Handbook of Formulating Dermal Applications

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Handbook of Formulating Dermal Applications

A Definitive Practical Guide

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WILEY

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Contents

Preface

Originally published by Allured in 2013 with the title "Apply Topically", this reissued book has the new title of "Handbook of Formulating Dermal Applications" and is published by Scrivener Publishing. It encases the same contents as the previous edition. In the three years since the original launch of this book, it has received rave feedback from industry colleagues as "the book" for experienced professionals and amateurs alike. The book idea stemmed from my experience and the understanding of the great and unmet need expressed by the many professionals I was teaching over the years. This understanding led me to the journey of collecting and organizing this precious information in one consolidated place.

The creation of semi-solid formulations to be applied topically is an area that requires multiple disciplines. Sciences, such as chemistry, physics and biochemistry, must complement artistic and creative talents, and engage mathematical and engineering skills.

Professionals that work in this industry are typically armed with an education in at least one of the above areas and acquire additional proficiencies over time in their workplace. Therefore, many of those skills are obtained by trial and error and by learning from experienced mentors.

As noted, having taught skin product development for many years, I have been constantly approached, most often by students but occasionally by colleagues as well, as to why there is no adequate book to refer when either beginning to formulate topical products or when a need for problem-solving arises that requires a deeper understanding in a specific area. In times past, I have been sympathetic, but unable to offer a reasonable answer. Perhaps this lack of foundation, this muddy ability to give a straight answer is what, ultimately, compelled me to construct the book you now hold/or accessing online.

Compiling such a book is challenging. The main reason is that advice and guidance is typically communicated verbally from one professional

to the other, in the same manner of loosely structured oral history—and it can be just as scattered. This book was created with the great collaboration of experienced and highly knowledgeable colleagues. It provides a comprehensive review of key elements in skin care product development and should serve as a basic guide for both beginners and advanced formulation chemists alike.

I sincerely thank my fellow contributors and hope that you, the reader, will find it valuable.

Nava Dayan PhD
Dr. Nava Dayan LLC
September 2016

Handbook of Formulating Dermal Applications: A Definitive Practical Guide.
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SECTION I:

Preliminary Considerations and Selection of Raw Materials

Handbook of Formulating Dermal Applications: A Definitive Practical Guide.
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CHAPTER 1

Pre-formulation Design and Considerations

Howard Epstein, PhD
EMD Chemicals

Key Words

Oil-in-Water Emulsification, Water-in-Oil Emulsification, Emulsifier Quaternary, Formulation Design, Global Intellectual Property, Marker Compounds, Oil/Water (octanol) Partition Coefficient, Anionic / Cationic / Amphoteric / Nonionic Sufactants, Tyrosinase

Introduction

The novice formulation chemist may be overwhelmed when challenged with developing a topical product suitable for a local or global market. The basic questions that come to mind are: *Where does one start? What criteria should a formulation chemist consider when selecting the ingredients to incorporate into a new product? How are safety and product performance claims established in different countries? What are the criteria for a patent? How does one ensure a patented formulation is not inadvertently being violated? Are any ingredients in the new formulation incorporated at levels restricted in a respective country where the formulation will be sold?* The ability to freely exchange information globally via the internet is a blessing and a curse. It is a blessing to have the ability to communicate and research information instantaneously and to conduct preliminary research conveniently from the desk prior to starting formulation activities. The curse is that the seeker of reliable information must have the ability to discriminate between opinion, facts and misinformation when accessing information from this resource.

This chapter is aimed at providing guidance to formulation chemists and other professionals involved in skin care product development, assisting them to produce innovative products. The goal is to provide insight with respect to planning and executing formulation development in an efficient and cost-effective process that is well-planned and intelligently executed.

Project Goals and Formulation Design

Prior to initiating project activity at the bench, a detailed description of the product design plan should be written. The project design sheet should provide a brief description of the project, including relevant background information of the rationale for the product. Product concept, goals, and objectives should be stated. The project description should contain the value proposition to the consumer, i.e., a statement of benefits that will be delivered by the product. It should include answers to the following questions: what unmet consumer need or needs will the new formulation provide and what is the formulation's cost constraints? Regulatory and other constraints should also be considered during the early phase in the design sheet. A thorough product description will assist the formulation chemist in the determination of appropriate technologies for consideration. The following product design checklist describes the types of questions a formulation chemist must satisfy before pressing forward on a potentially viable project:

- Project objective is clear and the concept and goals are stated.
- Value proposition is clear; benefit provided to the consumer is stated, budget for project is specified.
- Distribution (limited vs. global) is determined.
- Budget limitations are identified and isolated.
- Desired technologies are described in general terms.
- Desired claims for the product are defined; what is this product's end game?
- Target site of application is determined (i.e. the hair, face, body, or a combination of sites).
- An intellectual property search is conducted, where in known regulatory and patent restrictions are identified.
- Potential market analysis observations are conducted.

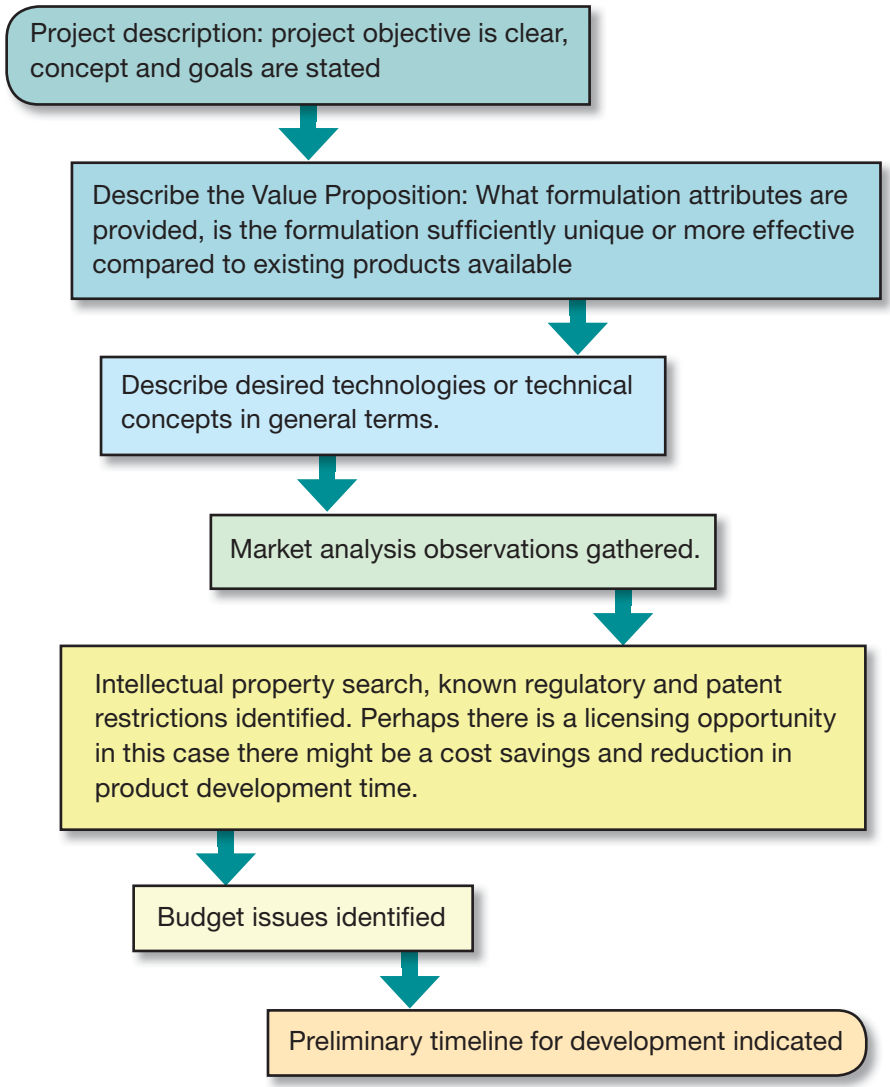
Once these questions have been considered and given a preliminary response, a product design flow will begin to form, following the logical tenets of initial formulative product scale-up. Such a workflow is shown in the following diagram:

Fleshing out a product design plan requires both satisfactory detail and the formulation chemist's willingness to address tough and complex questions. **Table 1** offers an example planning sheet for an SPF product, along with further questions the chemist must consider in pursuing the process.

Referencing the project design sheet, an intellectual property (IP) search should be conducted early on in the development stage. If the product is intended to be globally distributed, the formulation chemist should be familiar with the IP requirements of each region of the globe in which the product is intended for sale. For communication and assistance in the United States, the US Patent and Trademark Office (USPTO) can provide information regarding establishing and protecting IP.[1] An Intellectual Property Rights (IPR) Toolkit for protecting intellectual property rights overseas is likewise available from the USPTO.[2] The World Intellectual Property Organization (WIPO) is another valuable resource to obtain IP global information.[3] Varying

regulatory requirements can impact selection of ingredients, product claims and safety assessment. For example, China has a "positive list" of ingredients that may be used. Ingredients not listed will require a petition for approval, a process that is highly complicated and costly.[4] A complete battery of safety testing may be required by China utilizing animal testing. In contrast, the European Economic Union countries issued the 7th amendment to the EU Directive that bans animal testing of cosmetic ingredients and/or finished formulations.[5]

Product Design Workflow Diagram



Background and Project Description:

In 2011, the US Food and Drug Administration (FDA) issued its final Sunscreen Monograph in *Federal Register*, 76 FR 35620. This final rule addressed labeling and testing of sunscreen products. The final rule includes a broad spectrum test procedure for assessing protection across both UVA and UVB regions of the UV spectrum. The FDA acknowledges that not all sunscreen products are likely to pass the broad spectrum test criteria. In this case, these products may not bear a "broad spectrum" label claim. For the first time, the FDA acknowledges the need for UVA protection. The FDA also acknowledges that the test method required to meet the broad spectrum claim, a critical wavelength of 370 nm may be inadequate to fully protect in the UVA1 region (340-400 nm) of the spectrum. There is evidence to support the conclusion that exposure to UVA1 radiation can contribute to immune suppression and increase p53-positive cells. The cytokine p53 is a cancer and inflammation marker. The aim of this project is to design a sunscreen product that will exceed the new final sunscreen Monograph and provide enhanced protection in the UVA1 spectrum. The product should exceed the permitted SPF claim under *in vitro* and in *in vivo* testing, meet the broad spectrum requirement, and provide "superior" UVA1 protection. Superior UVA1 requires that appropriate testing to support a marketing statement "product designed for people who are concerned about exposure in the UVA1 spectrum and are concerned about resulting immune-compromised skin." There is a need for sunscreen products that provide maximum SPF and UVA1 and UVA2 protection.

Project Objective:

The aim of this project is to meet the need as described above with a product that consumers will find elegant and at a price perceived as mid- to high range in this market. Product will be distributed globally. Refer to market analysis report for further background information.

Project Milestones:

- Formulate a sunscreen product that conforms to the final FDA sunscreen Monograph.
- Determine what product form, i.e., cream or lotion, consumers will consider most elegant and be willing to purchase at the determined price point.
- Determine ingredients for formulation, combinations and levels permitted globally.
- Determine appropriate testing to establish product claims.
- Establish quality control specifications once a manufacturing process is determined for formulation.
- Determine facility with capability to manufacture the product.

Rationale for this Project as Regards Unfulfilled Consumer Need:

Consumers with sensitive skin and medical conditions that compromise health via exposure to UV radiation seek a sunscreen product that provides more protection from UVB and UVA radiation than currently available on the market. These individuals react more quickly to UV exposure, developing erythema and skin discomfort such as burning, stinging, and itching. This product is intended for use on any part of the body subject to UV exposure and must demonstrate an ability to minimize these conditions. Ideally this formulation should have global patent protection.

Additional Comments:

Budget must not exceed $XXX,XXX.00 without authorization.
Global intellectual property search required for this project.
Approval from regulatory department required for product launch.

Further Considerations to Be Addressed by Formulation Chemist:

1) When do polarity, hydrophobicity, lipophilicity, solubility, and viscosity become important considerations?
2) How do I increase the solubility of lipophilic ingredients in an aqueous-based formulation?
3) A sticky, greasy cream will not be suitable for a body cream. How do I formulate to avoid this outcome?
4) If the product is to be a sunscreen, what SPF claim will be made? Will the product have a broad spectrum UVA claim? If avobenzone is formulated, a photostabilzer will be necessary to maintain product performance. In this case what options are available?
5) What preservative system can I use and how do I optimize the efficacy of the selected preservative system? How do I ensure the preservative(s) does not interact with other ingredients within the package, resulting in a compromise of the package's integrity?
6) How do I select an appropriate emollient? For example, addition of a nonpolar lipid, paraffin oil, will improve moisture retention on skin, but may reduce spreading on skin.
7) Be aware that the selection of lipophilic ingredients of the emulsion may impact the selection of the emulsifier system.

Selecting The Right Ingredients for Your Design

Prototype starting formulations may be easily found in a variety of sources, such as the websites for ingredient suppliers' databases, trade magazines, and numerous textbooks, both online and in print. These formulations are frequently untested for their physical chemical properties, stability or interaction with the skin, and are intended to be used mainly for reference purposes. They may not be stable, adequately preserved, or optimized with respect to elegancy and performance. Their development is often limited and does not consider the optimal delivery of an "active" compound to desired skin or hair targets. Critical factors for formulation development should be considered when selecting the vehicle for the product that is the most appropriate when determining the project goal.

An active ingredient is incorporated into a carrier which is typically a mixture of ingredients that provide the product with its consistency. The carrier is referred to as a vehicle responsible for delivering the active ingredient into the skin. Topical product vehicles may be categorized by their intended us as follows: cleansing, decoration, care of skin, nails, and hair, hydration, and protection.[6] Classification of vehicles may be designed by function; shampoo or hair colorants for hair, polish or lacquer for nails, toothpaste, lipstick or lip-protection for the mouth, moisturizers, body lotion, aftershave, antiperspirant/ deodorant (AP/DEO), and sunscreen. Sensory feel and the chemical nature of the ingredients to be used will impact the decision to formulate in either o/w or w/o emulsion systems. The polarity of lipid components will also influence the selection of the emulsifier. To illustrate, microemulsions are small droplet size (5-50 nm) stable emulsions and may be considered when one desires to dissolve active substances with enhanced skin penetration and permeation or when certain components in the formulation should be protected for stability.[6] More recently the use of nano-emulsions, defined as emulsions with a particle size between 20–200 nm with a narrow distribution droplet size range, have become a popular approach for formulating more effective and elegant cosmetic products. In the European Union, products containing nanomaterials are required to be noted on the product label with the statement "contains noanomaterials."[5] At of this publication, no such requirement exists in the United States.

Pre-formulation Considerations—Vehicle Examples

Emulsions are the most common forms of vehicles for skin care products. Various emulsion types are available. Aqueous gels, w/o, o/w, and silicone-in-water (s/w), multiple emulsions, microemulsions, and nanoemulsions are a few examples. Selection of the emulsification system will determine the nature of the system. It is possible that certain emulsifiers having an identical designated chemical name in the International Nomenclature of Cosmetic Ingredient (INCI) Dictionary sourced from different suppliers will have a slightly different chemical composition.[7] For this reason, formulation chemists should keep records of the source of ingredients

and maintain a current specification sheet for each ingredient in the formulation as the project is initiated at the bench. If, for example, the product is targeted for children or for people with sensitive skin the selection of ingredients, particularly emulsifying agents, becomes increasingly important. Further considerations include application to the body site of intended use; what "time" the product is designed to be used (i.e., day vs. night cream);will clothing or bedroom pillowcases and sheets come into contact with the product; will other products be applied over or under the product? **Table 1** contains a list of resources available to identify common ingredients in topical formulations, their function, source of supply and other useful information for formulation chemists.

Table 1. Cosmetic Ingredient Reference Sources

Reference Source	Publisher
International Cosmetic Ingredient Dictionary and Handbook	Personal Care Products Council, Washington, DC
British Pharmacopoeia	The British Pharmacopoeia London
Title 21 of the U.S. *Code of Federal Regulations*, concerning food and drugs	United States Government
United States Patent and Trademark Office	United States Government
California Proposition 65	State of California
European Parliament Regulation EC No. 1223/2009	In effect as of July 2013. Addresses protection of human health by regulating cosmetic products. This legislation impacts products imported into the EU.
Cosmetic Ingredient Review	Personal Care Products Council, Washington, DC
Handbook of Cosmetic Science and Technology	Informa Healthcare, New York. Provides general information on all aspects of cosmetic science and technology.
Cosmetic Science and Technology	Marcel Dekker, Inc., New York. A series of textbooks, each reviewing different topics in the field of cosmetic technology.
Remington: The Science and Practice of Pharmacy	Lippincott Williams & Wilkins, MD, USA. An excellent resource for information for formulation bases for cosmetic and pharmaceutical products.
Harry's Cosmeticology	Chemical Publishing Company, MA, USA. Several chapters of information covering all aspects of cosmetic science and technology.

Choosing a Surfactant

Surfactants can be classified according to their charge being: anionic, cationic, amphoteric, or nonionic. Selection of the most appropriate surfactant will depend on a variety of considerations, including the purpose of the formulation, aesthetic considerations, the other ingredients to be formulated in the product, and the product form. Once the chemical class is selected the formulation chemist can select a surfactant or a combination of surfactants. Typically high surfactant solubility is desired for cleansing products, whereas medium solubility is required for emulsion spreading. Surfactants with low solubility in water can be formulated in w/o emulsions. A blend of surfactants is usually utilized for o/w emulsions. A surfactant molecule has a water-soluble component and an oil-soluble component. In an emulsion, these molecules reduce the interfacial thermodynamic tension at the water and oil phase, a process that lowers the energy needed to mix the oil into the water. Adding a surfactant therefore makes the emulsification possible, i.e., for the oil to disperse into the water phase as a discrete droplet. Each droplet is surrounded by a molecular layer of surfactant molecules around it which helps prevent the droplets around it from fusion and keeps them dispersed as distinct entities in the water.[8] Many resources are available to assist with the determination of the optimal selection of surfactants.[8-12] The Hydrophilic-Lipophilic Balance (HLB) system is a popular method used in the selection of the optimal emulsifier.[10] Formulation chemists should note that while the HLB system was designed for the evaluation of ethoxylated, nonionic emulsifiers, it may be applicable for the use of nonionic surfactants and should be used with caution in these cases. The HLB evaluation may not be as accurate for formulations containing ionic emulsifiers. Further, the required HLB is likely to change when the level of neutralizing agents, including triethanolamine, sodium oleate or potassium oleate are incorporated into the formulation. In these situations, it is advisable to monitor stability closely for signs of stability failure. These signs may be phase separation, color changes, pH changes, and viscosity changes.

Selecting a Suitable Emulsifier

Emulsifiers can act as solubilizers, and as spreading or dispersing agents. Selection of the appropriate emulsifier enables one to formulate homogeneous mixtures, allowing the dispersion of agents ordinarily difficult to disperse, and for oil phases to be mixed with water. Not all emulsifiers behave in the same way. The properties of a given emulsifier may dictate the emulsion type. Moreover, the emulsifying agent will impact the desired sensory properties of the product including color, odor, and consistency.

Nonionic emulsifiers are frequently selected to emulsify fats, oils, waxes, and powder suspensions. They may be suitable when the formulation requires high levels of electrolytes, acidic or basic formulations with a pH ranging roughly between 4 and 8 and good stability in hot environments and hydroalcoholic systems. Mild

quaternary emulsifiers may be selected for formulations having an extreme pH, hair conditioning products, emulsification of silicones, and structural agents for anhydrous sticks. Ethnic hair care products, for example, frequently require formulation at a pH range of 12-14. Therefore, a well-designed plan should include the following parameters: surfactants that can be considered, and emollients that can be used at that high level of pH, ensuring long-term stability. For formulations with a pH ranging between 4.0 and 7.0, but not above 8.0, stearyl alcohols and synthetic waxes will provide good compatibility with oils and should exhibit good batch-to-batch consistency. Polysorbates are the optimal surfactants for emulsification systems that contain waxes, silicones and solubilizing agents in o/w emulsions for hair, skin moisturizers, and skin cleansing formulations, while sun care formulations and long-wear lipsticks benefit from the use of rinse-off resistant ingredients, such as silicone, silicone derivatives, and ethylcellulose polymers. A variety of formulation approaches are possible to achieve water- or wash-off resistance. For sunscreen formulations, choosing a w/o system will assist in reducing the occurrence of re-emulsification of the product when applied to skin, along with subsequent exposure to water. Emulsions using hydrophilic emulsifiers are useful for this purpose.[13-15] Polyoxyethylene sorbitan monooleates and monostearates are common examples of hydrophilic emulsifiers. Long-wear and water-resistant properties for lipsticks and sunscreen formulations can be achieved by using silicone oils and film forming polymers. For these requirements, sucrose distearates are another optional class of ingredients. Phosphate esters can be used to assist in keeping a shampoo clear and stable, reducing the probability for precipitation developing, as may occur over time. For boosting foam in shampoos, enhancing skin feel, or modifying the viscosity of frequent-use products, amphoteric surfactants may be an option. Amphoterics are frequently used in baby formulations, because they are associated with low potential for irritation to skin, as exemplified by Johnson & Johnson's *"No More Tears" Baby Shampoo.*

Other Pre-formulation Considerations

A formulation intended to enhance percutaneous absorption requires that the formulation chemist consider the physical chemical properties of the active compound to be used so that an initial prediction can be assessed. Molecular weight in the range of 500 daltons, and thus appropriate for skin penetration and lipophilicity, may be expressed by calculating the octanol/water partition coefficient. Properties of the vehicle are another key factor, as these properties may either enhance or retard penetration. Particle size, pH in water, stability, and potential incompatibility of the actives and other ingredients should be considered at the pre-formulation stage as well. The chemical nature of the ingredients in the formulation may be impacted by the type of claims sought and the consequent testing required in order to validate the claim. (The reader is here referred back to the project evaluation process example as shown in Table 1.) Again, the formulation chemist should consider this possibility during the pre-formulation stage. In the design of sunscreen

formulations, it is desirable to minimize absorption of the sunscreen into the skin, because the sunscreen is intended to absorb and scatter UV light, thus protecting the skin. On the other hand, in the case of moisturizers that not only provide an occlusive barrier to skin but also deliver moisturizing and healing agents, skin-enhanced penetration would be desirable. For skin lightening formulations, if the target mechanism is, for example, tyrosinase inhibition, which is an enzyme that resides in the melanocytes in the epidermis of human skin, the formulation should be able to allow penetration beyond the outermost layer of skin. For skin lightening and smoothing formulations using an active that requires a low pH environment for stability or activity, the emulsifier of choice must be compatible with the pH of the active selected. For optimal activity when using lactic or glycolic acid as a peeling agent in the formulation, acidic pHs may be desirable.

In a published study in which alpha hydroxy acid (AHA) was employed, it was found that the stimulation of skin cell renewal was optimized at a pH below 6, with pH 3 being optimal; other investigators reported an improvement in the appearance of skin when AHA was tested after being neutralized to a salt form with sodium hydroxide.[16] Sodium ascorbyl phosphate, a derivative of ascorbic acid used in skin lightening formulations, requires a neutral pH to maintain stability. For increased absorption of hydrophilic actives, w/o emulsions may be a desirable option, as this form of emulsion may assist the active's passage through the lipid layers of the stratum corneum.[6,7,9] The rate of product absorption into skin will frequently depend on the nature of the vehicle, the skin site and body region, and the subject's state of hydration. Other factors are the molecular size of the active, pH levels, degree of dissociation, and volatility and solubility of the active in lipids and water. There is a direct correlation between the solubility of the compound in the vehicle when applied to skin and its penetration. The oil/water partition coefficient is a factor to be considered. A compound that is more compatible with the lipophilic nature of the stratum corneum may have a more favorable penetration to skin from the vehicle.[6,7,9,12] For lipsticks and other anhydrous stick products, good stick structure and application to the lips, termed "payoff," and describing the color smoothness of the product application, are important considerations. A stick formulation requires a balance of wax and emollients to maintain structure and stability and to prevent "sweating" of the ingredients on the stick. An application intended to be used on the lips should be smooth and creamy. Additional considerations include choice of the solvent used in order for the colorants to eliminate a tacky application on lips and prevent the color from bleeding, or"feathering," around the lip area. For more in-depth guidelines, please refer to Sango and Binder's chapter on lip care formulation strategies (Chapter 20).

Botanicals

The use of ingredients derived from plants, including botanical extracts used in topical semi-solid formulations, presents unique challenges. Color, odor, method of extraction, and residual solvents, as well as lot-to-lot consistency associated with

natural variations such growing seasons and the ingredient's geographical source, all are influential aspects of botanical usage. The same genus and species of a plant grown in different geographical locations where weather and soil conditions differ may result in variations in content and levels of key components. Other considerations are available safety testing conducted on the extract and prior use in other non-cosmetic applications, such as food and nutritional supplements. Natural compounds may contain chemical components that are photosensitizers with the potential to damage skin when exposed to ultraviolet light. When botanical resources are limited, there is always the possibility that future lots might be adulterated with a botanical having similar marker compounds or physical appearance as the desired botanical.

Choice of Preservation Systems

When selecting the appropriate system in which to preserve a formulation from potential contamination upon consumer use, the following key considerations should be reviewed:

- Consumer trends and media attitudes toward specific preservative compounds
- Regulatory considerations
- Formulation compatibility

The formulation chemist is advised to consult with suppliers and appropriate regulatory authorities for preservative selection and testing for preservative efficacy. Various factors can have a negative impact on the efficacy of any preservative system. Ingredient incompatibilities, packaging effects on the product's components, inadequate preservation and potential contamination concerns during product development should also be taken into consideration. For details on formulation preservation, the reader is referred to the chapters under the section heading **Stability and Preservation** in this book's table of contents.

Manufacturing Considerations

Formulation scale-up may present unexpected complications, depending on the complexity of the formulation, compounding procedure design, and the availability of manufacturing equipment. The formulation chemist should ensure that the formulation can be duplicated in scale-up. A formulation generated by a relatively small handheld homogenizer used at the laboratory bench may not be reproducible with the same appearance and tactile characteristics when a production-sized colloid mill is used. If large-scale production process and equipment application results in increased water loss from the process vessel, the lost water should be added after batch compounding is completed, following the formulation chemists approved procedure. The same considerations should be taken into account regarding pH and viscosity adjustments. For details on scale-up procedure, I refer you to Kimball's chapter on manufacturing topical formulations (Chapter 9).

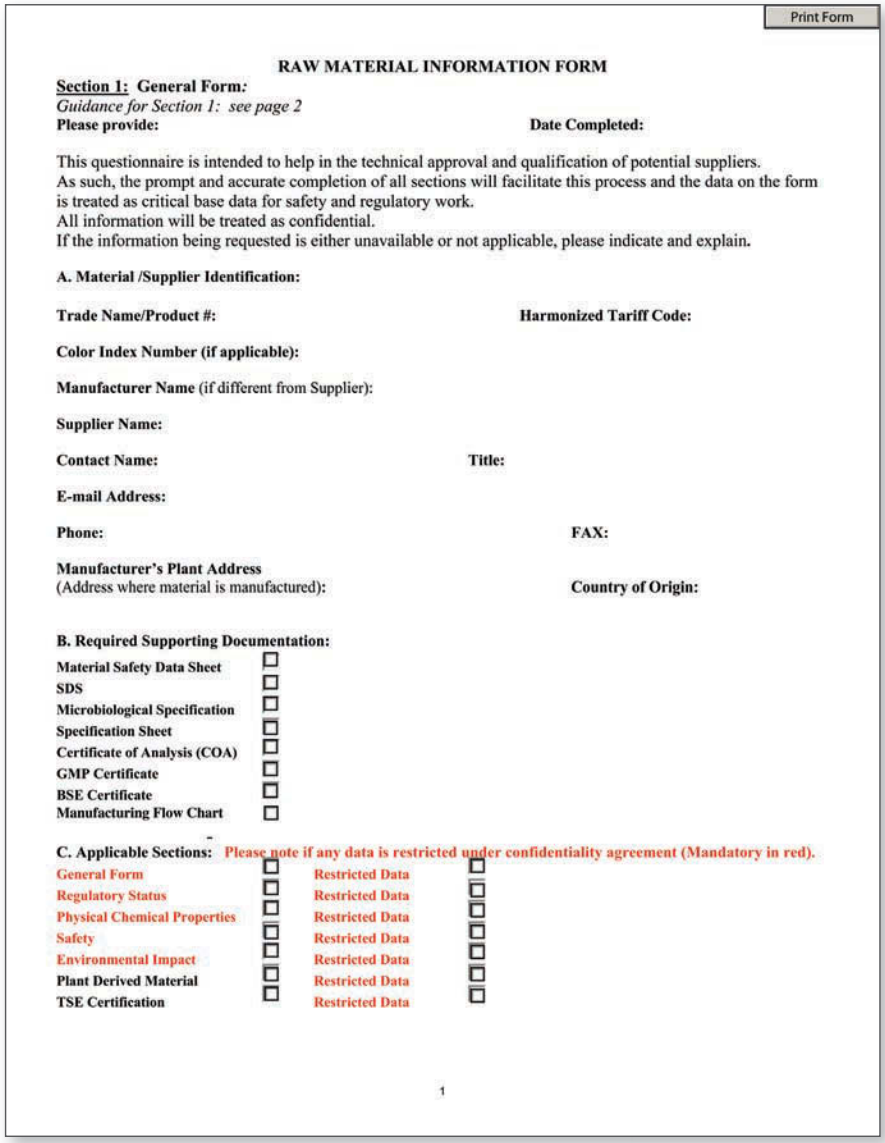
Reading a Technical Product Sheet

A well prepared Technical Product Sheet (TPS) should provide answers to the formulation chemist's most basic questions. Key information should include: the assigned name as listed in the INCI Dictionary, a brief description of the material and its main purpose for use in the formulation, a description of the purpose of the ingredient, the benefits provided using the ingredient, its required storage conditions and shelf-life, and a summary of performed efficacy tests. Frequently missing but no less important are references for biological, *in vitro* and *in vivo* studies conducted to support the claimed activity of the ingredient. Without credible references it is difficult to determine the reliability of the results obtained. In the case of data supporting the biologically active ingredients when either an *in vitro* or *in vivo* study is presented in the TPS, there should be reference to the controls and statistical analysis. The formulation chemist should question the reliability of the data if this information is not available. These documents may be one or more pages in length depending upon the amount of data a company wishes to convey. If the technical information included in the sheet references scientific studies, it is important to evaluate the validity of those studies with respect to safety and performance claims for the material. Small-scale pilot studies may not provide statistically meaningful or significant results; for this reason the sample number used in a test should be indicated with a well-run statistical analysis. The protocol should always be appropriate for the aim of the study and the function of the product. In addition to the TPS, a material safety data sheet (MSDS) should be available for the ingredient. The MSDS should be the first document generated, since it is required for appropriate shipping of the compound or formulation, as well as to advise on handling when human exposure is involved. Most companies will not permit a sample of any ingredient to be located in their facility unless an MSDS accompanies the material. The MSDS should contain safety and handling information and should be the first document to be reviewed by the formulation chemist prior to handling the ingredient.[18] The following is a list of key information that should be included in any MSDS:

- Hazard(s) identification
- Composition/information on ingredients
- First-aid measures
- Fire-fighting measures
- Accidental release measures
- Handling and storage
- Exposure controls/personal protection
- Physical and chemical properties
- Stability and reactivity
- Toxicological information
- Ecological information
- Disposal considerations

- Transport information
- Regulatory information
- Other information

At the permission of the Personal Care Products Council, an example of its Raw Material Information Form, aka Technical Product Sheet, is presented.[17,24] This is provided in effort to demonstrate the organization of a TPS, as well as the specificity of the information required in filling it out responsibly.



Print Form

RAW MATERIAL INFORMATION FORM

Section 1: General Form:
Guidance for Section 1: see page 2
Please provide: **Date Completed:**

This questionnaire is intended to help in the technical approval and qualification of potential suppliers.
As such, the prompt and accurate completion of all sections will facilitate this process and the data on the form is treated as critical base data for safety and regulatory work.
All information will be treated as confidential.
If the information being requested is either unavailable or not applicable, please indicate and explain.

A. Material /Supplier Identification:

Trade Name/Product #: **Harmonized Tariff Code:**

Color Index Number (if applicable):

Manufacturer Name (if different from Supplier):

Supplier Name:

Contact Name: **Title:**

E-mail Address:

Phone: **FAX:**

Manufacturer's Plant Address
(Address where material is manufactured): **Country of Origin:**

B. Required Supporting Documentation:

- Material Safety Data Sheet ☐
- SDS ☐
- Microbiological Specification ☐
- Specification Sheet ☐
- Certificate of Analysis (COA) ☐
- GMP Certificate ☐
- BSE Certificate ☐
- Manufacturing Flow Chart ☐

C. Applicable Sections: Please note if any data is restricted under confidentiality agreement (Mandatory in red).

General Form	☐	Restricted Data	☐		
Regulatory Status	☐	Restricted Data	☐		
Physical Chemical Properties	☐	Restricted Data	☐		
Safety	☐	Restricted Data	☐		
Environmental Impact	☐	Restricted Data	☐		
Plant Derived Material	☐	Restricted Data	☐		
TSE Certification	☐	Restricted Data	☐		

1

RAW MATERIAL INFORMATION FORM

Section 1: General Form

D. Composition & Material Identification:

Total target contents of the components should sum up to 100%. List all intentionally-added constituents in this table. Please be noted the data here is critical base data for safety and regulatory work.

Definition of Function:
Key Ingredients - defined as chemicals intended to function in finished products.
Additive Ingredients – defined as chemicals intentionally added to material to maintain its quality or stability, such as preservative, anti-oxidant, UV filter, that does not function in finished product formula.

#	Constituent name (Assigned INCI name)	CAS#	EINECS# / ELINCS#	Min (W %)	Target (W %)	Max (W %)	Constituent Function	Feedstock Origin
1								
2								
3								
5								
6								
7								
8								
9								
10								

General Comments:
If you selected the Feedstock Origin "Bovine" or "Animal-other", please attach TSE certification.
If you select the Feedstock Origin "Other", please explain:
Is the material a polymer according to the definition (ECHA)
Please note if the material is a polymer a detailed impurity profile should be provided in following table G.

E. Certifications: Please supply as applicable.

Kosher Certification	☐ Yes ☐ No	Halal Certification	☐ Yes ☐ No
Is the material Food Grade?	☐ Yes ☐ No	GRAS (Generally Recognized as Safe)?	☐ Yes ☐ No
USP?	☐ Yes ☐ No	EU Pharmacopeia?	☐ Yes ☐ No

Other? (Please describe and/or attach)

LOI Declaration:
Do you certify that all the lots you supply will comply with all the answers until further notice from you? ☐ Yes ☐ No
Comments/Notes:

RAW MATERIAL INFORMATION FORM

Section 1: General Form

F. Global Inventory Status: In the table below, please describe the inventory status of each constituent. Please choose the Inventory Status in each field below:

#	Constituent name (Assigned INCI name)	US TSCA	Canada Inventory	Australia AICS	China IECSC	Japan ENCS	Japan CLS	Korea ECL	Philippines PICCS
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									

General Comments/Notes:

G. Impurity Profile: Please refer to Guidance for explanation.

Impurities/Residues/Catalysts/Monomers/By-Products An impurity is any chemical substance that is unintentionally present. List all impurities (regardless of amount).	CAS #	Max Level in RM	% or ppm or ppb	Comments

RAW MATERIAL INFORMATION FORM

Section 2: Regulatory Status: *Guidance for Section 2: see page 5*

Instructions: Provide any known restrictions on this material for use in cosmetic products: For example, restrictions relating to UV Filters, colorants or preservatives or other restrictions noted in Annex III of the Cosmetic Directive, CIR. or Canadian Hot List

A. Restrictions:

Country	Restriction (% and approved use if any)
US	
Canada	
EU	
Australia	
China	
Japan	
Korea	
Other:	

B. Compliance:

Compliance with Regulations:	Yes or No?	Description
Are any of the ingredients a known Carcinogen, Mutagen or Reproductive Toxicant as defined in Annex I Directive 67/548 / EEC?		
Does the raw material as supplied contain any ingredients or impurities identified on the Substances of Very High Concern List under REACH?		
Are all of the ingredients compliant with the European Dangerous Substance Directive (67/548/EEC: 79/831/EEC)?		
Are all of the ingredients in compliance with the European Cosmetic Directive (76/768/EEC)?		
Are any of the ingredients or impurities listed by California Proposition 65?		
Are any of the ingredients declarable by California's SB 484?		
Are any of the ingredients or impurities found to be Carcinogenic by NTP?		
Are any of the ingredients or impurities found to be Carcinogenic by IARC?		

****Please attach the REACH status and summary (including any components that may require authorization) for the material.**

Animal Testing:	Yes or No?	Description
Are you in compliance with the 7th Amendment of the European Cosmetic Directive 76/768/EEC prohibiting animal testing after a certain date?		
Has your company conducted or commissioned any animal testing on this raw material, or are you aware of any such animal testing conducted by a third party? Please specify most recent testing date.		
If testing was conducted post September 11, 2004, please specify date; describe purpose and endpoints for the test(s).		

Volatile Organic Content	Description
Are any of this material's ingredients classified as a VOC?	
Total Raw Material VOC content in % (wt/wt) **HVOC**	
MVOC	
LVOC	
VOC Exempt?	

Section 2: Regulatory Status

4

RAW MATERIAL INFORMATION FORM

Section 3: Physical Chemical Properties

Guidance for Section 3: see page 6

A. Physical Form:

The material is supplied as If material is a powder please supply Particle Size Distribution data

The physical parameters reported here are applicable to the material as it is supplied.

If no is chosen, explain:

B. Physical Constants:

Physical Parameter	Value	Additional Information
Molecular Weight*		
Specific Gravity		
Partition Coefficient (K_{ow})		
Melting Point	°C	
Boiling Point	°C	
Freezing Point	°C	
Flash Point	°C	
Minimum Ignition Temperature	°C	
Spectral Data (As applicable)		
UV/Visible		
IR		
Mass		
Fluorescence		
NMR		
Separation/ Analysis Data		
GC		
HPLC		
HPTLC		

*Average molecular weight for key component.

Please indicate SMILES notation for the key component:

Note: If physical property data is included in the attached MSDS, check here: ☐

If Particle Size distribution data is on the agglomerate please check this box: ☐

Please also specify percentage of material that is less than 100 nm.

Section 4: Safety

5

RAW MATERIAL INFORMATION FORM

Section 4. Human Safety

Guidance for Section 4: see page 6

Please supply robust summaries of the tests performed as an attachment.

The testing identified here was completed on the material as it is supplied.

If the answer is "no," please explain.

Please specify when *in vitro* models are used.

A. Testing Summary:

Test	*Protocol*	*Date*	*Result*
Acute Oral Toxicity			
Sub chronic Toxicity (28 / 90 day test)			
Dermal Irritation			
Dermal Sensitization			
Dermal Absorption			
Mucous Membrane Irritation (Eye)			
Mutagenicity (Ames)			
Genotoxicity			
Carcinogenicity			
Inhalation Toxicity			
Reproductive Toxicity			
Comedogenicity			
Photo-irritation			
Photo-toxicity			
Photosensitization			
Other:			
Other:			
Other:			
Other:			
Other:			

General Comments/Notes:

Section 4: Safety

6

RAW MATERIAL INFORMATION FORM

B. Materials of Concern: *Guidance for a list of Materials of Concern, see page 7*

Material(s) of Concern	**CAS#**	***ALL SOURCES:* Total Inclusion Level %**	***Added Ingredient Contribution* Inclusion Level %**	***Natural Source Contribution* Inclusion Level %**

C. Declarable Allergens: Allergens other than those listed here may be dislcosed in the Botanical Section.

Regulated Allergens	**CAS#**	**Does not contain**	***ALL SOURCES* Total Inclusion Level %**	***Added Ingredient Contribution* Inclusion Level %**	***Natural Source Contribution* Inclusion Level %**
Alpha-Isomethyl Ionone	127-51-5	☐			
Amyl cinnamal	122-40-7	☐			
Amyl cinnamyl alcohol	101-85-9	☐			
Anise alcohol	105-13-5	☐			
Benzyl alcohol	100-51-6	☐			
Benzyl benzoate	120-51-4	☐			
Benzyl cinnamate	103-41-3	☐			
Benzyl salicylate	118-58-1	☐			
Butylphenyl methylpropional	80-54-6	☐			
Cinnamal	104-55-2	☐			
Cinnamyl alcohol	104-54-1	☐			
Citral	5392-40-5	☐			
Citronellol	106-22-9	☐			
Coumarin	91-64-5	☐			
Eugenol	97-53-0	☐			
Isoeugenol	97-54-1	☐			
Evernia Furfuracea (Treemoss) Extract	90028-67-4	☐			
Evernia Prunastri (Oakmoss) Extract	90028-68-5	☐			
Farnesol	4602-84-0	☐			
Geraniol	106-24-1	☐			
Hexyl cinnamal	101-86-0	☐			
Hydroxycitronellal	107-75-5	☐			
Hydroxyisihexyl 3-cyclohexene carboxaldehyde (Lyral)	31906-04-4	☐			
Limonene	5989-27-5	☐			
Linalool	78-70-6	☐			
Methyl 2-octynoate	111-12-6	☐			

Please Note: Allergens not included in this list may be disclosed under materials of concern section above or in the Plant Derived Scetion.

Section 4: Safety

7

RAW MATERIAL INFORMATION FORM

Section 5. Environmental Impact. *Guidance for Section 5: see page 8*

Please supply robust summaries of the tests performed as an attachment. The testing identified here was completed on the material as it is supplied. If the answer is "no," please explain.

Endpoint	*Protocol*	*Date*	*Result*
Aquatic Toxicity			
Short-term toxicity testing on *Daphnia**			
Long-term toxicity testing on *Daphnia*			
Growth inhibition study on algae			
Short-term toxicity testing on fish*			
Long-term toxicity testing on fish (OECD 210, OECD 212 or OECD 215)			
Activated sludge respiration inhibition testing			
Nitrification inhibition testing			
Degradation			
Biodegradability Study			
Simulation testing on ultimate degradation in surface water			
Soil simulation testing			
Sediment simulation testing			
Aerobic rate of biodegradation (please specify media)			
Anaerobic rate of biodegradation (please specify media)			
Hydrolysis as a function of pH			
Identification of degradation products			
Fate & Behavior in the Environment			
Life cycle analysis (LCA)			
Adsorption/desorption screening study			
Bioconcentration in an aquatic species			
Effects on Organisms			
Short-term toxicity testing on earthworms*			
Long-term toxicity testing on earthworms			
Long-term toxicity testing on soil invertebrates other than earthworms			
Effects on soil microorganisms			
Short-term toxicity testing to plants*			
Long-term toxicity testing to plants			
Long-term toxicity testing to sediment organisms			
Long-term or reproductive toxicity testing to birds			

Section 5: Environmental Impact

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RAW MATERIAL INFORMATION FORM

Section 6: Plant Derived: *Guidance for Section 6: see page 9.*

Please attach a manufacturing flow chart specifying mode of isolation or extraction. For materials that have identified plant or combination feedstock origin, or contain more than one plant species please fill out one for each species identified.

Please specify plant species

Please specify plant part(s) used to make this material

Extract % Solids %

If a marker compound is included, or available please identify and specify level.

Please specify Phylogenetic name:

Genetically modified? Yes ☐ No☐ Unknown ☐

If the INCI name includes the phylogenic name of the plant, please answer the following questions:

1. Is your Raw Material included in the IFRA guidelines? Yes ☐ No☐
2. If 'Yes', does the Raw Material meet the IFRA guidelines? Yes ☐ No☐
3. If 'Yes', please specify the amendment:
4. Revision Date:
5. Was the plant / botanical /fragrance screened for pesticides? Yes ☐ No☐
6. If 'Yes', what are the pesticide residue levels?
7. Do the pesticide residues present meet the European Pharmacoposia Guidelines? Yes ☐ No☐
8. Does the Raw Material contain any denatured alcohol? Yes ☐ No☐
9. If "Yes", please specify the denaturant(s):

Does the botanical contain, by addition or as a processing aid, any of the following nut/seed products?

Materials of Concern	Does Not Contain	All Sources Total Inclusion Level %	Added Ingredient Contribution Inclusion Level %	Natural Source Contribution Inclusion Level %
Tree Nuts --	☐			
Almonds	☐			
Brazil nuts	☐			
Cashews	☐			
Chestnuts	☐			
Cobnuts	☐			
Hazelnuts (Filberts)	☐			
Macadamia nuts	☐			
Pecans	☐			
Pistachio nuts	☐			
Shea nuts	☐			
Seed products, oils or derivatives --	☐			
Peanuts	☐			
Sesame seed	☐			
Sunflower seed	☐			
Cotton seed	☐			
Canola (Rapeseed)	☐			
Other (please specify and describe) ☐	☐			

Section 6: Plant Derived Material

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RAW MATERIAL INFORMATION FORM

Section 7: TSE Certification: *Guidance for Section 7: see page 9*
The information captured here is intended to collect details on components that are derived from internal organs or connective tissues of animals.

	Ingredient	Identify Animal Species	Identify Source Organs	Age of Animal	Country of Origin	BSE Country Status GBR**
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

** Category rating based on the EU Commission scientific steering committee (SCC) Regulation 999/2001-Geographical Risk of Spongiform Encephalopathy (GBR) Adopted on January 11, 2002. Updated on October 31 2007. As noted on the .EFSA Website

NOTE: Level I--Highly Unlikely, Level II--Unlikely but Not Excluded, Level III--Likely but Not Confirmed or Confirmed at a Lower Level, Level IV--Confirmed at a Higher Level

Certification of Isolation Method:
The material described in the table above is certified to be classified as a Category 3 under **Regulation (EC) No. 1174/2002.** As such the material shall be compliant with Articles 6 & 7 including:

(b) processed in a processing plant approved in accordance with Article 13 using any of processing methods 1 to 5, in which case the resulting material shall be permanently marked, where technically possible with smell, in accordance with Annex VI, Chapter I, and disposed of as waste either by incineration or by co-incineration in an incineration or co-incineration plant approved in accordance with Article 12 or in a landfill approved under Directive 1999/31/EC;
(c) processed in a processing plant approved in accordance with Article 17;
(d) transformed in a technical plant approved in accordance with Article 18;

and suitable for its intended use.

Name of Certifying Person Title

Date

Section 7: TSE Certification 10

Regulatory Considerations

Each region of the world has a designated regulatory agency that provides the framework to which the skin care industry should adhere, and though these agencies may vary in their organizational structure and methods of compliance, the formulation chemist should be familiar with their respective requirements in order to be able to formulate a globally accepted product and to have the latitude to consult with experts when necessary.

In the United States, the Food and Drug Administration (FDA) is responsible for the regulation of cosmetic product safety under the authority of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drugs Act of 1906 was the first of more than 200 laws that constitute one of the world's most comprehensive and effective networks of public health and consumer protections. Initially the Federal Food, Drug, and Cosmetic Act of 1938 (FD&C Act) passed after a legally marketed toxic elixir caused the death of 107 people, many of whom were children. The FD&C Act completely overhauled the public health system. Among other provisions, the law authorized the FDA to demand evidence of safety for new drugs, issue standards for food, and conduct factory inspections. Currently, the FDA regulates $1 trillion worth of products per year. It ensures the safety of all food except for meat, poultry, and some egg products; ensures the safety and effectiveness of all drugs, biological products (including blood, vaccines and tissues for transplantation), medical devices, and animal drugs and feed; and ensures that cosmetics and medical and consumer products that emit radiation do no harm. Further information is provided by the United States government in volume 21 part 700 of the *Code of Federal Regulations* (CFR). On April 18, 2012, a bill to amend the FD&C Act was proposed in the House of Representatives, referred to as H.R. 4395. H.R. 4395 is intended to further establish new procedures and requirements for the registration of cosmetic product manufacturing establishments.[20] US labeling requirements are enforced under the FD&C Act and 21 CFR 1.3(a).[21]

Canada has a regulatory structure similar to the United States. Further guidelines for cosmetic safety, labeling and packaging of cosmetic products may be found in Health Canada's Food and Drugs Act, Chapter 869 on Cosmetics Regulations.

Member states of the European Union (EU) decided to harmonize their national cosmetic regulations to provide free circulation of products within the member countries. The EU published rules and regulations for the safety of cosmetic products introduced into the EU market under Regulation (EC) number 1223/2009 of the European Parliament. The regulations are very comprehensive and outline the general requirements to establish product safety including testing and labeling. A responsible person must be designated to be legally responsible for product compliance for products commercialized within the European community. This includes products manufactured outside EU member nations, but imported into the member countries.

In Japan, the Ministry of Health and Welfare is responsible for the regulation of cosmetics and pharmaceuticals. There is a categogy known as "quasi drugs" which is somewhat comperable to the FDA category of "over-the-counter" or OTC, drugs. Japan maintains a list of ingredients that are prohibited for use in skin and hair care formulations; a positive list of ingredients with limits on levels of use also exists for various ingredients including preservatives and sunscreens.

Chinese products are regulated under the State Food and Drug Administration (SFDA) over seen by the Ministry of Health. Manufacturers and distributors are

subject to licensing requirements from the SFDA. The Ministry maintains a positive list of ingedients that may be used in cosmetic products; ingredients not on this list must be registered and approved for use by the agency.

The Australian Department of Health and Ageing and the Therapeutic Goods Administration regulate ingredients used in the production and importation of cosmetic products into Australia. The regulations are similar to those in the United States and EU. The agency maintains a list of ingredients classified as industrial chemicals. New cosmetic ingredients not listed in the Australian Inventory of Chemical Substances may be subject to an application for exemption by the agency. In addition, to regulation of the ingredients used in a formulation, there are label requirements that may differ between the countries.

Beyond the regulation of ingredients, there is usually a requirement for specific ingredient labeling that may vary in different regions of the world. If there is an ingredient that one desires to keep as a trade secret, appropriate regulations should be consulted for that region of the world.[23]

Safety of the Formulation

You would be hard-pressed to find any two given countries' governments that agree fully as to the proper safety requirements for a formulation that is meant to be applied to the skin. In most cases, while safety protocols are lettered out quite specifically for over-the-counter (OTC) and prescription-strength pharmaceutical products (i.e. drugs), cosmetic formulations are merely "recommended," though sometimes strongly, to have such protocols outlines. The liability for safety of cosmetic products in the United States lies with the entity (company) that is placing them in the marketplace. For example, products intended for use in proximity to the eye area or that may come in contact with the eye should be tested for eye irritation. Products should also be evaluated for skin irritation and sensitization. Since for many of the toxicological end points validated methods do not exist, careful consideration should be given to the study protocol, concentrations of the product to be tested, intended use, and regions of the globe the product will be commercialized. Other studies should be conducted to confirm that the product is not toxic to the user nor to the environment through either application or disposal. California Proposition 65 contains a list of chemicals that may cause cancer or reproductive toxicity. All products manufactured, distributed, or sold in California must comply with the exposure and or labeling requirements that are specified in the proposition.[25] Appropriate regulatory and safety authorities should be consulted to determine the most appropriate testing protocols for a given formulation. The following is a generalized list of standard safety tests that all topical care products should undergo.

- Toxicity
- Percutaneous Absorption
- Skin Irritation
- Eye Irritation

- Skin Sensitization and Photosensitization
- Subchronic Toxicity
- Mutagenicity/Photogenotoxicity
- Microbiological Testing

Summary

Formulating, developing, and commercializing cosmetic products for a global market does not look to get any less complex and challenging in the future. Complications arise as each of the world's regions' regulatory bodies proffers its own product preferences and safety and regulatory requirements. Pre-formulation planning, therefore, which should encompass knowledge of the ingredients to be used in the formulation and the regulatory and safety requirements of each region of intent, will shorten the development cost and save the formulation chemist much time in the process. Currently in the United States and other regions of the world, the cosmetics and pharmaceutical industries are growing increasingly more cost-conscious; there is a widespread reluctance to invest large sums of money to support the testing and safety of new active ingredients. This fact declares the role of safety, testing standards, and intelligent pre-formulative design to be more important than ever.

As the reader navigates the course of this book, they are reminded to be in constant awareness of the crucial impact of a well-designed plan.

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CHAPTER 2

The Use of Thickeners in Topically Applied Formulations

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Key Words

Topical; Sensory; Surface active; Stabilize; Hydrated; Hydrophobic; Hydrophilic; Lipophilic; Translucent; pH; Thickening

Introduction

The use of thickeners is ubiquitous in topically applied products. They function to provide products a desired feel, look, and flow properties. They help stabilize emulsions, suspend particles, and turn liquids into gels, pastes, and semisolids. This chapter will review the different chemical key classes of thickeners and their mechanisms of action. It will further offer advice on choosing the right thickener for different applications. Thickeners enhance consistency and contribute to product appearance by providing volume and luxurious sensory properties. Thickeners generally provide increased stability to a formulation and in most cases enhance performance for a particular application.[1]

Viscosity, suspension, and rheological properties are the key factors to consider when using thickeners in topical formulations. Some thickeners act as humectants, since they have the ability to attract and retain water on the skin or hair, and therefore have the potential to act as skin moisturizers. Other classes of thickeners have primary or secondary emulsifying properties. When primary, they can be used as standalone polymeric surfactants with no additional surface active agents to stabilize the formulation. When secondary, thickeners will suspend, thicken, and provide co-emulsification benefits in conjunction with other ionic surfactants. Classes of thickeners can be completely natural or synthetically derived. Examples of natural thickeners are waxes, polysaccharides (sugars, starches), gums, modified cellulose, clays, and proteins. Synthetic polymers, because of their relatively higher purity

and batch-to-batch consistency, are more uniform in their performance and present fewer variables when compared to natural thickeners. Thickeners can be used in most types of topically applied formulations. These can be creams, lotions, cleansing washes, gels, and serums. In addition, they can be used in hair care formulations to produce styling aid gels, sprays, creams, lotions, and pomades. Thickeners for skin and hair care can be nonionic (neutrally charged), cationic (positively charged) or amphoteric (having both positive and negative charges). Chitosan derivatives are a good example—e.g., **Carboxymethyl Chitosan and Hydroxyethyl Chitosan**—of this latter thickener class. Thickeners are also widely used in color cosmetics. They build structure in anhydrous color formulations such as lipstick, lip gloss, eye shadow, and mascara. They are used in foundation color liquid makeup and primers to thicken, stabilize, and improve performance properties of such formulations.

Rheology

Rheology is the science of how materials flow. When a force is applied to a fluid, it begins to flow in response. This applied force is called the sheer stress and is defined as force per unit area, usually measured in Pascals (Pa). The flow is fastest at the point where the force is applied and drops off the further the distance from the point where the force is applied. The sheer rate is the velocity (cm/sec) divided by the distance from the boundary (cm), with units of cm^{-1}. Rheological fluid flow is illustrated in **Figure 1**.

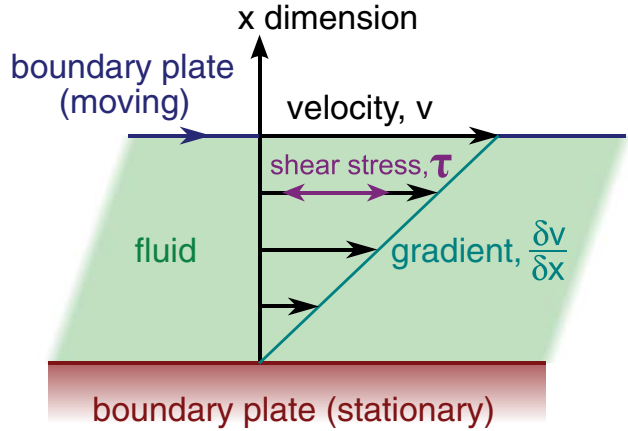

Figure 1. Rheological Fluid Flow Showing Sheer Rate

Viscosity is a measure of flow resistance; the higher the viscosity, the more resistant or "thicker" the fluid. Viscosity is defined as sheer stress divided by shear rate, with common units of pascal-seconds (Pa-s) or centipoise (cP); 1 cP = 1 mPa-s = 0.001 Pa-s. Fluids can exhibit various kinds of flow behaviors. In a Newtonian liquid (**Figure 2**), the viscosity is independent of the sheer rate. Water and thin motor oils are examples of Newtonian fluids.

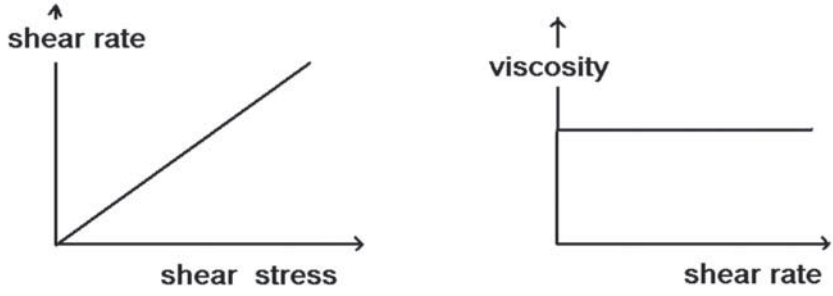

Figure 2. Newtonian Fluid behavior

In a pseudoplastic or sheer thinning fluid the viscosity decreases as the sheer rate increases (**Figure 3**). Most topically applied emulsions exhibit this behavior, which allows them to be spread smoothly on the skin.

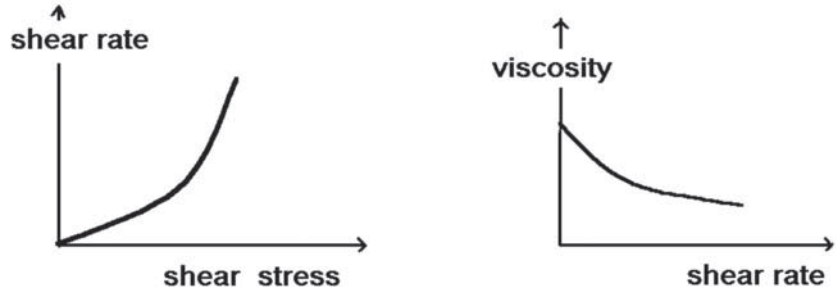

Figure 3. Pseudoplastic Fluid behavior

A dilatant fluid increases in viscosity as the sheer rate increases (**Figure 4**). Examples of dilatant fluids include corn starch or sand in water.

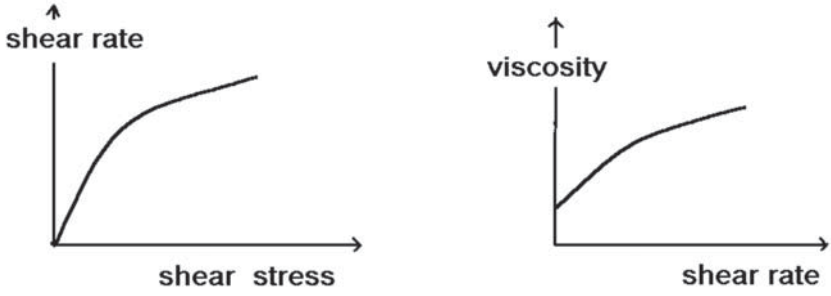

Figure 4. Dilatent Fluid behavior

In a thixotropic fluid, the viscosity decreases over time (**Figure 5**). Greases, heavy printing inks, and paints are examples of thixotropic materials.

Rheology modifiers or thickeners can be added to fluids to change the flow property of a formulation in order to give it desired properties in terms of thickness, appearance, stability, and feel. Many types of compounds have been used to thicken topical formulations, including natural and synthetic polymers and inorganic materials. For a more detailed review of rheological properties, the reader is referred to Hemi Nae's chapter on the subject in the Testing and Measurements section of this book.

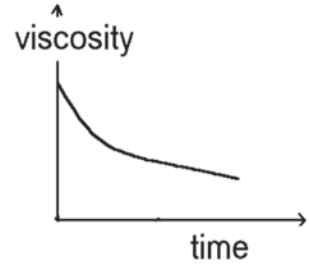

Figure 5. Thixotropic Fluid behavior

Classifying Thickeners

The following sections describe the chemical and physical properties of these compounds, the mechanism of their action, and advice on how to choose and use thickeners for topical formulations. Thickeners can be grouped into three major categories: natural polymers, synthetic polymers, and inorganic materials. Natural polymers were the first thickeners, with starches and other polysaccharides being used since antiquity. They have the advantage of fitting into the "green" trend in personal care that favors using compounds derived from nature that underwent minimal processing, but may be more limited in their functionality than synthetic materials. Synthetic polymers can be designed from scratch to impart the desired rheological properties to cosmetic formulations.

Natural Polymers: The most common natural thickening agents are polysaccharides, i.e. polymers of sugars. Examples include cellulose derivatives, xanthan gum, alginates, and carrageenan. These are effective for thickening aqueous systems or oil-in-water emulsions.

Cellulose is a polymer consisting of a linear chain of beta-(1,4)-linked D-glucose units and is the major structural component of green plants. The major commercial sources of cellulose are wood pulp and cotton.

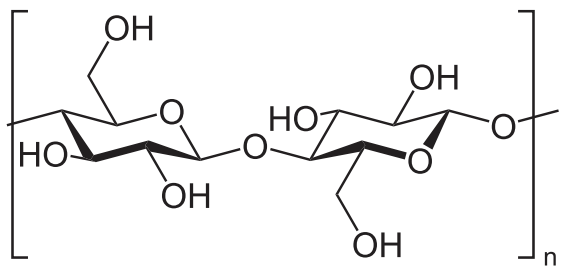

Figure 6. Chemical Structure of Cellulose

In order to function effectively, cellulose must be chemically modified to compounds such as methyl cellulose, hydroxypropylmethyl cellulose, and hydroxyethyl cellulose (**Figure 7**). These cellulosics build viscosity due to their long polymer chains and high molecular weights—as the length of the polymer chain increases, the more effective the material is at increasing viscosity at a given concentration.

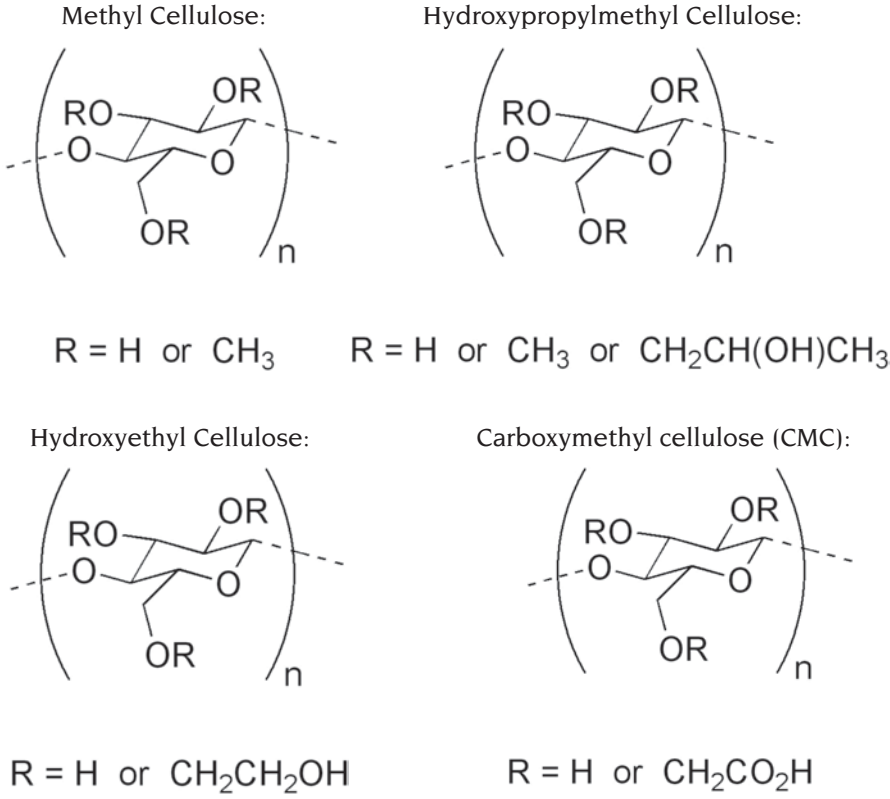

Figure 7.

Another commonly used derivative of cellulose is carboxymethyl cellulose (CMC) or cellulose gum, often used as its sodium salt

Xanthan gum is a polysaccharide produced by fermentation of carbohydrates from corn, wheat, soy, or dairy using the *Xanthomonas campestris* bacteria (**Figure 8**). In aqueous solution, it can produce high viscosities at concentrations of less than 1%. Products thickened with xanthan gum are pseudoplastic (sheer thinning).

Alginates are anionic polysaccharides with carboxylate groups attached to the sugar monomers. These are derived from brown algae and are very hydroscopic, being able to bind many times their weight in water (**Figure 9**).

Carageenan is another marine-derived polysaccharide, derived from red seaweed. It consists of repeating galactose units and 3,6-anhydrogalactose (3,6-AG), both sulfated and nonsulfated. The units are joined by alternating alpha 1–3 and beta 1–4 glycosidic linkages. There are several varieties of carrageenan, e.g. kappa, iota, and lambda, which differ in which sugars are present.

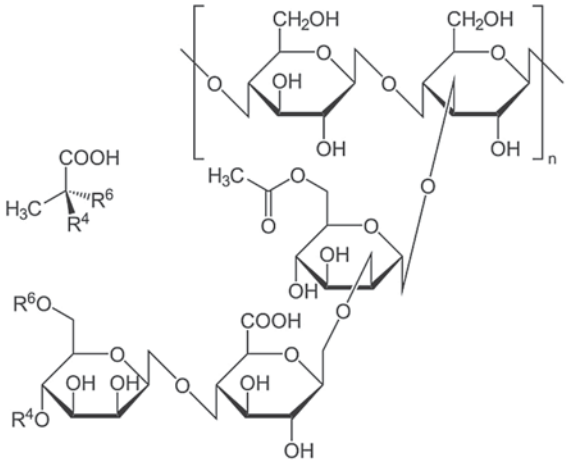

Figure 8. Chemical Structure of Xanthan Gum

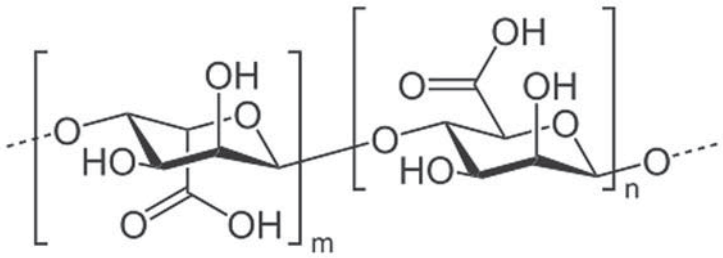

Figure 9. Chemical Structure of Alginate

Advantages and Disadvantages of Natural Thickeners

These thickeners have the advantage of being perceived as "green" or "natural" by the consumer, allowing a "clean" ingredient label without long, unfamiliar chemical names. Moreover, they have a long history of use with an excellent safety record. There are, however, several disadvantages to these materials. Their esthetic tactile properties may not be ideal, imparting sticky or tacky properties to formulations when used at higher concentrations. They may also give an unpleasant "snotty' appearance and texture to some formulations. In general, they have a lower yield value and are not as effective as synthetic polymers at suspending particles.

Synthetic Polymers*:* The two major classes of synthetic polymeric thickeners

are polyethylene glycol derivatives (PEGs) and acrylic polymers.

PEG thickeners have the general structure, R-(OCH_2CH_2)-OR, where R is a hydrophobic group (H) such as a fatty acid or alcohol. Examples of commonly used PEG thickeners are PEG-150 distearate, PEG-100 stearate, **PEG-15 Glyceryl Tristearate, PEG-180/Laureth-50/TMMG Copolymer**, **PEG-150/Decyl Alcohol/SMDI Copolymer**, and **PEG-45M**. Being hydrophilic in nature, these high molecular weight polymers uncoil in aqueous solution and thicken by occupying a large volume.

Acrylic polymers include the commonly used thickener carbomer, which is a homopolymer of acrylic acid cross-linked with an allyl ether of pentaerythritol, an allyl ether of sucrose, or an allyl ether of propylene. The cross-linking provides the polymers with a three-dimensional structure, as illustrated in **Figure 10**. When the carboxylic acid groups are neutralized with a base, such as sodium or potassium hydroxide or triethanolamine, the resulting negatively charged carboxylates repel each other, causing the polymer to swell, thereby occupying a large volume and increasing the viscosity of the solution.

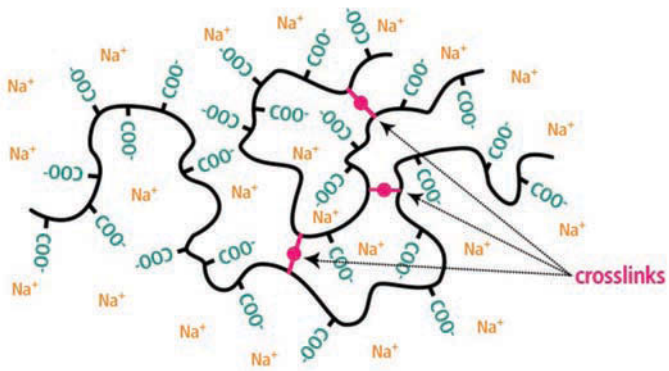

Figure 10. Cross-linking in Polyacrylic Thickeners

Associative thickeners are designed to elevate formulation viscosity by a different mechanism when compared to ionic or conventional polymeric thickeners. These compounds have a hydrophilic polymer backbone to which hydrophobic groups are attached. In aqueous solution, while the polymer backbone is hydrated and dispersed, the hydrophobic groups attract and interact, forming temporary cross-links between the polymer chains (**Figure 11**). This generates a three-dimensional network and thickens the solution. Because the interaction of the pendant groups is based on relatively weak hydrophobic interactions, they can be broken when shear is applied, and reform when the shear is removed. This mechanism gives solutions of associative thickeners their pseudoplastic properties. The hydrophobic groups can also form bridges to other hydrophobic components of a mixture, such as oil droplets in an emulsion or solids in a suspension, and thicken these materials by a similar mechanism.

Commonly used associative thickeners include Acrylates/Steareth-20 Methacrylate Copolymer, PEG-150/Decyl Alcohol/SMDI Copolymer, and PEG-180/Laureth-50/TMMG Copolymer.

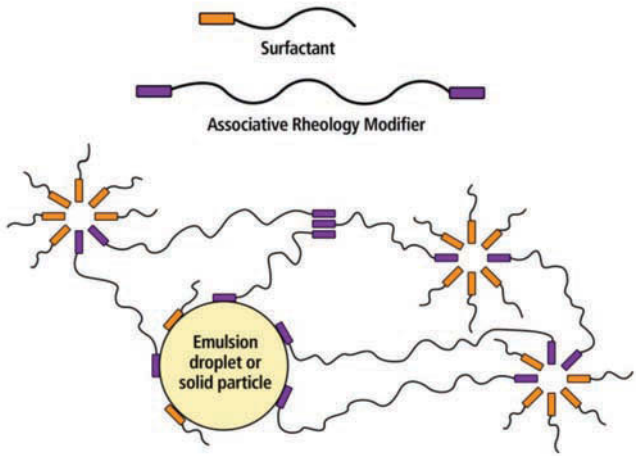

Figure 11. Associative Thickeners

Inorganic Thickeners

Inorganic materials can be used to thicken aqueous or non-aqueous systems. Examples of such compounds used in topically applied formulations are categorized as follows:

Clays: Hydrophilic clays can be used to thicken aqueous mixtures. The most commonly used clays are hectorites with the chemical formula $Na_{0.3}(Mg,Li)_3Si_4O_{10}(OH)_2$, bentonites (aluminium phyllosilicate), and magnesium aluminum silicates. These materials are hydrophilic and readily disperse into the aqueous matrix, thickening by a volume exclusion mechanism.

Organoclays are hydrophilic clays modified with quaternary amines, thus increasing their hydrophobicity and making them compatible with non-aqueous systems. They are used to thicken oil-based products such as mascaras, antiperspirants, nail polishes, and lipsticks.

Silica: Fumed silica is formed by flame pyrolysis of silicon tetrachloride or quartz sand to produce a fine powder with an extremely low bulk density and high surface area. It can thicken oil systems by forming inter-particle hydrogen bonds, thus creating a three-dimensional matrix.

Newer thickeners: Most new thickeners introduced in the past few years by topical ingredient suppliers have been derivatives or modifications of existing polymers rather than completely new classes of materials. This is done to impart specifically desired properties such salt tolerance, pH stability, or unique rheological properties. For example, in Acrylates Crosspolymer-4 a carbomer-type polyacrylate is cross-linked to allow it to thicken low pH systems. PVP polymers can also be cross-linked

to impart stability across a very wide pH range. Other copolymers such as Sodium Acrylates/ Beheneth-25 Methacrylate cross-polymer can be used in systems with high electrolyte concentrations.

Formulating With Thickeners

a) Choosing the right thickener

Selecting the right thickener is formulation dependent. There is no one universal thickener that transcends all application categories for hair care, skin care, cleansing products, sun care, color cosmetics, or antiperspirants and deodorants. It is therefore crucial that the thickener selected is compatible with other formulation ingredients and actives. The thickener must not interfere, block, react, or complex with performance enhancing ingredients, or the formulation will be ineffective or have a lower level of performance or simply become unstable. Thus, the formulation chemist should evaluate the compatibility between the thickener and type of formulation and decide upon a way to control viscosity thru selecting the correct compound. There is an extensive list of thickening agents available for topically applied products. Quite extensive. Weeding thru this vast list is beyond time-consuming and would require hours upon hours of formulation trial and error testing—which obviously exceed the scope of this chapter. The instructional guidance of this chapter, however, is to create a faster track towards successful and stable thickened formulations.

b) Viscosity

Viscosity building is one of the main criteria for choosing thickeners. The selection of any thickener(s) should be well thought and based on its properties and interaction with other formulation ingredients. A product's ability to flow freely in a continuous mass may also be controlled by the type of product dispensing package used to deliver the formulation. Properties of the dispensing package that may affect the dispensing are orifice opening, bottle flexibility, delivery rate, and dispensing pressure. These properties should be matched with the formulations viscosity to generate the desirable flow. This is also relevant to pump foaming packaging as well as to aerosols and sprays. For more detailed guidelines for foam products, the reader is referred to Dov Tamarkin's chapter on foams. Consumers' ease-of-use and delivery expectations of using retail products also fall into reasons for viscosity flow control of formulations. A good example of the importance of such measures is where a skin care oil is squeezed from a bottle with a product-specific orifice design; if the oil is too thin it will run between the fingers of one's hand and will drip before one is able to apply it to the skin. It will also be messy, runny, and difficult to spread and control on the skin's surface. By adding an oil compatible thickening agent, the formulation chemist can increase the viscosity to a desired level and thus aid the controlled dispensing and spreading properties of the oil. The consumer will benefit from this improved dispensing and product delivery based on viscosity flow control.

Building viscosity in oil-in-water emulsion creams and lotions to provide extra

"body" to a formulation encompasses a vast list of potential thickener choices. The main role of thickeners in formulations is not to impart stability but rather to control its flow by stiffening the bulk. The stabilization is an added value. Most common types of emulsion thickening agents are the solid thickening agents that require melting and incorporation into the oil phase. These include: fatty alcohols such as cetyl, stearyl and cetearyl; aliphatic alcohols such as isostearyl; fatty acids such as stearic acid; and natural and synthetic waxes. Other thickening agents that can be dispersed in the water phase and hydrated encompass naturally derived and synthetic additives and polymers, as discussed.

Cleansing surfactant systems are another major class where thickeners are employed to build viscosity. The majority of surfactant cleansers are water-based, as water acts as both solvent and dispersing media. Market category products range from shampoos, facial cleansers, liquid hand soaps, institutional and industrial hand cleaners, shower gels and body washes, to hand sanitizers. For anionic based surfactant systems, it is widely known that sodium chloride (NaCl) will shift the salt curve and is the most inexpensive thickener to use to increase viscosity. There may be a synergistic effect between amphoteric compounds such as cocamidopropyl betaine, which is a secondary surfactant, and primary detergents such as sodium laureth sulfate.[2] This enhanced viscosity is due to the formation of micelles and their interaction and intermolecular association. When a secondary surfactant such as an alkanolamide or a low ethoxylated fatty alcohol interacts with a primary surfactant such as an alkyl ether sulfate, this results in a re-organization on the molecular level. The primary surfactant, normally organized in solution in isometric spherical micelles, will undergo a structural change that can result in a transformation to anisometric rod- or disc-like micelles and even to dynamic networks. The consequence of this type of re-organization is a macroscopically observed increase in viscosity.

Interaction between sulfate surfactants and betaines is well known for building viscosity. Here again the importance of controlling product delivery is essential so the product does not flow too thin and the dosed amount is used effectively and efficiently. With anionic surfactant cleansing systems, it is very important that the thickening agent chosen is electrolyte tolerant. This requirement ensures stable viscosity for the life of the retail product and does not exhibit an immediate or gradual viscosity loss. Choices for such thickeners include acrylic polymers, PEG-150 distearate, PEG hydrogenated castor oil variants.

Aqueous gels and gel stick products are major, important classes of formulations that require special different classes of thickening agents. Gels are a key form of delivering a formulation in a controlled manner for dispensing and spreading on the skin or hair. Aqueous gels can vary in viscosity from a flowing thickened fluid to a rigid stick structure. They can be clear, translucent, or opaque in appearance. Gels and gel sticks can be developed with special thickening agents to improve their aesthetic properties and minimize a tacky feel, when desired. Many of the natural gums, alginates, cellulose, acrylic polymers, and synthetic associative polymers work well as gel-thickening agents. Other applications such as hair styling gels

require that a thickening agent provide hold upon drydown. Acrylic polymers are efficient in producing the playtime and hold needed for hair styling. Aqueous gels have a broad range of use in skin care, serums, hair care, and some color cosmetics. The aqueous gel sticks are a special class, in that a rigid structure can be formed in whatever shape will match and fit the dispensing package chosen. Sticks can be round, ovular, or customized to a shape desired in either a twist-up or push-up style package mechanism. These sticks can likewise be clear, translucent, or opaque in appearance. Structural gelling agents include those of sodium stearate, dibenzylidene sorbitol, polysaccharides, hydroxystearic acid, calcium sodium pyrophosphate, and organopolysiloxanes.

Suspending properties: Not all thickeners will exhibit suspending properties, although they provide viscosity, gelling, or body to a formulation. Proper and efficient suspension of solid particles in a semisolid formulation is challenging. The solid particles can be used solely as a visual color signal for aesthetic reasons or the particles can be a functional additive and/or an encapsulated additive providing both functional and aesthetic properties. If the inappropriate thickener is used it will cause the solid particles to either migrate upwards or settle downwards in the specific formulation. This direction of migration is dependent upon the specific gravity of the suspended powder. The use of the appropriate thickening agents will maintain the solid particles in suspension even if the formulation is subjected to temperature changes. Specific polymers and some natural gums display this property. Examples of thickeners for clear systems (water-soluble or water-dispersible thickeners that are neutralized to a pH of 5.5 and higher) are a**crylates copolymer, synthetic smectite, and acrylates/C10-30 alkyl acrylate cross-polymer**. Natural gum thickeners that produced translucent systems are xanthan, guar, and carrageenan.

c) Clarity

Some formulation categories such as serums can be semi-clear to translucent in appearance. But clear, thickened formulations hold a special attraction since they are perceived to exhibit purity in the eye of the consumer. They are visually appealing and present the appearance of mildness, which can be enticing to the consumer with concerns about what substantiates her products. Clear formulations provide eye-catching product differentiation on store shelves since they denote a clean appearance and generate the perception of product benefits. A clear formulation can be colored with water-soluble or oil-soluble dyes depending on the type of formulation or can be maintained with a natural water-clear appearance. Another marketable benefit is that a clear formulation most often allows for the use of clear packaging. This aids with showcasing the aesthetics of clear formulations. Clear containers can employ the use of UV absorbing additives to both protect the plastic as well as the actives in the formulation. Light stable and water-white thickeners are key attributes to be made in the selection process. Both polymeric and certain clay thickeners allow for the formulation of clear, thickened, stable systems. Rheological property selection can cover a wide variety of thickeners based on the means of formulation dispensing. For squeeze bottle-type dispensing, there are many ideal

thickening additives for controlled dispensing flow. These comprise polyacrylic acid polymers, water dispersible hydrocolloids derived from wood fibers (cellulose), and organo-clays.

For spray pump gel applications the preferred thickeners will exhibit pseudoplastic or thixotropic flow properties, as explained previously. These shear thinning thickeners will impart viscosity loss when the pump mechanism is actuated and allow the thickened formulation to spray/dispense. The secondary benefit for this thickening agent's class is that viscosity of the packaged formulation is not affected, only the portion of the product being pumped and sprayed. The end benefit of such thickeners is that the sheared dispensed product will rebuild viscosity on the skin and allow for a controlled application without being runny and messy.

d) pH effect

The electrolyte pH of ingredients and overall final formulations alike has a great influence on thickening and stability. Most thickening agents cannot tolerate acidic pH in the range of 3 to 4—and this is often applicable to topical products. They simply will not thicken, gel, or emulsify, or if they do initially thicken, they will eventually breakdown with time. Some formulations with acidic pH are antiperspirants, anti-acne products, and skin exfoliating products that use alpha- and/or beta hydroxy acids or other actives. Only special classes of ingredients will thicken, and those types are very limited to select clays, organosilicones, silicone polyols, silica, associative thickeners, and nonionic emulsifiers. The same principal applies for alkaline pH thickeners. Alkaline formulations in the pH 8-14 range are difficult to thicken and stabilize, as well. These formulations include depilatories, hair relaxers/straighteners, skin exfoliators, and rinse-off hair and scalp treatments, as well as skin care with other actives. In most cases relatively low or high pH in such formulations is maintained to allow better effectiveness of the active compound. Thickening agents that can be used in extreme pH formulations encompass, but are not limited to: guar derivatives, xanthan gum, nonionic emulsifiers, polyethers, fatty alcohols, silica, and cellulose derivatives.

e) Dispersing performance

Ease of dispersion is a key property required for the performance of a thickening agent. Ease of incorporation into either the aqueous phase or the oil phase of an emulsion or into an anhydrous formulation is a necessity. Formulation processing time is a key requirement, especially for scale-up and production manufacturing batches. The thickening agent must disperse easily, wet out quickly, swell or hydrate rapidly, or blend easily with heat. Time and energy is of the essence in production manufacturing as many points need to link properly in time sequence such as batching, analytical check points, QC clearance, filling, warehousing and shipping. A formulation is not cost-effective timewise if the thickening agent takes an extremely long time to process.

f) Heat vs. cold processing

There are two methods for thickening formulations through process manufacturing. The first involves heat. The overall single formulation batch can be

heated or multiple phases of a batch can be heated sequentially as in the preparation of an emulsion, or a particular phase of a batch can just be heated by itself. Heating a batch or phases aids dispersion, swelling, hydrating, or solubilization of the thickening agent. Heating further aids overall uniformity, and specific thickeners, especially those at the solid state, require application of heat.

Inversely, cold processing, or ambient temperature processing, is a desirable trait, as no heat expenditure is required. Cold processing for the most part speeds up manufacturing time, saves energy, and cuts down on cooling times. Also, in some locations of the world, heating capabilities are not available. These formulations do not use solid ingredients which require heat to melt and blend with other ingredients. Cold processing is used in some emulsions, gels, serums, and anhydrous thickened systems. Be it hot or cold process manufacturing, the selected thickening agent must be chosen carefully based on suppliers' technical information. Thickening agents within the same class can vary as to whether they need heat or cold processing.

The following is an example of a cold processing formula:

SEQUENCE	% OF WHOLE	NAME OF ADDITIVE/INGREDIENT
1	3.00	Polyacrylamide (and) C13-14 Isoparaffin (and) Laureth-7
1	7.00	Cyclomethicone (and) Dimethicone Crosspolymer
2	75.50	Water
2	0.50	Preservative
2	2.00	Aloe Barbadensis Leaf Extract
2	1.00	Lamium Album (White Nettle) Flower Extract
2	0.50	Polysorbate 20
2	0.50	Vanillyl Butyl Ether
3	4.00	Hydrogenated Polydecene
3	6.00	Neopentyl Glycol Dicaprylate/Dicaprate
	100.00%	

PROCEDURE:

1. Mix Sequence #1 ingredient well, at room temperature. A thick, uniform, viscous gel forms.
2. Combine Sequence #2 ingredients and mix until uniform.
3. Slowly add Sequence #2 to Sequence #1 with constant mixing. Product will gel to a cream.
4. Combine Sequence #3 and slowly add to the batch with constant mixing. Product will re-thicken into a cream gel.

Further Example Formulations

The formula examples offered below depict typical personal care formulations that are created using thickening agents. Each of the thickening agents used in these example formulas is described in more detail in prior sections of this chapter. Percentages of all ingredients can be adjusted to change feel and texture of a formulation and are prototype in form.

FORMULA A: COOLING SHAMPOO PRODUCT

A shampoo with a creamy foam texture that leaves the hair soft and refreshes the scalp. Thickening is provided by PEG-150 distearate ingredient.

pH: 7.0 ± 0.2

Viscosity: LVT #4 @ 30 rpm; 5,000 cps ± 10%

1	40.20	Water
1	0.50	Ricinoleamidopropyl Ethyldimonium Ethosulfate
1	0.10	Panthenol
1	2.50	Glycereth-26
1	1.00	PEG-150 Distearate
2	25.00	Sodium C14-16 Olefin Sulfonate
2	15.00	Sodium Laureth Sulfate
3	10.00	Cetyl Betaine
3	1.00	Cocamide MEA
4	2.00	PEG-6 Caprylic/Capric Glycerides
5	2.00	Butylene Glycol
5	0.20	Menthol
5	0.50	Menthoxypropanediol
	100.00%	

Procedure:

1. In the main manufacturing vessel, pre-mix Sequence #1 ingredients and heat to 78-80°C with slow stirring.
2. Add Sequence #2 ingredients one at a time to main vessel. Start cooling to 60°C.
3. Add Sequence #3 and Sequence #4 ingredients one at a time to main vessel.
4. At 35°C, pre-mix Sequence #5 ingredients and add to main batch when completely dispersed.

Summary

Thickening agents are an integral part of formulating personal care topical products. They help create aesthetically pleasing products that are more favorable to consumer needs. Thickeners provide enhanced consistency along with volume and luxurious sensory properties. Moreover, increased formulation stability and, in most cases, enhanced application performance are crucial benefits of proper thickener usage. This chapter is tailored to aid formulating chemists in the selection and use of specific classes of thickeners. The focus is on choosing which specialized thickener derivative best fits a product category need, and then optimizing a topically applied formulation. Thickening agents are not universal and require thought and knowledge in their selection process. A clearer understanding is provided to shorten this selection process and aid the formulator in quicker development times. Thickening agents are being used extensively in many topical formulations. They help with formulation stabilization as well as creating aesthetically pleasing products

that are more favorable to consumer needs. Thickeners provide better consistency along with volume and luxurious sensory properties. The stability enhancement allows, in most cases, for better application performance. These attributes are crucial benefits of proper thickener usage. There is a plethora of thickening agents available for the formulation chemist to choose from. The choices have been narrowed down to those thickening agents that provide the best performance and aesthetic benefits. Formulating topical products is both a science and an art in meeting consumer and changing market needs. This is why the specific choice of thickening agents is of great value in creating flexibility in formulation characteristics. As technology evolves and new products are launched, novel thickening chemistries are introduced to the marketplace. Thickening agents provide that leeway for creativity, modified feel enhancements, improved performance and appearance of formulated personal care products. The use of thickening agents with the proper suspending rheology segues into the next chapter on the use and importance of using submicron spheres.

FORMULA B: MOISTURIZING FACIAL SERUM

A soft, smooth gliding, lubricious serum with the superior moisturizing benefits. Thickening is provided by use of carbomer ingredient.

pH: 6.8–7.0

Viscosity: LV4 @ 3 rpm: 70,000 cps

1	93.70	Water
1	0.10	Disodium EDTA
2	0.30	Carbomer
3	0.80	Sodium Hydroxide
4	3.00	Glycereth-26
4	2.00	Sodium Hyaluronate Cross-polymer
5	.10	Calcium Sodium Borosilicate (and) Silica (and) Titanium Dioxide
6	qs	Preservative
	100.00%	

Procedure: (cold process)

1. In main vessel mix Sequence #1 with high speed propeller stirring. Slowly sprinkle in Sequence #2. Mix until fully dispersed at ambient room temperature. Once fully hydrated, the mixing speed can be lowered to medium.
2. Add Sequence #3 to main vessel, batch will thicken, continue mixing.
3. Add Sequence #4 ingredients with medium mixing.
4. Add Sequence #5 ingredient to main vessel with medium mixing.
5. Add Sequence #6 and mix until homogeneous.

FORMULA C: WRINKLE REDUCTION GEL

A smooth gliding, opaque gel that illuminates the skin to diminish the appearance of fine lines and wrinkles. Thickening IS provided by sodium magnesium silicate, sodium polyacrylate, and carbomer.

pH: 6.8–7.0

Viscosity: LV TF spindle @ 0.6 rpm; 700,000cps + 10%

1	65.90	Water
1	0.20	Sodium Magnesium Silicate
2	0.10	Tetrasodium EDTA
2	3.00	Glycereth-26
3	0.30	Carbomer
4	qs	Preservative
5	0.50	Triethanolamine
6	10.00	Glycerin (and) Sodium Polyacrylate
7	1.00	Water
7	qs	Preservative
8	1.00	Sodium Hyaluronate
9	15.00	Water
9	3.00	Nylon-12 Fluorescent Brightener 230 Salt (and) Polyvinylalcohol Cross-polymer
10	qs	Triethanolamine (99%)
	100.00%	

Procedure:

1. Mix the water from Sequence #1 with high speed propeller agitation. Slowly sprinkle in the remaining Sequence #1 ingredient, mix until clear.
2. Add Sequence #2 ingredients to Sequence #1 and keep mixing speed on high.
3. Slowly sprinkle in Sequence #3 ingredient with high speed propeller mixing. Mix until free of any lumps and batch is homogeneous. Mixing speed can now be reduced and Sequence #4 ingredient added with mixing.
4. Heat the batch to 75ºC with medium speed propeller mixing. Once batch is at 75ºC and uniform, then the batch can be slowly cooled to 60ºC.
5. Add Sequence #5 to batch. Batch will thicken and continue mixing until clear and uniform.
6. Continue slow cooling of batch and add Sequence #6 with mixing.
7. At 35ºC, add premixed Sequence #7 ingredients to batch with mixing.
8. Add Sequence #8 ingredient to batch, mix until dispersed completely.
9. Add premixed Sequence #9 slurry, which was mixed with high speed propeller agitation, to the batch and mix until completely dispersed. Batch will turn white color.
10. If necessary, adjust pH to within specification using Sequence #10.

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CHAPTER 3

The Incorporation of Delivery Systems into Topical Formulations: A Case Study on the Use of Salicylic Acid for Acne Treatment

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Key Words

Particulate Delivery Systems, Acne, Topical Application, Sub-Micron Spheres, Functional Ingredient Compatibility, Skin-friendly Formulations

Abstract

The major challenges in effectively formulating anti-acne products are related to the desired balance between efficacy and skin-friendly characteristics. One of the ingredients that consistently presents issues in both of these areas is salicylic acid (SA). The current chapter focuses on formulations that employ an encapsulated form of salicylic acid in order to solve the challenges mentioned above and, in the process, heighten the efficacy of the acid in use. Several delivery systems are commercially available that provide an encapsulated form of SA such as cyclodextrin, liposomes, and a proprietary, innovative sub-micron sphere technology. The advantages and application principles of working with these delivery systems in skin care formulations are discussed.

Background

Topical lotions should contain the right concentration of actives, stability features, programmed release kinetics and clinical efficacy[1] in addition to being skin-friendly and esthetically pleasing. The area of acne treatment is presently discussed in part because of the levels of over-the-counter (OTC) ingredients required by US Food and Drug Administration (FDA) monograph in order to claim efficacy. This monograph sets the allowable range of salicylic acid in these treatments at 0.5–2.0% thereby highlighting the need for a way in which to meet the remaining requirements of stability, kinetics, and enhanced efficacy. At the 0.5–2.0% range, salicylic acid can cause skin irritation, especially for those consumers that have sensitive skin, as well as present formidable challenges for formulators working to incorporate SA into their products. In effort to balance these needs, a number of delivery systems have become available in the market with the intention of assisting with the creation of formulations that are potent, stable, and skin-friendly.

Acne vulgaris (also known as acne) is a skin disease that affects the porous intrusions of the follicular-sebaceous unit. Acne is the most common skin disorder in the United States, afflicting 40 to 50 million Americans.[2] The primary source in the development of acne begins with a plug or cap formation within the pores of the epidermis. This plug is mainly caused by dead skin particles that mix with human sebum (a naturally produced oil within the sebaceous gland). As this mixture begins to saturate and congest the pores, it becomes a hospitable environment for pathogenic bacteria (known as *P. Acnes*) to trigger an inflammatory cytokine response.[3] Once inflammation of the sebaceous gland becomes prevalent, signs of comedones, papules, and pustules, along with occasional nodules, appear on the outer surface of the skin.

While there are several ingredients used in preventing and/or treating the infectious components of acne, SA has been widely accepted as a primary anti-acne agent, due to its efficacy as an exfoliator. Use of SA extends beyond anti-acne applications into products designed for the treatment of dandruff, psoriasis, corns, and warts.

SA, a beta hydroxy acid, is utilized in concentrations ranging from 0.5% to 10% with the maximum strength allowable in non-prescription acne products in the United States being 2% as set by the aforementioned FDA Final Acne Monograph.[4,5] The exfoliating action of SA causes the cells of the epidermis to shed more readily, opens clogged pores, and prevents them from clogging again through the following mechanisms of action.[6] Specifically, SA dissolves the protein that binds dead cells to the surface of the skin, making it easy to slough off the dead skin layer during cleansing. This removal of binding proteins is also the mechanism that unclogs pores and exposes *P. acnes* to the air, thereby accelerating antibacterial activity.

Motivation For Encapsulaton Of Salicylic Acid

Despite its widespread use as an anti-acne agent, SA presents the noted problems of skin irritation and formulation difficulties. In fact, approximately 60% of patients

relying on anti-acne medications report high levels of side effects including skin dryness and even a flare up in acne with low levels of efficacy due to the keratolytic activity of SA[7] resulting from a use level of up to 2%.[8] Thus, there exists a poignant need for a technology to provide SA in a form with which it is easy to formulate and will result in reduced side effects.

The secondary challenge of formulating with SA originates from the fact that it is poorly soluble in water (2 g/L at 20°C) and has a pKa of 2.97. As a result of its low solubility, formulators often must use organic solvents or harsh surfactants in order to suspend the SA in finished products. However, most of the organic solvents are not approved by the Personal Care Products Council (PCPC) and the use of surfactants, such as Polysorbate 80, can exacerbate irritation. As a result, SA should be incorporated in a skin-friendly medium that will deliver it via a water-based acne emulsion in an effective manner to eliminate irritation.

The issue of low pH has traditionally been addressed through addition of a base such as sodium hydroxide (NaOH) to bring the product to a pH that is more tolerable on the skin. The resulting reaction of the NaOH and SA, however, forms a salt (sodium salicylate) that is minimally effective in treating acne and significantly reduces the exfoliating effect of SA.[9] Therefore, an encapsulation system for SA should not only provide a skin-friendly solution that will lower irritation, but should also isolate the acid from a final product formulation to a degree that the formulation maintains a pH of 4.5 to 5.5 without necessary additions of a base. Further, this system should not chemically alter the salicylic acid, but should deliver it to the skin in pure form in order to achieve the highest efficacy possible. A trio of possible encapsulation systems is discussed in detail below.

Liposomes: Phospholipids are widely used as delivery systems due to the fact that they are comprised of a special class of phosphate lipids (phosphatidylcholine (PC), sphingomyelin (SM) and other phospholipids[10]) that resemble the lipid layer surrounding cells that facilitate penetration. The lipid component of phospholipids is hydrophobic and non-polar, while the phosphate component is hydrophilic. When mixed with hydrophobic and hydrophilic ingredients, liposomes will arrange in a micelle structure around these ingredients with the lipid ends of the micelle surrounding the hydrophobic ingredients and the phosphate ends surrounding the hydrophilic ingredients. They are currently available in the market for use with SA.

Encapsulation of SA in liposome systems has major drawbacks,[11,12] including a limited shelf-life stability, formulation issues,[13] and low loading of the SA. The shelf life stability of liposomes in a formulation depends on the interaction of the liposomes with the other base ingredients and the ability of the liposome lipid bi- or multi-layer structure to maintain its physical integrity in the product base. If this structural integrity is not maintained, agglomeration of the liposomes can occur resulting in a significant increase in particle size and formulation instability. In addition, liposomes have the inherent limitation in formulating where procedures as well as raw materials must be considered carefully in order to avoid adverse effects, such as shifts in pH, which could have detrimental effects on their stability.

Cyclodextrins: Cyclodextrins are obtained from the enzymatic degradation of starch. These molecules are composed of polysaccharides and possess an inner radius of 0.5-0.85 nm that can host cosmetic functional ingredients. The outer faces of this complex are hydrophilic, while the cavity is hydrophobic. The cavity is where a cosmetic active is surrounded, thereby protecting these actives from thermal, chemical, and mechanical degradation, retarding loss via evaporation and retaining poorly water-soluble actives. There is a commercial formula of SA that is solubilized in cyclodextrin complexes for anti-acne applications. The claims are enhancement of exfoliation and suitable for acne treatments.

While promising, both liposome and cyclodextrin technology do not fully address the issues presented herein relating to the balance between efficacy and skin-friendly attributes. Sufficient data does not exist on the effect of these delivery systems on skin pH nor on release kinetics and how these kinetics impact performance of the SA. Basically, the formulation comprising of the technology does not result in skin friendly pH upon topical application. The adhesion from a rinse-off is not guaranteed due to lack of suitable anchoring complexes. Slow gradual release is not validated and confirmed by published data. Thus, there is a need for an intelligently engineered delivery system that solves all of these issues.

Sub-micron Technology: A hydrophobic sub-micron technology employs a unique delivery system designed to encapsulate SA, and slowly release it over several hours from small vesicles called sub-micron spheres (**Figure 1**). These tiny (0.1 µm in diameter), hydrophobic (lipid matrix) spheres encase SA and suspend it in an aqueous medium via a hydrophilic outer shell that possesses a cationic charge. Once applied to skin, the charge moiety on the shell anchors the sphere for deposition while the hydrophobic matrix gradually dissolves into lipid architecture of skin, releasing the functional ingredient in a controlled manner over time.[14,15]

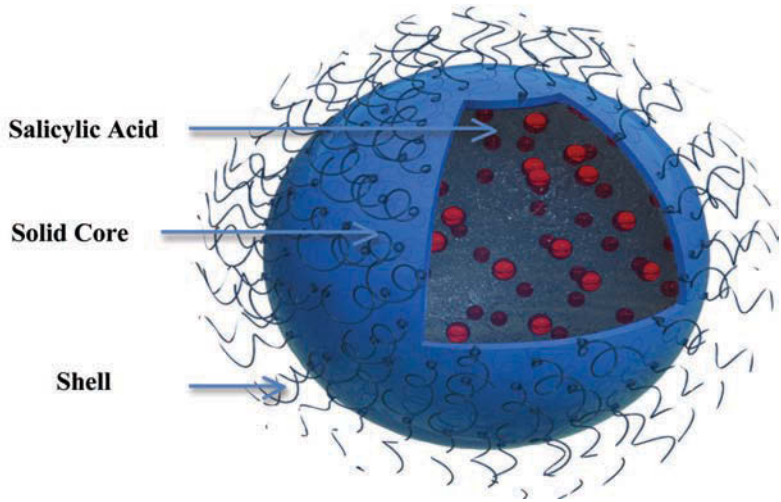

Figure 1. Structure of sub-micron spheres.

Overcoming Solubility and Compatibility Issues: The hydrophobic sub-micron technology encapsulates SA at loadings up to 30% without any phase separation or discoloration and maintenance of assay levels, particle size, pH, and color under accelerated aging conditions of three months at 42°C. As discussed earlier, the encapsulation causes no chemical alteration to the acid. Rather, the hydrophobic spheres enrobe the SA and suspend it in a water-based medium in shells that are composed of inert materials. The outer portion of these shells is treated with a cationic polymer that, in addition to contributing to better skin adhesion via electrostatic attraction, helps to suspend the shells in an aqueous medium via ionic interactions. Therefore, the formulator does not need to utilize additional solvents or surfactants in order to suspend the acid in their products. The sub-micron technology is easily incorporated under either rotary mixing or homogenization, depending on the viscosity of the formula. Once diluted down to the active level of 0.5–2.0% in a final OTC (or 6% for R_x) anti-acne treatment, the sub-micron technology lends minimal opacity, which results in an additional benefit of being able to formulate largely translucent rinse-off products (**Figure 2B**). Because the SA is encased in a hydrophobic vehicle, it is largely isolated from the rest of the formula. As a result, formulations using this technology can be created at pH ranges of 4.5–5.5. This alleviates the formulator's dilemma of having to limit their ingredient choices or having to use extra suspension or dissolution agents for the SA. Seeing a reduction of pH in a final product would indicate the release of free SA into the medium. When testing a commercial face wash product containing SA, acidic pH of 3.12-3.76 was observed, while the sub-micron technology in face wash, at the same level of SA as the commercial product, exhibited a pH of 5.7. Thus, the technology has the ability to maintain a skin-friendly pH in formulations.

Figure 2. Sub-micron technology as (A) raw material and (B) in a facial cleanser at 2% SA.

Reducing Skin Toxicity and Addressing Issues for Sensitive Skin: The second issue discussed, and not addressed by earlier delivery systems, is the low skin pH that is related to using a product loaded at effective levels of SA. As mentioned, an alkaline ingredient is commonly used to raise the pH of the formula that reduces the efficacy of the SA as it is neutralized. The sub-micron technology approaches skin-friendly pH in a different manner. The technology releases on skin through a gradual dissolution of the hydrophobic components of the sub-micron shell into lipid architecture of skin. This dissolution delivers the encased ingredients to the skin in a slow-release pattern, which allows the skin pH to re-balance itself and not decrease to a degree that might cause irritation to occur. Solving this sensitivity issue leads to a third benefit which is an extended efficacy in the activity of the SA. The controlled release pattern ensures a continual dose of the acid, in a controlled manner, for an average of 6–8 hours. The technology maintains a constant advantage over free SA in terms of overall percentage that is retained on skin for this period. There is always more SA present on the skin that aids in a more pronounced reduction of acne when compared to free. This advantage is discussed in more detail in a subsequent section of this chapter.

When testing skin-friendly pH on skin, two different body wash formulations were prepared: 1) 2% free SA and 2) 6.67% of technology which yields 2% salicylic acid. Volunteers washed their forearms with cleansers containing either the technology or free SA. The pH was tested with a Hanna, HI99181 pH meter. The sub-micron technology has the distinct advantage of providing the functional ingredient in a formula at skin-friendly pH of 5.

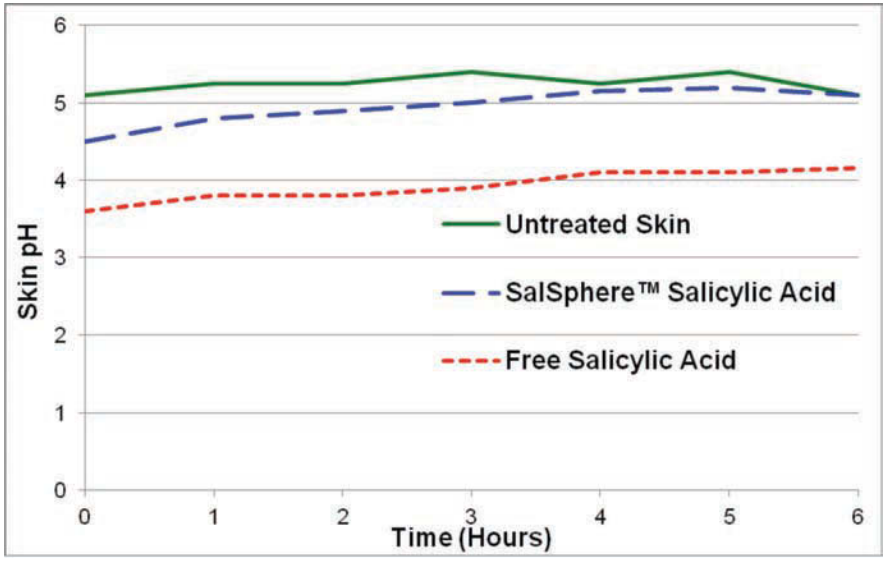

Figure 3. Skin pH after treatment with sub-micron technology comprising of SA.

The results show a final skin pH that is ~ 5 upon using the technology, while the free displays a reduced pH which may lead to potential irritation (**Figure 3**).

Improving Performance and Compliance: It has been shown that sustaining the release of SA on the skin reduces percutaneous absorption and thus limits side effects. During most attempts to deliver free SA to the skin surface using a rinse-off application such as body wash over 99% of SA is lost, reducing deposition on skin. Therefore, the primary goal in delivering SA is to stabilize the compound in an applicable complex, which can efficiently be deposited onto the skin, and specifically to the pimples or comedones. Traditional rinse-off products deposit a low amount of SA on skin.[2] Therefore, sub-micron technology was developed to deposit SA and control its release rate on skin for a longer period of time. Because the technology delivers the SA to the skin gradually, the acid remains at an increased activity level over free SA (**Figure 4**).

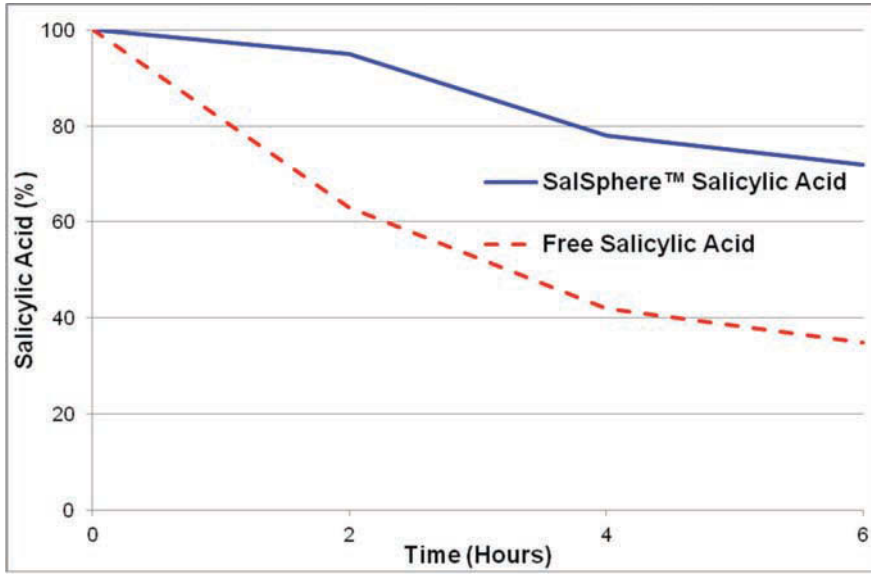

Figure 4. Longevity of SA from sub-micron technology vs. free over a six-hour period.

Clinical Deposition Test of SA (Rinse-off): The ability of the sub-micron technology comprised of SA to provide enhanced deposition of SA on skin was studied in vivo by skin extraction using an extraction apparatus (circular bulb 15.5 cm^2 in area). A measured amount of the product, approximately 0.25 grams, was applied to the target area. The samples were left on the target site for one minute. The applied area was rinsed with 100 mL of water and tapped dry with a paper towel.

A 3 mL disposable syringe was filled with 1.5 mL of ethanol, and the ethanol was placed into the skin extraction apparatus and carefully inverted over the application area, tightly holding the bulb in place and swiveled for 30 seconds. The ethanol

fraction was collected into a labeled glass jar. The extraction step was repeated a total of three times per marked area on the test subject's arm, as depicted in **Figure 5.**

Figure 6 shows the sub-micron technology resulted in threefold higher deposition of SA onto skin vs. free. In a separate study, all tested human volunteers (n = 12)

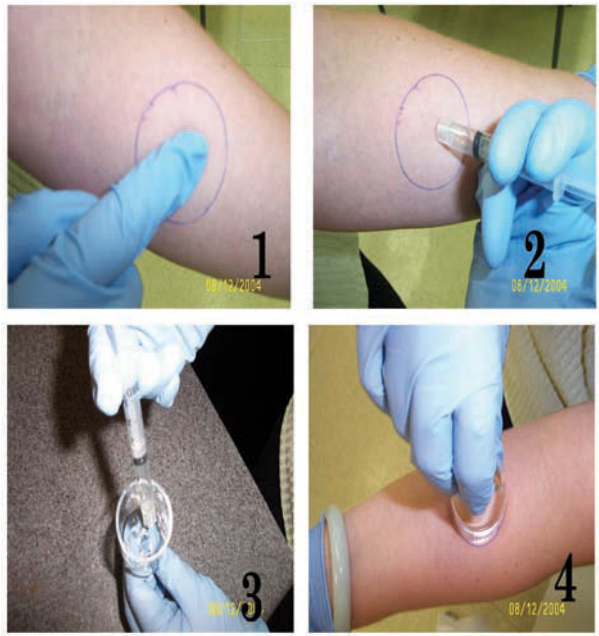

Figure 5. Skin Extractions for validation of controlled release of SA.

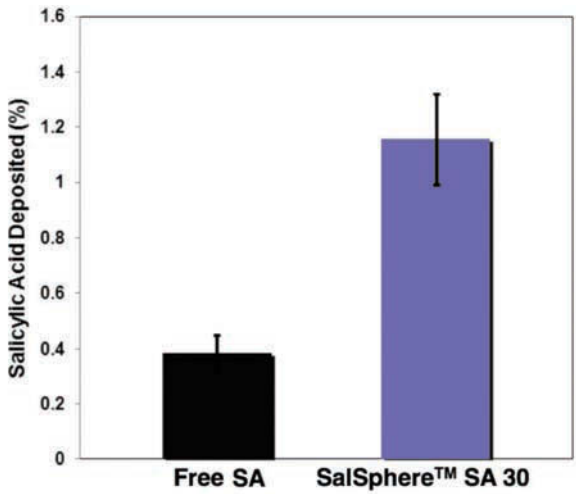

Figure 6. Enhanced deposition of SA after treatment with 2 % SA from free vs. sub-micron technology from a body wash.

reported the sub-micron technology in sulfate-free body wash as clear, smooth, gentle, non-itchy, non-irritating, and clean. Additionally, more than 70% of the volunteers displayed significant reduction in artificial sebum using the sub-micron technology formula in a facial cleanser vs. a commercial product (data not shown).

Formulations With Sa And Encapsulation Technologies

The following are practical ways in which to formulate with sub-micron technology comprised of SA for effective acne treatment. To begin, below is a lotion formulation wherein the pH of the final mixture is 3.51. Note that this pH is very acidic, and thus may lead to irritation on the skin.

Cyclodextrin Technology: A clear water-soluble spray comprised of moisturizing agents in addition to cyclodextrin enabled encapsulation of SA was made as shown below. The adjusted pH of the finished product was in the range of 3.8-4.2.

Formula of Free SA in Lotion

Phase	INCI	W/W %
A	*Butyrospermum Parkii* (Shea Butter) Fruit	16.5
	Cetearyl Alcohol and Ceteth-20 Phosphate	8
	Octadecyl Alcohol	2.8
	Partially Hydrogenated Oil	6.8
	1-Hexadecano	2
B	Water (*aqua*)	58.9
	Glycerin	2
C	Salicylic Acid	2
D	Phenoxyethanol/ Ethylhexlglycerin	1
	Total	100

Mixing instructions:
1. Combine Phase A ingredients and heat at 75°C until melted.
2. Combine and mix Phase B, then slowly add to Phase A ingredients. Continue heating and mixing.
3. Mix until homogenous.
4. Add Phase C ingredients to mixture after cooling to 40°C.
5. Add Phase D ingredients and mix until homogenous.

pH of final mixture=3.51

Hydrophobic Sub-micron Technology: A sub-micron technology that addresses multiple benefits over formulating with the functional ingredient alone bears out significant advancements.[16] A few examples will follow. Hydrophobic sub-micron technology comprised of SA can be readily formulated into a body wash, facial cleanser, gel, alcohol-free toner, or body cream. The advantage of formulating with

technology include: the ability to process at low temperatures, stable emulsion appearance, a product performance superior to controls, and skin-friendly pH. Foaming issues, especially during mixing, may occur, but can be resolved with a number of anti-foam agents available commercially, though incompatibility with anionic, carbomer-containing bases may be a disadvantage.

Formula of Cyclodextrin Encapsulated SA in Moisturizing Clear Gel**

Phase	Raw Material/ INCI Name	W/W %
A	Deionized Water	76.55
	Phenoxyethanol, Methylparaben, Butylparaben, Ethylparaben, Propylparaben	0.3
	Glycereth-26	2.5
B	Carageenan	0.5
C	Hydroxypropyl Cyclodextrin (and) Salicylic Acid	12.5
D	Glycerin, Urea, Saccharide Hydrolysate, Magnesium Aspartate, Glycine, Alanine, Creatine	2
E	Deionized Water	1
	Imidazolidinyl Urea	0.25
F	1 % Soln. Water (aqua) (and) HA	4
G	Sodium Chloride (25 % Soln.)	0.4
H	Triethanolamine, 99 %	q.s.*
* to adjust pH		100

Mixing instructions:
1. Heat Phase A to 75°C on overhead mixer at medium/high speed.
2. Slowly add Phase B to Phase A and mix until completely hydrated.
3. Cool combined Phase A and Phase B to 40°C and add Phase C at medium/low speed.
4. Add Phase D to vessel at medium/low speed and cool to 35°C.
5. Add premixed Phase E to vessel at medium/low speed and cool to 25°C.
6. At 25°C, add Phase F and Phase G to final mixture in order of addition at medium/low speed.
7. Adjust pH to 3.8-4.2 using Phase H.

pH of Final Mixture: 3.8-4.2

***Referenced in EW Flick, Cosmetic and Toiletry Formulations, Beauty Aids, 2001, 2 ed., Vol. 8, Section 6, Page 48.*

Summary/Conclusion And Future Perspectives

In this chapter, we have introduced the various delivery systems and have rationalized as to why encapsulation of SA is necessary. The chapter provided data on a novel sub-micron technology that is a stable, clear, water-based solution. The sub-micron technology based encapsulation of lipophilic SA is formulation friendly and has been proven to maintain skin friendly pH while enabling deposition on skin. The ultimate benefit of this technology is a clear, smooth product that can be used for reduction of fine lines, spots, and wrinkles.

Formula of Sub-micron Spheres Containing SA in Sulfate-free Body Wash

Phase	INCI	W/W %
A	Deionized Water	55.33
	Alpha Olefin Sulfonate	25
	Water, Cocamidopropyl Dimethylamine, Salicylic Acid, Polysorbate 80, Butyrospermum Parkii (Shea Butter) Fruit	6.67
B	Cocamidopropyl Betaine	10
	Cocamide MC	2
	Sodium Chloride	q.s.
	Citric Acid	q.s.
C	Phenoxyethanol/ Ethylhexylglycerin	1
	Total	100

Mixing instructions:

1. Mix Phase A ingredients together with constant mixing and heat to 45°C.
2. Remove from heat and continue to mix until homogenous.
3. Combine ingredient in Phase B in a separate vessel, add to Phase A and continue mixing until homogenous.
4. After the combined Phase A and Phase B has cooled to room temperature, adjust pH to 5.5 with citric acid.
5. Then add phase C and mix.

pH of final mixture = 4.95

Formula of Sub-micron Technology Containing SA in Clear Facial Cleanser

Phase	INCI	W/W%
A	Water (*aqua*)	52.73
	Ammonium lauryl sulfate	21.9
	Cocomidopropyl betaine	8.8
	Water, Cocamidopropyl Dimethylamine, Salicylic Acid, Polysorbate 80, *Butyrospermum Parkii* (Shea Butter) Fruit	6.67
B	Glyceryl cocoate	8.8
	Polysorbate 20	0.1
C	Phenoxyethanol/ Ethylhexlglycerin	1
	Total	100

Mixing instructions:

1. Mix Phase A ingredients together with constant mixing and heat to 45°C.
2. Remove from heat and mix until homogenous.
3. Add Phase B to the mixture, and continue mixing until homogenous.
4. Once combined Phase A and Phase B has cooled to room temperature, add Phase C and mix thoroughly.

pH of final mixture = 5.60

Formula of Sub-micron Technology Comprised of SA in Gel

Phase	INCI	W/W %
A	Water (*aqua*)	80.83
	Guar Hydroxypropyl Trimonium Chloride	1.5
B	Water, Cocamidopropyl Dimethylamine, Salicylic Acid, Polysorbate 80, Butyrospermum Parkii (Shea Butter) Fruit	6.67
	5% NaOH Solution	1.3
	Water (*aqua*)	8.7
C	Phenoxyethanol/ Ethylhexlglycerin	1
	Total	100

Mixing instructions:

1. With constant propeller mixing of the water at 700 rpm and low heat of 40-45°C, slowly disperse the guar gum into the water phase (A).
2. Allow guar gum to hydrate for about 60 minutes, until a gel-like consistency forms.
3. Once mixture has cooled to 30°C, add sub-micron technology containing SA with constant mixing at 700 rpm (B).
4. Add 5% NaOH solution to adjust pH of mixture to 5.0, followed by addition of residual water and Phase C ingredients while mixing.

pH of final mixture = 4.93-5.04

Formula of Sub-micron Technology Containing SA in Body Cream

PHASE	INCI	W/W %
A	Water (*aqua*)	34.33
	Hydroxyethyl Acrylate, Sodium Acryloydimethyl Taurate Copolymer, Isohexadecane, and Polysorbate 60	10
B	C-12-15 Alkyl Benzoate	5
	Glycerin	5
C	Water (*aqua*), Cocamidopropyl Dimethylamine, Salicylic Acid, Polysorbate 80, Butyrospermum Parkii (Shea Butter) Fruit	6.67
	Deionized Water	38
D	Phenoxyethanol/ Ethylhexlglycerin	1
	Total	100

Mixing instructions:
1. Incorporate water of Phase A in main tank, add the polymer and start mixing.
2. Once the gel is homogenous, add the Phase B ingredients to the main tank. Mix well.
3. In a separate beaker, combine Phase C ingredients and then add this phase to the mix. Mix well.
4. Add Phase D to the mixture and mix until homogenous.

pH of final mixture = 5.26

Formula of Sub-micron Technology Containing SA in Alcohol-free Toner

PHASE	INCI	%
A	Deionized Water	73.33
	Water (*aqua*), Cocamidopropyl Dimethylamine, Salicylic Acid, Polysorbate 80, Butyrospermum Parkii (Shea Butter) Fruit	6.67
B	Dimethyl Isosorbide	5
	Glycerin	5
	Sorbitol Solution 70% USP	5
	Myristamidopropyl PG-Dimonium Chloride Phosphate	4
	Phenoxyethanol/ Ethylhexlglycerin	1
	Total	100

Mixing instructions:
1. Mix ingredients in Phase A and heat to 40°C or until mixture is homogenous.
2. Remove from heating.
3. Sequentially mix ingredients from Phase B to Phase A.

pH of final mixture = 4.50

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CHAPTER 4

Formulating Skin Care Products with Silicones: Approaches and Strategies

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Key Words:

Silicone, Silicone Polyether, Silicone Elastomers, Siloxane, Polymer, Dimethicone, Cyclomethicone, Amodimethicone, Skin Care, Hair Care, Emulsions.

Introduction to Silicones

Silicones are a large and diverse family of synthetic compounds that were first discovered by British chemist F.S. Kipping in 1901.[1] They were not commercially developed in the United States until the 1940s. Like many new technologies, commercial development of silicones was prompted by demand from the U.S. military that arose during the Second World War. The first silicone products were electrically insulating greases that were needed to prevent arcing in airplane engines flying at high altitudes.[2]

The term silicone refers to polymers and other materials that contain siloxane bonds (i.e. the repeat unit –Si-O–). The siloxane backbone is very strong but yet flexible, and it is these characteristics that are responsible for many of the unique properties of silicones. The ability to attach different organic groups to the siloxane backbone leads to a wide variety of different materials. Methyl groups as well as longer chain hydrocarbons make siloxane polymers hydrophobic, while the grafting of polar groups can produce water-soluble silicone surfactants. Silicones used in commercial applications, including personal care formulations, are most often based on dimethyl siloxane.

Since they were first introduced to the personal care industry in the 1950s, silicones have come to be indispensable ingredients in many personal care formulations. The first silicone that was used is now referred to by the International Nomenclature for Cosmetic Ingredients (INCI) name **Dimethicone**. At the time of their initial use,

dimethicone polymers were viewed as exotic (and expensive) ingredients, but the unique combination of properties and benefits of silicone has led to steady growth in personal care formulations over the past sixty years. During this period, the silicone industry has developed hundreds of different silicone materials. The rapid proliferation of new silicone materials for applications in personal care product began shortly after the introduction of Cyclomethicone in the late 1970s. This proliferation was reflected in the growth in the number of unique INCI names for silicones. The INCI nomenclature system was created by the Cosmetics, Toiletries, and Fragrances Association (CTFA; now re-named the Personal Care Product Council; PCPC) to provide ingredient names for use on package labeling. By 1988, when the second edition of the CTFA's *INCI Dictionary* was published, there were more than sixty silicone ingredients with unique INCI names listed. The most recent edition of this dictionary published by the PCPC now lists more than 600 different INCI names for silicone ingredients.[3]

It is beyond the scope of this chapter to review all of the different silicones used in formulations today. Rather, this chapter is focused on the most widely used categories of silicones, and within each category a list of the most popular classes is provided as examples. The specific silicones are referred to herein by their INCI names. The first use of an INCI name in this chapter will appear in bold type and INCI names will be capitalized to distinguish them from chemical names.

Major Categories of Silicones and Their Properties

Most silicones that are used in personal care formulations are based on polydimethylsiloxane (PDMS). The INCI name for methyl-terminated PDMS is the aforementioned Dimethicone; when the terminal groups on PDMS are silanols (Si-OH groups), the INCI name is **Dimethiconol**. The structures for these basic silicone polymers are shown in **Figures 1 and 2**. Dimethicone is the oldest and most widely used silicone in personal care formulations. It provides many important benefits in skin care, hair care, and color cosmetic formulations. Dimethicones are good emollients that provide a unique combination of physical properties that set them apart from other cosmetic oils. Their low surface energy and highly flexible siloxane polymer backbone allows for effective spreading and a pleasant skin feel. The physical and esthetic properties of Dimethicones can be controlled by varying the chain length and molecular weight of the polymer. As chain length increases, the viscosity of the Dimethicone also increases. Low viscosity Dimethicones spread quickly and easily while providing a light, silky skin feel. High viscosity Dimethicones form more persistent hydrophobic films with good water barrier properties.

Dimethicone fluids with viscosities below about 5 cSt are somewhat volatile, but Dimethicones with lower viscosities such as 1 cSt are volatile enough to be noticeable to consumers. A related material called **Disiloxane**, which is essentially a methyl siloxane dimer, has volatility comparable to ethanol. **Trisiloxane**, another

volatile low molecular weight silicone, is the shortest possible PDMS with only one dimethyl siloxane unit.

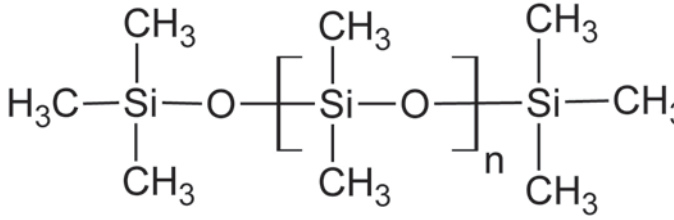


Figure 1. Dimethicone

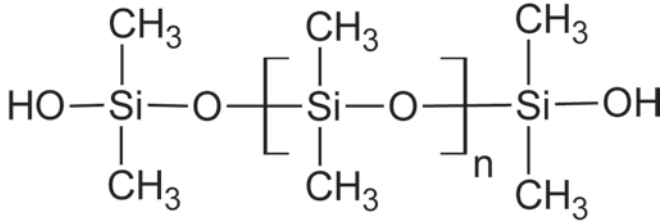


Figure 2. Dimethiconol

Dimethiconols are more polar than Dimethicones because of their silanol end groups and have somewhat limited reactivity. Silanol groups are weak acids and can condense with each other to form longer chains over time.[5] This affects the shelf life of Dimethiconol itself, but has little practical significance for the formulation chemist. Because of their polarity, short chain (low viscosity) Dimethiconols can impact the solubility of other ingredients with which they are mixed, but as the chain length increases, the effect of the silanol group's polarity rapidly diminishes. Many of the Dimethiconols used in personal care formulations are very long-chain PDMS (silicone gums) and the effect of the silanol end groups is minimal. The term *silicone gum* is used for very long-chain PDMS because physically they resemble a soft putty or dough-like consistency. Despite their appearance, silicone gums are liquids and will flow, albeit very slowly. High molecular weight Dimethiconols (and Dimethicones) are often sold as blends with low viscosity silicones. These blends (solutions) are relatively low viscosity liquids that are easier to handle when compared to the silicone gums themselves and easier to emulsify. If silicone gums are blended with volatile silicone or hydrocarbon solvents, unique skin interaction effects may be achieved in formulations, because the volatile solvent serves as a carrier or delivery system for the silicone gum. Normally the silicone gum would be too viscous to easily apply as a film on surfaces. Creating a low-viscosity solution of silicone gum in a volatile carrier allows for relatively easy application to skin and leaves a film of silicone gum when the volatile carrier evaporates.

As mentioned earlier, very low molecular weight Dimethicones are volatile, but their use is limited by higher cost compared to long-chain Dimethicones. Another class of volatile silicones that was introduced to the market in the late 1970s has become the dominant technology for providing transient silicone benefits in formulations. These are low molecular cyclic PDMS oligomers that have been assigned the generic INCI name **Cyclomethicone**. The INCI name Cyclomethicone covers a family of compounds that contain four, five, or six dimethyl siloxane units. These cyclic siloxanes are often referred to by an industry shorthand notation as D_4, D_5, and D_6 according to the number of dimethyl siloxane units. The INCI names for these compounds are **Cyclotetrasiloxane**, **Cyclopentasiloxane**, and **Cyclohexasiloxane**, respectively. Cyclopentasiloxane (**Figure 3**) is the most widely used of the Cyclomethicones. They exhibit esthetic properties similar to low viscosity Dimethicones but are volatile and odorless. They also have a very low heat of vaporization, and so produce no cooling effect on the skin. The first formulation to incorporate large percentages (>70%) of Cyclomethicone was an antiperspirant called *Dry Idea* that was introduced by Gillette circa 1980. This was an anhydrous formulation (i.e. containing no water) in which the aluminum salts (the active antiperspirant ingredient) were suspended in Cyclomethicone (in those days, D_4).[6] The name of the product reflected the use of the novel vehicle that provided a pleasant "dry" feel on the skin during application and then evaporated to leave the active ingredient on the skin.

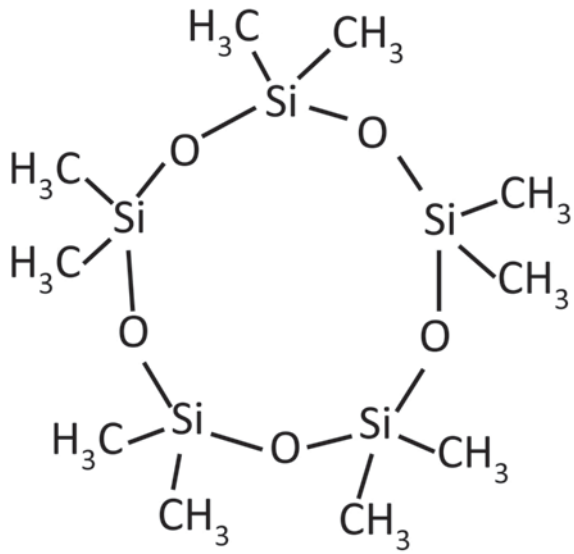


Figure 3. Cyclopentasiloxane

Anhydrous antiperspirant formulations based on Cyclomethicone still occupy a significant market share despite the cost associated with the silicone vehicle. A survey of the leading antiperspirants in the United States by the authors revealed

that all of them contain Cyclomethicone. Another popular use of cyclic dimethyl siloxanes is in color cosmetics. Here they serve as spreading agents for pigments. Pigments are usually derived from inorganic compounds such as iron oxide and titanium dioxide that are used in the form of small particles. These pigment particles need to be spread evenly on the skin surface, and various cosmetic oils are blended with the pigments to facilitate spreading. Cyclomethicone is ideal for this purpose because it provides good spreading and then evaporates leaving a pigment film that resists smearing.[4] When combined with a silicone resin, the pigment/cyclomethicone combination is effective for producing wear-resistant cosmetics. When the surface of the pigment particle is treated to impart a more lipophilic character, pigment spreading is facilitated in a silicone-based formulation because the pigment particles are more easily wetted. In fact, a case could be made that the evolution of surface treatments for pigment was spurred by the use of Cyclomethicone and other silicones as carriers in color cosmetic formulations.

From applications in antiperspirants and color cosmetics, the use of Cyclomethicone has grown steadily due to its versatility alone and in combination with other silicones. In hair conditioning formulations, the use of Cyclomethicone in combination with organic hair conditioning agents such as long-chain quaternary ammonium salts (e.g. **Cetrimonium Chloride**) was shown to provide very effective hair conditioning.[16] Cyclomethicone works with other hair conditioning agents to provide lubrication for improved wet combing, but evaporates as the hair is dried and leaves a minimal feel of residue. Using silicone emulsifiers, novel inverse emulsions based on Cyclomethicone allow the esthetic properties of the silicone to be maximized while improving the delivery of active ingredients. This approach has been used by formulation chemists to prepare clear antiperspirant emulsion gels where an aqueous solution of antiperspirant salts is emulsified into a continuous phase of Cyclomethicone. Similarly, inorganic pigments are delivered from an invert emulsion foundation that has an elegant feel because of silicone in the external phase. The introduction of hydrophobic surface-treated pigments into the color cosmetic market helped drive the trend towards silicone-based invert emulsion formulations because these pigments are ideal for use in this type of formulation. (Invert emulsions are discussed later in this chapter in the section on Formulation Considerations.)

Any discussion of the Cyclomethicones would be incomplete without some mention of the potential toxicity and environmental concerns related to the two most commonly used Cyclomethicones: Cyclotetrasiloxane (D_4) and Cyclopentasiloxane (D_5). The rapid growth in use and expanding applications of these compounds since the late 1970s prompted the silicone industry to conduct extensive studies on the toxicity and environmental fate of these silicones. The Cosmetic Ingredient Review (CIR), an organization sponsored by PCPC, first published its assessment of the safety of Cyclomethicone in 1991. More recently, the CIR has published an article that provides a comprehensive review of safety studies conducted on the individual members of the Cyclomethicone family.[7] This publication also includes

a review of the usage of the Cyclomethicones in various formulation categories. Because of their volatility, inhalation toxicity was tested using several animal species. Data from D_4 inhalation studies using rats showed that there was a potential for reproductive toxicity, although it was later concluded that these results are not relevant to humans. Nevertheless, this concern led the industry to shift from D_4 to D_5 in many applications beginning in the late 1990s. The overall conclusion of the most recent CIR panel was that all of the Cyclomethicones used today (D_4, D_5, D_6, and D_7) "are safe as cosmetic ingredients in the practices of use and concentration as described in this safety assessment."[7]

Although concerns about potential human toxicity for D_5 have been addressed by extensive testing with no evidence of a harmful effect, the high volume of its use and hence exposure led to concerns about its potential environmental effects. The environmental fate of these cyclic siloxanes in the atmosphere was established many years ago. Studies showed that they rapidly break down when exposed to oxygen and UV radiation from sunlight, producing silica and carbon dioxide.[8] A more recent field study on D_5 confirmed that it is effectively removed from the atmosphere.[9] The environmental fate of D_4 and particularly D_5 after they have been released into oceans and lakes (via sewage discharges) has been difficult to establish. Since they are not biodegradable and hydrophobic (potentially fat-soluble) the concern is for a potential bioaccumulation in the food chain. Because D_5 is not broken down biologically, it may persist in the bodies of organisms and thereby accumulate in growing concentrations as these organisms are eaten by animals higher in the food chain. One model that is widely used to predict lipophilicity and can be used in the estimation of bioaccumulation potential is the partition coefficient between water and octanol. High solubility in octanol correlates with high bioaccumulation potential for many compounds. Data from this model suggested that D_5 has a high potential to accumulate in animals imparting unknown and potentially toxic effects. To answer questions about bioaccumulation, the silicone industry sponsored environmental sampling studies in multiple aquatic systems around the world. Results from some of the studies have been published,[10,11] but others have not and the results so far are inconclusive. Regulatory bodies in the European Union, United Kingdom, and Canada have been considering rules that could restrict the usage of D_5 for several years. The Canadian government was the first to issue a conclusion concerning D_5 based on data presented by the silicone industry. The conclusion was that "D_5 is not entering the environment in a quantity or under conditions that constitute a danger to the environment."[12]

The silicones that have been discussed so far are referred to as methyl silicones because they have no other type of organic group attached to the silicon atoms. A large class of modified methyl silicones exists that contain other types of organic groups. These organic groups are introduced into the silicone to provide a specific functionality. These silicones are often referred to as "organo-modified" silicones. The different organic groups are introduced for various reasons such as to change the

solubility of the silicone or increase the affinity of the silicone for particular types of surfaces. Organo-modified dimethyl silicones developed for use in the textile industry were found to be effective hair conditioning agents and began to appear in hair conditioning products in the mid 1970s. One of the first of these silicones used for hair care was **Amodimethicone**, a dimethyl siloxane onto which amine groups are grafted (**Figure 4**). The polar amine groups which acquire a positive charge in water help to deposit the silicone onto both textiles and hair. The amine groups anchor the silicone to the surface of the hair fibers while the dimethyl siloxane backbone provides lubrication to facilitate combing and detangling. The INCI name Amodimethicone now refers to a diverse group of silicones that contain ethylenediamine groups that are very basic (i.e. ionize in water to generate hydroxide and ammonium ions and therefore generate a positive charge on the polymer over a wide pH range). Amodimethicone can also contain silanol groups that can produce further polymerization after the silicone is deposited, leading to a relatively durable coating. Silanols on Amodimethicone are more reactive because the ethylenediamine groups catalyze the silanol condensation reaction. Variants of Amodimethicone were developed over the years that contain other types of amine groups and quaternary nitrogen groups with the intention of improving hair conditioning performance. (**Table 1** provides examples of the most commonly used amine-modified silicones.)

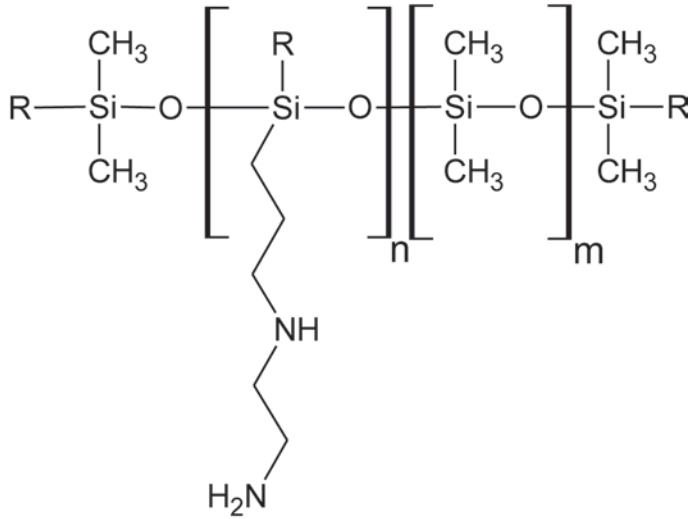


Figure 4. Amodimethicone (where R is –OH or –CH3)

Silicone surfactants that were originally developed for use in the manufacture of polyurethane foams have also found applications in personal care formulations. These silicones, like the Amodimethicones, are dimethyl siloxane polymers that have been modified by grafting polar groups onto the siloxane. For this family of silicones that are commonly referred to as silicone polyethers, the polar groups are

polyethylene glycol (PEG), polypropylene glycol (PPG), polybutylene glycol, or some combination of these. Since the dimethyl siloxane backbone is very hydrophobic and the polyethers are hydrophilic, silicone polyethers are essentially a type of nonionic surfactant. The properties of silicone polyethers are dependent on the type and ratio of silicone to glycol in the polymer. If the silicone polyether contains enough PEG, it will be water-soluble and exhibit a variety of properties one would expect from an organic nonionic surfactant. These properties include foaming, wetting, and emulsification of oils. As with other nonionic surfactants, silicone polyethers can be assigned an HLB value using the formula: wt. % polyether/5. Silicone polyethers with an HLB value of 10 or greater is water-dispersible.

The growth in popularity of Cyclomethicone-based formulations led to the development of high molecular weight silicone polyethers for stabilizing "invert" emulsion preparations. The term invert emulsion refers to the characteristic that these emulsions consist of the water phase dispersed in the oil phase, which is the inverse of conventional emulsions where the oil phase is dispersed into the water phase. This emulsifier technology enabled the production of novel antiperspirant and color cosmetic formulations, as discussed earlier. These special-purpose emulsifiers generally have an HLB of less than 5 and are not water-dispersible. They must be mixed with the oil phase prior to the preparation of an emulsion. (Information about the preparation of water-in-oil emulsions can be found in this chapter's section on Formulation Considerations.)

Silicone polyethers have been assigned a wide variety of INCI names because the INCI nomenclature system requires that the chain length of each type of polyether be included in the name. This nomenclature requirement was put in place circa March 2001. Prior to that time, silicone polyethers were assigned a generic INCI name, **Dimethicone Copolyol**. Despite the fact that the INCI name Dimethicone Copolyol was eliminated from the INCI dictionary more than ten years ago, some manufacturers still use it for ingredient labels. In addition to reflecting the lengths of the polyether chains in the INCI name, the nature of the polyether (block versus random) must also be reflected in the INCI name, therefore the INCI name contains information about how the silicone polyether is made. For example, the INCI name **PEG-12 Dimethicone** refers to a family of dimethyl siloxane polymers onto which polyethylene glycol chains that contain an average of 12 PEG units have been grafted (**Figure 5**).

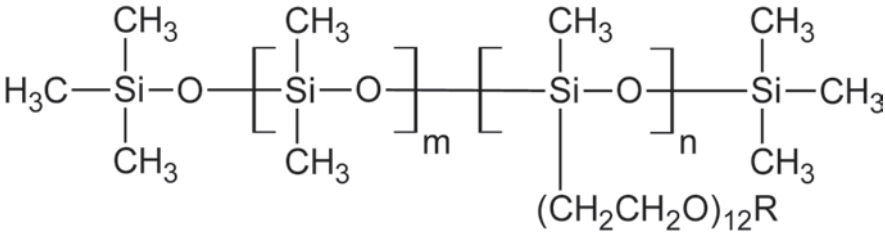


Figure 5. PEG-12 Dimethicone

The INCI name does not provide any information about the relative amounts of PEG versus dimethyl siloxane. PEG-12 Dimethicone may be water-soluble, but only if it contains a sufficient number of PEG-12 chains to overcome the insolubility of the dimethyl silicone backbone. The polyether chains can be grafted along the dimethyl siloxane polymer chain, or attached to the ends of the siloxane polymer. An example of the latter case is ***Bis*-PEG/PPG-14/14 Dimethicone**. The *bis* in the name indicates that the polyethers are attached to each end of the dimethyl siloxane polymer and in this case the polyethers are random copolymers with about 14 PEG units and 14 PPG units. The water solubility of this silicone polyether will depend upon the ratio of the polyether to the dimethyl siloxane, which for this copolymer is determined by the length of the dimethyl siloxane chain. Examples of some of the most common silicone polyethers are given in **Table 1**.In addition to methyl groups, silicones are produced that contain other types of hydrocarbon groups. Many of these have found their way into topical formulations.

Silicones with phenyl groups have been used for many years and the most widely used of these is **Phenyl Trimethicone**. This compound is not based on dimethyl siloxane and is usually a mixture of oligomeric (short chain) siloxanes that have both phenyl and trimethyl siloxy groups (**Figure 6**). Phenyl Trimethicone is soluble in a much wider variety of oils and waxes compared to Dimethicone and this makes it very easy to formulate with. In addition solubility modification of the silicone, phenyl groups raise the refractive index and this can produce higher gloss films. Other phenyl-containing silicones such as **Diphenyl Dimethicone** have been introduced more recently.

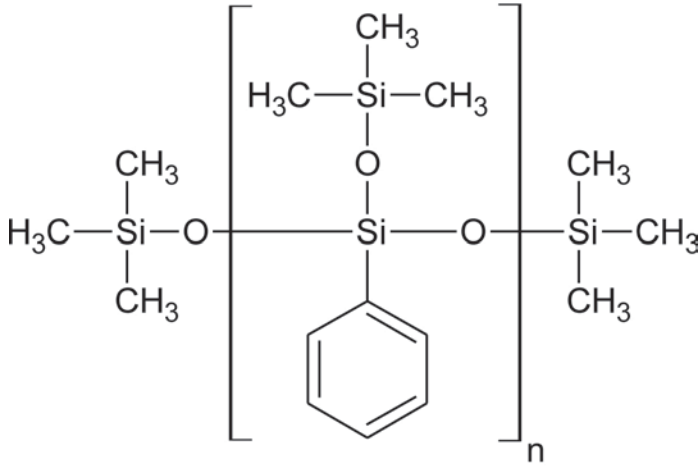


Figure 6. Phenyl Trimethicone

The silicones discussed so far in this section are all liquids at room temperature. There are several important classes of silicones used in topical formulations that are solids. These include alkyl-modified silicone waxes, silicone resins, and silicone

elastomers. The alkyl-modified silicone waxes are based on dimethyl siloxanes that have various amounts of methyl groups replaced with long-chain (C16 or higher) alkyl groups. The melting point of the silicone wax depends upon the degree of alkyl substitution and the chain length of the hydrocarbon. For example, two commercial waxes that conform to the INCI names Cetyl Dimethicone and Stearyl Dimethicone have roughly the same amount of alkyl substitution but different melting points. The structure for Cetyl Dimethicone is shown in **Figure 7**. Cetyl Dimethicone melts at slightly below room temperature while Stearyl Dimethicone melts at about 32° C which is, interestingly, the temperature of the surface of the skin. In addition to raising the melting point, replacing methyl groups with long-chain hydrocarbons changes the solubility of the silicone and also makes the films more impermeable to small molecules like water. Some alkyl-modified silicones such as C30-45 Alkyl Methicone, which has half of the methyl groups replaced with a mixture of long-chain hydrocarbons, are nearly as occlusive as petrolatum. **Figure 8** shows the relative occlusivity of several alkyl-modified silicones as measured in-vitro using the Payne Cup method. The *in vitro* data was shown to correlate with transepidermal water loss (TEWL) results[13].

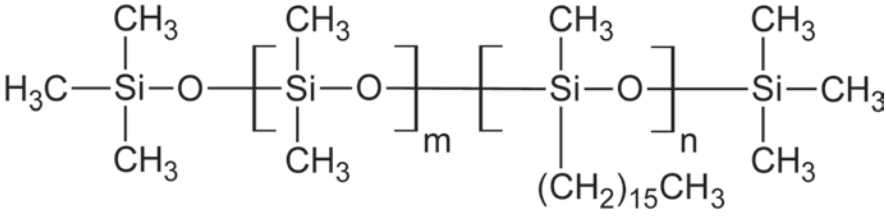


Figure 7. Cetyl Dimethicone

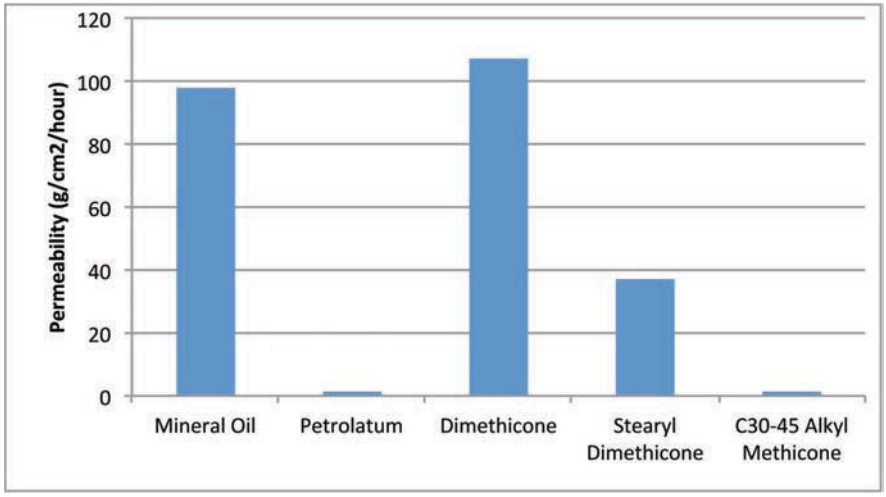


Figure 8. Water Permeability for Alkyl-Modified Silicones versus other selected materials

Silicone resins are a family of highly branched siloxane polymers that are used in the coatings industry. Silicone resins are not based on dimethyl siloxane. Instead, they are usually built from a silsesquioxane repeating unit. A silsesquioxane can be represented as the $RSiO_{3/2}$ unit where R represents the organic substituent (e.g. methyl) and $O_{3/2}$ indicates that each silicone atom is bonded to three oxygen atoms that are in turn bonded to other silsesquioxane units. Since each oxygen atom is "shared" with other silsesquioxane units, this type of resin has an average ratio of silicon to oxygen of 1 to 1.5, hence the use of the "silsesqui" prefix, which means 1.5. Silicone resins are solid materials with extremely high melting points. They are used as film-formers in color cosmetics and are typically added to the formulation in the form of solutions where the resin is dissolved in Cyclopentasiloxane or other volatile cosmetic solvent. Another type of silicone resin that is popular in color cosmetics is **Trimethylsiloxysilicate**. This resin is based on silica sol that has been modified by adding very hydrophobic trimethylsiloxyl groups (**Figure 9**). A silica sol is a water-soluble form of silicon dioxide and during the production of Trimethylsiloxysilicate, the silica is converted to a hydrophobic resin. As Figure 9 suggests, Trimethsiloxysilicate consists of very small silica particles that are coated with trimethylsilyl groups. This resin has similar physical properties and solubility as silsesquioxane resins. Silicone resins can be used in combination with dimethyl silicones and the dimethyl silicone (e.g. Dimethicone) will soften the normally brittle silicone resin. The inclusion of the resin makes the silicone mixture resistant to removal by surfactants.[14]

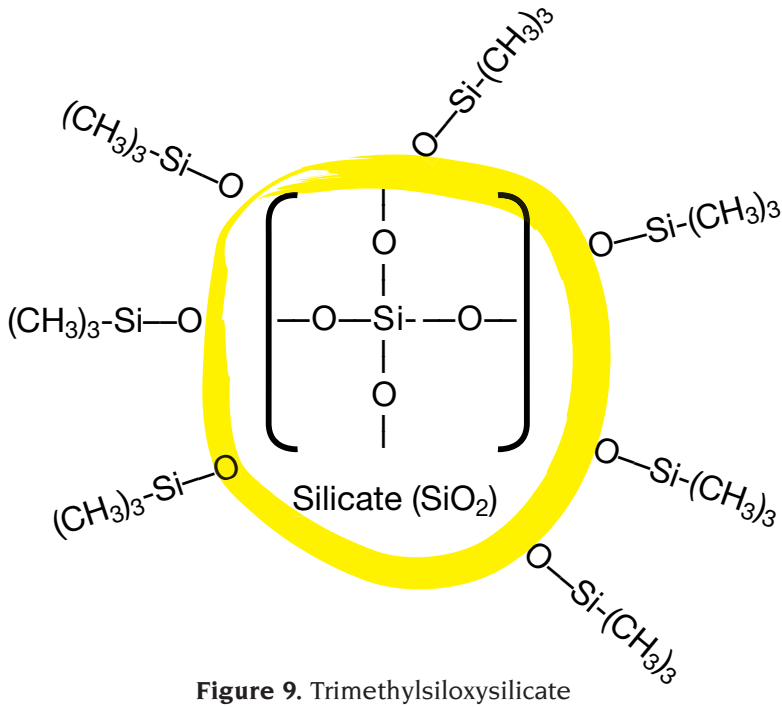


Figure 9. Trimethylsiloxysilicate

For color cosmetic preparations, silicone resins are usually dispersed in a volatile solvent prior to incorporation into the formulation. Cyclomethicones are particularly well-suited as solvents for silicone resins, and the volatile silicone improves spreading as well as serving as a carrier for the resin. After application, the silicone resin forms a film as the solvent evaporates. When properly formulated, silicone resins are very effective for producing durable color cosmetic films that will not smear and provide transfer resistance (e.g. reduce the tendency of lipstick pigments to transfer to a glass or coffee cup).

One of the more recent developments in silicone technology for personal care has been the introduction of silicone elastomers. As the name implies, silicone elastomers are rubbery solids and they are generally made by cross-linking dimethyl siloxane polymers. Cross-linking converts liquid silicone polymers into elastomeric solids. Silicone elastomers have a variety of uses in consumer products such as baby bottle nipples, non-stick bakeware, and cell phones, where silicone elastomers membranes are used to seal the keypad and form the buttons that are pushed to dial the phone. It would not seem obvious that silicones that are used to fabricate solid components would have applications in topical applications, but this category of silicone ingredients has grown rapidly in the number of ingredients and variety of applications over the past 15 years. The key to using silicone elastomers in topical formulations is to produce them in the form of small particles that are suitable for incorporation in formulations. The first silicone elastomer for skin care applications was introduced in Japan in the late 1990s. It is a powder made of spherical elastomer particles that provides a very soft, silky skin feel.[15] Silicone elastomer's esthetic properties are quite different from those of liquid silicones, and they can be easily incorporated into powder cosmetics. The lubrication provided by these particles is a consequence of their spherical shape; they behave like tiny ball bearings to produce a dry slippery feel. Other spherical particles (e.g. silica, nylon) provide the ball-bearing effect but are harder, so they give less of a cushion effect. The optical and esthetic effects of silicone elastomer powders can be modified by swelling them with a suitable solvent. For most of silicone elastomer powders, the ideal solvent is Cyclopentasiloxane, but hydrocarbon solvents, low viscosity Dimethicone, and some esters can be used as well. Silicone elastomers will absorb several times their own weight of Cyclopentasiloxane and when enough solvent is blended into the powder, the mixture will form a paste.

The other type of silicone elastomer for topical skin care formulations was introduced shortly after silicone elastomer powders. Commonly referred to as silicone elastomer blends or gels, these ingredients contain silicone elastomer that is already swelled with solvent. Physically, they are translucent pastes that typically contain 10-20% silicone elastomer, with the rest being the solvent. These particles in the paste are soft irregularly shaped gels with an average diameter of 40-70 microns. When spread on the skin, they provide an elegant silky feel and a "mattifying" effect (non-shiny appearance) in which the oily appearance of shine on the skin is eliminated.

Table 1 provides examples of the most frequently used silicones for each major category of silicones that have been discussed in this section. Key benefits for each silicone category are also listed.

Table 1. Silicone Types and Benefits by Category

Silicone Type	Examples	Benefits in Formulation
Polydimethylsiloxanes (PDMS)	Dimethicone, Dimethiconol	Emolliency, Skin protection, Gloss
Volatile silicones	Cyclopentasiloxane, Disiloxane, Caprylyl Methicone, Methyltrimethicone	Transient emolliency, Transient hair conditioning, Improved pigment spreading and film formation, Delivery of other silicones
PDMS with Amine functionality	Amodimethicone, Aminopropyl Dimethicone	Hair conditioning and Shine, Substantivity from aqueous formulations
Silicone Polyether PDMS with Polyol functionality (formerly Dimethicone Copolyols)	PEG-12 Dimethicone, PEG/PPG-18/18 Dimethicone, Cetyl PEG/PPG-10/1 Dimethicone, PEG-10 Dimethicone	Water solubility, Foaming, Emulsification
Phenyl silicones	Phenyl Trimethicone, Diphenyl Dimethicone	Emolliency, Improved solubility in organic oils, Gloss
Silicone waxes	Stearyl Dimethicone, Cetyl Dimethicone	Occlusivity, Texture & rheology control
Silicone resins	Trimethylsiloxysilicate, Polymethylsilsesquioxane,	Film formation, Durable films for color cosmetics
Silicone Elastomers	Dimethicone/Vinyl Dimethicone Crosspolymer, Dimethicone Crosspolymer, Polysilicone-11	Superior esthetics, Mattifying, Thickening

Silicone Applications and Benefits in Personal Care Formulations

There are a number of existing publications that provide detailed information about personal care applications for silicones,[4,16] which are recommended for further reading. The intent of this chapter is to provide practical information regarding benefits provided by silicones and approaches for formulating with silicones to achieve specific sensory and consumer benefits. As stated previously, silicones have

been key ingredients in the cosmetic and toiletries industry since their introduction in the 1950s, and this section will review various topical applications and highlight formulation strategies where silicones are commonly used.

Moisturizers (Hand and Body Lotions)

When Dimethicone fluids were introduced to the industry in the 1950s, their distinctive physical and sensory properties led to the development of products that featured their ability to form a protective film on the skin. Several early patents disclosed the use of silicone fluid in skin protective formulations.[17,18] One such product, *Silicone Glove* from Avon, is still on the market. The relatively high cost of Dimethicone fluids compared to other emollients limited their use at high concentrations in most skin care formulations, but they are often used in combination with other emollient and moisturizing skin occlusive ingredients such as mineral oil and petrolatum. Silicones also perform well in combination with natural oils such as jojoba, sunflower, and evening primrose.[19] In spite of its perceived higher cost versus organic emollients, mass-market formulations nearly always contain a small amount of Dimethicone as a defoamer to reduce lathering that can be generated when a lotion is based on a soap emulsifier (such as TEA-stearate). Currently, Dimethicone fluids are one of the most widely used silicones in skin care formulations because of their spreadability, smooth skin feel, and skin protection claims. The improvement of spreadability can be achieved at relatively low concentrations (<1-2%) and have been used to reduce the stickiness of moisturizers that contain humectants such as glycerin. Penetration of Dimethicones (and other silicones) into the personal care market also was encouraged by dropping prices in the 1960s and 1970s as their production volume increased and more silicone producers entered the market.

According to the U.S. Food and Drug Administration (FDA), Dimethicone can also be formulated as an "active" ingredient for over-the-counter (OTC) skin protectant drug products when used in a concentration range from 1-30%.[20] The National Formulary provides further specifications for Dimethicone as used in skin protectant OTC formulations in order to be in compliance to the Food Drug and Cosmetic Act. It is also important to note however that the National Formulary monograph for Dimethicone, NF grade is limited to viscosities between 20cst and 30,000 centistokes (cSt).

For body care products that are typically lower cost formulations, Dimethicone and Cyclomethicone fluids such as Cyclopentasiloxane and Cyclohexasiloxane are excellent choices to modify the spreadability and properties of formulations to achieve the desired esthetics. Low viscosity Dimethicone fluids (~ 10 cSt or 20 cSt) spread quickly and easily while providing a light, smooth skin feel. Higher viscosity Dimethicone fluids (10,000-30,000 cSt) form more persistent hydrophobic films with good water barrier properties. The broad range of viscosities of Dimethicone fluids offers a wide variety of esthetics and functional benefits that formulation chemists can leverage to create consumer claims. The choice of silicone to use in the formulation can be based on a variety of factors. Dimethicone fluids most commonly

used in topical formulations are typically in the viscosity range of 100-1000 cSt.[21]

The selection and use level of the appropriate silicone is a key factor in the esthetics of a formulation, both during and after application. Therefore, when formulating a body care product, a useful strategy to consider is to initially select a mid-range viscosity dimethicone fluid, in the range of 50 cSt to 350 cSt, and incorporate it into the oil phase at 1-2%. The viscosity of the Dimethicone will affect various esthetic properties such as spreadability, lightness/heaviness, oiliness/greasiness, and speed of perceived absorption. Lower viscosity Dimethicones will be perceived as more oily and faster-absorbing, while high viscosity Dimethicones will feel greasier and slower-absorbing. Of course, the use of other emollients in combination with silicone will affect formulation esthetics. Dimethicones with a viscosity above about 100 cSt are less miscible with organic emollients so they provide a characteristic silicone feel that is less affected by the presence of other emollients. A lighter skin feel and faster perceived absorption can be achieved by the inclusion of volatile, low viscosity Dimethicone fluids (<2 cSt) or Cyclomethicone. The term "play time" is used, especially in color cosmetics, to describe the period during which the formulation is spread over the skin and can be moved around relatively easily with the fingers. After a certain period, the formulation "sets" and becomes harder to spread around. For moisturizers, consumers usually perceive this effect as the completion of the absorption of the product. The perceived absorption is mostly caused by the evaporation of water and the breaking of the emulsion during rub-in. As the water evaporates, the emollients, waxes, and other ingredients become more concentrated on the skin and the oil phase ingredients separate from the remaining water (emulsion break). This produces a change in viscosity and signals the end of play time. The use of volatile silicones provide short-term benefits of spreadability, lubricity, and extension of the play time, while yielding a light skin feel with very low residue.

Conversely, a heavier skin feel and longer play time can be achieved by using higher viscosity dimethicone fluids or silicone gum blends. If compatibility is an issue with the oil phase, the formulation chemist could opt to include a low viscosity Dimethicone fluid (<5cst), Cyclopentasiloxane, alkylmethylsiloxane, or phenyl siloxane. Dimethicone fluids with viscosities less than 5 cSt and Cyclomethicone are compatible with a broad range of non-polar organic ingredients, and some of these are soluble in organic solvents such as ethanol and isopropanol. Similarly, alkylmethylsiloxanes and Phenyl Trimethicone exhibit increased solubility in non-polar organic ingredients due to the increased level of organic functionality versus silicon in the siloxane polymer. Phenyl Trimethicones are one of the few silicones miscible in 95% ethanol.

Facial Care (Anti-aging Products)

Facial care products include facial moisturizers, facial cleansers, anti-aging products, facial masks, toners, and lip care. Of these, anti-aging products represent the largest and fastest growing category of facial care products.[22] The goal of these

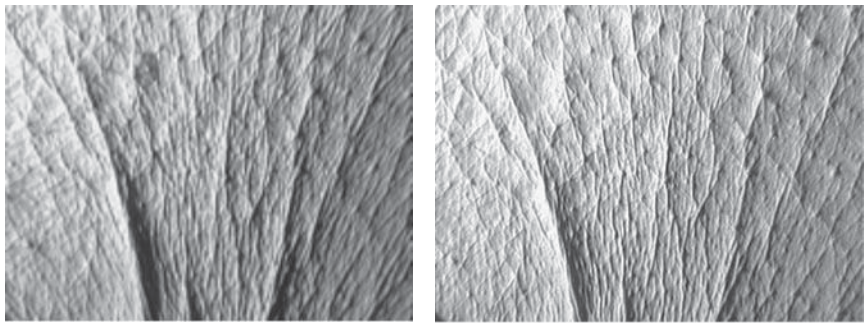
products is to impart a perception of healthy and more youthful skin. This is often driven by touch (skin smoothness, softness), visual effects (reducing the appearance of wrinkles, improved skin tone), and enhanced skin hydration. Facial moisturizers are distinguished from hand and body moisturizers by providing a lighter skin feel and faster perceived absorption. Facial moisturizers (and anti-aging products intended for daytime use) usually include sunscreen ingredients to provide a sun protection that is expressed by the sun protection factor (SPF). Silicones have become key cosmetic ingredients in anti-aging products over the past decade and provide a broad range of benefits to this market segment because of their unique esthetics and other mentioned properties. Silicones such as Dimethicone provide a light, smooth skin feel and the use of volatile silicones may reduce the amount of perceived residue on the skin after application. Silicone elastomers, which were introduced in the 1990s, have become popular ingredients in facial products because they provide a silky smooth skin feel and wrinkle-masking effects that cannot be achieved with liquid silicones. Reduction of wrinkle appearance, also referred to as "soft focus" or optical blurring, is due to light scattering by silicone elastomer particles. Unlike liquid silicones, these silicone elastomer particles create a rough (matte) surface on the skin that scatters light, thereby obscuring the underlying shadow that the fine wrinkles create. Many kinds of small particles can produce this effect, but silicone elastomers are especially well-suited because the elastomer particles are very soft and essentially transparent.

The types of silicones used in facial care products can be broken down into several categories:

- *Silicone fluids and gum blends* that are used to enhance spreading of formulations and impart smoothness.
- *Silicone emulsifiers* that impart formulation flexibility for water-in-silicone (W/Si), water-in-oil (W/O), and water-in-oil-in water (W/O/W) emulsions.
- *Alkylmethylsiloxanes* that provide improved compatibility with organic ingredients, wash-off resistance, barrier protection, skin hydration (moderate to good occlusive agent which yields low TEWL) and improved UV protection in sunscreen formulations.
- *Si Powders and Silicone Elastomer Blends* that provide silky to powdery esthetics, wrinkle masking, soft focus/blurring effect, sebum absorption, unique product textures, and actives delivery.

Silicone elastomers such as Dimethicone Crosspolymer, Dimethicone/Vinyl Dimethicone Crosspolymer, and Polysilicone-11 have been predominant cosmetic ingredients for anti-aging products over the past few years and have provided key benefits to this market segment because of their unique esthetics and properties. Silicone elastomers enable the formulation chemist to develop visually pleasing products with unique textures and esthetics turning a "simple" formulation to an elegant one. While the smooth-powdery skin feel is the key attribute driving the broad use of these compounds through various skin care segments, silicone elastomers provide an immediate and dramatic impact in reducing the visual appearance of

wrinkles following application to the skin. **Figure 10** illustrates the wrinkle-masking effect of Dimethicone/Vinyl Dimethicone Crosspolymer. The photographs are of skin impressions before and after application of a cream, which was a w/o emulsion containing 4% of the silicone elastomer powder. The study from which these photos were taken showed reduced appearance of wrinkles for 75% of the panelists (n = 21).



Before Treatment One hour after Treatment

Figure 10. Wrinkle-masking Effect of Silicone Elastomer Powder

Cosmetic powders based on silicone elastomers have an elegant, silky feel and provide a matte finish when applied to the skin. When included in the oil phase of facial care formulations, Dimethicone/Vinyl Dimethicone Crosspolymer has the ability to absorb various oils and reduce sebum on the skin as measured with a sebum analyzer (e.g. Sebumeter SM 810 from Courage + Khazaka). **Figure 11** shows the results from an *in vivo* sebum control test performed on eight volunteers.[23] The treatment was an anhydrous dispersion containing 21% silicone elastomer powder. This type of formulation is similar to facial primers, which are applied under makeup.

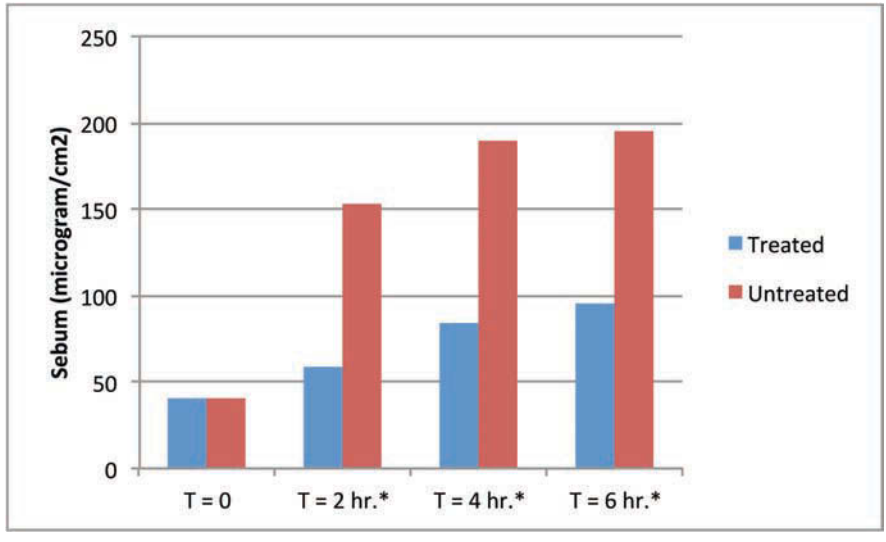


Figure 11. Sebum Control with Silicone Elastomer Powder; *indicates significant difference at the 99% confidence level

Silicone elastomers are recognized for their superior esthetics in skin care formulations, but until recently have had limitations with certain formulations. First generation silicone elastomer blends and powders are very effective at absorbing large amounts of silicone oils, and thereby swelling to produce soft particles that create unique esthetics and textures. These are compatible with typical non-polar cosmetic or topical formulation ingredients, but exhibit limitations in formulating with more polar ingredients, such as some of the sunscreen actives (e.g. Ethylhexyl Methoxycinnamate, Ethylhexyl Salicylate). Because of this, it was often difficult to incorporate silicone elastomers into sunscreen formulations at levels significant enough to achieve the desired esthetics.

The development of second generation silicone-organic elastomer blends such as Dimethicone/Bis-Isobutyl PPG-20 Crosspolymer has expanded the formulation options for this family of compounds due to the increased compatibility with polar organic ingredients and actives. This benefit allows the formulation chemist to combine higher levels of the silicone-organic elastomer with polar ingredients and maintain dry feel, smoothness, and a light, silky, lubricious sensation desired by consumers. Silicone-organic elastomer blends also enable clear formulations with organic components and would be suitable for use as a facial primer.

Color Cosmetics

Silicones have a long history of use in color cosmetic products because of their spreading properties, compatibility, and ability to improve texture and sensory properties[18] and continue to penetrate the color cosmetics market because of their distinct consumer benefits. Silicones offer and have allowed the use of new product claims such as "long wearing," "light feel," "oil-free," "smudge proof," and "transfer resistance."[24]

In liquid foundations, mascaras, and lip products, a key to achieving esthetically pleasing products and even color is to create uniform pigment films with good spreading properties. Volatile silicones such as Cyclopentasiloxane, Trisiloxane, and low viscosity Dimethicone are ideally suited for these applications due to their volatility, hydrophobicity, and spreading properties. These silicones have a non-greasy, light feel and contribute to a smooth and uniform application of the product. Treated pigment particles having a hydrophobic coating are more compatible with silicone fluids and are well-suited for delivery from a silicone-based formulation. This facilitates even spreading of the pigments and improved application and payout for stick formulations. The term *payout* refers to the transfer of the desired amount of formulation to the skin from the stick.

Alkylmethylsiloxanes and silicone resins such as Trimethylsiloxysilicate are film-forming polymers that improve the adhesion of pigments on the skin. These can be incorporated into the oil phase of formulations and used to improve the substantivity of color cosmetic formulations, therefore reducing transfer products by creating hydrophobic water-resistant films. These contribute to claims such as

"long-lasting," "waterproof," and "sweatproof." Phenyl Trimethicone is used to impart gloss to lipsticks and improve the compatibility of silicones with organic waxes.

Table 2 outlines various silicone families and key consumer benefits that silicones provide for color cosmetics.

Table 2. Silicone Benefits, as Arranged by "Family"

Silicone Family	Key Benefits
Volatile Silicone Fluids (Cyclomethicones, Dimethicone, Disiloxane, Trisiloxane)	Carrier for pigments and actives. Provide short-term lubricity and spreadability and their fast dry time yields a light, smooth skin feel.
Si Fluids and Si Gum Blends (non-volatile)	Si Fluids: Improve spreadability of formulations and provide a silky, soft sensory feel. Generate breathable films and are used to reduce tackiness in formulations. Si Gum Blends: Also improve spreadability of formulations, but provide thicker films that are more substantive and long-lasting. Depending on the carrier fluid, esthetics can range from a velvety to very lubricous feel. Si Fluids and Si Gum Blends both improve spreading, and reduce tackiness in formulations; however the higher viscosity fluids and Si gums also lubricate the skin and provide water barrier properties and substantivity.
Silicone Emulsifiers (Si Polyethers)	W/Si emulsions are used in foundations and mascaras.
Alkylmethylsiloxanes,	Long-lasting, wash-off resistance, barrier protection, skin hydration (occlusive agent reduces TEWL), potential SPF enhancement
Phenyl Silicones (Phenyl Trimethicone)	High refractive index that imparts gloss; for example. in lipstick formulations
Silicone Resins, Silsesquioxanes, and Silicone Acrylate Copolymers	Long-lasting/long wear characteristics, wash-off resistance
Silicone Elastomer Powders and Silicone Elastomer Blends	Unique silky to powdery skin feel, wrinkle masking, soft focus, sebum absorption, mattifying effect, delivery of actives. These can be used to create a broad range of product forms and textures (gels, powders and aqueous suspensions).

Sun Protection

Sun protection products include daily wear facial moisturizers and facial anti-aging products with SPF, which have been discussed in an earlier section. Other

products, often simply called sunscreens, provide protection from sun exposure during outdoor recreation. The goal in formulating effective sun protection products is to create formulations that will provide the following benefits: protection against ultraviolet solar radiation (UVB and UVA), high SPF with photostability, and water resistance. They must also be safe and non-irritating. Here the formulation challenge is to provide the functional benefits in combination with good esthetics since sunscreens that are unpleasant to use will not be applied in sufficient amounts to provide sufficient protection.

A broad range of silicone technologies have helped formulation chemists achieve these benefits, as demonstrated by the esthetic profile and performance of recent sun care formulations. Here, silicones may reduce the oiliness of sunscreen formulations and impart a light, non-greasy silky feel, which may improve the consumer's acceptance of and repeated use of the product. This is critical in the case of sunscreens because they cannot provide the labeled SPF unless a sufficient amount of product is applied and if the product has an unpleasant feel, consumers tend to apply less product and apply it less often.[25]

Sunscreen actives have limited compatibility with medium to higher viscosity silicone fluids and silicone gums, but are compatible with a variety of silicones including low viscosity, volatile dimethicone fluids, selected silicone polyethers, and alkyl-modified silicones. Alkyl-modified silicones such as Stearyl Dimethicone and Cetyl Dimethicone have been shown to improve sunscreen performance.[26] This work suggested that improved sunscreen performance was correlated with changes in formulation rheology due to the inclusion of alkyl methylsiloxanes. Rheological testing showed that alkylmethylsiloxanes affected formulation thixotropy, which is the recovery of the initial formulation viscosity after spreading the formulation by applying shear. The hypothesis is that viscosity recovery (thickening) produces a thicker sunscreen film, thereby improving protection.

Volatile dimethicone fluids (with typical viscosity of <2 cSt) are particularly well suited as co-solvents for alcohol-based recreational sunscreens due to their spreading characteristics and compatibility with non-polar sunscreen actives and ethanol. These are typically simpler formulations which contain ethanol, a combination of sunscreen actives, and an organic or silicone film former to impart wash-off resistance to the formulation. A number of different polymers are used to increase water resistance of sunscreen formulations. These include organic film formers such as VP/Eicosene Copolymer, VP/Hexadecene Copolymer, and hybrid silicone-acrylate polymers, such as Acrylates/Dimethicone Copolymer. Silicones and silicone acrylate copolymers such as Dimethicone, Trisiloxane, and Acrylates/Dimethicone Copolymer present in a number of commercial recreational sun protection products offer fast drying and water resistance benefits. **Table 3** lists the key benefits that silicones exhibit in sun protection applications.

Table 3. Benefits of Silicones for Sun Care Development, as Arranged by "Family"

Silicone Family	Key Benefits
Volatile Silicone Fluids (Disiloxane, Trisiloxane, Dimethicone and Cyclomethicone)	Carrier for sunscreen actives in recreational and daily wear products. These provide short-term lubricity and spreadability and their fast dry time yields a light, smooth skin feel
Si Fluids (non-volatile)	Low to medium viscosity fluids improve spreadability of formulations and provide a silky, soft sensory feel. These create "breathable" films and are used to reduce tackiness in formulations. Higher viscosity silicone fluids and gums are less soluble in sunscreen actives.
Silicone Emulsifiers (Si Polyethers)	W/Si emulsions are used in foundations and mascaras
Alkylmethylsiloxanes	Long-lasting, wash-off resistance, barrier protection, SPF enhancement
Phenyl Silicones (Phenyl Trimethicone)	Provide compatibility of silicones with organic sunscreens
Silicone Resins, Silsesquioxanes, and Silicone Acrylate Copolymers	Long-lasting/long-wear characteristics, wash-off resistance with comfort
Si Powders and Silicone Elastomer Blends	Silky to powdery skin feel, sebum absorption, mattifying effect, SPF enhancement

Shampoos

While the applications described in previous sections focus on leave-on formulations, this section will focus on rinse-off (or wash-off) formulations. Rinse-off formulations refers to the category of products that are applied to skin for short time and are washed with water to leave minimal or no residue. Of these, shampoos are the largest and most diverse category of products. Shampoos are formulated for the purpose of cleaning the hair by removing dirt and oils, especially sebum (oil excreted at the base of the hair follicles). Shampoos also remove residue from other hair treatment products (e.g. hair fixatives such as hairspray). The use of shampoo is often followed by application of a hair conditioner, which is formulated to deposit conditioning ingredients that lubricate the surface of the hair to make it easier to comb and style after shampooing. Silicones have several properties that make them effective hair conditioning agents. They spread easily over the hair surface forming a thin film that reduces inter-fiber friction. The film-forming action of silicones also produces a lustrous coating that imparts hair shine.

Shampoo formulations that most often contain silicones are referred to as "2-in-1"

shampoos, because they bring the added benefit of conditioning to the shampoo. These formulations are designed to both clean and condition the hair. In fact, the use of silicones as conditioning agents in these formulations has been the object of formulation efforts since the 1950s. One early patent[20] reveals the use of PDMS (Dimethicone) in a hair cleansing composition. Formulating a shampoo that cleans the hair while at the same time depositing conditioning agents is one of the more difficult formulation challenges in the industry. This is because the surfactants used in shampoos are as likely to remove hair conditioning agents as they are the dirt and oils that prompt the use of a shampoo in the first place. And non-polar, water-insoluble silicone fluids such as Dimethicone can produce undesirable effects such as reducing the amount of lather produced by the shampoo (due to the defoaming effect). The essence of the approach is to disperse small amounts of such silicones into the shampoo formulation in the form of small droplets that will deposit onto the hair when the shampoo is diluted during application to the hair. Several patents issued by major players in the shampoo business illustrate various schemes for solving this problem.[27-30] Generally, higher viscosity Dimethicones deposit more efficiently on hair, but achieving a uniform dispersion of small droplets of viscous silicone oils presents its own challenge. For this reason, emulsions of high molecular weight Dimethicones and Dimethiconols supplied by silicone manufacturers are popular for easy incorporation into a shampoo base.

The use of silicone polyethers that are water-soluble or water-dispersible in shampoos addresses many of the formulation challenges that other silicones pose, and the silicone polyethers have much less of a defoaming effect. Silicone polyethers can be used to formulate clear shampoos; however, the increased solubility of the silicone also makes it more likely to be washed away and not deposit on the hair. So the hair conditioning effects provided by silicone polyethers in shampoos are subtle at best. A better choice of organo-modified silicone for increasing deposition from a shampoo formulation is Amodimethicone or other amine-modified silicones. The amine functional groups develop cationic charges in an aqueous environment and this can drive deposition onto the hair surface, which has a net positive charge when wet. Once deposited onto the hair the dimethyl siloxane backbone of the amine-modified silicone provides lubrication and detangling. These types of silicones are costly and can significantly elevate the cost of the shampoo formulation, so Dimethicone is more commonly used.

Hair Conditioners

As mentioned above, many types of silicones can provide the benefits associated with the appearance of healthy, conditioned hair: detangling, easier combing, reduced static flyaway, and luster (gloss). It is far easier to achieve silicone deposition from a rinse-off hair conditioner than a shampoo, since in a typical conditioner there are no detergents. Many different types of silicones may be used in hair conditioning formulations: methyl silicones, silicone polyethers, and amine-modified silicones.

Silicones work well in combination with traditional organic hair conditioning agents, generally quaternary ammonium compounds with long alkyl chains (e.g **Cetrimonium Chloride**) that develop a cationic charge in water.

Cyclomethicones are particularly suitable for use in hair conditioners when combined with organic quaternary ammonium conditioning agents. The quaternary ammonium conditioning agents help to deposit the volatile silicone onto the hair surface and this combination provides a detangling and improved combing effect when the hair is wet. When the hair is dried, the Cyclomethicone evaporates, and therefore the amount of residue left on the hair is minimal. A patent from the late 1980s[31] provides examples of formulations with different volatile silicones in combination with **Dicetyldimonium Chloride.** When using non-volatile silicones such as Dimethicone in hair conditioning formulations, care must be taken to prevent excess deposition of silicone as this will cause the perception that the hair is greasy. Amine-modified silicones are deposited more efficiently from aqueous formulations than Dimethicones and can replace organic quaternary ammonium compounds.

Skin Cleansers and Body Washes

Liquid body wash formulations have a similar composition to shampoo formulations, although they are tailored to a different cleansing task. Body washes are designed to clean skin, and this task generally requires a milder detergent than is typically used in shampoos. In fact, many consumers find a typical shampoo to be harsh and drying to their skin because of its effectiveness in removing natural skin oils.

Body washes first appeared on the market in Europe and Japan and were introduced to the United States in the early 1990s. Like shampoos, the development of the body wash market has led to a variety of formulations tailored to different consumer needs. Body washes can be divided into three distinct categories:[32]

- Regular Body Wash formulations, which are intended to cleanse the skin.
- Moisturizing Wash formulations, which are intended not only to cleanse but to provide a skin benefit and minimize levels of skin dryness that is typically associated with the use of detergents.
- Specialty Body Wash formulations, which are intended to cleanse, moisturize, and provide additional benefits (deodorizing effect, sensory cues such beads and fragrance).

Moisturizing body washes are somewhat analogous to 2-in-1 shampoos in the sense that they are formulated to deposit skin care ingredients (moisturizers) onto the skin during and after the cleansing process. The difficulties presented by this task are every bit as difficult to achieve as previously described for the 2 in 1 shampoos—with the added difficulty that the skin presents a smaller surface upon which to achieve deposition, as opposed to a head of long (~10 inch) hair. Common moisturizing ingredients that affect the skin by occlusion and therefore may reduce TEWL include petrolatum and natural lipids (such as shea butter). Humectants such

as glycerin are often used to provide moisturization benefits as well. Silicones can be included to provide a moisturized skin feel and as with shampoos, high molecular weight dimethyl silicones are used to increase deposition.

Divinyldimethicone/Dimethicone Copolymer is a very high molecular weight silicone that was developed specifically for body wash applications. It is produced in an emulsion form by a suspension polymerization process using nonionic surfactants to maximize compatibility with the anion surfactant used in body washes and shampoos. The size of the silicone emulsion droplets formed by this method is large enough to scatter light and restrict the use of these large particle size emulsions to opaque formulations.

Silicone polyethers are also versatile ingredients for body wash formulations. Because of the vast solubility differences between the siloxane and polyether portions of these polymers, they have provided esthetic and functional benefits to skin cleansers and body washes. When combined with anionic surfactants, water-soluble/dispersible silicone polyethers such as PEG-12 Dimethicone or **Bis-PEG-18 Methyl Ether Dimethyl Silane** are known to improve the foam quality and create a creamier, more stable foam.[33]

Silicone polyethers and silicone surfactants such as silicone sulfosuccinates are also known for their mildness and are useful in cleansing formulations where low irritation is required. The use of **Disodium PEG-12 Dimethicone Sulfosuccinate** in personal cleansers is cited in several patents[34,35] as a mild cleansing agent and foam-enhancing surfactant for skin and hair. The silicone-based sulfosuccinate provides gentle and effective cleansing using low concentrations of surfactants, therefore lessening skin dryness. Additionally, the silicone-based sulfosuccinate provides a solubilization function, which prevents separation of oil-soluble components, such as fragrance components, vitamin extracts, plant extracts, and essential oils.

Antiperspirants and Deodorants

The term deodorant is sometimes used interchangeably with the term antiperspirant but these two types of formulations have different functions. Deodorants mitigate malodors produced by bacterial action upon perspiration. Therefore, deodorants usually contain antimicrobial ingredients in combination with a fragrance. Antiperspirants are intended to suppress perspiration. However, the active ingredients used in antiperspirants in addition to their main function generally have the effect of suppressing bacterial growth. Therefore, most antiperspirants are also deodorants, but the reverse is not true. Deodorants are usually very simple formulations that consist of alcohol, perfume, and often an antibacterial agent (such as Triclosan). Silicones are sometimes used in deodorants for the same reasons that they are used in other leave-on skin care products (i.e. emolliency, improved skin feel). But the use of silicones in antiperspirants has led to significant improvements in the formulation that deserve more detailed discussion. Silicones are broadly used in antiperspirant applications and are largely responsible for enhancing the consumer

acceptance of stick and roll-on formulations. Antiperspirant products are designed to deliver actives such as aluminum and aluminum-zirconium chlorohydrates to the skin thereby reducing sweat secretion. Antiperspirants are regulated as OTC drugs in the United States. Accordingly, the types of actives and use levels must conform to FDA rules.[36]

The predominant silicones used in the AP/DEO category are Cyclomethicones, which were introduced to this market in 1970s. Cyclomethicone was a breakthrough technology for antiperspirants because it provided unique properties compared to other formulation vehicles. They were first incorporated into aerosol formulations due to their dry feel and volatility, which eliminated fabric staining. Cyclic siloxanes (i.e. Cyclopentasiloxane) are an effective volatile carrier for antiperspirant stick formulations while providing the typical light lubricious silicone feel. Cyclomethicones provide even spreading and reduce the tackiness of the active ingredients during application and drydown.[37] Although this was a major breakthrough in product esthetics, there were limitations in using Cyclomethicones in AP formulations. Antiperspirant salts such as aluminum or aluminum zirconium are not soluble in these low viscosity silicone fluids and without the presence of an effective thickener; these would rapidly separate to the bottom of the formulation. For this reason, anhydrous antiperspirants based on volatile silicones include a thickener to retard the settling of the antiperspirant salts.

The introduction of silicone elastomers, which swell in the presence of Cyclomethicones, provides an elegant method of thickening anhydrous antiperspirant formulations. Because of the better esthetics of silicone elastomers relative to conventional thickeners, they can be used at sufficient levels to produce a soft paste antiperspirant formulation that does not require shaking. However, the high cost of such formulations has prevented widespread adoption of silicone elastomers in this product category.

Formulation Considerations

Conventional Emulsions (oil-in-water):

Since most silicones are hydrophobic (water-insoluble), they need to be emulsified in order to generate stable formulations. Formulations where the water-insoluble ingredients (oils, silicones, waxes, etc.) are dispersed into the water phase and stabilized by surfactants are called oil-in-water (o/w) emulsions (the reverse case of w/o emulsions is discussed in the next section). The general strategy for an emulsion formulation is to select a surfactant or mixture of surfactants that will effectively emulsify the particular combination of oils and waxes that are used in the formulation. There is a large variety of emulsifiers available to formulation chemists so the task is to select the suitable emulsifier that will be compatible with the specific silicones chosen. The selection of suitable emulsifiers for a given combination of oils and waxes or silicones, is as much art as it is science. Formulation chemists are often guided in their selection of emulsifiers by past experience with emulsifiers that

have worked for particular combinations of oil phase ingredients. But emulsifiers can also be selected using a systematic approach based on technical considerations.

One approach to the selection of emulsifiers that was introduced in 1949 by Griffin[38] is called the HLB system. HLB stands for Hydrophilic Lipophilic Balance and this system can be used to assign a numerical value to emulsifiers that roughly correspond to the degree of water solubility. The HLB system was designed primarily for use with nonionic emulsifiers made by ethoxylation of various fatty alcohols and other hydrophobic molecules and for fairly simple emulsions that contain a limited number of ingredients. The HLB values range from one to twenty where the polarity (degree of ethoxylation) increases with the HLB value. Emulsifiers with an HLB above about seven are dispersible in water and become water-soluble above ~ HLB 13. For preparing o/w emulsions, surfactants with HLB values in the range of 6-18 are used. As a general rule, emulsions made with two or more emulsifiers are more stable and easier to prepare than emulsions based on a single emulsifier. Therefore, it is a common practice to use combinations of emulsifiers where one emulsifier has an HLB lower than the targeted HLB and the other emulsifier has an HLB above the targeted HLB. The HLB for combinations of surfactants is determined by calculating a weighted HLB average where the weighting factor is the percentage of each emulsifier in the mixture of emulsifiers. The targeted HLB for specific oil phase is also referred to as the required HLB for that oil. The required HLB for various oils can be found in supplier literature[39] and in reference books.[40] More polar oils such as esters have a higher required HLB compared to non-polar oils. For example, Isopropyl Myristate has a required HLB of ~ 10 while mineral oil has a required HLB of ~ 9, as does Dimethicone. Cyclomethicones have a required HLB in the range of 7-8. The authors have not found required HLB estimates for other silicones in the literature, but our experience has been that phenyl and alkyl-substituted silicones are easily emulsified.

Inverse Emulsions (water-in-oil):

Most commercial emulsion products are the conventional o/w emulsions that were discussed in the previous section. Emulsions that are composed of an aqueous (water) phase that is dispersed and stabilized in an oil phase are termed water-in-oil (w/o) emulsions. These emulsions are often referred to as "inverse" emulsions because they represent the flip side of conventional (o/w) emulsions. The commercial application of w/o emulsion technology in the skin care industry is somewhat limited by higher formulation cost, the need for special emulsifiers, and the generally unappealing esthetics due to an oily heavy sensation when applied to skin.

The growing popularity of Cyclomethicone in the late 1970s prompted the development of silicone polyethers designed to stabilize w/o emulsions where the oil phase contains a large amount of Cyclomethicone. Such formulations overcame the esthetic problems of conventional w/o emulsions because of the spreadability, light skin feel, and volatility of the Cyclomethicone. The silicone polyethers suitable for preparing these emulsions are high molecular weight, water-insoluble (low HLB)

emulsifiers. They stabilize w/o emulsions by adhering to the water/oil interface and preventing coalescence of the water droplets. Coalescence is the process whereby small droplets of the dispersed phase in an emulsion join together to form larger droplets. If this process is not prevented, it will eventually lead to phase separation. The driving force for coalescence is the surface tension of the dispersed phase and since water has a very high surface tension, coalescence is particularly hard to overcome for inverse (water-in-oil) emulsions. For these emulsions using a high molecular weight polymeric emulsifier is effective because these polymeric emulsifiers are less likely to be displaced from the surface of the water droplet compared to short polymers or conventional low-HLB emulsifiers. The silicone polyether w/o emulsifiers form a protective film around the water droplets and this is critical because the high surface tension of water favors coalescence. Therefore large water droplets are energetically favored over small droplets, and if the formation of larger water droplet is not prevented, the emulsion will not be stable.

Another cause of instability for w/o silicone emulsions is settling that is driven by the difference in density between the droplets of the water phase and the surrounding oil phase. Since the density of water is typically greater than the oil phase, water phase droplets will sink over time. This problem is exacerbated when the water phase contains dissolved ingredients such as glycerin or electrolytes, which increase the density of the water phase. Stokes Law provides guidance about how to reduce the rate of settling for emulsions where the two phases have different densities. According to this law, the rate of settling can be reduced by two methods. First, making an emulsion with smaller droplets will reduce the rate of settling. This can be accomplished by using sufficient shear during emulsification to break down the droplets of water phase and by incorporating enough emulsifier to cover the surface of the emulsion droplets. The second factor that affects settling rate is emulsion viscosity. Increasing emulsion viscosity will inhibit settling. The viscosity of w/o emulsions is strongly dependent upon the volume ratio between the oil and water phases. Increasing the proportion of water phase will produce a thicker emulsion.

When preparing w/o emulsions, special attention must be given to the agitation used when dispersing the water phase into the silicone phase. The high surface tension of water usually requires more intense agitation for a w/o emulsion compared to an o/w emulsion. In addition more shear is needed for a w/o emulsion than that provided by a marine propeller (a simple propeller with three rounded lobes tilted at an angle designed to maximize vertical movement in the batch). The higher shearing energy is needed to overcome the tendency of water to coalesce into large droplets. In the authors' experience, mixing blades that generate high turbulence such as a Cowles disperser (Morehouse Cowles, Chino, CA) or a turbine blade with vanes perpendicular to the plane of rotation are suitable for making w/o emulsions with the most commonly used commercial emulsifiers. In addition to turbulent agitation, a second type of mixing is needed to move the emulsion through the shear zone of the turbine. Because w/o emulsions thicken as the water phase is added,

moving the emulsion through the shear zone becomes more difficult towards the end of the process. If the top of the batch is not moving as the last part of the water phase is added, this part of the water phase will not be properly incorporated into the batch. Good mixing of the entire batch can be achieved by the use of side-sweep blades or a secondary marine propeller. For small lab batches, we have experienced relatively easy processing by using a marine propeller mounted on the same shaft as the turbine blade. The key is to observe the batch as the water phase is added and set the addition rate so that water phase is rapidly incorporated into the emulsion. If the water phase is added to the top of the batch and it begins to collect on the surface, more agitation is needed.

Two other formulation techniques that are helpful for preparing W/Si emulsions involve additives for the water phase. Small amounts of salt added to the water phase improve emulsion stability. The mechanism for this effect is not well understood but salt in the water phase is thought to affect the configuration of the silicone polyether at the water/oil interface. For this, only small amounts of salt are needed, typically 1-2%. Sodium chloride, magnesium sulfate, buffered alpha hydroxy acids, and the aluminum salts used in antiperspirant formulations are all suitable. Another option to enhance stability is to include a small amount (< 0.5%) of a water-dispersible nonionic emulsifier such as Polysorbate-20 in the water phase. This reduces the surface tension of the water phase, making it easier to disperse into small droplets. Of the two options, the addition of salt is used most often. If the emulsion can be stabilized without the use of a nonionic emulsifier, it is best to leave it out of the formulation. For production of these emulsions on an industrial scale, it can be useful to pass the batch through a high-shear mixer such as a homogenizer or a colloid mill as the last step. This can be done as the batch is pumped out of the mixer. This final step is recommended as it improves batch uniformity by breaking up larger particles in the batch.

Translucent w/o emulsions based on silicone polyether emulsifiers can be produced by carefully adjusting the refractive index of the oil phase and the water phase. When the refractive indices of the two phases are matched, an emulsion that is nearly transparent can be achieved. Generally, the refractive index of the water phase must be increased to match that of the oil (silicone) phase and this can be done by including salts or polyols in the water phase. The requirement to accurately match the refractive indices of the two phases together with the special mixing requirements for w/o emulsions present difficulties in a manufacturing environment but it can be done, as demonstrated by clear antiperspirant gels; an example of such a formulation is provided in the Formulary section of this chapter.

Aqueous Solution Formulations:

Aqueous formulations that are clear and appear homogeneous can be produced if all of the ingredients are mutually soluble or if the oil phase ingredients are dispersed in the form of droplets that are smaller in size than the wavelength of visible light. In the latter case, the formulations are called a microemulsions. Special techniques

are used to generate microemulsions where the dispersed droplets are invisible to the naked eye; average droplets sizes ranging from 10 to 50 nm. Since most silicones are water-insoluble, the preparation of clear aqueous formulations with silicones requires fairly sophisticated emulsion techniques or the use of water-soluble silicone polyethers. These silicone polyethers are the easiest to use for preparing homogeneous aqueous formulations. If the silicone polyether contains enough water-soluble PEG units, it will dissolve in water and thus will be easy to incorporate into clear aqueous formulations. These silicone polyethers are essentially nonionic surfactants and exhibit behavior expected for such compounds; they reduce surface tension and generate foam in aqueous solution. Other than water-soluble silicone polyethers, insoluble silicones like Dimethicone can be used and are sometimes preferred since silicone polyethers do not provide the same degree of silicone esthetic properties as Dimethicone. However, the use of such silicones in clear formulations requires special techniques to create a microemulsion. Some silicone manufacturers offer pre-made silicone microemulsions that can be simply added to aqueous formulations

Anhydrous Formulations:

The first anhydrous formulations (apart from aerosols) based on silicone appeared shortly after Cyclomethicones were introduced. These were antiperspirant roll-ons and sticks. In both types for formulations, the antiperspirant actives (aluminum/zirconium salts) are dispersed in volatile silicone. For roll-ons the challenge is to suspend the salts, which are insoluble in silicone. This proved to be essentially impossible for roll-ons because they need to be low viscosity in order to dispense properly from their container. Including organically modified clays (e.g. **Quaternium-18 Bentonite**) in the formulation reduces the rate of settling and facilitates re-suspension of the antiperspirant salts. Other thickeners such as fatty alcohols and acids, or silica are also used in anhydrous antiperspirant formulations. For stick formulations, the thickener assists in suspending the antiperspirant salt actives while the formulation is molten during processing, filling, and cooling. Keeping the salts suspended prior to solidification of the stick allows for uniform distribution of the actives in the finished product. In roll-on products, the thickener helps to suspend the salts during application. Such formulations must always be shaken prior to use because the low viscosity needed for use as a roll-on precludes thickening the formulation to the point that the salts can be permanently suspended. The thickener in the roll-on formulation also reduces the tendency of the salt to pack tightly after settling so that they can be re-suspended by gentle shaking.

Color cosmetics such as lipsticks, pressed powders, and mascaras are usually anhydrous formulations. It has become common practice to include silicones, especially volatile silicones in color cosmetic formulations. Silicones are ideally suited to assist in even spreading of pigments on the skin. Volatile silicones provide these benefits and then evaporate so that smearing of the pigment film after drying can be minimized. The inclusion of silicone resins in the color cosmetic formulation can produce cosmetics that are wear-resistant. A more recent development in cosmetics

is what's known as"primers." These are typically anhydrous formulations based on volatile silicone and silicone elastomers. Primers are applied to the skin to provide a smooth matte surface onto which makeup (e.g. foundations) are applied. Primers assist in minimizing the appearance of wrinkles and skin imperfections, absorb sebum, and thus enhance the effect provided by other cosmetics applied afterwards.

Silicone Processing and Equipment Cleaning:

Silicon-based materials may be perceived to be difficult to process or remove from various surfaces. Silicones are typically added to the oil phase or silicone phase in an emulsion formulation. This section of the chapter is focused on highlighting key considerations related to the processing and equipment cleaning associated with silicone-containing formulations.

Equipment design and materials of construction are two important factors that require consideration prior to designing formulations with silicones. With the range of potential silicones available, physical properties such as volatility, melting temperature, particle size, and viscosity are all factors in determining the type of equipment and process to be used.

The key aspects to consider are as follows:

- Proper and safe handling of volatile silicones is critical during all phases of the product development and scale-up of formulations containing volatile silicone fluids. These need to be formulated in a closed system to prevent evaporation of the volatile fluid from the product; however, more importantly volatile silicone fluids such as Disiloxane, Trisiloxane, and Cyclopentasiloxane are classified as either flammable or combustible liquids based on their flashpoints. Special care (closed system, purging, and creating an inert environment with nitrogen) should be taken when handling these liquids and especially if heating the formulation is required.
- Due to their high viscosities, the use of silicone elastomer blends or some silicone gums can present a challenge during the scale-up or manufacturing process. While viscosities of silicone elastomer blends such as Dimethicone Crosspolymer are approaching 300,000 to 600,000 cSt, they exhibit shear thinning properties that may assist with handling. This means that the viscosity of the silicone decreases as the material is mixed and begins to flow. Silicone elastomer blends can be transferred into formulations using mixers or shear devices, such as a Graco Bulldog 10:1 pump with follower plate (Graco Incorporated, Minneapolis). In this case, pressure and contact with a follower plate will result in shear thinning of the silicone elastomer blend and processing as a lower viscosity fluid. Silicone elastomer and silicone gum blends can also be diluted with Dimethicone or Cyclomethicone fluids to reduce viscosity and assist in processing.
- As silicone gums are not compatible with many organic oils, they are often added *after* the emulsion has been formed and neutralized but will emulsify and remain suspended. Due to these issues and difficulties associated with

cleaning, some formulation chemists choose to use pre-emulsified silicones for their formulations. Silicone emulsions are post-added or added at the final stages of processing. These are typically added slowly and at lower temperatures (< 50°C) as excessive heat can impart instability and break some emulsions.

There are different methods that can be utilized to effectively remove silicones (emulsions, fluids, compounds) from equipment. These methods include the use of aqueous or solvent-based solutions but are dependent on the following factors:

- Type of silicone to be removed; its chemical and physical properties
- Type of emulsion (Si/W, W/Si, O/W)
- Equipment type and materials of construction
- Safety, environmental, and regulatory considerations*

To begin the cleaning process, it is imperative to remove as much of the silicone-containing formulation as possible prior to introducing cleaning agents. This can be done by purging to expel, scraping, or absorbing the bulk of the material. Once this initial step has been completed, then:

- Aqueous solutions of various surfactants, detergents, or degreasers, such as Shocon, Aqueous Reactivator, or Power Purge (ReNew Systems, Inc., Bay City, MI), can be used to partially emulsify silicone-based fluids to effectively clean equipment. Heated caustic solutions (i.e., KOH) are also very effective at cleaning silicone emulsions or cured silicone–based systems.
- Various solvent-based techniques can be used to remove siloxanes from process equipment. These include the use of aliphatic and aromatic hydrocarbons (hexane, mineral spirits, toluene), isoparaffins, higher alcohols, and higher ketones. Cyclic and volatile linear siloxanes are also effective solvents at removing silicones from equipment.
- Isopropyl alcohol (IPA) is generally not an acceptable solvent for washing due to its incompatibility with most silicones. In addition to this, if silicone elastomer is present in the formulation the addition of IPA will "dry up" the elastomer and leave small balls of residual elastomer which may be difficult to remove. However, IPA may be used for miscellaneous cleanup of equipment and floors.

Following the removal of the silicone containing material, it may be desirable to sanitize the equipment using a chlorine compound or quaternary ammonium based disinfectant. In any process development, the appropriate cleaning validation should be completed to confirm the effectiveness of the cleaning regiment, as well as the ability to detect any remaining silicon-based material or residue cleansing agents.

*The selection of cleaning procedure is also dependent on the waste handling capabilities of the facility and subject to local, state, and federal regulations for water, land and air. Therefore these should be studied prior to choosing a path for an appropriate cleaning practice.

Formulary

The following section contains formulations selected by the authors to illustrate the applications for silicones described throughout the chapter. The formulations are simple prototypes that are robust, stable, and reasonably easy to make. They can be modified to suit particular consumer needs; however, the stability of the formulation may be affected when other ingredients are added, or substituted for what is listed. Many of the formulations provide a suggested preservative that is suitable for the formulation in the authors' experience, but none of these formulations have been rigorously tested for microbial stability.

CATEGORY: Moisturizers

Basic Lotion Formulation

This basic lotion formulation is an o/w emulsion that utilizes the stearate-cetyl alcohol emulsifier combination to create a low cost, but esthetically pleasing lotion. The primary emulsifier for this formulation is TEA stearate, which is formed from the neutralization of Triethanolamine and Stearic Acid. A National Formulary (NF) grade of Dimethicone could be used as an OTC active for skin protectancy claims.[41]

Ingredients / Oil Phase (Phase A)		Wt. %
1.	Dimethicone (350 cSt)	3.0
2.	Mineral Oil	1.5
3.	Petrolatum	1.0
4.	Stearic Acid (50% minimum)	3.0
5.	Cetyl Alcohol	1.0
Water Phase (Phase B)		
6.	Water (*aqua*)	89.4
7.	Triethanolamine (99%)	1.2
Phase C		
8.	Preservative, fragrance	qs.

Procedure:
Heat the oil phase and water phase ingredients to approximately 70°C in separate containers and mix until uniform. Add the hot oil phase (Phase A) to the hot water phase (Phase B) while mixing with a propeller-type mixer. The mixer speed and addition rate should be such that the oil phase is rapidly dispersed in the water phase during addition. However, the mixer speed should not be so high as to create a vortex that will entrap air bubbles. Continue mixing until the batch is approximately 40°C and add Phase C (preservative, fragrance, and any other temperature sensitive ingredients). Mix until uniform and package.

Hand and Body Cream with Natural Lipids

This is a simple cream o/w emulsion formulation that illustrates the use of silicone in combination with natural butters. Cetyl alcohol is included to thicken the formulation and provide a creamy texture. The main emulsion stabilizer is a liquid dispersion polymer based on Sodium Polyacrylate and Trdeceth-6. Liquid dispersion polymers are ingredients that provide both thickening and emulsification. They consist of a thickening polymer and surfactant that are dispersed in an oil or solvent.

Ingredients / Phase A		Wt. %
1.	Water (*aqua*)	74.8
2.	Cetyl Alcohol	4.0
3.	Mangifera Indica (Mango) Seed Butter	2.0
4.	*Garcinia indica* Seed Butter (Kokum Butter)	4.0
5.	*Butyrospermum parkii* (Shea) Butter	4.0
6.	Dimethicone, 350 cSt	2.0
Phase B		
7.	Sodium Polyacrylate (and) Cyclopentasiloxane (and) Trideceth-6 (and) PEG/PPG-18/18 Dimethicone	4.0
Phase C		
8.	Glycerin	5.0
9.	DMDM Hydantoin	0.2

Procedure:
Heat the water to about 60°C and combine the rest of the ingredients for Phase A in a mixing vessel. The addition order is not critical, but it is important to ensure that the Cetyl Alcohol and the butters are completely melted before adding the Dimethicone. Begin cooling the batch and add Phase B. As Phase B is mixed into the batch, it will begin to thicken and the mixer speed should be increased to maintain good agitation. When the batch cools to 45°C, add Phase C and mix until uniform.

Variations:
Different natural butters and oils can be substituted for the three butters listed in the formulation. If oils are used in replacement of butters, the cream may have lower viscosity. The Cetyl Alcohol level can be increased to compensate for loss of viscosity. Other liquid dispersion polymers can be used in place of the one listed above, but the amount of Dimethicone should be increased to maintain the same esthetics.

CATEGORY: Face Care Formulations

Facial Moisturizer with SPF and Natural Lipids

This is a facial moisturizer that contains both UVA and UVB filters. It provides a smooth, silky feel from the use of a silicone elastomer gel and has a light afterfeel due to the volatility of the Cyclopentasiloxane. The main emulsion stabilizer in this formulation is a liquid dispersion polymer based on Polyacrylamide and Laureth-7.

	Ingredients / Oil Phase (Phase A)	**Wt. %**
1.	Ethylhexyl Methoxycinnamate (Octinoxate)	3.0
2.	Butyl Methoxydibenzoylmethane (Avobenzone)	1.5
3.	*Butyrospermum parkii* (Shea) Butter	1.0
4.	Glycerl Stearate (and) PEG-100 Stearate	4.0
5.	Stearyl Dimethicone	3.0
6.	Cetyl Alcohol	1.0
7.	*Camelina sativa Seed Oil*	4.0
8.	Isononyl Isononanoate	3.0
9.	Cyclopentasiloxane	8.0
10.	Cyclopentasiloxane (and) Dimethicone Crosspolymer	5.0
11.	Phenoxyethanol (and) Methylparaben (and) Ethyparaben (and) Propylparaben (and) Butylparaben	0.5
Phase B		
12.	Glycerin	2.0
13.	Water (*aqua*)	60.0
Phase C		
14.	Polyacrylamide (and) C13-14 Isoparaffin (and) Laureth-7	4.0

Procedure:
Combine the first two ingredients for Phase A and heat to about 60o C. Mix gently until the Avobenzone dissolves, then add the next four Phase A ingredients, making sure that each is melted before adding the next. Add the remainder of the Phase A ingredients and mix until uniform. Next, combine the ingredients for Phase B and heat to 60o C then add to Phase A with rapid mixing. Begin cooling the batch and when it drops below 30o C, add Phase C. As Phase C is mixed into the batch, it will begin to thicken and the mixer speed should be increased to maintain good agitation. After all of Phase C has been added, mix the batch until uniform.

Variations:
Different combinations of natural butters and oils can be used in this formulation as well as other liquid dispersion polymers.

Anhydrous Vitamin C Formulation

Ascorbic acid (Vitamin C) can be very difficult to stabilize in aqueous formulations. This formulation is stable because the vehicle for the Ascorbic Acid is glycerin. It is a non-aqueous emulsion with silicone as the external phase.

	Ingredients / Oil Phase (Phase A)	Wt. %
1.	PEG-10 Dimethicone*	5.5
2.	Caprylyl Methicone	9.0
3.	Dimethicone (and) Dimethicone Crosspolymer	22.5
4.	Tocopheryl Acetate (Vitamin E acetate)	1.0
Phase B		
5.	L-Ascorbic Acid (Vitamin C)	8.0
6.	Glycerin	54.0

*There are several different PEG-10 Dimethicones on the market. This formulation was developed using Dow Corning® ES-5612 Formulation Aid.

Procedure:
Combine the ingredients for Phase A in a suitable mixing vessel. In a separate vessel, heat the Glycerin to 95°C and add the Ascorbic Acid. Mix at 600 rpm until the Ascorbic Acid is dissolved. Slowly add Phase B to Phase A while mixing. See the prior section of this chapter on invert emulsions for guidance on mixing technique.

Anhydrous Sebum Control Gel (Facial Primer)

This formulation is designed to control sebum and impart a smooth, matte appearance to the skin. When applied under makeup, this type of formulation is called a "primer." NOTE: This formulation was the treatment used for the sebum control test discussed in this chapter's discussion of Facial Care/Anti-Aging Products. The results from this test are shown in **Figure 11**.

	Ingredients / Phase A	Wt. %
1.	Dimethicone/Vinyl Dimethicone Crosspolymer	21.0
2.	Cyclopentasiloxane (and) Cyclohexasiloxane	66.5
3.	Dimethicone (5 or 10 cSt)	12.5

Procedure:
Combine the silicone fluids in a suitable mixing vessel and begin mixing using a high shear mixer (Cowles mixer or rotor/stator). Add the elastomer powder into the vortex and increase mixing speed as the batch thickens. The mixture will be a thick paste. Continue mixing until all agglomerates (lumps) disappear and the texture is smooth.

Variations:
Different silicone elastomer powders can be used in this formulation. Some may be easier to incorporate and not require a high shear mixer. These are often supplied as a mixture with silica to de-agglomerate the silicone elastomer powder. Some of the silicone elastomer can be replaced by silica, with some sacrifice in esthetics. Many commercial primers incorporate anti-aging ingredients such as **Retinyl Palmitate**. Oil-soluble ingredients such as this can be included in the formulation above, but care should be taken to ensure that the anti-aging ingredients are uniformly dispersed.

Wrinkle-masking Cream

This is an invert (w/o) emulsion formulation that is intended to provide moisturization and delivers silicone elastomer powder to provide a wrinkle-masking effect.

	Ingredients / Phase A (Oil Phase)	**Wt. %**
1.	Dimethicone/Vinyl Dimethicone Crosspolymer (and) Silica	4.0
2.	Cyclopentasiloxane (and) PEG/PPG-18/18 Dimethicone	10.0
3.	Cyclopentasiloxane	16.0
4.	PPG-3 Myristyl Ether	0.5
Phase B (Water Phase)		
5.	Water (aqua)	
6.	Sodium Chloride	2.0
7.	Glycerin	5.0
8.	DMDM Hydantoin	0.4

Procedure:
Combine the ingredients for Phase A and Phase B in separate vessels. The vessel used for Phase A should be large enough to contain the entire batch. Slowly add Phase B to Phase A with turbulent mixing. The agitation should be sufficient to rapidly incorporate Phase B as it is added. Homogenize the batch using a high shear mixer, e.g. Ultraturrax or Silverson (IKA Works, Wilmington, NC; Silverson, UK). See the prior section of this chapter on invert emulsions for guidance on mixing technique.

Variations:
The viscosity of this formulation can be modified by varying the ratio between the silicone and water phases. More water will produce a thicker emulsion. Different types of water-soluble actives can be included in the water phase.

Blemish Balm ("BB Cream")

This type of formulation, which first became popular in Asia, is intended to provide multiple benefits. In addition to delivering moisturization and anti-aging ingredients, the formulation contains pigments that provide an even skin tone and conceal blemishes. The UV absorbers help to maintain skin whiteness by preventing tanning from sun exposure.

Ingredients / Phase A (Oil Phase)		**Wt. %**
1.	Lauryl PEG/PPG-18/18 Methicone	4.0
2.	Caprylyl Methicone	16.0
3.	Ethylhexyl Methoxycinnamate	7.0
4.	Ethylhexyl Salicylate	2.5
5.	Trimethylsiloxysilicate (and) Polypropylsilsesquioxane	2.0
6.	Dimethicone/Vinyl Dimethicone Crosspolymer (and) Silica	3.0
7.	Tocopheryl Acetate	0.5
Phase B (Water Phase)		
8.	Sodium Ascorbyl Phosphate	0.5
9.	Glycerin	8.0
10.	Sodium Chloride	0.7
11.	Water (*aqua*)	39.8
Phase C		
12.	Titanium Dioxide	5.6
13.	Iron Oxides, Yellow	0.25
14.	Iron Oxides, Red	0.1
15.	Iron Oxides, Black	0.05
16.	Phenyl Trimethicone	9.2
17.	Zinc Oxide	0.8

Procedure:
Combine the ingredients for Phase A in a vessel large enough to contain the entire batch. Combine the pigments for Phase C and blend well to ensure an even color and then add to Phase A. Alternatively, the pigments can be ground together with a ball mill using the Caprylyl Methicone from Phase A as the vehicle. Combine the ingredients for Phase B and slowly add Phase B to Phase A/C with turbulent mixing. The agitation should be sufficient to rapidly incorporate Phase B as it is added. Homogenize the batch used a high shear mixer such as an Ultraturrax or Silverson mixer (IKA Works, Wilmington, NC; Silverson, UK).See the prior section of this chapter on invert emulsions for guidance on mixing technique.

CATEGORY: Color Cosmetics

Liquid Foundation

This formulation illustrates a w/o emulsion formulation that delivers pigments from the silicone continuous phase.

Ingredient / Phase A (Oil Phase)		Wt. %
1.	Cyclopentasiloxane (and) PEG/PPG-18/18 Dimethicone	10.0
2.	Caprylic/Capric Triglyceride	5.0
3.	Dimethicone (and) Dimethiconol	3.0
4.	Dimethicone (Volatile Fluid < 5 cSt)	2.0
5.	Sorbitan Trioleate	0.5
6.	Volatile Dimethicone (and) Dimethicone Crosspolymer	10.0
Phase B		
7.	*bis*-Hydroxyethoxypropyl Dimethicone	2.73
8.	Iron Oxides, Red	0.18
9.	Iron Oxides, Yellow	0.45
10.	Iron Oxides, Black	0.09
11.	Titanium Dioxide	6.55
Phase C (Water Phase)		
12.	Glycerin	15
13.	Sodium Chloride	1
14.	Deionized Water	43
Phase D		
15.	Propylene Glycol and Diazolidinyl Urea and Iodopropynyl Butylcarbamate	0.3
16.	Perfume (choice)	0.2

Procedure:
Combine the ingredients for Phase A in a vessel large enough to contain the entire batch. Prepare Phase B by dispersing the pigments using high shear to ensure uniform color in the finished formulation. Combine Phase B with Phase A. Mix together the ingredients for Phase C and slowly add Phase A/B with turbulent mixing. The agitation should be sufficient to rapidly incorporate Phase B as it is added. Mix Phase D ingredients into the formulation. Homogenize the batch used a high shear mixer such as an Ultraturrax or Silverson mixer (IKA Works, Wilmington, NC; Silverson, UK). See the prior section of this chapter on invert emulsions for guidance on mixing technique.

Lipstick

This is a solid formulation that delivers pigments and dyes to the lips. The use of Cyclopentasiloxane helps spreading of the pigments and then evaporates after application, leaving the pigments and non-volatile ingredients on the skin. The choice of pigments and dyes is left open. The amount and type of pigments and dyes will affect the shade produced and the coverage.

Phase A		**Wt. %**
1.	Ozokerite	5.0
2.	*Euphorbia cerifera* (Candelilla) Wax	11.0
3.	Octyl Dodecanol	27.0
4.	C30-45 Alkyl Methicone	5.0
5.	Cyclopentasiloxane	4.8
6.	Petrolatum	3.0
7.	Lanolin Oil	9.0
8.	*Persea gratissima* (Avocado) Oil	2.0
9.	Oleyl Alcohol	8.0
10.	Methylparaben	0.2
Phase B		**Wt. %**
11.	Pigment blend in Cyclopentasiloxane	25.0

Procedure:
Heat the ingredients for Phase A to 80-90°C and gently mix until all of the waxes are completely melted. Prepare Phase B by dispersing the pigments and dyes into the Cyclopentasiloxane using a suitable high shear mixers or mill. Begin cooling Phase A and slowly add Phase B with mixing while adjusting the cooling to keep the batch above the solidification temperature (about 50°C). Mix until uniform and pour into lipstick molds.

Pressed Powder

Pressed powders consist of a mixture of pigments and dyes that are combined with a binder and then pressed into a suitable mold to produce a semi-solid formulation. A silicone elastomer blend is used as the binder. The silicone elastomer blend with a non-volatile silicone carrier prevents the formulation from dying out.

Ingredient / Phase A		Wt. %
1.	Talc	79.7
2.	Iron Oxides, Yellow	1.0
3.	Titanium Dioxide	14.0
4.	Methylparaben	0.2
5.	Propylparaben	0.1
Phase B		
6.	Dimethicone, 5 cSt (and) Dimethicone Crosspolymer	5

Procedure:
Combine the ingredients for Phase A and blend thoroughly to ensure a uniform color. Add Phase B and mix, then press into a suitable container.

Variations:
The use of yellow iron oxide will provide yellow color on the skin. Using a mixture of different iron oxides (yellow, red, black) will produce a variety to earth tones.

Facial Primer (for use under makeup)

This anhydrous formulation will provide some sebum control, but not as much as the formulation in the previous section. This formulation includes UVA and UVB absorbers and a silsesquioxane resin film-former.

Ingredient / Phase A		Wt. %
1.	Isododecane (and) Dimethicone Crosspolymer	25
2.	Dimethicone, <5 cSt (and) Dimethicone Crosspolymer	25
3.	Caprylyl Methicone	19.3
4.	C30-45 Alkyldimethylsilyl Polypropylsilsesquioxane	16
5.	*Theobroma cacao* (Cocoa) Seed Butter	5
Phase B		
6.	Butyl Methoxydibenzoylmethane	1.5
7.	Ethylhexyl Methoxycinnamate	4
8.	Octocrylene	2
Phase C		
9.	Squalane (and) Ubiquinone (and) Tocopheryl Acetate	1
Phase D		
11.	Perfume	1
12.	BHT	0.2

Procedure:
Combine the ingredients for Phase A in a covered mixing vessel equipped with a condenser and an inert atmosphere in the headspace. This is necessary to prevent loss of the volatile Isododecane and prevent the generation of explosive mixtures that can form if the Isododecane vapors mix with air. Heat Phase A to 85°C and mix until uniform. Combine the Phase B ingredients in a separate mixing vessel, heat to 85°C, and mix until all of the solids have dissolved. Cool both Phase A and Phase B to 30°C and add Phase B to Phase A. Add Phase C and Phase D, and then mix until uniform. The formulation is a thick paste, so a vessel equipped with side-sweep blades is needed to ensure proper mixing.

Triple Phase Makeup Remover

This is a novel formulation that will separate into three distinct layers if left undisturbed after shaking. It contains a mild surfactant and volatile silicones that will effectively remove cosmetics that contain hydrophobic pigments and silicone resins.

Phase A (Water Phase)		**Wt. %**
1.	PEG-8	37.6
2.	Deionized Water	9.0
Phase B		
3.	PEG-7 Glyceryl Cocoate	19
Phase C (Oil Phase)		
4.	Dimethicone (and) Trisiloxane	16.4
5.	Caprylyl Methicone	16.4
6.	Tocopheryl Acetate	0.4
Phase D		
7.	Phenoxyethanol (and) Methylparaben (and) Butylparaben (and) Ethylparaben (and) Propylparaben (and) Isobutylparaben	0.5
Phase E		
8.	Red 40 (0.1% in water)	0.1
Phase F		
9.	Violet 2 (0.1% solution in PEG-7 Glyceryl Cocoate)	0.3
Phase G		
10.	Perfume	0.3

Procedure:
Combine the ingredients for Phase A and Phase C in separate mixing vessels and mix until homogeneous. Mix Phases A, B, and C together, and then Phases D, E, F, and G. Mix thoroughly and then fill quickly while continuing to mix because the formulation will begin to separate as soon as mixing is stopped.

CATEGORY: Sunscreens

Sunscreen Stick

This is an anhydrous sunscreen stick formulation that combines a silicone wax with a natural butter. The volatile silicone is included to soften the stick and aid payout. After the stick is applied, the volatile silicone evaporates and therefore minimizes the greasy feel.

	Ingredient / Phase A (Oil Phase)	Wt. %
1.	Cetearyl Alcohol	20.0
2.	C30-45 Alkyl Methicone	3.0
3.	*Mangifera indica* (Mango) Seed Butter	20.0
4.	*Helianthus annuus* (Sunflower) Seed Oil	3.5
5.	Ethylhexyl Salicylate (Octisalate)	5.0
6.	Ethylhexyl Methoxycinnamate (Octinoxate)	7.5
7.	Homosalate	7.0
8.	Benzophenone-3	6.0
9.	Oleyl Alcohol	8.0
10.	Octocrylene	8.0
11.	Cyclopentasiloxane	20.0

Procedure:
Combine all of the ingredients except for the Cyclopentasiloxane into a suitable mixing vessel. Heat to 75-80°C and mix until all the waxes are melted and the Benzophenone-3 is completely dissolved. The mixture should be clear at this point. Begin cooling and add the Cyclopentasiloxane when the temperature drops below 60°C. Mix until uniform and pour into stick molds and cool to room temperature.

Variations:
Different combinations of sunscreen actives can be used in this stick to adjust the SPF and the UVA/UVB balance. Other natural butters can be substituted for the mango butter.

Sunscreen Cream

This is an o/w emulsion formulation that contains a mixture of UVA and UVB sunscreen actives. When tested *in vivo*, it produced an SPF of about 50. The main emulsifier (Potassium Cetyl Phosphate) is relatively water-insoluble and this improves the water-resistance of this formulation.

Ingredient / Phase A (Oil Phase)		**Wt. %**
1.	Ethylhexyl Methoxycinnamate (Octinoxate)	6.0
2.	Butyl Methoxydibenzoylmethane (Avobenzone)	3.0
3.	4-Methylbenzylidene Camphor	3.0
4.	Phenyl Trimethicone	3.0
5.	Stearyl Dimethicone	2.0
6.	Glyceryl Stearate	1.2
7.	C12-15 Alkyl Benzoate	4.0
8.	Cetyl Alcohol	2.0
9.	Methylparaben	0.15
10.	Propylparaben	0.10
11.	BHT	0.05
Phase B		
12	Potassium Cetyl Phosphate	2.0
Phase C (Water Phase)		
13.	Carbomer (1% dispersion in water)*	10.0
14.	Propylene Glycol	2.5
15.	Potassium Hydroxide (1% aqueous solution)	q.s.
16.	Disodium EDTA	0.1
17.	Water (*aqua*)	qs to 45%
Phase D		
18.	Cyclopentasiloxane	4.0
19.	Tocopheryl Acetate	0.5
Phase E		
20.	Phenylbenzimidazole Sulfonic Acid (Ensulizole)	2.0
21.	Water (*aqua*)	qs to 24%
22.	Potassium Hydroxide (10% aqueous solution)	~3.75.
23.	*bis*-PEG-18 Methyl Ether Dimethyl Silane	2.0

*There are many different Carbomers on the market. This formulation was developed using Carbopol 980 (Lubrizol Advanced Materials, Inc.)

Procedure:
Combine the ingredients for Phase C in a suitable mixing vessel. The potassium hydroxide should be added last. The mixture will gel as the base is added. Add sufficient potassium hydroxide to bring the pH to about 7 and then add enough water to bring the total for this phase to 45%. Heat Phase C to 75°C. Combine the ingredients for Phase A into a separate mixing vessel that is large enough to hold the entire batch and heat to 85°C. Mix until the solid ingredients are dissolved. Add Phase B to Phase A with gentle mixing. Add Phase C to Phase A/B with strong agitation. Continue mixing and begin cooling. When the batch cools to 45°C, add the ingredients for Phase D with strong agitation. Combine the ingredients for Phase E except for the last ingredient in a separate mixing vessel. Approximately 3.75% of a 10% potassium hydroxide solution will be required to neutralize the Phenylbenzimidazole Sulfonic Acid and render it soluble in the water. After a clear solution is obtained, adjust the pH to 7.0 using the Potassium Hydroxide solution. Heat Phase E to 30°C and add the 2501 *bis*-PEG-18 Methyl Ether Dimethyl Silane. Mix Phase E until uniform and add to the batch. Check the pH and, if necessary, adjust to pH 7.0. Cool to room temperature and add water to replace water lost to evaporation.

Oil-free Sunscreen with TiO_2

This is a w/o emulsion formulation where the sunscreen actives are titanium dioxide and Phenylbenzimidazole Sulfonic Acid (Ensulizole), a water-soluble UV absorber. This formulation has very good esthetics because it does not contain any of the traditional UV absorbing oil actives. The use of a hydrophobic powder provides a dry afterfeel.

Ingredient / Phase A		**Wt. %**
1.	Titanium Dioxide*	3
2.	Cyclopentasiloxane	19.5
3.	Cyclopentasiloxane (and) PEG/PPG-18/18 Dimethicone	7.5
4.	Aluminum Starch Octenylsuccinate	5
Phase B		
5.	Phenylbenzimidazole Sulfonic Acid (Ensulizole)	2.0
6.	Water (*aqua*)	qs to 65%
7	Sodium Hydroxide (10% solution in water)	~2.7
8.	Polysorbate 20	0.2

*A hydrophobic sunscreen-grade of Titanium Dioxide with a small particle size should be used. This formulation was developed using Titanium Dioxide that was surface-treated with Triethoxycaprylylsilane.

Procedure:
Disperse the Titanium Dioxide in the Cyclopentasiloxane using a high-shear mixer such as a Dispersator (Model 50 Lab Dispersator from NETZSCH Premier Technologies, Exton, PA). Combine the Titanium Dioxide dispersion with the rest of the ingredients for Phase A in a mixing vessel large enough to contain the entire batch. Prepare Phase B dispersing the Phenylbenzimidazole Sulfonic Acid in the water and then neutralizing with the Sodium Hydroxide solution. The Phenylbenzimidazole Sulfonic Acid will not go into the solution until it is neutralized. The process can be accelerated by warming the solution. Add the Polysorbate 20 and then add Phase B to Phase A with turbulent mixing. The agitation should be sufficient to rapidly incorporate Phase B as it is added. Homogenize the batch used a high shear mixer such as an Ultraturrax or Silverson mixer (IKA Works, Wilmington, NC; Silverson, UK). See the prior section of this chapter on invert emulsions for guidance on mixing technique.

Clear Sunscreen Gel

This is an anhydrous sunscreen gel based on one of the newer silicone elastomer blends that is much more compatible with organics than the first generation of silicone elastomer blends. It contains both UVA and UVB sunscreen actives and was tested *in vivo* on a small human panel, during which the SPF for this formulation was 20 and the UVA protection factor was 7.

	Ingredient / Phase A	**Wt. %**
1.	Isododecane (and) Dimethicone/*bis*-Isobutyl PPG-20 Crosspolymer	77.55
2.	Ethylhexyl Salicylate (Octisalate)	5.00
3.	Butyl Methoxydibenzoylmethane (Avobenzone)	3.00
4.	Stearyl Dimethicone	3.00
5.	Oxybenzone	0.45
6.	Octocrylene	2.00
7.	Diethylhexyl 2,6 Naphthalate	4.00
8.	Butyloctyl Salicylate	3.00

Procedure:
Heat all of the ingredients except for the Isododecane (and) Dimethicone/*bis*-Isobutyl PPG-20 Crosspolymer (silicone organic elastomer blend) combination to about 50°C and mix gently until all of the solids are dissolved and a clear mixture is obtained. In a separate container, heat the silicone organic elastomer blend to about 50°C. The time at about 50°C should be kept as short as possible to minimize evaporation of the solvent (Isododecane). On a manufacturing scale, a vessel equipped with a condenser can be used to return evaporated solvent to the batch. Combine the elastomer blend with the rest of the ingredients while mixing in such a way as to reduce incorporation of air bubbles. Cool to room temperature.

CATEGORY: Antiperspirants

Anhydrous Roll-on

This formulation illustrates the use of organo-modified clay as a thickener for an anhydrous roll-on (low viscosity) formulation based on silicone. The first commercial formulations of this type used Cyclotetrasiloxane, Cyclopentasiloxane, or a mixture of the two. This formulation is based on short-chain linear dimethyl silicones, but will works equally well with any type of Cyclomethicone.

Ingredient / Phase A		Wt. %
1.	Dimethicone (and) Trisiloxane	65.0
2.	Cyclomethicone and Quaternium-18 Hectorite and SD Alcohol 40	15.00
3.	Aluminum Zirconium Tetrachlorohydrex GLY	20.00

Procedure:
Combine ingredients 1 and 2 and mix until uniform. Add ingredient 3 and mix with high speed stirring. Homogenize.

Variations:
Any type of powdered antiperspirant salt can be used and other powders (e.g. Talc) can be included to change the esthetics of the film left behind when the volatile silicone evaporates from the skin. This formulation will accommodate a small amount of oil-soluble fragrance.

Clear Gel Antiperspirant Gel

Ingredient / Phase A (Silicone Phase)		Wt. %
1.	Cyclopentasiloxane (and) PEG/PPG-18/18 Dimethicone	8.0
2.	Cyclopentasiloxane	12.0
Phase B (Water Phase)		
3.	Aluminum Sesquichlorohydrate	48.0
4.	Deionized Water	16.0
5.	Propylene Glycol	16.0

Procedure:
Mix ingredients of phase A together and measure the refractive index. Mix ingredients of phase B together and measure the refractive index. Match the refractive index of phase A to that of phase B by adjusting with propylene glycol or water. If the refractive index of phase B is higher than that of phase A, add some water (~2%) to the aqueous phase to match. Once the refractive indexes are within +/- 0.0003 units of each other, increase the mixing speed of Phase A to a tip velocity of 900 ft/min (i.e. a 2-inch blade at 1,376 rpm) and very slowly add Phase B. Continue mixing for the same time period required for the addition.

Antiperspirant Stick

This is a stick (solid) formulation that incorporates Stearyl Alcohol as the structurant with a small amount of Hydrogenated Castor Oil to make the stick harder. This type of formulation was first introduced commercially with Cyclopentasiloxane as the volatile silicone**.** This version uses short-chain linear dimethyl silicones, but will work equally well with any type of Cyclopentasiloxane.

Ingredient / Phase A (Oil Phase)		Wt.%
1.	Hydrogenated Castor Oil	5
2.	Stearyl Alcohol	16
3.	Dimethicone (and) Trisiloxane	38
4.	Phenyl Trimethicone	15
Phase B		
5.	Aluminum Zirconium Tetrachlorohydrex GLY	25
6.	Talc	1

Procedure:
Heat phase A ingredients to 80-90°C until completely melted. Add ingredient 5 with mixing. Add ingredient 6 with mixing. Stir until the mixture is homogeneous and then cool to 60°C with mixing. Pour into stick molds.

CATEGORY: Cleansers and Shampoos

Body Wash with High Molecular Weight Silicone Emulsion

As mentioned in the Skin Cleansers/Body Washes section of this chapter, high molecular weight silicones are used in cleansing products because these silicones show improved deposition compared to low molecular weight silicones. This formulation contains Divinyldimethicone/Dimethicone Copolymer that is supplied as an emulsion.

	Ingredient / Phase A	Wt. %
1.	Sodium Laureth Sulfate (30%)	30.0
2.	Decyl Glucoside	5.0
3.	Cocamidopropyl Betaine	10.0
4.	Laureth-4	2.0
5.	Deionized Water	45.2
	Phase B	
6.	Polyacrylamide (and) C13-14 Isoparaffin (and) Laureth-7	2.0
	Phase C	
7.	Divinyldimethicone / Dimethicone Copolymer (and) C12-13 Pareth-3 (and) C12-13 Pareth-23	4.6
	Phase D	
8.	Sodium Chloride	q.s.
9.	DMDM Hydantoin	0.2
10.	Fragrance	0.1

Procedure:
Mix Phase A ingredients together until all ingredients are completely dissolved. Mix well, then turn the mixer off for several minutes to allow air bubbles to escape. Add Phase B to Phase A with mixing. Mix until well dispersed. Add Phase C with mixing and mix until uniform. In order, add ingredients 8, 9, and 10 with mixing to adjust viscosity. If necessary, de-air under slight vacuum or using a centrifuge.

Clear Shampoo with Amodimethicone

As mentioned in the Shampoos section of this chapter, amine-modified silicones have a greater tendency to deposit onto hair from a shampoo due to the cationic charge that the silicone acquires in water. This formulation contains Amodimethicone that is supplied as a microemulsion. The particle size of this emulsion is small enough to produce a transparent shampoo.

Ingredient / Phase A		Wt. %
1.	Water (*aqua*)	32.3
2.	EDTA	0.1
3.	Polyquaternium-10	0.2
Phase B		
4.	Sodium Laureth Sulfate, 28% Aqua	50.0
5.	Cocamidopropyl Betaine	5.0
6.	Cocamide DEA	2.0
Phase C		
7.	Amodimethicone (and) C11-15 Pareth-7 (and) Laureth-9 (and) Glycerin (and) Trideceth-12	3.0
8.	Polyglyceryl-2 Tristearate (and)PEG-6 Caprylic/Capric Glycerides	4.0
9.	Propylene Glycol	2.0
10.	Panthenol	0.3
11.	Propylene Glycol (and) Diazolidinyl Urea (and) Methylparaben (and) Propylparaben	0.5
12.	Fragrance	0.6

Procedure:
Mix Phase A ingredients together and heat to 60°C. Mix Phase B ingredients together and add to Phase A with mixing. Add phase C ingredients one at a time in order with mixing. Mix until homogeneous and package.

CATEGORY: Hair Conditioners

Leave-In Conditioner

This formulation contains several silicones that impart shine (luster) and facilitate both wet and dry combing.

	Ingredient / Phase A	Wt.%
1.	Sodium Polyacrylate (and) Dimethicone (and) Cyclopentasiloxane (and) Trideceth-6 (and) PEG/PPG-18/18 Dimethicone	2.0
2.	Dimethicone, 5 cSt	7.0
3.	Dimethicone (and) Dimethiconol	3.0
	Phase B	
4.	Water (*aqua*)	80.6
5.	Butylene Glycol	5.0
	Phase C	
6.	*bis*-Diisopropanolamino-PG-propyl Dimethicone/*bis*-Isobutyl PEG-14 Copolymer	1.8
7.	Fragrance	0.1
8.	Preservative	0.5

Procedure:
Mix Phase A ingredients together. Mix Phase B ingredients together and add to Phase A with mixing. Add phase C with mixing.

Rinse-off Conditioner

This formulation contains a traditional quaternary ammonium conditioning agents in combination with silicone conditioning additives. It improves wet and dry combing and a soft feel.

Ingredient / Phase A		Wt.%
1.	Behentrimonium Chloride	2.0
2.	Cetearyl Alcohol	5.0
3.	Water (*aqua*)	88.5
Phase B		
4.	Dimethicone, 5 cSt	2.0
Phase C		
5.	Dimethicone (and) *bis*-Hydroxy/Methoxy Amodimethicone	2.2
6.	Fragrance	0.1
7.	Preservative (choice)	0.2

Procedure:
Heat the ingredients for Phase A to 80°C with mixing until completely melted. Add Phase B to phase A slowly, with mixing, and maintain mixture temperature at 70°C. Cool to 50°C while stirring. Add the ingredients for Phase C with mixing. Mix until homogeneous.

Curl Defining and Styling Lotion

This formulation is based on a novel cross-linked silicone that provides a soft hold when applied to the hair.

Ingredient / Phase A		Wt.%
1.	Water (*aqua*)	60.3
2.	Polyquaternium-7	0.5
3.	Polyquaternium-55	3.0
Phase B		
4.	Cocamidopropyl Betaine	5.0
5.	Cocamide DEA	2.0
6.	Silicone Quaternium-16 Glycidoxy Dimethicone Crosspolymer (and) Undeceth-11 (and) Undeceth-5	4.2
Phase C		
7.	Polysorbate 20	1.0
8.	Fragrance	0.5
Phase D		
9.	Water (*aqua*)	20.0
10.	EDTA	0.1
11.	Panthenol	0.2
12.	PEG-12 Dimethicone	2.5
13.	Raspberry seed oil/ Palm oil	0.2
14.	Propylene Glycol (and) Diazolidinyl Urea (and) Methylparaben (and) Propylparaben	0.5

Procedure:
Mix the ingredients for Phase A together and heat to 60°C. Mix the Phase B ingredients together. Add Phase B to Phase A, mixing until homogeneous. Premix the ingredients for Phase C until homogeneous. Add Phase C to Phase AB with gentle mixing. Add the Phase D ingredients one at a time in the mixture of ABC. Mix until homogeneous and package.

Summary

The use of silicones in topical formulations has increased dramatically since they were first used in the 1950s. This growth has been driven by several factors. These include the proliferation of new silicone ingredients that improve performance in specific applications and the economies of scale in the silicone industry that have

reduced the cost of dimethylsiloxanes, which are the backbone for most commercial silicones. One class of silicones, the Cyclomethicones, introduced in the late 1970s has been particularly important in the penetration of silicones into new applications in topical products. Cyclomethicones provide a combination of physical properties that are unlike any other cosmetic solvent and have enabled many other silicone technologies that probably never would have been developed if widespread use of Cyclomethicones had not occurred.

The personal care market for silicones has penetrated into nearly all formulation categories. One sign of the ubiquity of silicones in topical skin care is the fact that new silicones are often developed to replace older silicones in the same application. Growth of this market is now being driven by the same forces that are important for the topical skin care industry as a whole. These include geographic expansion to underserved markets (e.g. Brazil, Russia, India, and China), increasing affluence by consumers who will pay for innovative formulations, and the aging of the population especially in the developed countries (e.g. the U.S. and the E.U.). These trends support sales for more sophisticated formulations that usually include silicones.

The success and wide adoption of silicone technologies has also invited scrutiny on issues on health and environmental safety. Scrutiny that has prompted the silicone industry to conduct extensive testing and has made this family of ingredients one of the most studied among all ingredients used in the topical skin care market. The results of these studies have continued to support the safety of silicones for these applications. Nevertheless, continued growth of silicone applications may also be threatened by the "greening" of the cosmetic industry, which is driving development of more sustainable and environmentally friendly ingredients. The trend toward natural ingredients is particularly difficult for the silicone industry to respond to because silicones are synthetic ingredients that do not exist in nature. The key factor that supports the current use of silicones for these applications is performance. Silicones have chemical and physical properties that are unmatched (at least so far), and cannot be duplicated by ingredients derived from natural sources.

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CHAPTER 5

The Use of Corn-derived Ingredients in Personal Care Applications

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Key Words:
Corn wet-milling process, Zea Mays (corn) starch, Modified corn starch, Hydrolyzed corn starch

Introduction

Western society in the past two decades is driven by increased desire to "get back to nature" with the recognition that generally industrialized lifestyle may bring with it many problematic health-related outcomes. Personal care product manufacturers are therefore looking to deliver more natural multifunctional products. With this shifting need of a more diverse and eco-conscious society, the formulation chemist is challenged to develop products that will satisfy consumer desires for more natural products without compromising those products' performance. A ripple effect of this influence is an upward demand for transparency in manufacturers' practice and sourcing.

While this notion triggers suppliers to seek exotic plant derived compounds, oftentimes it is the simplest ingredients that are overlooked, but with this surge of consumer awareness in personal care products, and since nature somewhat equates with simplicity, this chapter will focus on natural corn-derived ingredients. These multifunctional ingredients, which are also used in the food industry, have found a way into topical personal care formulations. They are easy to incorporate and can assist in the promotion of a more natural concept of topically applied products.

Corn kernel is a natural, complex, multifunctional, and sustainable compound. When the kernel is broken down and extracted, the extract contains a multitude of components with a variety of properties and functionalities. Corn-derived ingredients are produced through the corn wet milling process and can be made to perform in

a versatile range of personal care topical applications.

Corn wet milling is a continuous process that separates the corn kernel into various components. A general overview of the corn wet milling process begins with taking the corn kernels and steeping them in a dilute aqueous solution of sulfurous acid. The acid softens the kernels, which are then coarsely ground to begin the separation of the other components. The germ, which contains the oil, is separated by centrifugation. Once the germ is separated, the remaining assortment of starch, gluten and fiber are finely ground and the fiber is separated through a filtering process. The starch and gluten mixture is then separated by weight through centrifuging, followed by various cycles of washing. After washing, the starch slurry can be dried to make unmodified corn starch, or can be pumped to make modified or hydrolyzed starches using acid or enzyme conversion technology.[1]

Common ingredients derived from the wet milling process include unmodified (native) starch (INCI: Zea Mays (corn) Starch), modified starches, liquid hydrolyzed starches, maltodextrins, dextrose, gluten, and corn oil. These corn-derived ingredients have been used for many decades in the food industry and continue to expand their versatility into other applications, such as topically applied consumer products. There is an abundance of corn-derived ingredients that seems to have penetrated markets across many different types of industries including food, mining, industrial, paper, and corrugating. The main focus of this chapter is to introduce those corn-derived ingredients that can provide a more natural touch to personal care topical formulations since they are mildly processed from a sustainable, renewable resource.

Zea Mays (Corn) Starch

Unmodified starch (INCI: Zea Mays (corn) starch) is one of the most common ingredients extracted from corn utilizing wet milling technology. The starch polymer is composed of repeating glucose units with hydroxyl groups that participate in hydrogen bonding. It is a high molecular weight biopolymer consisting of two major units, the linear amylose (1,4-glucoside linkage) and the branched amylopectin (1,6-glucoside linkages) which takes the shape of a polygonal granule. On average, unmodified corn starch is composed of approximately 30% amylose and 70% amylopectin and has a particle size range between 10 to 14 microns.[1]

Zea mays (corn) starch exhibits versatility in offering both functional benefits and sensorial enhancements to topical applications. Perception of a silky, soft feel is imparted by the rolling motion of the granules over the skin. Typically, these granules can be delivered in either cream or lotion form. The porous nature of these granules functions to absorb oil, resulting in a reduced greasy sensation associated with creams with higher oil content. With these functionalities in mind, zea mays (corn) starch can be formulated into many powder products, ointments, creams, soap bars, and even color cosmetic products.

Powdered product applications are one of the most common ways to formulate zea mays (corn) starch and can be delivered in either pressed or loose form. The

porous nature and structure of the starch granule allows it absorb both oil and moisture. This physical arrangement allows it to be applicable for topical products such as body, foot, and baby powders. Different usage levels can alter the degrees of these attributes that compose the sensory profile to best suit the end performance of a topical product. The polygonal chemical shape allows the granules to glide over the skin surface creating this perceivable "rolling" sensation during spreading and application.

Depending on the technique and the method of incorporation into a formulation, corn starch can impart versatile properties. For topical formulations, unmodified starch is used in its raw granular form and is recommended to be blended with other dry ingredients by the use of a mixer or blender. On the other hand, if it is a hot processed formulation that requires heat, then it is recommended that the unmodified starch be added during the cool down phase of the system (typically below 50°C), so the granules remain intact and are not hydrated. This method of incorporation allows the native starch to impact the sensory profile of the formulation. With high oil content emulsion systems such as water-in-oil, the addition of unmodified corn starch can be used to mitigate the sensation of tackiness or greasiness and allow for an enhanced product experience.

Typical usage levels for unmodified corn starch are broad, ranging from 1% to 90% depending on the application. The following sampling of starter formulations demonstrates the wide range of usage levels for unmodified corn starch.

Botanical Foot Powder

#	Ingredients	Wt. %	Function
1	Zea Mays (Corn) Starch	86.25	Absorbent
2	Sodium Bicarbonate	12.00	Odor Control
3	Silica Dioxide	0.80	Flow Agent
4	Lavender Oil (INCI: *Lavandula angustifolia* oil)	0.60	Antimicrobial/ Antiseptic
5	Tea Tree Oil (INCI: *Melaleuca altenafolia* Leaf oil)	0.20	Antimicrobial/ Antiseptic
6	Methylparaben	0.15	Preservative

Procedure:
Mix all dry ingredients in a ribbon blender until uniform. Add Lavender and tea tree oil to powder mixture and blend until uniform

Appearance: White, free-flowing powder.

This Botanical Foot Powder formulation contains more than 85% (by weight) unmodified corn starch as the base or bulk of the formulation. This usage level may

also be appropriate for other topical applications such as body and baby powders. For topical powder products, especially in baby care, formulation chemists should select ingredients that are safe and mild and would not have any irritation potential. In powder applications, unmodified corn starch can be also formulated into compact powder products. One such example is the following Natural Compact Powder formulation, which uses 10% unmodified corn starch. Here again, the starch functions as an absorbent. These usage levels are starting points and should be used as guidelines for designing topical formulations.

Natural Compact Powder

	#	Ingredients	Wt. %	Function
A	1	Micronized Titanium Dioxide	45.80	UV Blocker
	2	Zea Mays (Corn) Starch	10.00	Oil Absorbent
	3	Lauroyl Lysine	4.50	Conditioning agent
	4	Mica	15.30	Texturizer
	5	Calcium Starch Octenyl Succinate	8.00	Skin feel modifier
	6	Iron Oxide – Russet	0.80	Pigment
	7	Iron Oxide – Yellow	8.00	Pigment
	8	Iron Oxide – Black	0.10	Pigment
	9	Iron Oxide – Brown	2.50	Pigment
B	10	Caprylic/Capric Triglyceride	4.00	Plasticizer, Emollient
	11	Preservative	qs to 100	

Procedure:
Combine Phase A ingredients and micro-pulverize for 4 min. Combine Phase B ingredients and blend. Add Phase B to Phase A and micro-pulverize for up to 4 min in 30 sec intervals to avoid excessive heating of material. Press into foundation pan using appropriate die press.

Appearance: Tan colored pressed powder

Though many conventional applications use unmodified corn starch in its raw powder form, it can also be easily incorporated into other topically applied semi-solid formulations. For example, in the cream powder formulation which follows, Zea Mays (corn) starch is incorporated into a cream powder at 30% usage level and is added during the cool down phase to make sure the granules remain intact and do not hydrate and swell. Once this high viscosity cream is rubbed and spread on the skin, the corn starch remains deposited on the skin surface, creating a dry afterfeel sensation. Delivering a powder in a cream form would be advantageous in baby care because it eliminates certain disadvantages such as clouding and dusting

when applying loose powder. In parallel, this cream-to-powder formulation could be promising for color cosmetics such as cream eye shadows or other matte finish applications.

Cream Powder

	#	Ingredients	Wt. %	Function
A	1	Water (*aqua*)	58.18	
	2	Glycerin	5.00	Humectant
	3	Propylene Glycol	2.00	Humectant
	4	Carbomer	0.25	Viscosity Stabilizer
	5	Urea	0.50	Emollient
	6	Cyclomethicone	3.00	Emollient
B	7	Preservative	0.60	
	8	Aloe Vera 100x	0.01	Conditioning Agent
	9	dl-Panthenol	0.05	Conditioning Agent
	10	Zea Mays (Corn) Starch	30.00	Viscosity builder, Absorbent, Skin Feel Modifier
	11	Fragrance	0.20	
C	12	TEA (85%)	0.21	pH Adjuster

Procedure:
Mix Phase A with mixer to 55°C. Cool to 40°C and add Phase B in order. When homogenous, add TEA (85%).

Appearance: Off-White cream

Zea Mays (corn) starch can also be incorporated into hair care products. The dry shampoo concept has resurfaced in recent years and it is a product category in hair care that unmodified starch plays a role in. Dry shampoo is a powder product, usually in an aerosol that functions to absorb the sebum from the hair. Dry shampoo uses a combination of unmodified corn starch and aluminum starch octenylsuccinate, which is a modified starch. The aluminum starch octenylsuccinate is anionic and has lipophilic characteristics which allows it to absorb the sebum (oil) generated from the scalp.[2] Afterwards, the dry shampoo is removed by brushing the powders off the hair. Below is a starter formula for a dry shampoo consisting mainly of unmodified corn starch and aluminum starch octenylsuccinate. Note that the formulation is delivered in loose powder form and not via an aerosol.

Dry Shampoo

	#	Ingredients	Wt. %	Function
A	1	Zea Mays (corn) Starch	80.0	Oil Absorbent
	2	Aluminum Starch Octenylsuccinate	10.0	Oil Absorbent
	3	Silica	5.0	Flow Agent
	4	Sodium Carbonate	2.0	Odor/Oil Absorbent
	5	Fragrance, Preservative	qs to 100.00	

Procedure:
Add components in order to a ribbon blender. Evenly spray in the fragrance and preservative while blending. Blend until completely homogenous.

Appearance: White, free-flowing powder.

Modified Starches

While providing a sustainable raw material for personal care formulations, native corn starch presents certain performance limitations. Starch is known to help thicken and build texture when properly hydrated, especially as it is applied in the food industry. However, one of the undesirable attributes of heated and hydrated corn starch is its tendency to retrograde after cooling, resulting in congealing that creates a rubbery texture. Retrogradation—the reassociation of starch molecules after the starch granules have already been hydrated and dispersed—transforms the texture which impacts the overall viscosity of a formulation. As a result, this change in viscosity imparts instability to the product, and a result of this instability is that native corn starch can be altered through either chemical or physical modification.

Due to the limitations associated with the use of unmodified starch previously outlined, chemical modifications are necessary to alter the starch molecule in order to enhance its stability, as well as to impart different functional characteristics. Stability is a critical part of formulation development because products need to withstand changes in temperature and pH during processing, manufacturing, and even throughout the shipping process. Chemical modification of corn starch can be classified into three categories: *depolymerization*, *substitution*, and *cross-linking*. Depolymerization reduces the starch viscosity through acid conversion or acid-thinning. Substitution involves either esterification or etherification reactions, which allow the introduction of substituent groups onto the starch molecule. Different substituent groups provide different functionalities. Cross-linking involves the bridging of molecular chains to form a more rigid network. Cross-linking starches help to stabilize the starch granule. Physical modification of starch includes pre-gelatinization, which allows for rapid viscosity development and instant dispersion of the starch without requiring heat. Combinations of these types of modifications

are also common. A variety of modified starch compounds that are readily used in the food industry have been introduced into the personal care category offering similar functionalities such as thickening, rheology modification, and film-forming.[1]

One type of modified starch that is both substituted and cross-linked is hydroxypropyl starch phosphate. It can be used in topical formulations such as creams and lotions, where it provides both viscosity and texture. An example of this is shown in the following silky body cream formulation. The hydroxypropyl starch phosphate is used mainly as a thickener enhancing viscosity and texture in the formula.

Silky Body Cream

	#	Ingredients	Wt. %	Function
A	1	Water (aqua)	qs	
	2	Xanthan Gum	0.10	Emulsion Stabilizer
	3	Tetrasodium EDTA	0.10	Chelating Agent
	4	Hydroxypropyl Starch Phosphate	3.00	Thickener
	5	Hydrogenated Starch Hydrolysate	4.00	Humectant
B	6	Glyceryl Stearate	1.00	Emulsifier
	7	Ceteareth-20	1.50	Emulsifier
	8	Cetearyl Alcohol	2.50	Viscosity Adjuster
	9	Caprylic/Capric Triglyceride	5.00	Emollient
	10	Isopropyl Palmitate	2.00	Emollient
	11	Zea Mays (corn) oil	3.00	Emollient
C	12	Camelia sinensis (green tea) Leaf extract, Glycerin and Water	0.15	Antioxidant
	13	Preservative	qs	Preservative
	14	Fragrance	qs	Fragrance
	15	Citric Acid	qs	pH Adjuster

Procedure:
Add xanthan gum in water and mix until clear. Add hydroxypropyl starch phosphate into Phase A and heat up to 80-85°C until opaque gel forms. Add ingredients #3 and #5 into Phase A and blend with heat until uniform. In a separate vessel, heat Phase B to 70-75°C until all has melted. Pour Phase B into Phase A and blend until a white uniform mixture is obtained. Cool to 45°C and ingredients 12-13. Cool to 35°C and add fragrance. Adjust pH with 10% citric acid solution to 5.5-6.0.

Appearance: White emulsion (cream).

To incorporate into oil-in-water emulsions, modified starches are typically added into the water phase and heated up to 80-85°Celsius for 20-25 minutes to allow for proper hydration. The starch granules go through various stages of swelling until the point of gelatinization in which the amylose and amylopectin are dispersed from the granular structure. [1] This dispersion forms a firm network providing both viscosity and texture to the body of the formula. Heating is required for modified starches to transform into a gel-like paste texture. Although modifications are involved, modified corn starches offer formulation chemists with a variety of functionalities on a biodegradable, sustainable resource.

Hydrolyzed Corn Starches

Hydrolyzed corn starches are also derived from the corn kernel and can be produced using a specific enzymatic molecular cleavage process similar to depolymerization.Hydrolyzed corn starches are physically present in both liquid and powder form. Usually, products of starch hydrolysis are blends of saccharides consisting of shorter molecular chains with lower molecular weights than starches.

Hydrolyzed corn starches undergo a certain degree of hydrolysis and vary in their dextrose equivalent (DE). This is the total amount of reducing sugars calculated as dextrose on a dry weight basis. In other words, this indicates the degree of hydrolysis of a starch molecule. Generally, it can be viewed that the higher the dextrose equivalent, the shorter the chain due to the higher degree of cleaving.

Hydrolyzed corn starches are hygroscopic in nature and function as humectants in personal care formulations. Humectants are able to attract water to both skin and hair surfaces and can act as moisturizing agents. Humectants contain hydroxyl groups allowing the molecules to participate in hydrogen bonding.[2] The ability to draw in moisture allows a formulation such as a cream, lotion, or the following example of a body wash, to retain the water content over time, thus helping to improve the overall stability and extending the shelf-life of a product.

Honey Lemon Body Wash

#	Ingredients	Wt. %	Function
1	Deionized water	42.34	Diluent
2	Tetrasodium EDTA	0.10	Chelating Agent
3	Sodium Laureth Sulfate	35.00	Surfactant
4	PEG-80 Sorbitan Laurate	3.00	Co-surfactant
5	Disodium Cocoamphodiacetate	3.00	Secondary Surfactant
6	Cocoamidopropyl Betaine	8.00	Foam Booster
7	Hydrolyzed Corn Starch	7.00	Humectant
8	Caramel Color	0.01	Natural Colorant
9	Preservative	0.15	Preservative
10	Fragrance	0.50	Fragrance
11	10% Citric Acid Solution	qs	pH Adjuster
12	Sodium Chloride	0.70	Thickener, Viscosity Adjuster

Procedure:
Add Tetrasodium EDTA to water and mix until crystals dissolve. Add Phase A ingredients 3-6 individually and slowly into water; mix slowly until they yield a clear solution. Add the hydrolyzed corn starch to batch. Add caramel color to give desired color to your formulation. Add preservative to batch, and add fragrance. Adjust pH with 10% citric acid solution to 6.0-6.5, and then adjust viscosity with NaCl.

Appearance: Light, golden clear color.

Hydrolyzed starches are saccharides that impart a tacky sensation when used at high concentration, typically above 15-20% usage level. The key to formulating a successful topical product is balancing the right ingredients to form an alluring sensorial experience for the end-use consumer. Often this results in the need to formulate multiple formulations at different usage levels and testing their stability as well as their performance in consumer panels.

Natural Moisturizing Shampoo

	#	Ingredients	Wt. %	Function
A	1	Deionized Water	qs	
	2	Hydrolyzed Corn Starch	12.0	Humectant
	3	Ammonium Lauryl Sulfate (30%)	40.0	Primary Surfactant
	4	Lauramidopropyl Betaine (30%)	5.0	Foam Booster
	5	Isostearamidopropyl Morpholine Lactate (25%)	4.5	Conditioning Agent
	6	Preservative	qs	
	7	Fragrance	qs	

Procedure:
Add ingredients 2-5 to deionized water. Heat to 40°C and blend until clear. Add fragrance, dye, and preservative during cool down. If needed, adjust pH to 5.0-6.0 with dilute sodium hydroxide.

Appearance: Clear viscous with slight yellow tint.

Within the category of hydrolyzed starches, maltodextrins can be used in topically applied products. Typically, maltodextrins have a dextrose equivalent (DE) of less than 20. They contribute to formulations by adding "body" without building additional viscosity. Maltodextrins are completely water-soluble and will work in clear formulations. This bodying effect is achieved by adding solids to the formula. One property of maltodextrins is their ability to form a film.[2] With that functionality in mind, it has potential to be used in a variety of applications including skin creams, lotions, mascara, and even as a styling aid, as exemplified by the following styling cream formula, in which film formation is demonstrated. By incorporating maltodextrin into the water phase of the emulsion at a relatively high percentage, it functions as a mild styling aid because of the tackiness it imparts while leaving a film.

Hair Styling Cream

	#	Ingredients	Wt. %	Function
A	1	Water (*aqua*)	qs	
	2	Maltodextrin	7.00	Film Former, Styling Aid
	3	Tetrasodium EDTA	0.10	Chelating Agent
	4	Starch Acetate Adipate	3.00	Thickener
B	5	Cetearyl Alcohol (and) Polysorbate 60	2.00	O/W Emulsifier
	6	Glyceryl Stearate	0.60	Thickener
	7	Cetyl Alcohol	1.50	Viscosity Adjuster
	8	Behentrimonium Chloride	0.75	Conditioning Agent
	9	Dimethicone	0.60	Emollient
C	10	Polyquaternium-7	0.75	Conditioning Agent
	11	Preservative	qs	Preservative
	12	Fragrance	qs	Fragrance

Procedure:
Mix Phase A ingredients and heat to 65-70°C until dispersed. In separate container, combine Phase B ingredients and heat to 65-70°C. Pour Phase B into Phase A and mix until uniform. Begin cooling of mixture. At 45-50°C, add Phase C and continue mixing. Cool to 30°C and fill containers.

Appearance: White viscous cream

Additional Applications for Corn-derived Ingredients in Topical Formulations

Natural and modified starches are functional biopolymers that can be applied in a range of topical formulations. In addition, some of the other components extracted from the ubiquitous corn kernel can be functionalized in topical products and are presented in formulations to follow. These other ingredients, including but not limited to corn oil, dextrose and corn fiber, are demonstrated, respectively, in a sugar body scrub and a lip balm. The major component of the sugar body scrub formulation is dextrose (powder), which serves as an exfoliant by physically removing dead skin cells on the surface of the skin. This formula is an oil-based formulation that allows for the dextrose crystals to remain intact until their point of contact with water. Dextrose dissolves completely in water and so there is no issue of residue or clogging of the drain during the showering process. During the application of the sugar scrub, the zea mays (corn) oil, along with the other emollients, is spread onto the skin surface; some emollients remain deposited even after rinse-off, creating a soft, moisturized feel for the consumer.

Sugar Body Scrub

		Ingredients	Wt. %	Function
A	1	Zea Mays (corn) oil	18.00	Emollient
	2	Butyrospermum parkii (shea butter) Fruit	11.80	Emollient
	3	Caprylic/Capric Triglyceride	16.60	Emollient
	4	Sorbitan Stearate	3.00	Emollient
	5	Glyceryl Stearate/ PEG-100 Stearate	2.50	Emulsifier
B	6	Dextrose	45.00	Exfoliant
	7	Zea Mays (corn) gluten protein	2.00	Exfoliant
C	8	Fragrance	qs	
	9	BHT	0.10	Preservative
	10	Methylparaben	0.20	Preservative

Procedure:
Prepare Phase A, heat to 65-70°C and blend for 10 min or until uniform. Add components of Phase B, in order, into Phase A, blend and begin cooling to 45°C. Add components of Phase C, in order, into the combined mixture and blend. Cool and fill.

Appearance: Grainy, opaque off-white cream with fiber particles.

The moisturizing lip balm formula contains 28.00% zea mays (corn) oil and can help extend some of the other types of oils such as jojoba, sweet almond, olive, etc. Since majority of actives used in personal care are oil based and used in such small amounts (0.10-1%), zea mays (corn) oil performs as a carrier and delivery system for those actives. When combined with the other emollients and waxes, corn oil functions as an added occlusive agent.

Moisturizing Lip Balm

	#	Ingredients	Wt. %	Function
A	1	Petrolatum	20.60	Emollient
	2	Ozokerite wax	7.00	Viscosity Enhancer
	3	Bees wax	9.00	Viscosity Enhancer
	4	Zea Mays (corn) oil	28.00	Emollient
	5	Carnauba wax	6.00	Viscosity Enhancer
	6	*Euphorbia cerifera* (Candelilla) wax	2.00	Viscosity Enhancer
	7	Cetyl Alcohol	3.00	Viscosity Enhancer
	8	*Butyrospermum parkii* (shea butter)	5.00	Emollient
	9	C13-C16 Isoparaffin, C12-C14 Isoparaffin (and) C13-C15 Alkane	10.00	Emollient
	10	Caprylic/Capric Triglyceride	6.00	Emollient
	11	Tocopheryl Acetate	0.70	Antioxidant
	12	BHT	0.10	Antioxidant
	13	Preservative	qs	
B	14	Flavor	qs	

Procedure:
Heat Phase A to 75-80°C with stirring until melted. Cool to 70°C. Add flavor and mix until uniform. Pour into molds and let cool.

Appearance: off-white to light yellow

Summary

With an influx of ingredients developed for topically applied personal care products, formulation chemists have a daunting task of deciphering and selecting the most suitable compounds to achieve the formulation goal in terms of functionality and feel as well as safety and minimized adverse effects.

The corn kernel is a versatile ingredient with multifunctional components that can deliver performance in topical personal care products. For many consumers, the allure behind topical products is their tendency to play upon the senses, notably the sensation of touch. The way the product spreads on the skin and the sensation it imparts when first applied, the process and feel during application, and the afterfeel are all essential to the overall product experience. Corn-derived ingredients help provide a key sensorial enhancement with a "natural" touch because they stem

from a biodegradable and renewable source. A unique balance of functionality and sensorial aesthetics can support more innovative avenues toward creative formulating for both new and seasoned formulators.

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Handbook of Formulating Dermal Applications: A Definitive Practical Guide.
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SECTION II:

Formulation, Processing and Production Techniques

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CHAPTER 6

Emulsions and their Characterization by Texture Profile Analysis

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Key Words

Emulsion, Sensorial Analysis, Textural Attributes, Texture Profile Analysis.

Introduction

Emulsions are the underlying basis of personal care formulations for skin. They are seemingly simple, yet complex systems, which allow the skin care chemist to combine otherwise immiscible ingredients into effective, commercially desirable skin care products.[1] Emulsions are very versatile vehicles that can incorporate a variety of ingredients and allow simultaneously delivery of hydrophilic and hydrophobic ingredients to the skin. This gives the advantage of developing custom-made formulations designed for various skin types or addressing many skin disorders or conditions. Over the last several decades significant advances in the understanding of emulsion behavior were accompanied by the availability of many new products, especially emulsification agents. Coupled with consumer demand for biologically functional actives, this trend persists. The success of a product often depends on its sensorial attributes, in which case the consumer is the best candidate to judge. Many of these sensorial perceptions stem from the textural properties of the formulation. Carrying out consumer tests is oftentimes expensive and time consuming. With this in mind, there is much interest to establish instrumental techniques to objectively quantify textural attributes of formulations, which may serve as rapid screening protocols allowing formulators to fine tune particular attributes into the final product. In this chapter, methodology is presented to perform such tests to characterize *firmness*, *compressibility*, *integrity of shape*, *tackiness*, *spreadability*, *cohesiveness*, *resilience*, and *elastic resistance to deformation*.

Basic Principles of Emulsion Technology

Emulsions

The majority of skin care formulations are complex multi-phase systems based on solid-liquid dispersions (suspensions) or liquid-liquid dispersions (emulsions).[2] Emulsion systems are used universally in skin care formulations to create creams and lotions for application to skin. An emulsion is a heterogeneous system in which two or more immiscible liquids or semi-solid materials are dispersed in another liquid in discrete droplets. The materials that are dispersed (or emulsified) form the dispersed or internal phase, while the rest of materials form the continuous phase or external phase. There are a variety of emulsion types that consist of oil-in-water (o/w), water-in-oil (w/o), multiple (oil-in-water-in-oil; water-in-oil-in-water), nano-, micro-, and Pickering emulsions (a type of oil-in-water emulsion). O/W emulsions are probably the most commonly employed vehicles in skin care formulations, which contain an oil phase dispersed in an aqueous continuous medium (**Figure 1**). These types of emulsions tend to feel less greasy because the water is the external phase (Epstein, 2006).[1] W/O emulsions, on the other hand, feel greasy due to the fact that the oil phase is the external phase. A schematic representation of a dispersed droplet in a w/o emulsion is shown in **Figure 2**. Generally, the type of emulsifier and the phase volume ratio dictate what type of emulsion will be formed.[3] In terms of physical properties, the o/w and w/o emulsions, also known as macroemulsions, have particle sizes greater than 1,000 nm and appear opaque/white in color.

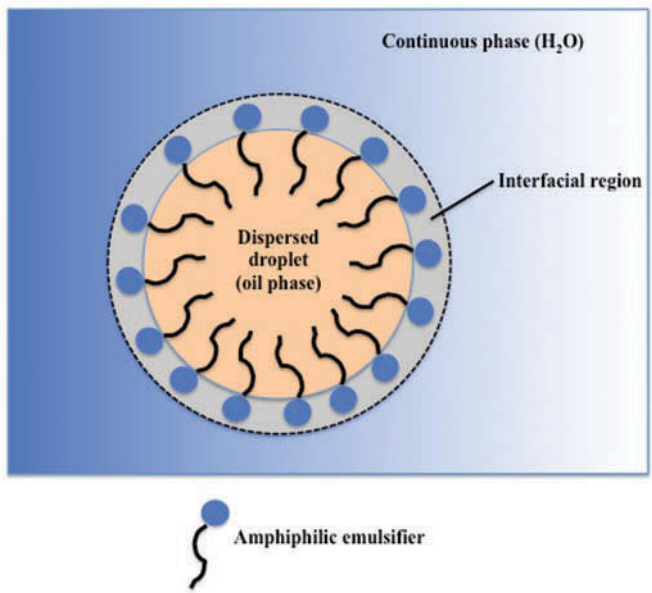

Figure 1. Illustration of a dispersed oil droplet in a typical o/w emulsion stabilized with an emulsifier.

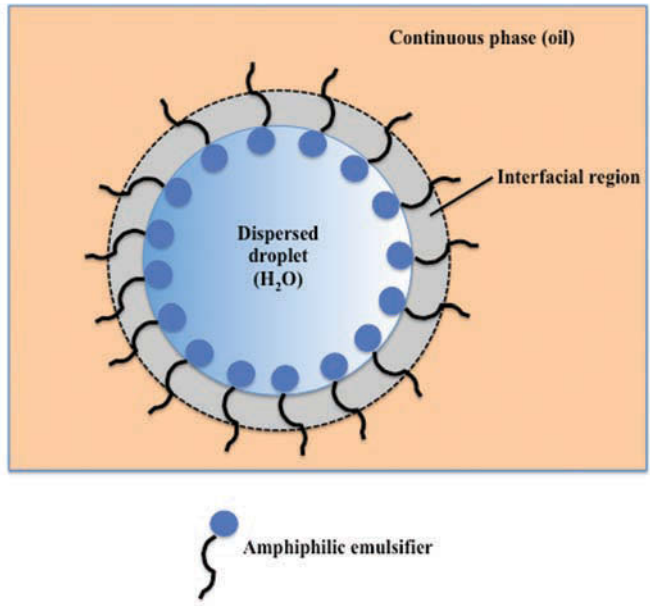

Figure 2. Illustration of a dispersed water droplet in a typical w/o emulsion stabilized with an emulsifier.

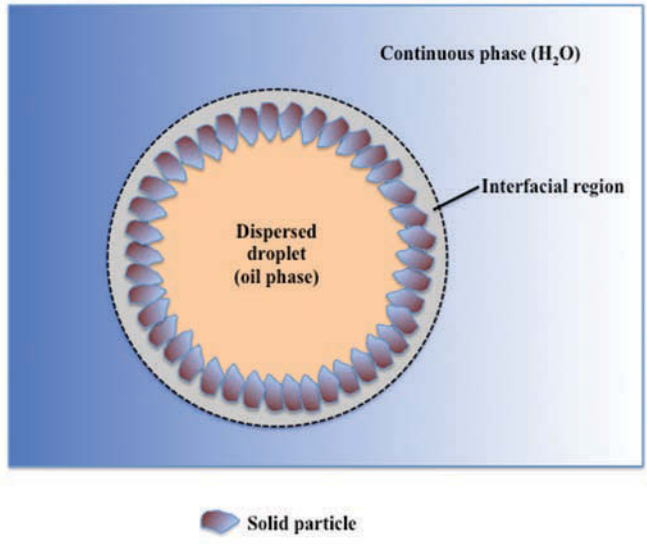

Figure 3. Example of a Pickering emulsion, a type of o/w emulsion, stabilized with solid particles at the interface of the oil and water phase.

The use of the terms "nanoemulsion" and "microemulsion" has created a lot of confusion in the literature. Nanoemulsions usually refer to a size range of 50–200 nm, while microemulsions are clear or transparent emulsions with a particle size between 5–50 nm.[2] O/W and w/o macroemulsions are thermodynamically unstable. In order to circumvent such instability, microemulsions evolved as alternative vehicles. In contrast, nanoemulsions are not thermodynamically stable.[4] Pickering emulsions are another type of o/w emulsion system in which stability is conferred by solid particles present at the interface of the two phases, thereby reducing the surface energy (**Figure 3**). Multiphase o/w emulsions constitute a special type of emulsion in which lamellar gel phases form a complex network in the continuous water phase to hold the oil phase droplets in place preventing coalescence, as well as enhancing the viscosity and stability of the system.[5,6]

Emulsion formation

Most emulsions are formed by dispersion or condensation methods. Dispersion techniques usually refer to mechanical agitation (e.g., with a homogenizer) resulting in the formation of a coarse dispersion, which is then further sheared producing a finer dispersion. During the course of such a process, emulsifiers are added to stabilize the increasingly unstable system (higher surface energy) due to the creation of a much larger interface. Condensation methods rely on the dissolution of the discontinuous phase molecules in the continuous phase. As an example, an o/w emulsion is formed by pouring the oil phase into the water phase with proper mixing or homogenization. There are also phase inversion (e.g., PIT emulsions) and electrical techniques to form emulsions. Phase inversion occurs when the concentration of the dispersed phase becomes so high that it inverts and the continuous phase becomes the dispersed phased and vice-versa. Electrical techniques refer to emulsions formed by the basis of electrostatic interactions.

Emulsifiers

An emulsifier (or emulsifying agent) is an amphipathic molecule, which arranges itself at the interfaces between the two immiscible phases (o/w), thus reducing the surface (interfacial) tension between the two phases, and is able to disperse oil droplets in water. When used with o/w emulsions, they arrange themselves with the hydrophobic tails in the oil (internal) phase and hydrophilic heads in the water (external) phase. The mechanism of action of emulsifiers and many other details will be discussed more in-depth later in this chapter.

Typical emulsion compositions

As an illustrative case, the oil phase of an o/w emulsion contains various chemical classes of organic ingredients such as: emollients and occlusive agents (e.g., esters, mineral oil, vegetable oils, waxes, and silicones); emulsifiers (anionic, nonionic, and cationic); and consistency agents/thickeners (e.g., fatty alcohols). The water phase of an o/w emulsion, on the other hand, typically contains: water as the solvent; humectants (e.g., glycerin, propylene glycol, and butylene glycol); chelating agents (Na_2EDTA); and thickeners (cellulose derivatives and gums, as well as carboxyvinyl polymers). Other ingredients normally found in an o/w emulsion are: preservatives,

pH adjusters, colorants, fragrances, botanicals, biofunctional ingredients, and antioxidants. **Table 1** contains a typical o/w emulsion composition.

Table 1. A typical o/w emulsion composition.

1.	Emulsifier systems ~ 3-5%
2.	Hydrophobic thickeners/consistency agents/stabilizers ~ 0.50-2%
3.	Oil phase ~ 10-35%
4.	Hydrophilic thickening agent ~ 0.1- 1%
5.	Humectants ~ 3-5%
6.	Preservatives, antioxidants, botanicals ~ as required
7.	Water (qs to 100%)

Phenomena Involved in Emulsion Instability

Emulsion stability is a major concern for the formulator. Without a properly designed system, some of the phenomena listed below may occur. Since macroemulsions are inherently unstable, such effects may be produced when an improper (or inadequate amount of) emulsifier or a rheology modifier/consistency agent is used. Such outcomes may also result due to excessive amounts of the dispersed phase employed in the formulation. In any event, brief definitions are provided for some of the most common phenomena that occur during emulsion instability. **Figure 4** contains an illustration to accompany this section.

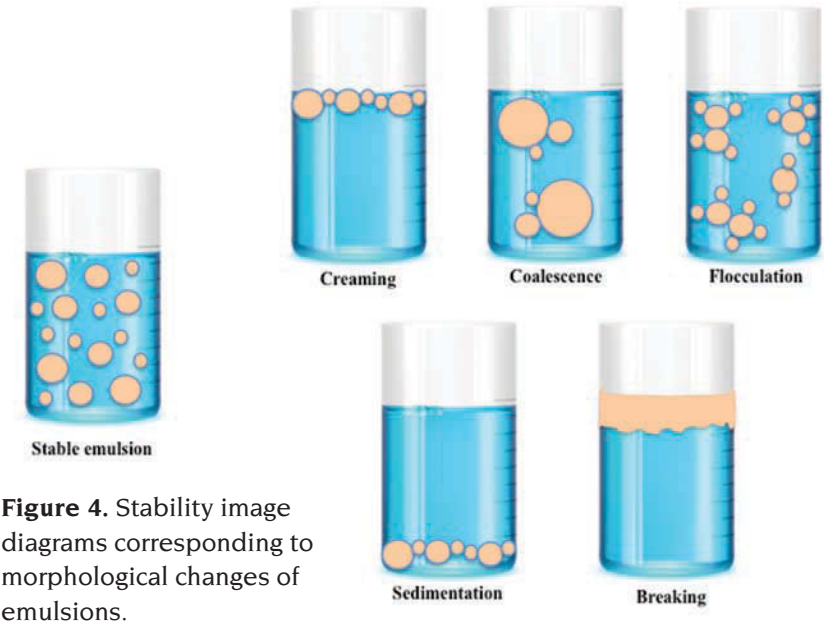

Figure 4. Stability image diagrams corresponding to morphological changes of emulsions.

Creaming: Oftentimes emulsion droplets cluster together in a process known as flocculation. This phenomenon refers to the case when particles cluster together without actually merging.[7] This is very common in o/w emulsions as the dispersed oil phase flocculates, and then rises to the surface, a process known as creaming.

Sedimentation: Emulsion droplets may also settle to the bottom of the vessel in a process known as sedimentation. Such instability, in some cases, may be reversible by mechanical agitation or shaking.

Flocculation/aggregation: As already stated, flocculation occurs when particles (droplets) aggregate together without merging together; they clump together. In this case, flocculated particles retain their individual characteristics and may be re-dispersed by agitation (or shaking).

Coalescence: In contrast to flocculation, coalescence is the actual merging together of droplets forming a new entity. Droplets lose their distinctness and may not be easily re-dispersed in the continuous phase.

Breaking: An emulsion is said to break when the dispersed phase settles out of the continuous phase. Normally, this occurs first by flocculation (clumping of droplets together) followed by coalescence (actual merging of droplets).

Inversion: Inversion occurs in an emulsion when the dispersed phase becomes the continuous phase and vice versa.

Improving stability of emulsions

To prevent creaming, sedimentation, and aggregation in emulsions, several strategies may be employed. A first measure would be to reduce the particle size of the internal phase by homogenization. In this way, one obtains a more uniform particle size distribution, ultimately leading to an increase in viscosity. Further, the addition of thickeners (natural gums or synthetic acrylic acid polymers) to the external phase will increase the viscosity of the continuous phase and enhance the high temperature stability.[8] Emulsion stability is also conferred by the addition of emulsifiers. Typically, nonionic emulsifiers provide steric stabilization, while ionic emulsifiers provide electrostatic or charge stabilization. In any event, emulsifiers prevent dispersed phase droplets from coalescing.

Mechanisms of Emulsion Stabilization by Emulsifiers

Normally, creaming, sedimentation, and aggregation are prevented by employing emulsifiers with specific stabilizing properties. For example, nonionic and polymeric emulsifiers are used to provide steric stabilization, while ionic emulsifiers are employed to provide repulsive electrostatic interactions, which keep emulsion droplets apart. In addition, coalescence may be prevented by adding amphiphilic surfactants that form lamellar gel phases (multiphase systems) or other agents that improve emulsion stability or increase consistency of the dispersed and continuous phase.

Electrostatic/charge stabilization (repulsive electrostatic forces)

Ionic emulsifiers, both anionic and cationic, stabilize emulsions by formation of an electrical double layer on the surface of the droplet, creating a repulsive electrostatic

barrier to keep droplets apart. Fatty acid salts (soaps) are typical examples of anionic emulsifiers that provide electrostatic charge stabilization.

Steric stabilization

An emulsion may also be stabilized by the presence of molecular entities on the surface of the dispersed phase droplet; in many cases, a nonionic or polymeric emulsifier is employed. Portions of the molecular structure of the emulsifier branch out into the continuous phase and impede droplets from coalescing together. Block copolymers and polyethylene glycols are especially useful for such applications, as one segment of the molecule will be in contact with the dispersed phase droplet and the other will extend into the continuous phase. In particular, one example of a block copolymer is a polymeric surfactant that contains a hydrophobically modified segment.[9] To reiterate, the portion of the molecule in the continuous phase provides steric hindrance to interaction of other oil droplets in the case of an o/w emulsion.

Stabilization by lamellar gel phases

The formation of lamellar gel phases can stabilize an emulsion by forming a third phase or third layer (a rigid film about 1 μm thick) between the oil and water phases. These lamellar gel systems form a network of bilayers, which surround the oil interface, and extend into the continuous phase, forming a third phase between oil and water, thus preventing coalescence (oil droplets are less likely to rise and collide with each other) and stabilizing the emulsion (the lamellar network increases the viscosity of the water phase). While such vehicles can be classified as three-phase systems (e.g., oil-in-lamellar gel-in-water), they contain two interfaces, one shared by the oil-lamellar gel and the other, lamellar gel-water.[6,10] An example of such a system consists of a commercial product based on a customized blend of glyceryl stearate, behenyl alcohol, palmitic acid, stearic acid, lecithin, lauryl alcohol, myristyl alcohol, and cetyl alcohol.[11]

Measurement of Emulsion Stability

A number of general techniques are available to monitor emulsion stability. In this section we cover some of the most fundamental methods that can be carried out in most laboratories. More advanced techniques to study phenomena associated with emulsion technology are available; however, for the sake of brevity these methods are not discussed herein.

Formulation pH measurements

General pH measurements should be carried out utilizing a probe designed for more viscous systems, such as creams and lotions. The pH of the system is of utmost importance, as this will determine the electrostatic conditions of the head group of any of the added emulsifiers, as well as polymeric thickeners in the continuous phase of an o/w emulsion. Increasing or decreasing the charge will affect the interactions between the dispersed phased droplets. Oftentimes, the emulsion is stabilized by opposing electrostatic forces that keep droplets from coalescing together. If the head group of an emulsifier is pH sensitive, it could convert from a negatively to a

positively charged species when the pH is lowered below its pKa. This could result in agglomeration of the dispersed phased droplets, eventually leading to instability in the emulsion.

Rheological techniques

Rheological measurements provide extremely important physical and aesthetic information about emulsions. Formulation and processing parameters of emulsions influence a number of its characteristics, including dispersed phase volume, size distribution, particle-particle interactions, and particle deformability.[12] Traditionally, standard viscometers capable of measuring the linear viscoelastic shear properties were used routinely to characterize the viscoelastic properties of emulsions. In recent years, this has changed (to some extent) due to the availability of more sophisticated dynamic instruments, which allow for measurement of important rheological parameters such as the storage modulus (G'), loss modulus (G''), and loss factor (tan δ).

Optical microscopy

The visualization of emulsions is a straightforward process that can provide extremely useful information to characterize the nature of the dispersed phase droplets, including their shape, size, and interaction with each other. If bright field microscopy is employed, colorful lipid-soluble dyes can be added to the emulsion in order to provide a striking image with clear contrast between the dispersed and stationary phase. Fluorescence microscopy may also be employed in conjunction with a fluorescent probe; however, this requires a more technically specialized fluorescence microscope.

Liquid conductivity measurements

Emulsions are commonly characterized by electrical conductivity measurements. Emulsion electrical resistivity can provide important information with regard to emulsion stability with temperature, ion concentration, and emulsifiers or other surfactants employed in the formulation. Its most practical use is to determine the amount of oil present in an emulsion. The measurement determines the electrical conductivity of water, which decreases as the oil phase increases.

Size distribution

One of the most popular instruments for measuring emulsion size is a Coulter Counter. It is an extremely common method that is used universally in the pharmaceutical and medical industries to measure the particle size of ingested or injected emulsions used for treatment protocols or diagnostic exams. The Coulter Principle (electrical sensing zone method) uses the proportionality between the volume of a particle and the height of the electric pulse generated from passage of the particle through a small aperture to directly count it and measure its size. The measurement is not affected by color, shape, and optical characteristics of particles.[13]

Zeta potential

Zeta potential is a measure of the repulsive/attractive electrostatic forces between particles, and is a very good indicator of emulsion stability.[14,15] Its measurement

can shed light on the causes of instability whether it be flocculation/aggregation, coalescence, breaking, or inversion. In most cases, emulsion droplets normally bear an electrical charge at their surface. In addition, the outer surface of the emulsion is surrounded by a cloud of ions (from the continuous phase liquid) consisting of both negative and positive charges (**Figure 5**). The zeta potential is the voltage difference between the surface charge of the droplet and the collective charge of the ion cloud from the surrounding continuous phase. Zeta potential measurements are especially useful for charge stabilized emulsions and can provide us with a measure of the electrical repulsive force between dispersed droplets. Even in sterically stabilized emulsions, knowledge of zeta potential can provide us with information related to the state of the droplet surface. Overall, increased emulsion stability is normally associated with larger (either more negative or positive) zeta potential values, which indicates that the repulsive forces are great enough to keep particles apart.

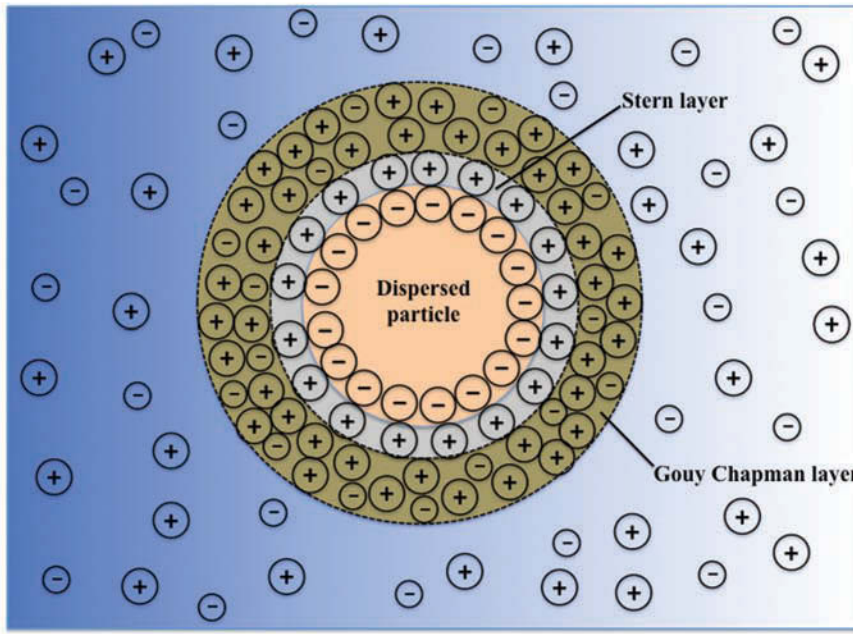

Figure 5. Zeta potential diagram of a negatively charged emulsion droplet.

Definitions of Key Phenomena in Emulsion Technology

Bancroft's rule: The phase in which an emulsifier is more soluble is considered the continuous phase.

Cloud point: The temperature at which two phases are not soluble with one another. In the case of emulsions, increasing cloud point indicates increased stability of the system.

Gibbs-Marangoni effect: A situation that occurs when there is insufficient

coverage by surfactant on the droplet surface. As two droplets come together this causes coalescence due to the resulting interfacial tension gradient between the surface of adjacent droplets.

Hydrophile-lipophile balance: A guideline, which allows the formulator to predict the hydrophilicity or lipophilicity of a molecule. It is based on a scale of 0 to 20 with 0 corresponding to the most lipophilic/hydrophobic compounds and 20 to the most hydrophilic/lipophobic materials. The values are calculated based on a weighted grading system that takes into account hydrophilic and lipophilic components of a molecule.[16,17]

Janus particles: These are nanoparticles that have dual functionality in terms of their surface properties (e.g., it can have hydrophilic and lipophilic sections). Amphiphilic Janus particles are used to stabilize Pickering emulsions.

Ostwald ripening: This phenomenon is common in w/o emulsions, in which case oil molecules tend to migrate through the water phase to agglomerate with large lipid particles.

Phase inversion temperature (PIT): An existing emulsion, e.g. an o/w emulsion can undergo phase inversion to a w/o emulsion as the temperature of the system is raised. These PIT emulsions, when prepared properly, have very good long-term stability.

Sensorial and Textural Properties of Emulsions

The sensorial and textural properties of an emulsion play an integral role in a formulation's acceptance as a final product by the consumer. Typical sensorial properties consist of odor, color, consistency, spreadability (initial and rubout), and stickiness or tackiness.[18] Many sensorial attributes correspond to the textural properties of the skin care preparation. In addition, several other important parameters are governed by the textural properties of the emulsion and include pick-up, stringiness, cushion, and slipperiness.[19]

Early on, a skin feel index was developed to characterize the skin feel after application of a skin care treatment, examining the initial slip of a product in relation to its end feel. In a systematic comparison of the structure-property relationships of various molecules, it was found that molecular weight, oiliness, polarity, unsaturation, and chain branching were found to be key contributing factors to observed skin feel.[20]

In the early 1990s, an ASTM standard was developed as a guideline for sensorial analysis of skin creams and lotions.[21] This dossier provides guidelines and procedures for qualitative description and quantitative assessment of the sensorial properties of skin care products, and continues to be an updated model for panel studies. Using this methodology, products are graded on appearance, pick-up, rub out, immediate afterfeel, and afterfeel at additional time points. Appearance refers to the visual attributes of the product and may deal with its optical or rheological properties. Integrity of shape and gloss are two key components of appearance and, respectively, deal with the ability of a product to retain its shape and the amount of reflected light

from a product. Pick-up describes the rheological properties of a product when it is manipulated between the fingers (usually the index finger and thumb) and consists of several components: firmness, stickiness, and cohesiveness. Rub out describes the physical and rheological attributes of a product during application; i.e. from initial application until the product has been absorbed by skin. Several characteristics are normally evaluated with respect to rub out and consist of: wetness, spreadability, thickness, waxiness, greasiness, and absorbency. As its name implies, afterfeel is an attribute corresponding to the skin feel after application of the product. Usually, gloss, stickiness, slipperiness, amount of residue, and type of residue (waxy, greasy, silicone, powdery, or chalky) are evaluated immediately after application and at prescribed time points following the treatment.

In recent years, significant efforts have focused on better understanding the sensorial properties of skin care emulsions by sensorial profiling.[22] Traditionally, there were two analytical procedures for the sensorial evaluation of products: Spectrum Descriptive Analysis and Quantitative Descriptive Analysis. The Spectrum Descriptive Analysis method is a very detailed characterization of the sensorial attributes of a product.[23] It provides detailed information on how to carry out such sensorial tests and provides guidelines for statistical analysis of the data. More recently, this technique was applied specifically to the sensory evaluation of skin care products in which panelists were trained and surveyed a pool of samples for 26 attributes.[24] Principal component analysis was performed and revealed that oiliness, viscosity, adhesiveness, thickness, transparency, wetness, coolness, and spreadability were in the first principal component, while gloss and stickiness were the basis of the second principle component.

The Quantitative Descriptive Analysis method, developed by Tragon Corporation in collaboration with the Department of Food Science at the University of California Davis, was designed for the food industry to provide enhanced statistical treatment of sensorial data.[25] In this test, greater weight is given to panelists' ability to make relative sensory judgments rather than to distinguish absolute differences among products.

The two descriptive techniques discussed above provide a nice alternative to the traditional tests that utilize a trained panel. However, despite the utility of Spectrum Descriptive Analysis and Quantitative Descriptive Analysis, they have their drawbacks. For example, these tests can be laborious, requiring panelists to undergo a significant amount of training and to develop vocabulary specific to the test product. An alternative approach to gather consumer preferences is to use check-all-that-apply (CATA) questions. This methodology has had considerable success in the evaluation of foods, and was also successfully implemented for the evaluation of skin care products.[22]

Despite the benefits of panel testing, oftentimes a more rapid approach to evaluate and screen numerous products with quantitative, objective data is desirable. Great efforts have been put forth to correlate sensorial properties with

instrumental approaches. A number of research groups have concentrated much effort on correlating rheological measurements to sensorial properties of skin care emulsions.[19,26-30] Brummer and Godersky correlated rheological parameters to the skin feel of the formulation, at the onset of application (primary skin feel) and after the product has been applied and rubbed into the skin (secondary skin feel).[31] According to their studies, the primary skin feeling correlates with the shear stress at the onset of flow (τ_F) and the dynamic viscosity (η_{dyn}). The secondary skin feeling correlates with the value of the stationary viscosity (η) for the rate of shear prevailing at the end of application to the skin.

Gilbert and coworkers investigated various sensorial properties of skin care emulsions, including integrity of shape, firmness, compression force, stringiness, and difficulty of spreading, comparing panel sensory tests with rheological measurements (flow, creep, and oscillation tests) and texture analysis (with a Texture Analyzer).[32] They found very good correlation between subjective evaluation and instrumental analysis for most of the parameters, although this required developing empirical models of analysis.

Likewise, other physicochemical parameters (spreadability, surface tensiometry, and viscosity) measured by instrumental techniques also correlated with sensorial analysis of emollients.[33] These data suggest that gloss, residue, and oiliness correlate well with surface tension and spreadability measurements. Viscosity measurements, on the other hand, were found to correlate with spreading, thickness, softness, and slipperiness. In a separate study, another research group correlated *in vitro* physicochemical properties of several emollient esters with *in vivo* sensorial characteristics perceived by panelists. The results showed that spreading, contact angle, surface tension, dielectric contact, viscosity, refractive index, and molecular weight of the emollient esters correlated well with perceived sensorial attributes such as initial spreading, skin feel after application and absorption, shine, residue after spreading, and tackiness. This approach in correlating *in vivo* perceived sensory attributes with physicochemical parameters can provide insightful information for the skin care formulator in selecting specific emollient esters for topical products and ultimately predicting a product's sensorial profile.[34]

Texture Profile Analysis (TPA)

The principles of texture profile analysis have been well established in the food industry to provide sensorial and textural descriptions of food as it feels in the mouth including its anatomical components: lips, tongue, palate, gums, and teeth.[35] Some of the most common words used to describe food texture in the United States are: crisp, dry, juicy, soft, creamy, crunchy, chewy, smooth, stringy, and hard.[36] As should be expected, each culture has distinct ways of describing food texture, and some have many more descriptive indicators of texture than others. Such accurate descriptions lead to the development of instrumental techniques to characterize the textural properties of foods. Utilizing Texture Profile Analysis, characteristics such

as resilience, chewiness, gumminess, springiness, and cohesiveness may be easily measured for a variety of foodstuffs.[37] The most commonly employed instrument for carrying out such measurements is a Texture Analyzer. It should be pointed out that while similar instruments with load cell capacity may also be employed for these purposes, the Texture Analyzer is particularly suited for Texture Profile Analysis due to its software development and variety of available probes. Not surprisingly, adaptations of techniques for measuring food texture with Texture Profile Analysis have been employed to perform similar measurements of skin care formulations.[32] In the section that follows, we provide a comprehensive examination of the adaptation of the Texture Profile Analysis technique to measurement of important sensorial attributes of typical skin care emulsions used in skin care preparations.

Determination of Textural Attributes from Texture Profile Analysis

The aforementioned description of Texture Profile Analysis provides alternative nomenclature to that employed for the analysis of food texture; furthermore, we have also offered insight into other calculable parameters that are especially useful for the descriptive analysis of skin preparations. As stated, the most common instrument used for carrying out Texture Profile Analysis is a Texture Analyzer (see **Figure 6**).

Figure 6. Image of a Texture Analyzer (TA.XT Plus, Texture Technologies, Scarsdale, NY).

It is essentially a mechanical device with a load arm that contains a load cell with either 2 Kg or 5 Kg capacities. The formulation is placed in a sample cell underneath the probe, which is attached to the load arm, and then the emulsion is subjected to deformation by the probe. There are a number of probes available to use with the Texture Analyzer and custom designed pieces may also be employed. **Figure 7** contains photographs of several probes, fabricated from both acrylate and stainless steel, which have been utilized to conduct Texture Profile Analysis of skin care emulsions.

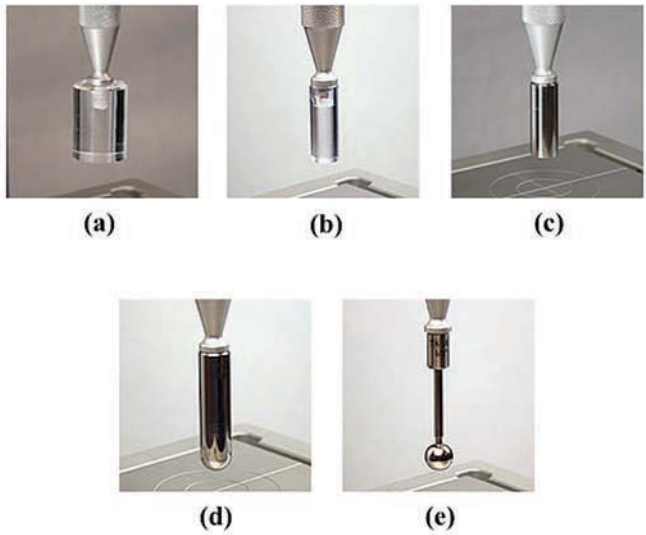

Figure 7. Probes utilized to conduct Texture Profile Analysis: (a) TA-11; (b) TA-10; (c) TA-10ss; (d) TA-23; and (e) TA-18.

Probe TA-11 is a standard multi-purpose acrylic probe with a 1-in diameter. Probe TA-10 (0.5-in diameter) differs from Probe TA-11 only in its dimensions. Probe TA-10ss has the same dimensions as Probe TA-10, but is constructed with stainless steel. Probe TA-23 has the same diameter as Probe TA-10, and is constructed with stainless steel, but has a rounded bottom (0.25-in radius end), analogous to the anatomical structure of a human finger. Probe TA-18, also constructed of stainless steel, contains a spherical structure (0.5-in diameter) that comes into contact with the sample, which was originally designed for food texture analysis applications. It should be noted that the surface energy of the probe, due to the material of which it is constructed, affects the magnitude of forces encountered by the probe. Overall, regardless of the probe type employed, similar trends are observed when comparing skin care creams and lotions.

In a typical test, two deformations are carried out during the course of Texture

Profile Analysis. Data, similar to that shown in **Figure 8**, is obtained in which case each peak corresponds to a deformation of the sample. Typical settings are: probe speed, 1.0 mm/s; deformation, 2.0 mm; deformation time, 1 s; initial trigger force (point where the 1.0 mm deformation begins), 2 g. From the plot in Figure 8, we can calculate several parameters that can be related to textural properties of the cream or lotion. Area 1 and Area 2 are the calculated areas under the first and second peaks, corresponding to the first and second deformation. These values are used to calculate the *cohesiveness* (Area 2/Area 1) and *compressibility* (1-Area 2/Area 1) of the emulsion. Peak 1 is the maximum value of the first peak and corresponds to the *firmness* or penetration force required to deform the sample. The first peak can further be analyzed by taking the ratio of Area 5 to Area 4, which provides a measure of *resilience*. *Adhesiveness of the emulsion to itself* can be taken to be Area 3, while *adhesiveness of the emulsion to the probe* corresponds to Area 6. *Integrity of shape* corresponds to the springiness of the sample and may be calculated by taking the ratio of Length 2 to Length 1. *Elastic resistance to deformation* corresponds to: (Area 2•Peak 2•Length 2)/(Area 1•Length 1). Finally, *stringiness* corresponds to Length 3, which begins in the negative force region of Area 6 and ends when the force becomes asymptotic to zero force.

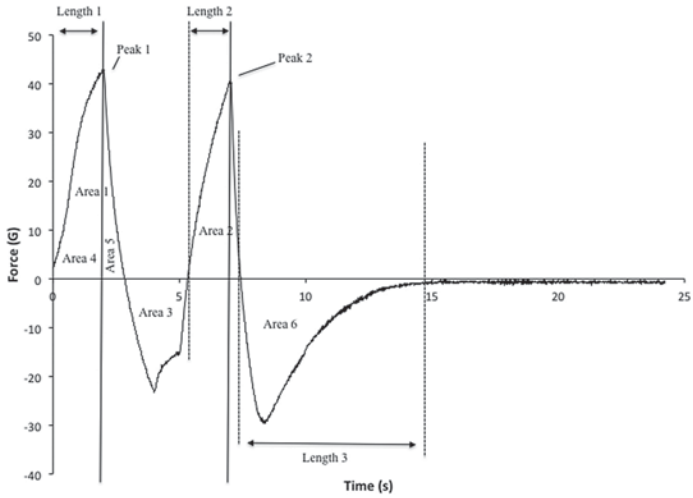

Figure 8. Example of a typical Texture Profile Analysis curve denoting specific length, peak height, and area measurements used to calculate textural attributes.

To measure *spreadability* and *tackiness* requires two separate tests with the Texture Analyzer. First, a simple measure of spreadability is attained by placing a small amount of emulsion in a weighing boat and applying a given force that partially deforms the sample, causing it to spread. Using a digital camera mount with fixed

dimensions and a scale included in the photograph, image analysis provides the area dimension of the spread emulsion. Tackiness, on the other hand, is measured by placing a small amount of the emulsion on a flat surface and bringing the probe in contact with sample. The adhesive forces corresponding to tackiness are measured as the negative peak forces and averaged from five deformations.

Analysis of Commercial Lotions and Creams by Texture Profile Analysis

Creams and lotions available in the skin care market can vary considerably in their textural properties. For example, a typical anti-aging cream would be distinctly different from a body milk formulation. The anti-aging cream normally would have much more consistency or structure as well as a distinct rub out profile, cohesiveness, etc. The body milk, on the other hand, would spread very easily, even without additional external forces, such as spreading by fingers. These characteristics are captured in Texture Profile Analysis experiments. In the current study, a total of fourteen commercial products were evaluated by Texture Profile Analysis. All of these samples were skin care emulsions in the form of either a cream or lotion. **Table** 2 identifies four of the commercial products and their key structure-modifying ingredients, which provide viscosity and stability to the product. The ingredients listed include emulsifiers/co-emulsifiers as well as rheology modifiers/thickeners for both the oil and water phases of the emulsion.

Table 2. Selected commercial products subjected to Texture Profile Analysis. Viscosity data, courtesy of Timothy Gillece, were obtained with an Ares G2 strain controlled rheometer utilizing parallel plates geometry.

	Product type	Viscosity (Cp)	Key structure-modifying ingredients
Product A	Thick cream	29,000	Stearyl alcohol, Cetyl alcohol, Glyceryl stearate, Carbomer, Sodium polyacrylate
Product B	Low viscosity lotion	1,840	Glyceryl stearate, Cetearyl alcohol, Carbomer, Hydroxymethylcellulose
Product C	Medium viscosity lotion	10,450	Glyceryl stearate, Cetearyl alcohol, Steareth-21, Distearyldimonium chloride, Behentrimonium methosulfate
Product D	Very low viscosity lotion	1,960	Glycol stearate, Carbomer, Glyceryl stearate, Cetyl alcohol, Magnesium aluminum silicate

Table 3 contains the results of selected textural attributes for several of the analyzed commercial creams and lotions. Upon inspection of the data, it is immediately apparent that *firmness* is the greatest for the cream sample (Product A), which is, by far, the most structured/viscous of the tested products. Products B and D, which are much lower viscosity lotions require less force to penetrate the sample at a fixed distance. The *compressibility* is more difficult to discern upon initial inspection. The very low viscosity lotion (Product D), which contains very little body, is the most compressible system. The cream (Product A), on the hand, is the least compressible. Likewise, the *integrity of shape* does not adhere to basic rheological parameters and depends on the complex interactions of the product with itself and with the probe. The analysis is pretty straightforward when we observe the properties of the product with the most structure and viscosity (Product A). As we would expect, the cream changes shape the most without returning to its original state. In addition, it is not surprising that Product B (low viscosity lotion) loses a significant amount of its body. However, Product C (medium viscosity lotion), which appears to have properties similar to Product A upon physical inspection, loses its shape upon deformation. In the case of Product B, this very low viscosity lotion is almost like water and does not change shape upon deformation.

The results of *elastic resistance to deformation* follow a trend corresponding to the consistency of the sample. The products with the highest consistency (Products A and C) have the greatest *elastic resistance to deformation*. Finally, we also report the *adhesiveness to the probe*, which more than likely also contains a strong cohesive component for the emulsion. Again, the two products with the greatest structure (Products A and C) have the strongest adhesion. The data for *adhesiveness of the emulsion to the probe* correlate well with the *adhesiveness of the emulsion to itself* (data not shown), again demonstrating the important role of the cohesiveness of the sample.

Table 3. Selected textural attributes of several commercial creams and lotions.

	Firmness (g)	Compress-ibility	Integrity of shape	Elastic resistance to deformation (g)	Adhesive-ness to probe (g•s)
Product A	87.85 ± 9.10	0.31 ± 0.0059	0.88 ± 0.0068	54.02 ± 1.48	255.80 ± 4.64
Product B	10.93 ± 2.68	0.32 ± 0.0064	0.94 ± 0.038	6.61 ± 0.22	38.16 ± 0.43
Product C	51.28 ± 4.39	0.35 ± 0.011	0.95 ± 0.0096	28.12 ± 1.32	135.00 ± 2.20
Product D	9.10 ± 0.13	0.37 ± 0.011	0.90 ± 0.0074	4.78 ± 0.15	22.63 ± 0.24

Overall, Products A and C follow the same trends in terms of *firmness*, *elastic resistance to deformation*, and *adhesiveness to the probe*. As already mentioned, these two products contain more structure than Products B and D, and it is probably safe to conclude that the structure/viscosity in the product correlates well with these parameters. On the other hand, we do not find such a clear correlation when examining the calculated values for *compressibility* and *integrity of shape*. These parameters may be less dependent on the formulation's physical properties and may rely more on the chemical properties of particular ingredients.

Table 4. Composition of four selected cream base emulsions subjected to Texture Profile Analysis.

Phase	Ingredient Trade Name	A % wt/wt	B % wt/wt	C % wt/wt	D % wt/wt
A	Deionized water	76.40	76.40	73.30	76.70
	Carbomer (Ashland 940 Carbomer, ASI)	0.5			
	Acrylic acid/VP crosspolymer (Ultrathix P-100, ASI)		0.5		
	PVM/MA decadiene crosspolymer (Stabileze QM, ASI)			0.5	
	Sodium polyacrylate (Rapithix A-100, ASI)				0.5
	Glycerin (99.7%) (Ruger)	2.00	2.00	2.00	2.00
	Disodium EDTA (Versene NA, Dow Chemical)	0.1	0.1	0.1	0.1
B	Isodecyl neopentanoate (Ceraphyl SLK, ASI)	7.00	7.00	7.00	7.00
	Ethylhexyl palmitate (Ceraphyl 368, ASI)	10.00	10.00	10.00	10.00
	Glyceryl stearate and PEG-100 Stearate (Arlacel 165, Croda)	2.75	2.75	2.75	2.75
	Cetyl Alcohol (Lanette 16, Cognis)	0.25	0.25	0.25	0.25
C	Triethanolamine (99%) (Dow Chemical)	0.30	0.30	0.40	
D	Propylene glycol (and) Diazolidinyl urea (and) Iodopropynyl butylcarbamate (Liquid Germall Plus, ASI)	0.70	0.70	0.70	0.70

Analysis of O/W Emulsions by Texture Profile Analysis

In order to discern the influence of thickening polymers on the properties of emulsion systems, we studied four o/w emulsion systems composed of the same vehicle and that only differed in composition by their thickening polymer. For simplicity, **Table 4** provides the example of the polymer used at 0.5% (w/w). The behavior of neat polymer solutions containing the same polymer were also examined, although the rheological profile was considerably different and did not present a suitable system for Texture Profile Analysis.

As already stated, a number of textural attributes were determined for the emulsion systems described in Table 4. All of the emulsion systems were evaluated at two concentrations of the selected polymers, 0.25% and 0.50% (w/w). Before delving into the Texture Profile Analysis data, there are several factors we should consider about the structural properties of the tested polymers.

Normally, when we think about rheology modification and structuring in relation to polymers, the concept of chain entanglements tends to come to mind. In this case, a polymer chain may be in a random coil conformation forming a small compact structure. By increasing the pH of the polymer solution, for example, the acid groups on the polymer chains become deprotonated, thereby bearing a negative charge and repulsing one another. As a result, chains of the polymer extend and entangle with neighboring chains. Overall, this transition causes an increase in the viscosity of the polymer solution. This is the typical situation for sodium polyacrylate, which is a linear polymer. The other three polymers included in the emulsion system, carbomer, acrylic acid/VP copolymer, and PVM/MA decadiene crosspolymer, are highly cross-linked and form microgels in solution. In this case, neutralization results in profuse swelling of the microgels and ensuing increases in the viscosity and measurable rheological structuring attributes such as the yield stress and G'. Further, factors such as the concentration, neutralization level, electrolyte type and level, cross-link density, and mole fraction of carboxylate in the repeating unit affect the way the microgels associate and respond to shearing forces. For example, at the same concentration and neutralization, a lower cross-linked microgel may produce a softer, or less elastic bulk gel than its more highly cross-linked analogue. In any event, we must keep in mind that the current study involves emulsions with many other components, which present a much more complex system than simple polymer in water gel solutions.

Figure 9 contains a graph of *firmness* at two concentrations for the four tested emulsion systems. The system containing carbomer provides high resistance to penetration at the low concentration, relative to the other systems; however, at 0.5% solids the systems based on acrylic acid/VP crosspolymer and sodium polyacrylate perform similarly, while PVM/MA decadiene crosspolymer requires much greater force to penetrate its structure. The requirement for such strong forces in PVM/MA decadiene crosspolymer may stem from the polymer's inherent networked structure due to chemical cross-linking as manifested by swelling of its microgels.

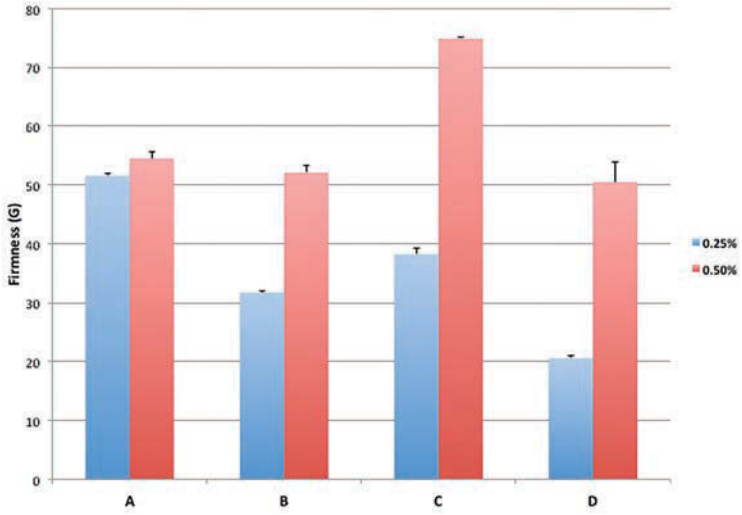

Figure 9. Chart of firmness for emulsion systems based on (A) carbomer, (B) acrylic acid/VP crosspolymer, (C) PVM/MA decadiene crosspolymer, and (D) sodium polyacrylate.

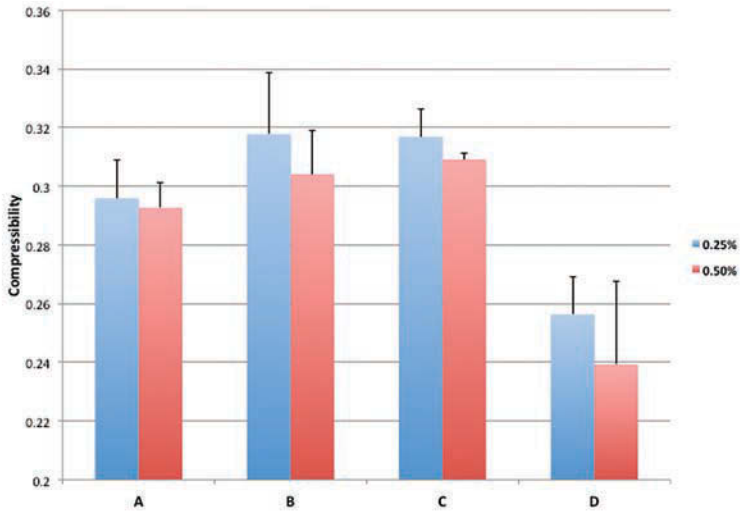

Figure 10. Chart of compressibility for emulsion systems based on (A) carbomer, (B) acrylic acid/VP crosspolymer, (C) PVM/MA decadiene crosspolymer, and (D) sodium polyacrylate.

From a slightly different perspective, the *compressibility* of each cream is reported in **Figure 10**. One should bear in mind that compressibility is proportional to the ratio of Area 2 to Area 1 in the Texture Profile Analysis plot. The three cross-linked systems—acrylic acid/VP crosspolymer, carbomer, and PVM/MA decadiene crosspolymer—are more compressible than sodium polyacrylate. Such a result is in contrast with what one might expect for highly cross-linked systems, which should be more elastic in nature. In this case, the shearing forces between the microgels may play a more prominent role.

Figure 11 contains *resilience* data, demonstrating the ability of the cream to break down as a result of shear forces. Such a result may be rationalized by the chemical structure of the polymer. A highly cross-linked system would be more likely to bounce back to its original structural, rather than to become molded by the deformation, as is the case with the linear, non-branched sodium polyacrylate system.

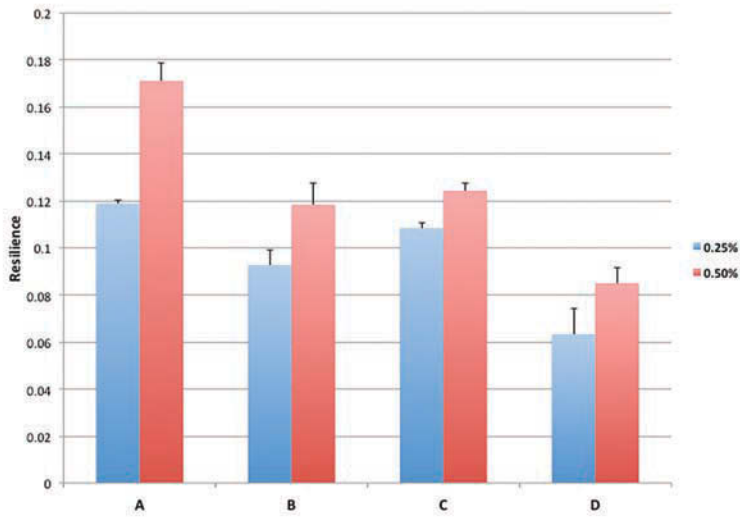

Figure 11. Chart of resilience for emulsion systems based on (A) carbomer, (B) acrylic acid/VP crosspolymer, (C) PVM/MA decadiene crosspolymer, and (D) sodium polyacrylate.

Concluding Remarks

In this chapter, we provide a broad overview of emulsion technology and its fundamental concepts. We also take a preliminary look at the textural attributes of skin care formulations as determined by Texture Profile Analysis. It is a promising and novel technique that can help us better engineer finished formulations with desired sensorial characteristics. It is our hope that future studies will include a full comparison of this technique to the sensorial attributes as determined by a pool of panelists.

Acknowledgements

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CHAPTER 7

High Internal Phase Water-in-oil Emulsions

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Key Words:
HIPEs, Polyhedral, Elastic Solids

Introduction

The protective, moisturizing, and healing properties of water-in-oil (w/o) emulsions have been recognized by cosmetic chemists and pharmacists for many decades. The main reason is that unlike oil-in-water (o/w) formulations, w/o formulations provide a more continuous occlusive film when applied to skin and therefore are more occlusive. Occlusion is known to promote healing in chronic inflammatory skin disorders. Nevertheless, the use of this therapeutic emulsion vehicle has been limited because of its heavy, oily, and occlusive properties that lead to diminished consumer compliance. Fortunately, over the past fifty years incremental technical and scientific advances have made it feasible to formulate w/o emulsions with reduced oil phase content, aqueous phase concentration beyond 70%, and improved application aesthetics.

This chapter will identify and describe some of the significant incremental advances that have made it possible to formulate stable and aesthetic high internal phase water-in-oil emulsions (HIPEs).

Shortly after entering the cosmetic industry in mid-1955, I was assigned a project involving the formulation of a more stable and aesthetic version of a then-popular w/o emulsion hair care product. Even though our product development R&D group had made some progress with this task, marketing professionals decided on an alternate, less greasy, formulation based upon o/w emulsion composition that was more desirable by consumers. However, I continued to be intrigued by w/o

emulsion technology, since it presented numerous opportunities and challenges. In spite of the recognized protective and moisturizing benefits of w/o emulsions, their use was limited to a 15–20% share of the emulsion market. The main reason for this limitation is believed to be the unfavorable sensory profile of classical w/o emulsions. This was considered to be a major drawback. The paradoxical task was the following: would it be possible to formulate stable, low viscosity w/o lotions with minimum oil phase content that possessed good application properties?

The main reason that classical w/o emulsions were greasy and occlusive was because in most instances the classical formulation contained a high concentration of oil/wax/petrolatum phase and a much lower concentration of water phase. Some of the original Eucerin brand w/o formulations are good examples of this. They were quite occlusive and functional; however, the aesthetics and application properties were inferior. The breakthrough with HIPEs is that the aqueous concentration, with the use of the polymeric emulsifiers, can be from 70% to 85%.

This chapter presents a group of technical advances abstracted from scientific literature and United States registered patent information that has contributed to the development of effective w/o emulsions, particularly those that have provided the foundation for a variety of stable and aesthetic HIPEs over the past 50 years.

Early studies of a group of emulsifiers to formulate w/o emulsions with relatively high water content offer fundamental background information as provided in the 1955 paper, titled, "The Influence of the Emulsifying Agent on the Viscosity of Water-In-Oil Emulsions of High Water Content."[1] In this study, the role of the emulsifying agent in determining the viscosity of w/o emulsions of identical water volume concentration disperse phase (65%) was investigated. Ten nonionic emulsifying agents were examined. The viscosities of the emulsions prepared from six of these emulsifying agents were of the same order, but appreciable divergences from the mean were exhibited by the remainder. It was concluded that the chemical constitution of the emulsifying agent does affect the resultant emulsion viscosity, presumably through the physical state of the film formatted at the interface and its relationship to the two phases.

Emulsion stability tests were performed by transferring samples to graduated cylinders, which were maintained at 35°C for 8 weeks. Samples were also centrifuged at 6000 rpm for 10 min and the degree of separation estimated. Among the low Hydrophilic-Lipophilic Balance (HLB) emulsifiers that demonstrated good rheology and emulsion stability in this study were Sorbitan Sesquioleate, Sorbitan Monooleate, Sorbitan Trioleate, Polyethylene Glycol (200) Monooleate, and Glyceryl Polyricinoleate. An important stability test not employed in this early study was three freeze/thaw cycles, which many w/o emulsions fail. Since the HLB had been only introduced by William Griffin of Atlas Chemical in the late 1940s, this study was a confirmation of the utility of this system as a practical guide to formulate stable w/o emulsions.

High Internal Phase Water-in-oil Emulsions (HIPEs)

In emulsion research literature prior to 1950, it was frequently stated that if the water phase of w/o emulsions exceeded 70%, emulsion inversion would occur, meaning that regardless of the nature of emulsifying agents, the formulation's outer phase will be water. However, several years later, after a variety of new nonionic, film-forming emulsifiers were commercialized, it was found that formulation of w/o emulsions with water content in excess of 74% was feasible.

K. J. Lissant, who worked for the Petrolite Corporation, St. Louis, Mo, is recognized as one of the foremost workers in the areas of HIPEs. He published numerous papers in the field and was granted numerous patents related to HIPE technology.[2-21] In his studies, he learned that continued incremental addition of water to the internal phase of a w/o emulsion would reach an upper limit of 0.74 assuming the water droplets remain uniform in size and spherical in shape. Interestingly, he did find that an HIPE is achieved with the addition of more of the aqueous phase by producing smaller droplets than can be located in between larger droplets, and/or by causing a deformation of the droplets. This results in the formation of a polyhedral foam-like structure.[2-4]

One of Lissant's US patents provides a very fine and concise definition of HIPEs: "Emulsions comprising greater than about 75% by volume internal phase (dispersed phase) are referred to as high-internal-phase-ratio emulsions (HIPEs). The droplets present in HIPEs are deformed from the usual spherical shape into polyhedral shapes and are locked in place. Thus, HIPEs are sometimes referred to as "structured" systems and display unusual rheological properties which are generally attributed to the existence of the polyhedral droplets. For example, when HIPEs are subjected to sufficiently low levels of shear stress, they behave like elastic solids. One of the most important and useful attributes of these emulsions is their rheology. Despite being comprised solely of fluids, emulsions can nevertheless be elastic solids. This elasticity is achieved due to droplet fluidity. Elasticity can result from the energy stored by additional deformation of the shape induced by an applied strain. As the level of shear stress is increased, a point is reached where the polyhedral droplets begin to slide past one another, whereby the HIPE begins to flow. This point is referred to as the yield value. When such emulsions are subjected to ever-increasing shear stress, they exhibit non-Newtonian behavior, and the effective viscosity decreases rapidly."[22] (Hemi Nae discusses rheology and its terms in **Chapter 11**).

Stabilization in HIPEs

The feasibility of formulating stable, low viscosity w/o lotions with minimum oil phase content that exhibit desirable aesthetic properties came into closer focus during the 1980s. This resulted from the confluence of new developments, particularly the introduction of low HLB polymeric emulsifiers, specialty silicone emulsifiers, and methodologies to improve freeze/thaw stability of w/o emulsions, examples of which—to be discussed later in this chapter—are cetyl dimethicone copolyol,

PEG 30 dipolyhydroxystearate, and polyglyceryl-4 diisostearate polyhydroxystearate sebacate and polyglycerol oleate.

A US patent assigned to Lever Brothers Corp. in 1986 provided useful insights related to stabilization techniques for HIPEs at a range of storage conditions. The abstract for this patent reads as follows: "An improved high-internal-phase emulsion having increased stability under conditions of long-term storage at elevated temperatures and freeze-thaw conditions, methods for preparing and stabilizing said emulsions, and cosmetic preparations based thereon are disclosed. The improvement comprises incorporating into said emulsion an amount sufficient to increase the stability of said emulsion of an electrolyte contained in the aqueous phase of the emulsion."[23] Prior to this disclosure, many HIPEs that were claimed to be stable had proven disappointing when those emulsions were subjected to tests approximating conditions that would be expected to be encountered by commercial products. Previously, stability at room temperature for 30 to 45 days was held to be an indication of HIPE stability. However, based upon storage conditions that approximate what a commercial product might be exposed to, this testing is far too mild.

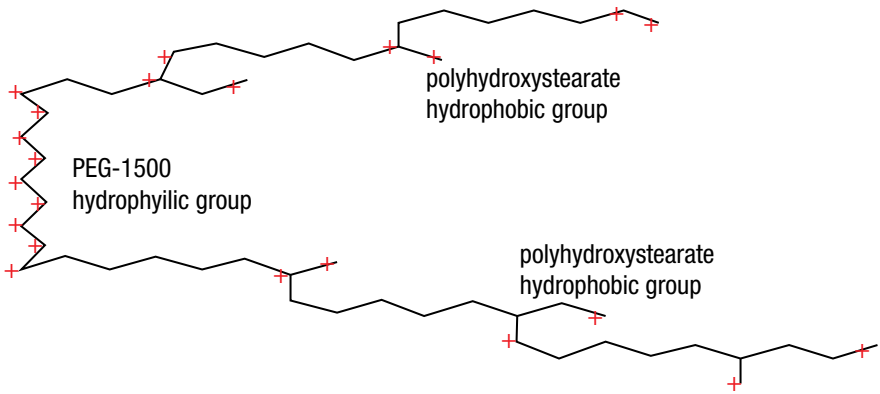
Researchers disclosed that HIPEs exhibiting increased stability can be obtained by the inclusion of appropriate levels of electrolytes. Among the electrolyte types disclosed in this patent are the following water-soluble salt types: monovalent inorganic salts, divalent inorganic salts, trivalent inorganic salts, and mixtures thereof. Some specific examples are magnesium sulfate, sodium chloride, and calcium chloride, which are used at concentrations ranging from 0.201.50% depending upon the composition of the specific HIPE. Additional confirmation for the merits of using electrolytes to stabilize HIPEs was given in a 2003 article titled, "Emulsion stability of cosmetic creams based on water-in-oil high internal phase emulsions."[24] The emulsion stability of HIPEs containing water, squalane oil, and cetyl dimethicone copolyol was investigated with various compositional changes, such as electrolyte concentration, oil polarity and water phase volume fraction; the following conclusion was drawn: "The rheological consistency was mainly destroyed by the coalescence of the deformed water droplets. Emulsion stability was shown to be dependent on the addition of electrolyte to the water phase. Increasing the electrolyte concentration increased the refractive index of the water phase, and thus decreased the refractive index difference between oil and water phases. This decreased the attractive force between water droplets, which resulted in reducing the coalescence of droplets and increasing the stability of emulsions. Increasing the oil polarity tended to increase emulsion consistency, but did not show a clear difference in cream hardness among the emulsions."

Based upon subsequent studies conducted by Dahms and Zombeck, it was documented that the impact of electrolytes in water-in-silicone (W/Si) emulsions are primarily on interfacial tension and interfacial viscosity.[25]

A more recent publication authored by researchers at Unilever, of which the abstract follows, describes the influence of electrolytes on the stability of highly concentrated w/o emulsions according to alternate colloidal mechanisms:[26]

"Concentrated water-in-oil emulsions of over 95% internal phase by volume were prepared using a variety of low HLB emulsifiers. These emulsions coarsened with time to produce a fraction of large droplets that grow at the expense of smaller droplets. This resulted in a decrease in yield stress and eventually to visible phase separation of water. There was a significant effect of emulsifier type, and the optimum HLB appears to be ~5 for mineral oil. None of the emulsions prepared with distilled water as the internal phase could withstand a single freeze/thaw cycle. In contrast to the gradual coarsening process at room temperature, freeze/thaw instability was sudden and involved an inversion process that took place in the frozen state. The properties of these concentrated emulsions changed dramatically when electrolyte was introduced into the aqueous phase at concentrations as low as 0.02 M. The rate of coarsening decreased and coalescence of water droplets during the freeze/thaw process was inhibited. The emulsions retained their yield stress over prolonged storage and a lower droplet size was often produced under the same conditions of emulsification. These effects seemed to be general and were observed with a variety of emulsifiers and electrolytes. The electrolytes appeared to enhance the stability of these water-in-oil emulsions by increasing the resistance of the water droplets to coalescence. It is proposed that this was achieved by a higher adsorption density of emulsifier at room temperature storage, and in the frozen state by the fractionation of a concentrated electrolyte solution that wetted the ice crystals and prevented their fusion. Analysis of emulsion rheology and processing suggested that this enhanced coalescence stability was adequate to account for the changes in yield stress and droplet sizes observed."

PEG 30 Dipolyhydroxystearate was introduced by Uniqema in the late 1990s.[27] It is a versatile w/o emulsifier with an HLB of 5.5 that has the unique ability to produce very stable, fluid, low-viscosity emulsions that spread easily on the skin while creating a light, non-oily skin feel. It is claimed to produce HIPEs, with emulsifier concentrations as low as 1%, display excellent high temperature stability, very high internal phase volume (90%), and fine emulsion droplet size (0.44mm). This polymeric emulsifier with a molecular weight of 5000 is currently marketed by Croda as Cithrol DPHS.



A prototype HIPE emulsion, a w/o light moisturizing cream, provided in the original Uniqema literature for Arlacel P-135, is as follows:[27]

Phase	Ingredient	% Wt.
A	PEG 30 Dipolyhydroxystearate	1.0
	Cyclomethicone and PPG-15 Stearyl Ether	3.0
	Isohexadecane	6.0
B	Sorbeth-30	4.5
	Magnesium sulfate	0.8
	Water (aqua)	84.7
	Preservative	qs
C	Fragrance	qs

Procedure:
Heat Phases A and B separately to 75-85°C. Slowly add Phase B to Phase A while stirring vigorously. Homogenize for one minute. Allow to cool to 35°C while stirring. Once cooled, add fragrance (Phase C).

This formula was stable at room temperature, elevated temperature (up to 50°C), freezing and low temperatures, and across five freeze/thaw cycles after one month. It is stated that the finished emulsion must be homogenized. Heating and production time can affect the final viscosity; both should be kept constant with every batch to avoid fluctuations. In 90% internal phase emulsions, adding more PEG 30 Dipolyhydroxystearate will increase the viscosity. This literature also indicated that this HIPE showed significant promise for the formulation of stable water-in-oil-in-water (w/o/w) emulsions.[27]

A patent assigned to Beiersdorf AG in 2004 titled, "Flowable preparations of the water-in-oil emulsion type having an increased water content" illustrates the use of PEG-30 Dipolyhydroxystearate to formulate HIPEs.[28] Four example formulations abstracted from this patent are as follows:

Formulation name	Ingredient	% Wt.
W/O Lotion (A)	PEG-30 Dipolyhydroxystearate	2.0
	Isohexadecane	4.5
	Paraffinum liquidum	12.5
	Glycerol	3.0
	Magnesium sulphate	0.70
	Fragrance, preservatives, dyes, antioxidants	qs
	Water	qs to 100

Formulation name	Ingredient	% Wt.
W/O Lotion (B)	PEG-30 Dipolyhydroxystearate	2.0
	Cycloparaffin	10.0
	Paraffinum liquidum	7.50
	Tocopherol acetate	0.50
	Glycerol	3.0
	Panthenol	0.30
	1,3-Butylene glycol	1.0
	Serine	0.30
	Biotin	0.10
	Di-starch phosphate	1.0
	Magnesium sulphate	0.70
	Fragrance, preservatives, dyes, antioxidants	qs
	Water (aqua)	qs to 100
Sunscreen Lotion	PEG-30 Dipolyhydroxystearate	2.0
	Isohexadecane	4.0
	Paraffinum subliquidum	8.0
	4-(tert-Butyl)-4'-methoxydibenzoylmethane	1.0
	Octyl methoxycinnamate	1.5
	4-Methylbenzylidene camphor	1.5
	Tris[anilino(p-carbo-2'-ethyl-1'-hexyloxy)]triazine	0.50
	Titanium dioxide	1.0
	Zinc oxide	1.0
	Glycerol	1.0
	Magnesium sulphate	0.70
	Fragrance, preservatives, dyes, antioxidants	qs
	Water (*aqua*)	qs to 100
Liquid Emulsion Make-up	PEG-30 Dipolyhydroxystearate	2.0
	Isohexadecane	3.0
	Paraffinum liquidum	13.0
	Glycerol	1.5
	Magnesium silicate	0.50
	Mica	0.50
	Iron oxides	0.50
	Titanium dioxide	0.50
	Talc	0.50
	Magnesium sulphate	0.70
	Fragrance, preservatives, dyes, antioxidants	qs
	Water (*aqua*)	qs to 100

A recent article by Meyer et al. titled, "A Novel PEG-free Emulsifier Designed for Formulating W/O Lotions with a Light Skin feel" provides extensive information about applications for the use of ***Polyglyceryl-4 Diisostearate Polyhydroxystearate Sebacate*** to prepare HIPEs.[29] This polymeric emulsifier is a yellow, clear to turbid, viscous liquid with a HLB of ~ 5. It has good skin compatibility and provides a pleasant, non-oily skin feel. It is compatible with all types of cosmetic oils and silicones. It requires no additional co-emulsifiers and makes the cold processing of emulsions possible. This emulsifier enables the formulation of HIPEs with oil phase content as low as 18% depending upon the emollients selected. In addition, the formulation has low viscosity and desirable light application properties.

A example formulation for an After Sun w/o lotion with just 18% oil phase content is shown in the following table:

Phase	Ingredient	% Wt.
A	Polyglyceryl-4 Diisostearate/Polyhydroxystearate/Sebacate	3.00
	Hydrogenated Castor Oil	0.25
	Microcrystalline Wax	0.25
	C12-15 Alkyl Benzoate	10.70
	Diethylhexyl Carbonate	10.00
	Tocopheryl Acetate	0.60
	Salicyloyl Phytosphingosine	0.20
B	Glycerin	3.00
	Sodium Carboxymethyl Betaglucan	0.20
	Creatine	0.50
	D-Panthenol	0.50
	Magnesium Sulfate Heptahydrate	1.00
	Water (aqua)	69.80
	Fragrance	qs

Procedure:
Heat Phase A to approx. 80°C. Add Phase B premixed (80°C or room temperature) slowly while stirring. Homogenize for a short time. Cool with gentle stirring below 30°C and homogenize again.

Topical Delivery Systems Based Upon HIPEs

A patent assigned to KV Pharmaceuticals in 1983 titled, "Stable high internal phase ratio topical emulsions"[30] discloses the following via abstract: "Delivery systems for topical preparations which are commercially stable. The emulsions are water-in-oil, in which the water phase comprises at least 75% of the emulsion by volume. The emulsifier is a nonionic, oil-soluble straight or branched chain ester, or combination thereof, composition having at least two hydrogen bonding sites per

molecule." The HIPEs of this invention are claimed to be effective for delivering topical actives based upon the stability of the emulsion vehicle, as well as the invention's nonlipoidal media in a lipoidal media emulsion, in which the nonlipoidal phase is at least 75% of the emulsion. The first prototype stated in this patent, which contains Benzocaine 10%, is a good example, because the HIPE displays good emulsion stability and provides and oil adherent system for the active ingredient without using a high concentration of oil.

Protective Lotion 3 (Initial Viscosity = 250-450 K cPs)	**Ingredients**	**% Wt.**
Internal Phase	Deionized Water	75.19
	Sorbitol 70% sol.	8.00
	Polyquaternium 15	0.10
	Methylparaben	0.14
	Silicone Fluid 200, 100 CS	5.00
External Phase	Microcrystalline Wax	0.50
	Gloria Mineral Oil	5.00
	Glycerol Monoisosterate	3.00
	Polyglycerol Oleate	3.00
	Propylparaben	0.03
	Fragrance	0.025
Benzocaine 10% (Initial Viscosity = 100-400K cPs)	**Ingredients**	**% Wt.**
Internal Phase	Deionized Water	69.30
	Glycerine	8.00
	Benzyl Trimethyl Ammonium Hydrolyzed Animal Protein	1.00
	Methylparaben	0.15
	Propylparaben	0.05
	Silicone Fluid 200, 100 CS	1.00
External Phase	Carnation Mineral Oil	7.00
	Polyglycerol Oleate	3.00
	Microcrystalline Wax	0.50
Active Phase	Benzocaine 10%	10.00

Other examples of HIPE usage exist in this patent, such as for a protective lotion product. It is stated in this patent that its prototype formulations display

good freeze/thaw stability, despite the fact that no electrolytes have been included. In this author's view, the inclusion of high levels of glycols accounts for the good freeze/thaw stability properties in these formulations.

Future Prospects for HIPEs

With our current knowledge that stable, aesthetic, and functional HIPEs can be formulated and scaled-up with the availability of a series of specialty emulsifiers and appropriate stabilizers, it is apparent that opportunities exist to employ this innovative emulsion technology for a range of new products. Among the prime product categories that merit exploration are improved protective and water-resistant sunscreen vehicles, aesthetic and protective skin care lotions, HIPEs for over-the-counter (OTC) delivery systems, lotion-type makeup applications, and the formulation of a variety of w/o/w compositions for topical and pharmaceutical delivery systems.[31] This latter is due to the fact that multiple emulsions based on conventional nonionic surfactants have been reported to produce multiple emulsions with a limited shelf life, whereas polymeric surfactants have recently been shown to maintain the physical stability of w/o/w emulsions.[31]

Summary

A series of incremental technical and scientific advances that have contributed to the development of high internal phase water in oil emulsions (HIPEs) over the past 50 years have been described. Numerous researchers and firms have contributed to provide innovative technical paths to resolve the long sought-after challenge of formulating low-viscosity, stable, and aesthetic w/o lotions with high water content. HIPE technology has opened new possibilities to formulate w/o lotions and creams for a wide range of applications, such as moisturizing body lotions, water-resistant applications, high SPF sun care formulations, and color cosmetics with high pigment loadings.

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CHAPTER 8

Manufacturing Topical Formulations: Scale-up from Lab to Pilot Production

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Key Words:

Scale-up, QbD, Design of Experiments, Design Space, Control Strategy, Critical Material Parameter, Critical Process Parameter, Critical Quality Attribute, Body of Knowledge, Risk Management, Technology Transfer

Introduction

Scale-up is generally defined, in the pharmaceutical and cosmetic industries, as the process of safely and efficiently utilizing a process to increase the batch size of the product. It usually involves an increase in the physical mass of product, such as when increasing a mix size from a bench top unit handling a few hundred grams, to a pilot scale mixer of several kilograms. When approached methodically, with the proper tools, foresight, and attention, scale-up can go smoothly, with few surprises, or, when tackled in casual, haphazard fashion, can be most unforgiving, often leading to project delays, lost capital, and damage to organizations and careers.

This chapter is intended to cover scale-up of topical products used in both pharmaceutical and cosmetic applications, from laboratory scale to pilot scale. It is not intended to address scale-up from pilot to commercial scale, although many of the principles and ideas contained herein can easily be applied to commercial scale-up. While the principles and requirements are quite similar, the pharmaceutical avenue represents a more highly-regulated environment in which regulatory guidance and scale-up principles are more developed. As such, the focus of the discussions in this chapter will be geared to a pharmaceutical approach, with the understanding that adapting such principles in a cosmetic product environment is often done in any event, and is certainly advisable from a product development standpoint to varying degrees depending on your particular business environment.

The goal of this chapter is to present and advocate a holistic approach to the challenges of scale-up. Volumes have been written on the raw theory of scale-up principles; many papers are beginning to appear on the application of Quality by Design principles (QbD), and there is abundant literature on statistical methods, designed experiments, and many of the other topics touched upon here. This work intends to tie these pieces together in such a way as to give the engineer or formulation chemist an overview which provides a reasonably comprehensive high-level synopsis of all facets of pilot-level scale-up in order to avoid major mistakes and pitfalls. This chapter is not intended to be a comprehensive reference work on the technical details of scale-up.

This chapter is organized as follows: this introductory section will touch upon high-level concepts and philosophical considerations, as well as list keywords associated with topical product scale-up and their definitions. Next, an **Overview of Key Scale-up Considerations** is presented as a transition into the more detailed sections that follow. After the overview, **Process Design** is discussed, with attention to documentation, Quality by Design (QbD) principles, critical process parameter and critical quality attribute identification, and general scale-up principles. A working example is used to illustrate the principles in the Process Design section – that of a topically applied gel product for local pain supplied in a metered-dose pump dispenser. This product will be referred to in other sections where appropriate to provide a working example. Following the Process Design section, **Process Equipment** for manufacturing topical dosage forms is discussed in modest detail, with a particular focus on mixing equipment, as the mixing or blending process is typically more sensitive to scale-up than filling and packaging with topical dosage forms. Next, **Facilities and Engineering** considerations are discussed at a high-level; it is not the intent of this chapter to delve into facilities design, but certain considerations merit mention when selecting from available facilities for pilot scale-up. **Raw Material** considerations are then discussed, also at a fairly high level, with the intent to capture the major issues the engineer or chemist need be aware of when moving into the pilot plant with a new product or process. The chapter is concluded with a summary of key points and a list of references.

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Pharmaceutical Development Guideline Q8(R2) notes: "Strategies for product development vary from company to company and product to product . . . An applicant might choose either an empirical approach or a more systematic approach to product development, or a combination of both." Scale-up is of course a key element of product development, and product development decisions are inextricably linked with the scale-up process, and vice versa. Much has been written about theoretical aspects of scale-up. This chapter will address what the author believes are the most useful elements of scale-up theory, while focusing on day-to-day practical considerations and working within the very real constraints one often finds in a business-industrial setting, while keeping substantially within a QbD paradigm.

The purest theoretical elements of scale-up do provide a useful framework through which practical, real-world scale-up requirements can, at a minimum, be evaluated for probability of success, but in many (if not most) cases, do not represent the path the process engineer is able to take. In this author's experience scaling up topical and transdermal products in a real-world industrial setting, practical constraints predominate the majority of scale-up and process development decisions.

For example, scale-up theory may dictate a fourfold increase in mixer horsepower and blade-speed in order to ensure a high probability of success for a particular topical formulation mixing process. Real-world limitations, either from a space, time, or capital constraint standpoint, may prohibit this option, or instead require the engineer make do with a mixer having only half the capability available. Purchasing a new production line for each new product is seldom an option. Time to market is a major constraint that, along with budget limitations, often compels the engineer to make do with what is already available. Herein lays the true challenge. Engineering is by nature a field requiring creativity and innovation in addition to rote mathematical skill. The engineer is truly in his element and "earning his pay" when he is forced to innovate outside the strict requirements of the textbook theory.

On the plus side, over time, the engineer who is forced to successfully perform scale-up with a limited palette will find himself developing what the industry refers to as a "body of knowledge" that can be drawn upon for subsequent scale-up projects. Drawing on similar experiences for similar products will become a vital tool for the engineer expected to rapidly scale-up products with limited time and funds. For an organization, it is imperative this body of knowledge be captured and cross-pollinated throughout the organization in order to sustain long-term product development efficiency. Many projects sputter and stall because the engineering team was not privy to similar experiences of other teams within the organization. In addition, QbD principles have been developed with all of this in mind and anticipate the practical constraints the engineer is faced with, and do provide a sound framework in which to empirically operate.

Overview of Key Scale-up Considerations

The key elements of scaling up a topical formulation manufacturing process can be broadly broken down into the following categories: process design, including QbD principles, equipment and facilities considerations and limitations, raw materials, and regulatory considerations. In all aspects of industrial scale-up (as opposed to an academic or laboratory setting), practical considerations predominate, although some companies may, as a matter of practice, place more emphasis on theory than do others. For example, most engineers and formulation chemists reading this chapter are likely to work in an established facility with existing pilot plant equipment, with little or no option for major equipment acquisitions or modifications. As a result one will need to compromise and improvise to some extent. Herein lays the art of successful scale-up – combining the appropriate mix of prior knowledge,

process design principles, and common sense, in order to achieve success within the confines of your working limitations. In an established plant setting, an applicable prior body of knowledge generally provides the best foundation, or starting point, with which to begin applying QbD and process design principles. Prior knowledge is extremely useful in identifying the candidates for critical quality attributes as well as critical process parameters, because it was likely done so for a similar, prior product. Application of this knowledge allows large numbers of potential critical process parameters to be culled down to a manageable set that will more easily lend itself to statistically based process design. Early experimentation using this foundation will of course, on occasion, uncover surprises that must be considered as the process is refined, and perhaps ultimately validated at a larger, commercial scale.

QbD principles are becoming important aspects of scale-up and process development, particularly for the pharmaceutical industry, both on the brand as well as generic side of the industry. Not following basic QbD principles when developing drug products will no longer be an option in the near future. The US Food and Drug Administration (FDA) has stated that beginning in 2013, generic Abbreviated New Drug Applications (ANDAs) should contain elements of QbD.[1]

Equipment and facilities considerations provide a skeletal framework of sorts in which the process design space must be fleshed out. If one only has a mixer capable of 2,000 rpm, then 2,000 rpm obviously becomes a fixed limit for that parameter.

Raw materials are a critical element of scale-up in any of several ways. It is not uncommon (for example) for lab samples of key ingredients to be used during bench top formulation, and for the engineers in the pilot facility to source materials from different suppliers capable of meeting larger supply and/or regulatory requirements. Supplier change or even a change of grade within the same supplier may introduce unexpected variability to a process which can be difficult to detect.

Regulatory considerations are often tied into raw material selection and sourcing issues. As an example, consider the change from a lab-quantity raw material source to a bulk supplier as part of scale-up. While certification of compliance to the common compendia, such as the United States Pharmacopeia (USP) or National Formulary (NF), may not have been critical during bench top formulation work, it is critical to begin using the grade (both compendial and physiochemical) intended for commercialization, early on during product development, and certainly by the time the process is introduced to the pilot-scale plant. Scale-up factors from pilot to commercial are often more significant than those associated with lab-to-pilot increases in scale, and keeping easily controlled variables such as these to a minimum when undertaking larger scale-up steps is critical for success.

The next section, Process Design, begins the more detailed discussion of scale-up theory and practice for topical formulations.

Process Design

General Considerations

For sound scale-up and process design to occur, an established framework of administrative support systems is essential. These systems should have a basis in Current Good Manufacturing Practice (cGMP) and will ensure a consistency in approach from project to project and across different scale-up teams. Such a system will necessarily include documentation and record keeping procedures that ensure key elements of experimentation, i.e., a "prior body of knowledge," are recorded for future use, as well as a system of practices which ensure consistent and appropriate methodologies are used when operating manufacturing equipment and analytical instruments. Weak or absent documentation systems severely hamper the ability of the engineer or scientist to consistently perform technically sound product and process development and may create regulatory and compliance problems.

Documentation and Record Keeping

Effective scale-up to pilot plant manufacturing should occur within a cGMP framework. Many pilot plants, especially in the pharmaceutical industry, serve as both a stepping-stone to full-scale commercial manufacturing as well as the source of product for human clinical trials. Documentation and records are a key element of any cGMP manufacturing system.

A record keeping system supporting high-quality scale-up and process design is necessarily a multi-faceted collection of interrelated documentation subsystems which must mutually support one another and, when taken as a whole, should be designed to fulfill the regulatory requirement for your target marketing region and product type. Regulatory requirements may be different for drug products (as well as combination drug-cosmetic products) versus products that are strictly cosmetic. While it is not the object of this book to provide a comprehensive discussion of regulations, which are covered extensively elsewhere, it nonetheless is beneficial to give a brief overview of how regulations worldwide tie into documentation requirements for the production of topical pharmaceutical or cosmetic formulations, which in turn should drive the documentation system used in support of pilot plant scale-up. The following section briefly summarizes differences in documentation requirements for drugs versus cosmetics in the two major Western markets: the United States and the European Union. Again, it should be stressed that cosmetic or drug product manufacturers ultimately must comply with the regulations of the region where the product is to be marketed.

Drug Products

United States:

In the United States, drug manufacturing regulations are driven by the Food, Drug, and Cosmetic Act of 1938, which, under section 501(B) of the act, established Title 21 of the Code of Federal Regulations.[2] Parts 210 and 211 of Title 21 are commonly known as the "cGMPs," or Current Good Manufacturing Practice (cGMP) requirements. The cGMP principles strictly apply to the manufacture of

drug products or they may be viewed as adulterated by the FDA. Specifically, Subpart F 211.100 states: "There shall be written procedures for production and process control designed to assure that the drug products shall have the identity, strength, quality, and purity they purport or are represented to possess."

Documentation systems may be maintained on paper, electronically, or a combination of both. Electronic documentation systems are touched upon briefly later in this section, as they may be subject to regulation as electronic records under 21 CFR Part 11 in the United States, if drug product manufacturing is involved. Key elements of cGMPs related to documentation include: equipment logs, component labeling, master and batch production records, laboratory records, distribution records, product complaint files, and prescribed periods for record retention.

European Union:

The cGMP procedures within the European Union are established under the authority of the European Commission and enforced by the European Medicines Agency (EMA). Specifically, EU cGMPs for human drug products are set forth in Commission Directive 2003/94/EC, last updated in 2003. Guidance on interpreting the good manufacturing principles established in the Commission Directive is published in Volume 4 of *The Rules Governing Medicinal Products in the European Union,* titled: "Guide to Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use."[3] Chapter 4 of this volume describes documentation requirements for EU good manufacturing practice compliance. The EU requirements are, not surprisingly, similar to the requirements in the United States, and include: site master file, specifications, manufacturing and testing instructions, SOPs, protocols, technical agreements, production and testing records, certificates of analysis, and reports. Document retention requirements are also outlined in the guidance.

Other Markets:

Approximately 25 countries maintain their own cGMP requirements for the manufacture of drug products. However, most are based on either the United States' or European Union's requirements, with occasional local variation. Much recent effort has been undertaken to harmonize cGMP requirements across markets. The Pharmaceutical Inspection Convention (PIC), also known as "The Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products," formed in 1970, is a multinational organization formed to streamline and harmonize the compliance inspection process across different markets and countries. The PIC was originally comprised of a few Western European nations that were members of the European Free Trade Association (EFTA), an organization of European states which at that time did not belong to the European Union's predecessor organization, the European Economic Community (EEC). The goals of the PIC were "mutual recognition of inspections, harmonization of GMP requirements, uniform inspection systems, training of inspectors, exchange of information, and mutual confidence." In the early 1990s it was realized, due to conflict between European law and the Convention, that non-European states

could not be admitted. As a result, the PIP Co-operation Scheme was formed in 1995 which would allow non-European countries to participate in a less formal and non-legally binding cooperation arrangement. At present, the PIC/S includes numerous regulatory and governmental agencies from Western and Eastern Europe, South America, North America, and the Middle East.[4]

Cosmetic Products

United States:

Cosmetic manufacturers in the United States are not legally required to follow the cGMPs for drug products (21 CFR 210 and 211). However, the Food, Drug and Cosmetic Act (FD&C) "prohibits the introduction or delivery for introduction into interstate commerce of cosmetics that are adulterated or misbranded (Sec. 301)." Adulteration may occur essentially due to any of four reasons, according to section 601 of the act:

1. "It may be injurious to users under conditions of customary use because it contains, or its container is composed of, a potentially harmful substance
2. It contains filth.
3. It contains a non-permitted, or in some instances non-certified, color additive.
4. It is manufactured or held under insanitary conditions whereby it may have become injurious to users or contaminated with filth."[5]

Misbranding may also be an unfortunate result of failure to follow cGMPs. The act considers a cosmetic product misbranding in any of the following circumstances:

1. "False or misleading labeling.
2. Failure to state prominently and conspicuously any information required by or under authority of this act.
3. Misleading container presentation or fill."[5]

In order to avoid adulteration or misbranding of cosmetic products, it is essential to adhere to key principles of cGMPs, including those related to documentation and record keeping. Section 704(a) of the FD&C act invests the FDA with authority to enter cosmetic manufacturing establishments for inspection and enforcement purposes to ensure compliance with the act. In addition, FDA publishes on its website a Good Manufacturing Practice Guidelines/Inspection Checklist of key cGMP principles for cosmetic manufacturers. The points in this checklist are excerpted from the FDA's Operations Inspection Manual and provide a convenient means for cosmetic manufacturers to self-inspect their operation to ensure compliance.

Record keeping and documentation guidelines are, not surprisingly, very similar to those outlined for drug products and include:

1. "Records. Check whether control records are maintained of:
   a. Raw materials and primary packaging materials, documenting disposition of rejected materials.
   b. Manufacturing of batches, documenting the:
      iii. Types, lots and quantities of material used.

iv. Processing, handling, transferring, holding and filling.
v. Sampling, controlling, adjusting and reworking.
vi. Code marks of batches and finished products.

c. Finished products, documenting sampling, individual laboratory controls, test results and control status.
d. Distribution, documenting initial interstate shipment, code marks and consignees."[5]

European Union:

In the European Union, new regulations are in place that require cosmetic finished product manufacturers to comply with cGMPs as outlined by ISO 22716. The International Organization for Standardization (ISO) is a worldwide network of national standards organizations which collectively publish technical standards for a multitude of industries, including manufacturing. At present there are 164 member countries in ISO, which maintains its headquarters in Geneva.[6] Cosmetic ingredient suppliers are also encouraged and expected to follow cGMPs. In 2005, the European Federation for Cosmetic Ingredients (EFfCI), a trade group comprised of chemical and natural ingredient suppliers who serve cosmetic manufacturers, published a guide for industry to aid in cGMP compliance. This guide, *GMP Guide for Cosmetic Ingredients*, was produced by the EFfCI GMP working group using the IPEC-PQG GMP guide as a foundation. The International Pharmaceutical Excipients Council (IPEC) is a worldwide trade organization comprised of both manufacturers and end users of pharmaceutical excipients. The Pharmaceutical Quality Group (PQG) was formed in 1977 "to promote development of a consistent approach to pharmaceutical quality and good manufacturing practices."[7]

The EFfCI GMP Guide uses as the basis for its quality management system the ISO 9001:2008 framework. ISO 9000 represents the set of standards defining international consensus on GMP, and the EFfCI GMP guide essentially builds certain hygienic and quality system requirements on top of the ISO 9000 framework.

Other Markets:

The third major market for cosmetics, Asia, is regulated primarily by the Association of Southeast Asian Nations (ASEAN). The ASEAN Harmonized Cosmetic Regulatory Scheme, approved by member states in 2003 to standardize requirements and lower barriers to trade, provides a set of guidelines cosmetic manufacturers are expected to follow. The scheme is comprised of three parts, the signed agreement, Schedule A, the ASEAN Mutual Recognition Arrangement of Product Registration Approvals for Cosmetics, and Schedule B, the ASEAN Cosmetic Directive. Article 8 of Schedule B, Product Information, outlines documentation and record keeping requirements for cosmetic manufacturers wishing to market their products in the region. These requirements are similar to those of the EU, and require the marketing authorization holder to maintain the following documents for potential inspection by regulatory authorities: qualitative and quantitative composition of the product, specifications, method of manufacture as defined by the ASEAN Guidelines for Cosmetic Good Manufacturing Practice, Appendix VI of the scheme. The ASEAN

Guidelines for Cosmetic GMP read remarkably like 21 CFR parts 210 and 211 and outline the following record keeping requirements: history of each batch of product, including "executed activities for maintenance, storage, quality control, primary distribution and other specific matters related to GMP," specifications, production documents (master and batch production records), and quality control records.[8]

In the sections that follow, each type of record is discussed in some detail, with comments and suggestions this author has found of use in his experience when scaling up products to the pilot plant operation.

SOPs

Written procedures, typically in the form of Standard Operating Procedures (SOPs) are an essential element to a quality manufacturing operation and GMP across all markets. The importance of SOPs stems from the fact that if no written procedure exists for performing a critical manufacturing step, there can be no assurance that step is done consistently from batch to batch. When scaling up a topical cosmetic or drug product, a key element to the process characterization work is consistency of procedure when performing critical steps which may affect experimental outcome. For example, operating or setting up a piece of equipment, or charging in ingredients, if not performed the same way, may confound process characterization experimental results and make investigation extremely difficult. On the other hand, when critical steps are known to have been performed in a prescribed, consistent manner, those steps are no longer variables in process characterization work. Furthermore, when a process is successfully scaled up using well-defined SOPs to govern key steps, one has added assurance that subsequent batches of product intended for clinical use will be consistent with experimental process characterization batches. In short, use of SOPs assists in minimizing variability caused by human factors when scaling up a manufacturing process.

Technical Reports

Good science mandates good reports, and process scale-up is no different. The body of technical knowledge an organization has collected for a particular type of product, process, or equipment comprises an important element of QbD. How that knowledge is collected and documented can be a make-or-break factor for subsequent, similar scale-up projects. Here, there are two critical junctures in the scale-up to pilot batch where technical information must be captured: 1) formulation activities in the lab, including bench top manufacturing methods that were used, and 2) scale-up work within the pilot plant itself. The former activity may be documented in a formulation report, which is ideally intended as the initial technology transfer package handed to the pilot plant engineer by the formulation scientist. It should include a number of elements in order to be considered complete. The following list is intended as a reasonably comprehensive guide based on a topical drug product, but can easily be adapted to a cosmetic formulation:

- Description of the physiochemical properties of the active substance (if present).

- Characterization of physical and chemical compatibility between the active substance and excipients.
- Test method description for any analytical methods necessary to characterize the product.
- Description of any screening studies used to select formulation components and their chosen concentrations.
- *In vitro* Franz cell skin flux characterization of the active component (if present and/or appropriate).
- Physical stability assessment of the formulation. This may include both visual and microscopic observation of formulation over time, at multiple storage conditions to assess attributes such as phase-separation, precipitation, visual indicators of degradation such as discoloration and any other perceivable observational evaluation such as change in odor and feel upon application.
- Chemical stability of the formulation under multiple storage conditions, including stress conditions (elevated temperature, conditions of oxidation and hydrolysis, photostability as appropriate).
- Physical and chemical characterization of formulation, which may include, as examples, attributes like viscosity, rheology, pH, appearance, and cohesion.
- *In vitro* and/or *in vivo* evaluation of formulation safety, including any appropriate skin irritation and sensitization studies.
- Preliminary risk assessment of formulation and process attributes.

This report will assist the pilot plant engineer or scientist, along with a Target Product Profile, in identifying critical quality attributes which will be the focus of any process characterization work during scale-up.

The second instance where high-quality technical reports must be generated is at the conclusion of scale-up, in order to support the next leg of tech transfer, from the pilot plant to the commercial manufacturing facility. This report may be combined with the product development report, because there is much overlap between general product development activities and manufacturing scale-up. Tech transfer from pilot to commercial scale remains one of the most significant challenges for the industry, and inadequate or incomplete scale-up/product development reports can create a major pitfall leading up to commercialization. These challenges arise in a large part due to the business pressures that come to bear on the science and engineering work needed to properly characterize a process.

Equipment and Facilities Logs

It is a common practice in the pharmaceutical and cosmetic industries to keep logbooks for major pieces of equipment. Machine logbooks are essential to track equipment use, cleaning, calibration, and maintenance activities, and are an essential component of cGMP compliance. The absence of such logs makes the efficient and

safe use of equipment extremely difficult. For example, the inability to discern what active component was last used on a piece of equipment makes verification of cleanliness impossible and can result in the adulteration of subsequent products, a serious manufacturing compliance deficiency that can result in regulatory citation and product recalls. In addition, equipment logs can provide an invaluable record of the general state of the equipment during periods in which an investigation into a particular manufacturing process or event is warranted. For example, a log may record the specific set-up procedure used for the equipment, allowing one to ascertain how the equipment was configured during the manufacturing event in question. This ability can prove invaluable as part of scale-up and process characterization, particularly when the unexpected or unexplainable occurs.

Production and Labeling Records

Production and labeling records are also an essential element of any cGMP or ISO-certified manufacturing operation. cGMP principles typically require a pre-approved master production formula which is duplicated or issued as a working document for each batch of product. The master production formula should be a stepwise set of instructions that allows documentation of each significant step in the manufacturing, packaging, and holding of the product. The production formula facsimile, when filled out by production personnel during manufacturing, becomes the batch manufacturing record, and must include the names of individuals performing and verifying key steps and the dates those steps were performed.

The record should include:

- Identification of raw materials or intermediate lots used
- Identification of major pieces of equipment
- Weights and measures taken
- Relevant in-process or laboratory test results
- Yield and reconciliation calculations
- Labeling specimens or copies
- Container/closure description
- Record of any sampling performed
- Description of any investigations undertaken related to the batch manufacture

Some organizations prefer simple, minimalist production records that are largely table-based, where the operators fill in blanks with required information; in this style of record, the majority of instructional text is contained in separate SOPs or records. Alternately, one may opt for a more comprehensive and detailed set of instructions within the master production formula, with only limited reference to external SOPs. The latter style of record is the author's preference because the textual instruction can be clearly laid out in a more readily accessible, stepwise manner. In a relatively stressful work environment, if one has to access a separate SOP manual to perform every step for details, there is a chance that a step that will be incorrectly followed when the manual is not open. In the author's experience

with regulatory inspections and audits, this latter format has been much better received by investigating or auditing personnel, perhaps in part because the format provides a convenient, stand-alone document that can more easily be followed and understood by persons not familiar with the operation or process.

A few odds and ends are worth noting when discussing production records. A small but potentially very important detail is the use of indelible ink in production (or laboratory) environment. While not likely to save a record from a strong acid spill, a good, indelible ink can mean the difference between saving and discarding a batch of product in the event of a liquid spill on the bench top. Some companies identify only certain pens that may be used in the manufacturing suite. At the other extreme, some organizations, particularly those operating under an ERP program may use batch records that are entirely electronic, where operators use a computer interface or automated/networked production equipment to generate the batch production record. Such systems must be carefully selected, specified, and appropriately validated to comply with any applicable electronic records regulations.

Laboratory Records

As in the manufacturing environment, the testing laboratory must also keep records in accordance with the cGMP requirements of the target market. These may be written records or, in the case of larger organizations, computer-based via the use of an enterprise laboratory information management system (LIMS) for managing data, inventory, and user permissions. Typically, laboratory records should specifically include the following:

- Description of sample tested
- Test method used
- Statement of the weight or measure of the sample tested
- Record of all data collected
- Calculations performed
- Statement of test results, including comparison to know standard or specification
- Initials or signature of the analyst and a second qualified individual who reviewed the testing

Other Records

Distribution records are also a critical cGMP requirement. It goes without saying that recalling a problem batch from the marketplace would be next to impossible without a record of where the batch was distributed and sold to consumers.

Change Control

As processes and test methods are used, there is often learning and discovery of alternate techniques which may improve accuracy or efficiency. While it is understood that consistency is the beneficial byproduct of having written procedures and master production formulas, it is also understood that written procedures must evolve and improve, or be corrected if they contain errors. Nevertheless, such change must be

carefully managed to ensure minimization of unforeseen negative impact. Change control is therefore another essential element of GMP and by extension, product and process development during the scale-up to the pilot plant. The broader term "change management" is often applied, in a pharmaceutical manufacturing setting, in a more global sense, to refer to a higher level set of processes intended to capture and effectively manage the more detailed, lower-level "change control." For example, a new product being introduced to the pilot plant may require wholesale changes to an established set of SOPs, which, in accordance with cGMPs requires written justification of change. A change management policy or process enables strategic-level tracking of the overall process, while change control ensures each individual change is adequately documented, justified, and approved.

Record Retention

A brief mention of record retention is warranted, as it is an essential element of cGMP record-keeping, particularly with regard to pharmaceutical products. Specific requirements vary across markets, but general principles typically involve retaining production, control, labeling, and distribution records for a prescribed number of years following expiry or distribution of the batch in question. Some organizations may wish to adopt internal policies specifying longer periods; however, one must be aware of the possible pitfalls of keeping information for longer than the legally mandated period. These include storage cost as well as potential for legal discovery during, for example, patent litigation with a competitor.

Electronic Records

More and more organizations are moving to electronic document management and storage systems. In the pharmaceutical industry, such systems are subject to specific regulatory requirements centering on validation and security issues. For example, 21 CFR Part 11 Electronic Records, Electronic Signatures, outlines the requirements for industry to follow in order for the FDA to consider valid the use of electronic records and signatures. Electronic records meeting the requirements of 21 CFR Part 11 may be legally used in place of paper records. Although it is more common to find electronic records in use by larger organizations and more frequently in commercial manufacturing settings, pilot plants and R&D groups can benefit from the convenience and efficiencies afforded by automation in document and record handling, especially considering the speed and leanness with which R&D operations are expected to operate in our highly competitive industries.

Scale-up Principles

When to Scale-up?

A key question the engineer or scientist will face is when to scale-up a product. Scale-up is largely an issue of economics. A Target Product Profile should include a marketing profile and forecast. Strategic planning within the organization should include an assessment of the forecast against current and projected line capacities

within the commercial plant. The final anticipated commercial scale can be a useful starting point in planning a scale-up strategy. If a pilot plant with multiple mixers of various sizes is available, there is the option of choosing a scale that will minimize risk when scaling up to the commercial line. In the pharmaceutical industry, regulatory guidance and expectation generally limits scale-up to 10x or less when expanding from pilot to commercial scale, and this magnitude is a useful rule of thumb. The greater the magnitude of increase in scale, the greater the likelihood one will encounter unanticipated challenges.

Common problems of overreaching scale changes for topical formulations include: inadequate mixing; too extensive mixing, i.e., shearing that may be damaging to polymer components or chemical bonding that is required for stability; non-homogeneity; and equipment failure. An example of the latter might include discovering the commercial-scale mixer lacks the capacity to cool and lubricate its shaft seals, resulting in mechanical failure. Formulations that tend to push equipment to the limits of their design capability, such as highly viscous creams or gels, are likely to pose the highest risk to successful scale-up.

Key considerations that play into the decision to scale-up to the pilot plant include:

- Overall risk tolerance: "speed to market"; what is the timeline in your business plan that requires you to commercialize? An organization may be willing to accelerate the scale-up timing at increased technical risk if business needs and outcomes justify it.
- How well-characterized is the formulation? Is the formulation stable and compatible?
- Pilot plant work load and project prioritization.

Ultimately the decision of when to scale-up should be approached as a risk management exercise. All relevant factors need be weighed, with consideration to probability of success alongside the costs of failure, keeping in mind the fact that premature scale-up, or scale-up without a QbD paradigm, may often result in longer product development timelines with significantly increased cost, as well as potential post-commercialization problems.

Prior Body of Knowledge

One needs to start somewhere when planning an increase in scale for a topical product. For a mature organization, this starting point is quite understandably the knowledge gained from past, similar products, scaled-up on the same or similar equipment. Prior knowledge provides a baseline from which the process engineer can approach theoretical scale-up calculations as well as adhering to a systematic QbD approach to developing a scale-up manufacturing process. Prior knowledge will typically include a rough estimate of an anticipated process design space, based on knowledge of equipment capabilities as well as process parameter ranges that proved successful with similar products.

An existing prior body of knowledge is not of itself a fail-safe and fully contained

approach to scale-up; it should only be viewed as a starting point which must be appropriately challenged experimentally to demonstrate success. It is, however, very useful in the risk assessment process which will be discussed, in terms of guiding the experimental process in a focused and efficient manner.

If no prior body of knowledge exists, as in the case where the pilot plant is either new or being designed, or the product type is novel to the existing equipment, the equipment vendors themselves can provide an excellent resource to the scale-up engineer.

Theoretical and Empirical Concepts

The complexities involved in scaling up multiple unit operations in pharmaceutical or cosmetic product manufacturing remain challenging in terms of developing theoretical models that can be reliably and simply applied. For topical products, the mixing step is, in most cases, by far the most difficult and challenging unit operation to scale-up, and accordingly receives the most attention in the literature. Filling and packaging operations are much more easily scaled up by means of introducing replicates of existing systems at the current scale. Mixing will therefore be the focus of the discussion to follow. Given the many different types of mixers and products, there are far too many semi-theoretical and empirical models of scale-up to adequately cover them all in one chapter; instead, the following discussion touches upon the high level key concepts of common methods used to scale-up processes within impeller-type mixers and includes an example approach for a typical topical product. This chapter does not purport to comprehensively cover scale-up theory and empirical work, nor could it. The reader is encouraged to be mindful of the basic principles while consulting the available literature, which is quite extensive and can provide more detailed and application-specific relationships based on the type of equipment and formulation at hand.

Theoretical concepts are also somewhat limited by the fact that pilot plant equipment is rarely specified and purchased with the intent to be dedicated to a single product or even class of product; more probable is the engineer finding him- or herself faced with adapting existing pilot plant equipment to the introduction and scale-up of new products and formulations which may be completely different than those conceptualized when originally selecting the pilot plant equipment.

Mixing

The two most common and effective approaches to scaling up mixing in geometrically similar impeller-type mixers are generally acknowledged to be:

- Equal impeller tip speed
- Equal power per unit volume[9]

In a majority of situations, there is no well-established, comprehensive body of theory that can tell the engineer how to properly scale a mixing process. Rather, there exist a set of principles and models which can to some degree inject a level of science and rationality into the approach. This scientific approach most often derives from

and is simplified by the principles of *dimensional analysis* and *similarity*. Michael Levin defines dimensional analysis as "a proven method of developing functional relationships that describe any given process in a dimensionless form to facilitate modeling and scale-up or scale-down."[10] Dimensional analysis represents an approach partly theoretical and partly empirical which provides the engineer with a means of bridging the gap between purely theoretical concepts that are difficult to apply, and a simple trial-and-error approach to scale-up.

Michael Levin's (ed.) useful textbook on theoretical aspects of pharmaceutical scale-up provides a very detailed discussion of the use of dimensionless numbers and principles of similarity to aid in scale-up calculations. This work, *Pharmaceutical Process Scale-Up* (Marcel Dekker, 2001), includes an excellent chapter on non-parenteral liquids and semisolids, by Lawrence H. Block. Dr. Block's discussion highlights what are known as principles of similarity, when scaling up a process and applying dimensionless number theory to these principles to achieve scale-up success. Principles of similarity include: *geometric similarity, mechanical similarity, thermal similarity, and chemical similarity.*[10] Principles of geometric similarity are often used as the primary means of simplifying scale-up of a mixing operation. Geometric similarity can be characterized between scales through the use of dimensional analysis methods. Dimensional analysis, used throughout the various engineering disciplines, as noted by Zlokarnik in Levin, is based on the principle or recognition that a mathematical characterization of a "physicotechnological problem can be of general validity only when the process equation is *dimensionally homogenous*, which means that it must be valid in any system of dimensions."[11] Zlokarnik also astutely notes one of the major challenges facing the process engineer working on a scale-up problem: that there is little to no research in universities on applying dimensional analysis techniques to the problems of scale-up because there is little motivation for academic entities to do so, for reasons of both not having to face industrial challenges of scale-up while also lacking the relatively large-scale equipment necessary to do the work.[11] The use of dimensionless numbers to simplify engineering problems has been around for many years and was first applied a century ago by Lord Rayleigh to problems involving fluid mechanics . Dimensional analysis is a method for reducing the number of variables involved in a physical problem using a simplification technique. This technique distills a problem down from n dimensional variables to k dimensionless variables in the following relationship: $n - k = i$, where i is the number of primary or fundamental dimensions governing the phenomenon of interest. Typically, in fluid mechanics and mixing, the fundamental dimensions are taken to be mass M, length L, Time T, and temperature Θ.[12]The above relationship derives from the Buckingham pi theorem; in mathematics the notation Π denotes a product of variables; or more specifically in this case the dimensionless groups used to simplify complex relationships.[12]

Mixing Scale-up: Dimensional Analysis

Scale-up theory aims to express the process as a set of dimensionless numbers

which provide a means of comparative characterization of processes across scales. In so doing, process similarity is maintained across scales due to the dimensionless nature of the relationship. The three most important dimensionless numbers in fluid and semisolid mixing are the Power (or Newton) number (Po), Reynolds number (Re), and Froude number (Fr). These numbers have been derived using traditional dimensional analysis techniques and detailed background can be found in most fluid mechanics textbooks. The Power number characterizes inertial and resistance forces. The Reynolds number is an indication of the fluid's viscous behavior, and the Froude number relates to surface vortexing.

$$Po = \frac{P}{\rho N^3 D^5} \qquad (1)$$

$$Re = \frac{\rho N D^2}{\mu} \qquad (2)$$

$$Fr = \frac{N^2 D}{g} \qquad (3)$$

Where: P = impeller power requirement, N = impeller rotational speed, r = density of liquid, μ= viscosity of liquid, D = impeller diameter.

Edwards and Baker in Harnby et al. provide a useful discussion of how dimensional analysis can be employed to aid in determining a mixer impeller power requirement across scales.[13] In the case of a Newtonian liquid, or, in other words, a liquid where apparent viscosity is independent of shear rate, it is known that the power requirement of the impeller is a function of the following independent variables:

$$P = fn(r,m,N,g,D,T,W,H, \text{ other dimensions}) \qquad (4)$$

W, in this case is the height of the impeller blade (propeller type blade) and H is the height of the fluid in the tank.

Edwards and Baker use dimensional analysis to reduce equation (3) to the following dimensionless relationship:

$$\frac{P}{\rho N^3 D^5} = fn\left\{\frac{\rho N D^2}{\mu}, \frac{N^2 D}{g}, \frac{T}{D}, \frac{W}{D}, \frac{H}{D}, etc.\right\} \qquad (5)$$

Or, using dimensionless notation:

$$Po = fn\left\{Re,\ Fr, \frac{T}{D}, \frac{W}{D}, \frac{H}{D}, etc.\right\} \qquad (6)$$

Further, these two authors note that the Froude number dependence can be neglected when the Reynolds number is less than 300 (Skelland, 1967). Additionally, Froude number effects can be minimized through the use of baffles or off-center stirring.[13]

Estimating the power requirement for a scaled-up process on geometrically similar equipment then reduces to this greatly simplified relationship, known as the power curve for a given type of impeller system:

$$Po = fn\{Re\} \qquad (7)$$

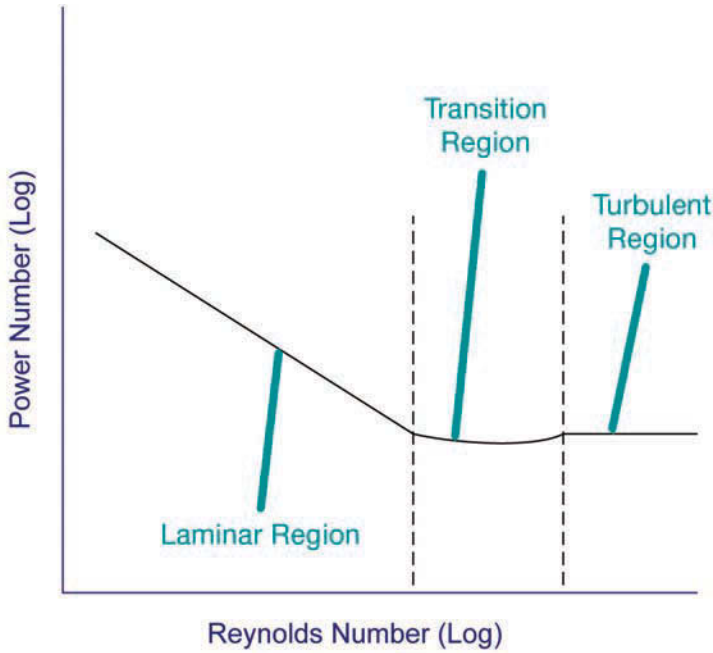


Figure 1. shows the general shape of a mixer power curve, on log-log coordinates.

More precise relationships between power requirement and Reynolds number can then be empirically determined for a given mixer geometry and impeller type using varying conditions of rotational speed and fluid physical properties.

Laminar vs. Turbulent Conditions

The dimensionless Reynolds number has long been used in fluid mechanics to characterize flow conditions as either laminar, turbulent, or in transition between the two. Flow conditions have implications in both impeller power consumption as well as mixing efficiency. For highly viscous liquids, mixing typically occurs under laminar conditions, such as with a slower moving anchor and/or helical ribbon impeller.

In the laminar or low Reynolds number region (typically Re < 100, depending on impeller geometry), viscous forces are predominant and the relationship is linear; once turbulent conditions are reached at higher Reynolds numbers (Re > 10^4) the power requirement becomes constant and independent of Reynolds number. Once established, perhaps at a laboratory scale at lower cost, this relationship can be of use in sizing larger-scale equipment for the pilot plant.

In the transition region between laminar and turbulent flow, the Power number cannot reliably be correlated to Reynolds number.

Example: Scaling up a Gel

Consider the example of a topical pain treatment gel that needs to be scaled up to the pilot plant mixer. The gel is a Newtonian liquid. The laboratory mixer is 1 gal in volume and the existing pilot plant mixer is 10 gal in volume, a typical difference in scale. Let's assume both mixers are geometrically similar and are of similar type: a traditional single blade impeller. We'll approach the problem using both scale-up techniques: (1) matching power per unit volume and (2) matching blade tip speed. A schematic of the mixer is shown in **Figure 2**.

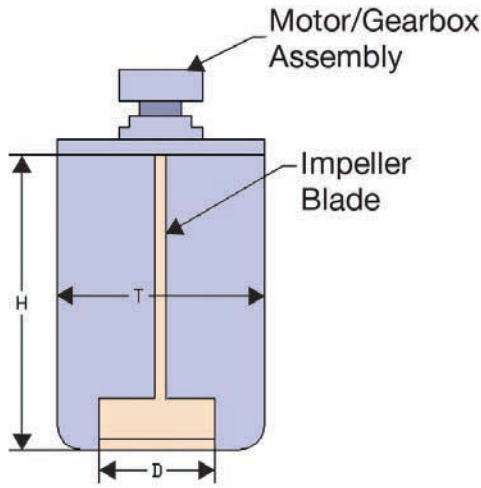


Figure 2. Mixer Schematic

Equal Power per Unit Volume:

In assessing power per unit volume, it has been demonstrated in the laminar flow regime that the agitator power input to the mixed fluid in a tank can be calculated using the following relationship between the Power and Reynolds numbers:

$$PoRe = A \tag{8}$$

Where A, the laminar energy constant, depends only on agitator type and vessel geometry.[14] Using the definitions for the two dimensionless parameters, Power input to the agitator can be expressed as:

$$P = \rho N^3 D^5 \left(\frac{\mu A}{\rho N D^2} \right) \quad (9)$$

Here: P = power input, Po = Power number, N = rotational speed, rev/sec, D = impeller anchor blade diameter, ρ = Fluid density. For a cylindrical, flat-bottomed mixer of diameter T and height H, power per unit volume can be expressed as:

$$\frac{P}{V} = \rho N^3 D^5 \left(\frac{\mu A}{\rho N D^2} \right) \left(\frac{4}{\pi T^2 H} \right) = A \frac{4\mu}{\pi} \left(\frac{D}{H} \right) \left(\frac{D}{T} \right)^2 N^2 \quad (10)$$

For geometrically similar mixers, the two geometric ratios (D/H) and (D/T) are essentially equal. Keeping power per unit volume the same for the 1 gal mixer and the 10 gal mixer therefore means:

$$\frac{\frac{P_{10}}{V_{10}}}{\frac{P_1}{V_1}} = 1 = \left(\frac{N_{10}}{N_1} \right)^2 \quad (11)$$

For the ratio to be unity, N must be constant across scales, in the laminar regime. In other words, to keep constant agitator power across scales in laminar flow conditions, the rotational speed must be constant.

In the case of turbulent flow, eq. (7) no longer holds, as the Power number is constant; in this case the rule of scale, which can be derived in a similar manner, is: $ND^{2/3}$ is kept constant.[14]

Equal Tip Speed:

Matching blade tip speed can be of critical importance in applications where the formulation is subject to permanent damage from high shear, such as biologic products and some polymer-based formulations. For testing sensitivity to shear such as in a case of a topical gel, one needs to ensure that at the 10 gal scale the formulation is not exposed to a higher level of shear than was used at the 1 gal scale. Shear is greatest at the liquid-solid interface where blade velocity is highest. The tip velocity of an impeller blade of diameter D, rotating at N rpm, can be calculated as follows:

$$v = 2\pi N — = \pi N D \quad (12)$$

If we choose to keep the blade tip speed across the two scales:

$$\frac{v_{10}}{v_{10}} = \frac{N_{10} D_{10}}{N_1 D_1} = 1 \quad (13)$$

Or:

$$N_{10} = N_1 \frac{D_1}{D_{10}} \quad (14)$$

Rotational speed of the impeller scales linearly as a function of ratio of impeller diameters. At times, one finds matching tip speed during scale-up may result in an operating condition at the larger scale that uses only a small fraction of the mixer capability. In such cases, it may be worth experimentally determining whether a faster blade tip speed can be safely used, in order to take advantage of equipment capability to keep the mixing process as efficient and short as possible.

Mixing Time

Mixing time is generally defined as the time required to achieve a predetermined level of uniformity throughout the vessel. Mixing time can be empirically determined by the use of tracer compounds in the mixer whose concentrations can be measured over time at discreet locations within the mix. From the above relationships (10) through (12) it can be shown that the power per unit volume is proportional to fluid velocity, as represented by tip speed, squared. If P/V is kept constant while scaling-up, the fluid velocity remains constant while the flow path increases with increasing mixer size. As a result, keeping mix time constant across an increase in scale can require massive and impractical increases in impeller power. Therefore, if the principle of keeping P/V constant is applied during scale-up, an increase in mixing time should be expected; however, in cases where the larger-scale mixer has greater power per unit volume output than the smaller mixer, mixing time may be shortened as long as no other deleterious effects are expected, such as unacceptable heat transfer, thermal degradation, or shear damage.

For Newtonian fluids in geometrically similar systems, a dimensionless mixing time has been shown to be a function only of Reynolds number: [13]

$$Nt_m = fn(Re) \qquad (15)$$

Specific empirical relationships between dimensionless mixing time and Reynolds number can be found in the literature and vary according to vessel geometry and impeller type.

Newtonian vs. Non-Newtonian Fluids

A non-Newtonian fluid is defined as a fluid in which the apparent viscosity varies according to shear rate, either decreasing (shear-thinning) or increasing (shear-thickening). Examples encompass many topical formulations including many carbomer-based gels, pastes, creams, and ointments. The majority of the literature on mixing scale-up is focused on Newtonian fluids. Wilkens et al. propose a useful scale-up algorithm the engineer can employ when scaling up a non-Newtonian fluid.[15] This approach recommends using constant P/V as a scale-up principle for the case of non-Newtonian fluids when no other principle is obvious. For more comprehensive knowledge about system's rheology please refer to Hemi Nae's chapter on rheology.

Particle Size Reduction

Emulsion behavior in mixing is often characterized by the dimensionless Weber number:[11]

$$We = \frac{\rho v^2 d_0}{\sigma} \qquad (16)$$

Where the density of the suspended phase droplet is, is its relative viscosity, is its diameter, and is the interfacial tension between phases. The Weber number can be thought of as a ratio of the forces disrupting the drop to the forces maintaining it. Above a critical value of Weber number, drop disruption occurs and smaller droplets result. Homogenization refers to the sub-category of liquid mixing in which the dispersed droplets of one phase are reduced in size through the use of impellers which are capable of maximizing drop disruption forces. Emulsification can be achieved by a number of different impeller designs, including rotor-stators, high-speed dispersers, colloid mills, high-pressure homogenizers, ultrasonic disruptors, and membrane homogenizers.[16]

The Weber number can also be expressed in terms including mixer parameters, in what is sometimes called the agitation Weber number, as noted by Levin:

$$We_a = \frac{\rho_c D_i^3 v^2 N^2}{\sigma} \qquad (17)$$

In this case, is the continuous phase density, is the impeller diameter, N is the impeller rotational speed. The tendency of a drop of the dispersed phase to break apart is a function of the pressure across it relative to the interfacial forces holding it together. The forces applied to the droplet can be related to the energy dissipation in the turbulent region of the mixed fluid. Peters notes this relationship can then be expressed in a dimensionless manner as follows:[17]

$$\frac{d_{32}}{D} = CPo^{-0.4} We_a^{-0.6} \qquad (18)$$

Here d_{32} is the Sauter mean drop diameter. The scale-up of systems processing emulsions to the pilot plant can proceed using the usual principles, with appropriate attention given to the Newtonian or non-Newtonian nature of the formulation and selection of a homogenizing device that maximizes droplet reduction efficiency. Emulsification can be sensitive to numerous parameters, including temperature, visco-elastic properties of the phases, the type and concentration of the emulsifier, and the physical introduction point of the second phase. Peters suggests an approach for non-Newtonian emulsions based upon consideration of the process as a series of discreet steps between which the rheological properties can vary significantly, with the idea of selecting which scale-up parameter is best kept constant for each step. The fundamental scale-up equation takes the form:

$$N_2 = N_1 \left(\frac{D_1}{D_2}\right)^x \qquad (19)$$

Where x is dependent on the scale-up parameter selected to remain constant. For example, x = 1 for maintenance of constant tip speed; desirable towards the end of a typical oil-in-water emulsification process as the fluid increases in viscosity and becomes more shear-thinning.[17]

Non-geometrically Similar Systems

In cases where geometric similarity is not an option, such as when pilot plant and laboratory scale equipment are already in place and not geometrically similar, a non-geometric scale-up approach such as the one advocated by Dickey can be effective in achieving successful mixing scale-up. Dickey outlines a systematic algorithm for approaching non-geometrically similar scale-up by conducting a stepwise calculation of key mixing variables such as tip speed, power per unit volume, Reynolds and Power numbers for the larger-scale mixer based initially on geometric similarity and selection of the scale-up parameter to keep constant (e.g., tip speed). Then, the same key mixing parameters can be re-calculated incrementally based on step-wise changes to the mixer such as increased impeller diameter or type, volume, etc. Each important variable is re-calculated and assessed with each incremental change, and parameters within the engineer's control, such as impeller diameter and rotational speed, can be adjusted as needed to maintain the desired scale-up principle.[9]

Summary of Scale-up Principles

Table 1, adapted from Peters, summarizes the key scale-up approaches as a function of impeller speed and diameter and depending on which parameter is desired as constant for the increase in scale. As noted above, the two most used principles involve maintenance of equal power per unit volume and equal blade tip speed.[17]

Table 1. Summary of Mixing Scale-up Principles

Parameter	Function	Scale-up Equation	Exponent x
Blend Time	$\frac{1}{N}$	$N_2 = N_1$	$x = 0$
Froude No.	$\frac{N^2D}{g}$	$N_2 = N_1\left(\frac{D_1}{D_2}\right)^{\frac{1}{2}}$	$x = 1/2$
Power/Volume	$\frac{N^3D^5}{D^3}$	$N_2 = N_1\left(\frac{D_1}{D_2}\right)^{\frac{2}{3}}$	$x = 2/3$
Solids Suspension	ND	$N_2 = N_1\left(\frac{D_1}{D_2}\right)^{\frac{3}{4}}$	$x = 3/4$
Tip Speed	$ND^{\frac{3}{4}}$	$N_2 = N_1\left(\frac{D_1}{D_2}\right)$	$x = 1$
Weber No.	$\frac{N^2D^3\rho}{\sigma}$	$N_2 = N_1\left(\frac{D_1}{D_2}\right)^{\frac{3}{2}}$	$x = 3/2$
Reynolds No.	$\frac{ND^3\rho}{\mu}$	$N_2 = N_1\left(\frac{D_1}{D_2}\right)^{2}$	$x = 2$
Pumping No.	$\frac{Q}{ND^3}$	$N_2 = N_1\left(\frac{D_1}{D_2}\right)^{3}$	$x = 3$

Source: Adapted from Reference 17, pp 318.

Quality by Design Principles

QbD Overview

Quality by Design (QbD) is defined as a systematic approach to process development which starts with a set of predetermined objectives (Quality Target Product Profile, or QTPP) and emphasizes product and process understanding as well as process control, based on good science and appropriate risk management.[18] QbD is scientifically based and incorporates risk management to enable optimum time and resource allocation to product development and scale-up. Although not the subject of this chapter, QbD can be applied not only to new products, but to existing products as part of a continuous improvement program. ***A QbD approach is an essential complement to theoretical or semi-theoretical approaches to scale-up, because it focuses efforts and outcomes, providing the process engineer with not only a framework in which to operate but a means by which successful application of scale-up models can be measured***. Application of a scale-up model without elements of QbD has the potential to be aimless and inefficient.

In short, QbD represents a paradigm shift in the pharmaceutical and cosmetic industries—from the approach of testing quality into a product, to a new concept of designing quality into both the formulation and manufacturing process *a priori*. The current approach of limited characterization, lack of understanding around CPPs, and conservative specification settings have resulted in an inefficient cycle of cautious product review on the part of regulatory professionals and significant industry resources wasted on trouble-shooting post-commercialization product and process issues. QbD necessarily encompasses formulation activities; however, as this chapter is concerned with scale-up, it will be assumed our formulation is essentially established, and will instead focus on the process aspects of QbD.

For purposes of illustration, this section will reference a simulated product for scaling up to pilot plant manufacture: a topically applied hydro-alcoholic gel for local pain, provided in a metered-dose pump. This product may have more complexities than the typical topical product (i.e., using a simple squeeze tube rather than metered-dose pump) but for purposes of the exercise, elements from several product types are deliberately discussed in order to provide more detailed analysis.

Product development in the topical pharmaceutical and/or cosmetic world is driven, typically top-down, by any of several triggers. These can be driven by the business development function, either by identifying an unmet therapeutic or marketing opportunity leading to indigenous development, or by a licensing opportunity that gives rise to a need to transfer established bench-top technology into a pilot plant setting, as two examples. In either case, the defining document for any new product is known as the Target Product Profile, or TPP. The overall cycle of product development, from identification of a TPP to the application of QbD as a product and process are developed and scaled-up, is illustrated in **Figure 3**. This illustration shows how QbD principles and scale-up are inextricably linked, making it impossible to discuss one without the other. Other key elements of QbD include

risk management, design space determination, and the development of a suitable process control strategy. The scale-up engineer or scientist should begin to address these factors as part of pilot plant scale-up and a discussion of findings ought to be an element of the tech transfer package. This will create a better defined path for the commercial support engineers.

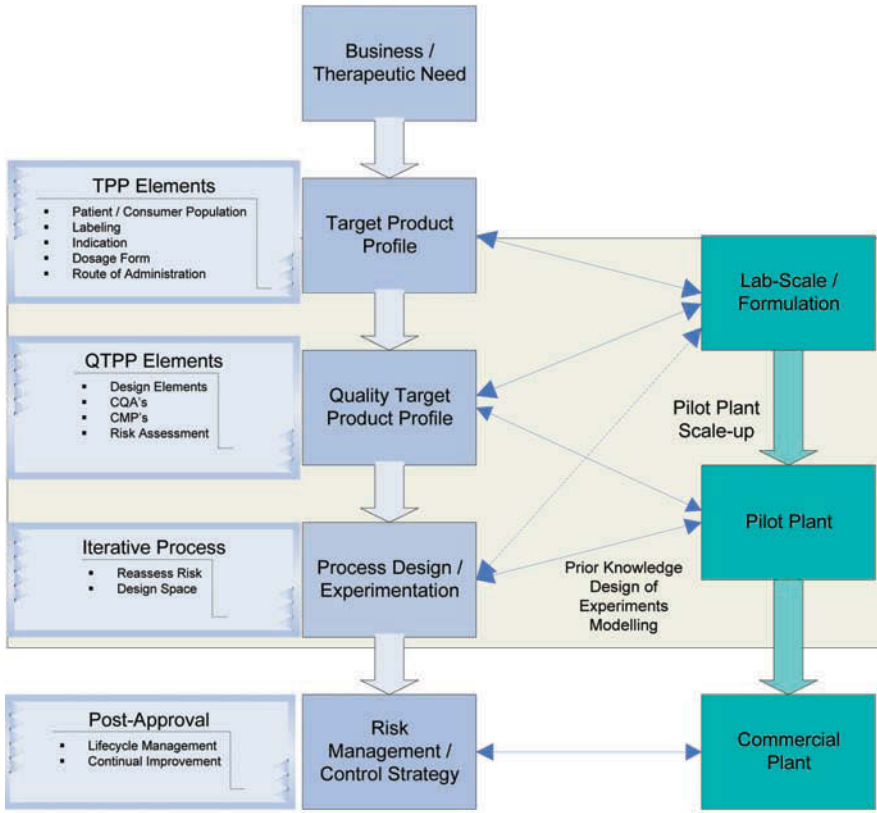


Figure 3. Pilot Plant Scale-up and Quality by Design

Target Product Profile

No universally accepted definition of a TPP exists; the FDA's recently issued draft *Guidance for Industry and Review Staff: Target Product Profile — A Strategic Development Process Tool* defines the TPP loosely as "a format for a summary of a drug development program described in terms of labeling concepts."[19] Others have defined the TPP as "defining the use, safety, and efficacy of the product."[20] The importance of a TPP to scale-up, whether for a drug product or cosmetic product,

comes from its importance as a foundational reference for the desired product characteristics, which in turn determine critical quality attributes necessary to establish those characteristics. The TPP is generally viewed as a dynamic, living document that may evolve through the course of product development.

Often, a more focused and quantitative Quality Target Product Profile (QTPP) is developed as a bridge between the broad-based TPP and wheels-on-the-ground process and product development activities, such as identifying critical quality attributes and the critical process parameters which affect them. The QTPP may include attributes that are not tested in the analytical laboratory, such as bioequivalence, as an example for a topical generic drug product. Lionberger et al. note: "It is the role of a pharmaceutical scientist to translate the qualitative TPP into what we define as the target product quality profile for further use in a quality by design exercise."[20]

As a working example, the case of a topically administered gel for treatment of local pain is considered in the sections that follow. **Table 2** shows key linkages between TPP elements and product requirements comprising a QTPP, for our example product. As a TPP is a strategic document, it will contain elements not directly relevant to process characterization and scale-up; only those elements which directly drive the quality profile of the product are considered here. The TPP described in this example is significantly simplified for purposes of this exercise and may also include additional characteristics such as warnings and precautions, contraindications, adverse reactions, usage in specific population, and others.[19]

The QTPP comprises an overall product quality/performance framework which must be attained and ensured by the identification of appropriate Critical Quality Attributes. During the formulation stage, the Critical Quality Attributes (CQAs), once determined, will drive the identification of critical process parameters to experimentally challenge during process characterization and scale-up to the pilot plant.

Table 2. Example Target Product Profile: Topical Pain Treatment Gel in Metered-Dose Pump

Desired Attribute / Label Element (TPP)	Product Requirement (QTPP Element)	Target	Justification
Indication and Usage: Local pain Relief; applied once/ daily	Active or Functional Ingredient	API for Pain Relief	Needed for effective product
Efficacy: Provides local pain relief	Dosage Strength (Potency); Adequate Delivery	10%	Demonstrated effective in clinical trials
Dosage Form: Suitable for relief of local pain	Dosage Form	Hydroalcoholic Gel	Proven effective dosage form; convenient and protective container-closure
Route of Administration: Effective in treating local pain	Route of Administration	Topical	Safest and most effective route for treating local pain
Aesthetics: Consumer acceptance	Pleasing Appearance and Feel	Clear, colorless, free of visible contamination	Indication of purity, safety, and pleasantness of use
Shelf Life	Stable Product	2-year Expiry	Consumer acceptance, business need, industry standard
How Supplied	Container/ Closure (CC) System	Suitable CC to provide protection, shelf-life and # of doses	Metered-dose pump with multiple-dose supply
Acceptable Quality and Safety Profile	Quality Attributes	Various (see Table 3)	Meet required standards for identity, strength, purity, quality

Critical Quality Attributes

Critical quality attributes (CQAs) are defined as quality attributes for which deviations from established limits may result in a significantly decreased assurance of quality, safety, and/or efficacy of the resulting topical product.[21] CQAs must be clinically important and should exclude irrelevant attributes. In developing a list

of CQAs, one should consider the severity of impact to the end user while factoring in any uncertainty.

For the working example of the topical pain treatment product, to illustrate, viscosity has been identified as a CQA during lab-scale formulation. During formulation activities two aspects were analyzed and revealed: (1) consumer focus groups evaluating the product prototype may have found a particular viscosity to be more aesthetically pleasing in terms of feel and ease of application, and (2) early trials with the metered-dose pump determined a product over a certain viscosity would prevent the pump from achieving prime and dispensing product.

Further, process inputs such as machine parameters and raw material attributes which affect CQAs can be assigned a relative measure of significance as part of process and product risk assessment during scale-up, which will in turn guide the resource expenditure during process characterization and experimentation. Table 3 provides an illustration of how QTPP elements tie into CQAs, along with an example specification. Having some idea up front of the desired specification for a CQA provides a target framework when beginning process characterization at the pilot plant scale and, ultimately, the development of a design space that can be beneficial to additional increases in scale and/or commercialization. In fact, as the pharmaceutical industry is increasingly adopting a QbD approach to product development, defining the design space at the pilot scale is likely to become more common. CQAs may be identified for drug substances, process intermediates, as well as finished products. For purposes of this working example, the focus will be on the finished product.

A helpful discussion of quality attributes for topical products can be found in the recently published General Chapter of the United States Pharmacopeia, *USP <3>, Topical and Transdermal Drug Products – Product Quality Tests*. This recent USP chapter distinguishes between attributes which affect product quality and those which affect performance; specifically, the following attributes are noted as potentially affecting product quality: "description, identification, assay, impurities, physicochemical properties, uniformity of dosage units, water content, pH, apparent viscosity, microbial limits, antimicrobial preservative content, antioxidant content, sterility," as well as others that may be unique to the specific product.[22]

Drug release is noted as a performance attribute; however, for purposes of most QbD discussions, CQAs are inclusive of attributes which affect performance.

Table 3. Topical Pain Treatment Gel in Metered-Dose Pump: Example Quality Target Product Profile vs. Critical Quality Attributes

QTPP Element	Critical Quality Attribute	Specification
Appearance and Feel	Appearance	Clear, Colorless Gel, Free of Visible Contaminants
Quality Attributes (Safety)	Identity	Matches Standard
	Assay	90–110% of Label Claim
	Impurities & Degradation Products (Purity)	Meets Required Limits
	Drug Release	Meets Requirements
	Microbial Enumeration	Meets Requirements
Stable Product	Impurities & Degradation Products (Purity)	Meets Required Limits
Appearance and Feel	Viscosity	1,000–10,000 cP
	pH	5.0–7.0
Potency/Efficacy	Assay	90–110 % of Label Claim
	Drug Release	Meets Requirements
	Delivered-Dose Uniformity	Meets Requirements
	Uniformity of Dosage Units	Meets Requirements
	Homogeneity	Meets Requirements
Container / Closure	Ethanol Content	90–110 % of Label Claim
	Weight Loss	Not More Than 5%
	Minimum Fill Weight	Not Less Than 100% of Label Claim

Critical Process Parameters

Once a QTPP and CQA profile is developed, the engineer or scientist can begin to assess what process parameters may be acute in terms of affecting critical quality attributes. Critical process parameters (CPPs) are the key process inputs which affect the important outputs as defined by critical quality attributes of the product. Process mapping can be a valuable tool in the initial identification of possible CPPs and assessing their relative risk to overall product quality.

Risk Assessment

Risk assessment is an essential element of an integrated QbD approach to process design and scale-up. International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline Q8 (R2) emphasizes that risk assessment provides a key link between process inputs, such as raw material attributes, formulation characteristics, and manufacturing

process parameters to process outputs of interest, notably the CQAs identified for the product. Risk assessment can provide the scale-up engineer with added product and process knowledge by conveying an analysis-based snapshot of the expected magnitude of impact for each CPP on the accordant CQAs, and in turn guide the experimental design approach. In other words, the output of the risk assessment exercise can be used to develop an experimentation strategy, including consideration of techniques that are most appropriate for each parameter. ICH Q9 guidance, Quality Risk Management, provides a useful overview of how risk assessment can be implemented as part of QbD-based product development and scale-up effort for pharmaceutical and cosmetic products. The main elements of risk management are: risk identification, risk analysis, risk evaluation, and risk control.[23] Performing risk assessment early in development is highly recommended. Recognizing that the risk assessment process should be applied broadly, to include both raw material attributes and formulation characteristics, the focus in this chapter's example is on the manufacturing process which is to be developed as part of the scale-up effort. It's worth emphasizing that regulatory authorities look favorably on risk assessment as an indicator that the product development and scale-up process have been thoroughly examined from a "bird's eye" view.

Process Mapping

The first step in risk assessment is mapping the process and breaking up the overall process into smaller, more manageable focus areas. For each area, process inputs parameters (critical and non-critical) as well as quality attributes are identified and listed. For each unit operation, Lionberger et al. define four categories of parameters and attributes:[20]

- Input material attributes
- Output material attributes
- Input operating parameters
- Output process state conditions

Further, Lionberger et al. propose three categories for parameters or attributes: unclassified, critical, and non-critical. Unclassified attributes remain so until experimentation determines they can be reclassified as either critical or non-critical.

For each focus area, a simple relative risk assessment exercise can be conducted in which each process parameter is ranked according to significance in terms of its effect on associated quality attribute(s). Prior experience and existing process knowledge are used to assign a numerical rating to each parameter. An alternate and more in-depth method of risk assessment, FMECA, is discussed in more detail in the section that follows. This risk assessment process will aid in the identification and classification of possible process inputs, including material attributes and process parameters, and it can be iterative—driving a cycle of experimentation and re-classification that will further refine product and process knowledge during scale-up.

Process mapping typically involves the creation of a graphical representation of

the significant steps in the process being scaled-up. **Figure 4** shows the example of the topical pain product process flow. Additionally, the process is generally broken into discreet focus areas, each of which can be the subject of targeted experimentation. For purposes of this working example, the raw materials/dispensing, mixing/vacuum step and the filling/capping steps are broken out as distinct focus areas.

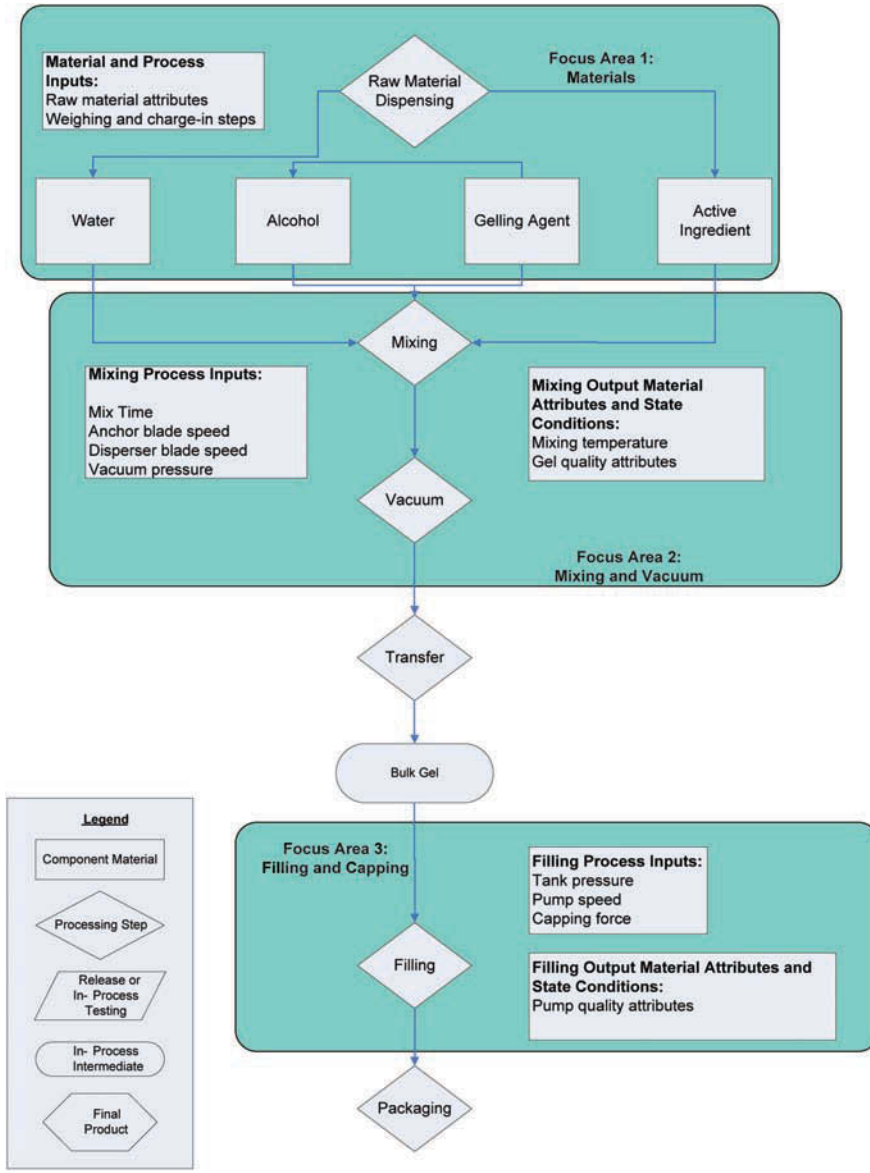


Figure 4. Topical Pain Gel in Metered-Dose Pump: Process Flow Chart with Focus Areas

Once the process has been mapped and subdivided into focus areas, which may be chosen to coincide with unit operations, each process input may be analyzed and given a score or qualitative rating (i.e., low, medium, or high) based on potential impact to the product or intermediate CQAs.

In this example, the process is considered as a relatively straightforward powder-in-liquid mixing operation using a multi-shaft mixer with a slow-moving anchor and high-speed disperser blade. The gel is then transferred to a pressure vessel and transferred to the filling operation. The second unit operation is a filling step involving pressurizing the gel vessel and pumping the gel using an electrically driven positive displacement pump. The gel is dispensed through a nozzle into each metered-dose pump container, at one pump per cycle.

For each area of focus, which in this example corresponds to the unit operation, process inputs, including any relevant raw material attributes or characteristics, as well as process parameters, are tabulated along with the CQAs they can potentially impact. **Table 4** illustrates this process for the working example. This example is somewhat simplified; all possible process inputs can be considered in this type of exercise. Focus area 1, raw material dispensing, accounts for raw material characteristics and how they may potentially impact final product quality attributes. As an example, consider the particle size of the active or functional ingredient. As part of the process mapping exercise and risk assessment process, particle size has been identified as a critical process (formulation) parameter. A large particle size distribution may present challenges in terms of solubilizing the component within the formulation. The resultant product may look and feel grainy, not to mention having the potential for bioavailability impairment due to un-dissolved active ingredient failing to penetrate the skin—a course that may lead to ineffectiveness.

Table 4. Topical Pain Gel in Metered-Dose Pump: Process Map

Focus Area	Unit Operation	Equipment	Process Inputs (all classes)	Response (Quality Attributes)
1	Raw Material Dispensing	Scales Balances	Raw Material Attributes (e.g., particle size of active) Dispensed Qty	Assay Drug Release Ethanol Content pH Appearance
2	Mixing / Vacuum	High Shear Mixers	Anchor Blade Speed Disperser Blade Speed Mixing Time Mix Temperature Vacuum Pressure Transfer Pressure	Assay/Content Uniformity Drug Release Viscosity Ethanol Content Degradation Appearance Fill Weight
3	Filling	Pressure Vessel, Metering Pump, Filling Head, Capper	Pump Speed Tank Pressure Nozzle Diameter Nozzle Speed Capping Force	Assay/Content Uniformity Drug Release Fill Weight Appearance

The output of our risk assessment process for process inputs (of all classifications) in focus area 2 is summarized in **Table 5**. In this relative risk assessment technique, each process input associated with the mixing/vacuum unit operation is assessed for its potential impact on final product CQAs. Each parameter is assigned a rating of low, medium, or high, depending on its potential to affect each CQA; this rating should incorporate both severity of effect and probability of occurrence. A numerical rating system such as the one described in Table 4 can be used, which may then be translated into one of the three qualitative categories. How relative risk is assigned is a function of prior knowledge, mechanistic and/or empirical information. For example, prior knowledge in our case includes the awareness that mixing certain gelling agents at a high level of shear can cause viscosity breakdown; no new experimentation is needed to facilitate that basic risk assessment. However, that does not mean focused, specific experiments should not be undertaken to determine acceptable ranges for the disperser blade—they, in fact, should be performed. Similar risk assessments can be undertaken for the other focus areas of the process.

Some organizations are known to use a well-trained cadre of risk facilitators who may work across multiple products as well as bridge both R&D and commercial manufacturing areas. Such cross-pollination of technical information also ties into the efficiency with which prior knowledge is used across the organization.

Table 5. Topical Pain Treatment Gel in Metered-Dose Pump: Risk Assessment, Focus Area 2: Mixing / Vacuum

Process Parameter ->	Anchor Speed	Disperser Speed	Mixing Time	Mix Temperature	Vacuum Pressure	Transfer Pressure
Product CQA						
Assay	**High**	**High**	**High**	Medium	Low	Low
Content Uniformity	**High**	**High**	**High**	Medium	Low	Low
Viscosity	Medium	**High**	**High**	Low	Low	Low
Ethanol Content	Low	Low	Low	Medium	Low	Low
Degradation	Low	Low	Low	**High**	Low	Low
Appearance	Medium	Medium	Medium	Medium	**High**	Low
Fill Weight	Low	Low	Low	Low	**High**	Low

Relative risk ranking:

Low risk: no additional investigation needed.

Medium risk: additional investigation may be needed.

High risk: additional investigation needed.[24]

Anchor Speed

Anchor blade speed is a measure of the rpm's of the slow-moving anchor-shaped blade in our mixer, which provides bulk fluid circulation. If the bulk fluid is not well-circulated to allow frequent turnover of the well-mixed region near the higher-speed disperser blade, it is possible to have regions in our gel mix where the active or functional ingredient (or other ingredient) is either not dissolved or not fully dispersed throughout the mixer. The resultant outputs of assay (potency) and content uniformity of our final product can be adversely affected. Anchor blade speed was therefore classified as high risk and requiring further investigation. Due to the slow speed of the anchor, it is less likely than the disperser to cause damage to the polymer chains of any gelling agent; however, there is some uncertainty here, so a medium level of risk to viscosity should be assigned. Ethanol content is expected to be unaffected as well, as is degradation of the active ingredient. However, if one or more components do not get mixed well, it is possible the gel appearance could be affected; it is therefore assigned a medium-risk rating.

Disperser Speed

Similar to the anchor blade, the disperser blade speed represents the rotational speed of the smaller high-speed blade which provides a small region of high intensity mixing as well as axial motion of the fluid. Like the anchor blade, the disperser is known, from a mechanistic standpoint, to have an obvious effect on mixing of the

components, including the active (if present). Therefore both assay and content uniformity of the active are considered high risk. Additionally, the disperser has the potential to permanently shear-thin a gel containing a polymer-based gelling agent; therefore viscosity is tagged as high risk as well. The disperser blade speed is expected to have a similar effect as the anchor blade on the remaining three parameters.

Mixing Time

The duration of mixing is known to mechanistically affect several key parameters: assay and content uniformity of the active, as well as viscosity of the mixture/gel/product. Longer mixing time is expected to favor better dispersion and dissolving of components, yet may result in damage to the polymer gelling agent if too extreme and if used in conjunction with sufficiently high disperser blade speeds. Mixing time is not expected to have a mechanism for affecting either ethanol content or degradation, so long as the mixer is sealed to prevent loss of ethanol and longer mix times do not contribute to significant temperature increases. Appearance is tied to the dissolution of components; mixing time is therefore assigned a medium risk to affect that parameter.

Mix Temperature

The temperature of a mixture during processing is mechanistically known to affect the rate of dissolution of components whose solubility depends on temperature. Mix temperature is assay, therefore assigned a medium risk for affecting the assay and content uniformity attributes. Permanent viscosity breakdown is typically a mechanical process; temperature is therefore assigned a low risk for impacting viscosity. High temperatures could cause excessive volatilization and loss of ethanol from the formulation if the mixer needs to be breached during processing for observation, sampling, or other reasons; it is therefore assigned a medium risk. If the active component is sensitive to temperature-induced degradation, mix temperature should also be treated as high risk to this attribute.

Vacuum Pressure

In our example, as well as in the case of many other types of topical formulations, gas entrapment during mixing can present manufacturing difficulties downstream, particularly in the filling process. Accurate control of fill weights in the final container is difficult for formulations having excessive air entrapment due to inconsistent density. The remedial step in processing is often the application of vacuum pressure at the conclusion of mixing to de-aerate the gel. In many cases, high gel viscosity prevents natural de-aeration in any reasonable period of time. As a result, finished product fill weight is tagged as a high risk to variation in this parameter. None of the other parameters are expected to be affected by vacuum pressure.

Transfer Pressure

The pressure used to expel the mixed gel out of the mixer into a portable pressure vessel was also assessed for risk. For low to medium viscosity products, past experience has shown that reasonable variation in the pressure head used for transfer does not result in gas entrapment or any other deleterious effects. This process parameter is therefore judged low risk, and is unlikely to be slated for further investigation during the experimental phase of the design/scale-up process.

A More Detailed, Alternate Risk Assessment Methods: FMECA

A number of alternate risk assessment techniques are available to the process engineer or chemist in charge of process development and scale-up, in addition to the more simplified relative risk assessment method used above. ICH Q9 Quality Risk Management provides an overview of various risk assessment techniques. A detailed treatment of all possible methods is not practical here; however, Failure Modes, Effects and Criticality Analysis (FMECA) has been chosen for inclusion due to its long history of successful use by a number of industries, including the United States military and space agencies. Failure Modes, Effects and Analysis (FMEA) is a systems reliability assessment procedure developed and used by NASA extensively in the 1960s, which was the heyday of the US manned space program. FMECA combines FMEA with a criticality assessment, and although it is most often used with established systems and processes, it can be useful as an additional or alternate risk assessment tool in early and mid-stage product development, a time which may well coincide with pilot plant scale-up work. FMECA does require a basic understanding of the manufacturing process; this can include prior knowledge from similar products, or, if overall process understanding is poor, FMECA can be used in a second iteration of the risk assessment process, following an initial cycle of relative risk assessment, as described above, and initial process experimentation. FMECA is generally performed as two separate analyses: FMEA followed by a criticality assessment; for purposes of discussion they are combined in our example. In addition, FMECA can be performed as an iterative process, similar to the relative risk assessment approach.

Application of this technique, like other QbD risk assessment tools, can provide focus in terms of which parameters of the process can impact critical quality attributes, and may to some degree help guide the prioritization and selection of scale-up principles. For example, if impeller rotational speed (proportional to blade tip speed, or shear rate) is determined using FMECA to be a potential CPP because the formulation is known to shear-thin, a scale-up approach of maintaining constant impeller tip speed may be the first choice. In contrast, if the formulation is not sensitive to shear effects, maintaining equal mixing power per unit volume may be chosen instead.

FMECA assessment begins with defining the system to the best of our knowledge, which in our example will be the manufacturing process for the topical pain gel,

and listing all possible risk factors in tabular form, including process parameters, raw material properties, and any other input to the process with a potential effect on outcome. Each risk factor is given a row entry and assessed for possible failure modes. A process map of the manufacturing process such as Figure 3 is useful in identifying and tabulating inputs to the FMECA table. An alternate and equally suitable means of compiling all possible inputs to the process is an Ishakawa or fishbone diagram.

Each risk factor is then assigned a numerical value between 1 and 10 (or 1 and 5; this is somewhat arbitrary) for the three elements of FMECA: severity, occurrence, and detection. These assessments can be somewhat subjective, but should be based on data, scientific judgment, and prior knowledge. Severity (S) is a measure of the magnitude of the worst-possible effect of the failure. A ranking of 10, for example, may indicate a health and safety hazard to the patient. A rating of 1 indicates no effect. Occurrence (O) is an estimate of the probability that the cause will result in the failure mode as well as its associated effect. A rating of 10 indicates very high probability of occurrence; a rating of 1 indicates a very remote probability of occurrence. Detection (D) represents a relative numerical estimate of the effectiveness of controls which are currently in place to prevent or detect the failure mode before it impacts the patient. A detection rating of 10 represents near absolute uncertainty of detection and/or control; a detection rating of 1 indicates near certain detection.[25] **Tables 6 through 8**, adapted from the Department of the Army's Technical Manual TM 5-698-4's slightly more detailed tables, summarize the Risk Priority Numbers (RPN) for Severity, Occurrence, and Detection.[25]

Table 6. Risk Prioritization Numbering System: Severity

Rating	Effect	Comments
1	None	No expected effect on product safety or efficacy
2- 3	Low	Minor impact on product safety or efficacy
4 - 6	Moderate	Moderate impact on product safety or efficacy
7 - 8	High	High impact on product safety or efficacy
9 - 10	Critical	Critical impact on product safety or efficacy

Table 7. Risk Prioritization Numbering System: Occurrence

Rating	Failure Rate	Comments
1	Remote	Unreasonable to expect failure to occur
2- 3	Low	Very low to low failure rate expected
4 - 6	Moderate	Moderate failure rate expected
7 - 8	High	High failure rate
9 - 10	Very High	Failure rate very high; problems almost certain

Table 8. Risk Prioritization Numbering System: Detection

Rating	Detection	Comments
1	Almost Certain	Current controls almost certain to detect failure
2- 3	High	High to very high probability current controls will detect failure
4 - 6	Moderate	Moderate probability of detection
7 – 8	Low	Low probability of detection
9 – 10	Remote	Detection probability remote to impossible

A risk prioritization number (RPN) can be calculated for each possible failure mode by taking the product of the rankings for severity, occurrence, and detection:

The use of a multiplicative RPN is not universally embraced due to the skewed RPN distribution that results by multiplying all possible O, S, and D combinations of 1 through 10; nonetheless, the author finds it a useful way to analyze and categorize risk.

The outcome of the FMECA assessment is intended to assist in the identification of CPPs and Critical Material Properties (CMPs) and aid in the development of effective control strategies to ensure the process results in a finished product having acceptable quality attributes. The information gathered in an FMECA exercise can and should be used to design an experimental plan. Experiments should be prioritized on the basis of relative risk; for example, for a low RPN (< 100) no further experimentation is needed; however, those identified as medium or high risk should be considered for further investigation. These studies should be designed to evaluate the effects of CPPs and CMPs in practice on the product or intermediate CQAs.

This example exercise has been simplified relative to the techniques outlined in the aforementioned Technical Manual TM 5-698-4. This manual provides a more detailed treatment of the conduct of FMECA on military systems; the procedure for applying FMECA to manufacturing processes is very similar and textbook resources specifically geared towards manufacturing processes are readily available.

In addition to the relative risk ranking process described above, **Tables 9 through 11** provide a simplified illustration of the use of FMECA as an alternate means of risk assessment and identification of CPPs and CMPs as part of the scale-up and process development process. Following a preliminary risk assessment such as this, experimentation outcome may result in a final, modified risk assessment based on increased process and product understanding.

Table 9. Topical Pain Gel in Metered-Dose Pump: Example FMECA Exercise, Focus Area 1: Selected Raw Material Attributes

Risk Factor	Possible Failure Mode	Possible Causes for Failure	Possible Effects	Quality Attribute Impacted	S	O	D	RPN	Controls	CPP or not?	Classification Rationale
Selected Raw Material Attributes											
API Particle Size	Too large or small	Vendor error	Does not dissolve	Drug release	7	10	2	140	Testing	Yes	Undissolved API in FP may impact absorption
Gelling Agent Viscosity	Too high or low	Vendor error	OOS gel viscosity	Viscosity	3	7	2	42	Testing	No	A wide range of FP viscosity not likely to affect performance
Alcohol Purity	Contam-inant	Various	API precipitation	Drug release	7	5	2	70	Testing	No	Visual detection highly probable; not likely to reach patient
Dispensing / Charge-in Qty	Over or under target	Weigh error	Super or sub-potent gel	Assay, drug release, viscosity, pH	7	7	5	245	Visual, weigh tape	Yes	Charge-in of components directly impacts several CQAs

S=Severity
O=Occurrence
D=Detection
RPN = Risk Priority Number, the product of S, O, and D.
FP = Finished Product
OOS = Out-of-Specification
PM = Preventative Maintenance

Table 10. Topical Pain Gel in Metered-Dose Pump: Example FMECA Exercise, Focus Area 2, Mixing Process Parameters

Risk Factor	Possible Failure Mode	Possible Causes for Failure	Possible Effects	Quality Attribute Impacted	S	O	D	RPN	Controls	CPP or not?	Classification Rationale
Process Parameters											
Achor speed	Too low or too high	Operator error; mech. failure	Poor mixing	Assay, drug release	7	7	7	343	Inspection	Yes	Inhomogeneity will impact various FP CQAs.
Disperser Speed	Too low or too high	Operator error; mech. failure	Poor mixing, shear damage	Assay, drug release, viscosity	7	7	7	343	Inspection	Yes	Inhomogeneity and low viscosity will impact various FP CQAs.
Mix Time	Too short or too long	Operator error; mech. failure	Poor mixing, over- heating	Assay, drug release, purity	7	7	7	343	Inspection	Yes	Inhomogeneity will impact various FP CQAs.; excessive mixing time may cause API or other degradation
Vacuum	Too low	Operator error; mech. failure	Gas entrap-ment	Assay, dose uniformity	7	7	7	343	Inspection	Yes	Inadequate vacuum will not properly de-aerate gel, causing under-filling of pump and possible low-potency doses.
Mix Temp.	Too low or too high	Operator error, cooling system failure	API degrada-tion	Assay, purity	7	5	7	245	Inspection Alarm	Yes	High temperature may cause API degradation
Addition Order	Too slow or fast	Operator error	Clumping, poor mixing	Assay, dose uniformity	7	5	5	175	Inspection	Yes	Clumping, inhomogeneity will impact various FP CQAs
Transfer Pressure, Post Mixing	Too low or too high	Operator error, line break	Slow or no transfer	None	1	1	1	1	Inspection Sensor	No	No impact to product likely; lack of pressure easily detectable.

Table 11. Topical Pain Gel in Metered-Dose Pump: Example FMECA Exercise, Focus Area 3, Filling Process Parameters

Risk Factor	Possible Failure Mode	Possible Causes for Failure	Possible Effects	Quality Attribute Impacted	S	O	D	RPN	Controls	CPP or not?	Classification Rationale
Process Parameters											
Tank Pressure	Leak, over-pressure	Seal failure, operator error	OOS fill weight, gas entrap-ment	Priming, assay, drug release	7	5	7	245	Gage, PM, FP testing	Yes	Aeration of gel may cause under-filling of pump and possible low-potency doses.
Capping Force	Too low or too high	Operator error, mechanical failure	Pump seal damage	Priming, assay, drug release	7	5	7	245	Inspection FP testing	Yes	Poor seal on FP pump may introduce air during patient use, causing low doses.
Tube Diameter	Too small	Operator error	Can't fill pump	All	7	7	1	49	Easily observed	No	Go/no-go situation
Filling Pump Speed	Too low or too high	Operator error, mechanical failure	Over or under filled pumps	Priming, assay, total doses	7	8	5	280	Inspection FP testing	Yes	Overfill can cause poor sealing; under fill will result in insufficient doses in pump.
Fill Nozzle Diameter	Under or oversized	Blockage, wrong size installed	Equip-ment damage, no filling	None	1	5	1	5	Easily observed	No	Go/ No-go situation – process will not run if this failure occurs.
Nozzle Speed	Too slow or fast	Operator error, mechanical failure	Nozzle may not dive or retract	None	1	5	1	5	Easily observed	No	Filling unlikely to be affected; both fixed and moving nozzles have been used with success for similar products.

Experimental Design

Those CPPs that have been identified as "high risk" in either the relative risk assessment or FMECA process is targeted for further experimental investigation, in accordance with risk management principles. The more formal aspects of experimental design for scale-up and process characterization can be approached in a number of ways; one of the most useful is statistical Design of Experiments.

Design of Experiments

Design of Experiments (DoE) is a controlled statistical experimentation methodology in which the effects of predetermined, variable inputs on an output of interest are evaluated. In our application, the inputs are CPPs and the output(s) is a CQA. The statistical basis of the experimental design allows efficient and meaningful conclusions to be drawn from the experimental results. DoE can be viewed as a more rigorous and efficient outgrowth of what is known as "one factor at a time" experimentation, in which only one process input is varied while investigating an output. The one factor at a time approach has the disadvantages of both inefficient use of time and resources, as well as an inability to capture variable interaction and therefore can provide only partial information.

In this example we are interested in the effects of three CPPs (inputs or factors) on one CQA (response variable); that is, viscosity. Our initial risk assessment process points out that disperser blade speed and mixing time are high risk factors and warrant further investigation. Anchor speed was identified as medium risk, meaning additional investigation may be necessary. The anchor blade speed factor is fairly straightforward in our set of experiments and therefore should be included. After having identified the CPPs that have potential to affect our CQA of interest, the first step is to determine a range of values over which those CPPs will be allowed to vary in the experiment. This range is often dictated by factors such as equipment capability, past experience, and consideration of effect on other attributes. For example, our disperser blade motor may be capable of 10,000 rpm; however, in past experience we may have found an unacceptable temperature rise above 3,000 rpm and so we choose to limit our maximum speed accordingly. We may also wish to apply theoretical aspects of mixing scale-up to guide in our selection of speeds; specifically, matching blade tip speeds to what proved successful on the bench top scale could be a useful starting point.

Factors can be continuous or categorical. A mixing blade speed or mixing time, for example, can vary continuously over a range. Continuous factors are typically challenged at the extremes of the range of investigation and, sometimes, the center point of the range. Non-numerical inputs are an example of categorical factors. Perhaps the most common designed experiment in process scale-up is the factorial design, which involves performing testing at all possible combinations of factors. A designed experiment having three factors to be evaluated at their maximum and minimum would then have 2 x 2 x 2 or 8 possible combinations to evaluate. In general, for k factors (k = 3 in our case), the numbers of conditions to test are given

by the relationship: 2^k. Center points, or face points, representing values between the extremes of all factors, are often included to detect curvature in the data and additional points or interactions may be included if quadratic and other relationships are suspected, depending on the proper model fit.

Obviously, as the number of factors increases, the number of possible conditions increases, at times making it cost- and time-prohibitive to test all possible conditions. The following equation, known as a fractional factorial design, is often used in this case, minimizing the number of conditions by eliminating certain combinations with reduced probability or significance. Fractional factorial designs take the form of:

$$i = 1^{(k-p)} \qquad (20)$$

where:

i = the number of conditions to run,
l = the number of levels for each factor
k = the number of factors
p = the number of generators; an estimation of the scope interaction between factors.

As an illustration, we could in our example opt to perform a ½ factorial design, or $2^{(3-1)} = 4$ conditions if time and cost were prohibitive for the full eight-condition experiment. In so doing, we sacrifice an estimation of certain interaction effects between factors.

Many resources exist which discuss DoE in great detail, including the *National Institute of Standards and Technology*, or *NIST, Handbook of Engineering Statistics*.[26]

For our example, **Table 12** summarizes the factors chosen for evaluation, including their maximum and minimum. Maximum, center point, and minimums are often given a relative shorthand designation of +1, 0, and -1 when designing experiments.

Table 12. Topical Pain Treatment Gel in Metered-Dose Pump: Example Designed Experiment

Critical Quality Attribute	Critical Process Parameter	Minimum	Target (center)	Maximum
Viscosity	Mixing Time, hrs	1 (-1)	2 (0)	3 (+1)
	Anchor Blade Speed, rpm	25 (-1)	50 (0)	75 (+1)
	Disperser Blade Speed, rpm	1000 (-1)	2000 (0)	3000 (+1)

Table 13 lists the randomized experimental plan for the full factorial, eight-condition experiment. Randomization of the experimental order is typical, in order to minimize bias. The Pattern column designates the pattern among the three factors, (-) = minimum level, (+) = maximum level, and 0 = center point or target level. The

final column represents the viscosity data gathered during performance of the eight hypothetical mixing experiments. These data are simulated and intended solely for the demonstration of statistical principles.

Table 13. Topical Pain Treatment Gel in Metered-Dose Pump: Designed Experiment – Full Factorial Experimental Plan (Randomized)

Run No.	Pattern	Mix Time, hrs	Anchor Speed, rpm	Disperser Speed, rpm	Viscosity (Output), cP
1	- + -	1	75	1000	5000
2	- - -	1	25	1000	4800
3	+ - +	3	25	3000	1100
4	- - +	1	25	3000	4750
5	- - +	1	25	3000	2000
6	+ + +	3	75	3000	900
7	+ + -	3	75	1000	3500
8	0 0 0	2	50	2000	4500
9	0 0 0	2	50	2000	4650
10	- + +	1	75	3000	1650

Numerous statistical software packages are available for designing DoE experiments as well as analyzing the results. The full theory behind the analysis is beyond the scope of this chapter; however, a simple analysis of our viscosity results is tabulated in **Table 14**.

Table 14. Topical Pain Treatment Gel in Metered-Dose Pump: Designed Experiment – Full Factorial Experimental Plan (Randomized) Modeling Results, Effects Testing

Source	p value
Mixing Time	0.1133
Anchor Speed	0.4068
Disperser Speed	<0.001*
Mixing Time*Anchor Speed	0.4978
Mixing Time*Disperser Speed	0.9579
Disperser Speed*Anchor Speed	0.7923

Statistical significance is indicated by any result with a p-value of less than 0.05. In our example, results show a p value of < 0.001 for disperser speed, which not surprisingly indicates that the high shear of the disperser is indeed critical in terms

of affecting the gel viscosity. Most modern software packages capable of DoE work include a wide array of modeling and analytical algorithms. For this example, JMP 8.0 software was used (SAS Institute, Carey, North Carolina). JMP can generate a bewildering variety of visual representations of experimental data. For example, Figure 5 andFigure 6 show three-dimensional surface contour plots of predicted viscosity based on varying values of inputs. **Figure 5** plots anchor blade speed and mixing time on the horizontal axes, and viscosity on the vertical axis.

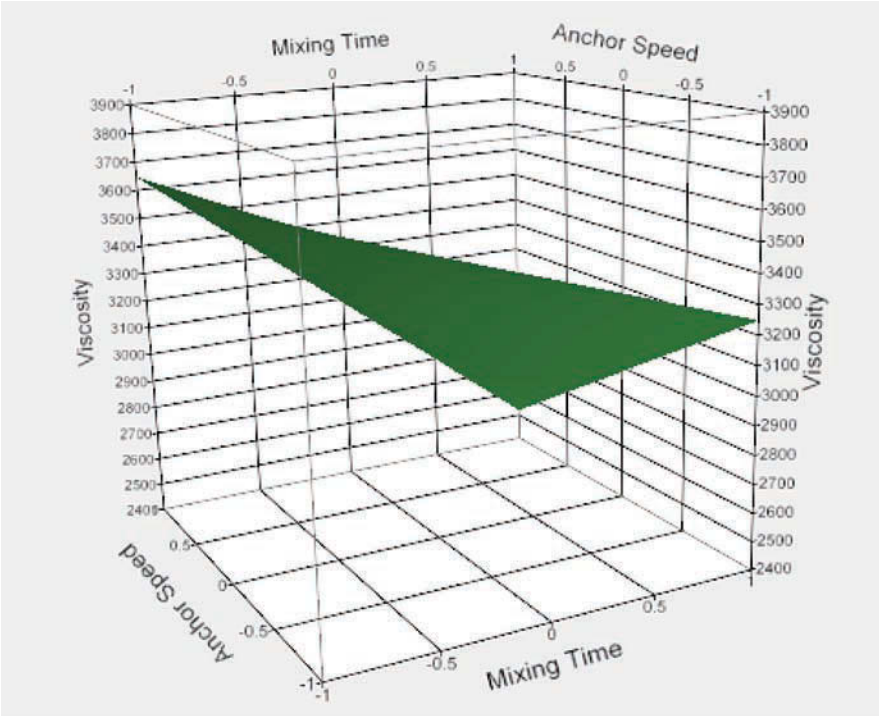


Figure 5. Contour Plot: Mixing Time and Anchor Speed Effect on Viscosity

These plots are interesting in that they provide an immediate visual illustration of how relative variation in two CPPs of interest, in conjunction, can affect the output, or CQA we're studying (viscosity). Inspection of Figure 5 shows a general downward trend in viscosity with increasing mixing time and anchor speed, although the power of our experiment could not prove statistical significance of these two parameters' effect on viscosity. The p value for mixing time, 0.1133, is approaching significance, and this is evident by the more extreme slope of the contour as mixing time increases for any given value of anchor blade speed. Figure 6 shows a more dramatic effect of disperser blade speed on viscosity for any given value of mixing time. These plots are the tip of the iceberg in terms of what a statistical software package like JMP is capable of when it comes to modeling and analyzing DoE output. In addition,

JMP's stepwise DoE algorithm can identify significant interaction effects between factors as well as eliminate insignificant main effects.

A useful element of DoE is the capability of modeling for generating an empirical algorithm for optimizing inputs (CPPs) for a given, desired range of output (CQA). For example, if one decides to target the viscosity at 5,000 cP, the software model will use generated data to return values for our CPPs most likely to result in this desired viscosity.

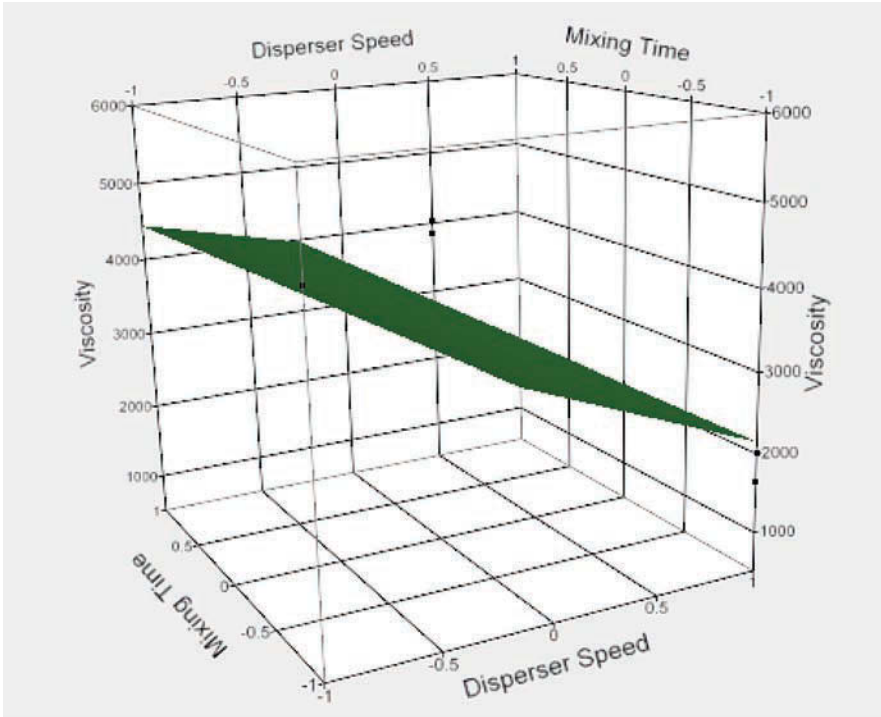


Figure 6. Contour Plot: Mixing Time and Disperser Speed Effect on Viscosity

Re-Assessment of Risk

The initial risk assessment can be re-assessed based on initial experimental results. In some cases, risk reduction may be possible if no significant effect on CQAs was observed over the evaluated range of a process parameter. The re-classification of risk can shift a parameter designation to non-critical, which in turn changes the approach to both design space and control strategy.

Design Space

The resultant ranges of CPPs and CMPs predicted to result in acceptable product is often referred to as the design space. Ideally, during scale-up CPP targets are selected near the center of a design space; this principle helps ensure both scalability

and robustness of a process, because the probability of inadvertent operation outside the space is minimized. In addition, changes to a process which stay within the established design space is viewed quite favorably by regulatory authorities and may not be considered a significant change. One may choose to operate a process within a more narrow CPP range; a subset of the Design Space sometimes called the Operating Space. Conversely, the totality of process information may include data gathered from CPP ranges which exceed the Design Space; this region of information is known as the Knowledge Space.

Control Strategies

Once a design space has been established one can begin thinking of a control strategy to ensure the process stays within it. Process Analytical Technology (PAT), which can provide real-time measurement of key in-process parameters and attributes, is gaining acceptance in the pharmaceutical industry, though it is not an essential element of a QbD strategy. PAT is discussed in more detail later. Pilot plants can be difficult environments to implement a robust control strategy, due in no small part to their ever-changing mix of products, processes, and equipment; nevertheless, the exercise of determining a potential control can be useful in terms of providing a foundation or starting point for the fully scaled commercial process.

Laboratory and Testing Considerations

Assessment of scale-up success is only as good as the analytical test methodology used to make that assessment. A frequent pitfall of tech transfer and scale-up is changing the testing laboratory alongside the change of manufacturing scale, whether due to company practice or issues of physical proximity and logistics. The safest approach to this issue is to maintain the testing laboratory and methods the same as one increases manufacturing scale, eliminating a potentially significant set of variables that can be extremely difficult to ferret out in the event of unexpected or unexplainable scale-up results.

Absent the option to keep the lab unchanged, the next best approach is to ensure a thorough and robust test method transfer occurs between laboratories in advance of testing product at the new scale. Ideally, even at the lab scale, test methods should be adequately assessed for key performance attributes such as accuracy, precision and ruggedness, understanding of course that method validation is generally not practical this early in product development. Physical methods such as viscosity are not generally validated; nevertheless, in the case of physical methods particular attention should be given to the nuances of sample preparation and overall analyst technique, because the most minor of differences can lead to confounding results and inappropriate conclusions during the scale-up process.

Process Equipment: Pilot Scale

General Considerations

As is true in myriad facets of life outside the laboratory and factory floor, in

manufacturing pharmaceuticals and cosmetics there may be multiple approaches to accomplish an objective, and each respective approach, while different, may be equally valid. This is certainly the case when selecting equipment for scaling up and manufacturing topical formulations. The section that follows represents, to a large extent, the author's personal experience of what is known to be effective. This is not to suggest there are not other equally valid choices when it comes to selection of equipment. The mixing step is generally the most scale-sensitive and critical unit operation in the manufacture of a topical dosage form or cosmetic, and as such will receive the most attention. Filling and packaging unit operation tends to be less scale-sensitive; the scale-up principle often involves adding multiples of the same process, i.e., more pumps, stations, filling nozzles, etc.

Materials of Construction

In pharmaceutical applications, requirements for materials of construction for processing equipment are outlined in US Code of Federal Regulations, Title 21 CFR 211.65, which states that equipment shall be constructed "so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."[27] This principle applies equally well for equipment used to make cosmetic products. In practice, this requirement usually dictates the use of inert, resilient, and readily cleanable materials such as stainless steel, silicone, and, in some cases, glass. The various grades of stainless steel are the most common material of construction for product contact parts in pharmaceutical pilot plants. Attention should be made to issues of machinability, hardness, corrosion resistance to a particular type of formulation, and cost. For particularly corrosive formulations, additional surface treatment such as passivation may be needed even for stainless steel, which is not completely impervious to chemical attack. Passivation removes impurities and creates a thin protective oxide film on the material surface; it is commonly performed on stainless steels using an acid treatment.

Electropolishing is an electrochemical process that can also be applied to stainless steel to improve corrosion resistance. In electropolishing, an electric potential is applied to the metal while it is submerged in an electrolyte bath as a cathode, removing metal ions from the surface. Electropolished surfaces generally do not require passivation.

Other metals such as aluminum can be protected from corrosion by an anodizing process. Anodizing is similar to electropolishing, although the treated part is in this case the anode (hence "anodizing") versus the cathode in traditional electropolishing.

When polymer materials such as silicones are employed, chemical compatibility with the product as well as cleaning agents must be addressed.

Cleaning Issues

In pharmaceutical and cosmetic pilot plants, verification of cleanliness is a particular challenge. This challenge exists for several reasons. First, most pilot plants are extremely busy and fast-paced, and cleaning time, like maintenance

and changeover, is down time. In addition, pilot plants usually see a wide variety of different formulations and active substances, each of which may have unique cleaning and verification procedures. There are several approaches available to demonstrate cleanliness, including a "visually clean" standard as well as the more rigorous approach of post-cleaning surface swabbing for residuals of active substances, therapeutic agents, or other formulation materials of concern. Surface swabbing involves chemical analysis of a swab sample taken from a representative, and typically hard-to-clean, location on the equipment of interest.

The importance of surface selection to the cleaning process cannot be overstated. Product contact surfaces of pilot plant equipment must be carefully selected to ensure cleaning is effective and efficient. Surface swabbing procedures usually require the assessment of active compound recovery from each major surface material type. Porous materials such as polymers and ceramics can be much more problematic than stainless steel. Inadequate assessment of a therapeutic compound's recovery from a machine surface can create cross-contamination issues in a pilot plant, and is an acute challenge in high-use R&D facilities. In some applications, recovery of the cleaning agents themselves may need investigation; in rare cases one may find critical attributes of the product exhibiting sensitivity to residual cleaning agents on machine surfaces. While the importance of a chosen cleaning agent may not be perceived as a critical process parameter, it can be. Proper attention to cleaning issues when selecting equipment and surfaces is also an important part of an overall QbD-based product development approach. Subsequent scale-up to a commercial process will occur more smoothly if equipment surfaces have been appropriately addressed from a product compatibility and cleaning standpoint. In some cases, demonstrating cleanliness via surface swabbing for small or frequently used inexpensive equipment may not be cost-effective, and the use of disposable equipment should be considered.

Mixing Equipment

In most cases there is no one right way to mix a liquid or semisolid topical formulation; rather, there may be several valid options that will work equally well, along with choices which should clearly be avoided. Several of the more common mixer types have significant areas of performance overlap. The reader may have different experiences than the author in choice of mixing equipment, and these choices may of course be equally valid. There is abundant literature on impeller selection and design, and this section is intended to provide a high-level overview of the more common mixer types used in pilot plant applications for the manufacture of topical products, with some commentary as to what works and what doesn't.

Impeller Types

Table 15 provides a very brief overview of several common mixing impeller types and the viscosity ranges and applications for which they are best suited. There is abundant information in mixing literature on impeller selection and operating characteristics. Impellers are classified as either axial-flow or radial-flow, depending on how they circulate the fluid. Axial-flow impellers have blades which are mounted

at an angle of less than 90 degrees relative to the impeller shaft axis and include pitched-blade turbines, marine propellers, and hydrofoils. Radial-flow impellers generally have multiple blades mounted parallel to the impeller shaft axis. Examples include flat-blade turbines, paddles, and anchor blades. Some impellers, like pitched-blade turbines, achieve a combination of axial and radial flow.

Marine-type **propellers**, **turbines**, and **dispersers** are typically driven at higher speeds and are most effective at mixing low-to-medium viscosity liquids. **Flat-blade turbines** are effective for gas-dispersion and emulsification. **Pitched-blade impellers** are often used for suspension of solids.[28] **Anchor** blades are typically very slow-moving horseshoe-shaped impellers and can be used in a variety of applications, often in tandem with higher-speed impellers such as dispersers and/or **rotor-stator homogenizers** by improving heat transfer and providing bulk circulation. They are not suitable for low viscosities unless used in conjunction with another impeller. A variant of the anchor having a single blade resembling a hollow gate (known as a gate anchor) is intended for high viscosity applications. **Hydrofoils** are a close relative of propeller-type impellers and feature variable blade angle-of-attack as opposed to the fixed orientation of turbine blades in addition to a hydrofoil blade shape. They provide high axial fluid flow and generate excellent top-to-bottom turnover within the vessel. Very-high viscosity fluids can be mixed with **helical ribbon** or **helical screw** type impellers.

Table 15. Selected Impeller Characteristics

Impeller Type	Power Number (Approx.)	Approximate Viscosity Range, cP	Best Use
Marine Propeller	0.8	< 4,000	Blending, solid suspension, liquid dispersion, heat transfer
Flat Blade Turbine	5.0	< 100,000	High-shear, gas-liquid dispersion; liquid dispersion,
Pitched Blade Turbine	1.3	< 100,000	Solids suspension
Curved Blade Turbine	1.0	< 100,000	High solids content, fibrous materials dispersion, heat transfer, low fluid level
Hydrofoils	0.3–0.6	< 75,000	General blending, solids suspension, gas dispersion
Anchor Blade	0.6	20,000–100,000	Moderate to high viscosity, heat transfer, laminar flow
Helical Ribbon	variable	100,000–25,000,000	Ultra-high viscosity
Multi-Shaft Anchor – Disperser	various	< 1,000,000	High-shear, changing viscosity

Source: Adapted from References 28-36.

Vessels

Mixing vessels in the pilot plant are most often stainless steel cylinders with a slightly dished bottom. Maximum process flexibility can be obtained when the vessel is equipped with a fluid jacket to aid in heating or cooling, as well as the capability for pulling a vacuum within the vessel. Glass vessels may also be advantageous and practical at smaller scales in order to provide greater visibility and insight into the behavior of the mixing process.

Figures 7 through **9** show three different scales of mixing vessels common to topical dosage form pilot plants: 1.5 gal-, 15 gal-, and 35-gal multi-shaft mixers. These three vessels, fabricated by Charles Ross and Son, Inc., Hauppauge, New York, share a similar geometry and operating principle; each having a central anchor blade complemented by high-speed disperser impellers. A third shaft is sometimes present which can be equipped with a rotor-stator homogenizer or emulsifier. The smaller, 1.5-gal unit provides a low-volume pilot-scale option for products containing potent or expensive ingredients. The largest, 35-gal unit is near-commercial scale, and has the potential to provide an effective 1:1 scale bridge to a commercial manufacturing unit. The intermediate-scale mixer is a versatile unit that provides a modest amount of capacity while maintaining scalability with the largest unit. In combination, these three mixers provide a great deal of versatility and capability within a pilot plant.

Photo courtesy of Marc Moesser

Figure 7. Multi-Shaft Mixer: 1.5 Gal Unit

Photo courtesy of Michael Fowler

Figure 8. Multi-Shaft Mixer: 15 Gal Unit

Photo courtesy of Michael Fowler

Figure 9 Multi-Shaft Mixer: 35 Gal Unit

Figure 10 shows a close-up of an anchor-disperser impeller combination. Two saw-tooth type high-speed dispersers are attached to the disperser shaft. A one or multiple-blade configuration can be used, depending on application and fluid depth. This configuration provides a great deal of versatility and can be used for a wide variety of topical formulations over viscosities ranging from 1 cP to as much as 1,000,000 cP.

Photo courtesy of Michael Fowler

Figure 10. An Anchor-Disperser Impeller Combination

Figure 11 shows a three-shaft configuration where a helical auger impeller is added to the anchor-disperser combination. This configuration provides even greater flexibility in the high-viscosity region due to the ability of the augur (also called a screw impeller) to provide good top-to-bottom mixing. The off-set rod just above the disperser blade is an immersed temperature sensor which provides real-time indication of the fluid temperature.

Photo courtesy of Michael Fowler

Figure 11. Anchor-Disperser-Augur Impeller Combination

Figures 12 and 13 show a close-up view of the saw-tooth disperser blade and a rotor-stator homogenizer impeller, respectively. There is overlap in application between high-speed dispersers and rotor-stator homogenizers; both can be effectively used for particle size reduction and emulsification. The user is advised to consult manufacturers' technical bulletins such as those provided by Charles Ross and Son, Inc., to make the best choice for their application.

Photo courtesy of Michael Fowler

Figure 12. High-Speed Disperser Blade

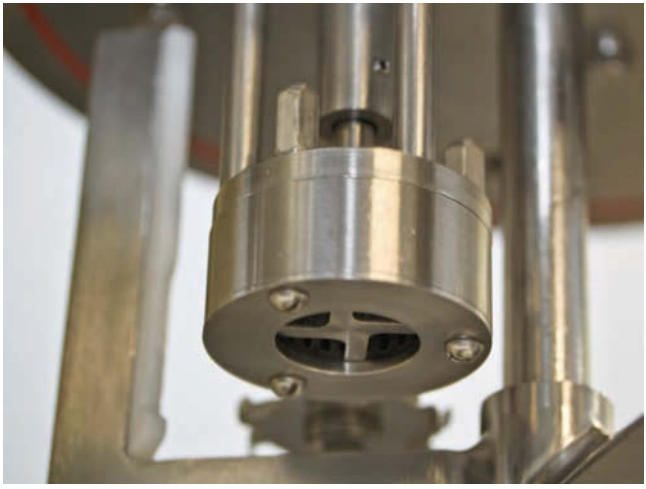


Photo courtesy of Michael Fowler

Figure 13. Rotor-Stator Homogenizer

Baffles

The inclusion of fixed baffles in a mix tank can be an effective aid in mixing process involving low-viscosity liquids in vertical, cylindrical vessels to prevent gross vortexing.[13] Baffles are more frequently used with turbine, paddle, or propeller-type impellers; anchor blades often have scraper attachments designed to sweep the tank walls, precluding the use of a baffle arrangement.

Temperature: Effects on Formulation

Heat transfer characteristics of mixing operations inevitably change with scale; the engineer should anticipate that they may become a limiting factor during scale-up. As scale increases, the volume-to-surface area of mixing and reactor vessels also increases. As a result, heat transfer processes will take much longer. In cases where the process is significantly affected by heat, this element of scale-up can prove critical. For example, consider a topical gel formulation containing solute crystals. Crystallization processes are highly sensitive to cooling and heating rates; a bench-scale mix may be cooled within the vessel via ambient convection or using a cooling jacket surrounding the mix vessel. However, at pilot scale, cooling the entire mass *in situ* may not be possible at the rates required for proper crystal formation. Instead, the cooling may have to be performed using an inline heat exchanger during the transfer process in order to keep the crystallization process consistent.

Vacuum and Pressure Considerations

As formulation viscosity increases, gas entrapment during mixing can become problematic. Entrapped gas leads to downstream issues in filling operations due to the volumetric operating principle of most pumps used in filling steps. By displacing a constant volume in each filling cycle, error will be introduced in the fill weight if a significant portion of the displaced volume is air (or nitrogen). When scaling up high viscosity formulations, it is advisable to ensure that pilot-scale mixers are properly equipped with vacuum pumps capable of degassing the formulation one plans to process. Most standard mixers are not typically certified to handle high pressures and vacuum (a 15 psi maximum pressure is typical) and exceeding these vessels' design pressures can cause mechanical problems such as shaft seal failure.

Power Source: Pneumatic or Electrical

Mixers that are fixed in place are typically powered electrically. If flammable or combustible formulations are processed, the electrical fixtures must comply with the appropriate safety code to prevent ignition. Pilot plants may benefit significantly from the versatility of portable mixing vessels equipped with pneumatically powered impellers. Such vessels, typically in the 2–15 gal volume range, can provide enormous flexibility in designing and developing new processes. In addition, such vessels are relatively inexpensive and can be purchased in greater quantity than fixed, electrically powered mixers.

Cleaning

The cleaning of pilot-scale mixers can be a time-consuming and expensive activity. Fixed mixers of large enough scale, typically 50 gal or larger, can be purchased with clean-in-place (CIP) systems, which greatly optimize cleaning efficiency. Mixing impellers are typically used to enhance the cleaning action of solvents and other cleaning agents.

Material Charge-in, Charge-out, and Transfer

Laboratory-scale charge-in of components and their mixing, as noted by Block, can occur quite rapidly due to the small quantities involved. Conversely, the charge-in and mixing of components at larger scales necessarily takes longer, which in turn alters the mass-transfer characteristics of the process. Such temporal differences across scales can create local conditions in the process that result in unfavorable and unexpected consequences to the formulation.[37] The engineer must be cognizant of this potential when determining charge-in procedures and component addition sequences during scale-up.

Consideration also should be given to how a completed mix will be transferred to the next phase of the process, whether to a storage tank, or directly into the next unit operation, such as filling. Low-to-medium viscosity liquids may be transferable using a pressure head through either a dip tube or bottom valve. Highly viscous liquids and semisolids can be difficult to transfer with pressure alone and generally are best moved from the mixer through a bottom valve using a pump while maintaining a pressure head within the mixer. In extreme cases, such as viscosity on the order of 1,000,000 cP or higher, a hydraulic piston or similar apparatus may be required to force the material from the mixer. Transfer of the material through the piping system to the next process phase is governed by basic fluid mechanics theory, and equipment can be sized according to the many rules of thumb which can be found in chemical engineering and fluid mechanics handbooks. When designing a material transfer system, particular care should be given to suspensions or dispersions where buildup of the suspended phase can occur in "dead spaces" within the piping system, thus leading to uniformity and potency problems in the finished product as well as possible pumping problems.

Formulation Specific Requirements

The type of topical formulation plays an important but not necessarily dominant role in equipment selection, particularly in the case of mixing. Having said that, certain mixer designs are more versatile than others and with limited space in pilot plants, having the ability to make multiple types of topical formulations using the same equipment is an obvious advantage. Low-to-medium viscosity formulations can typically be manufactured using the same or very similar equipment. The most versatile mixer type for a range of viscosities is a double- or triple-shaft mixer with independently driven agitators, having a slow-moving anchor blade supplemented

by a high-speed disperser blade or rotor/stator assembly. Such mixers have the ability to effectively process materials that undergo significant viscosity changes during mixing, such as gels and emulsions, in addition to formulations of constant, low-to-moderate viscosity. Multi-shaft mixers are also very capable in dealing with non-Newtonian liquids, which comprise the majority of high-viscosity topical formulations, especially those having a polymer-based thickening agent. Very high viscosity formulations may stretch the capability of the multi-shaft mixers and require more specialized equipment such as a planetary mixer. The most common types of topical formulations are discussed below.

Gels

Gels are semisolid dosage forms comprised of a colloidal dispersion of a solid phase dispersed within a continuous liquid phase. The solid phase is typically a three-dimensional cross-linked network of biocompatible polymer such as a cellulose, carbomer, or povidone. Topical gels are usually non-Newtonian in behavior, water-based or hydro-alcoholic, and formulated at moderate-to-thick viscosities (approximately 10,000 to 100,000 cP) to allow ease of application. Gels are in most cases easily mixed using standard multi-shaft mixers and do not require highly specialized equipment. Mixing of gels having viscosities on the lower end of the range may be successfully achieved using single-impeller mixers such as pitched-blade turbines, hydrofoils, and marine propellers.

*Hydrogels:*A subset of gels, hydrogels are semisolid gels in which a hydrophilic solid phase is dispersed in water only. Hydrogels may be stand-alone dosage forms or they may be applied to a backing in the form of a topical patch such as the Lidoderm or Flector brands. Hydrogels can be mixed using multi-shaft mixers such as anchor-disperser combinations. In some cases, hydrogels are comprised of two phases which, when combined, involve a cross-linking reaction that increases hydrogel cohesion and viscosity. In such cases more than one mixer may be used to prepare the individual phases, which are then combined during the next unit operation (extrusion coating or dispensing onto a web, in the case of patches) in the process via an inline mixer.

Emulsions

Emulsions are mixtures of two normally immiscible phases, such as an oil and water, in the presence of a stabilizing agent, or emulsifier. Emulsions represent a broad class of topical formulations that include creams, liniments, ointments, pastes, and lotions, depending on the ratio of the oil and water phase. Lotions and liniments tend to be low-to-medium viscosity and ointments, creams, and pastes are mid-to-high viscosity. Emulsions typically require two mixers to independently process the oil and water phases prior to emulsification. The emulsification process itself is best performed in a mixer capable of particle or droplet size reduction, such as a high-speed disperser blade or rotor-stator homogenizer. For more detailed information about emulsions, please refer to Chapters 6 and 7.

Gel-Emulsions

Gel-emulsions combine elements of both gels and emulsions; they involve two immiscible liquid phases, such as an oil and aqueous phase, in the presence of a dispersed solid phase. Such formulations may involve discontinuous oil-phase particles containing an active ingredient suspended within a continuous aqueous phase. Gel-emulsions can require very specific types of mixing equipment in order to properly emulsify the gel without undue damage to the solid, or polymer phase component (i.e., shear-thinning). However, the standard multi-shaft mixer is generally adequate for most gel-emulsions intended for topical application due to the desired viscosity for proper application common to many topical formulations.

Solutions

Solutions are low-viscosity formulations that lack solid-phase thickening agents or emulsifiers, and in which the active component(s) and excipients are fully dissolved. Solutions are of low enough viscosity that traditional single or multiple shaft mixers are generally adequate, with a variety of impellers appropriate for low viscosities. If viscosity is very low, baffles may be needed to break up vortexing.

Topical Patches

Although not as common as the liquid or semisolid based formulations, patches may also be used to topically deliver therapeutic agents. The most scale-critical aspect of manufacturing topical patches is generally the mixing step, where a therapeutic agent is mixed into a low-to-medium viscosity solution, gel, or dispersion. The resultant liquid or semisolid intermediate is then processed further in any of several different ways: film coating and die cutting/packaging in the case of matrix-type patches, or form, fill, and seal in the case of the less common liquid reservoir design. The common multi-shaft mixer is generally adequate for processing most topical patch formulations. Low-to-moderate viscosity intermediates can also be successfully mixed by single-shaft impellers such as marine propellers and pitched-blade paddles or turbines. Discussion of the highly specialized extrusion coating and form/fill/seal equipment used in the latter unit operations is beyond this chapter's scope.

Filling & In-process Analytical Equipment

Lab-scale filling of finished packages such as tubes, pumps, and bottles is typically performed manually, using syringes, pipettes, or similar devices. Scale-up to the pilot plant will usually involve a semi-manual operation capable of increased throughput. Instead of hand filling, the use of semi-automated pump-based filling equipment is common at the pilot scale. A single nozzle filling machine with electric or pneumatic operation is capable of filling several hundred multiple-dose containers per shift. If manufacturing thousands of multiple-dose units is required at the pilot plant scale, such as for supplying large clinical trials, multiple dispensing nozzle-pumps can be combined in order to fill multiple units per cycle. Such machines are typically economical and simple to build/customize. In addition, filling operations lack the

complexities and scale-up factors associated with the mixing step and scale-up can generally be accomplished by adding replicates of each pump/tubing/nozzle assembly along with the desired level of automation and control. Care should be given to areas where geometric or dynamic similarity cannot be maintained, such as when longer tubing is necessitated at the increased scale. For example, tubing diameter may need to be increased at the larger scale to compensate for pressure losses due to longer length. But this is rarely an issue when scaling up from the bench-top, due to the improbability of using semi-automated pump-driven filling processes at such a small scale in early development.

Figure 14 depicts a single-station filling machine using an electrically driven positive-displacement piston pump to fill bottles, jars, syringes, or similar containers with low to relatively high viscosity formulations (1–100,000 cP). A separate capping press would typically be used alongside this machine. This type of machine provides a great deal of versatility to a pilot plant making a wide array of topical formulations.

Photo courtesy of Michael Fowler

Figure 14. A Single-Station Filling Machine

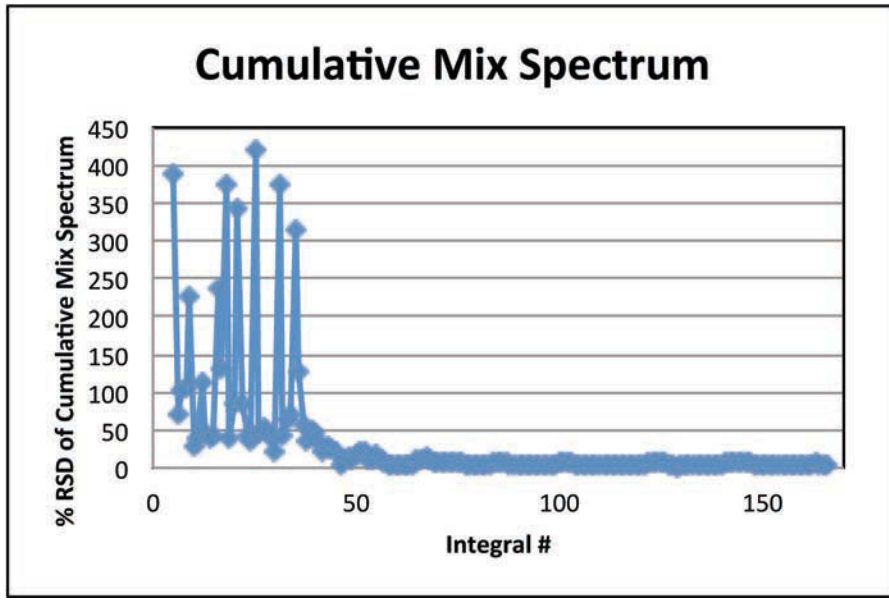
Figure 15 shows a typical pilot-scale tube filling machine, which can be configured to use either a cold- or hot-seal crimp. Filling machines like these have a small footprint and may be used for both pilot and commercial-scale production.

Photo courtesy of Michael Fowler

Figure 15. A Typical Tube Filling Machine

Process Analytical Technology (PAT) can be an essential, although not mandatory, element of a QbD-based scale-up control strategy. PAT devices capable of flexible operation without extensive calibration and recipe development are most useful in a frequently changing R&D environment. Finding and implementing such devices in an R&D operation remains a challenge, although some of the more recently developed devices are quite versatile and can provide useful real-time analytical feedback during manufacturing. For batch mixing processes, an example of a promising and useful PAT device is a near-infrared (NIR) probe capable of analyzing local spectrographic variation within a mixer during processing.

Figure 16 illustrates the output of an NIR probe manufactured by Bruker Optics, Inc. (Billerica, MA) during the preparation of a 15-gal batch of a topical gel product. The NIR probe generates a local, real-time cumulative spectrum of the components being mixed. The vertical axis, which shows the cumulative mix spectrum, is a representation of homogeneity and the horizontal axis is an indication of time. The region where the slope becomes essentially zero indicates homogeneity. This device's sensor is clad in stainless steel and easily attaches through a sanitary port in the mixer lid. It operates using fiber optics, which allows safe operation near flammable or combustible materials.



Courtesy of Michael Fowler

Figure 16. NIR Spectrum for Mixing of a Gel

Facilities and Engineering Issues

A detailed treatment of facilities and engineering issues is far outside the scope of this chapter and many excellent resources exist; however, a few salient points of consideration are worth noting. It is relatively rare that the engineer finds the opportunity to design or specify pilot plant facilities in advance of a scale-up project; more often he must adapt to existing facilities and equipment. Still, for those occasions where opportunity arises to modify or improve pilot plant facilities, making decisions with foresight around the broadest possible product and process range can ease the process when an unusual scale-up project arises.

Process Segregation

Avoiding product cross-contamination is a significant challenge in the pilot plant setting, with the fast-paced and frequently changing work environment common in R&D. Physical separation of each unit operation, along with a well-designed and implemented Heating, Ventilation, and Air Conditioning (HVAC) system that provides pressure differentials between rooms and common spaces is advised whenever possible. Processes which don't generate airborne cross-contaminants such as powdered ingredients and organic solvents, either inherently or through engineering controls, can be segregated using temporary barriers such as curtains, ropes, or chains. Modular pilot plants have gained popularity in recent years; these types of designs allow quick rearrangement of working space as dictated by changing project needs, while still providing adequate process segregation.

Utilities

A pilot plant with a diverse array of potent process utilities is much more versatile and quick in terms of adapting to different scale-up requirements. Equipping each room with basic process and equipment aids such as water, compressed air, nitrogen, and electrical outlets of sufficient voltage and amperage can provide a maximum amount of flexibility when new equipment or scale-up processes need be introduced. Utilities should have appropriate monitoring and control, such as filtration for gases, to ensure ongoing quality and absence of contamination. An in-house source for USP-grade water can be an economical and convenient means of supplying a key ingredient for many formulations as well as a highly pure cleaning aid.

Environmental Monitoring and Controls

Pilot plants involved in cGMP production activities need appropriate environmental monitoring and controls systems. Maintaining a consistent ambient temperature and in some cases humidity can eliminate a frequent source of problems or questions during product development and process scale-up. It is not uncommon to unexpectedly find a product or process sensitivity to temperature or humidity. Monitoring of pilot plant environmental conditions can be a useful investigative tool in such cases.

Room Surfaces

Like machines, a well-designed pilot plant should be constructed with chemically resistant surfaces such as specialized epoxy finishes on walls and floors. Floors are typically coated with chemically resistant and non-slip surfacing. Areas where frequent chemical contact is expected are best clad in stainless steel. Soft, inert mats can be placed around machines to reduce operator fatigue.

Safety

Pilot plants are inevitably fast-paced and constantly introducing new technologies and chemicals. This combination can be a significant challenge to employee health and safety. Often, the exposure hazards associated with a new process may not be fully understood at the pilot plant stage. It is imperative that pilot plants be supported by a capable and highly involved safety staff that can administer a robust employee safety training program as well as ensure the appropriate safety equipment such as eyewash and shower stations, spill kits, drains, and personal protective equipment (PPE) are available. Safety specialists can assist in implementing appropriate engineering controls around processes which use particularly potent compounds. Employee exposure monitoring may be advisable when introducing especially potent materials for the first time, in order to benchmark expected dosing and ensure the appropriate PPE is mandated.

Some operations may involve flammable or explosive materials, and attention must be paid to the appropriate regulations in terms of purging, sealing, or protecting from potential sources of ignition.

Raw Material Considerations

Sourcing

A major element of successful scale-up necessarily involves securing a reliable, adequate, high-quality supplier for each ingredient, *as early as possible in the formulation process*. Raw material attributes, like test methods, can be particularly insidious variables, affecting scale-up in subtle ways that can ultimately be as catastrophic as they are hard to identify. It is important to ensure a constant material supplier to maintain uniformity and consistency, while controlling Critical Material Attributes for key ingredients over the course of product formulation, development, and scale-up to eliminate a major source of potential product variability. Lionberger astutely summarizes this point by noting "monitoring material properties makes scaling less equipment dependent."[20]

Key ingredients should be sourced in duplicate whenever time and resources permit. This is certainly not limited to the active component, and in many cases, the inactive components of a formulation can prove to be even more critical. Active components, such as active pharmaceutical ingredients, typically have to meet strict compendial requirements that can represent a level of control that may exceed those imposed on excipients; yet slight variations in excipients can prove to have dramatic effects on finished product quality and performance.

A sound raw material sourcing program should include some level of supplier compliance and quality assessment. Larger organizations may have the resources to perform periodic on-site supplier quality audits. Smaller organizations can find this prohibitive, but paper audit via quality/compliance questionnaires can be a suitable alternative. Suppliers should be required to inform the organization of any change to raw materials or process; such a requirement can, as one option, be spelled out on your purchasing specification as a part of the purchase contract when an order is placed.

Confidentiality or non-disclosure agreements are highly recommended for key ingredient suppliers; particularly those with whom you anticipate process development / troubleshooting discussions.

Summary

Scale-up can be as much an art as a science. A holistic, multivariate approach can be the key to quick success. Scale-up success means designing and implementing an efficient, cost-effective process resulting in a product which consistently meets a comprehensive and appropriate set of pre-determined quality attributes. A combination of the appropriate application of theoretical principles and prior knowledge within a focused framework based on QbD principles will ensure the highest probability of success. Working within a structured system of good recordkeeping, documentation, and good manufacturing practices is a necessary foundation to successful scale-up. Understanding the end goal by adequate

recognition of the key attributes of the target product is essential. In turn, it is vital to the process to identify as early as possible in the formulation stage the key critical steps, properties, and material parameters that may affect the critical attributes of the product. Risk management can be an invaluable tool by which experimentation and process characterization can be made highly effective and efficient. A well-designed experimental plan can identify a design space in which pilot plant equipment will be assured of producing an acceptable finished product as well as providing a solid process foundation for the increase to commercial scale.

The goal of this chapter has been to provide a high-level overview of the multivariate aspects of topical product scale-up, and provide guidance through example of how to address key issues and concerns. For drilling down to a greater level of detail, there are many valuable resources and guidance documents available to the scale-up scientist. These range from the highly technical and specialized texts such as Levin's excellent *Pharmaceutical Process Scale-up*, to more high-level guidance documents including but not limited to the key ICH guidances: Q8(R2) (Pharmaceutical Development) and Q9 (Risk Management) in particular. Additionally, there is an ever-growing body of literature concerning QbD in the pharmaceutical space.

We can learn as much from our failures as our successes; they become an essential element of our ever-growing body of knowledge. Scale-up can be a frustrating process fraught with great challenge, occasional disappointment, and inspiring reward. All of us use topical cosmetic and pharmaceutical products, as do our loved ones—and there are few things quite as professionally rewarding as the sight of a high-quality, safe, and effective commercial product rolling off the store shelves that, as an engineer or scientist, one can look at and say,"I figured out how to make that product."

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CHAPTER 9

Foam: A Unique Delivery Vehicle for Topically Applied Formulations

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Key Words:

Foam, Hydrophilic Emulsion Foam, Lipophilic Emulsion Foam, Nanoemulsion Foam, Aqueous Foam, Hydroethanolic Foam, Potent-Solvent Foam, Suspension Foam, Ointment Foam, Hydrophilic Ointment Foam, Oil Foam, Saccharide Foam

Introduction

The paramount objective of pharmaceutical and skin care product development is to create effective products based on state-of-the-art active ingredients with improved patient compliance and usability. The vehicle used to deliver topical active ingredients can considerably influence the performance of the active ingredients. The vehicle can have a direct effect on the condition of the skin as a barrier, as it can enhance or retard the delivery of the active agent to the target site of action. In addition it can affect the skin's physical appearance and sensory properties, attributes that can influence patient compliance. While semi-solid compositions, such as creams, lotions, gels, and ointments are commonly used by consumers, new forms are desirable, in order to achieve improved control of the application, increased skin absorption, and to maintain or bestow the skin promised beneficial properties.

Foam is becoming a prominent delivery system for topical active agents in skin treatment. This platform provides an innovative, easy to apply, modern alternative to creams and ointments. A significant advantage of the foam formulation is that it spreads easily on large skin areas, does not leave a greasy or oily film on the skin after application and does not impart a greasy feeling upon and after application.

The use of foam in dermatology was first reported in 1977 by Woodward and Berry who studied the therapeutic benefit of Betamethasone benzoate, in hydroalcoholic "quick-break" foam in comparison with a corresponding semi-solid dosage form.[1] The activity of the foam, as determined by a vasoconstriction

test, was similar to the corresponding ointment and better than a cream. In 1995, Deaffontio et al. investigated the anti-inflammatory and analgesic profile of a topical foam formulation of ketoprofen lysine salt, which exhibited anti-inflammatory and analgesic effectiveness and favorable usability properties.[2,3]

A comprehensive review on foam drug delivery in dermatology was written by Carryn et al. in 2003.[4] Tamarkin et al. published a broad review, titled "Emollient foam in topical drug delivery" in 2006;[5] and an additional review, titled "Foam: The Future of Effective Cosmeceuticals" was published in *Cosmetics & Toiletries* magazine in 2006.[6] More recently, in 2010, Steckel et al. wrote a review on foam technology, titled "Foams for pharmaceutical and cosmetic application."[7]

Overview of the Market: Current Foam Technologies

Currently, only a few dermatological foam products are commercially available.

EpiFoam (Alaven Pharmaceutical LLC), which contains hydrocortisone acetate 1% and pramoxine hydrochloride 1%, is based on an aqueous foam vehicle. It is indicated for the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.[8]

Olux Foam and Luxiq Foam (Stiefel, a Glaxo SmithKline (GSK) company), which contain 0.05% clobetasol propionate and 0.12% betamethasone valerate, respectively, are both thermolabile (temperature-sensitive) steroid hydroethanolic foams (containing about 60% ethanol).[9,10] Evoclin (Stiefel) is another hydroethanolic foam, comprising 1% clindamycin, which is indicated for acne.[11-12]

Stiefel, a GSK company further markets four emollient foams, namely Olux-E (0.05% clobetasol propionate) Foam and Verdeso (0.05% desonide) Foam for corticosteroid-responsive dermatoses, Sorilux (0.005% calcipotriene) Foam for psoriasis, and Fabior (0.1% tazarotene) foam for acne.[13-14]

Scytera (Promius Pharma, developed by Foamix), is a non-prescription foam containing 2% coal tar for the treatment of psoriasis, which is effective and highly convenient.[15] While coal tar preparations in general are associated with poor patient compliance as they cause skin irritation, staining to clothes, hair and skin, and are malodorous,[16] Scytera's color intensity is off-white, and thus does not cause staining; moreover, its **fragrance is pleasant**. Stiefel and Foamix are both market leaders in foam technology and are engaged in the development of innovative foams in collaboration with several pharmaceutical companies.

This chapter will describe what foam is, survey the various types of foam available today commercially along with those presently under development, and exemplify their uses in skin therapy. It will further account for the physiochemical properties of foam products and explain how to evaluate them. Please note that the term "drug" is used extensively throughout this chapter, as the source of much discussion is based on such research; however, the principles of foam delivery systems apply equally well to personal care product types and so for the purposes of this writing, the terms, as regards their methods of application, may be considered synonymous.

The Rosetta Stone Of Foam

To date, all foams are collectively designated as "Medicated Foams" by the European Pharmacopoeia, and the U.S. Pharmacopoeia simply lists "Foam Aerosol" as a sub-part of its Aerosol section.[17]

Most foams used in pharmacological and cosmetic applications are aerosol foams, which comprise a semi-solid formulation, packaged in an aerosol can and pressurized by a propellant. It is imperative to understand that while a foam preparation exhibits distinct characteristics that differentiate it from other generically used vehicles, not all foams are similar and they can be tailored to fulfill product properties requirements. While in the past there were just a few types of medicated foam, i.e., aqueous foams, hydroethanolic foams and emulsion-based emollient foams, today there are several new classes of foam formulations under development, mainly by Foamix, which are distinct in their composition and functionality from each other. Examples of new classes of foams are petrolatum-based foam, which is the foam version of an ointment; hydrophilic solvents (such as PEG and propylene glycol) based foam, which is the foam version of a hydrophilic ointment; and oil-based foam, which corresponds to oil solutions or suspensions. Foams that are based on "potent" solvents, such as dimethyl isosorbide and dimethyl sulfoxide (DMSO) contribute to high solubility and enhanced transdermal drug delivery of active agents. Also under development are hydroethanolic foams (containing high levels of ethanol) which are suitable mostly for scalp treatment because they collapse easily and do not impart greasiness to the scalp and hair. Foams can be also used to further stabilize suspensions and there are foams that contain high levels of saccharides and honey for wound and burn therapy.

These versatile foam classes have been used to develop a large number of foam products, containing a variety of active ingredients, such as antibiotic agents, antifungals, antiviral agents, immunomodulators, corticosteroids, steroid hormones, anti-acne agents, anti-psoriasis agents, vitamins A, B, C, D and E, a-hydroxy and b-hydroxy acids, and skin barrier-building agents for the treatment dry skin conditions.

It is important for the formulation scientist to understand the differences between the above classes of foam formulations, and be able to select the right type of formulation for a given clinical condition. The current review presents the "Rosetta Stone" of foam. It introduces the various types of foam technology platforms and suggests a functional transformation of their respective traditional topical dosage forms. **Table 1** lays out a series of foam classes, which correspond to their current topical dosage forms, with a summary of the main features and attributes of each class of foam; and the following sections will provide further features of each of these classes.

Table 1. Classification of foam technology platforms, corresponding to traditional topical dosage form designations

Foam		Traditional topical dosage form designation (USP and EP, combined)	Attributes
Class	**Main formulation characteristics**		
Water-containing Foams			
Hydrophilic Emulsion Foam	Oil-in-water emulsion	Emulsion, Cream, Hydrophilic cream	Emollient, skin conditioning vehicle Can carry lipophilic and hydrophilic drugs and retain their stability Favorable usability- enhance compliance
Lipophilic Emulsion Foam	Water-in-oil emulsion	Emulsion, Cream, Lipophilic cream	
Nanoemulsion Foam	Oil-in-water nanoemulsion		Emollient, skin conditioning vehicle Improved solubility and skin delivery of active agents
Aqueous Foam	Main ingredients = water, gelling agents and surfactants	Gel	Non-greasy
Hydroethanolic Foam	Main ingredients = ethanol and water	Solution, Tincture	Serves to solubilize drugs, thereby increasing their bioavailability Suitable for oily skin areas Does not require preservatives
Potent-Solvent Foam	Water and strong solvents	Gel, solution	Serves to solubilize drugs, thereby increasing their bioavailability Induces skin penetration Suitable for transdermal drug delivery Does not require preservatives
Suspension Foam	Suspended drug in a foam formulation	Topical suspension	Emollient, skin conditioning vehicle Can carry suspended drugs and retain their stability Favorable usability

Foam		Traditional topical dosage form designation (USP and EP, combined)	Attributes
Class	Main formulation characteristics		
Water-free Foams			
Ointment Foam	Single phase, petrolatum main ingredient (up to 90%)	Ointment, White ointment, Hydrophobic ointment	Occlusive, builds up skin barrier Prolongs drug skin residence Compatible with water-sensitive drugs Does not require preservatives
Hydrophilic Ointment Foam	Single phase, PEG, propylene glycol, glycerin or other hydrophilic solvents main ingredients	Polyethylene glycol ointment, Hydrophilic ointment	Greaseless ointment base Humectant, provides skin moisturization Serves to solubilize drugs, thus rendering them more bioavailable Compatible with water-sensitive drugs Does not require preservatives
Oil Foam	Single phase, liquid oil main ingredient	Oil solution or suspension	Builds up skin barrier Nourishes and lubricates the skin Prolongs drug skin residence Compatible with water-sensitive drugs Does not require preservatives
Saccharide Foam	Mono-saccharides, disaccharides, honey main ingredients (up to 90%)		Hygroscopic, absorbs exudates Antibacterial Useful for wounds and burns treatment

Water-containing Foams

The early generation of medicated foams included the aqueous foam, the hydroethanolic foam and the newer platform of emulsion-based foam, also termed

"emollient foam," which was initially introduced by Stiefel and is now also being extensively developed by Foamix.

Water-containing foams have several general advantages:

(1) **Usability.** Foam formulations containing water offer cosmetically pleasing advantages over traditional topical vehicles such as ointments and creams. These include easy application, minimal residue after application, and quick absorption into the skin. Studies have revealed that patients using foam preparations spent less time applying medication when compared with other topical medications.[18]

(2) **Stability.** The pressurized aerosol container is an impermeable packaging system, which prevents formulation contact with air, light, and contaminants during storage, as well as during the use period. This differentiates foam packaging from tubes, which, although minimally, are exposed to the environment once they are opened. Hence, drugs prone to oxygenation or sensitive to light can have longer shelf life and in-use life when formulated in a foam.

(3) **Skin hydration and conditioning.** In emulsion-based foams, the hydrophobic components, which are primarily liquid oils, act to mitigate skin dryness through their emollient properties. The mechanism is thought to involve increased skin hydration (water content) and reduction in water evaporation (transepidermal water loss, or TEWL) a process which contributes to the softening and pliability of the external layer of the skin (epidermis). Humectants, such as alpha hydroxy acids, propylene glycol, hexylene glycol, glycerol and urea, can be added to the aqueous phase of the emulsion.

The following sections will review the compositions of the various water-containing foam platforms.

Cream Foam (Emollient Foam)

The term emollient foam relates to foams that exert soothing and moisturizing effects when applied to the skin. Emollient foams are emulsions, comprised of water and oil, and as such possess vehicular properties similar to traditional creams and lotions. The emulsions can be oil-in-water (o/w) or inverted (water-in-oil; w/o) emulsions, which correspond to "hydrophilic creams" and "hydrophobic creams," respectively.

The oil components of the foam contribute to improved skin condition and provide symptomatic relief of dry skin and associated skin diseases such as psoriasis and atopic dermatitis. [19,20]

Emollient Foam Composition: The primary components of emollient foams are water and oil, which are present in the formulation as the form of emulsion. The composition of the oil phase can be selected from all cosmetically and pharmaceutically acceptable oils, including mineral oil; plant-derived oils and esters, such as capric/caprylic triglycerideisopropyl myristate, isopropyl palmitate and diisopropyl adipate; and silicone oils, which are known for their emolliency, wetting and spreading characteristics and ability to provide unique aesthetics. Petrolatum is a less desirable hydrophobic component, due to its greasy nature.[21]

Formulations that include high concentrations of petrolatum leave a greasy and sticky feeling after application and occasionally stain clothing. The foaming agents that are required to stabilize the emulsion and produce foam with desirable texture include surfactants, polymers, and foam adjuvants. The surfactants should be carefully selected. Ionic surfactants are effective as foaming agents but they are generally known as irritants, and therefore, nonionic surfactants are preferred, especially when the target area of treatment is inflamed or infected or is a mucosal surface or body cavity. A gelling agent is a useful component for the creation of foam with desirable texture and spreading properties. A variety of gelling agents also possess film-forming properties, which serve to maintain drugs at the site of application. Another group of components that contribute to the stability and sensory properties of the foam are the aforementioned foam adjuvants, which assist the surfactants in stabilizing the emulsion and forming stable foam. The adjuvants are selected from the variety of fatty alcohols and fatty acids.[22,23] Optionally, polar solvents such as glycerol, propylene glycol, hexylene glycol, dimethyl isosorbide, and DMSO are added to the foam composition, in order to increase the solubility of the active agents and to enhance skin penetration.[24] The propellant can be a hydrocarbon propellant (mix of butane, propane, and isobutene) or a fluorocarbon gas. A pharmaceutical or cosmetic emollient foam product may include a single active agent or a combination of active agents, which can be dissolved in the water phase or the hydrophobic phase of the carrier composition. Yet, in certain cases, the foam as a vehicle can still allow the dispersion of the drug even when it is not fully soluble in either the water or oil phases. Examples of drugs that have been successfully incorporated in emollient foam formulations include antibiotics, antifungals, antivirals, corticosteroids, non-steroidal anti-inflammatory agents, retinoids, keratolytic agents, immunomodulators, anesthetic drugs, anti-allergic agents, and anti-proliferative drugs.[25-26]

Emollient Foam Properties: Emollient foams possess several advantages, when compared with hydroethanolic foams:

(1) **Breakability.** The emollient foam is thermally stable. Unlike hydroethanolic foams, it does not readily collapse upon exposure to skin temperature. Shear-force breakability of the foam is clearly advantageous, since it allows comfortable application and well directed administration to the target area.

(2) **Skin hydration and skin barrier function.** The oil components of the foam provide skin conditioning and enhance the skin barrier function, thereby improving the condition of damaged skin.

(3) **Reduction in adverse effects.** Due to the lack of alcohol and improvement in skin barrier function, skin irritability is reduced.

(4) **Usability.** Foam provides significant usability advantages. When the foam is released from its container, it expands and allows easy spreading on the target area, and is absorbed into the skin without any extensive rubbing. This feature is particularly important with regard to the treatment of large skin surfaces. The fact

that when applied to skin the foam remains on the applied area and does not leak or drip is an additional usability advantage.

The following examples demonstrate the implications of the above mentioned advantages.

Betamethasone Valerate Emollient Foam

An emollient foam composition, containing 0.12% of betamethasone valerate, was developed with the aim of treating patients with psoriasis and atopic dermatitis. The composition includes delicate oils and nonionic surfactants, in order to minimize skin irritation. A Phase II, randomized, blinded, right-left comparison within patient clinical trial was carried out with 30 patients with mild to moderate psoriasis. Two similar plaque areas of psoriasis, i.e. both knees or both elbows, were selected for treatment for each patient. Foam was administered on one side and a commercially available betamethasone valerate 0.12% cream was administered on the other side for a period of six weeks. The following results were recorded:

Efficacy: Both treatments were equally effective in the treatment of the psoriatic lesions. After three weeks of treatment, there was a statistically significant improvement from baseline in all parameters, including thickness (4243% improvement), redness (3644%), scaling (4956%), itch (7778%) and global score (4244%). These clinical improvements persisted following an additional three weeks of treatment (**Figure 1**).

Usability: Patients rated the foam as better than the cream in skin absorption, oily residue, shiny look, stickiness, and odor (**Figure 2**). The favorable usability of the foam is a major advantage, which contributes to enhanced patient compliance and better clinical outcome of treatment.

Safety: No drug-related adverse effects were recorded in both treatments.

In conclusion, the emollient foam offers an attractive alternative to mid-potency steroid cream. As such, it is more likely that psoriasis patients will use their medication as frequently as prescribed and will gain the desirable therapeutic benefits.

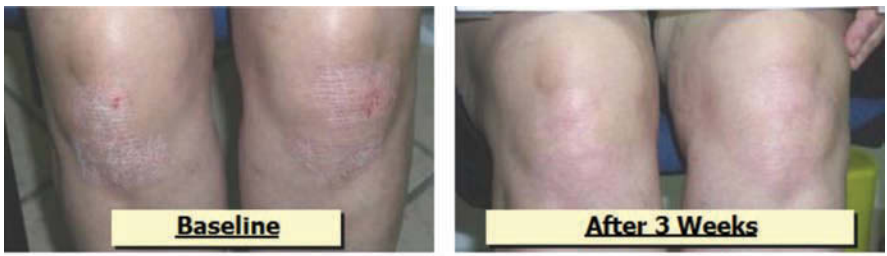

Figure 1. Betamethasone Emollient Foam—clinical improvement of psoriasis lesions following three weeks of treatment

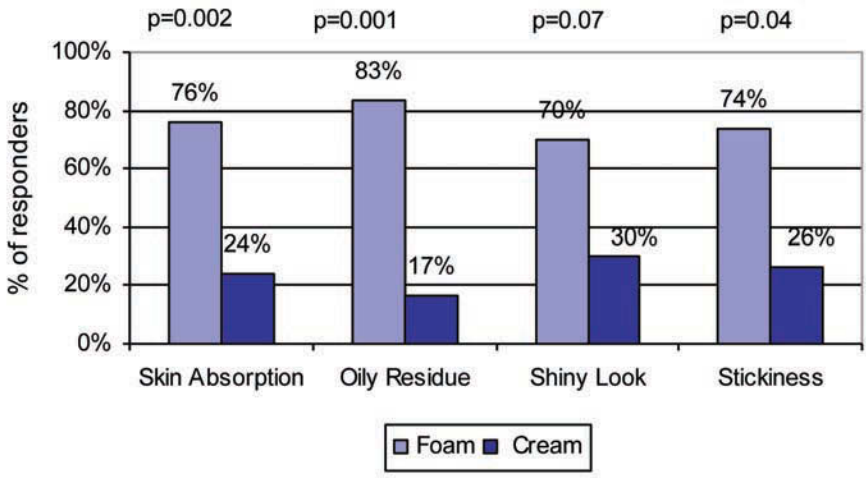

Figure 2. Usability preference–Foam vs. Cream

Metronidazole 1% Emollient Foam – *Demonstration of Efficient Drug Solubilization and Favorable Skin Bioavailability*

Metronidazole, the leading topical drug for rosacea, is currently available in gel, cream, and lotion at 0.75% and 1% concentrations. Since the saturation solubility of metronidazole in water is relatively low (≤ 0.75%), 1% metronidazole is not expected to fully dissolve in an aqueous vehicle.

Emollient foam compositions, including delicate emollient oils and nonionic surfactants, were designed with the aim of dissolving 1% metronidazole. Surprisingly, the foam fully solubilized the active ingredient, as shown in **Figure 3**.

An *in vitro* skin penetration study was conducted using excised human skin, aiming to evaluate the penetration profile of 1% metronidazole from two types of emollient foams. Two foam compositions were tested–one with 2.5% propylene glycol as a penetration enhancer and the other without propylene glycol (MZPG and MZ, respectively). These were compared to a commercial 1% metronidazole cream. As shown in **Figure 4**, the total cutaneous penetration of metronidazole following 16 hours' exposure was two- to threefold higher for the two foams when compared to the commercial product. Propylene glycol increased significantly the delivery of metronidazole through the skin. The full solubility of the active agent in the foam formulation, as shown in Figure 3, is conceivably the explanation for the better penetration from the foam products. Particles will obviously not penetrate the stratum corneum.

Thus, the enhanced solubility of the drug in the emollient foam is useful in enhancing the effectiveness of topical metronidazole.

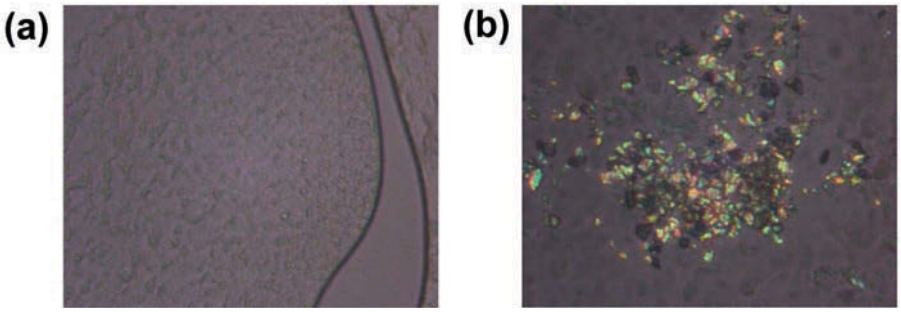

Figure 3. Metronidazole 1% emollient foam versus commerical cream.
(a) No crystals in the 1% emollient foam.
(b). Metronidazole crystals in commercial product.

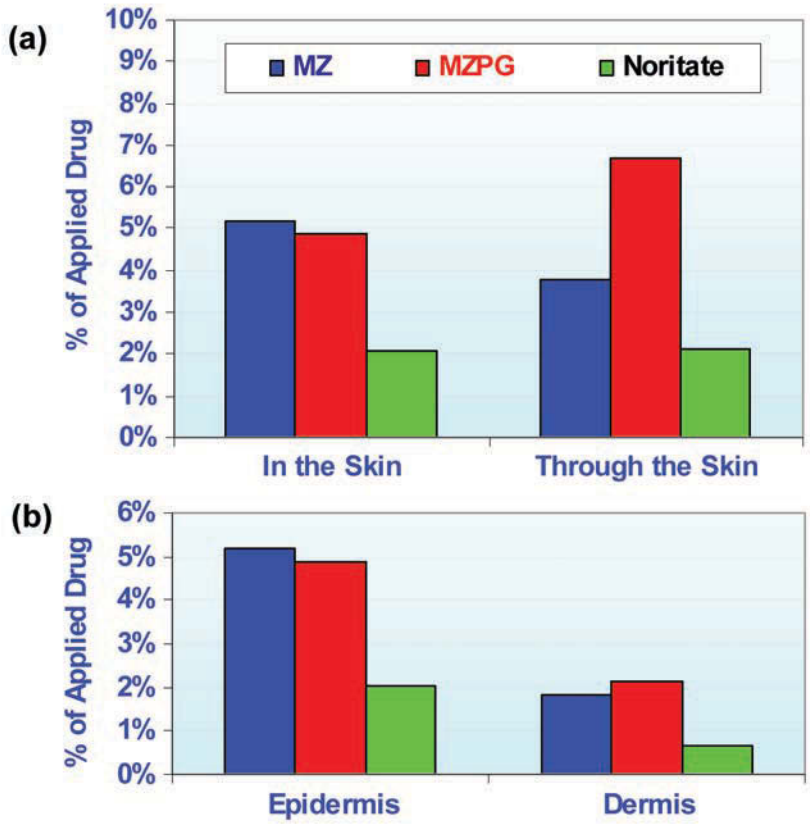

Figure 4. The skin penetration profile of Metronidazole 1% emollient foam with 2.5% propylene glycol as a penetration enhancer (MZPG) and without propylene glycol (MZ) vs. cream.

(a) enhanced intradermal delivery and controllable transdermal delivery by both foams; and further, induction of transdermal delivery by propylene glycol
(b) delivery of metronidazole to all skin layer

Numerous cosmetic and over-the-counter (OTC) products have been conceived as suitable for a foam delivery format. Several such products are at various stages of development. **Table 2** describes some of these cosmetic foams, their active ingredients and their properties.

Table 2. Examples of Cosmetic and Nonprescription Emollient Foams.

Product	Active Agent
Salicylic Acid Acne Foam	2% Salicylic Acid
BPO Anti-acne Foam	5% Benzoyl Peroxide
Scytera	2% Coal Tar
Skin Whitening Foam	3% Mg Ascorbyl Phosphate (MAP)
"Instant" Skin Whitening Foam	MAP + Titanium Oxide
Anti-cellulite and Body Firming Foam	5% Caffeine
Sunscreen Foams Type I: chemical Type II: physical Type III: combination chemical and physical	Type II: Micronized zinc oxide & Titanium dioxide

Properties	Comments
Non-greasy o/w emulsion Alcohol-free (no skin drying or irritation) Moisturizing effect, to mitigate the drying effect of the active agent	Salicylic acid is listed as an anti-acne agent under the FDA OTC monograph.
Non-greasy o/w emulsion Contains the Natural Moisturizing Factor (NMF) , to mitigate the drying effect of the active agent Alcohol-free Preservative-free	Benzoyl peroxide is a highly effective anti-acne agent, approved by FDA for OTC use.
Non-greasy o/w emulsion The foam presentation decreases color intensity of coal tar from dark brown to off-white, making it stain-free The unique formulation neutralizes the typical smell of coal tar. Suitable for the treatment of scalp and whole body psoriasis. Suitable for the treatment of dandruff and seborrheic dermatitis.	Coal Tar is a highly effective anti-psoriasis and anti-seborrheic agent, approved by FDA for OTC use. The product is currently marketed in the United States and will become available worldwide.
O/W emulsion Alcohol-free Moisturizing effect Skin lubricating and conditioning effect Drip-free Cosmetically elegant	Based on the emollient foam technology platform. Proprietary product. Active approved in Japan for skin whitening.
As above with instant “cosmetic” whitening provided by titanium oxide Sun protection as an added benefit	Based on the emollient foam technology platform. Proprietary product. Unique combination product.
O/W emulsion Alcohol-free (no skin drying or irritation) Moisturizing effect (builds skin barrier) Refatting effect Drip-free Cosmetically elegant–spreads easily on large areas	Based on the emollient foam technology platform. Proprietary product. Uses penetration enhancers, to increase efficacy.
Alcohol-free (no skin drying or irritation) Moisturizing effect (builds skin barrier) Drip-free Cosmetically elegant–spreads easily on large areas	O/W or w/o emulsion foams. Proprietary products. Ability to include solids in foam based on Foamix’s suspension foam technology.

Nanoemulsion Foam

Nanoemulsion foam is a thermodynamically stable system with a typical droplet size in the range of 20-200 nm. Nanoemulsions show great promise for the future of topical drug therapies and cosmetics. They enable the solubilization of hard-to-dissolve active agents and increase their bioavailability, resulting in improved efficacy.

The technology is suitable for a variety of actives, including water-soluble and oil-soluble molecules, vitamins, hydroxyl acids, peptides and proteins, retinoids, antimicrobial, antifungal and antiviral agents, NSAIDs and hormones.

Hydroethanolic Foam

Hydroethanolic foams are the foam version of alcohol solutions and tinctures. Olux Foam and Luxiq Foam (Stiefel Laboratories), which contain 0.05% clobetasol propionate and 0.12% betamethasone valerate, respectively, were the first commercially available dermatological foams, and they gained high acceptance by physicians and patients. These are thermolabile foams, consisting of ethanol (about 60%), water, propylene glycol, cetyl alcohol, stearyl alcohol, polysorbate 60, citric acid, potassium citrate, and a hydrocarbon propellant. The launch of these products was followed by Extina Foam (ketoconazole foam 2%) and Evoclin Foam (clindamycin foam 1%). Studies conducted *in vitro* demonstrated that drugs, formulated in hydroethanolic foam exhibit delivery at an increased rate compared with other vehicles. For example, an *in vitro* skin penetration study, using Franz cells, demonstrated that the hydroethanolic foam vehicle delivered more clobetasol propionate through the skin (5.3%) than the comparator solution, cream and lotion vehicles (2.8%, 2.7%, 2.1% and 1.8% respectively).[11] These findings suggest that components within the foam (probably the alcohol) act as penetration enhancers, and alter the barrier properties of the outer stratum corneum, thus driving the delivered drug across the skin membrane via the intracellular route.

Since alcohol evaporates quickly from the skin, it also promotes fast drying of the skin and therefore is used to ameliorate the sticky feeling left by many topical formulations after application. However, alcohol extracts stratum corneum and sebum lipids that naturally moisturize the skin and therefore may cause skin to become dry and cracked. Due to this undesirable property, hydroethanolic foams have not been proposed for the treatment of atopic dermatitis, a childhood inflammatory skin disorder that involves dry, itchy skin and rashes on various body areas. Atopic dermatitis is also characterized by impaired skin barrier and enhanced penetration, and the use of ethanol can further promote percutaneous absorption instead of targeted delivery to skin layers.

The high incidence of skin irritation (burning, itching and stinging) as noted, for example, in the package insert of Luxiq Foam (54% ethanol content) is probably due to the high content of alcohol content, in combination with surfactants which are known skin irritants. Moreover, an even higher incidence of skin irritation was reportedly caused by this foam vehicle (75%); 27% of the population tested/ using

the product reported moderate-to-severe irritation. Furthermore, since alcohol is an irritant to mucosal surfaces, the label of these products states, "Avoid getting the foam in or near your eyes, mouth, lips, or broken skin."

In addition, the current hydroethanolic foams are thermolabile and their usage is hindered by the recommendation not to dispense them directly onto the hands, as the foam melts immediately upon contact with skin temperature. Instead, the foam is to be dispensed onto a cool surface, and then small amounts of foam should be picked up using the fingers and gently massaged into affected area.[27]

Thus, while alcohol is useful in solubilizing an active agent and enabling effective dermal penetration of drugs, the development of less irritable foam vehicles, which overcome the evident skin drying and irritation caused by the combination of alcohol and surfactants, was warranted. One of the means to achieve this goal is adding emollient oils to the foam composition. Such emollients provide skin conditioning effects, build up the skin barrier properties, and reduce skin irritation. An example of such commercially available foam is Scytera (Promius Pharma, developed by Foamix), a product containing 2% coal tar for the treatment of psoriasis. Scytera contains alcohol, but it also contains emollients. This novel foam vehicle is versatile and may be used to treat psoriasis even in areas of the body where the application is challenging, such as the scalp, palms, and soles.[28-29]

An additional way to overcome the usability limitations of the traditional hydroethanolic foams, which was developed by Foamix, is to omit the surfactants or to replace them by polymeric agents, resulting in foams which are thermally stable.[30,31] The absence of surfactants in the formulation further decreases the irritation potential of such formulations.

Potent Solvent Foam

A new platform of foam formulation is intended to promote transdermal skin delivery of drugs via the addition of high concentrations of skin penetration enhancers. Following the recent FDA approval of products containing up to 40% DMSO, an aqueous foam comprising 40% DMSO was developed by Foamix, which is suitable as a carrier for non-steroidal anti-inflammatory drugs that are intended to treat osteoarthritis, as well as other drugs that can be administered transdermally.[32]

Water-free Foams

The creation of foam formulations without water is counterintuitive. It is known in the art that foams can easily be formulated based on high amounts of water, in combination with surface active agents, foam adjuvants, and polymeric agents. As described in the literature, hydrophobic excipients, such as petrolatum, oils, and hydrophilic solvents, can have a de-foaming effect which makes the formulation of foams based on such solvents challenging. To overcome this challenge, substantial levels of surfactants that act as foaming agents have been used in the past; however, many surface active agents are known to be irritating to skin, especially ionic surface

active agents, and repeated application to the skin or mucosa in high concentrations can damage the integrity of the skin barrier and cause dryness and irritation.

Newly-developed water-free foams, which contain limited amounts of surfactants or no surfactants at all, are currently under development. While water-free foams are as-yet unavailable commercially, several products based on such foams that are under development are described in following sections.

Water-free foams have several advantages:

(1) **Stability.** The first and foremost advantage is that water-free foams are perfect vehicles for drugs and cosmetic active agents that undergo decomposition or are unstable in water. Many active agents, including corticosteroids, steroid hormones, immunomodulators, antibiotics, and water-soluble vitamins such as vitamin C, as well as other actives that contain ester groups, tend to degrade in the presence of water, so a vehicle that does not contain water is preferred. Moreover, the pressurized aerosol container is an impermeable packaging system, and as such, it prevents contact of the formulation with ambient moisture even during the use period, unlike tubes which are exposed to the environment once they are opened.

(2) **Self-preservation.** Microorganisms require water to grow and reproduce. A water-free foam formulation prevents the growth of bacteria, molds and fungi during storage, and, as mentioned, the entry of moisture into the aerosol pressurized can is prevented during the use period, so water-free foams do not require the inclusion of preservatives.

(3) **Usability.** Today's water-free topical formulations are primarily ointments, which are characterized by being thick and greasy, and they require extensive rubbing for efficient topical application. In contrast, foams are structurally soft and their application is facile. They spread easily onto the skin and absorb quickly.

(4) **Skin hydration and conditioning.** Hydrophobic excipients such as petrolatum and liquid oils act to mitigate skin dryness and ameliorate inflammation through their emollient and humectant properties. They make the external layers of the skin (epidermis) softer and more pliable, thereby increasing the skin's hydration (water content) by reducing water evaporation. Hydrophilic excipients, such as polyethylene glycol, propylene glycol, and glycerin are hygroscopic—they attract ambient water and retain skin moisture. Water-free foams are rich with such emollients and humectants, so they maximize skin hydration and conditioning.

Ointment Foam – Petrolatum-based Foam

Ointment foam is the foam version of traditional petrolatum-based ointments.[33] When applied to skin, petrolatum can generate an occlusive layer and lower TEWL.

Petrolatum-based foam formulations may be complicated to make, especially due to the high viscosity of the hydrocarbon; however, there are now under development ointment foams that contain up to 90% petrolatum. The foaming agents in such formulations include small amounts of foam adjuvants and nonionic surfactants. The propellant is typically hydrocarbon.

Due to the unique texture of the foam, it instantly liquefies and spreads easily

onto the skin upon application, and no extensive rubbing is required. Thus, the benefit of petrolatum's occlusive shield is retained without the thick texture and greasy feel of traditional ointments. This usability feature is especially valuable in the treatment of infants and children who suffer from dry skin conditions like atopic dermatitis. In such cases, the effect of the drug is accompanied by the synergistic skin barrier buildup, and lubricating and protective properties of the vehicle.

Examples of drugs that can benefit from this type of formulation include corticosteroids, which are typically applied to large areas of dry, inflamed and damaged skin, anti-infective agents (antibacterial, antifungal, and antiviral drugs) and immunomodulators (such as pimecrolimus and tacrolimus) which are used to treat atopic dermatitis. An illustrative example is a unique petrolatum-zinc oxide foam (petrolatum and natural oils, 91%; zinc oxide, 15%). Petrolatum is approved by FDA as an OTC active ingredient that helps treat and prevent diaper dermatitis, seal out wetness, and temporarily protect against and provide relief from chapped or cracked skin, as well as minor cuts, scrapes, and burns. Likewise, zinc oxide, the active ingredient in many diaper dermatitis products, is a skin protectant and an antimicrobial agent. It protects by forming a protective barrier on the skin, preventing wetness and other irritants from reaching the skin underneath. Unlike traditional petrolatum-based pastes for diaper dermatitis, which are very thick and hard to apply to the baby's sensitive skin, the petrolatum-zinc oxide foam is easy to apply, and still provides the same protective and healing effects. This synergistic composition can be further enhanced by the addition of an antimycotic agent (such as miconazole, ketoconazole, clotrimazole, or nystatin) to eradicate yeast infections.

Oil Foam

Oil foam is the foam version of traditional oil-based solutions and suspensions.[34] Oil foam is one of the most promising foam platforms for use in dermatology, as it can utilize a broad range of pharmaceutical liquid oils, including mineral oil, plant-derived oils (e.g., olive oil, soybean oil, and castor oil), emollient esters and alcohols (e.g., isopropyl myristate, isopropyl palmitate, diisopropyl adipate, isostearic acid, and oleyl alcohol), and silicone oils.

Despite the fact that oils are generally known as de-foaming agents and their incorporation in foam formulations is challenging, studies have shown that use of a unique proprietary technique can yield a foamable composition containing more than 90% oil content. Such a composition contains very small amounts of foaming agents and no water whatsoever. The foaming agents include lipophilic surfactants with low HLB, foam adjuvants (fatty acids and fatty alcohols), waxes, and polymers. In certain cases, when a drug is to be included in the vehicle that is incompatible with surfactants, the aforementioned technique even allows the creation of foam compositions with no surfactants at all.[35-36] The most suitable propellants for such foams are hydrocarbon propellants.

Oil foams have a very soft and airy texture; they spread effortlessly on the target surface and quickly absorb into the skin, leaving no greasiness at all. In fact, oil

foams are so cosmetically elegant that they can be used for the treatment of facial conditions, even if those conditions are associated with oily or sensitive skin, as in the cases of acne and rosacea.

Oil foam is the most suitable form to accommodate unstable drugs. For example, it has been used as a vehicle for calcipotriene and calcitriene, two vitamin D3 analogs to treat psoriasis and atopic dermatitis, resulting in stable drugs with more than two years of shelf life. The most advanced oil foam product in private development is Minocycline Foam (1% and 4%).[37,38] Minocycline is an antibiotic known to be very unstable, since it is degraded by a wide range of commonly used pharmaceutical excipients. For example, it degrades readily in the presence of hydrophilic solvents (such as water, glycerin, sodium PCA, propylene glycol and polyethylene glycols), polymers (such as xanthan gum, poloxamers, carbomers, and methocel), and surfactants (such as polysorbates, sorbitan esters, polyoxyalkyl esters, and lanolin-based surfactants). Hence, the development challenge was to attain a stable foam composition without the hydrophilic compounds, which are usually used as foaming agents. A series of development efforts resulted in a water-free, alcohol-free, and surfactant-free formulation which contains more than 80% liquid oils, where the foaming agents are fatty alcohols, fatty acids, and waxes.

The Minocycline foam has the following features:

Stability: Minocycline Foam 1% and 4% exhibit high stability. They remain within the designated specifications following 12 months' storage at 40°C and over 24 months at 25°C.

Antibacterial effects: In vitro studies have demonstrated that Minocycline Foam 1% and 4% effectively inhibited the growth of *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, a methicillin-resistant strain of *Staphylococcus aureus* (MRSA), and *Propionbacterium acnes*, the causative microorganism in acne.

Inhibition of inflammation and apoptosis: UVB irradiation of the skin is known to decrease cell viability and total antioxidant capacity, while increasing the levels of inflammation (pro-inflammatory cytokines secretion) and epidermal cell apoptosis. Exploratory studies have revealed the beneficial effects of Minocycline foam on cell viability and apoptosis of skin cells: treatment prior to irradiation results in more than 50% inhibition of apoptosis, as measured by caspase 3 activity; and treatment after irradiation results in 60% inhibition of apoptosis, as measured by caspase 3 activity. Capsase 3 is a cytokine that plays a key role in apoptosis, defined as programmed cell death that is accelerated in inflamed tissues.[44]

Targeted delivery of Minocycline into the skin: The transdermal penetration of Minocycline was tested using the Franz cell *in vitro* diffusion system, with porcine ear skin. Approximately 500 mg of product was placed in each cell; the receiver compartments were sampled at baseline and 3, 6, 9 and 24 hours following application, respectively. After 24 hours the amounts of Minocycline in the upper and lower stratum corneum layers (SC1 and SC2) and viable skin were analyzed. As shown in **Table 3**, the drug was delivered exclusively into the skin. The mean amount of

Minocycline in the skin following 24 hours of exposure was 9.5 μg/cm² for the 1% formulation and 43 μg/cm² for the 4% formulation. The weight of skin at the delivery area is about 100 mg, which implies that the concentration of Minocycline in the skin following 24 hours of exposure is about 168 μg/gr of skin for the 1% formulation and about 760 μg/gr for the 4% formulation. This amount is an effective dose for the treatment of bacterial skin infections. No transdermal passage of Minocycline was observed, indicating that Minocycline foam should not generate any systemic adverse effects.[44]

Table 3. Minocycline Foam 1% and 4%; Measure Skin Delivery Comparison

	Minocycline Foam 1% (n=5)		Minocycline Foam 4% (n=6)	
	Minocycline μg/cm²	STD	Minocycline μg/cm²	STD
Stratum Corneum SC1	7.77	4.32	33.63	20.41
Stratum Corneum SC2	0.93	0.77	7.49	8.67
Total Stratum Corneum	**8.70**	**4.97**	**41.12**	**16.89**
Viable Skin	0.79	0.19	2.00	0.81
Total Intradermal Delivery	**9.49**	**4.99**	**43.12**	**17.48**
Receiving Compartment (Transdermal Delivery	0.00	-	0.00	-

Minocycline foam is safe and effective in the treatment of acne:[39] A randomized double-blind dose-ranging Phase II clinical study was conducted to assess the efficacy and safety of Minocycline foam in 150 patients with moderate to severe acne who received placebo or one of two Minocycline foams (1% or 4%) once daily.

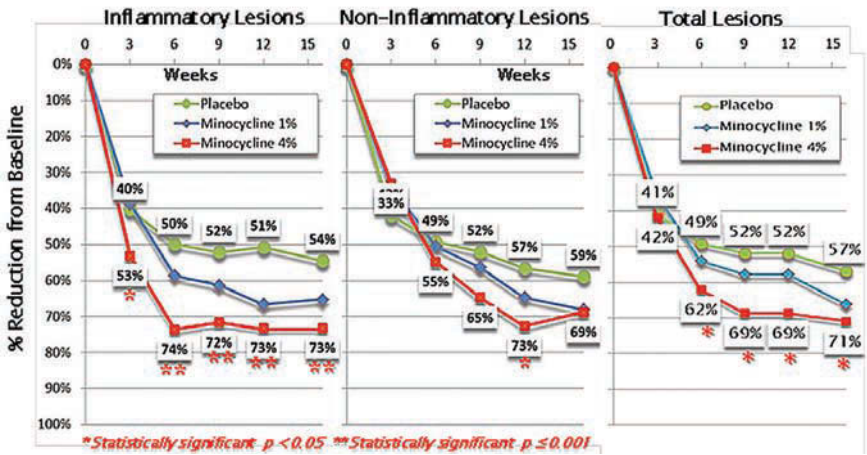

Figure 5. Percent reduction of inflammatory, non-inflammatory and total count of acne lesions

As shown in **Figure 5**, six weeks' treatment was enough to reach more than 70% reduction in the inflammatory lesions. Even after three weeks of treatment the reduction of inflammatory lesions was 53% and statistically significant. The effects were dose-dependent, as demonstrated by the higher effects of the 4% foam and the placebo (Figure 5). **Figure 6** exemplifies an acne patient who had 49 lesions at baseline (23 inflammatory lesions, 26 non-inflammatory lesions) and who improved dramatically after nine weeks of treatment.

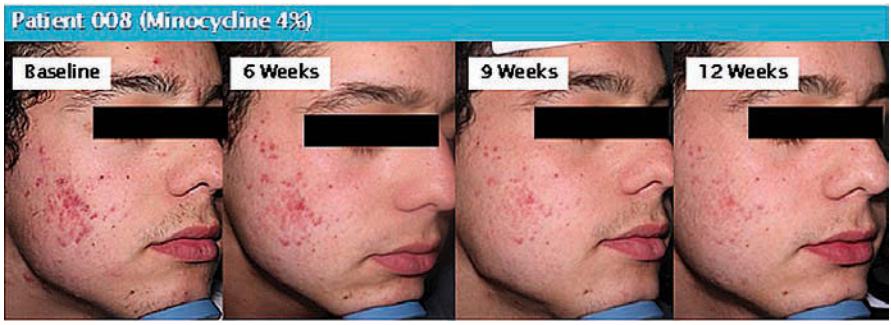

Figure 6. Photographic documentation of the effect of Minocycline foam in a severe acne patient. Dramatic improvement is observed after 9 weeks of treatment

Minocycline foam is safe and effective in the treatment of impetigo[39]*:* A randomized double blind dose-ranging Phase II clinical study was designed to assess the efficacy, safety, and tolerability of two strengths of the Minocycline foam in pediatric patients with impetigo. Impetigo is a highly contagious bacterial skin infection. The study enrolled 32 pediatric patients ages 2 to 15 with at least two impetigo lesions. Patients applied the foam twice daily for 7 days; and they were checked again on day 14. Strong efficacy was demonstrated in both 1% and 4% levels. Clinical effectiveness was defined as the absence of treated lesions, or treated lesions that had become dry without crusts with or without erythema compared to baseline, or had improved (defined as a decline in the size of the affected area, number of lesions, or both) such that no further antimicrobial therapy was required. Notably, about 80% of the patients in both groups saw improvement, or disappearance of the lesions, and met the efficacy criteria after 3 days of treatment. Clinical response at the end of the treatment was 92% and 100% respectively for the low or high doses; and all patients (100%) demonstrated improvement on day 14 (**Table 4** and **Figure7**).

Eleven of the study patients had methicillin-resistant *Staphylococcus aureus* (MRSA) infection at baseline, and in all cases the infection was eradicated on Day 7.

Minocycline foam was well-tolerated and no drug related side effects were recorded in any of the patients throughout the study. Questionnaires, filled by the patients' caregivers revealed high satisfaction from treatment.

Table 4. Minocycline Foam 1% and 4%: Success rate at Day 3, Day 7 (End of Treatment) and Day 14 (Follow-up)

	1%	4%	All
Day 3	81.3%	78.6%	80.0%
Day 7 (EOT)	92.3%	100.0%	95.8%
Day 14 (FU)	100.0%	100.0%	100.0%

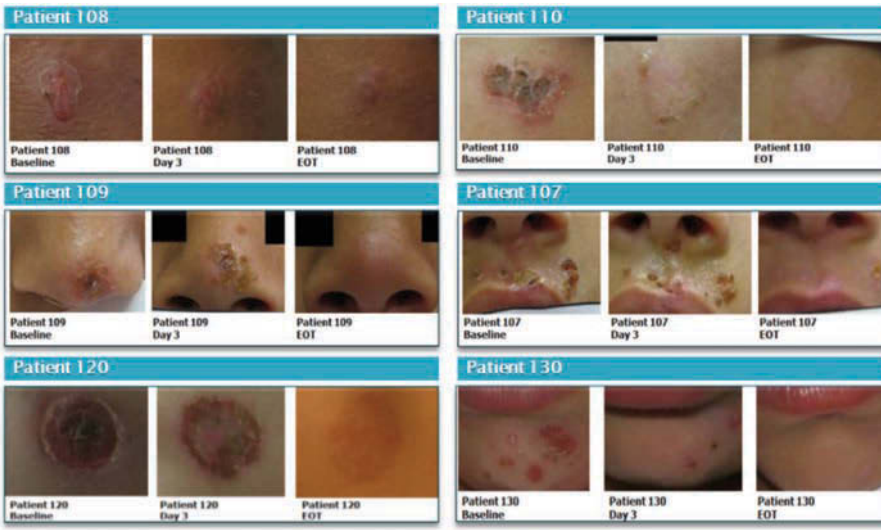

Figure 7. Photographic documentation of the effect of Minocycline foam in pediatric patients with impetigo, demonstrating visible improvement or clearance of lesions within 3 to 7 days of treatment.

Hydrophilic Waterless Foam

Hydrophilic waterless foam is the foam version of traditional hydrophilic ointments.

This foam can contain up to 98% polar hydrophilic solvent, which may be selected from the following groups of compounds: (1) polyols (organic solvents that contain at least two hydroxy groups in their molecular structure); and (2) polyethylene glycols (PEGs). The polyols can be selected from the group of di-alcohols, such as propylene glycol, butanediol and diethylene glycol, and tri-alcohols, such as glycerin. The PEGs can be primarily low-molecular weight liquid PEGs, such as PEG 200, PEG 400, PEG 600 and PEG 1000; however, mixes of the liquid PEGs with higher molecular weight such as PEG 4000, PEG 6000, and PEG 8000 may be used as long as the viscosity, prior to filling of the composition into aerosol canisters, is less than about 10,000 CPs. The addition of secondary polar solvents, such as dimethyl isosorbide, ethoxydiglycol, DMSO, and alpha hydroxy acids, such as lactic acid and glycolic acid, is sometimes warranted in order to enhance solubilization and skin

permeation of the drug.[40] These properties enable increased permeability across the skin, resulting in an enhanced therapeutic effect.

The foaming agents include up to 5% surfactants and small amounts of polymers, and the propellants can be hydrocarbon propellants and fluorocarbons.

Polyols, PEGs, and other polar solvents have a great affinity for water; as such, they exhibit hygroscopic properties. Microorganisms require water to grow and reproduce, thus the high concentration of polar solvents that absorb and hold free water in order that it be unavailable for bacterial population, the result being an inhibition of the growth of bacteria and fungi. Consequently, waterless hydrophilic foams do not require preservatives in their composition; furthermore, their application onto an infected skin surface can be used as a topical treatment for superficial infectious conditions. It is further possible to add an anti-infective (antibacterial or antifungal) element that may enhance the formulation's effect and, consequently, render higher treatment success.[41,42]

Saccharide Foam

Saccharide foam, which contains up to 90% monosaccharides, disaccharides, or honey was developed for the treatment of wounds and burns.[43] The foam is soft and easy to apply on the target site of treatment, with no need for extensive rubbing. It is hygroscopic, and thus it has anti-infective attributes and absorbs exudates. In addition, high percentages of sugars in the formulation are known to generate a high-osmolality environment that is hostile to microbial proliferation.

How to Formulate Foam Products

Most foams used in pharmacological and cosmetic applications are aerosol foams, which comprise a semi-solid formulation, packaged in an aerosol can and pressurized by a propellant.

An aerosol is made up of several basic components:

- An aerosol can
- The bulk product (semi-solid formulation)
- The propellant
- A valve
- An actuator
- A dust cap

The preparation of the semi-solid bulk (termed pre-foam formulation or PFF) depends on the type of composition used. For example, emollient (emulsion-based) foams are produced in the following sequence:

1. PFF production

(a) *Aqueous Phase preparation:* Gelling agents and surface-active agents are dissolved in water with agitation. The solution is warmed to 50-70°C. Water-soluble cosmetic or pharmaceutical active ingredients and optional water-soluble ingredients are added with agitation to the aqueous phase mixture.

(b) *Hydrophobic phase preparation:* The hydrophobic solvent is heated to 50-70°C. Foam adjuvants (e.g., fatty alcohols and/or fatty acids) are added to the hydrophobic solvent with agitation; followed by the addition of oil-soluble cosmetic or pharmaceutical active ingredients and other optional oil-soluble formulation ingredients.

(c) *The warm hydrophobic phase* is gradually poured into the warm aqueous phase, with agitation, followed by homogenization. The mixture is allowed to cool down to ambient temperature. In case of heat-sensitive active ingredients, they can be added with agitation to the mixture after cooling to ambient temperature.

2. Packaging and pressurization

The mixture, at ambient temperature, is added to an aerosol container, the container is sealed with a valve and an appropriate amount of propellant (typically 6-12% of the composition) is added under pressure into the container.

The most commonly used propellants are hydrocarbon mixtures, which comprise n-butane, isobutane, and n-propane in various ratios. These hydrocarbons are gasses at ambient temperature; however, when stored under pressure, they are liquefied. Alternatively, fluorocarbon propellants, such as 1,1,1,2 tetrafluorethane and 1,1,1,2,3,3,3 heptafluoropropane, can be used.

When single-phase foams are prepared, such as aqueous foams and hydroethanolic foams, as well as oil foam and waterless hydrophilic foams, the primary solvents and foaming agents are mixed together to form a uniform bulk PFF, which is in turn added to the aerosol can and pressurized as described above.

While the preparation of PFFs can be performed in any formulation laboratory, the stages of packaging into the aerosol cans and the pressurization require specialized equipment. The assembly of the valve to the can is carried out using a specialized crimper, which compresses the edges of the valve and secures tight attachment of the valve to the can. This is a very critical operation and the crimping machinery has to be carefully set up to ensure that the can/valve seal does not leak. The preferred crimper for this operation is a "vacuum crimper," which is capable of drawing the air from the can prior to sealing it with the valve.

The pressurization of the product also requires specialized equipment, as the propellant is injected into the can under pressure, through the valve. The propellant may be in the form of a liquefied gas, or a compressed gas. When a liquefied gas is used it will exist as both a liquid, and vapor in the aerosol can head space. A significant part of the propellant will be dissolved in the PFF, resulting in an increase of the volume of the semi-solid bulk. To ensure product integrity, each can is immersed in a water bath at 50°C to check for any leaks. Any cans that leak are rejected.

Once the process of preparing the PFF, packaging it in the aerosol can, and pressurizing it is completed in laboratory scale, it is usually readily scalable to commercial amounts, using industrial manufacturers.

Methods of Evaluation of Foam Products

The following section provides test methods for the evaluation of foam products. The chemical analysis is important to ensure the compliance of a product with the specified concentration of active ingredients, and to follow-up the stability of the active agents. The physical parameters are also related to the integrity, uniformity, and stability of the product; moreover, they are important properties in terms of the usability of the product.

Chemical Analysis

Active ingredients and preservatives are commonly quantified in pharmaceutical and cosmetic preparations as part of the quality control and stability evaluation of such products. Foams are unique in the sense that the composition within the aerosol container includes a propellant, which evaporates immediately upon dispensing. Therefore, it has been accepted that the quantitation should be done *in the absence of* the propellant to mimic real "in use" conditions.

Accordingly, the testing sample preparation includes (1) shaking the canister well and dispensing an initial quantity to waste; (2) transferring to a beaker a sufficient quantity for duplicate preparation; (3) de-aerating the dispensed foam by mixing with a glass rod. Aliquots of the de-aerated sample are then weighed accurately and processed for analysis by chromatography (e.g., GC, HPLC or UPLC) using customary methods.

The method of analysis of preservatives in Scytera was recently published by Dr Reddy.[44]

Physical Foam Properties

The physical characteristics of the foam are important for ensuring acceptance and facile usability of the product by the consumer. The principal physical properties of foam are presented below, alongside with the methods to quantify them.

Foam quality:

Foam quality can be graded as follows:

Grade E (excellent): Very rich and creamy in appearance; does not show any bubble structure or demonstrates a very fine (small) bubble structure; does not rapidly become dull; upon spreading on the skin, the foam retains the creaminess property and does not appear watery.

Grade G (good): Rich and creamy in appearance; very small bubble size; "dulls" more rapidly than an excellent foam; retains creaminess upon spreading on the skin and does not become watery.

Grade FG (fairly good): A moderate amount of creaminess is noticeable; bubble structure is noticeable; upon spreading on the skin, the product dulls rapidly and becomes somewhat lower in apparent viscosity.

Grade F (fair): Very little creaminess is noticeable; larger bubble structure than a FG foam; upon spreading on the skin, it becomes thin in appearance and watery.

Grade P (poor): No creaminess is noticeable; large bubble structure; when spread

on the skin, it becomes very thin and watery in appearance.

Grade VP (very poor): Dry foam, large very dull bubbles; difficult to spread on the skin.

Topically administrable foams are typically of quality grade E or G, when released from the aerosol container. Smaller bubbles are indicative of more stable foam, which does not collapse spontaneously immediately upon discharge from the container. The finer foam structure looks and feels smoother, thus increasing its usability and appeal.

Foam density:

Density is also a distinguishing factor in at the assessment of the quality of foams. The density of a foam product is quantified by dispensing into vessels (including dishes or tubes) a known volume and weight of the foam product, as follows:

The foam product is allowed to reach room temperature. The canister is then shaken well to mix the contents and 5-10 g of product are dispensed and discarded thereafter. Then, foam is dispensed into a pre-weighed tube, filling it until excess is extruded from the other side of the tube. The excess of foam at both ends is removed and then the tube, filled with foam, is weighed on an analytical balance. The density is calculated by dividing the net weight of the foam by the volume of the tube. Replicate measurements are recommended.

The density of the foam is related to the foam class, as provided above. Water-containing foams are less dense and their density is typically less than 0.1 g/mL. Frequently, the density of hydroethanolic foams and emollient foams is in the range of 0.03-0.06 g/mL, which makes their application very easy.

Water-free foams are "heavier" when applied and their density can range from 0.1-0.25 g/mL. Even such dense foams spread very easily and absorb quickly into the skin.

Breakability and collapse time:

An important property of foams is breakability, i.e., the way the foam breaks down or collapses upon release from the aerosol can. Foams can be classified into three classes: stable, quick breaking foam, and breakable.

A typical example of stable foam is shaving foam. Shaving foams possess remarkable stability upon release from the aerosol can, and they do not break down even upon extensive rubbing onto the skin. Such stable foams are not suitable for topical therapy of skin conditions as they do not absorb into the skin upon application.

By contrast, quick breaking foams are inherently unstable and thermolabile, i.e., they readily collapse or melt upon exposure to body temperature.[45] The quick breaking property is usually caused by the presence of ethanol in the foam composition, and the breaking temperature can be somewhat modulated by changing the alcohol to water ratio in the quick-breaking temperature sensitive foam composition. The usability of quick breaking foams is hindered by the fact that the foam quickly collapses upon dispensing to one's fingers prior to application to the target area.

Breakable foams are thermally stable, yet break under shear force. Shear-force

breakability of the foam is clearly advantageous over thermally induced breakability. The breakable foam does not collapse quickly upon expulsion, and it does not readily collapse or melt upon exposure to skin temperature, allowing for comfortable application and well directed administration of the preparation to the target area. The difference between quick breaking thermolabile foam and breakable foam is illustrated in **Figure8**. In the figure, the breakable foam is stable, resulting in facile application and spreading, while the hydroethanolic foam instantly melts on the fingers, which makes the application to the target site challenging and difficult spreading over large skin areas

The tendency of a foam to collapse upon exposure to skin temperature is examined by dispensing a given quantity of foam and photographing sequentially its appearance over time at 36°C. This "collapse time" is determined as the time that elapses until the height of the foam is reduced to 50% of its original value. Preferably, to ensure convenient application, the foam should maintain its structural stability at skin temperature for at least 1 minute and, more preferably, more than 2 or 3 minutes.

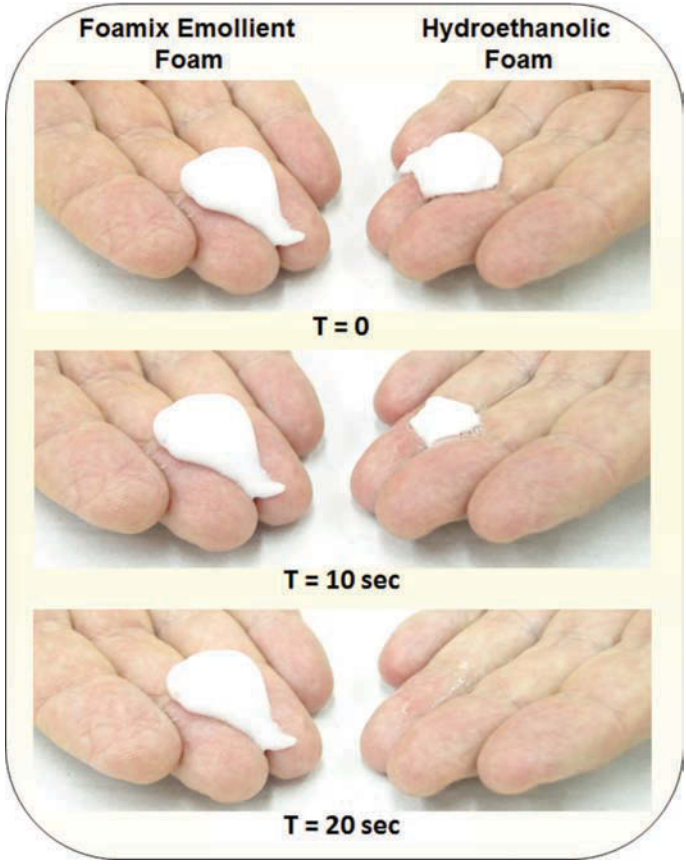

Figure 8. Breakable emollient foam (Foamix) vs. quick breaking hydroethanolic foam

Summary

Creams and ointments have been used historically in skin care and dermatology. Foams offer an innovative and more convenient means of topical treatment of the skin. The continuing development of versatile foam technology platforms will facilitate achieving new topical products, including valuable drugs for the treatment of dermatological mucosal and body cavity conditions. The advantages of foam in terms of enhanced usability and compliance, improved clinical safety, tolerability and efficacy, stability, and targeted drug delivery will enhance therapy and the future development of therapeutic and topical treatments and products.

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SECTION III:

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CHAPTER 10

Using Experimental Design to Optimize Formulations

Joseph Albanese

Key Words:

Design of Experiments, Synergy, Optimization, Cost Reduction, Enhanced Performance, Claim Substantiation, Mixture Designs, Factorial Design, Cornell, Ingredient Interactions

Introduction

Carefully constructed, statistically designed experiments facilitate the analysis of collected data in a logical and expeditious fashion. Such a sound scientific approach offers the best chance of success for the experienced cosmetic chemist hoping to find and take advantage of synergistic interactions between ingredients in a formulation and/or manufacturing process. This chapter will provide a very specific definition for synergistic ingredient interactions.

The rationale behind the search for such synergies is the prospect of achieving an optimized product that will be the most cost-effective, while still offering the best overall performance and customer satisfaction. Furthermore, a well-planned statistical approach will provide in-depth knowledge and greater understanding of the product with a minimal amount of experimentation, thereby saving both time and money. It will provide a good measure of experimental error, which is useful for making performance predictions with confidence. Reproducible results will lead to the development of a more robust product able to endure the vagaries of the manufacturing environment. It certainly is also possible to accelerate speed to market, and potentially uncover new patent opportunities otherwise overlooked or left undiscovered. From an additional marketing perspective, it may also help sell a treatment regimen because it might demonstratively substantiate a claim that multiple products work in harmony to give a synergistic effect. In stark contrast, statistical analysis of data gathered from a set of experiments run in a helter-skelter

fashion or by changing only one-factor-at-a-time (OFAT), while holding all other factors constant, often fails to garner any valuable learning.

This chapter will not delve into the complicated mathematical proofs and computer algorithms used in the sophisticated experimental design software programs of today. The scope of this chapter will be limited to mixture designs, with only brief reference to factorial, mixture/amount and mixed designs.

What is Experimental Design?

Statistics began when William Sealy Gossett developed the "t-test" to analyze data collected at the Guinness Brewery. Since that time, the field of statistics continues to evolve. Today, more and more product and process development groups no longer limit their use of statistics to the analysis of historical data. Wise researchers also use statistics to design the experiments that will generate the data. Experimental Design is a scientific statistical approach to experimentation known as DoE, which is simply an acronym for *Design of Experiment*. Using DoE the scientist plays a proactive role in developing a comprehensive strategy that is an efficient and expedient way to gain much information with a minimum amount of time, effort, and cost. More importantly, it allows the simultaneous examination of multiple independent variables, which are under the control of the experimenter. Examples of these independent "control variables" (also known by statisticians as "factors") manipulated by the researcher as he/she designs the experiment may be the components or ingredients in a formulation, the process parameters used in the making procedure or other quantitative variables measured on a continual scale. There may also be certain categorical factors that examine, for example, differences between ingredient suppliers that a researcher may wish to investigate.

What one wants to see and understand are how these deliberate and simultaneous changes to various control factors affect the measured responses, or what statisticians refer to as "dependent variables." DoE permits simultaneous changes of multiple controlled variables and examines their effect on one or more dependent variables (responses). It is far superior to the "knock out approach" where only one ingredient (factor or parameter) at a time can change. That is because one likely will miss interactions that may point to synergy, an optimized formula or set of conditions. DoE is a powerful tool that can predict responses for batches that one has not even made yet. In order to determine the direction for optimization it is essential that each response is quantifiable on a continuous scale. In order to satisfy this requirement, one can use a ranking or rating scale for sensorial responses.

Harry's Cosmetology agrees that the role of computer statistical software programs in identifying synergistic ingredient interactions and formula optimization is increasing. It is an interesting historical sideline to note that researchers at Helene Curtis optimized the original *Finesse* shampoo this way.[1]

"Unfortunately, many chemists still spend their energies on experimental programs that produce much data but little information. Part of this failure stems from a reluctance to recognize the important influence of experimental error, to part from the study-only-one-factor-at-a-time syndrome, and to part from the habit of searching for that unique set of successful experimental conditions in absence of a model, however empirical. The good news is that more and more chemists are becoming aware of the power of statistical design of experiments."

J. Stuart Hunter,
"Applying statistics to solving chemical problems", CHEMTECH, March 1987

Some of the reasons for not wanting to utilize DoE are simply not justifiable.[2] These include:

- "We have always done things this way." In my book, this is never an excuse for not learning a new technique.
- "I don't want a computer program to create my formulas." The programs are only as good as the information you, the scientist, input; the old adage, "garbage in, garbage out" still applies.
- "The results I get from only investigating two, three or even four ingredients (factors) will not be reproducible in the final formula due to uninvestigated effects of additional ingredients like perfume, which we did not include in the experiments." There is some validity to this reasoning. It is true that a higher number of variable factors and levels investigated may exponentially increase the number of experiments, or trials, which may have to be conducted. However, there are DoE programs and computer algorithms that allow the investigation of many different factors with far fewer batches (trials) than you might imagine.
- "If I optimize for one response, another one will be compromised." No doubt, this is often the case. However, you may assign a weighted value to each response to give more or less importance to it. In addition, many programs allow you to find the best compromise (or "sweet-spot") for all the responses.
- "It's an unnecessary luxury that I do not have time for." Well, that certainly may be. Sometimes people need an answer immediately and any improvement will do, even if it is not the best possible answer.

To repeat, perhaps the most important reason for using DoE to optimize a formula is the possibility of discovering hidden synergies that are impossible to find by changing only one factor at a time. These synergistic interactions are useful in enhancing performance and in reducing the total percent solids (saves money)

required to achieve a desired effect. Although adding variables increases the number of possible trials exponentially, DoE software algorithms will significantly reduce the percentage of trials actually needed to optimize a formulation.

Factorial Designs

The simplest type of experimental design consists of two-level [high (+) and low (-)] factorials that may have anywhere from two to 24 different factors of interest and one or many more responses.

If researchers want to know how lemons and sugar water affect the taste of their company's new lemonade, they might set up a traditional factorial design. With only two ingredients (factors) in the formula, the experiment is simple and they are only interested in testing two different use levels of each ingredient, the aforementioned high (+) and low (-). They are interested in just the one response, namely taste.

The full factorial design for this simple experiment, shown in outline below, includes all possible combinations of the two ingredients and their respective use level. Both Run#1 and Run#4 are precisely the same formula because the ratio of lemons to sugar water remains unchanged. Doubling the amount of both ingredients simply yields twice the amount of lemonade. It has no effect whatsoever on taste. Therefore, the extra run is just wasted effort.

As we will see later, this very simple experiment with two ingredients at two different use levels does not comply with the constraint that the total amount must remain constant. This is why factorial designs do not work for optimizing formulations.

Run #	Cups of Lemon Juice	Cups of Sugar Water Total	Ratio of (Lemons/Water)	Response (Taste)
1	1 (-)	1 (-)	2 / 1	Good
2	2 (+)	1 (-)	3 / 2	Too Sour
3	1 (-)	2 (+)	3 / 0.5	Weak
4	2 (+)	2 (+)	4 / 1	Good

Please note the following notation employed in describing these experiments. The base number indicates the number of use levels and the "exponent" the number of factors. Thus,

2^3 = three factors at two different use-levels (low and high)
3^2 = two factors at three different use-levels (low, middle, and high)

If you have more than four factors to consider, it is not necessary to start with a full factorial design. Start with a fractional factorial; you will still be able to get information on any interactions. Usually one will discover that embedded in the full factorial are the partial factorial runs. So, if the partial does not provide all of

the answers, one is already well on the way to completing the extra runs needed for a full factorial. However, for optimizing formulations it is far better to run a mixture design.

Mixture Designs

The formulation chemist works with a plethora of cosmetic raw materials.[3-4] Through education, experience and knowledge of cosmetic chemistry, one selects the most suitable ingredients to try. From this refined palette, the first prototype formulations come together. Once these prototypes are tested against the objectives of the project, the formulator must often return to the lab bench. Where, through a process of trial and error a finished marketable formulation gradually begins to emerge.

However, going back and forth changing and then re-testing just one parameter at a time, which still seems to be the norm in the personal care industry, is an inferior approach. This is because there was no significant learning acquired on how ingredients and/or processes interact to affect product attributes. By changing only one factor at a time, it is impossible to identify synergistic interactions and opportunities to take advantage of them are lost. In addition, one ends up losing valuable time preparing many unnecessary batches that provide no direction to guide formula enhancements in a timely fashion. To exacerbate the situation, as development costs increase, the speed to market slows down.

More reliably, DoE allows the experimenter to change multiple parameters at once to see how a *combination of changes* affects the key attributes under investigation. Even in complex sophisticated formulations, the ingredients having the main effects on the desired responses (attributes) become obvious. Be forewarned, DoE is *not* going to replace much needed formulation skills and creative artistry, gained only through education and on-the-job experience, but it will complement and expedite the formula development process.

A pure mixture design is an experiment in which the response depends only on the relative proportions of the ingredients present in the mixture and not on the amount of the mixture. When the total amount is constant then the behavior of the measured response is purely a function of the combined blending properties of the ingredients in the formula.

For a cosmetic formulation, no matter how simple or complex, the primary constraint of the design is that all of the ingredients add up to a constant. If expressed as fractions of the formula, they must always sum to unity:

$$X_1 + X_2 + X_3 = 1/3 + 1/3 + 1/3 = 1, \text{ or } 2/3 + 1/3 + 0 = 1, \text{ etc.}$$
$$0 \leq Li \leq Xi \leq Ui \leq 1$$
Where Li = lower level, Xi = unknown and Ui = upper level

Therefore, unlike in a factorial design, the factors in a mixture design really are

dependent upon one another. They are still under the control of the experimenter but the use level of one determines the use level of the others. Thus if one knows the use level of two of the three factors (ingredients) in a batch, it is easy to calculate the third by simply solving the proportion. Solve for X3 if both X1 and X2 = 1/3 …

$$X_1 + X_2 + X_3 = 1 = 3/3$$
$$1/3 + 1/3 + X_3 = 3/3$$
$$X_3 = 3/3 - 1/3 - 1/3 = 1/3$$

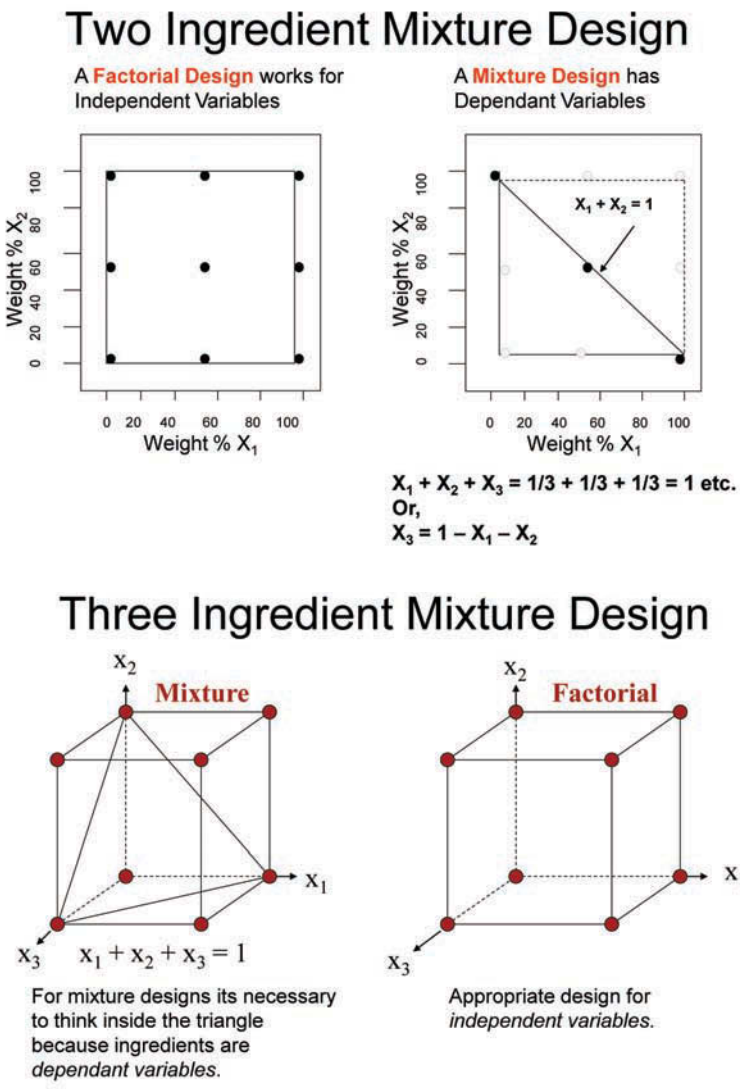

Figure 1. Comparison schematic: Mixture Design vs. Factorial Design

Mixture/Amount Design

A mixture/amount design is an experiment where the amount of the mixture varies as well. In this case, the response depends not only on the relative proportions but also on the total amount of the ingredients. **Figure 1** offers a comparison of mixture and factorial design. It is a great way to screen for the lowest possible threshold amounts of ingredients required to reach a desired and quantifiable response. For example, is 12% enough total surfactant to achieve desired cleansing and foam attributes? On the other hand, does the formula need 18%? It is not the recommended way to find or demonstrate synergistic interactions of formulation ingredients, but it is a great first step.

Exactly What Is Synergy?

Buckminster Fuller popularized the word "synergy" and now, it seems, everyone is using it.[35] Nearly everyone accepts that synergy means, or implies, that the sum measure of something is greater than the expected sum of its component parts. It is more than an additive effect, and its antithesis is antagonism.

- 1 + 1 = 2 is an additive effect.
- 1 + 1 > 2 is a synergistic effect.
- 1 + 1 < 2 is an antagonistic effect.

There are various approaches for identifying synergistic interactions depending upon the field of research. Two ways are the Beta (β) Parameter[6] used by scientists looking for synergistic interactions between surfactant blends and the Kull Equation[7-8] used by microbiologists (and other disciplines) to calculate the Synergy Index. In the paper, "What is Synergy?" printed in the *Pharmacological Review*, researcher/author M.C. Berenbaum uses an Isobole Method to determine if drugs are interacting together in a beneficial way (synergy; when the dosage required to achieve the desired effect is reduced to a concentration below what can be predicted) or against one another (antagonism).[9]

The Kull Equation, which calculates a term called the Synergy Index (SI), can tell you if a synergy exists but it does not provide a strategy for determining what relative proportions of A + B to test. It rather puts the cart before the horse.

$$SI = CD/A + CE/B$$

Where: A = the minimum amount of component "A" to reach a desired endpoint; B = the minimum amount of component "B" to reach a desired endpoint; C = the minimum amount of component "A + B" to reach a desired endpoint; D = the Amount of "A" in "C"; and E = the Amount of "B" in "C"

Unlike the aforementioned approaches, one simply cannot support a true synergy claim in formulation optimization unless the following definition is satisfied:

In a controlled mixture, a synergistic interaction indicates that the combined effect of two or more ingredients, at a given concentration, is greater than the sum of

the contribution from each individual ingredient.

NOTE: The word "interaction" does not imply a chemical reaction.

The essential constraint inherent in the definition is that for every experimental batch the relative proportions of the ingredients under investigation must always sum to unity (1 or 100%). There is a second more common-sense constraint for formulations. It is that, for obvious reasons, the ingredient proportions must sum to, greater than or equal to zero. After all, an ingredient obviously cannot be present at a negative level. In a mixture design, control variables become dependent variables in a sense because the level of each ingredient depends upon the level of the other(s).

$$X1 + X2 \ldots + Xq = 1 = 100\%$$

Where q = the number of components in the mixture $0 \leq X1 \leq 1$ and $X1 \geq 0$.

In our case of formula optimization, the best way to satisfy the definition for synergy is to adhere to the teaching of John A. Cornell presented in his *Experiments with Mixtures*.[10]

The Cornell Approach

In defining the general mixture design, Cornell uses a very simple example of a binary blend of gasoline as the "independent or controllable factors" and the average number of miles per gallon as the single "measured response". (**Figure 2**) He explains that if a car gets 13 mpg with Gasoline A and 7 mpg with Gasoline B then if a gallon of each goes into the same car it is reasonable to expect it to travel 20 miles. However, because that is for two gallons of gasoline, one must divide the total by two to get mpg. If one adds one gallon of the 50/50 gasoline blend into the fuel tank and the car actually runs a measured distance greater than 10 mpg then the interaction can be termed "complementary." (Notice how Cornell deftly avoids using the word *synergy*.) A researcher who is faithful to the definition will realize that it is only the relative proportions of gasoline—and not the total amount of gasoline—in the fuel tank that can vary. The word interaction does not imply that the two gasolines have come together through some chemical reaction to form a new molecule.

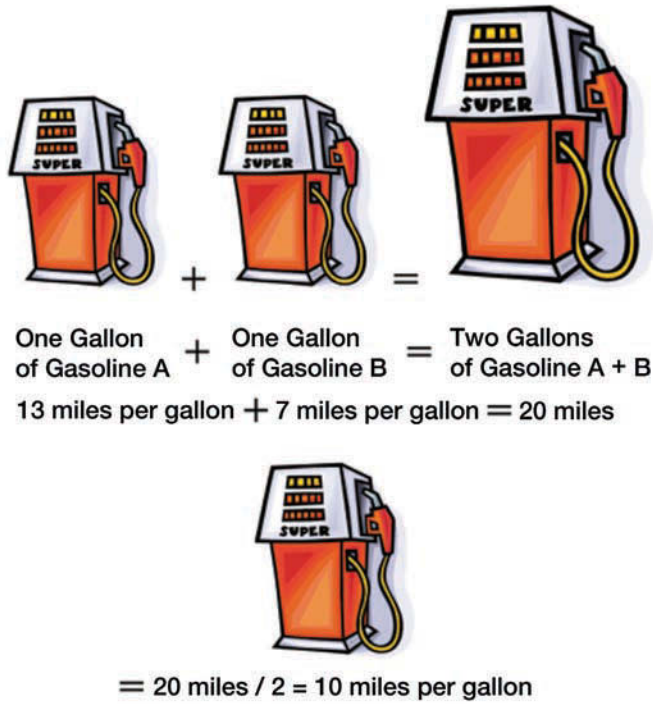

Figure 2. Calculating the miles per gallon Gasolines A and B

In his book, Cornell draws a line to connect the known mpg data for Gasoline A and Gasoline B (**Figure 3**). He calls this the Additive (1 + 1 = 2) Blending Line, which includes the predicted midpoint for the 50/50 binary blend. He then superimposes the curve generated by the actual experimental data. In the example, the curve is above the Additive Blending Line so there is a synergistic (1 + 1 > 2) interaction. If it is below the line, it is an antagonistic (1 + 1 < 2) relationship. This should be the criteria applied to cosmetic formulations whenever one is trying to prove that the combined interaction of two ingredients produces a synergistic effect on a measured response.

Of course, two data points are all one needs to draw a straight line. However, that assumes there is a linear relationship between the two ingredients, which is not always the case. The same is true about the curvature assigned to the actual experimental data. Naturally, one increases confidence in the data by testing other ratios of ingredients in additional mixtures and making replicate batches. Time and money can be the limiting factors.

Now that we know what is, and what is not, a synergistic interaction between two (or more) ingredients in a formulation, it is time to show how DoE optimizes a product and seeks synergy. DoE acts like a synergy-seeking guided missile, using statistics to plot course corrections and find the vectors needed to hit its intended

target(s). The guidance system is a model or equation used to make predictions and solve for unknowns.

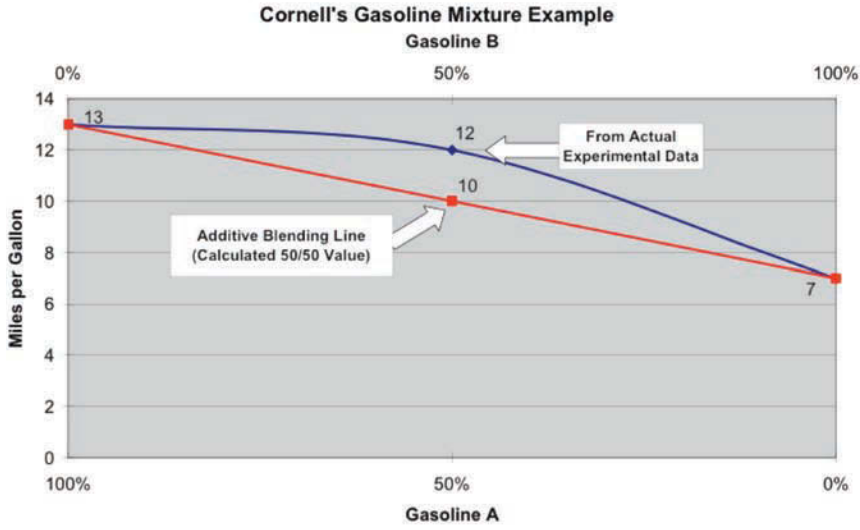

Figure 3. The Cornell Additive Blending Plot of Gasolines A and B

The objective in all of this is to be able to predict responses with a model defined by an empirically derived equation. Does the model (equation) accurately predict the response? The simplest of these is an additive association where the main factors are what have the greatest effect on a measured response. In this case, the interaction of two or more ingredients produces a linear equation and indicates that there are no inherent synergistic interactions. If there is curvature, or non-linear, response there is a quadratic equation. In situations that are more complicated the best-fitting model to predict the response will be either a cubic equation or a special cubic equation.

Model:

A, B, C	Main effects – linear equations
AB, AC, BC	2-way interactions – quadratic equations
ABC	3-way interactions – cubic equations

How To Get Started

The approach is simple. There are a few sequential steps involved in DoE:

1. Identify the objective(s)
2. Design the experiment
3. Make the batches and test the key responses
4. Enter the data
5. Analyze the data and interpret the results looking for possible synergies
6. Confirm the predicted optimization

If life were truly simple then there would be only unconstrained factors in

experimental design. However, this is not the case. For example, one is never told, "I don't care how much SLES/CAPB surfactant you need to use. Just give me the highest foaming shampoo." Well, someone might say that, but then upon further reflection, all sorts of considerations creep into play. Constraints are restrictions. There are very few unconstrained factors not restricted by things like cost limitation and safe use levels. Sometimes there may be multiple component constraints. For example, the combined level of two ingredients might be restricted to a sum less than 42% of the total formula: $X2 + X3 \leq 42\%$. Alternatively, there may be a ratio constraint: $1.2 < X1 / (X2 + X3) < 1.3$.

Identify the objective(s)

Initially, one must thoroughly understand the deliverables of the finished product. This is more than just the formula and actual production procedure, but also the packaging components, marketing concept, advertising, label copy, and claims substantiation. Meet with your marketing, engineering, and other groups and do a little brainstorming. What does everyone expect? This can be the most time-consuming stuff to face, and it may appear that nothing is happening yet. However, unless one accurately defines objectives and everyone on the team buys into them, it may be necessary to repeat all of the work that is to follow. It is extremely important to establish the purpose and the scope of the experiments at the onset.

It would be wise to invite a company statistician to help the group clearly define the independent variables (controlled variables or factors) and the dependant variables (responses) that you are interested in optimizing. However, do not dismay if you are not fortunate enough to have a statistician employed by your company. You can do a very acceptable job at DoE with proper training in the right software program. There are a number of commercial software programs available. Most are intuitive and user-friendly enough so that one does not have to be a statistician, or go to one, to get good results. (Note: Design-Expert from Stat-Ease and JMP from the SAS Institute are two such examples this author has used.[11-12] Others are Minitab, Statistica and ECHIP.)

Just be sure not to attempt to predict responses or draw conclusions for batches that lie outside the scope of the design; *make no extrapolations*. The set of factors and ranges included in the initial design phase will limit predictions. One must set the factors and ranges based on knowledge of the system under investigation and common sense.

Examples of Independent Variables (a.k.a. factors) that you can control:

Quantitative/Numeric	**Qualitative/Categorical**
Use-levels of ingredients	Order-of-addition
Batch temperature	Supplier of ingredients

Examples of Dependant Variables that are the measured responses from your experiments:

Viscosity	Hedonic scale (rating or ranking)
pH	Clarity
Cost	Foam attributes

Design the Experiment

The next step is setting the specifications for the design of the experiment. Knowing what, and how many, factors (x, inputs) there will be, the range over which they will be varied and how tightly the changes can be controlled (+/- *x* oC; +/- *x* minutes) will determine what kind of experiment is preferred. If there are only three factors at just two use-levels then a 2^3 Full Factorial design is okay. If there is more than that, a Partial Factorial or Box-Behnken design is better. If there are multiple factors (7 or more) and processing parameters (such as pressure, temperature, mixing speed, order of addition, and cooling/heating rates) to consider, then a cause and effect fishbone diagram and a Taguchi Method may be better. Discussion of these examples of possible alternate experimental design types (of which there are many) are well beyond the scope of this chapter.

If one is trying to optimize a formulation then a Mixture Design, where three or more ingredients and their use-levels are the variable factors (x), is the appropriate approach. The constraint is that the sum of all ingredients under investigation always adds to 1 (100%) so that the relative proportions are all important. Usually there are no more than one or two independent ("manipulated") variables; in mixture designs, there may be many.

Of course, the Cornell example demonstrating a synergistic blend of gasolines represents the simplest of experimental mixture designs, only two ingredients and just one response. **Figure 4** introduces something a bit more complex.

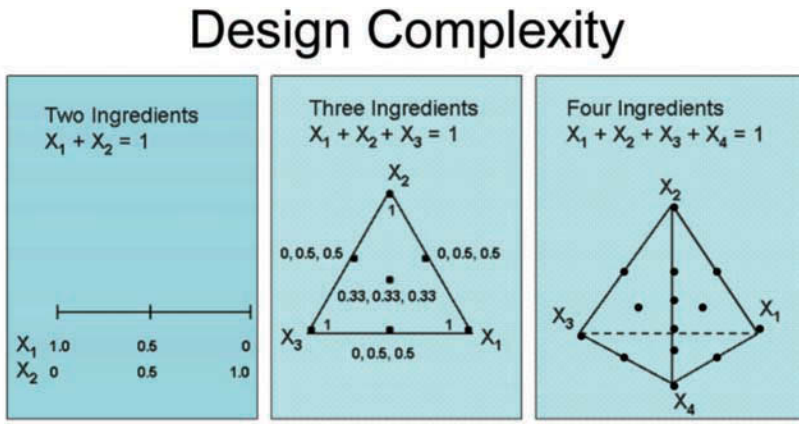

Figure 4. Diagram of multi-ingredient design concerns. Each end of the linear design space for a binary blend represents 100% of one ingredient and 0% of the other. Each apex of the equilateral triangle (three ingredients) or pyramid (four ingredients) represents 100% of the ingredient indicated while the side of the triangle (or pyramid) directly opposite represents that same specific ingredient at 0%.

Design Replicates

Experimentation is often an iterative process. This suggests that performing a fractional (or partial) factorial rather than a full factorial design may provide an early preview and initial insight to guide the next set of experiments.

Replication provides an estimate for pure error, helps guarantee reproducibility, and builds confidence in the ability of the model to predict desired responses. One replicate of the centroid blend provides only a single statistical measure of pure error (one degree of freedom) for estimation. Replicating each pure component gives a better estimate of pure error.

One uses the signal-to-noise ratio ($\Delta y / \sigma$) to estimate power. It is the ratio of the change in response (Δy) to the experimental error (σ) in measuring the response.

Using randomization minimizes the impact of controlled variables on results and reduces experimental error. One must be able to measure response variables precisely or additional error will creep into the experiment. Use calibrated and certified instruments with reliable accuracy and performance. If one suspects the accuracy of instruments, it might be wise to take multiple measures and enter the average. Make sure sensory panels are properly trained and capable of discriminating consumer perceivable performance attributes adequately. Make sure to properly define rating terms like "excellent," "fair," and "poor" for your panelists. Many software programs can also analyze ranking data.

Next one must decide upon the most important criteria for approval of the final formula. Some software programs allow the user to provide weighted values to those quantifiable responses (y, outputs) considered most important.

Make the batches and measure the key responses

Finally, the formulator is now ready to prepare his pre-determined batches in random order. Up until this point, supervisors may seem a bit dismayed that you were not standing at the bench, making batch after batch. Be patient with them. Explain what you are doing.

Uniquely suited for many designs requiring a large number of trials (batches) are the robotics available for combinatorial chemistry or high-throughput processing exemplified by the research done by Dr. Robert Lochhead and the Institute for Formulation Science and by those researchers doing high-throughput screening.[13-14]

Enter the data

When the batches are complete and all responses measured, one enters the data for statistical analysis and interprets the results. To help with the interpretation, it is a very good idea to run one or more replicate batches and test them to determine the reproducibility of the batches, accuracy and precision of analytical assessment panel or instrumental data, and reliability of the contour plots.

Look to see if the data is normally distributed. Do not categorically dismiss outliers, or "maverick data" without a closer examination. Eliminate them only if they are a mistake in measurement, data entry or typo errors then repeat the test and enter the corrected values.

Analyze the data and interpret the results looking for possible synergies

1. *Check the topography of the Response Surface Map:* Caution—An optimized formulation does not necessarily contain synergistic interactions between its ingredients. The output of any of these designs is often either a ternary diagram (a 2D graphical representation of a 3D space which is used when there are three factors) or a tertiary diagram (a 3D graphical representation of a 4D space which is used when there are four factors) that show contours of a single constant response (y). These contour plots, also known as Response Surface Maps, look a lot like a weather isobar chart. From this RSM, the optimum levels of each of the ingredients under investigation can be obtained. The map can also be used to predict how formulas that were not even made will perform. The best formula may be determined without even having prepared and tested it even once! With the shotgun approach, you are more likely to miss such an excellent opportunity.
2. *Check the Scheffé Coefficients:* If there is a significant interaction one must next consider the direction of change in the measured response to determine if it is either synergistic or antagonistic.
3. *Look at the ANOVA Table to test for significance:* Look at the Probability > F values. Values of "Prob > F" less than 0.0500 indicate model terms are significant
4. *Check JMP Leverage Plots* (discussion to come)
5. *Confirm the predicted optimization*

The reasonable thing to do last is to prepare the predicted optimum batch and test it to confirm the prediction. The advantages of DoE are that ingredients and/or processes can be changed independently so that main effects can be determined with fewer batches, saving both time and money. Synergies and other interaction effects can also be discovered in an efficient manner. With DoE, just one study will provide extensive knowledge of formula behavior. This can all provide insight for future improvements that can lead to new business opportunities in the form of "next generation" product launches.

Example

They will follow the lead of Professor Cornell and utilize a gasoline blend as an example to demonstrate the five step DoE approach to design and analysis of data to discover the optimal blend and then to subsequently find whether or not synergy between the ingredients exists.

1. *Identify the objective(s).*
   In this hypothetical example, the team members all agree that the only response of immediate importance is getting the highest mileage from a gallon of gasoline. These veteran researchers know their starting formula and ingredient constraints quite well. Because of their familiarity in

the industry, they quickly agree on the use levels as constrained by cost, environmental regulations, and the like. They already know what they can get with their current formula—a binary blend of two gasolines (A & B) in a pre-established ratio. They are satisfied with that binary blend, having arrived at it through an earlier set of experiments. Now they want to know if added Gasohol and/or a Fuel Additive will increase or decrease mileage. They also want to achieve an optimal formula and then look for possible synergies to take advantage of and patent, to secure and protect a winning proprietary position in the marketplace for an extended period.

2. *Design the Experiment.*
The researchers can chose from one of three different types of mixture designs—Simplex Lattice, Simplex Centroid, or Extreme Vertices, illustrated in **Figure 5**. The center triangle shows the typical use level settings for a Simplex Centroid design represented as pseudo-components.

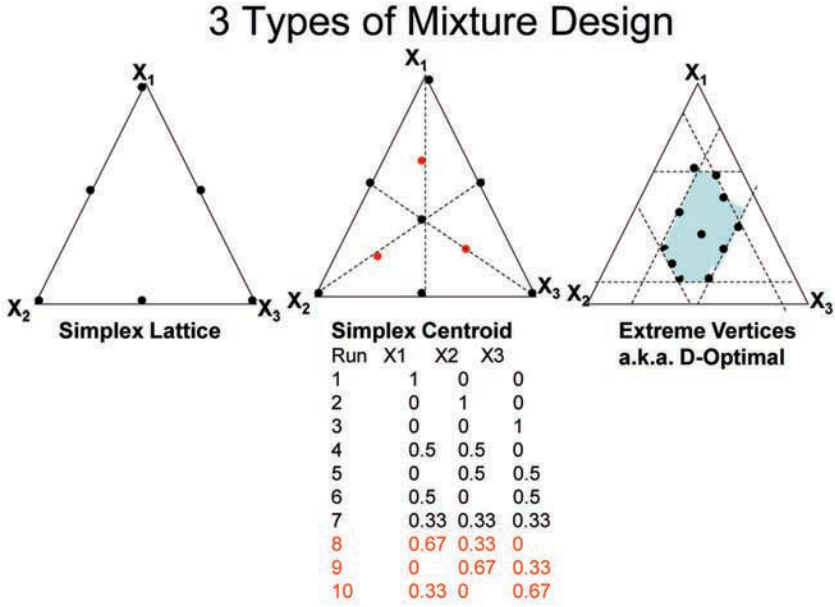

Figure 5. Mixture Design Types under discussion

In the initial design phase of work, despite extensive collective experience, they still do not know how the three factors will behave individually or how they may interact. Therefore, even though they've established critical constraints on the ingredients, they will decide to go with an enhanced Simplex Centroid design with three axial blends added. The apexes of the design space shown within the greater triangle represent values less than the 100% of each ingredient. The values used for the level of each component is shown in **Table 1**. At this stage, they have chosen to

not go with a D-optimal or Extreme Vertices design; the reason for this is that they simply do not have enough knowledge yet to restrict the design space so tightly.

The AB Blend (factor X1) is constrained to be 50-75%, Gasohol (factor X2) 25-50% and Fuel Additive (factor X3) to be between 0-25% of the total formula. Obviously, this limited experiment will not provide the results for all possible combinations of the three ingredients. For instance, it will not tell them anything at all about 100% of AB blend, and no Gasohol or Fuel Additive. The assumption is that either they are already familiar with the behavior of the ingredients outside the area under investigation, or that those formulas are impractical for any number of reasons. Note that in Table 1, after taking rounding into consideration, each of the rows representing the 14 trial runs or experimental blends all add up to 1 or 100%. Also notice that there are only 10 dots shown in **Figure 6**, each representing a batch, shown on the triangle. That is because the four replicate batches (one additional run each for the center point and as well as the three axial blends) are overlaid. The center point (33% of each of the three ingredients) is obvious to pick out in **Figure 5**. The axial blends are in red.

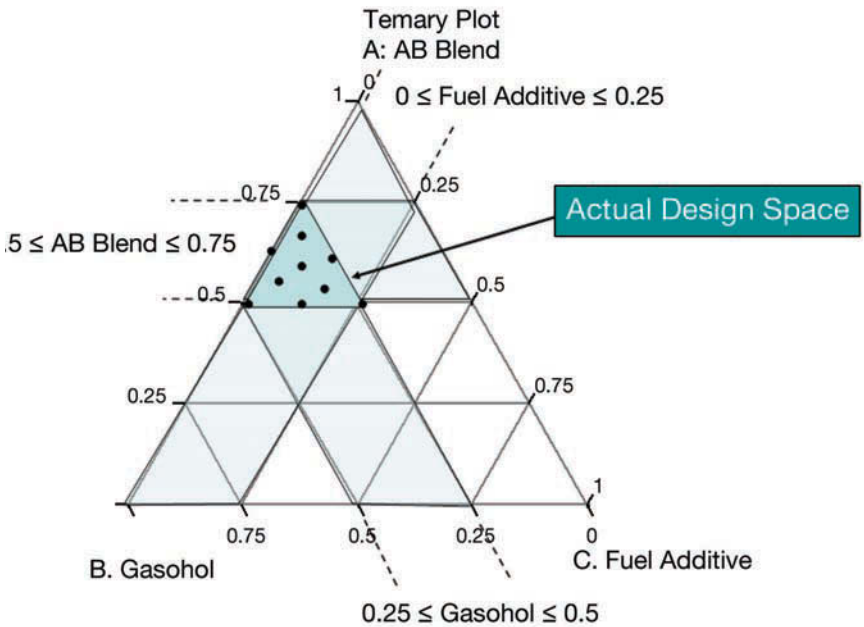

Figure 6. Batch display in actual design space

3. *Make the batches and measure the key response.*
   The 14 individual trials are now run in random order to eliminate experimental bias or other extraneous influences.
4. *Enter the data.*
   The data is entered as MPG in the right hand column of Table 1. This table shows the settings of the original components instead of the pseudo-components.

Table 1. the experimental batches and results

Extreme Vertices Design Fuel Mixture				
Contraint: **X1 + X2 + X3 =1**			**Additional Contraints:** **0.5 ≤ X1 ≤ 0.75** **0.25 ≤ X2 ≤ 0.5** **0 ≤ X 3 ≤ 0.25**	
Run#	**AB Blend**	**Gasohol**	**Fuel Additive**	**MPG**
1	0.75	0.25	0.00	18
2	0.50	0.50	0.00	19
3	0.54	0.29	0.17	16
4	0.50	0.25	0.25	17
5	0.50	0.50	0.00	19
6	0.54	0.42	0.04	18
7	0.50	0.25	0.25	17
8	0.75	0.25	0.00	18
9	0.58	0.33	0.08	20
10	0.63	0.38	0.00	15
11	0.50	0.38	0.13	9
12	0.67	0.29	0.04	18
13	0.63	0.25	0.13	16
14	0.63	0.38	0.00	15

5. *Analyze the data and interpret the results looking for possible synergies.* Using DoE software, the plotted data in the response surface maps is examined. **Figure 7** shows the 2-dimensional plot.

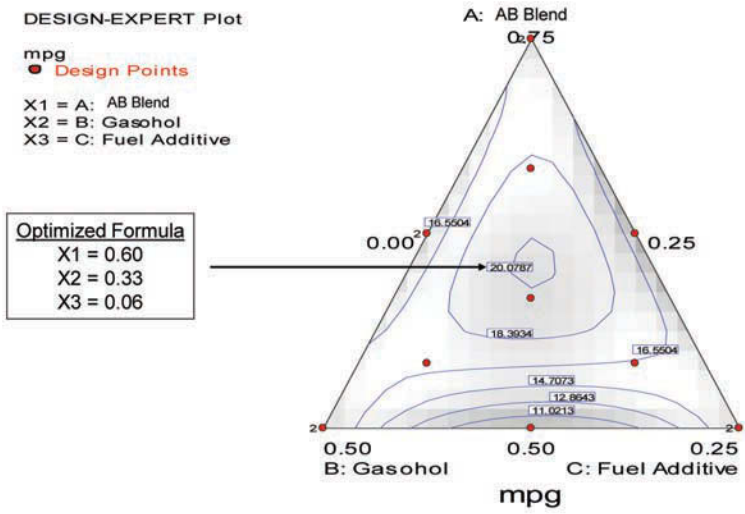

Figure 7. 2-D Data Plot

From the 3-dimensional contour plot (**Figure 8**), they can immediately visualize where the optimal formula lies, and also easily see where the *worse* possible combination of ingredients lies.

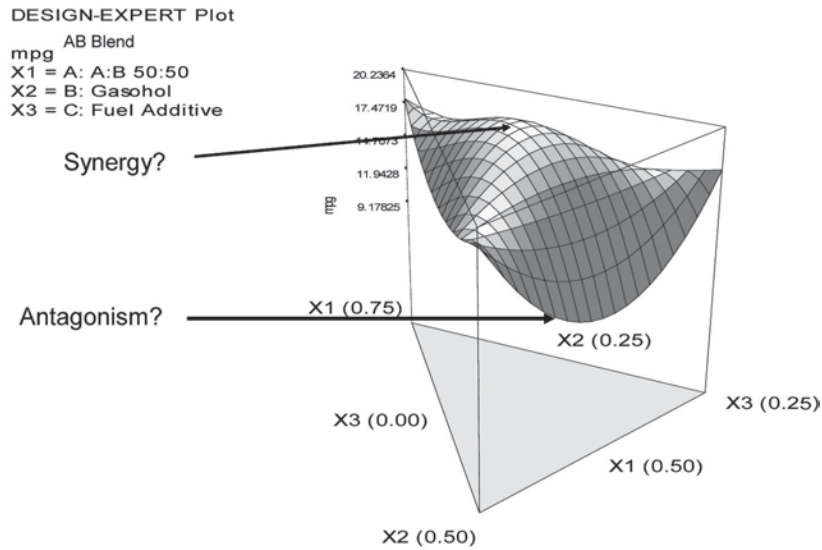

Figure 8. 3-D Data Plot

The question that remains is whether there is a synergy between the ingredients at that point; in order to determine this, we must next look at the Scheffé Coefficients. A

positive (+) Scheffé Coefficient may indicate synergy. A negative (-) Scheffé Coefficient may indicate antagonism. **Table 2** shows that each of the single components or main effects (AB Blend, Gasohol and Fuel Additive) as well as the ternary blend of all three ingredients have a positive effect on increasing MPG. What's more, the ternary blend suggests a possible synergistic interaction.

Table 2. Scheffé Coefficients

Final Equation in Terms of Actual Components:

mpg =	+	44.37562	AB Blend
	+	105.07093	Gasohol
	+	1951.73227	Fuel Additive
	-	222.20979	AB Blend* Gasohol
	-	3650.30170	AB Blend* Fuel Additive
	-	7639.43257	Gasohol* Fuel Additive
	+	14146.23776	AB Blend* Gasohol* Fuel Additive

+ Scheffé Coefficient = Synergy
- Scheffé Coefficient = Antagonism
CAUTION: Statistical Significance Required

Scheffé Polynominal

$$y = mpgX_1 + mpgX_2 + mpgX_3 + mpgX_1X_3 + mpgX_2X_3 + mpgX_1X_3 + mpgX_1X_2X_3$$

The Scheffé Coefficients show that the main effects (single ingredients) have a positive impact on MPG. However, none of the binary blends increases MPG. Surprisingly, the ternary blend shows a strong positive effect and therefore a possible synergy.

The Scheffé Polynomial equation defines the model that will best fit the results and used to make predictions about the probable responses of unprepared batches. The first three terms after the = sign are for when there are no interactions for X_1, X_2 *and* X_3 in which case there would be a linear model. The set of three terms, covering the possible binary blends, are for first order interactions, which is a quadratic model. The last term is for all three ingredients combined and represents second order interactions, a cubic model.

6. *Check the ANOVA table*

   Next, they must investigate the Analysis of Variance, or ANOVA, table. Focusing primarily on the "Prob > F" column, they see that everything—the model, linear mixture (single components), binary blends (AB, AC, BC) and the ternary blend (ABC)—is statistically significant.

The replicated data in **Table 3** can be compared to show that it "looks like" there is not much error, but a better conclusion can be made after looking at the ANOVA.

Table 3. ANOVA Table

Response:	mpg				
ANOVA for Mixture Special Cubic Model					
Analysis of variance table (Partial sum of squares)					
Source	Sum of Squares	DF	Mean Square	F Value	Prob > F
Model	92.36313686	6	15.3938561	54.04045591	<0.0001
Linear Mixture	5.217456758	2	2.60872838	9.157995868	0.0111
AB	16.19049722	1	16.1904972	56.83708117	0.0001
AC	2.625247908	1	2.62524791	9.215988021	0.0190
BC	65.0789814	1	65.0789814	228.4611336	<0.0001
ABC	52.87482576	1	52.8748258	185.6181884	<0.0001
Residual	1.994005994	7	0.284858		
Lack of Fit	1.994005994	3	0.66466866		
Pure Error	0	4	0		
Cor Total	94.35714286	13			
Std. Dev.	0.5337209		R-Squared	0.97887461	
Mean	16.78571429		Adj R-Squared	0.960753856	
C.V.	3.179613873		Pred R-Squared	0.693563815	
PRESS	28.91444284		Adeq Precision	28.38990972	

JMP Leverage Plots

The computer algorithms provided in statistic software programs use Multiple Regression Techniques, Ternary Plots, Response Surface Contours, and other data analysis techniques that are useful for investigating ingredient interactions and developing formulations optimized simultaneously for cost, performance, aesthetics, and any other measurable attribute desired. For example, by using JMP statistical software one can generate Leverage Plots to test for significant interactions. One uses Leverage Plots (**Figure 9**) to test a specific hypothesis using a sloped line to represent the full model and a horizontal dashed line showing the model constrained by the hypothesis. Dotted lines that are the 0.05 confidence curves surround the sloped line. The distance from each point to the sloped line is the residual from the full model, and to the horizontal line is the residual from the constrained model. Observe the generic Leverage Plots in Figure 10 for significant effect (left) and for non-significant effect (right).[11]

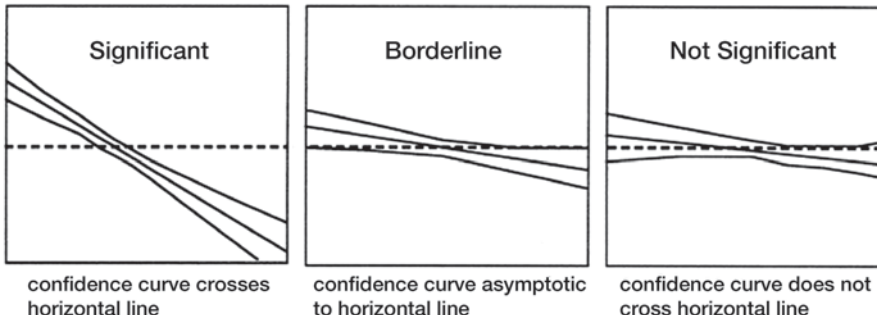

Figure 9. Comparison of Significance Shown in Leverage Plots

Next, we must check the Summary of Fit and a plot of the residuals. The Summary of Fit shown in **Table 4** suggests that a Special Cubic model is the best predictor and that a synergy between the three ingredients is likely. Each row in the Summary of Fit table shows a loss of one Degree of Freedom (under the DF column) because in mixture designs the level of the *n*th ingredient is set by the level of the others in the formula. That agrees with what was said earlier. Namely, that *n*-1 ingredient levels must be specified in mixture designs. Mathematically, for our three ingredient formula: X1+X2+X3 = 1 or, X3 = 1 – X1 –X2. In order to have statistical significance, the values under the "Prob > F" column must be less than 0.05 for 95% confidence. The liner model does not adequately explain how the ingredient levels effect mpg because Prob > F = 0.7314. This means each ingredient, considered individually, is not the best fit to the data collected. Likewise, quadratic or first order interactions (binary interactions) are also not the best fit. The model that best fits the data and best explains the way the ingredients interact is either the special cubic or cubic model. Cubic models are second order interactions and means that all three ingredients have an impact on the mpg response.

The plot of the residuals (**Figure 10**), which looks at the experimental error, seems normal, suggesting that there are neither outliers nor anything unusual about the data collected. The linear fit of the residuals provides an additional verification and bolsters confidence that the experiment was designed and conducted correctly and that all measuring instruments calibrated and functioning properly. At last, the researchers may conclude that the optimized formula shown in Figure 7 is correct, and that there are *statistically significant*, synergistic interactions between all three components of their gasoline of which they can take advantage.

Table 4. Summary of Fit

Response:	mpg				
Sequential Model of Sum Squares					
Source	**Sum of Squares**	**DF**	**Mean Square**	**F Value**	**Prob > F**
Mean	3944.64	1	3944.64		
Linear	5.22	2	2.61	0.32	0.7314
Quadratic	34.27	3	11.42	1.67	0.2505
Special Cubic	52.87	1	52.87	185.62	<0.0001 Suggested
Cubic	1.97	2	0.99	247.37	<0.0001 Aliased
Residual	0.020	5	3.990E-033		
Total	4039.00	14	288.50		

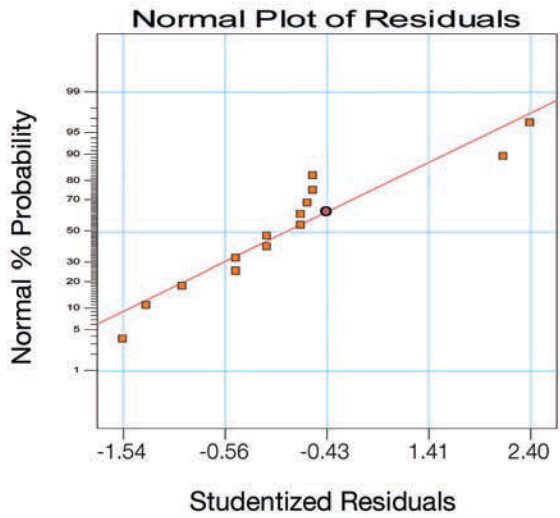

Figure 10. Plot of Residuals

Additional Thoughts

If the findings are unique and unobvious, then patent possibilities arise. Conversely, it is not surprising that, if one searches the US Patent database (*www.uspto.gov*), the words "synergy" and "synergistic" are pervasively employed. Of the 2,946,816 patents granted from 1976 to the present, across all markets, segments, and applications, that are searchable on-line, the word "synergy" is used as a primary term in 4,947 of them—and in five of those, the word is featured in the patent's title. The word "synergistic" is even more common, appearing in 33,164 patents, of which 834 patent titles bear it. In current patent applications, to say those filed within the last

decade, synergy is used 3254 times, four times in the title, while word synergistic is used 11,529 times, 156 times in the title. The pattern here is clear. These are terms that are growing in use and stature and are consistently being marketed. Obviously, the people who file these patents to protect their inventions intend on doing something with them, namely to create new business opportunities. In formula optimization, synergistic interactions are useful in reducing the total percent solids required to achieve a desired effect, implementing a cost savings initiative to reduce the use level of more expensive ingredients. If a supplier truly has a synergy, take advantage of it. In the case of synergy, it is a case of "buyer beware."

Conclusions

The author hopes that this chapter provided a good understanding of Design of Experiments for mixtures; for our purposes, a mixture is simply another term for a cosmetic formulation. In addition, the example and the step-by-step description of how to set up an experiment and analyze data with computer software provides the reader with a head-start on their own exploration into the realm of DoE. The word design refers to the sets of experimental batches utilized to fit an experimental model that can make predictions within the range of parameters (ingredient use-levels and/or relative proportions) established. The approach of John Cornell and other statisticians is perfect for accomplishing the goals of identifying synergistic ingredient interactions that can lead to a proprietary position in the market place, an optimized formulation, accelerate speed-to-market and achieve cost-savings. If you want to continue learning there are many great articles in the literature a very few of which are included in the reference section.[15-22]

Note: All figures and tables in this chapter are the product or adaptation of the author. All figures and tables in this chapter are slides taken from presentations given by the author at SCC Meetings.

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CHAPTER 11

Rheological Properties of Topical Formulations

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Key Words

Complex modulus, Creep/Recovery, Dilatant Flow, Dynamic viscosity, Flow, Flow curve, Flow models, Frequency sweep, Kinematic viscosity, Loss Modulus (G"), Newtonian Flow, Non-Newtonian Fluid, Oscillatory mode, Pseudoplastic Flow, Plastic flow, Rheological Additive (Thickener), Rheology, Rheometer, Rotational mode, Shear rate, Shear stress, Shear thickening, Shear thinning, Storage modulus (G'), Strain sweep, Thickening mechanism, Thixotropy, Viscoelasticity, Viscometer, Viscosity, Yield value

Introduction

This chapter reviews the principles of rheology and the rheological properties of topical formulations such as shear stress, shear rate, viscosity, yield value, viscoelasticity, storage and loss moduli. It discusses the measurement of these properties and the instruments typically used in measuring the rheological properties of topical formulations. It also describes various rheological additives, including natural gums, cellulose-based alkali-swellable polymers, associative thickeners, clay and organoclay rheological additives, and synthetic thickeners, their thickening mechanisms and the properties that they impart to topical formulations. The discussion and the sample of rheological measurements described in this chapter may serve as a general basic guide to the design and development of target rheological profiles for topical formulations.

The scope and goal of the formulation chemist is to compose the optimal formulation that would exhibit the best possible application properties. The formulation chemist has to balance the ingredients used so that the product is stable, easy to apply and functions as designed during manufacturing, on the shelf, during application, and after application. Therefore, characterization of the properties of the product throughout these phases is important and may eventually save time and resources in the search for the optimal formulation that would be appealing to the consumer.

Whether it is a pharmaceutical formulation, paint, ink, food, or a cosmetic

formulation, the desired combination of ingredients should provide the user with the most efficient way to use the product. This means the creation of a complex three-dimensional network structure that would retain the structure before the product is used, exhibit the proper flow when utilized, and recover the structure after the application. **Rheology** is the science that studies how materials deform and flow under the influence of external forces. The word, which derives from the Greek Rheo (= flow), was suggested by Markus Reiner and Eugene C. Bingham.[1] They formed a "new" scientific discipline and founded the Society of Rheology in 1929. Reiner and Bingham were inspired by a quotation attributed to the Greek philosopher Heraclitus: "Everything Flows" (in Greek: Παντα Ρει - Panta Rei; some sources attribute the quotation to Simplicius). Plato paraphrased this observation as "Everything Changes and Nothing Stands Still." Actually, the study of flowing systems has been progressing long before the formal inception of the field of rheology in 1929: Archimedes (~250 BC) studied the behavior of rigid bodies; Hooke (1678) studied the behavior of elastic solids; Newton (1687) studied rigid bodies and Newtonian liquids; Stokes (1845) studied the motion of fluids and the movement of rigid bodies in viscous fluids; Maxwell (1867) and Boltzmann (1878) studied linear viscoelasticity; Einstein (1906) studied the behavior of suspensions; and Trouton (1906) studied Newtonian liquids and extensional viscosity. Many other scientists contributed over the years to the evolution of the field of rheology. Details of these and other contributions to the development of the scientific field of rheology may be found in several reviews.[2,3]

Characterization of the rheological properties of the system is important not only in the design of the product and its application, but during its processing and to ensure long shelf-life. Consider the application of a skin care product: we use a product in a container where it is already under an external force, the gravitational force. We pick a portion to apply on the skin; this is another external force. We then rub it onto the skin, forcing it to flow so that it forms a thin layer. Then, we remove the external force, leaving the thin layer to regain its original structure under gravity.

These requirements seem to be contradictory: we force the product to exhibit homogenous flow to cover the application area but then require that it stops flowing and remain in place. To demonstrate the flow patterns of different systems, think about the difference between spreading honey on a slice of bread and spreading mayonnaise on that same slice. Honey is "thick" and seems to resists the "application," while mayonnaise becomes "thin" and spreads easily. However, if we apply honey and mayonnaise on pieces of wood and turn them vertically, allowing the samples to flow under gravity, honey starts flowing immediately, while mayonnaise does not flow.

In this chapter, we explore the rheological changes that our formulations experience when subjected to external forces, how the deformation and flow of systems used are measured, how we can modify the flow of systems we use, and how the formulation chemist may improve the application properties of the product by characterizing the rheological properties of the system. This chapter will also discuss various instruments that are available to the formulation chemist to measure the

rheological properties of the system and the variety of rheological additives that are available to tailor its rheological properties. It will address typical questions that are frequently asked by formulation chemists, such as:

- "We have several products that were formulated to have the same viscosity, so why do they behave so differently when we apply them?"
- "Our product settles/separates over time. How can we prevent it?"
- "We have two similar formulations. One regains its viscosity after application while the second formulation does not and continues to flow. Why does it happen and how can we fix it?"

To demonstrate the characterization of the rheological properties of skin care formulations, this chapter includes a discussion of a study in which a series of tests were performed on commercial products in order to differentiate their rheological attributes, aid in understanding their behavior, and assist in the redesign of their formulation.

Rheological Measurements

Flow Curves

When we apply a topical formulation, the external force F deforms the product or causes the system to flow. Let us assume that the force F is applied to an area A as shown in **Figure 1**.

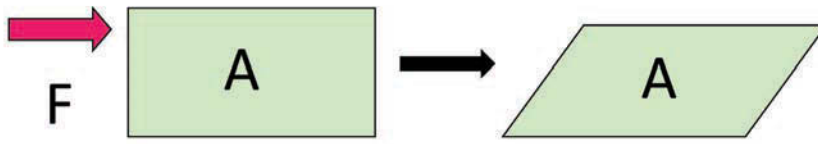

Figure 1. Applying force to an area

We define the **shear stress** (or pressure) σ as the force F over the area A:

$$\sigma = F/A$$

The units of the shear stress are Newtons per square meter (N/m^2) or Pascal (Pa). If the application of an external force results in the elongation of the system, such as stretching a rubber band, the material experiences **shear strain**. We define the **shear strain** γ as the change in length $\Delta L = (L - L_0)$ relative to the initial, un-deformed length L_0 of the material:

$$\gamma = (L - L_0)/L_0$$

The strain is dimensionless.

The resistance of the material to the deformation, sometimes described as its stiffness, may be defined by the ratio between the shear stress and the shear strain, usually referred to as **Young's modulus G:**

$$G = \sigma/\gamma$$

The units of the modulus are Newtons per square meter (N/m^2) or Pascal (Pa).

If we plot the shear stress σ as a function of shear strain γ, the modulus **G** is represented by the tangent of the angle (α) as shown in **Figure 2**.

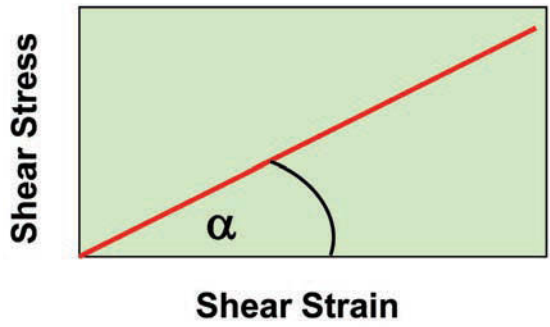

Figure 2. Shear stress as a function of shear strain

We may visualize our product as a three-dimensional system that is made of many layers, occupying the space between two plates where the external force is forcing the plates to move in a certain direction (**Figure 3**). At rest, the material has a thickness X_0, length L_0 and width W_0. Assuming that the bottom plate is stationary, and the flow is laminar (i.e. the plates are sliding on top of each other, as opposed to a turbulent flow), the upper plate would be displaced by dL and the thickness by dX.

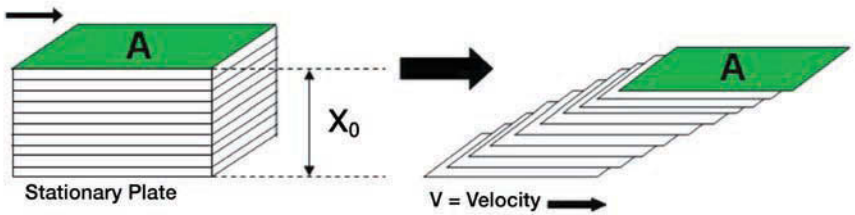

Figure 3. Basic model for flow under an external force

As a result, the system is moving in a speed (velocity) V. The **shear rate** $\dot{\gamma}$ is defined as the ratio between the change in velocity dV and the change in thickness dX:

$$\dot{\gamma} = dV/dX$$

The units of the shear rate are (meter/second)/meter = 1/second or reciprocal second (s^{-1}). If we mix a formulation with a laboratory mixer, for example, at a speed of 23 m/sec and the distance between the blade and the bottom of the beaker is 33 cm, the shear rate is 23/0.33 = 69.7 1/s. If we apply a cream on the skin at a speed of 25 cm/sec, forming a layer that is 75 microns thick, the shear rate is 3,333 1/s.

Isaac Newton discovered that in certain fluids, the ratio between the shear stress and the shear rate is a constant η.[4]

$$\sigma = \eta\dot{\gamma}$$

Fluids that exhibit a constant ratio of the shear stress to the shear rate are called **ideal fluids** or **Newtonian fluids**. Typical Newtonian fluids are water, various oils (such as olive oil and mineral oil) and most organic solvents. Newton defined the constant η as "the resistance which arises from the lack of slipperiness of the parts of the liquid, other things being equal, is proportional to the velocity with which the parts of the liquid are separated from one another." We refer to this "resistance" as the **viscosity**. The **absolute viscosity** is therefore defined as the ratio between the shear stress and the shear rate at any given experimental conditions (e.g., shear rate, temperature and pressure):

$$\eta = \sigma/\dot{\gamma}$$

The units of viscosity are Pascal/1/sec or Pascal*sec (Pa.s). Sometimes, the viscosity is quoted in units of Poise. 1 Pascal*sec equals 10 Poise and correspondingly, 1 milliPascal*sec equals 1 centiPoise (cP). For ideal Newtonian fluids, the viscosity is constant at a given temperature and a given pressure and is independent of the change in shear rate. The viscosity of water at 20°C and atmospheric pressure is 1 cP or 1 mPa.s. **Table 1** summarizes the units of the rheological properties discussed thus far.

Table 1. Units of rheological properties

Property	Units	Conversion
Stress	Pascal (Pa), Newton/meter^2 (N/m^2)	1 Pa = 10 dyne/cm^2
Strain	Dimensionless	
Shear Rate	1/second (1/s)	
Viscosity	Pa.s, Poise	1000 milliPa.s = 1 Pa.s 1 m Pa.s = 1 Centipoise (cP) 1 Pa.s = 10 Poise 1 Poise = 100 cP
Modulus	Pascal (Pa), Newton/meter^2 (N/m^2)	1 Pa = 10 dyne/cm^2

If we plot the shear stress as a function of shear rate for Newtonian fluids, the tangent represents the viscosity (**Figure 4**).

If we plot the viscosity, instead of shear stress, as a function of shear rate for Newtonian fluids, it would show a straight line across the shear rate range (**Figure 5**). However, the viscosity of most fluid systems we use, including semi solid topical formulations, is not constant but changes with increasing shear rate. These fluids are called **Non-Newtonian fluids**. If the viscosity of the system decreases with increasing shear rate, we define the system as **shear thinning**. **Figure 6** shows a **flow profile** of a Non-Newtonian fluid, in which the viscosity is plotted as a function of shear rate.

If the viscosity of the system increases with increasing shear rate, we define the

system as **shear thickening** or **dilatant**. Typical shear thickening systems are highly filled fluids such as highly pigmented systems and quicksand. **Figure 7** shows the flow profile of a dilatant system.

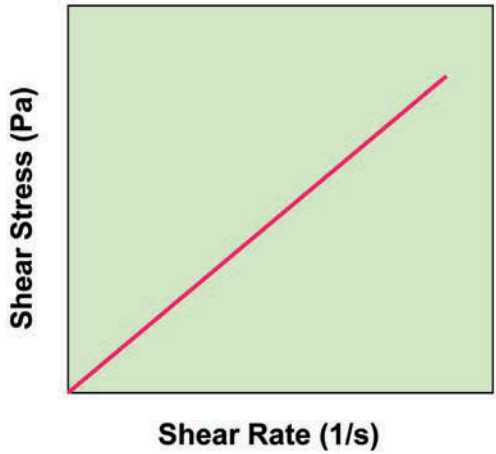

Figure 4. Shear stress as a function of shear rate for Newtonian fluids

Figure 5. Viscosity as a function of shear rate for Newtonian fluids

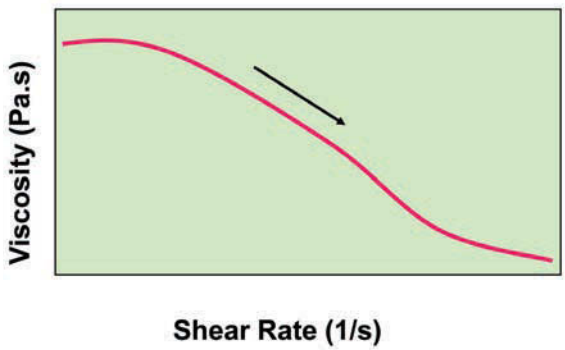

Figure 6. Viscosity as a function of shear rate for Non-Newtonian fluids (shear thinning)

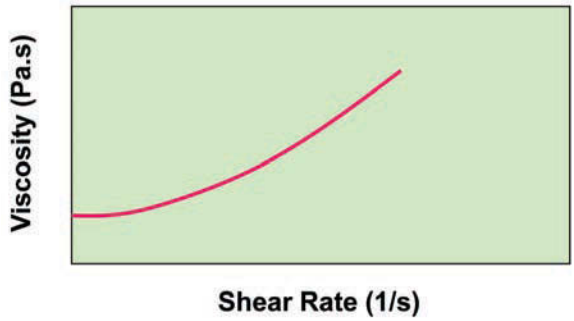

Figure 7. Viscosity as a function of shear rate for Non-Newtonian fluids (shear thickening)

Following the change in shear stress or viscosity as a function of shear rate emphasizes that in Non-Newtonian systems, the result of the external force is non-linear and therefore the corresponding shear rate at which the shear stress or the viscosity were measured needs to be specified. This means that the viscosity is described not just by a number but should be characterized by a curve that reflects relevant storage effects, processing and the application shear rate ranges. In addition, the measurement should include the temperature and the pressure applied during the test. Characterization of the flow properties of the system as a function of shear rate and understanding the possible interactions between the various ingredients in complex formulations, as well as the changes that occur in their network structure during the shearing process, may explain why these systems behave the way they behave. It can also provide a hint as to how to modify them in order to formulate new and improved products. A plot of shear stress as a function of shear rate may therefore reveal the nature of the system.

Flow profiles of **Newtonian** systems exhibit a linear increase of shear stress with increasing shear rate. Flow profiles of shear thinning Non-Newtonian systems exhibit an increase in shear stress with increasing shear rate but the increase in shear stress diminishes with increasing shear rate. We differentiate between systems that exhibit an initial resistance to shear at low shear rates and require a certain stress to induce flow and systems that yield to stress from the onset of an external force. The resistance to initial flow is defined as the **yield value** (to be discussed later in this chapter). Shear thinning Non-Newtonian systems that exhibit a yield value are labeled as **plastic systems** while those that yield immediately to an external force are labeled as **pseudo-plastic systems**. Flow profiles of **shear thickening (dilatant)** Non-Newtonian systems exhibit an increase of shear stress with increasing shear rate but the increase in shear stress becomes steeper with increasing shear rate.

Figure 8 shows flow curves (shear stress as a function of shear rate) depicting the rheological behavior of various types of systems.

Similarly, a plot of viscosity as a function of shear rate may reveal the nature of

the system: Flow profiles of **Newtonian** systems exhibit a constant viscosity with increasing shear rate. Flow profiles of **shear thinning** Non-Newtonian systems exhibit a decrease in viscosity with increasing shear rate. Flow profiles of **shear thickening (dilatant)** Non-Newtonian systems exhibit an increase in viscosity with increasing shear rate.

Figure 9 shows flow curves (viscosity as a function of shear rate) depicting the rheological behavior of various systems.

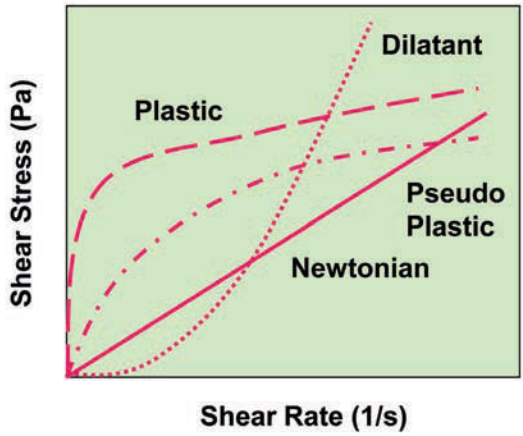

Figure 8. Flow profiles of Newtonian and Non-Newtonian systems: Shear stress as a function of shear rate

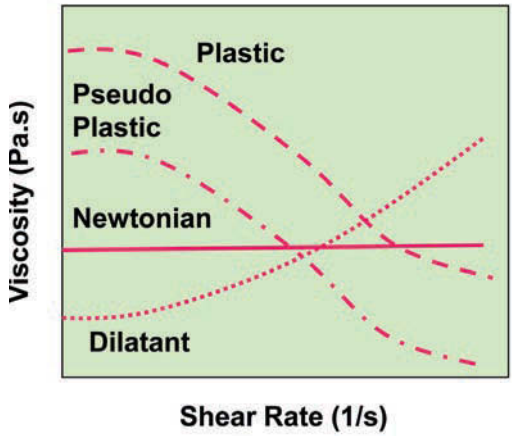

Figure 9. Flow profiles of Newtonian and Non-Newtonian systems: Viscosity as a function of shear rate

To properly describe the changes in shear flow, one needs to visualize the system as composed of volume elements and assign a mathematical model (or an equation) that describes the relationship between two or more physical properties such as shear

stress and shear strain. This relationship usually describes the properties of a volume element and integrates the properties over the whole system. Such a relationship is expressed by an equation that is often called the **constitutive equation**. For example, the KBKZ constitutive equation, proposed by Kaye, Bernstein, Kersley and Zapas,[5,6] describes the one-dimensional relationship between stress and strain. Additional background and the basics of the theory and modeling of the flow properties of complex systems may be found in numerous textbooks on the rheology of complex fluids.[7-11]

When measuring the shear rate and shear stress of the system, one has to ensure that the time scale of the system is faster than the time scale of the observation/experiment. If the changes measured in a specific test take a very long time, the experiment should run a very long time. An example is the pitch drop experiment at Queensland University, Australia.[12] In this experiment, which began in 1927, a sample of pitch (also known as bitumen, which is about 100 billion times thicker than water), was enclosed in a container and allowed to stand under gravitational force. So far it yielded eight drops since 1927 with a cycle lasting for about 9 years.

The ratio of the time scale of the system t_c, the stress relaxation time (also known as the Maxwell relaxation time) to the time scale of the observation t_p was defined by M. Reiner as the **Deborah Number**,[1] based on a line from Deborah's song "The mountains flowed before the Lord" (Judges 5:5):

$$De = t_c/t_p$$

In water based systems, t_c is very low (fast relaxation time: about 10^{-12} seconds) and therefore Deborah Number is low. This means that the system has plenty of time to reach its equilibrium during the measurement. In the pitch experiment, it takes a very long time for the system to relax, therefore the experiment takes a long time to perform and De is high. In practical terms, the shear stress and the shear rate range may describe the application properties of the system, as seen in **Table 2**. Note that these ranges are estimates and would depend on the system and the equipment used.

Table 2. Typical shear stress and shear rate ranges

Property	Shear Stress (Pa)	Shear Rate (1/s)
Storage/Sedimentation	1	<0.001
Sagging/Dripping	0.1 – 10	0.01 – 1
Leveling	0.1 – 10	0.01 – 10
Pouring/Mixing	1 – 100	0.1 – 100
Brushing	100 - 1000	100 – 10,000
Pumping	1000 – 10,000	100 – 10,000
Spraying	10,000 – 100,000	10,000 – 100,000

The formulation chemist designs the product to comply with a specific set of viscosities over a range of shear rates. If the shear rate is not taken into account, two different products may exhibit the same viscosity at a specific shear rate but different viscosities at other shear rates as shown in **Figure 10**.

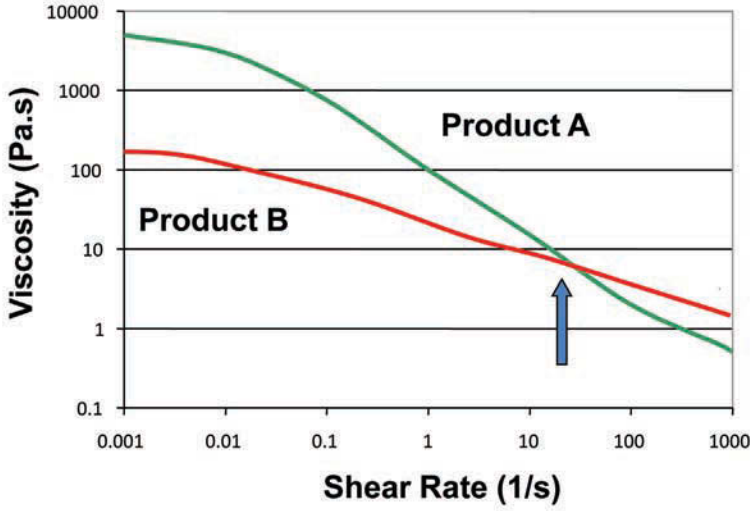

Figure 10. Flow profiles of two products formulated to the same viscosity

The graph in Figure 10 shows the flow profiles of two products that were formulated to exhibit the "same viscosity" (viscosity as a function of shear rate is plotted on a log-log scale). Product A exhibits higher viscosity at low shear rates relative to Product B. Product B exhibits higher viscosity at high shear rates relative to Product A. This may indicate that Product A would be more resistant to flow compared to Product B, that it would sag (drip) less than Product B and that the film it forms would be thinner than that formed by Product B. Product B would probably be easier to apply but may drip and may form a thicker film.

The minimum shear stress necessary to induce flow is defined as the **yield value.** One way to calculate the yield value is to interpolate the shear stress to shear rate = 0. In this case, one has to define the shear rate range for the interpolation since the slope of the graph is changing with increasing shear rate. **Figure 11** shows shear stress as a function of shear rate for three formulations and the interpolation to shear rate = 0.

It is obvious that the value calculated from the interpolation of the flow profile would change, depending on the shear rate range we choose. In Figure 11, the yield value for Formulation C is 0 Pa and the shear rate range is also close to zero. The yield value for Formulation D is 300 Pa and the shear rate range is 400 1/s to 1000 1/s. The yield value for Formulation E is 100 Pa and the corresponding shear rate range is 150 1/s to 1000 1/s. Note that the shear stress and the shear rate are plotted in Figure 11 on a linear-linear scale.

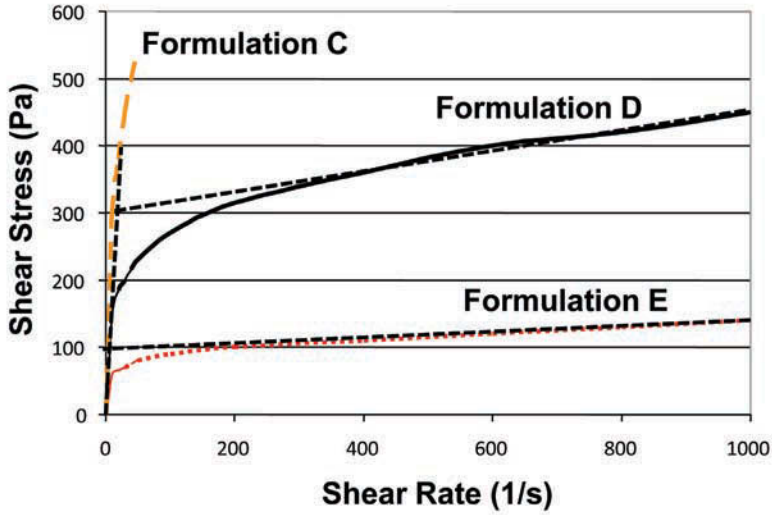

Figure 11. Calculating yield value by interpolation to shear rate = 0

Instead of drawing a straight line and interpolating to zero shear rate, one may describe the relationship between shear stress and shear rate by using a mathematical model. If we use a Newtonian model, the viscosity is constant and the yield value is zero. Bingham extended the Newtonian equation to include the yield value.[13] The shear stress of many Non-Newtonian fluids exhibits a power law relationship with the shear rate. Herschel and Bulkley[14] extended this model to include the yield value. The most popular flow models are shown in **Table 3**. With today's advanced computer technology it is easy to process the data and calculate the shear stress/shear rate relationship and to choose a model that best fits the measured values over the largest possible shear rate range. An example of using the flow models to calculate the best model that fits the measured data and the yield value of skin cream formulations is shown later in this chapter.

Table 3. Flow models

Model	Flow Equation
Newtonian	$\sigma = \eta\dot{\gamma}$
Bingham	$\sigma = \sigma_0 + \eta\dot{\gamma}$
Power Law	$\sigma = \eta\dot{\gamma}^n$
Herschel-Bulkley	$\sigma = \sigma_0 + \eta\dot{\gamma}^n$
Casson	$\sigma^{0.5} = \sigma_0^{0.5} + \eta^{0.5}\dot{\gamma}^{0.5}$
Williamson	$\eta = \eta_\infty + (\eta_0 - \eta_\infty)/(1 + \lvert\sigma\rvert / \sigma_{rel})$
Cross	$\eta = \eta_\infty + (\eta_0 - \eta_\infty)/(1 + \alpha\dot{\gamma}^n)$
Ellis	$\eta_0/\eta = 1 + (\sigma/\sigma_{0.5})^{\alpha-1}$
Carreau	$(\eta - \eta_\infty)/(\eta_0 - \eta_\infty) = [1 + \lambda\dot{\gamma}^2]^{(n-1)/2}$

Another way to measure yield values is by applying increasing stress in steps and following the strain as a function of time (see later the discussion about creep tests), until the formulation shows a significant increase in strain as a result of the applied stress.[15] The shear stress at this point is the yield value. A quicker way to calculate the yield value is to plot the strain as a function of increasing shear stress.[16] In this case, the stress at the inflection point is considered to be the yield value. After the formulation is sheared, the external force (other than gravity) is usually removed and the formulation attempts to recover to its original equilibrium, returning to its original network structure. In order to simulate this breakdown and recovery effect, one needs to mix the formulation at high shear rates and then follow the recovery at shear rate = zero (i.e., at rest). Since the viscosity would be infinite at shear rate equals zero, the next best experiment would be to follow the increase in viscosity at very low shear rates as a function of time after the external force has been removed. **Figure 12** shows the change in viscosity as a function of time during the initial application of the external force at a constant high shear rate, followed by the change in viscosity at a constant low shear rate after the external force has been removed.

Following the recovery after shearing may reveal whether the formulation is capable of reconstructing its network structure and the time frame required to do so. The ability of the system to exhibit lower viscosity as a function of increasing shear rate and to recover its structure over a period of time is called **thixotropy**. In a typical test, the formulation is sheared and the change in viscosity is monitored

as a function of shear rate. The process is then reversed and the change in viscosity is monitored as a function of decreasing shear rate. The flow diagram showing the viscosity as a function of both increasing and decreasing shear rates is called a **thixotropy loop**. **Figure 13** shows the change in viscosity as a function of increasing shear rate, followed by the change in viscosity as a function of decreasing shear rate.

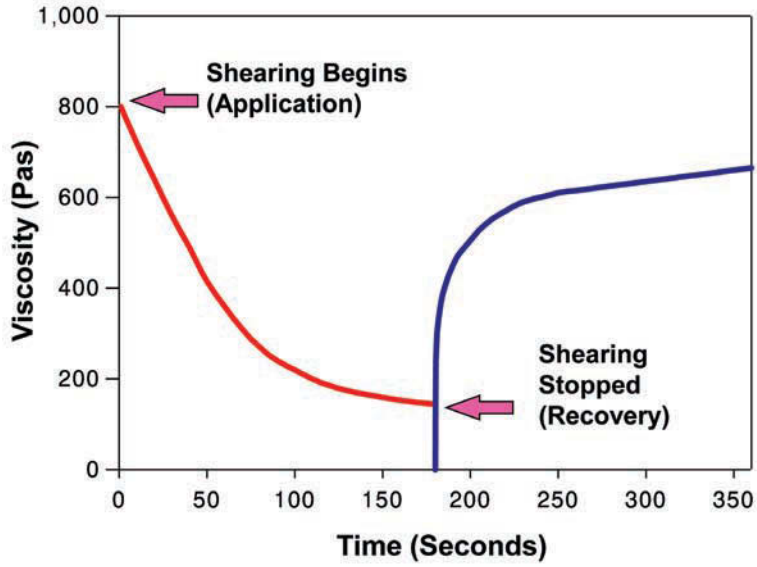

Figure 12. Recovery after application

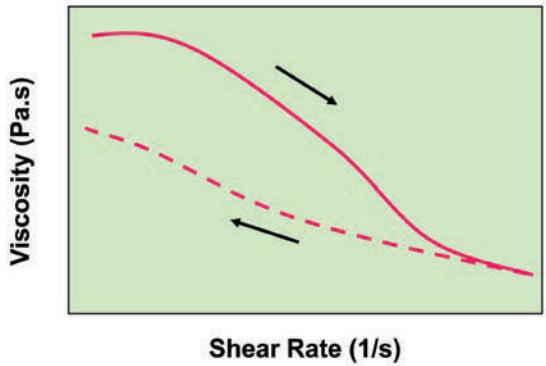

Figure 13. Thixotropy loop

If the "up" curve (i.e., increasing shear rate) overlaps the "down" curve (i.e., decreasing shear rate), the system is **non-thixotropic**. If the "up" curve is above the "down" curve, the system is **thixotropic**. If the "up" curve is below the "down" curve, i.e., the viscosity is increasing with decreasing shear rate after the initial

shearing, but is higher at each shear rate relative to the "up" curve, the system is **rheopectic**. Examples of rheopectic systems are certain lubricants, gypsum pastes, and inks that thicken during the "down" step, after they are mixed, to viscosities that are greater than the corresponding viscosities in the "up" step.

The area between the "up" curve and the "down" curve indicates how much energy (ΔE) the formulation is losing or gaining in the process:

$$\Delta E = \int \sigma_i \dot{\gamma}_{i(up)} - \int \sigma_j \dot{\gamma}_{j(down)}$$

Additional parameters that affect the formulation are temperature and pressure. The relationship between the viscosity and the temperature follows in many cases (but not in all formulations) the Arrhenius relationship:[7,17]

$$\eta = Ae^{Ea/RT}$$

Where A is a constant, Ea is the activation energy, R is the gas constant, and T is the absolute temperature. This relationship describes how the viscosity decreases with increasing temperature. The activation energy may be calculated by plotting log viscosity as a function of 1/T as shown in **Figure 14**.

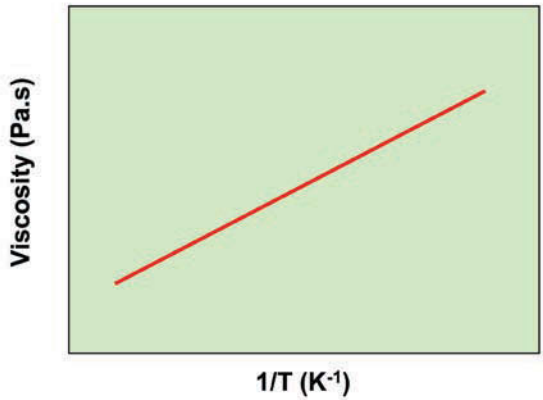

Figure 14. Arrhenius plot: Viscosity as a function of 1/T

Standard measurements are usually performed in the X-Y dimensions by shearing in one direction. However, the external force may result in a deformation in the third dimension Z. If the formulation experiences a force in the Z direction, also labeled as the **normal force**, the formulation may respond in an expansion in certain directions. Normal forces are important in extrusion, where the normal force may result in die swelling (the swelling of the material after it is forced through a die, usually to form a part having a specific geometry) and in certain polymeric solutions where the material is climbing up the rotating mixer shaft while mixing. In addition to temperature, other parameters that may affect the rheological properties of the formulation include pressure gradients during processing, extensional forces, and electric and magnetic fields.

Dynamic Properties – Viscoelasticity

When we pull a spring and remove the external force, the spring recoils to its original position, exhibiting an "elastic" behavior. Ideally, it would regain all its initial energy. The relationship between the force F and the extension X is described by Hooke's Law:

$$F = kX$$

where k is a constant. The energy E that is stored in the spring may be calculated as:

$$E = \frac{1}{2} kX^2$$

When we pull a piston in a cylinder filled with a Newtonian liquid (the device is known as a dashpot) and remove the external force, the liquid stays in its place and all the energy is dissipated to the environment. Since most formulations are neither fully elastic nor fully inelastic, some of the energy is stored and some of it is lost. A material that demonstrates both elastic and flow properties is a silicone polymer known, commercially, as Silly Putty. When shaped into a ball, it exhibits its elasticity over a short period of time and would bounce when dropped on a hard surface. However, when the ball is left on the surface, the material would flow like a liquid, exhibiting its flow properties over a long period of time.

Various models are used to calculate the viscoelasticity of the system by combining the elastic and the flow parts. Combining the behavior of a spring with the behavior of a dashpot may be done in series (The Maxwell model) or in parallel (The Kelvin/Voigt model). A schematic presentation of combining a spring behavior with a dashpot behavior is shown in **Figure 15**.

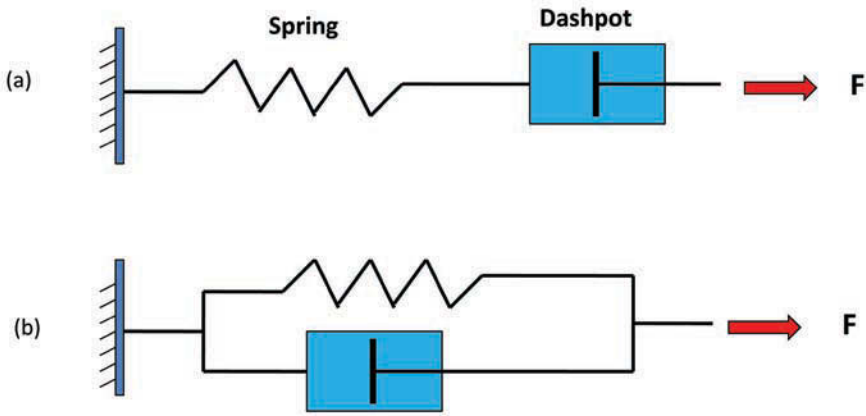

Figure 15. Viscoelastic models: (a) Maxwell model (b) Kelvin/Voigt model

The Maxwell model presents the shear rate as a combination of the elastic and the flow components:

$$\dot{\gamma} = \dot{\gamma}_E + \dot{\gamma}_V$$

$$\dot{\gamma} = \dot{\sigma}/G + \sigma/\eta$$

$$\sigma + \tau_M \dot{\sigma} = \eta\dot{\gamma}$$

Where $\tau_M = \eta/G$ is the time constant or the relaxation time. Therefore, the shear stress is:

$$\sigma = \eta\dot{\gamma}\,[1\text{-}\exp(-\tau/\tau_M)]$$

Where τ is the time.

The Kelvin/Voigt model presents the shear stress as a combination of the elastic and the flow components:

$$\sigma = \sigma_E + \sigma_V$$

$$\sigma = G\gamma + \eta\dot{\gamma}$$

Therefore, the shear strain is:

$$\gamma = (\sigma/G)\,[1 - \exp(-\tau/\tau_k)]$$

Where τ_k is the time constant.

Following the effect of the external force on the deformation and the recovery of the system after the external force is removed may be done by monitoring the changes in strain as a function of time while applying a constant shear stress and following the recovery immediately after the removal of the external force, as shown in **Figure 16**. This test is known as the **Creep/Recovery test**. Sometimes, creep/recovery profiles show the compliance J rather than the strain.

$$J(t) = \gamma(t)/\sigma = 1/G$$

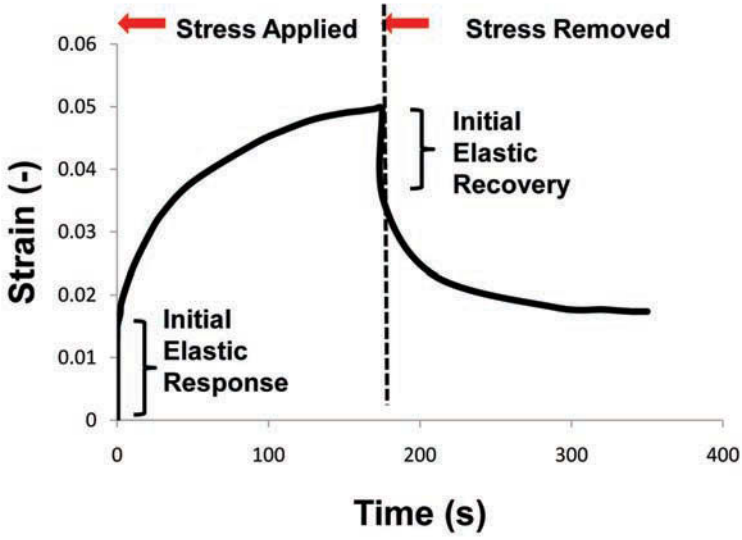

Figure 16. Creep/Recovery test (constant stress)

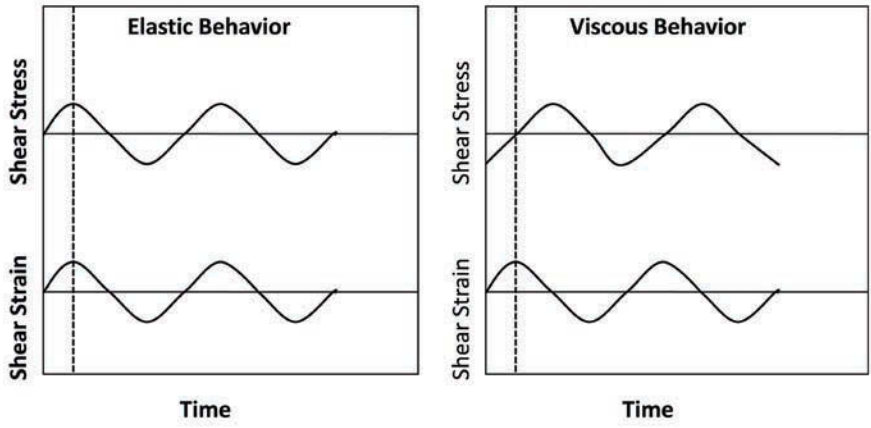

Figure 17. Oscillatory elastic and viscous behavior

Properties that may be calculated from a creep/recovery test are the shear rate at low stress, the initial (or zero shear) viscosity, yield value, compliance, percent elasticity, relaxation time and the elastic modulus.

Instead of pulling the sample in one direction, let us consider a dynamic test in which an oscillatory strain is applied to the formulation (**Figure 17**). By applying a sinusoidal oscillatory movement one may measure the distance (amplitude) the sample travels and the frequency of the oscillation. The complex oscillatory strain γ^* is therefore:

$$\gamma^* = \gamma_0 \exp(i\omega t)$$

Where γ_0 = strain amplitude, ω = angular frequency, τ = time and i is the imaginary unit ($i^2 = -1$).

For small strain amplitudes, the resulting complex stress σ^* is:

$$\sigma^* = \sigma_0 \exp[\, i\,(\omega t + \delta)]$$

Where σ_0 is the stress amplitude and δ is the phase angle between the stress and the strain. If the formulation is fully elastic, the shear stress would follow the shear strain during the oscillation and the phase angle would be $\delta = 0^0$. If the formulation is fully viscous, the shear stress would follow the shear strain with a phase delay of $\delta = 90^0$.

We define the **complex modulus G*** which describes the combined effect of the elastic and the viscous behavior of the system as:

$$G^* = \sigma^* / \gamma^*$$

The elastic part or the **storage modulus G'** may be defined as:

$$G' = G^* \cos(\delta)$$

And the viscous part or the **loss modulus G"** is correspondingly defined as:

$$G'' = G^* \sin(\delta)$$

The complex modulus **G*** is therefore defined as the square root of the complex combination of the elastic (or storage) modulus **G'** and the viscous (or loss) modulus **G":**

$$G^* = V\overline{(G'^2 + i\,G''^2)}$$

The tangent of the phase angle **Tan** (δ) is therefore:

$$\textbf{Tan}\ (\delta) = \frac{G^* \sin(\delta)}{G^* \cos(\delta)} = G''/G'$$

Correspondingly, the **complex viscosity** η* is defined as:

$$\eta^* = \eta' - i\eta''$$

where the **elastic viscosity** (sometimes referred to as dynamic viscosity) η' is defined as:

$$\eta' = G''/\omega$$

and the **loss viscosity** η" is defined as:

$$\eta'' = G'/\omega$$

In a typical **strain sweep** test, as shown in **Figure 18**, the moduli are measured as a function of increasing strain at a constant frequency (in most tests – 1 Hz).

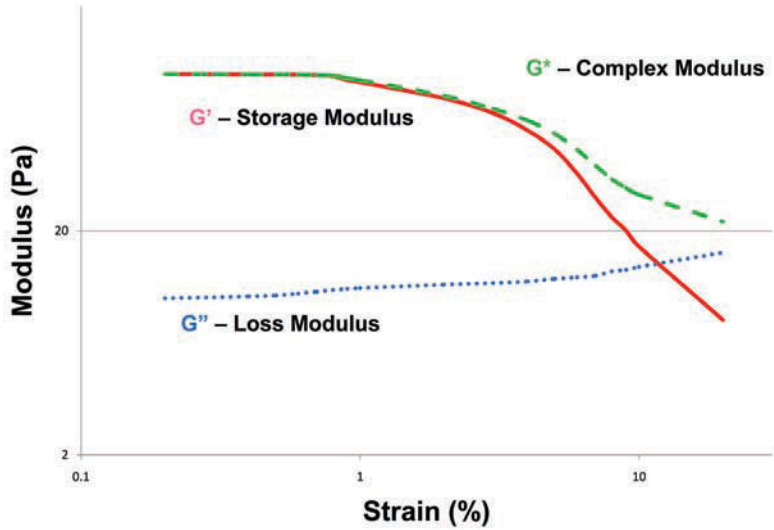

Figure 18. Strain Sweep: Modulus as a function of strain

At very low strains the modulus is (almost) constant until a certain strain is reached, at which the modulus deviates from linearity. This range of strains is called the **linear viscoelastic region**. When the modulus is measured as a function of increasing frequency, it is very important to confirm that the test is run at a

constant strain which is within the linear viscoelastic region. A **frequency sweep** may shed light on the internal interaction in complex fluids: If the components exhibit weak interactions with each other, the formulation is mostly viscous and G" > G' throughout the frequency range. If the components exhibit strong interactions with each other, the formulation is mostly elastic and G' > G" throughout the frequency range. A typical frequency sweep is shown in **Figure 19**.

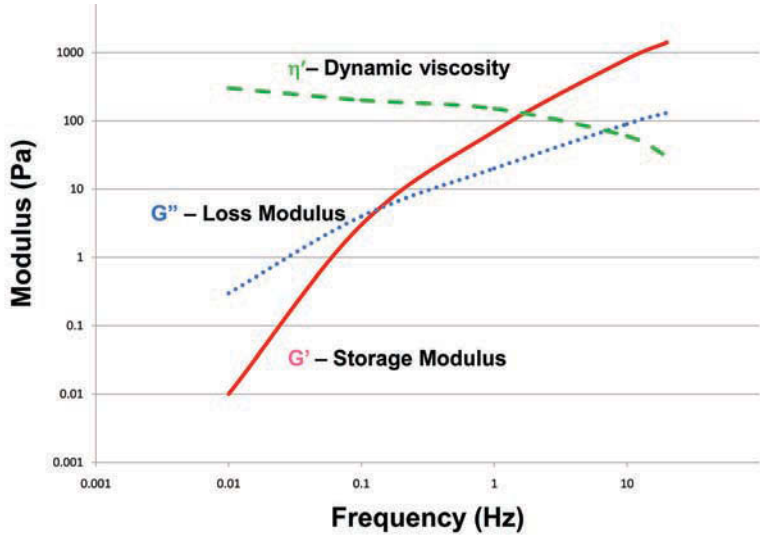

Figure 19. Frequency sweep: Modulus as a function of frequency

At low strains, in the linear viscoelastic range, we may assume that the absolute viscosity η obtained by a flow test (rotation) is the same as the dynamic complex viscosity η* obtained by an oscillation test.

$$\eta\,(\dot{\gamma}) \sim \eta^{*}\,(\omega), \text{ assuming that at low strains: } \dot{\gamma}\,(1/s) = \omega(rad/s)$$

This relationship is called the **Cox-Merz** Rule.[7-9,18] This rule is just an empirical rule and should not be considered a law. It has been shown that the Cox-Merz rule is valid for some systems (such as polymer melts, concentrated solutions, and semi-dilute solutions) but not for other systems (such as dilute solutions and cross-linked polymers). Since the formulation may undergo various transitions during the oscillation, its elastic and viscous components may be described by a combination of several models, such as the Burgers model,[2,7] which combines the Maxwell model and the Kelvin/Voigt model in series. This model may be expanded to a generalized model with many combinations of spring and dashpot models. With today's fast data processing technologies, it is easy to look for a model that describes best the transitions in the system and to calculate the relevant relaxation time for each transition. Most state of the art rheometers are equipped with software that analyzes such transitions and calculates the relevant relaxation times based on such models.

Instrumentation

The rheological properties one should follow when designing a formulation and the various tests that may provide insight about the behavior of the formulation and how it changes under external forces have been described thus far. This part discusses the various means of measurements and their use to describe the potential changes that the formulation might undergo during storage, processing and application.

One Point measurements

If the formulations we compose were 100% elastic, like a spring, we could have measured everything using an instrument similar to a balance and calculated the stored energy using Hooke's Law. A simple way to measure the properties of flowing formulations in a qualitative way is to use test tubes filled with known liquids, labeled A to Z. The tubes are sealed, leaving an air bubble inside. If we flip the test tube upside down, the air bubble travels upwards in a speed that depends on the viscosity of liquid. This method is known as the rising bubble measurement. We could then compare our sample to the known "viscosity" and label our formulation as having a viscosity similar to a reference liquid. Another method to measure the viscosity is to fill a cup with an opening in its bottom and record the time that it takes to drain the cup. If we have a master curve showing the viscosity as a function of time for known liquids, we may find the corresponding viscosity of our sample on the master curve. The **Zahn Cup** and the **Ford Cup** (See **Figure 20**) are examples of cups used in the industry.

Figure 20. Zahn and Ford Cups (courtesy of Byk-Gardner)

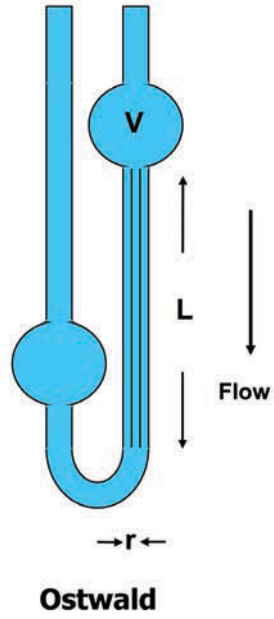

Figure 21. Ostwald capillary viscometer

For dilute solutions, we may use **capillary viscometers**. These are generally glass tubes that have a calibrated volume, usually in the form of a bulb. The capillary viscometer is filled with the sample, placed in a constant temperature bath and the time to drain the bulb under gravitational force is recorded. An **Ostwald capillary viscometer** is shown in **Figure 21**.

The viscosity may be calculated by using the **Hagen-Poiseille** equation:

$$\eta = \pi r^4 \Delta P t / 8VL \text{ or } \eta = Kt$$

Where V is the volume of the liquid, ΔP is the pressure drop, L is the length of the capillary, r is the radius of the capillary, and t is the time it takes to drain the bulb. If all the parameters are constant (K), the viscosity is easily calculated by measuring the time it takes to drain the bulb. The **kinematic viscosity** ν is calculated by dividing the measured viscosity by the density of the liquid. The units of the kinematic viscosity are Stokes.

$$\nu = \eta / \rho = Ct$$

Where C is K/ρ.

Various types of capillary viscometers with different geometries are available commercially. Examples are the **Cannon-Fenske capillary viscometer** and the **Ubbelohde capillary viscometer** as shown in **Figure 22**. High pressure capillary viscometers are used where there is a need to force the material through the capillary such as in the study of polymeric materials. The viscosity is calculated by measuring the pressure difference and using the Hagen-Poiseille equation.

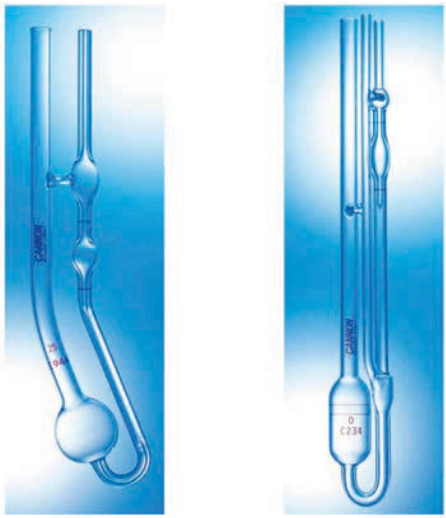

Figure 22. Cannon-Fenske and Ubbelohde capillary viscometers (courtesy of Cannon Instrument Company)

Other one-point measurement instruments include the **Falling Ball** and **Falling Rod** viscometers which are used for low viscosity formulations and the **Melt Indexers**, which are used for polymeric materials. In the falling ball viscometer, the sample is placed in a tube of known dimensions and a ball or a rod with known size and density is dropped into the sample. Electronic or magnetic sensors may be used for opaque formulations. The viscosity is correlated to the time it takes the ball/rod to travel a known distance and calculated according to the **Stokes equation**, where the frictional force $\mathbf{F_f}$ is:

$$F_f = 6\pi r\eta v$$

Where r is the radius of the spherical ball, η is the viscosity, and v is the velocity of the ball. Since the frictional force is balanced by the gravitational force, F_g:

$$F_g = 4/3\ \pi r^3 (\rho_p - \rho_f)g$$

Where r is the radius of the ball, ρ_p is the density of the ball, ρ_f is the density of the fluid and g is the gravitational acceleration. The resulting velocity is:

$$V = (2/9)\ r^2 g\ (\rho_p - \rho_f)/\eta$$

And the viscosity is therefore:

$$\eta = (2/9)\ r^2 g\ (\rho_p - \rho_f)/V$$

The falling ball/rod method is limited to Newtonian liquids and requires several balls/rods having different sizes and/or densities to cover a range of viscosities.

Extended range rheometers

The advantages of one-point measurements are the simple mechanism of the viscometers, their ease of use, and their relative low cost. However, since most formulations are Non-Newtonian, in order for the analysis to describe real changes in the behavior of the formulation, one has to measure the viscosity as a function of shear rate over a range of shear rates, not just a one-point measurement. For Non-Newtonian formulations, the viscosity measured by the one-point measurement instruments should be viewed just as an indication of the rheological properties of the system. Since the viscosity is changing as a function of changing shear rate, there is a need for an instrument that is capable of measuring the stress, the strain, the shear rate, the temperature and in some cases, the pressure, during the application of the external force. To study the viscoelastic properties of the formulation, an instrument that would measure the strain and the stress while oscillating at certain frequencies is required.

The formulation chemist has a choice of a variety of **rotational rheometers**, **oscillatory rheometers** and rheometers that combine both methods and provide a wide range of strains, stresses, and frequencies. The formulation chemist should define first the types of measurements and the ranges that are applicable to the formulation under investigation and then choose the rheometer that would best fit that definition. Most rheometers in use to date are based on rotating the sample inside a known fixture (also known as the geometry) following an extended range of parameters such as shear stress and shear rate. The rotation allows the continuous shearing of the sample between a stationary surface and a moving surface as shown in Figure 3.

There are two types of rotational rheometers: **Controlled stress rheometers,** in which the applied force is pre-determined and the resulting shear rate is monitored and **controlled rate rheometers**, in which the speed (shear rate) is controlled and the resulting shear stress is monitored, as shown in **Figure 23**.

A schematic structure of a controlled stress rheometer is shown in **Figure 24**. Various techniques are used to monitor the speed, such as an optical decoder, and various techniques are used to suspend the assembly, such as air bearing or magnetic bearing to enable measurement of the smallest possible torque and to ensure that the effect of inertia and other factors are minimal. With today's advanced calculations capabilities, standard computers can easily convert the data measured by either type of these instruments and accurately report the parameters measured, therefore practically, in most cases, the differences between the two types are minimal.

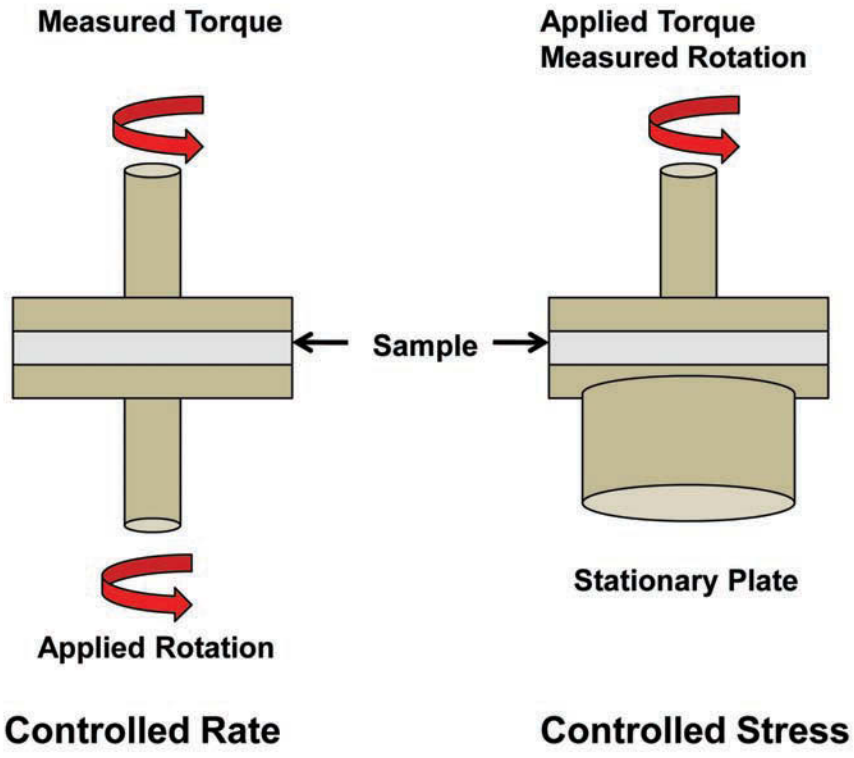

Figure 23. Differences between controlled stress and controlled rate rheometers

A typical viscometer that is used in many laboratories is shown in **Figure 25**. It measures the stress resulting from the rotational movement of a spindle inside a cylinder filled with the material. The spindle rotates at a fixed, pre-set rate, usually measured as rotations per minute (RPM). The corresponding shear rate may be calculated by multiplying the speed in RPM by a constant that is provided for each spindle. Some viscometers provide only a limited number of shear rates and therefore cover only a portion of the relevant shear rate range. The viscometer shown in Figure 25 provides 54 pre-set speeds from 0.01 to 200 RPM. It may be connected to a computer, so that the measurement is performed continually, hence, transforming the viscometer into a rheometer. The advantage of using this type of rheometer is its ease of use, the use of a number of shear rates (as opposed to the one-point measurement discussed earlier), and their relatively low cost.

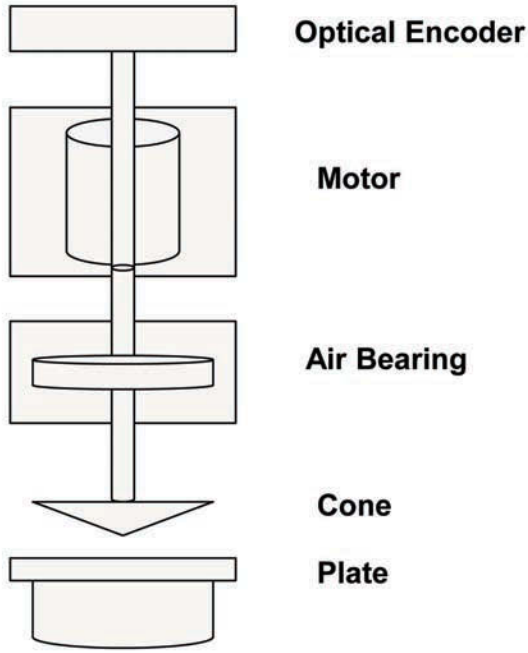

Figure 24. A schematic structure of a controlled stress rheometer

Figure 25. The DV II + Pro Viscometer (courtesy of Brookfield Engineering Laboratories)

When the viscosity is measured by rotating a spindle at pre-determined speeds inside a cylindrical container with a defined geometry, the material flows in the gap between the inner and the outer cylinders. This geometry is known as a "bob and cup configuration." This type of geometry, sometimes referred to as the "Couette Cell," in which the sample is placed in a narrow gap between an outer cylinder and an inner cylinder, was first used by Couette in 1890. As the outer cylinder is moving, a torque is applied on the inner cylinder which may be measured by a sensor, such as a torsion bar that is attached to the inner cylinder. The advantage of this type of measurement is that it separates the motor that determines the speed and the sensor that measures the torque. In a rheometer system that controls the stress, the same bob and cup configuration may be used but the motor creates the movement and controls the stress. The torque that is created by the motion of the fluid is monitored by a sensor, such as a spring, that is placed between the motor and the inner cylinder. The displacement of the inner cylinder is monitored by a special device such as an optical decoder. The speed may be pre-set, changed manually or continually changed by specific software. Figure 26 shows a schematic presentation of the concentric cylinder geometry.

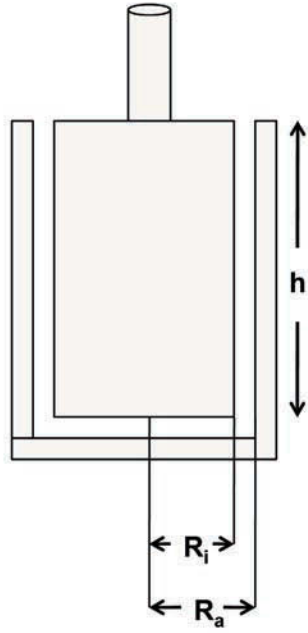

Figure 26. A schematic presentation of the concentric cylinder geometry

The shear rate in a cup and bob system is:

$$\dot{\gamma}_i = 2\omega R_a^2/(R_a^2 - R_i^2)$$

Where the angular viscosity is $\omega = 2pv/60$ (v is the speed in RPM), R_a is the radius of the outer cylinder and R_i is the radius of the inner cylinder. Therefore:

$$\dot{\gamma}_i = \{\pi R_a^2/[\ 15\ (\ R_a^2 - R_i^2\ )]\}v$$

Or:

$$\dot{\gamma}_i = Pv$$

Where P is a constant known as the shear rate factor.

The shear stress for this system would be:

$$\sigma_i = (1/2h\ R_i^2)\ M$$

Where h is the height of the rotor and M is the torque.

Or:

$$\sigma_i = f\ M$$

Where f is the shape factor. Therefore, if the instrument measures a signal S that is proportional to the torque, for example M = aS, the shear stress is:

$$\sigma_i = faS = QS$$

And the viscosity is:

$$\eta = \sigma / \dot{\gamma}_i = (M/4\omega h)\ [1/(\ R_a^2 - 1/R_i^2\ )] = (QS)/(Pv) = D\ (S/v)$$

Where D is a constant and the shear stress is calculated by monitoring the signal S and the shear rate is calculated by monitoring the speed v.

Since the concentric cylinder configuration is designed to simulate the movement of the fluid between two plates, it is important that the gap between the bob and the cup is kept so that the flow remains laminar and steady during the test. Therefore, the recommended ratio g, between the radius of the inner bob and the radius of the outer cup should be kept at $1.00 < g > 1.10$. As shown in Figure 25, concentric cylinder geometry may be attached to the controlled rate rheometer discussed earlier. This device may be equipped with a housing that circulates a fluid around the concentric cylinder to maintain a constant temperature during the test.

Other popular geometries are cone-and-plate and parallel-plate measuring devices. These geometries are designed to contain small quantities. In a cone-and-plate geometry, a schematic diagram of which is shown in **Figure 27**, the lower plate may be stationary while the upper cone is rotating (or oscillating) or the lower plate may rotate (or oscillate) and the applied torque on the upper cone is recorded.

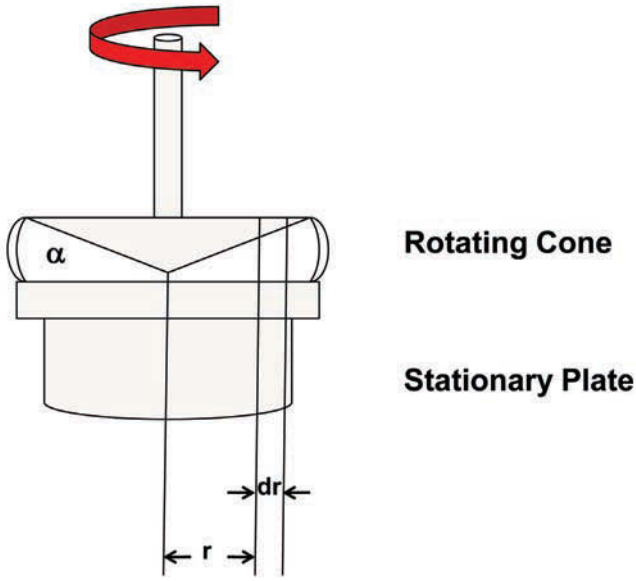

Figure 27. A schematic presentation of a cone and plate geometry

If the fluid is moving at an angular velocity ω and assuming that the cone angle a is very small (usually 0.1–3 degrees), so that sin (α) = α, the shear rate is:

$$\dot{\gamma} = \omega r/\alpha r = \omega/\alpha = 2\pi v/60\alpha = \pi v/30\alpha$$

Where v is the speed and r is the distance from the center of the cone.

The shear stress is calculated from the total torque M which is obtained by integrating over the entire radius:

$$M = \int \sigma 2\pi r^2 dr = \sigma 2\pi r^3/3$$

Or:

$$\sigma = 3M/2\pi r^3 = f_{cp}M$$

Where f_{cp} is the cone and plate constant. Since the cone and plate and the parallel plate configurations hold small amounts of material, the measurement is sensitive to drying and temperature change, as well as to errors as a result of edge effects. If the material is shear thinning to low viscosities, there is a risk of the material slinging out, especially at high shear rates.

For parallel plates, the "cone" angle is zero and therefore the shear rate is:

$$\dot{\gamma} = R\omega/h$$

Where h is the gap between the plates and correspondingly, the shear stress is:

$$\sigma = 2M/\pi r^3 = f_{pp}M$$

Where f_{pp} is the parallel plates constant.

(a)

(b)

(c)

(d)

(e)

Figure 28. (a) The Nova Rheometer (courtesy of ATS Rheosystems); (b) The Kinexus Rheometer (courtesy of Malvern Instruments); (c) The MCR Rheometer (courtesy of Anton-Paar); (d) The MARS Rheometer (photograph used by permission from Thermo Fisher Scientific); (e) The Discovery Hybrid Rheometer (courtesy of TA Instruments)

Additional measuring geometries for extended range rheometers include double gap geometry, tapered-plug geometry, and vane rotor and serrated plate geometry. These geometries have been designed to increase the accuracy of the measurement and to provide the geometry that would be adequate for specific conditions where other geometries may not be useful.

Full-scale **extended range rheometers** are capable of measuring the rheological properties over a wide range of shear stress and shear rate. The advantage of full scale rheometers is their ability to accurately measure the absolute viscosity. Most extended range rheometers provide an oscillation mode to measure the viscoelastic properties. These instruments are equipped with very good temperature control devices, for example, a controlled temperature bath, an oven or a thermoelectric cooler/heater, such as the Peltier device. Full-scale rheometers are fast and convenient. Their software allows fast and accurate analysis of the data, plotting a wide range of graphs and calculating various properties using mathematical models, comparisons of various tests, and seamless embedding of the results in comprehensive reports. They exhibit the flexibility of tailoring a specific sequence of tests for specific projects. For example, one may store a sequence of steps that could serve as a template for a repeat test designed for a specific research and development project or for a standard quality control testing procedure. The limitations of these rheometers are in their relatively larger size and relatively higher cost. Examples of standard extended range rheometers are shown in **Figures 28a to 28e**.

In addition, there are many instruments that are specifically designed for quality control, process control (on-line and off-line), very low viscosity, very high viscosity, melt viscosity, and extensional flow. Some rheometers have been developed for a specific industry (for example, for the ink or the drilling fluids industries). Other rheometers offer a combination of techniques such as a combination of a rheometer and a microscope to monitor simultaneously the rheological properties and the movement of particles or a change in phases. **Figure 29** shows an extensional rheometer (a) and a rheometer/microscope combination (b).

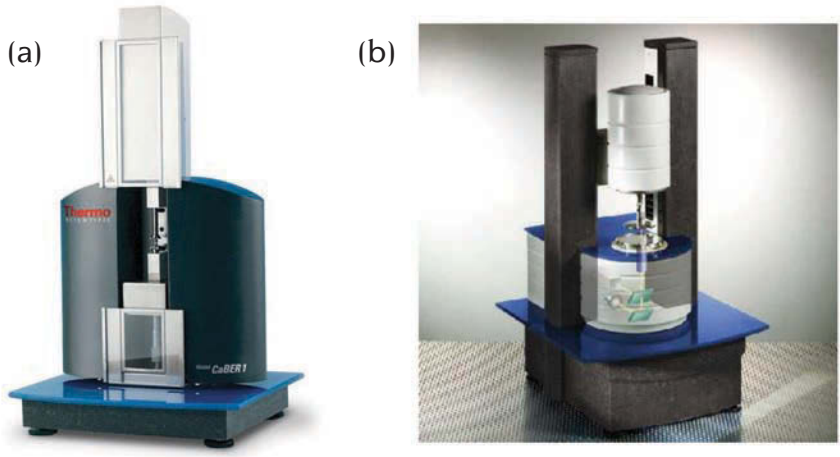

Figure 29. (a) A capillary breakup extensional rheometer and (b) a rheometer/microscope combination (photograph used by permission from Thermo Fisher Scientific)

For such measurements, a fresh sample should be used for each test. The order of tests depends on the objectives of the specific study. Generally, it is recommended to begin with flow tests: shear stress as a function of shear rate, viscosity as a function of shear rate, thixotropy loop, calculating yield values, and a shear/recovery test. This is in addition to a creep/recovery test, a strain sweep, and a frequency sweep. Sometimes it is impossible to perform all these tests using fresh samples, especially when the formulation chemist has only a small amount of the material under development available for testing. When the same sample is being used in all tests, the practical order of tests that may shed light on the rheological properties of the system, though it is not the ideal sequence of tests, would be: strain sweep, frequency sweep, creep/recovery, thixotropy loop, and flow curves.

When choosing a rheometer system for a research laboratory, a quality control laboratory or for a manufacturing plant, it is recommended that the formulation chemist prepares a list of tests, the range of viscosities, and shear rates that are relevant to the materials that are being tested as well as the temperatures, pressures, and other relevant parameters. Based on this initial assessment, a decision should be made that will lead to the use of the most appropriate commercial rheometer systems. Updated lists of manufacturers of commercial rheometers may be found online.[19]

Rheological Additives

Rheological additives are natural or synthetic compounds that may be **hydrophilic** (which means that they may be attracted to, interact with, or be compatible with

water-based systems), **hydrophobic** (which means that they may be attracted to, interact with, or be compatible with organic-based systems), or **amphiphilic** (combinations of hydrophilic and hydrophobic parts in the same molecule). Rheological additives are added in small quantities to the formulation in order to impart the desired rheological properties. Rheological additives are capable of creating and significantly changing the three-dimensional structure of the system by interacting with one or more key components of the formulation: the solvent, the binder, and/or with other additives. Rheological additives can range in size/molecular weight from small organic molecules to high molecular weight polymers. Their main feature is their ability to form a weak three-dimensional network structure in the continuous phase of the formulation. This weak structure should be capable of breaking down when an external force is applied to the formulation and be capable of re-forming when the external force is removed. A formulation that contains rheological additives exhibits, in most cases, shear thinning behavior: high viscosity at low shear rates and low viscosity at high shear rates. When the external force is removed, the formulation should recover gradually, over time, back to its original viscosity. In most cases, rheological additives impart thixotropy. The advantage of rheological additives is that they affect the system at very low levels, usually at 0.1% to 5% (w/w). The abundance of different types of rheological additives allows the formulation chemist to pick and choose the right additive (or a combination of additives) for a specific formulation. Note that each type of rheological additive may be available in a variety of grades which may be different in their molecular weight, polymer chain architecture, side chains, ionic nature, and their sensitivity to salts and surfactants, pH, and temperature. The disadvantage of using rheological additives is that most are sensitive to changes in the composition of the formulation and to external conditions such as temperature and pressure. Some rheological additives are very sensitive to changes in the pH of the formulation. This sensitivity to other ingredients in the formulation and to the physical conditions that the formulation experiences during processing should be taken into consideration in the design of the product and every time the product is being reformulated.

Rheological additives used in topical formulations may be classified into the following groups:

1. Rheological additives for water-based systems: natural gums, cellulose-based rheological additives, synthetic rheological additives, silicate minerals, synthetic silica, and their blends
2. Rheological additives for solvent-based systems: fumed silica, organoclays, and organic rheological additives
3. Miscellaneous rheological additives

Rheological Additives for Water-based Systems

Natural Gums:

Rheological additives based on natural gums are manufactured from natural sources such as trees and plants (from wood or from the fruit of the plant), algae or by

fermentation. Examples are carrageenan, alginate, guar gum, locust bean gum, and xanthan gum. These bio-based additives are widely used in the food, personal care, and oil-drilling industries. Natural gums are basically long-chain polysaccharide polymers based on various sugar units as the building blocks of the polymer chain with side chains that are unique to the specific gum.

Carrageenan is extracted from red seaweeds. Its chemical structure is based on a sulfated polysaccharide. It is used as a vegetarian replacement to gelatin in the food industry. There are three basic types of carrageenan: kappa, iota, and lambda. Kappa carrageenan contains about 25% ester sulfate and 34% 3,6-anhydrogalactose (3,6-AG). It forms rigid gels at room temperature in the presence of potassium ions. Iota carrageenan contains about 32% ester sulfate and 30% 3,6-AG. It forms soft gels in the presence of calcium ions. Lambda carrageenan contains about 35% ester sulfate with little or no 3,6-AG. It does not form a gel by itself but is used as a thickener. Heating carrageenan in water, or a mixture of water with other solvents, in the presence of the relevant ions and then cooling, leads to the formation of a gel. When heated, the polymer is present in the form of free coils and when the formulation is cooled, double helix structures are formed by hydrogen bonding. It has been shown that the gel formation occurs in two steps (**Figure 30**) and is thermo-reversible.[20,21]

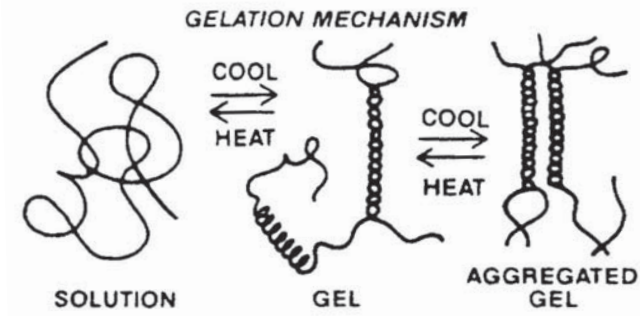

Figure 30. Schematic representation of the gelling mechanism of carrageenan (courtesy of FMC Corporation)

Alginate (Alginic Acid or Algin) is extracted from brown seaweeds. Its chemical structure is based on a polysaccharide copolymer of (1-4)-linked β-D-mannuronate and C-5 α-L-guluronate. Alginate, which is capable of absorbing 200-300 times its own weight in water, is used as sodium, potassium, or calcium alginate. The gelling mechanism of calcium alginate is thought to be attributed to the formation of microscopic super-molecular structures.[22]

Guar gum (Guaran or Galactomannan) is produced from the seeds of the guar bean plant. It is composed of a polysaccharide chain containing the sugars galactose and mannose. There are about two mannose residues for every galactose repeat unit. Guar gum and its derivatives may gel by forming a complex with multivalent metal

ions, in particular borate ions. At high (basic) pH, the borate ion forms junctions (similar to crosslinks) with the polysaccharide chains. This gelation process may be reversed by lowering the pH to acidic values. A modified derivative of guar gum is **Hydroxy Propyl Guar gum (HPG)** which is produced by reacting alkali guar gum with propylene oxide. HPG is nonionic, stable at pH ranging from 4–10 and is compatible with formulations containing alcohols and glycols.[23]

Locust Bean gum (LBG, Carob gum) is produced from the seeds of the carob tree. Similar to Guar gum, its chemical structure is based on a polysaccharide chain composed of galactose and mannose. The ratio of mannose residues to galactose repeat units is about 3-4:1.

Xanthan gum is produced by a fermentation process of sugars using the *Xanthomonas campestris* bacterium. Its chemical structure is based on a polysaccharide chain composed of glucose, mannose, and glucoronic acid. The mannose units are acetylated and the side chains may contain cetyl and pyruvate groups. The degree of substitution for pyruvate may be as high as 40% while the degree of substitution for the acetate units may be as high as 70%. A representative chemical structure of xanthan gum is shown in **Figure 31**.

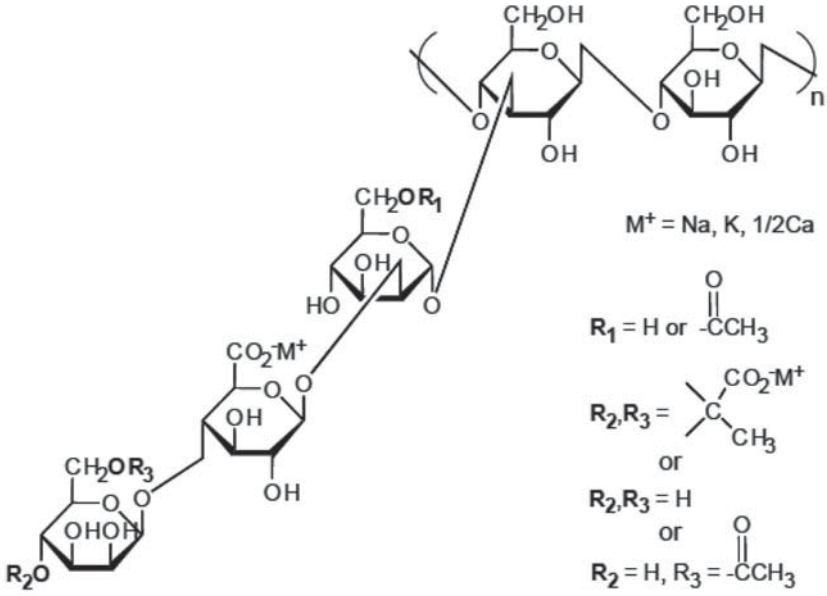

Figure 31. A representative chemical structure of xanthan gum (graph reproduced by permission of CP Kelco U.S., Inc. and affiliated companies; members of the J.M. Huber family of companies; © 2008 CP Kelco U.S., Inc., and its affiliates)

Xanthan gum is relatively resistant to enzymatic degradation. It is highly stable over a wide range of temperatures and is less sensitive to changes in salt concentrations, pH, and alcohol compared to other rheological additives. This

is due to the presence and position of its anionic side chains. It is highly efficient in water-based systems, i.e., it imparts very high viscosity at low shear rates and is almost non-thixotropic (i.e., fast recovery). The effect of salts and pH on the rheological properties of formulations containing xanthan gum has been widely studied.[24,25] A schematic presentation of the effect of heating/cooling and shear on the conformation of xanthan gum is shown in **Figure 32**.

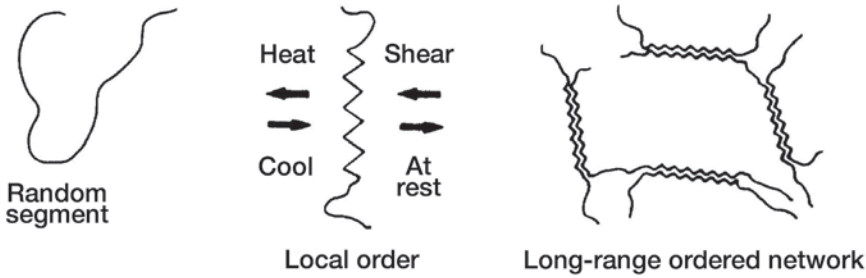

Figure 32. Effect of heating/cooling and shearing on the conformation of xanthan gum (graph reproduced by permission of CP Kelco U.S., Inc. and affiliated companies; members of the J.M. Huber family of companies; © 1988 CP Kelco U.S., Inc., and its affilates)

Blends of xanthan gum with other additives, such as locust bean gum, guar gum or carrageenan, exhibit a synergistic effect in most cases.[26-28] **Figure 33** shows the viscosity of blends of xanthan gum and guar gum at various ratios.

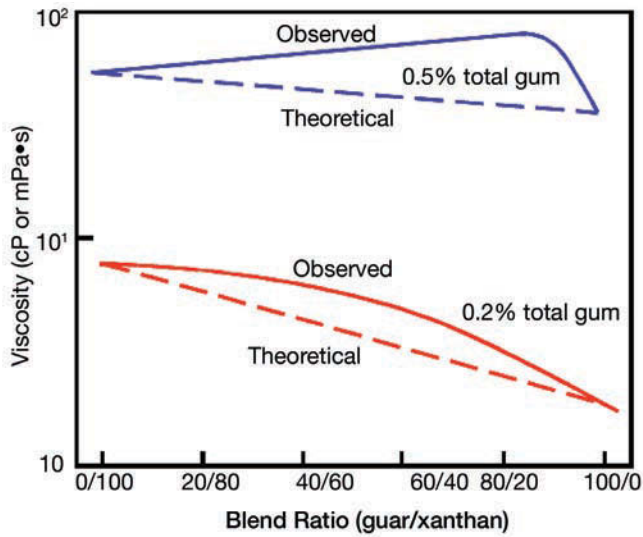

Figure 33. Synergistic effect of blends of xanthan gum and guar gum (graph reproduced by permission of CP Kelco U.S., Inc. and affiliated companies; members of the J.M. Huber family of companies; © 2008 CP Kelco U.S., Inc., and its affiliates)

Cellulose-based rheological additives:

Rheological additives based on cellulose are manufactured from wood pulp (about 40-50% cellulose) or from cotton (about 90% cellulose). Cellulose is a linear, insoluble polysaccharide polymer containing D-glucose units. The **degree of polymerization (DP)** is defined as the number of glucose units in the cellulose polymer chain. The DP of cellulose derived from wood pulp is in the range of 300 to 1700 while the DP of cellulose derived from cotton is in the range of 800–10,000. Cellulose molecules form fibrous bundles that contain crystalline and amorphous regions. Cellulose is used as a rheological additive in its microcrystalline form or in its modified form such as the addition of hydrophilic side chains. The hydrophilic side chains act like spacers, separating the main cellulose layers, thus allowing water molecules to interact with the polymeric chain. Cellulose-based rheological additives are used in the food, personal care, pharmaceutical, and paint industries.[29-31]

Microcrystalline Cellulose (MCC) is made from purified crystalline cellulose fibers. It forms a three-dimensional structure of the insoluble micro-crystals in water. This structure is stable at very low shear rates but collapses at high shear rates. This process is reversible: viscosity increases over time as the gel structure reforms.

Modified cellulosic rheological additives, such as cellulosic ethers, are made by reacting purified cellulose with various alkylating reagents, usually in a concentrated base (sodium hydroxide) which makes the hydroxyl groups (OH) of the glucose units readily accessible. The **degree of substitution (DS)** is defined as the average number of substitutes per glucose unit. Since each glucose unit has three free OH groups, DS may be 3 or less. Typical DS values range from 0.4–2.8. Some alkylating reagents, such as alkylene oxide, may generate an additional OH group, which may be further reacted to form an oligomeric side chain. The **molar substitution (MS)** is defined as the average number of moles of substituents per one mole of glucose unit. Typical MS values may range from 1.5–4.0.

Carboxy Methyl Cellulose (CMC) or the corresponding sodium salt is a cellulose-based rheological additive in which a carboxy methyl (-CH_2-COOH) group (or its sodium salt) is the substituent. It is manufactured by reacting basic cellulose with monochloroacetic acid. CMC is a water-soluble anionic thickener. The properties of CMC depend on its degree of substitution and the degree of polymerization. It is soluble in hot and cold water. While the rate of dissolution increases with decreasing molecular weight, its viscosity decreases with decreasing molecular weight. CMC is stable at pH ranging from about 4–9. **Figure 34** shows flow profiles of various rheological additives for water-based systems at a concentration of 0.5% in water.

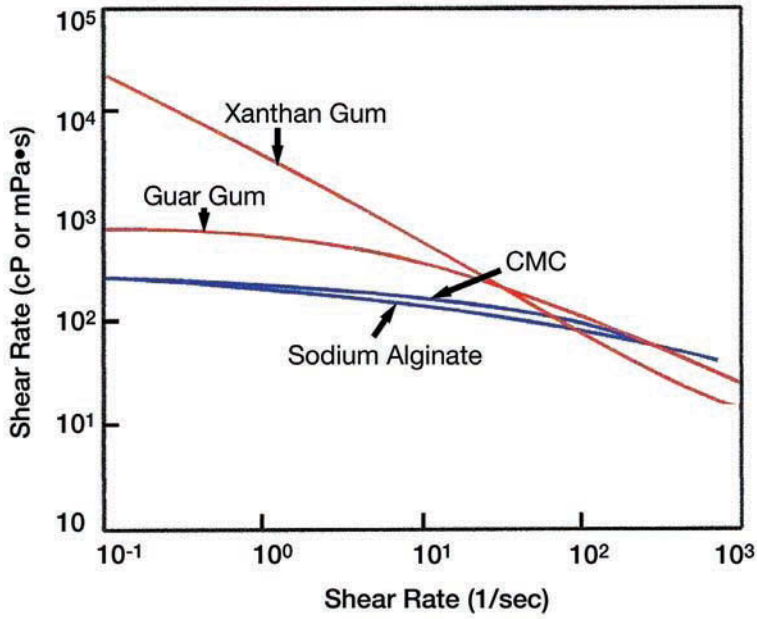

Figure 34. Flow profiles of various rheological additives in water at 0.5% concentration (graph reproduced by permission of CP Kelco U.S., Inc. and affiliated companies; members of the J.M. Huber family of companies; © 2008 CP Kelco U.S., Inc., and its affiliates)

Hydroxy Ethyl Cellulose (HEC) is a nonionic thickener in which the substituent is a hydroxy ethyl ($-CH_2CH_2$ (OH)) group. It is prepared by reacting basic cellulose with ethylene oxide. Its solubility in water depends on its molar substitution. Most commercial HEC grades are soluble in cold and hot water with MS ranging from about 1.8 to about 3.5. As a nonionic thickener, it is relatively tolerant to salt solutions. HEC tends to agglomerate, or lump, when it is hydrated. This issue can be solved by treating the surface of its particles with, for example, glyoxal, which delays initial hydration. The hydration time may be controlled by the pH of the formulation. When coated with glyoxal, the HEC surface OH groups are masked so that there is no wetting. The glyoxal/HEC bond is breaking down when the pH is increased. The rate of breaking down the glyoxal/HEC bonds and exposing the HEC depends on the pH. HEC is stable at pH ranging about 2–11 but may be oxidized at extreme pH and temperature conditions.

Similarly, Hydroxy Propyl Cellulose (HPC) is a nonionic thickener in which the substituent is a hydroxyl propyl ($-CH_2CH(OH)CH_3$) group. It is prepared by reacting basic cellulose with propylene oxide. Since the alkyl group is larger compared to HEC (i.e., more hydrophobic), MS has to be 3.5 or higher in order to be soluble in water. Its solubility in water depends on the temperature: it exhibits a lower critical

solution temperature (LCST) at 45°C. HPC may be dissolved in polar organic solvents such as short chain alcohols and glycols.

Methyl Cellulose (MC) and its derivatives, such as **Hydroxy Propyl Methyl Cellulose (HPMC)** are nonionic thickeners prepared by reacting alkali cellulose with methyl chloride with or without ethylene oxide or propylene oxide. Its solubility depends on the degree of substitution and the solution is usually stable at pH ranging from 3–11. MC is used in formulations containing high concentrations of surfactants due to its increased lipophilic nature compared to HEC.

Other rheological additives based on a cellulose polymer backbone include mixed ether derivatives of HEC (nonionic), **Carboxymethyl Hydroxyethyl Cellulose (CMHEC)** (anionic) and hydrophobically modified derivatives such as **Ethyl Hydroxyethyl Cellulose (EHEC)** and **Cetyl Hydroxyethyl Cellulose (HMHEC)**. The rheological properties of EHEC and HMHEC and their associative nature are discussed later in this chapter. CMHEC is available with carboxymethyl degree of substitution ranging from 0.3–0.5 and hydroxyethyl DS ranging from 0.7–2.0. Combining the properties of both the nonionic nature of HEC and the anionic nature of CMC results in an increased tolerance to salts compared to CMC.

Synthetic Rheological Additives

Alkali Swellable Polymers (ASP), also known as **Alkali Swellable Emulsions (ASE)** are used in paints, adhesives, oil drilling, and personal care products. ASP rheological additives are synthetic polymers or copolymers of ethylenically unsaturated monomers containing anionic groups such as acrylic or methacrylic acid with relatively high molecular weight. A typical copolymer structure of acrylic and methacrylic monomers is shown in **Figure 35**.

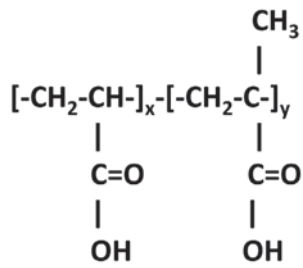

Figure 35. Chemical structure of an acrylic copolymer.

Polyacrylic polymers and copolymers swell in water-based systems when they are neutralized with a base such as sodium hydroxide, ammonium hydroxide, or triethanolamine. As the carboxylic groups are neutralized, the polymer chain, which is originally coiled, opens up to fill the space, as shown in **Figure 36**. The effect of pH on the viscosity of polyacrylic rheological additives is shown in **Figure 37**.

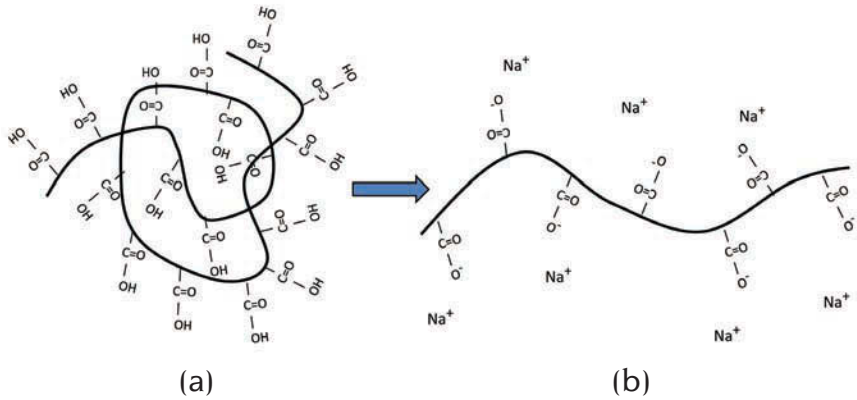

Figure 36. Schematic presentation of the neutralization of an alkali swellable polymer chain (a) coiled (b) uncoiled

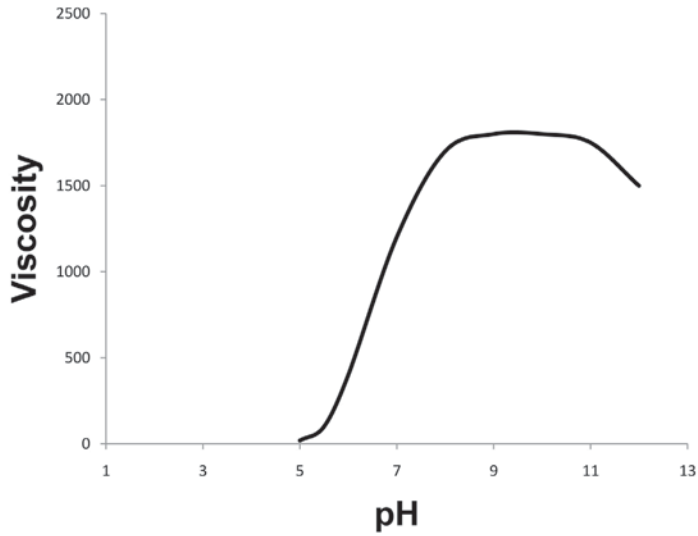

Figure 37. Change in viscosity of an alkali swellable polymer in water as a function of pH

Lightly Cross-linked Alkali Swellable Polymers, also known as **Carbomers,** are alkali swellable copolymers, mostly copolymers of acrylic acid, which are lightly cross-linked with cross-linking agents such as allyl pentaerythritol or allyl sucrose. The effect of the following properties on the rheological properties of carbomer rheological additives has been widely studied:[32-35.]

- Type of polymer
- Type of crosslinking agent and its concentration
- The molecular weight between crosslinking junctions

Cross-linked alkali swellable polymers are much less prone to bacterial growth compared to natural gums due to their chemical structure. The original carbomers have been manufactured using benzene as the solvent. Due to regulatory restrictions current carbomers are being manufactured using ethyl acetate or ethyl acetate/cyclohexane as the solvent.

Associative Thickeners (AT) for water-based systems are used in various formulations to impart improved application properties such as better leveling, homogeneous coverage of the application area, and smoother film formation. Associative thickeners are ionic or nonionic water-based polymers or copolymers containing hydrophobic groups with the following general structure:

R-X–water-soluble polymer–X-R'

Where X is a linkage group and R and R' are hydrophobic groups. Many types of molecular architectures have been proposed for associative thickeners, such as linear, comb, star, and complex structures. Commercial associative thickeners include hydrophobically modified polyether polyurethanes, hydrophobically modified polyether polyols, hydrophobically modified alkali swellable copolymers, and hydrophobically modified cellulosic thickeners.

While standard surfactant molecules contain, in most cases, one hydrophobic part and one hydrophilic part, associative thickeners for water-based systems may contain a hydrophilic part and at least two hydrophobic parts. Surfactants are typically low molecular weight molecules, while associative thickeners are typically low to medium molecular weight polymers. Representative molecular weights of associative thickener molecules are 2,000 to 100,000. The structure of a polymeric associative thickener may contain a hydrophilic backbone and hydrophobic groups attached to the ends of the polymer chain or to its side chains. The hydrophobic groups associate with each other to form micelles that connect several polymer chains and result in a three-dimensional network structure as seen in **Figure 38**.

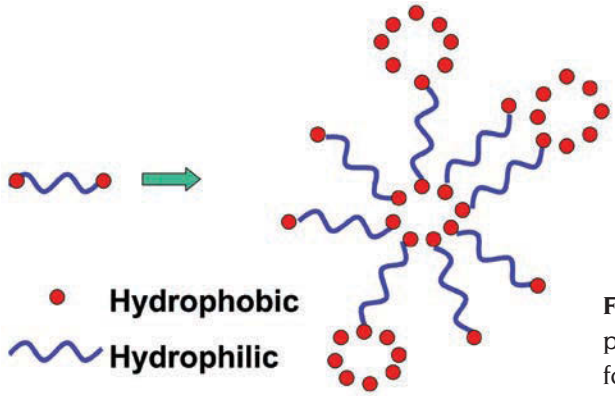

Figure 38. Schematic presentation of micelle formation

The chemical structure of the hydrophilic and hydrophobic parts of the polymer determines the nature and the size of the micelles and the response of the network to shear forces. Associative thickeners are also capable of interacting with other ingredients in the formulation (such as binders, pigments, surfactants, and co-solvents) to form an even more complex network structure. The use of associative thickeners, originally developed for use in paints,[36,37] in cosmetic formulations has significantly increased in recent years.

Associative thickeners have been the subject of numerous studies that include their synthesis, rheological properties and the effect of surfactants and co-solvents on the properties of the formulation.[38-41] Other studies have shown that the hydrophobic end groups strongly affect the relaxation time of the network. The structure of the network, the effect of temperature, and the number of different relaxation mechanisms have also been studied. Various techniques have been developed to follow the size of the micelles at rest and under shear forces, including flow birefringence and dichroism, small angle light scattering, neutron scattering, and fluorescent labeling.[42-49]

Hydrophobically Modified Cellulose Based Rheological Additives (HMCE), such as derivatives of **Hydroxy Ethyl Cellulose (HMHEC)**, were developed to improve the flow and leveling of water-based formulations and to decrease spatter while they are being brushed or sprayed. These additives are based on high molecular weight cellulose polymers that were modified with hydrocarbon chains having alkyl or aryl groups ranging from C_{10} to C_{24}, for example, Cetyl (C_{16}) side chains. A schematic model of HMCE is shown in **Figure 39**.

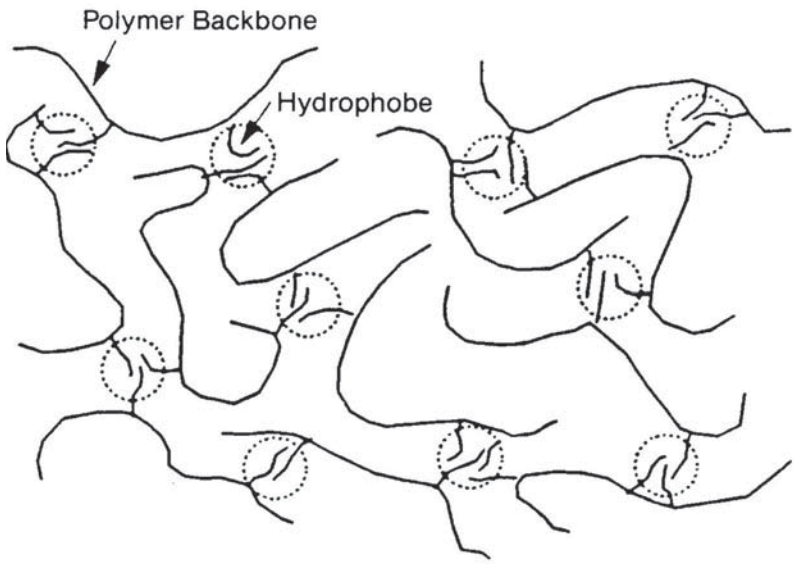

Figure 39. A schematic model of hydrophobically modified cellulose ether (HMCE) (reprinted with permission of Ashland Inc.; © 2013 Ashland Inc.)

The addition of hydrophobic groups to HEC results in lower viscosity at lower shear rates and higher viscosity at high shear rates in formulations containing HMCE compared to formulations containing HEC as seen in **Figure 40**.

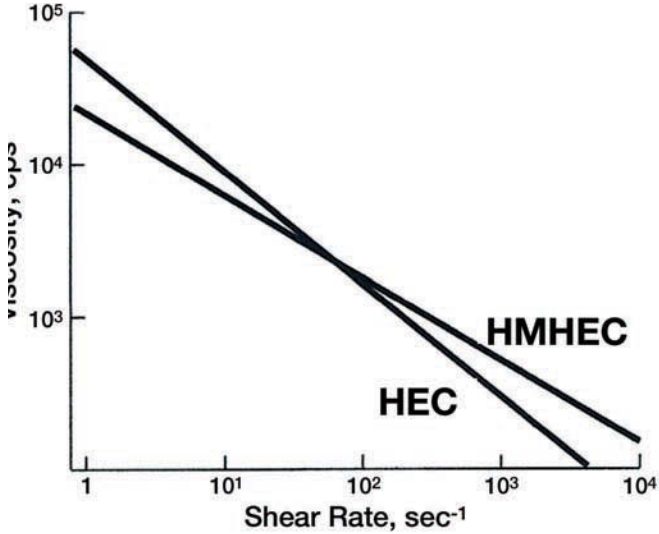

Figure 40. Viscosity as a function of shear rate in systems containing HMHEC and HEC (reprinted with permission of Ashland Inc.; © 2013 Ashland Inc.)

The rheological properties and the incorporation of HMHEC in various formulations has been widely studied.[50,51] Other hydrophobically modified cellulose ethers include hydrophobically modified ethyl hydroxyethyl cellulose (HMEHEC),[52,53] hydrophobically modified hydroxypropyl cellulose (HMHPC) and hydrophobically modified carboxymethyl cellulose (HMCMC). Examples of hydrophobically modified natural gums are hydrophobically modified hydroxypropyl guar gum (HMHPG) and hydrophobically modified alginate gum (HMAG).

Hydrophobically Modified Alkali Swellable Polymers (**HMASP** or **HASE**) are used in paints and in personal care products. The effect of the incorporation of hydrophobic groups in an acrylic polymer, as well as other types of alkali swellable copolymers on the efficiency of the polymer as a rheological additive has been widely studied.[54-60] Adding hydrophobic side chains to the copolymer results in a significant increase in viscosity but due to the presence of carboxylic acids, it strongly depends on the pH of the system, as shown in **Figure 41**. HMASP copolymers may contain monomers with a hydrophobic end group linked to the main chain through an acrylamide, sulfonate, or urethane linkage.

In addition to the pH, the rheological properties of HMASP depend on the molecular weight of the polymer, the length and type of the hydrophobic groups, and the concentration of these groups in the polymeric structure. The effect of the size of the hydrophobic group of a HMASP on the viscosity is shown in **Figure 42**.

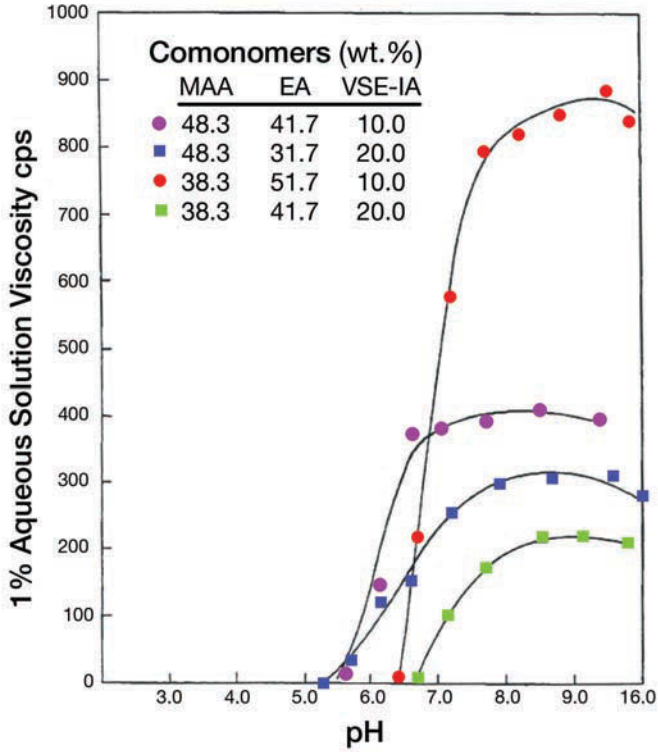

Figure 41. Viscosity of HMASP thickeners as a function of pH[61]

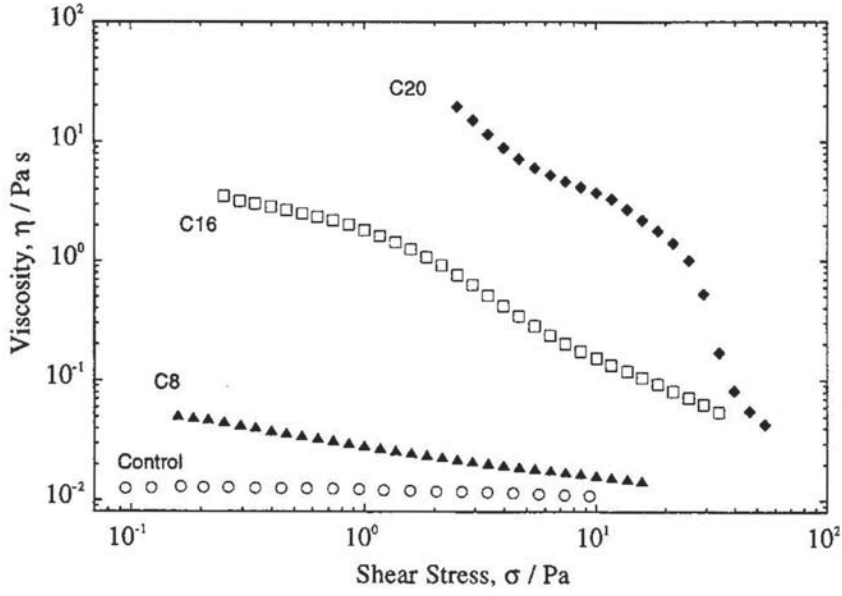

Figure 42. The effect of the size of the hydrophobic group of a HMASP on viscosity as a function of shear stress[56]

Nonionic hydrophobically modified rheological additives include **Hydrophobically Modified Urethane Polymers (HMUP)** and **Hydrophobically Modified Ether Polymers (HMEP).** HMUP and HMEP are used in paints and personal care products. HMUP, also known as **Hydrophobically Modified Ethoxylated Urethane (HEUR),** is prepared, for example, from a backbone of diisocyanate monomers and polyethylene glycol, capped with a hydrophobic isocyanate, an amine or an alcohol. The effects of the type of monomers, molecular weight, size and type of the hydrophobic groups, the formation of micelles and the effect of surfactants and co-solvents on the rheological properties of formulations containing HMUP and HMEP have been widely studied. [38-44,48-49,57-64] These studies demonstrated that every change in the composition of the associative thickener significantly affects the structure of the network it enters into when interacting with the other components of the formulation. **Figure 43** shows the viscosity as a function of the concentration of HMUP rheological additives in water with and without the hydrophobe. **Figure 44** shows the effect of concentration on the viscosity of two different HMUP rheological additives in water.

Figure 45 shows the effect of surfactant (sodium dodecyl sulfate, SDS) concentration on the viscosity of HMUP thickeners having different end groups. It demonstrates that there is a slight increase in viscosity at low concentrations as a result of increased participation of the surfactant in the formation of the micelles, followed by a decrease in viscosity as additional surfactant molecules disrupt the formation of micelles, thus breaking up the three-dimensional structure of the system.

Figure 46 shows the effect of the molecular weight of HMEP rheological additives on the low shear limiting viscosity (interpolated to shear rate = 0) compared to a polymer without the hydrophobes.

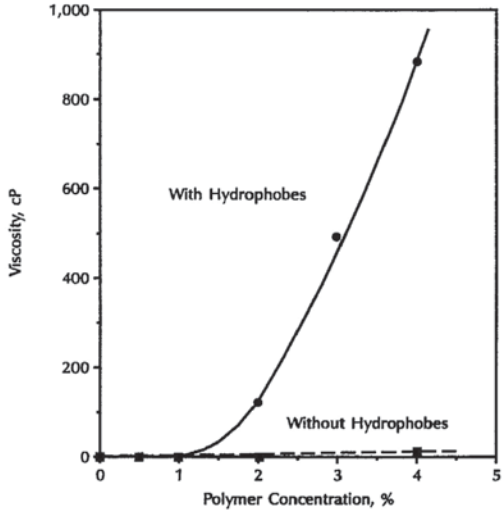

Figure 43. Effect of hydrophobic modification on the viscosity of HMUP in water (reprinted with permission from Reference 62. Copyright (1991) American Chemical Society)

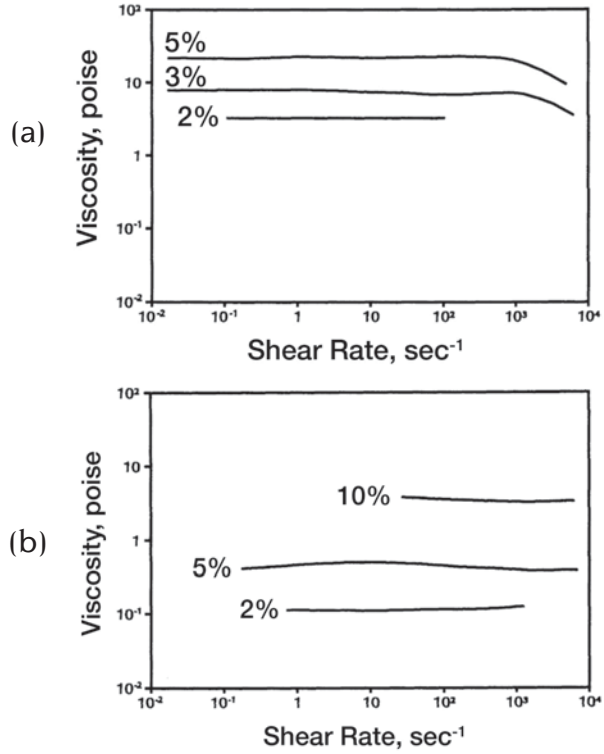

Figure 44. The effect of concentration on the viscosity of two HMUP rheological additives in water (reprinted with permission from Reference 62. Copyright (1991) American Chemical Society)

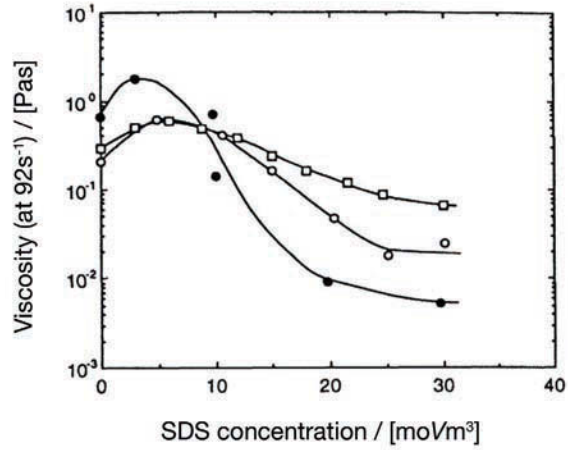

Figure 45. Effect of surfactant concentration on hydrophobically modified urethane polymers (HMUP) (●) 2% Associative Thickener (AT)18-19 HMUP with octadecyl end groups; (o) 2.5% AT15-19 with pentadecyl end groups; (□) 5% AT17:1-19 with 9- heptadecenyl end groups[63]

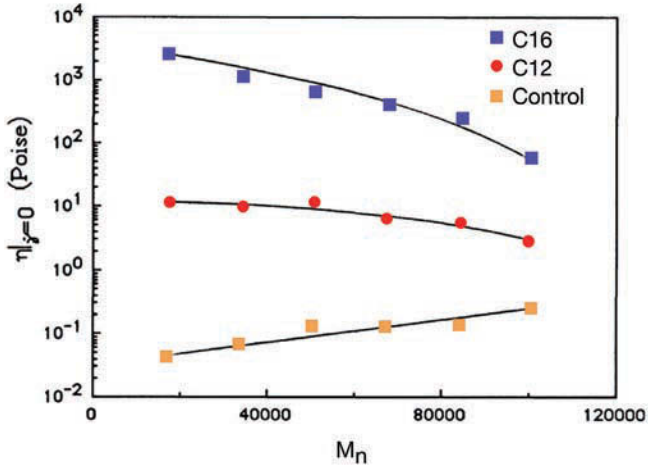

Figure 46. The effect of molecular weight and hydrophobic groups on low shear limiting viscosity of hydrophobically modified ether polymers (HMEP) (reprinted with permission from Reference 64. Copyright (1991) American Chemical Society)

Since associative polymers may be synthesized in practically endless molecular architectures, they may offer the formulation chemist a variety of ways to choose the right thickener (or a combination of thickeners) for the formulation. The formulation chemist should be aware of the sensitivity of associative polymers to other components of the formulation and the effect of pH on the thickening effect of HMASP additives.

Silicate Minerals—Clays

Silicate minerals, which constitute about 90 percent of the Earth's crust, are based on crystals containing silicon and oxygen. A sub-group of silicate minerals is **phyllosilicates** (from Greek φυλλον– phyllon = leaf), in which the crystals are arranged in the form of leaves or parallel layers, as opposed to the continuous three-dimensional tetrahedral structure of other silicate minerals such as quartz. Clay minerals that belong to the phyllosilicate sub-group are **montmorillonite** (or **smectite clays**), **attapulgite** and **kaolin**.[65] **Bentonite** and **hectorite** are examples of commercial smectite clays. Smectite clays or their blends are sometimes referred to as **magnesium aluminum silicates (MAS)**. The minerals are named after the location where they have originally been mined: Montmorillon, France; Fort Benton, Wyoming; Hector, California; Attapulgus, Georgia; and Kao-Ling, China. The layers, sometimes referred to as platelets, are formed due to the presence of aluminum and magnesium ions and other ions in their crystal structure.

Bentonite is used in a variety of applications from cat litter to oil drilling muds. Its general chemical formula is $(0.5Ca, Na)_{0.66}(Al, Mg)_4Si_8O_{20}(OH)_4$. Potassium, iron, and other cations may also be present in bentonite clay minerals.

Hectorite is used in paints and household and personal care products. Its general chemical formula is $Na_{0.66}(Mg,Li)_6Si_8O_{20}(OH)_4$. Bentonite platelets, with dimensions estimated at 800x800x1 nm, are larger than hectorite platelets, with dimensions of about 800x80x1 nm. The presence of the aluminum and magnesium ions imparts a negative charge on the surface of the clay platelets. This charge is balanced by additional positive ions such as sodium or calcium ions. The structure of the mineral can be determined by using X-ray diffraction. The crystal structure of clay minerals is classified according to the arrangement of the layers that are formed as a result of the tetrahedral silicate layers and the octahedral hydroxide layers. Smectite minerals exhibit a 2:1 structure of an octahedral layer sandwiched between two tetrahedral layers. A general structure of smectite clay (montmorillonite) is shown in **Figure 47**.

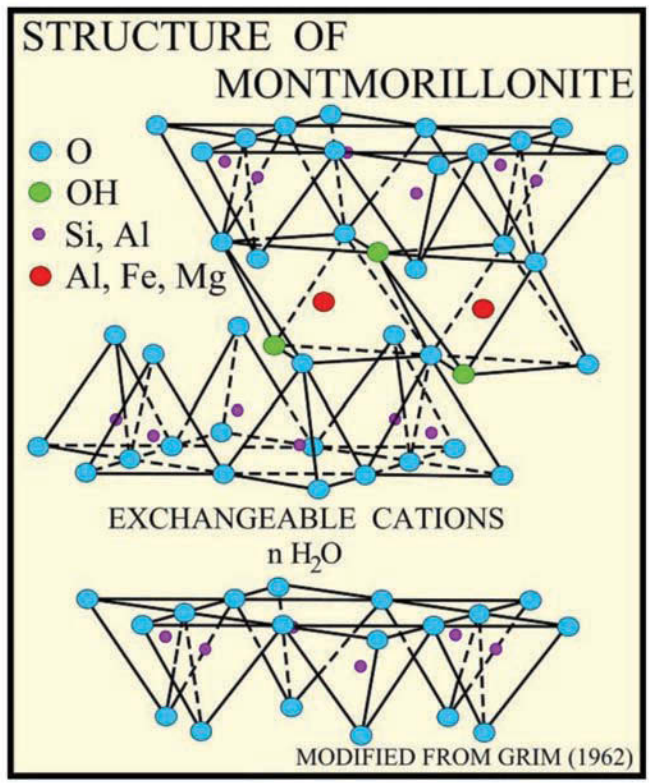

Figure 47. Mineral structure of montmorillonite clay (courtesy of US Geological Survey[66])

Clay minerals swell when they absorb water, as water fills the spaces between the silicate layers. They can be used as rheological additives due to their ability to disperse in water and form a three-dimensional structure of layers in a network that

is sometimes described as a "house of cards" arrangement. The interaction of clay minerals with water and its implications on the rheological properties of systems containing clay thickeners has been widely studied.[67] As shown in **Figure 48**, clay platelets may arrange in an edge-to-edge, edge-to-face or face-to-face structures.[68] The weak three-dimensional platelet structure collapses under shear and recombines when the external force is removed.

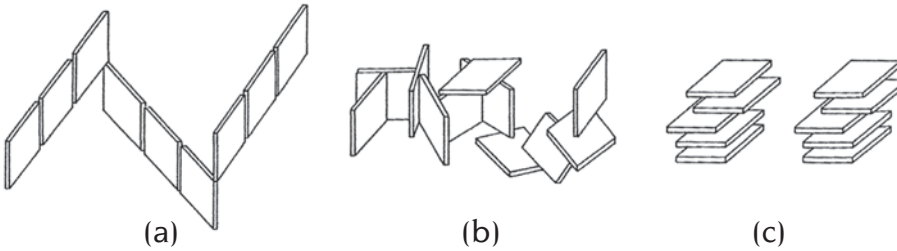

Figure 48. Possible arrangements of clay platelets: (a) edge-to-edge, (b) edge-to-face, (c) face-to-face, from Reference 68, reproduced with kind permission of The Clay Minerals Society, publisher of *Clays and Clay Minerals*

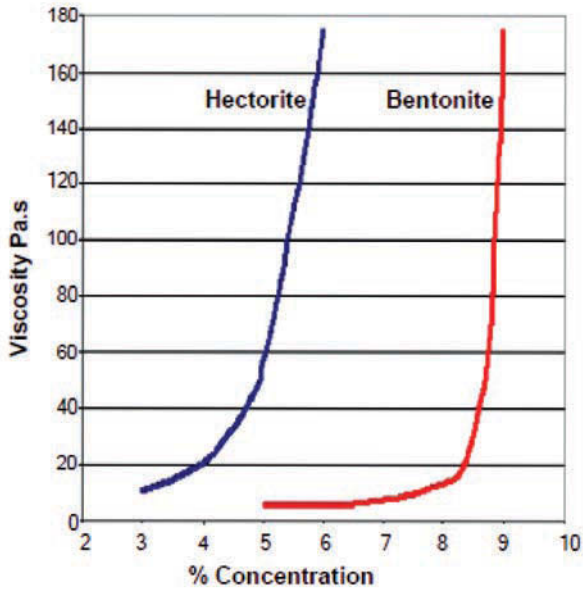

Figure 49. Viscosity as a function of concentration for bentonite and hectorite solutions (© 2008 Elementis Specialties, Inc.; reprinted with permission of Elementis Specialties, Inc.[69a])

Figure 49 shows the viscosity of bentonite and hectorite in water as a function of clay concentration. The increase in the viscosity of hectorite in water occurs at lower concentrations due to the smaller size surface area of the hectorite platelets, which, when dispersed, exposes a much larger surface area compared to the surface area of bentonite platelets.

Attapulgite, also known as **palygorskite,** is a magnesium aluminum phyllosilicate. Attapulgite is used in the manufacturing of coatings, drilling muds and cosmetic products. Its chemical composition is $(Mg, Al)_2Si_4O_{10}(OH)$. Attapulgite has a lower swelling capacity compared to bentonite and hectorite but may swell in fresh and in salt water.

Kaolin, which is also known as **china clay**, is an aluminum phyllosilicate. It is an important ingredient of china and porcelain dishes. It is also used in the manufacturing of paper, coatings, and personal care products. Its chemical composition is $Al_2Si_2O_5(OH)_4$. Kaolin has a much smaller surface charge and a smaller swelling capacity compared to bentonite and hectorite.

Synthetic Silica and Silicates

Fumed silica (silicon oxide) is manufactured by flame pyrolysis of silicon tetrachloride. It forms branched, chain-like particles of submicron-size amorphous silica spheres which may arrange in three-dimensional agglomerates in polar solvents via hydrogen bonding. This is due to the silanol groups located on the surface of the particles.[31] Fumed silica is used in the manufacturing of coatings, inks, adhesives and sealants, and personal care products. The three-dimensional structure formed by fumed silica spheres depends on the polarity of the system, the degree of dispersion of the silica, the presence of hydrogen bonding components in the formulation, and the pH of the system. The effects of various parameters on the rheological properties of systems containing fumed silica have been the subject of numerous studies.[70-72]

Synthetic smectites, which are manufactured from inorganic salts, are used in the manufacturing of paints, inks and personal care products. Synthetic hectorite, which has a crystal structure similar to that of natural hectorite, forms clear/transparent dispersions in water due to its small particle size. Synthetic smectites are more homogeneous and have higher purity compared to the natural smectites. Aging effects, that is, changes in physical properties due to deviations in internal structure, have been observed in dispersions containing synthetic hectorite.[73,74]

Blends

Enhanced rheological properties may be achieved when different types of rheological additives are mixed together. Synergistic effects have been reported when natural gums are used together with cellulose-based additives, hydrophobically modified and non-modified polymers, and various combinations of clays with polymers. Examples of clay/polymer blends are clay/CMC, clay/xanthan gum, clay/HMASP, and clay/carbomer blends. The synergistic effect has been widely studied and patented, covering various combinations of rheological additives, such as clay/HMASP.[75] With so many types of rheological additives for water-based systems

available to the formulation chemist and with so many grades of each type of thickener, the formulation chemist has a variety of properties to choose from to impart the optimal rheological properties to the formulation.

Rheological Additives for Solvent Based Systems

Fumed Silica

Hydrophilic fumed silica may be treated with hydrophobic materials, for example, by treating its surface with organosilanes, such as dimethyldichlorosilane, thus changing its nature from hydrophilic to hydrophobic. Surface treated fumed silica is used in coatings, adhesives, sealants, plastics, and cosmetic products. Various grades of fully or partially treated fumed silica are available with different degree of hydrophobicity. The formulation chemist may therefore choose the thickener that would be most compatible with the topical formulation that is being developed. The effects of various parameters on the rheological properties of systems containing surface treated fumed silica have been the subject of numerous studies.[70,76]

Organoclays

Silicate minerals may be transformed to become hydrophobic by reacting the hydrophilic clay mineral with a cationic hydrophobe, such as quaternary ammonium cations $[NR_1R_2R_3R_4]^+$. The quaternary ammonium cation exchanges the sodium or calcium cations on the surface of the clay platelets. The addition of an organic layer on the surface of the platelets results in the expansion of the spacing between layers. Typical interlayer spacing may increase, for example, from 10 Angstroms to 34 Angstroms, depending on the amount and the type of the quaternary ions that are exchanged. The modified clays are called organoclays. A schematic presentation of a reaction between a quaternary ammonium chloride and a clay mineral is shown in **Figure 50**.

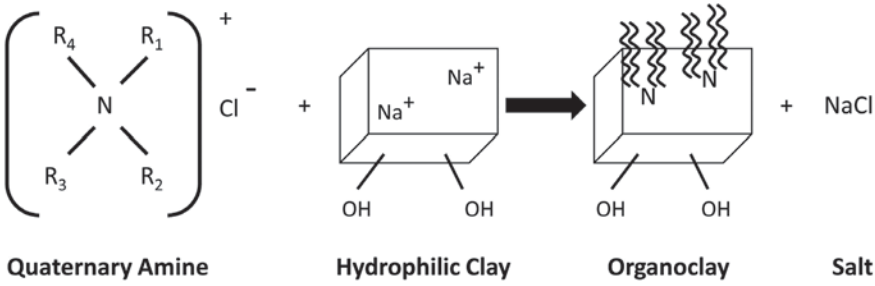

Figure 50. Schematic presentation of a reaction between a quaternary ammonium chloride and a silicate mineral

Typical quaternary ammonium cations are based on fatty acid derivatives, such as beef tallow, or plant oils such as palm oil. Tallow is a fat containing fatty acids such as palmitic, oleic, stearic, linoleic, and other fatty acids. An example of a quaternary ammonium chloride based on tallow fat is dimethyl, *bis*(hydrogenated tallow) ammonium chloride, sometimes abbreviated as 2M2HT ammonium quat. The type

and the size of the hydrophobic part of the organoclay determine its compatibility with organic solvents. For example, organoclays made by reaction with dimethyl, benzyl hydrogenated tallow ammonium chloride are more compatible with polar organic solvents. Since the organoclay layers are agglomerated, it is very important to separate the platelets by mechanical means such as the use of high speed dispersion mixers to expose their platelet surface to the system. If the agglomerates are not separated during the preparation of the product, the viscosity may continue to increase with time as additional organoclay surface becomes exposed to the solvent.

The organoclay swells in organic solvents and thickens the formulation by forming a three-dimensional "house of cards" of the clay platelets. Since the platelets are connected to each other via hydrogen bonding, organoclays require the addition of a polar activator, such as propylene carbonate, alcohol, or water to facilitate the connection. A typical polar activator is propylene carbonate/water (95%/5% w/w). The required amount of a polar activator may be up to two-thirds of the clay itself. It is important to disperse the organoclay in the formulation prior to the addition of the polar activator. Addition of polar activator in excess may disrupt the network structure, resulting in lower viscosity as shown in **Figure 51**.

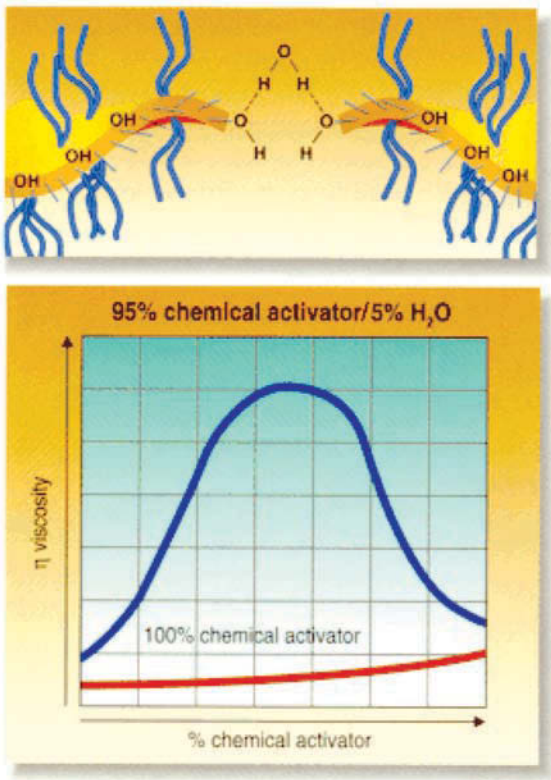

Figure 51. Effect of polar activation on the viscosity of organoclays (courtesy Elementis Specialties; © 2008 Elementis Specialties, Inc.; reprinted with permission of Elementis Specialties, Inc.[69b])

The proper process of incorporating an organoclay into a formulation therefore requires the following steps: Wetting and de-agglomeration under shear, addition

of a polar activator, additional shear to disperse the activated platelets, and allowing the system to form the three-dimensional network structure. Organoclay rheological additives which are mechanically pre-dispersed in a variety of solvents (pre-gels) are available commercially.

Organic Rheological Additives

Organic rheological additives for solvent based systems include those based on castor oil and castor oil derivatives such as hydrogenated castor oil (castor wax), polyesters, polyamides, polyesteramides, modified polyethylene, oxidized polyethylene, and copolymers of polyethylene such as ethylene/acrylic acid copolymers. The compatibility of organic rheological additives with various organic solvents depends on the nature of the thickener and the incorporation conditions. The choice of the correct heating temperature to dissolve or disperse the thickener in the formulation as well as cooling to the right temperature is a key to allow the formation of a three-dimensional structure. If the system is being cooled too fast to low temperatures, the organic rheological additive may separate and form crystallites (also referred to as "seeds") that will not contribute to enhanced rheological properties of the formulation.

Rheological additives based on **castor oil derivatives** (trihydroxystearin) are used in the coatings, paper, grease, petrochemical, and cosmetics industries. A typical incorporation procedure includes dispersing the additive in the oil phase of the formulation and heating to 55-60°C, applying high shear mixing at 55-60°C and cooling to below 35°C with low to medium shear mixing.[31] Blends with other organic rheological additives and organoclays are available commercially. In addition, derivatives of castor oil containing polyethylene glycol such as PEG-40 hydrogenated castor oil are also used as emulsifiers in personal care formulations.

Rheological additives based on polyethylene and its copolymers are mostly used as anti-settling additives to enhance the low shear rate viscosity of the formulation and to prevent heavy particles, such as pigments, from separating or settling due to gravity.

Miscellaneous Rheological Additives

The following are additional additives that the formulation chemist may consider:

Rheological additives based on alkylene oxide polymers and their esters, such as **polyethylene glycol**. The molecular weight of these additives ranges from about 200 to 2 million. Mono- and diesters of polyethylene glycol, such as **PEG distearate,** are available commercially, with molecular weight ranging from very low to very high, depending on the number of ethylene oxide units. In many cases, they are used as both the emulsifier and the thickener.

Aluminum/Magnesium Hydroxide Stearate (AMHS), are complexes between stearic acid and aluminum/magnesium hydroxide.[77] AMHS thickeners are used in various cosmetics and pharmaceutical products. They form alternating layers of anionic stearate and cationic aluminum/magnesium hydroxide with the general chemical formula $Al_5Mg_{10}(OH)_{31}(C_{17}H_{35}COO)_4$. These additives swell in organic solvents such as mineral oil, cyclomethicone pentamer, and fatty esters. The

viscosity of the gels they form is less sensitive to changes in temperature compared to formulations containing other rheological additives.

Hyaluronic acid (HA, also known as hyaluronan) is a biomaterial found in the human body, for example in skin, the umbilical cord and in synovial fluid. It is used in medicinal applications as a lubricant for eye surgery and treatment of osteoarthritis of the knee. Its chemical structure is based on a non-sulfonated polysaccharide with alternating β(1,3) glucoronidic acid and β(1,4) glucosaminidic bonds. The effects of various parameters on the rheological properties of systems containing hyaluronic acid have been the subject of numerous studies.[78-80]

The rheological additives mentioned so far represent most of the types of rheological additives that are available commercially. The list is intended to serve as a general guide. It is practically impossible to cover all the commercially available types, grades and blends of thickeners in the scope of a book chapter.

Formulation of Topical Products

Studies of skin cream formulations that seem to be similar at rest (when packaged) indicate that they may behave very differently when applied to skin. Testing the rheological properties of skin cream formulations is important for accurate and detailed characterization as well as for confirmation that the differences in their application properties may be attributed to their rheological properties. With the understanding of the effect of the formulation design on the rheological properties of the products, scientists and formulation chemists are able to reformulate the products to improve their application properties by tailoring the low and high shear rate viscosity, their recovery after shearing, and their storage and loss moduli.

A typical skin cream formulation consists mostly of

- Water (60–85%)
- Oil Phase (15–40%)
- Emulsifiers
- Preservatives
- Minerals
- Colorants
- Vitamins/Botanicals/Actives
- Rheological Additives
- Fragrance

Despite their small portion in the formulation, rheological additives exhibit a significant effect on the properties of the formulation, its manufacturing process and its application.

In order to characterize the rheological properties of skin care formulations that appear to be similar in their commercial container (as observed in a study conducted in a laboratory setup; data not published), four commercial products, labeled A, B, C and D were tested. A Thermo Scientific Haake Controlled Stress RS1 Rheometer equipped with a ThermoHaake C25 circulating bath with a

ThermoHaake F6 controller (all Thermo Fisher Scientific, Waltham, MA) was used in rotational and oscillatory modes. A cone and plate configuration was used in all tests. All measurements were performed at 25°C. A fresh sample was used for each test. **Figure 52** shows the flow profiles (viscosity as a function of shear rate) of all four creams. Note that the graph is a log-log presentation. All four products exhibit shear thinning behavior (high viscosity at low shear rates and low viscosity at high shear rates). Cream C exhibits the highest viscosity at low shear rates, while cream D exhibits the lowest viscosity at low shear rates. Cream D exhibits the lowest viscosity at high shear rates, while creams A and C exhibit the highest viscosity at high shear rates.

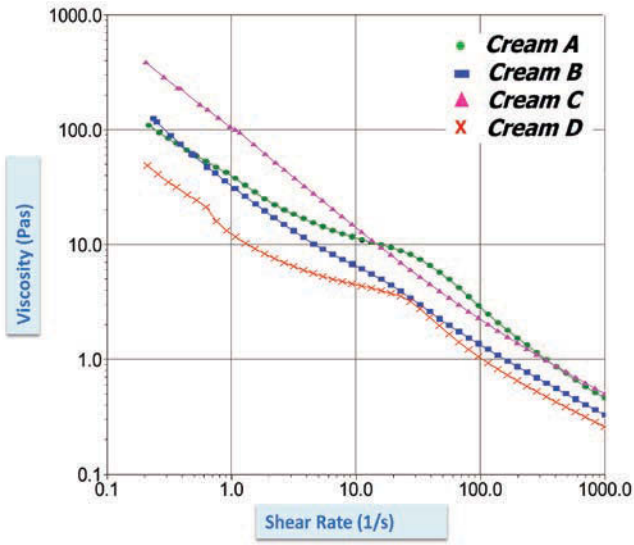

Figure 52. Flow profiles of skin creams: Viscosity as a function of shear rate

By plotting the viscosity as a function of shear stress instead of shear rate, the transformation of the product from a three-dimensional network structure to a broken-down structure may be better visualized. As shown in **Figure 53**, cream A experiences two transitions: one at about 40 Pa and a second transition at about 300 Pa. Cream B experiences transitions at about 30 Pa and 100 Pa. Cream D experiences a similar transition at 100 Pa. It is not clear whether the transition shown at low stress is a real transition or an instrument issue. However, cream C requires the highest stress in this series and its three-dimensional structure collapses gradually between about 100 Pa and 400 Pa. These transitions indicate that the changes in structure due to the external force are mainly due to two major events (one at a low shear stress and the other at a medium shear stress). Transitions that may indicate a change in the network structure of the system require further investigation.

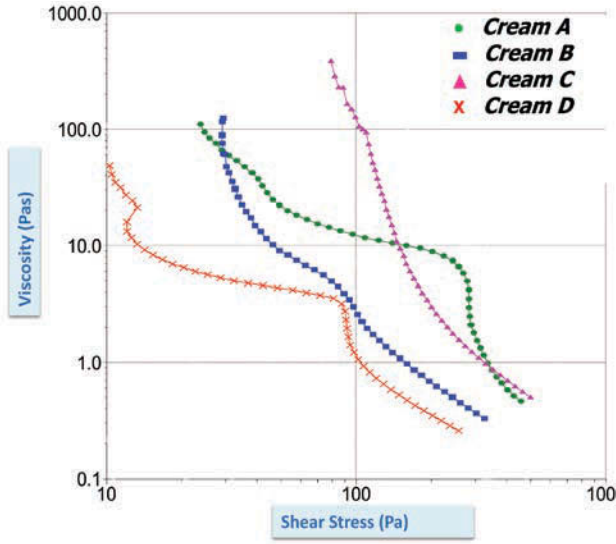

Figure 53. Flow profiles of skin creams: Viscosity as a function of shear stress

To follow the recovery of the formulation after shearing, we tested the thixotropy loop (**Figure 54**). This test revealed that all four creams recover to higher viscosities at low shear rate (when the shear rate is reduced from high shear rate to low shear rate) after the initial shear thinning (when the shear rate increases from low shear rate to high shear rate). It seems that cream A exhibits the largest area between the "up" and "down" curves (which indicates the energy loss in the process) while cream C exhibits almost a non-thixotropic behavior.

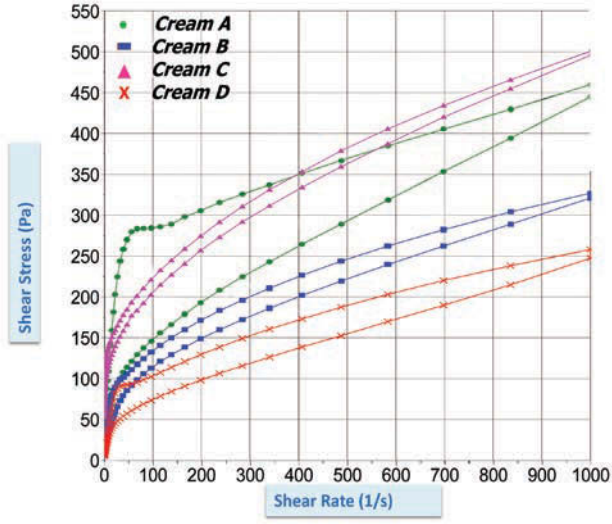

Figure 54. Skin creams: Thixotropic loop (shear stress as a function of shear rate: "up" and "down" curves)

The yield value, the minimum stress that is required to induce flow, may be calculated from the slope of the graph showing shear stress as a function of shear rate and interpolation to a shear rate of zero. Note that the plot in Figure 54 is a linear-linear presentation. The graph shows that cream A seems to exhibit the highest yield value (and therefore the highest initial resistance to flow). By continuing a straight line to shear rate = 0 we may conclude that the yield value for cream A is about 275 Pa. Similarly, cream C would have a yield value of about 150 Pa and creams B and D about 75 Pa. When scanning through the various mathematical models available and choosing the most appropriate one, we find that the best model fit for the data obtained is the Herschel-Bulkley model. As shown in **Figure 55**, the calculation was done over the shear rate range from about 100 1/s to 800 1/s. According to this analysis, the yield value for cream A would be 242.9 Pa, for cream C 92.74 Pa, for cream D 43.72 Pa, and for cream B 36.65 Pa. **Figure 55** shows that it is important to define the shear rate that is chosen as the basis for the calculation since the calculated yield value would be smaller as the shear rate range is closer to shear rate = zero.

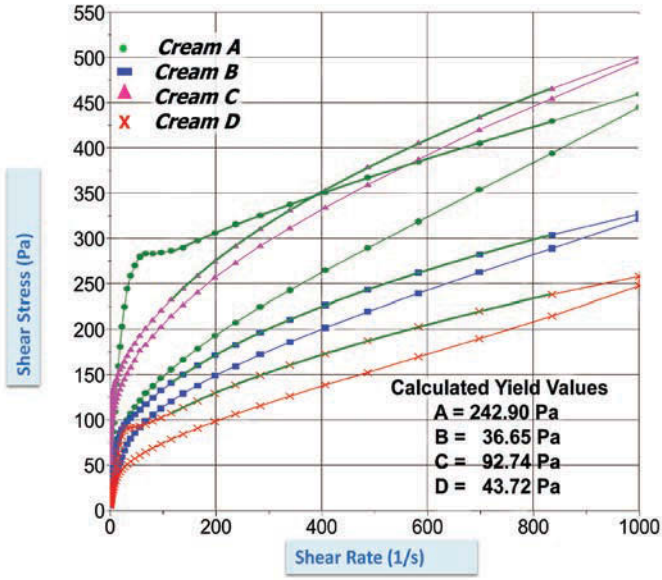

Figure 55. Skin creams: Calculating yield values

Another way to analyze the behavior of the formulation is to apply an external force and then remove it and follow the changes in strain as previously described in the creep test. Here the products were pulled at a constant stress and the change in strain was monitored as a function of time. As shown in **Figure 56**, cream B (which had the lowest yield value) elongates the most by applying an external force. Creams A and C exhibit the smallest strain and thus the highest resistance to an external force. Cream D was somewhere in the middle. When the external force was removed, the formulation recoiled to its original structure. The initial recoil is

therefore a measure of the elasticity of the formulation. As shown in Figure 56 cream C recoils the most (95.12% recovery), which implies that it is very elastic. Cream B recoils the least with only 13.92% recovery, meaning that is mostly non-elastic. Creams A and D exhibited recovery values of 62.70% and 45.47% respectively.

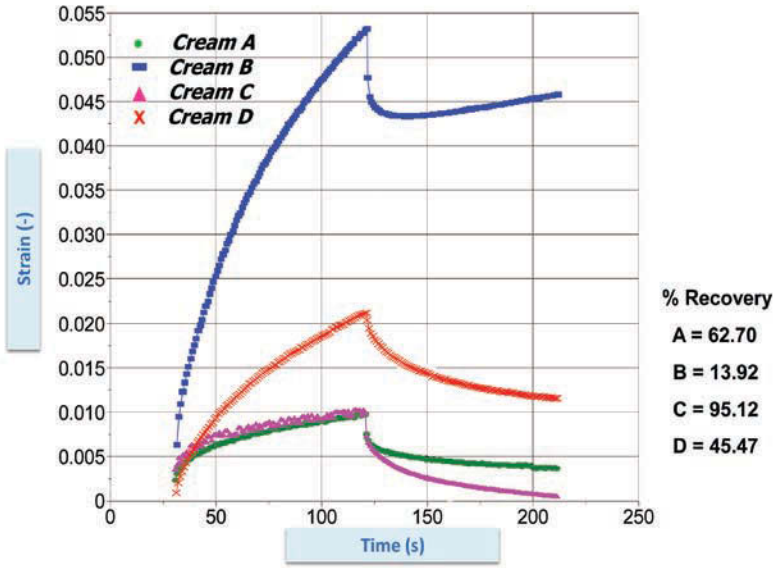

Figure 56. Skin creams: Demonstration of Creep/Recovery

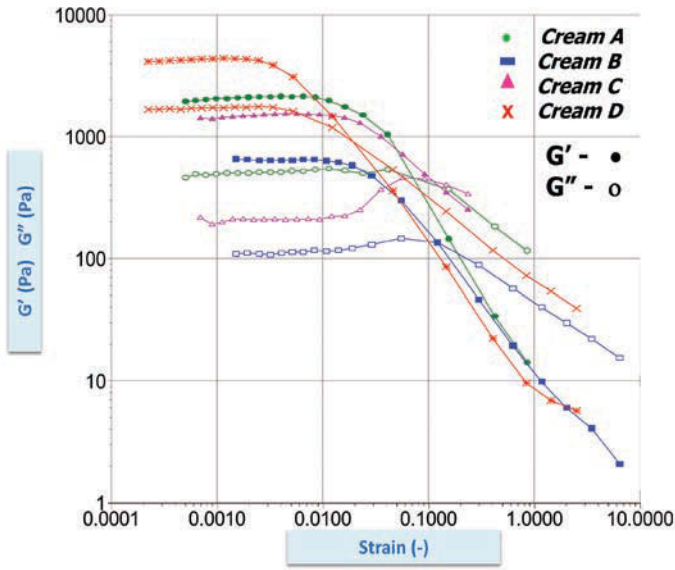

Figure 57. Skin creams: Strain sweep

The ratio between the elastic nature and the viscous nature of the formulation at very low strains may be obtained by a strain sweep using the oscillatory mode. In

this test, the storage and the loss modulus were measured as a function of increased strain at a frequency of 1 Hz. As shown in **Figure 57,** all four creams exhibit a linear viscoelastic region at low strains and then lose their elasticity with increasing strain. The elasticity portion (as shown by the storage modulus, G') of all four products is higher than their viscous portion (as shown by the loss modulus, G"). However, cream D, which shows the highest storage modulus in this test and has shown a medium yield value in the previous test, breaks down at the lowest strain (about 0.003). The other three creams start to break down at higher strains (about 0.03).

Table 4 summarizes the various properties of the four creams as demonstrated in the characterization tests:

Table 4. Rheological Properties of Skin Creams

Test/Product	A	B	C	D
Flow I: Viscosity	**as a Function of**	**Shear Rate**		
Low shear Rate	Medium	Medium	High	Low
High Shear Rate	High	Medium	High	Low
Continuous?	No	Yes	Yes	No
Thixotropy				
Energy Loss	High	High	Very Low	Medium
Flow II: Viscosity	**as a Function of**	**Shear Stress**		
Required Stress	Low/High	Low	High	Low/Medium
Transitions	2(?)	1(?)	No	2(?)
Yield Value	High	Low	Medium	Low
Strain Sweep				
G' > G"	Yes	Yes	Yes	Yes
G'	Medium→Low	Low→Low	Medium→Medium	High→low
G"	Medium	Low	Low	High
Creep				
Extension	Low	High	Low	High
Recovery	High	Low	Very High	Medium

Note: ? – The nature of these transitions requires further investigation

The behavior of the three-dimensional network that the rheological additive builds in the formulation determines the customer's sensory perception when the product is applied and as the system recovers its structure. The relationship between the rheological properties and the texture of the formulation and sensory parameters has been widely studied in the food industry (e.g. cheese, yogurt, soup, and porridge). Texture and viscosity have been related to many sensory parameters in foods.[81] However, very little has been published on the relationship between the rheological properties, such as dynamic properties and yield values, and the sensory parameters of topically applied products, such as skin feel.[82-85] An attempt

to find a correlation between the dynamic rheological properties and skin feel[86] indicates that firmness, spreadability, cohesiveness, and integrity of shape may be correlated to viscoelastic parameters (the crossover of the storage modulus and the loss modulus) and to creep analysis. Additional discussion about the relationship between the rheological properties of the formulation and sensory perception is covered in another chapter in this book.

Designing a formulation with "ideal" rheological properties is easier when the formulation chemist has the ability to characterize the system and to tailor the ingredients to exhibit the desired properties. Using a combination of rheological additives enables us to bring the actual rheological behavior of the formulation closer to the "ideal" target profile. **Figure 58** shows the use of such combination of two different rheology modifiers to achieve a formulation with the desired flow profile.

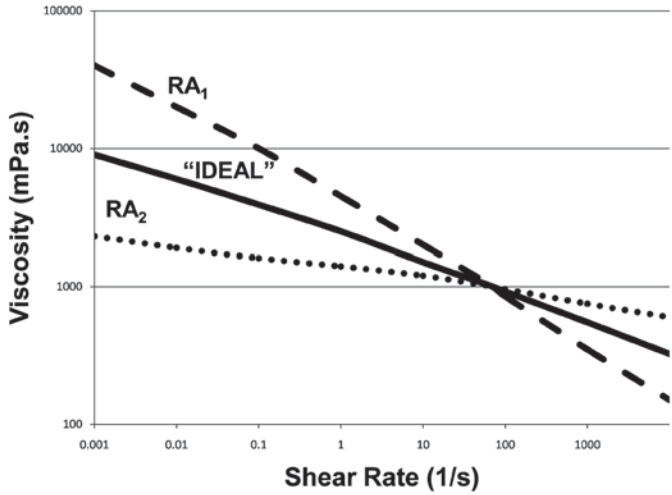

Figure 58. Combination of two rheological additives to achieve an "ideal" target flow profile

Summary

This chapter reviews the basic principles of rheology and the characterization of the rheological properties of topically applied formulations in light of the formulation chemist's need to balance the formulation's ingredients so that the product is stable, easy to apply and retains its properties during manufacturing, on the shelf, during application and after application. The chapter defines basic concepts, such as shear stress, shear rate, viscosity, yield value, viscoelasticity, storage modulus and loss modulus. Measurements methodologies are described and the rheological changes that the formulations undergo when subjected to external forces are described. The chapter also covers the basic characterization tests that are available to the formulation chemist: Flow profiles, creep/recovery, yield value measurements, viscosity recovery, strain sweep and frequency sweep. This discussion was followed by a description of

the various instruments employed: from tubes and glass viscometers to controlled rate and controlled stress rheometers, including rotational and oscillatory modes, together with various fixtures (geometries) that may be included in the rheometer system and how the various rheological parameters are calculated for each system. The chapter continues with a discussion of the various types of rheological additives that may modify the rheological behavior of the formulation, including rheological additives for water-based systems, such as natural gums, cellulose-based, alkali swellable polymers, associative thickeners, clay and fumed silica and for solvent-based systems, such as organoclay rheological additives, synthetic thickeners and treated fumed silica. The synergistic effect of using blends of various rheological additives was also discussed. We described the thickening mechanisms that the various rheological additives participate in and how they build a weak three-dimensional network structure. The chapter also describes the effect of temperature and the addition of salts and cosolvents on the formation of a network structure. It concludes with a demonstration of various rheological measurements used to characterize topical formulations and the various rheological parameters that they provide. The discussion and the sample of rheological measurements may serve as a general guide as to how to design and develop a target rheological profile for topical formulations.

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CHAPTER 12

Viscosity Measurement for Topically Applied Formulations

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Presperse

Key words:

Absolute Viscosity, Dynamic Viscosity, Flow Curve, Kinematic Viscosity, Newtonian Fluid, Non-Newtonian Fluid, Pascal (Pa), Poise (P), Rheology, Rheometer, Shear Rate, Shear Strain, Shear Stress, Shear Thinning, Spindle, Stoke (St), Thixotropy, Viscometer, Viscosity, Yield Value

Introduction

In the development of a semi-solid topically applied formulation, formulation chemists typically prepare a number of prototypes for evaluation. Due to formulation complexity, often the process to achieve the desirable final product is one of trial and error. Performance trade-offs and cost considerations during the formulation process result in the inclusion and elimination of ingredients, changing levels of components, and implementing different preparation methods. After a prototype is prepared, the product must undergo a comprehensive evaluation before it is approved for launch to the consumer market. Key questions that may be asked in the laboratory during the development of formulations are related to sensory attributes such as "do you like it?" and "how does it feel?" Answering these questions is challenging and may involve a variety of measurable and non-measurable parameters. Examples include thickness, texture, sensory impressions, cushion, slipperiness, color, and odor. Some of these properties rely on qualitative appraisals, which can differ depending on the individual assessing them. Other properties can be measured quantitatively, and should not vary with the person performing the measurement. One of the important parameters that can be quantified is the formulation *viscosity*, which is the topic of this chapter.

The *Merriam-Webster* online dictionary defines viscosity as *the property of resistance to flow in a fluid or semifluid*.[1] Viscosity is part of the field of *rheology*, defined by Merriam-Webster as "a science dealing with the deformation and flow of matter."[2]

These definitions appear similar, and often these words are used interchangeably. In practice, rheology covers a broader range of topics such as the behavior of solid materials, time dependency, and elasticity. Viscosity is generally used to refer to a value measured under a particular set of conditions (usually temperature and shear rate), and rheology is used to refer to a material behavior over the spectrum of test conditions.

A good understanding of rheology is important in the development process of topically applied formulations and may be crucial for consumer acceptance of the commercial product. For example, if a shampoo viscosity is too low, it can drip easily out of the bottle and would not be appealing to consumers; if a sunscreen lotion viscosity is too high, the user cannot dispense or apply it easily enough. If a body wash is intended to have the visual effect of evenly suspended beads, consumer reviews would be negative if the beads are no longer suspended while the package is still on the shelf. These are only a few practical examples of the many performance parameters that can be related to basic rheological characterization. While these properties may not relate directly to a product "feel," it is an important part of the final product performance. Understanding of viscosity measurements is important for formulation chemists, even those not directly involved in product characterization.

The goal of this chapter is to define key commonly used terms in viscosity measurements, and describe the instrumentation most frequently used in a topical formulation setting. This chapter is not intended to discuss rheological terms and measurement techniques in-depth. The chapter on rheology (Chapter 11) in this book delves into detail on this subject. In addition, there are several resources written for the cosmetic industry that can provide a deeper understanding of the subject.[3-5]

Definitions and Units of Viscosity

The term viscosity is typically envisioned as whether a fluid is "thick" or "thin." There are two types of viscosity terms used for topical raw materials and finished products—absolute (dynamic) viscosity and kinematic viscosity. Finished goods such as creams, lotions, and gels use absolute (dynamic) viscosity measurements in their specification. The viscosity of silicone oils and hydrocarbons is typically specified as kinematic viscosity.

a) Absolute or dynamic viscosity (typically just "viscosity")

The units commonly used for reporting absolute viscosity are either centipoise (cP) or milliPascal-seconds (mPa-s). The relationship between these two types of units used is:

1 cP = 1 mPa-s
The viscosity of water is 1cP, or 1 mPa-s.
The definition of "Poise" is:
1 P = 1 g/(cm-s)

These units can be understood by looking at the definition of viscosity. The

absolute or dynamic viscosity is defined as the resistance of a fluid to flow, under an applied stress. The result of the applied force is motion of the fluid. **Figure 1** depicts a fluid between two plates. The bottom plate is stationary, and the upper plate can move. The plates are a distance of *h* apart, and have area *A*.

Figure 1. Schematic illustration of a model of fluid between two plates

The viscosity is the ratio of the applied stress, and the resulting shear rate. The units used to report viscosity data are derived from the units of applied stress and shear rate.

Applied stress

Applying a force to the upper plate results in motion of that plate. This causes the fluid between the two plates to flow. Since the applied force required for moving the upper plate depends on the area of the plates, the applied *stress* is the parameter to consider. The SI (international system) units of stress are:

Stress = Force /Area, units of N (Newton) / m^2 (square meter)

The unit N/m^2 is defined as a Pascal (Pa).

As a review, the unit of force (Newton) is defined as:

Force = mass * acceleration, N = kg – m /s^2 (kilogram-meter per second squared)

Shear rate

The shear rate is calculated from the difference in velocity (speed) of the moving plate and the stationary plate. In terms of SI units:

Shear rate = (difference in velocity between the two plates) / distance between plates

From this definition, the units of shear rate are velocity/distance:

(Meters/second) / meters, which can be simplified as 1/s or s^{-1} (reciprocal second).

Viscosity units – SI system (International System of Units, also meter-kilogram-second)

Derived from the definitions above, the SI unit (International System of units) for viscosity is:

Shear stress/Shear rate, which is Pa/s^{-1}, which can be written as **Pa-s**

Viscosity is not typically reported in Pa-s, as the values may be low and awkward to use; for example, the viscosity of water in the SI units is approximately 0.001 Pa-s.

mPa-s (milli Pascal seconds)

In the metric system, the "milli" prefix refers to "one thousandth." As the viscosity value for water is approximately 0.001 (one thousandth) Pa-s, units of mPa-s are used. In these units, the viscosity of water is approximately 1 mPa-s.

Viscosity units – CGS (centimeter-gram-second) system

The CGS system is also a metric system, in which grams and centimeters are used rather than kilograms and meters. In the CGS system, the units of viscosity are called Poise (P), which is defined as:

1 P = 1 g/(cm-s)

The relationship between Poise (P) and Pascal-seconds (Pa-s) can be derived by converting units, and is:

1 P = 0.1 Pa-s

In this unit system, the viscosity of water is 0.01 P. In the metric system, the "centi" prefix refers to "one hundredth." Using this prefix, the viscosity of water is 1 cP (centipoises). From the description above: 1 cP = 1 mPa-s

b) Kinematic viscosity

The kinematic viscosity is the ratio of absolute viscosity (described above) to the density of the fluid. The kinematic viscosity is often used to characterize silicones or hydrocarbons. The unit used for kinematic viscosity Stokes (St):

Stoke = Poise/density = (g/(cm-s)) /(g/cm^3) = g/cm^2

Here again, as the value of kinematic viscosity for water is low, typically centistokes (cSt) are used. The kinematic viscosity of water is 1 cSt.

The numerical value of the dynamic viscosity and kinematic viscosity of water are equal (1 cP and 1 cSt), since the density of water is 1 g/cm^3. For other fluids, the numerical value of dynamic and kinematic viscosity could be different. For example, the viscosity of dimethicone oils is reported in units of cSt. The density of dimethicone oils is lower than 1, so the viscosity value would not be the same if reported in cSt or cps. For this reason, it is important when reviewing a technical data sheet to pay attention to the type of measurement reported.

Table 1 shows specification properties for a hydrocarbon used in formulations as a film former and wear extender (INCI: Polyisobutene; trade name: Permethyl 106A). The viscosity is given in units of cSt, showing that this is a kinematic viscosity value, and was measured at an elevated temperature (100°C).

Table 1. Specification properties for Polyisobutene (trade name: Permethyl 106A)

Property	Specification	Evaluation Method
Appearance	Clear, viscous liquid	Visual
Color, APHA	70 max.	ASTM-D 1209
Specific Gravity, @ 60°F	0.86–0.96	ASTM-D 4052
Viscosity @ 100°C:	3000–3400 cSt	ASTM-D 445
Water	50 ppm max.	ASTM-D 1744

Importance of Shear Rate

The previous section provided a mathematical description of shear rate. This

mathematical description can be translated into actual use conditions for a topically applied product. The applied shear rate may not be similar during all stages of a product's lifetime. For example, if a product is poured from a bottle (applying force of gravity only), the shear rate is low. When a lotion is rubbed onto the skin, a higher shear rate is experienced. An approximation of shear rates for different processes is given below[6-8].

Suspending particles: 0.001–0.1 sec^{-1} (10^{-3} – 10^{-1} sec^{-1})
Pouring from a bottle: 10–100 sec^{-1} (10^{1} – 10^{2} sec^{-1})
Rubbing on skin: 100–10,000 sec^{-1} (10^{2} – 10^{4} sec^{-1})
Applying lipstick: 1,000–10,000 sec^{-1} (10^{3} – 10^{4} sec^{-1})
Applying nail polish: 1,000–10,000 sec^{-1} (10^{3} – 10^{4} sec^{-1})
Spraying aerosols: 10,000–100,000 sec^{-1} (10^{4} – 10^{5} sec^{-1})

It is important to recognize that a product can undergo different shear rates during its lifetime: manufacturing, storage and use. These shear rates should be predicted and considered. For many materials, the viscosity can change as the shear rate changes. A common, industrial related example of different shear rates during a product's normal usage is the use of paint for painting a wall. When using a brush or roller to apply the paint, it should not be too "thick," otherwise it will be difficult (and tiring) to apply. But, after the paint is applied, it should "thicken," so it will not drip down the wall. Paints are formulated to have a relatively high viscosity at low shear rates, and a lower viscosity at high shear rates. The same is true of many topically applied products.

Definitions: Dependence of Viscosity on Shear Rate

As mentioned in the section above, the viscosity of a material can change as the shear rate varies. There are several classifications, for the different trends observed:

- **Newtonian:** Viscosity *does not change* with shear rate, for example, water
- **Shear thinning (pseudoplastic):** Viscosity *decreases* as shear rate increases, for example paint, shampoo, lotion
- **Dilatant (shear thickening):** Viscosity *increases* as shear rate increases for example corn starch in water ("oobleck," see description to follow)

These viscosity classifications are shown schematically in **Figure 2**. The variable on the X axis is the shear rate applied to the fluid, and the variable on the Y axis is the fluid viscosity.

The curves depicted are idealized, with the relationships being shown as straight lines. Real data would typically exhibit curvature, but the same trends (viscosity increasing or decreasing with shear rate) are seen. When viscosity measurements are presented, the scaling on the axes can be either linear or logarithmic. The exact shape of the curve will change depending on the scaling, but the trend will remain the same.

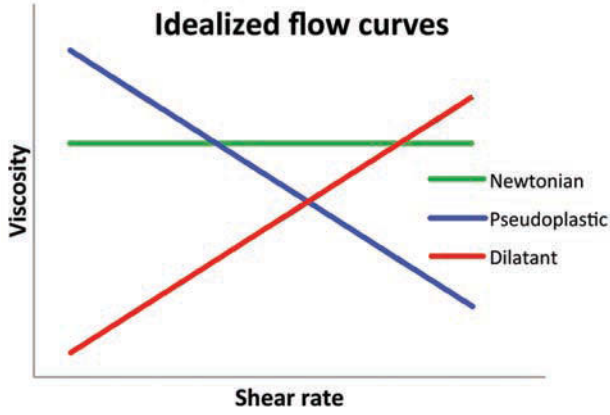

Figure 2. Dependence of viscosity on shear rate, for different fluid types

A shear thinning material could have a Newtonian plateau at low shear rates, as shown in **Figure 3**.

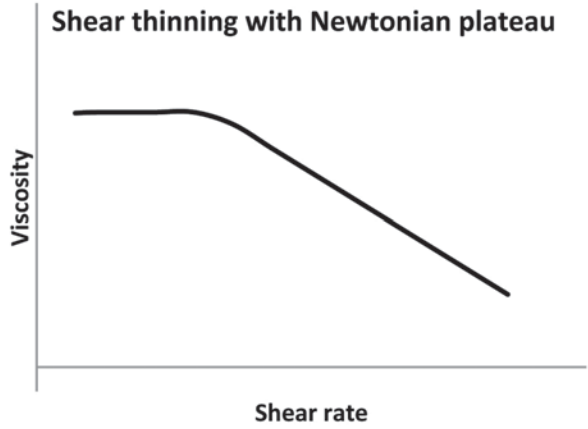

Figure 3. Flow profile for a shear thinning (non-Newtonian) fluid with a Newtonian plateau

The rheological behavior of raw materials (e.g. silicone oils, hydrocarbons) used in topical formulations can be Newtonian, while the behavior of finished formulations is often shear thinning. This shear thinning behavior explains why single point (measured at a single shear rate) viscosity measurements can be misleading.

Figure 4 demonstrates how a single point measurement can provide three different conclusions when assessing relative viscosities of fluids A and B. Both A and B are shear thinning fluids. In region I, fluid A has a higher viscosity. In region III, fluid B has a higher viscosity. In region II, the two fluids are equal in viscosity. The answer to "which fluid is more viscous" cannot be answered without specifying

the shear rate of interest. Therefore, for a comprehensive understanding of fluid behavior, the viscosity should be measured at several shear rates, to generate a *flow curve* or *viscosity profile*.

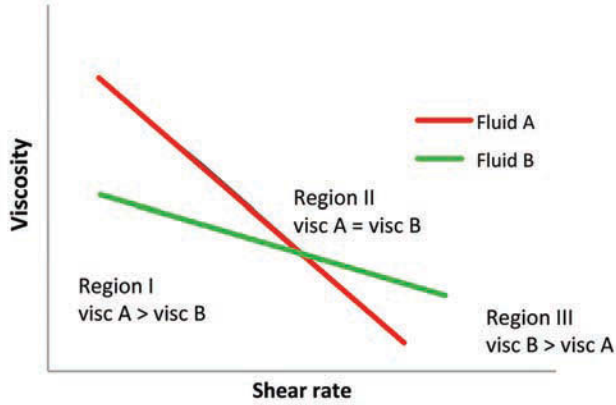

Figure 4. Flow profile of two fluids with different dependence of viscosity on shear rate

Dilatant behavior is rare, but one well-known example is the behavior of corn starch in water, called "oobleck." This was featured in an episode of the television show *MythBusters*[9] as well as many YouTube videos. One example of a demonstration is filling a pool with a water/corn starch mix. When running across the pool, the force applied to the water surface is high. If a person stops running no force is applied, and s/he sinks into the water.

Another rheological classification is based on the behavior of fluid viscosity with time:

- **Thixotropic:** Non-Newtonian fluid, in which the viscosity decreases if a constant shear rate is applied. After shearing is stopped, the viscosity returns to its initial value. This is due to a breakdown in the structure of the fluid during shearing. The structure reforms after shearing ends.
- **Rheopectic:** Opposite of thixotropic behavior, i.e. viscosity increases with time when a constant shear rate is applied; rarely observed.

Many lotions are thixotropic in behavior, which explains why a lotion can be poured more easily when the container is first shaken. A processed food example of a thixotropic formulation is ketchup.[10] The extent of thixotropy can be evaluated by preparing a flow curve, first increasing the shear rate ("up curve") and then decreasing the shear rate ("down curve"). This is shown schematically in **Figure 5**.

In Figure 5A, the "down curve" closely follows the "up curve". This material does not exhibit much thixotropy. The sample in Figure 5B does not recover as quickly, and exhibits *hysteresis*, the lagging of a physical effect on a body behind its cause. [11]

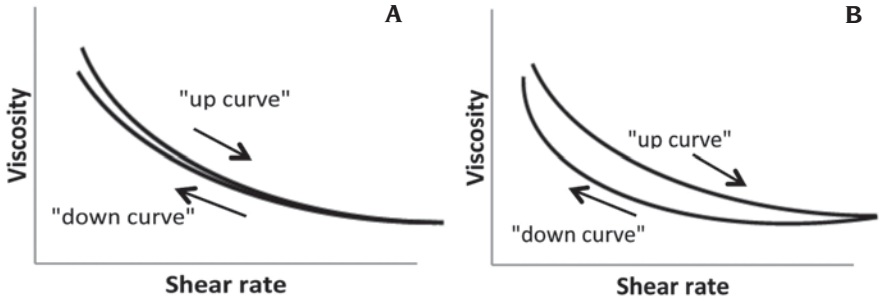

Figure 5. Flow curves showing fluids without (A) and with thixotropy (B)

Another rheological parameter that can be evaluated for formulations is the *yield value*. Flow occurs only if the stress applied is above the yield value. One well-known example of a consumer product with a yield value is toothpaste, which requires a minimum force to remove from the tube. In topical applications, an example of the importance of awareness of yield strength is a body wash with suspended beads. The formulation must have sufficient yield strength to keep beads suspended, at both room temperature and the higher temperatures that can be encountered during storage/transport. An estimate for the yield strength required to suspend particles is:[8,12]

Required Yield Value (dyn/cm^2) = 4/3 R (ρ_p - ρ_m) g

Where: R is particle radius (cm); ρ_p is density of particle (g/cm^3); ρ_m is density of medium (g/cm^3); and g is acceleration due to gravity (980 cm/s^2).

From this estimate, larger and denser particles are more difficult to suspend. Note that the viscosity of the medium does not appear in this estimate. It is important to remember that the yield strength of a fluid does not necessarily correlate with its viscosity. A study by Meyer and Cohen,[13] over 50 years ago, found that a particular solution of low viscosity could suspend sand. A solution with a different thickener, and a viscosity higher by an order of magnitude, did not suspend sand.

A major concept in rheology is viscoelasticity, the combination of both viscous and elastic behavior in a material. This concept is discussed in the chapter on rheology.

The Stages in Product Development for the Consideration of Viscosity Evaluation

Consideration of viscosity values is encountered in several stages of product development and commercialization. In the product development stage, the choice of a raw material under consideration for use in a formulation could include consideration of its viscosity. One example is when looking to offset one material with another. For example, the silicone oil dimethicone is widely used in topical applications and is commercially available from several suppliers. Grades available range in viscosity from 1 cSt to 1,000,000 cSt, covering six orders of magnitude.[14]

The difference in viscosity results from difference in molecular weight. Other properties also vary with molecular weight, such as volatility, solubility in solvent, and others.[14] Therefore, if grades of a raw material similar in chemistry from different suppliers are being evaluated, the formulation chemist should first ensure that they are equivalent in viscosity.

Another example of viscosity specifications in raw materials is a material that could be supplied with different active contents. Here, there is a trade-off to consider between ease of use (easy flowing) and lower use levels. For example, surfactants can be sold in different concentrations, for example a concentration of 30% (liquid form) or 70% (paste form). This would not affect the surfactant performance, but could have an impact on the manufacturing process.

One type of raw material in particular that will include viscosity specifications in the technical data sheet or product literature is rheology modifiers. Rheology modifiers are viscosity controlling agents, and are incorporated into a formulation with the aim of influencing viscosity. Viscosity controlling agents can either increase or decrease viscosity, and are chosen to be compatible with either the water or oil phase of a formulation. There are a large number of rheological modifiers commercially available, and their use in cosmetic formulations is increasing. A search via Mintel's market intelligence records shows that in the years 2000–2005, viscosity controlling ingredients were listed in less than 20% of the new product launches. In the years 2005–2010, viscosity controlling agents were listed in more than 30% of the new product launches.

Rheology modifiers differ in thickening efficiency and also the extent of shear thinning they impart to the formulation. One consideration in the choice of rheology modifier is the sensitivity, if any, to formulation pH or electrolyte content.

A supplier of rheological modifiers will provide viscosity information on the thickening as a function of concentration ("loading ladder"), pH ("pH curve") or electrolyte level ("salt curve"). An example for the dependency of viscosity on the electrolyte content, at several pH values of interest, is given for a synthetic rheology modifier, in **Figure 6**.

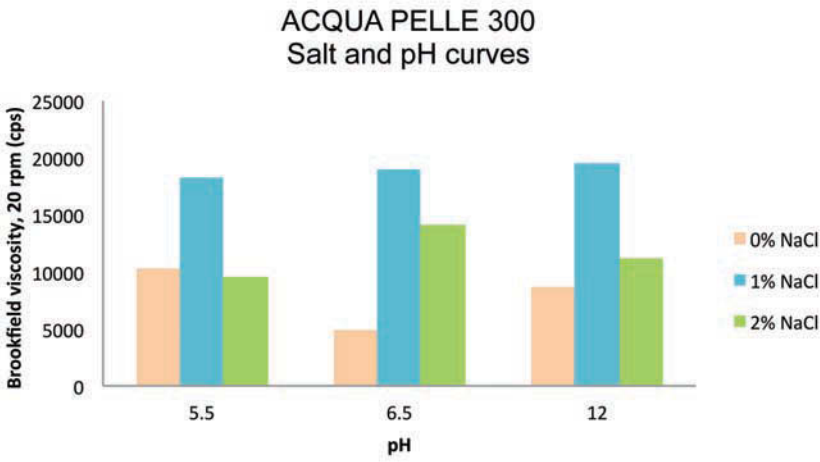

Figure 6. The viscosity as a function of pH, at different levels of salt content provided for a commercially available rheology modifier (reprinted by permission from Presperse Corporation)

Ideally, at the beginning of a formulation development project, a list of requirements for the product is set, including claims, benefits, costs, pH, regulatory requirements, and physical parameters (including viscosity). A successful prototype will meet all or most of the requirements, and some trade-offs are usually encountered along the way. The rheological additive is not the only ingredient that can affect the viscosity of a topical formulation. As a result, the product viscosity should be evaluated for each promising prototype. It is important to monitor the viscosity as formulation changes are made to ensure that the target viscosity is not missed.

Factors that can affect the viscosity of an emulsion include the volume fraction of the dispersed phase, the viscosity of the dispersed phase, the viscosity of the continuous phase, the size of the droplets (dispersed phase), and the emulsifier used.[15-17] A study by Tamburic[17] showed that the choice of oil for the dispersed phase of an emulsion (oil-in-water emulsion) affects the viscosity, thixotropy, and stability of the cream. A study reported by Schramm[7] shows that the amount of emulsifier present in an emulsion influences the emulsion viscosity and the droplet diameter of the dispersed phase.

The presence of components other than the rheological modifier in a formulation can have an effect on rheology. One component that is known to affect the viscosity of surfactant systems and emulsions, even though used in relatively small amounts, is fragrance.[18,19] Another component that can have an effect on surfactant systems is salt (electrolytes).[20] Therefore, formulation chemists should be aware that viscosity changes can result as formulations are developed and ingredient lists are modified.

An important aspect of product development that requires viscosity

characterization is evaluation of product stability. Before a formulation can be launched, the manufacturer must ensure that it has an acceptable shelf life, and will not lose its physical and chemical characteristics. The stability evaluation method involves measurements of critical parameters although details can differ between finished goods manufacturers. Parameters evaluated could include appearance, viscosity, pH, color, and odor. In a stability evaluation, samples are stored at different temperatures and are tested periodically. The pass/fail criteria should be set at the beginning of the stability protocol. Breakdown of an emulsion (phase separation) is a clear sign of instability. Other parameters, such as pH and viscosity, should not vary by more than a given amount after exposure to the stability protocol.

An example of stability results for a cleansing formulation is shown in **Figure 7**. The viscosity and pH were monitored over 4 weeks, with samples stored at RT, 45°C, and 50°C. Since no major changes occurred in viscosity or pH, this formulation passed the stability testing.

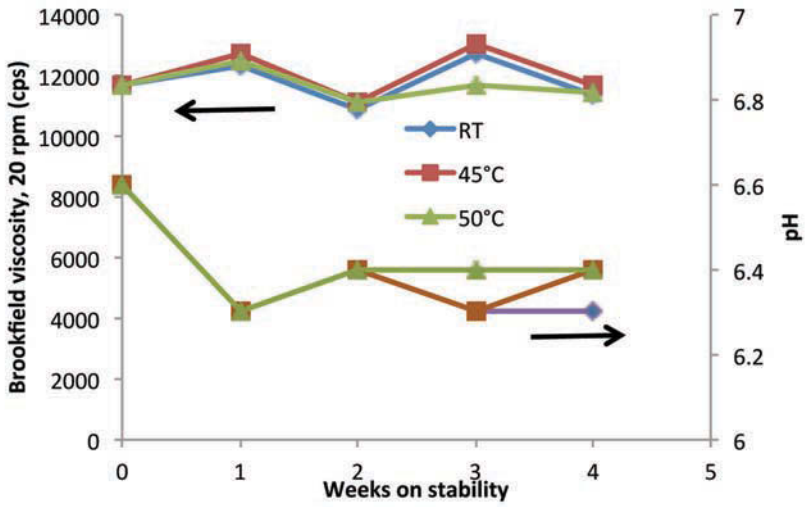

Figure 7. Viscosity and pH results for a model cleansing system monitored over 4 weeks of stability testing (reprinted by permission from Presperse Corporation)

After a formulation has passed lab scale evaluation, it is scaled up to pilot scale production in preparation for a commercial size run. The product produced on the pilot scale equipment is evaluated in comparison with the lab scale standard, to assess whether there are any manufacturing concerns. (See Kimball's chapter in this book on scale-up for a cogent analysis of this process.) It has long been recognized that large scale production of emulsions can provide different results than a lab scale process.[21,22] Finally, when a formulation is produced on an ongoing basis, each lot

should be evaluated for quality control (QC) requirements. The product viscosity is measured, and compared to the specification values set by the formulating chemist.

One exciting aspect of topical product formulation that is being studied in industrial and academic settings is the relationship between rheology and sensory characteristics of formulations. A study by Parente[23] found that the viscosity of emollients used in emulsions correlates with the stickiness, slipperiness, and softness of the emollients. Ozkan[24] found correlations between rheological parameters of gels with various thickeners, and sensory characteristics. Brummer[25] divided the sensory evaluation of emulsions into two stages, primary and secondary. The primary skin feel is the feel at the beginning of application of an emulsion, while the secondary feel is when the emulsion is almost completely rubbed into the skin. Results showed that different rheological parameters are correlated with the different stages of use of a topical emulsion. This area of research can lead to greater consumer satisfaction with the end product, and can provide a commercial advantage to a company that puts these types of studies to good use in its formulating practices.

Another aspect of product development that requires consideration of product rheology is the type of packaging that will be used for the commercial product. The product must have the right viscosity, at the appropriate dispensing shear rate. It is important to remember that the "right" viscosity for a formulation can be different for various product types. Also, the shear rate encountered by the formulation will vary with package type. Therefore, the type of packaging should be considered early on in the product development, and prototype formulations should be evaluated in the packaging chosen. For example, sunscreen can be purchased in stick form, tube form, and spray form. The SPF requirement is a crucial aspect of the formulation, but the remainder of the formulation has to support the chosen packaging type. A sunscreen stick must remain rigid enough to not deform when used, even on hot summer days. A sunscreen packaged in tubes is clearly not as stiff, and must be able to flow through the tube opening without the use of too much force. Too high a viscosity, and excess force would be required, too low a viscosity would lead to product squirting out of the tube. Sunscreen packaged as sprays or aerosols must have the appropriate rheology to be dispensed through the nozzle. Even within one sunscreen product form (lotion), the formulation rheology has been found to affect the effectiveness of the sunscreen obtained. Changing the product viscosity at high shear led to a change in product SPF.[26]

Similarly, moisturizers are commercially sold in jars, tubes, and pumps. The shear rate experienced during product dispensing is different in each package type. The "optimal" viscosity for a formulation packaged in a jar, and which is picked up by hand, is different from the "optimal" viscosity for a formulation dispensed through a pump. The formulation might need to be altered if the product package type is changed.

Instrumentation for Measurement

A comprehensive look at choosing instrumentation is beyond the scope of this chapter, since in most cases a formulation chemist is limited to using the instrumentation already available in the laboratory. However, there are measurement-related concerns the chemist ought to be cognizant of, as regards equipment choice and usage.

The first parameter to consider when acquiring an instrument is the range of shear rates that are expected for material analysis. Viscometers are typically low cost and easy to use, but limited in the shear rates that can be applied and the viscosity that can be measured. An advantage of viscometers is that they are relatively rugged and easy to use, making this type suitable for production and QC settings.

One disadvantage of a viscometer is that this cannot apply an oscillatory stress, which is used for viscoelastic evaluation. Rheometers measure over a wider range of shear rates, and can generate viscoelastic (oscillatory) data. Another advantage of rheometers is the flexibility to measure viscosity at different temperatures, as the viscosity can change with temperature. These instruments are more suited for research purposes. Some disadvantages of rheometers are higher cost and the requirement of greater expertise in order to operate and interpret their results.

Rheological measurements are used in a wide range of industries—including the pharmaceutical, food, plastics, petroleum adhesives, and coatings industries—and instrument suppliers have industry-specific case studies on their websites to highlight specific applications. Instrumentation suppliers often participate in industry trade shows, which is an opportunity for formulators to learn about different models and testing capabilities. A good practice for formulation chemists is to review case studies from other industries, to glean additional approaches to evaluating a topically applied raw material or finished product.

The viscosity measurement instrument found most commonly in topical formulations laboratories is a Brookfield viscometer (**Figure 8**), due to its ruggedness and low cost. This type of instrument is so universal that supplier formulation examples and general articles refer to a "Brookfield viscosity measurement."

There are several models of Brookfield viscometers, which differ in the range of viscosity values they can measure. These models, in increasing order of viscosity values that can be measured, are LV (low viscosity), RV (medium viscosity), HA (medium to high viscosity), and HB (high viscosity). The principle of operation is similar for the different models. A spindle (**Figure 9**) is immersed in a test fluid, to the immersion groove.

Figure 8. Brookfield DV-III Ultra viscometer (reprinted by permission from Brookfield Engineering)

Figure 9. Spindles used for Brookfield viscosity measurement (reprinted by permission from Brookfield Engineering)

During measurement of a sample's viscosity, the spindle is rotated at a constant speed. The time of measurement is also specified. The torque required to rotate the spindle through the fluid, at the set speed, is measured. The instrument displays the fluid viscosity, which is calculated from the measured torque. An error message

appears on the display if the fluid viscosity is out of range for the spindle and test conditions (rpm) chosen. The choice of correct spindle is based either on an existing test procedure, experience, or on a trial and error process. The spindle area required is smaller (spindle number increases) as fluid viscosity increases.

A helipath attachment is used for the measurement of high viscosity creams and lotions. This attachment is a motor which can elevate or lower the viscometer. T-bar spindles (**Figure 10**) are used with the helipath attachment. When using a helipath, the spindle is continuously rotating through fresh (unsampled) material, and so does not create a "tunnel" through the same area of the sample.

Figure 10. T-bar spindles for use with a helipath attachment (reprinted by permission from Brookfield Engineering)

As with the regular spindles, the choice of T-bar spindle size depends on the sample viscosity and the test conditions (rpm). The higher the fluid viscosity, the smaller the spindle needed.

Older Brookfield models did not indicate the shear rate that was applied during measurement; however, newer models may have a shear rate display option. Thus, viscosity measurements generated using Brookfield viscometers are reported specifying the rpm (measurement speed) used. Use of a Brookfield viscometer gives a single point value, as described in the previous section. A viscosity profile can be constructed by measuring Brookfield viscosity at several rpms. The Brookfield viscometer does not cover a wide range of shear rates, but can be sufficient to demonstrate non-Newtonian characteristics.

Figure 11 shows viscosity results for two commercial lotions, a baby lotion (1; blue line) and an adult moisturizer (2; red line). The Brookfield viscosity results are shown both on a linear scale and a logarithmic scale. Shear-thinning is clearly seen for both lotions, with the viscosity decreasing more than tenfold over the shear rate range evaluated. As the shear rate increases, the two lotions are closer in viscosity.

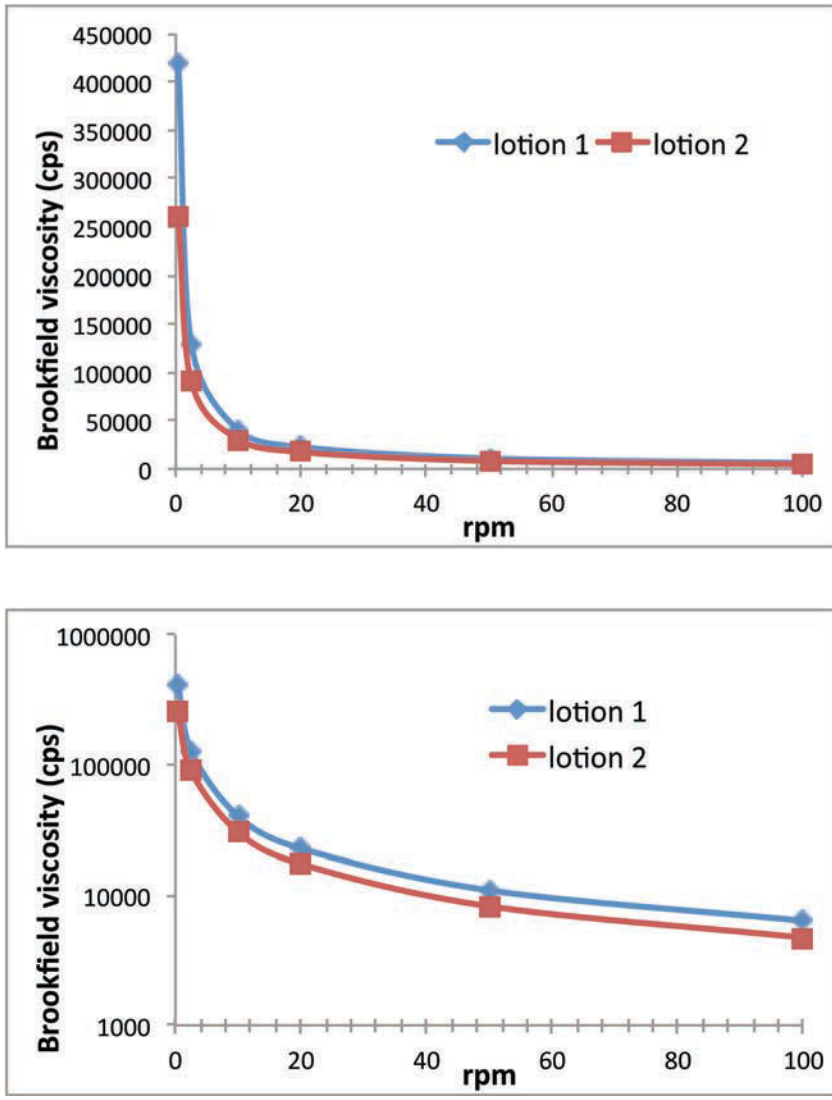

Figure 11. Example of flow curves for two commercial lotions, scaled linearly (top) and logarithmically (bottom)

Reading and Understanding Viscosity Specifications

Specifications describe the expected performance of a raw material or finished product. For example, a lotion might be specified as white, non-irritating, with certain claims and benefits, with a certain fragrance, and characterized by a specific viscosity range.

When reading a viscosity specification, there are several details to note—for example, instrumentation used, shear rate used (rpm for Brookfield measurement),

spindle number (for Brookfield measurement), and temperature of measurement. To illustrate, a lotion viscosity might be specified as 25,000–30,000 cps, measured at 20 rpm, using spindle 6. Two other details to note are the wait time before reading the Brookfield viscosity (e.g. 30 seconds or 1 minute after starting the measurement), and the length of interval between preparing the formulation and taking a reading. For example, a specification could state that a formulation be measured 3 hours or 24 hours after preparation. Again, consistency in measurement method is important to achieve reproducible results.

General considerations for reading a viscosity specification are:

- Note the units used, demonstrating either an absolute viscosity or kinematic viscosity
- Note the type of instrument used
- Note the shear rate/rpm/spindle applied
- Note the temperature at which the fluid was characterized

Measurement Key Considerations

When measuring viscosity, the first reference for test methodology should be an existing company Standard Operating Procedure document (SOP), if available. If an internal SOP is not available, an instrument operator's manual can be used to understand the steps used to set up and execute a test method.

Key considerations for accurate measurement using a Brookfield viscometer are:

- Verify that instrument is within the calibration period
- Verify that the instrument is properly aligned (bubble on top is centered)
- Verify that the correct model is being used (LV/RV/HA/HB) if more than one is in the lab
- Verify that the correct spindle is being used, if there is more than one spindle set present
- Verify that the spindle setting on the instrument is correct
- Verify that the rpm setting on the instrument is correct
- Ensure that the spindle is at the correct depth in the sample
- Ensure that the viscosity value reading is not at the high or low end of the scale
- When comparing viscosities of formulations, the measurements should be made under as close conditions as possible.
- If the viscosity value is not within range, change the spindle but not the rpm (shear rate)

If results are different than expected, the above considerations should be carefully reviewed. In addition, the operation of the viscometer can be assessed by measuring a calibration fluid or a sample of known viscosity if no calibration fluids are available.

Summary

This chapter reviews the definition of fluid viscosity and the importance of understanding the flow behavior of cosmetic raw ingredients and topical formulations. The chapter describes the types of flow profiles that are typically encountered by the formulation chemist. The importance of the concept of shear rate is described, as it relates to different processes encountered in the lifetime of a topical formulation. The chapter covers the types of flow curves that can be encountered—Newtonian, shear thinning (pseudoplastic) and dilatant. It defines thixotropy, the effect of time under shear on viscosity. It also defines the yield value, a stress below which flow does not occur. The chapter includes a discussion of when viscosity data should be used through the development cycle of a topical formulation.

Awareness of the importance of rheological understanding is expected to continue to grow in the personal care industry. New rheology modifiers are being constantly introduced by manufacturers, to meet formulating challenges or to provide multi-functional benefits. Cosmetic product innovation will put increasingly difficult demands on the performance of rheological modifiers.[27] The cosmetic chemist/formulator needs to be aware of new developments in the "toolbox" of rheology modifiers, and the advantages and limitations of each.

Examples of formulating challenges can be given in virtually every aspect of personal care application. In cleansing systems, there is a consumer trend towards sulfate-free surfactant formulations. These systems provide a challenge for thickening. The presence of electrolytes in a formulation can decrease the efficiency of some rheology modifiers. In skin care, some actives that are of interest in a topical formulation require a low pH for activity. The choice of rheology modifier could be different in low pH systems, and there could be a trade-off with other attributes of the product. When considering nail products, development of water-based nail polish requires a different approach to thickening, as compared to traditional nail polish formulations. Any type of consumer product must have a pleasing aesthetic, and new rheology modifiers are expected to contribute to that.

Other future advances in rheological understanding of consumer product behavior are expected through academic and industrial studies of the interaction of rheological properties with sensory or other performance properties. This is a growing area of research, and is of commercial interest as it can be used by finished goods manufacturers to differentiate their products. A better understanding of the relationship between rheology and sensory performance could shorten product development cycles.

Instrument manufacturers periodically introduce new models, designed for greater ease of use and measurement flexibility. Improvements in software make characterization simpler and more reproducible. These advances contribute to a greater comfort level in using viscosity measurements and rheological terminology, and support the anticipated growth in incorporation of rheological characterization in the consumer product development process.

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CHAPTER 13

Fourier Transform Infrared (FTIR) Spectroscopic Imaging Analysis of Topical Formulations

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TRI Princeton

Key words:
Spectroscopy, Imaging, FTIR, Formulation, Active Distribution

Introduction

Fourier Transform infrared (FTIR) spectroscopic imaging microscopy is a useful and unique tool with which to characterize molecular and chemical components in a stable sample as well as the molecular and chemical changes accompanying changes in sample composition and environment. The technique provides a molecular spectroscopic image through the acquisition of thousands of spatially resolved FTIR spectra. Of particular interest to formulation science is the ability to visualize changes in molecular distribution and chemistry that can occur as a function of relative changes in formulation components such as the evaporation of water and volatile emollients that can lead to the crystallization or redistribution of actives within formulation films. In addition, the formation of super-saturated conditions, loss of active solubility, and interactions between formulation components can all occur when a formulation dries to form a film. The applications of FTIR imaging spectroscopy described in this chapter provide the ability to measure and visualize much of this behavior and therefore can be helpful in understanding the in situ performance and efficacy of topical formulations.

FTIR spectroscopy is a ubiquitous tool in analytical and biophysical chemistry that provides information on chemical composition, organization, and dynamics based on molecular vibrations occurring in the mid-infrared spectral region. Most readers will be very familiar with the use of FTIR spectroscopy in organic chemistry and analytical quality control, where it is used for characterizing the products of

chemical reactions and for chemical identification. Perhaps less familiar to readers is the use of FTIR spectroscopy in biophysics and materials science, where it is often used to investigate molecular and supra-molecular dynamics and organization in diverse materials which result in changes in the FTIR spectra of materials that are indicative of molecular packing, hydrogen bonding, phase transitions, and other non-chemical changes occurring in the sample.

Advances in instrumentation techniques and mid-infrared detector technology led to the emergence of commercial FTIR spectroscopic imaging microscopy instruments in the late 1990s. This brought to molecular FTIR microspectroscopy the additional dimension of spatial resolution, a major enhancement for the study of heterogeneous samples. Spatial resolution in this context means that each of the many spectra collected in an imaging experiment comes from a known specific location on the sample. This is in contrast to conventional FTIR spectroscopy with a microscope in which one spectrum is collected from a large sample area and the spectrum then represents an average of all the information. The technique gives an interactive organizational (structural) and chemical "picture" through the acquisition of spatially resolved molecular spectra. This allows spectral identification and simultaneous spectroscopic images of almost all the molecular and chemical species present in a sample.

Biomedical and biomaterials applications of FTIR spectroscopic imaging methods have blossomed in recent years and in particular have been used to examine tissue sections including skin, bone, teeth, cartilage, brain, and breast tissue. In addition, significant and successful work has been applied to the development of FTIR imaging as a medical diagnostic tool.[1-9]

Beyond applications to biomedical and biomaterial samples, spectroscopic imaging has been successfully applied to the study of pharmaceutical formulations for questions concerning enhancing drug quality, understanding the impact of processing on active distribution, and to provide molecular imaging information on changes in physical attributes such as solubility, dissolution, stability, and crystallization.[10-11]

In related applications, our laboratory has developed a major interest in the applications of FTIR imaging microspectroscopy to the physical chemistry of topical pharmaceutical and consumer product formulations. In previous reports, we have discussed spectroscopic imaging applications as they relate to dermal and transdermal delivery of exogenous molecules including active drugs, pro-drugs, and formulation components such as skin penetration enhancers. The majority of such work has examined skin sections from topically treated *ex vivo biopsies*.[12-16]

The focus of the present chapter is to illustrate the use of FTIR imaging spectroscopy in order to interrogate the physical properties of topical formulations when they are spread to form films, as occurs in the application of virtually all topical formulations to skin. These particular studies, unlike those previous reported upon, are not concerned with questions of skin penetration, but rather in the distribution of drugs or actives within formulations as they are applied to a substrate and form films. Of particular interest are the changes in molecular distribution and chemistry

that occur as a function of the relative changes in formulation components, e.g., the evaporation of water or other volatile solvents and emollients that can lead to the crystallization or redistribution of actives within the films. The formation of super-saturated conditions, loss of active solubility, and complexation between formulation components can all occur after a "stable" formulation is applied to a substrate and forms a film. The ability to measure and visualize some of this behavior can be extremely insightful in understanding the performance and efficacy of topical formulations when applied, a significantly different issue than measuring the stability of a formulation in the jar.

The intention of this chapter is to illustrate that FTIR spectroscopic imaging can provide unique and useful information on the molecular dynamics, chemistry, and partitioning of molecules in formulations, and thereby assist in understanding how these parameters may change as a function of diverse variables including temperature, water concentration, polymer or surfactant chemistry and concentration, and formulation structure. Using a few selected examples for illustration this chapter will provide a brief introduction to the unique capabilities of FTIR spectroscopic imaging and address topics of considerable interest and relevance in understanding the physical chemistry of topical pharmaceutical and cosmetic formulations.

Experimental Methods

The details of specific instrument set-ups and the issues of initial data collection and processing have been reviewed elsewhere.[14,16] Accordingly, only a general overview will be provided here. The development of FTIR spectroscopic imaging has added a spatial resolution dimension to sample analysis by FTIR microspectroscopy. Whereas a conventional FTIR microscope collects a single spectrum which represents the average of all the molecular species present as the IR beam passes through a heterogeneous sample, an FTIR imaging system collects hundreds (or thousands) of spectra with each spectrum spatially correlated to a specific area of the sample.

FTIR spectra were acquired with a Spectrum Spotlight 300 or 400 Imaging System (Perkin Elmer Instruments, Shelton, CT), consisting of an FTIR spectrometer with a MCT (mercury-cadmium-telluride) focal plane array detector placed at the image focal plane of an FTIR microscope. Single spectra and images were collected in the transmission mode at a spectral resolution of 4 cm^{-1} or 8 cm^{-1} in the mid-infrared (MIR) frequency region between 4000 and 800 cm^{-1} with a pixel size of 6.25 μm x 6.25 μm or 25 μm x 25 μm. As with all transmission FTIR methods, materials samples and biological sections need to be thin to allow transmission of the FTIR signal. Routinely, after deposition on the FTIR window (CaF_2 or ZnSe) the formulation layer thickness must be between 4–20 μm, approximately, a thickness routinely used for optical microscopy. The very large data sets collected in an FTIR imaging experiment have necessitated the development of software specifically designed to process such large arrays of spectroscopic data. Indeed, a major objective in hyperspectral imaging is to extract the relevant information from the vast amount of data present in these

images and highlight the "useful" information as defined by the specific question being asked. Initial steps in processing may include baseline correcting in spectral regions of interest but can extend to generating arrays of difference spectra or derivative spectra. For the type of samples discussed in the current work, soft materials, a critical step is to define appropriate spectral parameters relevant for characterizing specific components within the formulation. All the data and images presented in this chapter were processed using ISys software from Spectral Dimensions (Olney, MD). Using this software any spectral parameter can be monitored. These can be peaks arising from protein or lipid vibrational modes or from a chemical within a formulation. In addition spectral factors may be quantitatively analyzed with a variety of univariate or multivariate techniques across the entire array of spectra. The schematic in **Figure 1** illustrates the experimental and data collection setup of an FTIR imaging microscope spectrometer. The resulting array of data is spatially resolved such that each pixel, which collects a complete IR spectrum, maps directly to a specific sample area.

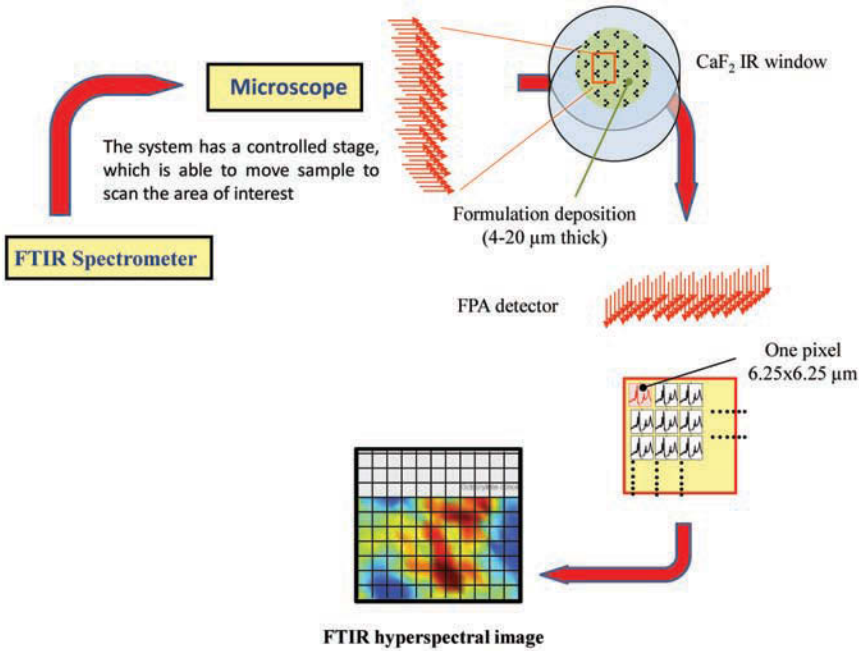

Figure 1. Schematic of a Fourier transform infrared (FTIR) imaging microspectrometer measurement. Complete IR spectra are collected at each pixel providing spatially resolved IR spectroscopic characterization of the sample area imaged.

Imaging Formulations: Examples

Figure 2 shows FTIR spectral images of a commercial sunscreen formulation film at 2 different spatial resolutions (25 x 25 µm/pixel) and (6.2 5x 6.25 µm/pixel). The band at 1,670 cm-1 is specific to the formulation and the one at 1,030 cm^{-1} is used to follow 2-ethylhexyl-2-cyano-3,3-diphenyl (octocrylene) one of the UV actives in the formulation. These images illustrate clearly the different information provide by a high and low spatial resolution. For questions of film stability or water resistance, collecting low resolution images over larger sample areas is likely more appropriate. However, to evaluate active distribution and its dependence on formulation design, high resolution images are necessary to discern the differences in active distribution that are critical to efficacy in sunscreen formulations.

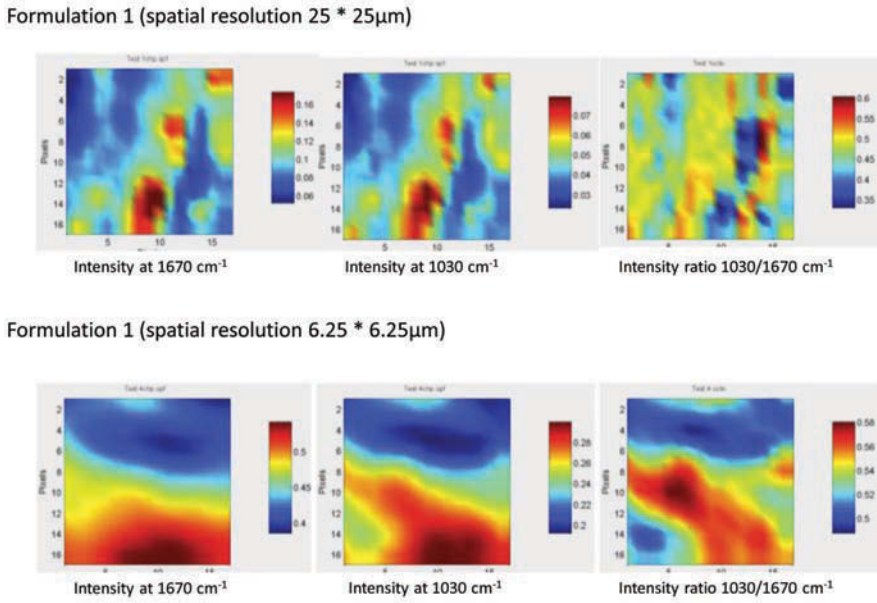

Figure 2. Spectroscopic images of a commercial sunscreen formulation at 2 different spatial resolution (25 x 25 µm/pixel) and (6.25 x 6.25 µm/pixel). The images show the distribution and intensity of a two chemical components in the formulation. The image of the 1,670 cm^{-1} peak is specific to the base formulation while the peak imaged at 1,030 cm-1 is specific to octocrylene, one of the UV actives in this formulation. The right-hand image in both rows shows the relative intensity of the octocrylene peak to the formulation peak thereby removing intensity variations associated with film thickness variations.

Figure 3 and 4 illustrate the use of FTIR imaging to monitor formulation dynamics and the change in relative chemical composition of a formulation film over time. The images of specific components with a commercial topical insect repellent formulation are shown. One image corresponds to the formulation active *N,N*-Diethyl-*meta*-toluamide (DEET) and the other to recipients of the formulation film. Imaging the ratio of these components provides an image of DEET distribution and concentration normalized for any differences in the thickness of the formulation film.

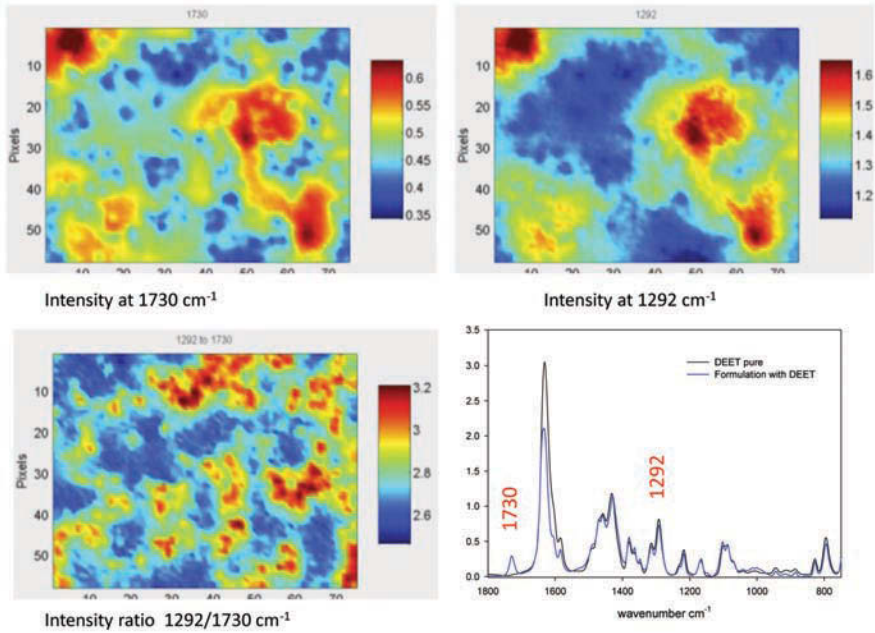

Figure 3. FTIR images of a commercial topical insect repellant formulation. The images show the distribution and relative concentration of *N,N*-Diethyl-*meta*-toluamide within the formulation. The spectral assignments are based on molecular FTIR spectra of the formulation and pure *N,N*-Diethyl-*meta*-toluamide, as shown in the figure.

The unique utility of FTIR spectroscopic imaging is illustrated in **Figure 4** in which the DEET distribution and concentration (normalized for film thickness) is imaged over time and provides a direct and semi-quantitative series of images of the changes in the film chemistry every 10 minutes for a 1-hour period. The images collected between 13 hours correspond to other sample areas across the formulation and show the continuing decrease in DEET concentration when the formulation film is sampled randomly.

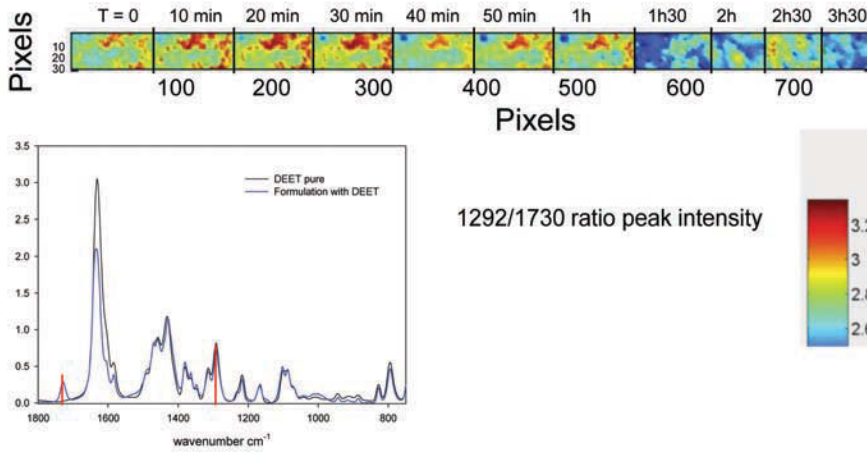

Figure 4. FTIR images showing the changing concentration of DEET within the formulation film over a period of several hours at room temperature. These images directly represent the spatial distribution and concentration changes of DEET within the formulation film.

As discussed in this chapter's introduction, FTIR imaging of samples can be conducted at pixel resolutions of 6.25, 25, and now 50 μm2. Imaging formulation films at lower resolution can be informative for following changes in overall concentration in simple formulations. The images in **Figure 5** are collected for a large area at a spatial resolution of 25 μm^2 and illustrate a progressive decrease in the overall concentration (red to blue) of medicinal alcohols in a simple topical petrolatum-based commercial formulation over a period of 150 minutes. The images are all collected from the same area of the formulation film and clearly show that the decrease in concentration of the formulation actives is quite uniform over time, although not completely, both with respect to the overall distribution and the average decrease in intensity (concentration). The intensity scale provides a semi-quantitative aspect to these spectral images and shows that average active intensity (concentration) decreases by 50% over 150 minutes.

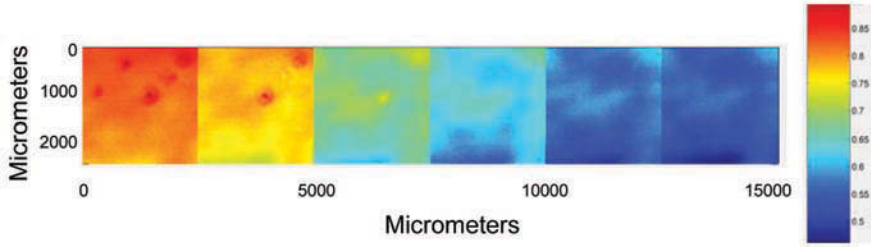

Figure 5. FTIR images showing the changing concentration (slow release) of medicinal alcohols from a petrolatum-based formulation. These images are generated from the ratio of the peak corresponding to the volatile active normalized to a peak from the non-volatile petrolatum base. Thus the images capture directly the changing distribution and concentration of specific chemical components within the formulation film.

In previous work, we have shown that the changes in the distribution of actives can be imaged as a function of other external variable such as water submersion.17,18 This can be important for water-resistant sunscreen formulations and related formulations in which efficacy depends on maintaining the concentration and even distribution of UV actives in the formulation film. By providing images of the specific functional chemical components in the film, FTIR spectroscopic imaging is a powerful tool in understanding and characterizing the behavior of soft materials.

By way of a final example, the images in **Figure 6** report the distribution of salicylic acid in a commercial topical analgesic formulation. Given that this active is not volatile, there is, as expected, little change in the concentration of the active over the 90-minute time period, during which the three images were collected. However, what the images do reveal is the highly non-uniform distribution of the salicylic acid and its crystallization in discrete domains within the spread film. By providing direct molecular images of salicylic acid distribution in the formulation film, this measurement approach provides a unique and useful method for the comparison of the role of formulation design on salicylic active behavior. Of course this imaging approach is general and can be applied to the physical chemistry of many pharmaceutical or cosmetic actives in wide range of different formulations.

While the majority of FTIR spectroscopic imaging applications are focused in materials science, biomaterials, and biomedical applications, the unique combination of structural, dynamic, chemical, and spatial information obtained by FTIR imaging of topical formulations, and soft materials in general, insures that applications in soft materials will continue to grow. This expansion will be furthered by the continued development of new technology, such as attenuated total reflectance (ATR) FTIR imaging which has recently become commercially available. Such new methods will expand to range of samples and experimental questions that can be addressed by FTIR imaging spectroscopy.

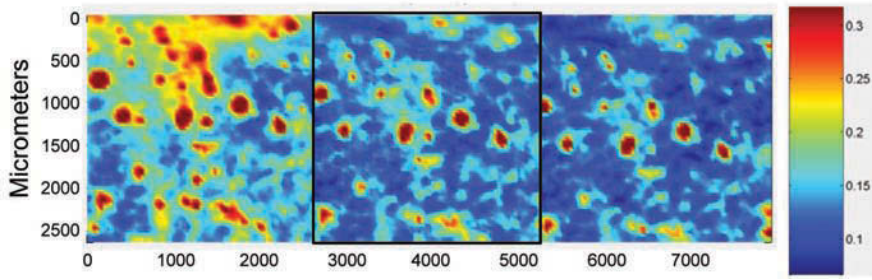

Figure 6. FTIR images showing the distribution of salicylic acid in a topical analgesic formulation generated by imaging an acid peak specific to the active. In this case the active peak intensity is not normalized to a component of the formulation base. The image is to illustrate the non-uniform distribution of the active and the apparent localization of crystals in the formulation film.

Summary

FTIR imaging microspectroscopy is now commercially available as a measurement tool that can be used to inform the design of topical formulations. To date, the majority of imaging applications have been in other fields, but hopefully this chapter has demonstrated that FTIR imaging of soft materials, such as topical formulations, provides new and unique insights into important aspects of product physical chemistry that are key to product performance. The unique insights provided by FTIR imaging spectroscopy into the physical chemistry of formulations include visualizing the molecular distribution of specific chemical species within the applied formulation film. This can be crucial in sunscreen films, for example, in which an even and complete distribution of UV absorbing molecules is essential to providing a protection benefit to the skin. Equally as important is the information provided by FTIR imaging of formulation films regarding changes in active concentration and distribution following exposure of the film to water, heat, friction, and related stresses. In the case of topical formulations designed to deliver molecules into or through the skin, FTIR imaging of the formulation film provides direct information on whether an active remains dissolved or crystallizes as the formulation dries. Such information is very useful for understanding bioavailability and the clinical efficacy of a specific topical formulation and how changes in the structure and composition of inert formulation components alter formulation performance through changes in the underlying formulation physical chemistry.

A final point is worth noting. The spectroscopic imaging approach discussed in this chapter relies on the intrinsic characteristic FTIR spectra of the samples; the technique does not require the use of dies, stains, fluorescent probes, or any other exogenous molecules to generate the images and is therefore devoid of the potential issues that can occur when imaging probes rather that the endogenous molecular

species of interest. It remains only to note that while this chapter highlighted a couple of examples of the approach and while the method is still new, it is general and should have wide applicability in topical formulation science.

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SECTION IV:

Sensory and Elegancy

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CHAPTER 14

Creating Appealing Topically Applied Formulations: Linking Physical Aspects to Marketing Psychology

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Key Words

Aesthetics, Skin Feel, Consumer Appeal, Facial Care, Luxury Goods, Rational Appeal, Emotional Appeal, Consumer Loyalty, Consumer Experience, Development Process

Introduction

For success in the skin care market, products should possess sensorial appeal that may trigger an emotional reaction in addition to their intended performance. From a study conducted in the late 1990s and early 2000s, we can learn that the primary determining variable for engineering the tactile aspects of an emulsion is the emulsifier choice. By using this information and thereby altering the development process, more aesthetically pleasing topical formulations that resonate with the target audience can be designed and scaled-up in a fraction of the normal time. One must use such approaches to build a sustainably profitable skin care business in an increasingly competitive marketplace.

Luxury Goods Business

There exists no distinct human physical need for skin care products. For survival, humanity can manage without them. Similarly, there is no real need for beautiful fast cars or works of art and music. Nonetheless, there are voids that are seemingly satisfied through the purchase and use of skin care products. Skin care products can make a person look better, which can provide him/her with a sense of wellbeing and help them achieve success in a modern society that values physical attractiveness.

There is also the aspect of the excitement of the purchase of a new product, and the subsequent initial and continuing use of the product. In that sense, every skin care product, regardless of its price point, can be perceived as a luxury item. This concept should be taken into consideration by formulation chemists and marketing groups throughout the development process of every new skin care product. Not only must such technical aspects of a product as performance and stability be considered, but also the emotional and psychological aspects that are associated with the experience of using the product.

The purchase of a luxury good has both rational and emotional aspects. The consumer is not only interested in what a product can do but also in the promise it holds. Deep down, the consumer is looking for an emotional lift from a product, as well as for an instant connection and satisfying experience. For the skin care business, the hope is that the emotional meets the rational and a long-term relationship is formed.

A bond with an artwork is not formed merely based on technical proficiency. The expectation is that the artwork will stir the emotions while performing on a high technical level. Art that is not involving a human control and merely done by a robotic computer rarely excites. (One may even argue that it is not truly art.) At the same time, a heartfelt performance poorly executed rarely elicits a request for an encore. We tend to be in a quest for beauty, not merely in appearance, but also in overall experience. This quest for beauty is complex. Theologian RC Sproul states, "Edgar Allan Poe understood that in beauty one encounters the dimension of the sublime, a dimension that is not irrational but may be transrational." That is, beauty, though it involves the mind, goes beyond the limits of mere cognition. When we are "moved" by great works of art, we are gripped by an affective sense that stirs the soul as well as the mind. To cultivate an appreciation for beauty is to set our course to follow after the sublime Author of all beauty."[1]

Skin care products are luxury items, whether they are mass-marketed hand lotions or prestige brand facial treatment creams. Mass-market products are sold at food/drug/discount retailers and are usually priced at the low end, while prestige products are normally sold at department store cosmetic counters or specialty shops and are priced high. The mass-market segment is between two and three times the size, in dollar terms, of the prestige market, as seen from comments from such industry experts as the NPD Group. While all skin care formulations should be designed to meet the claim and expectation for physical performance, they should also be appealing psychologically. Again, we do not *need* luxury goods to survive, but in a society where survival is not a major concern, we like them and want them and are willing to pay for them.

Consumer Perception—Multiple Factors At Play

Every skin care product is produced with a target customer in mind and therefore delivers a specific message. The message may be related to an effect usually attributed

to a featured ingredient or a combination of ingredients. It may be related to a target group in the general population such as age group, ethnicity, a group that is committed to a certain activity (such as sports), or tailored for a specific area of the body that may require special care such as the feet or hands. When a new formulation is being designed, the intended message needs to be communicated clearly to all parties involved in the process of its development and launch.

Messages to end-consumers can be delivered in many ways. The first announcement is generally made through advertising and promotion. This enticement may work on the emotions as well as the intellect, and also may provide a financial incentive to purchase. Sampling is another avenue of promotion, both for prestige and mass-marketed products. The more aggressive marketing may be confined to the point of purchase, with an in-store display, eye-catching packaging, or strategic shelf placement. With prestige products sold at a cosmetics counter, it is more about the approach of the salesperson and the initial impression that the product gives when tested at the counter.

All this work, accompanied often by a considerable amount of investment, is leading to a certain moment of truth, when the consumer is trying the product for the first time. Many aspects are judged at that moment, leading to the decision to purchase. Following purchase, especially if the product has not been sampled beforehand, the consumer is looking for validation of the cash outlay from the initial experience. The experience either makes the sale or confirms the sale.

The promotional message first attracts the senses. Later, the product is experienced, both with the sense of touch and the sense of smell. If the promotional message, both in emotion and effect, is delivered as promised simultaneously and can be connected to the aesthetics of a product, both in terms of sensory feeling and smell, then the product has a much greater chance of success, consistent use, and repeat purchase. The issue of consistent use is especially important with prestige facial creams and topical drug products. If the consumer does not faithfully use a product as directed because the experience is not appealing, it has very little chance of delivering its promise. Since so much is invested nowadays in product development, the manufacturer should strive for a long product life in the market. This is difficult to achieve given the flood of new products being withstood by a marketplace that generally allows a life cycle between 2 to 3 years.

The importance of the aesthetic attributes therefore needs to be defined, refined, and communicated to the formulation chemist early in the development process. Moreover, the marketing group and formulation chemist need to stay engaged throughout the development process. Designing the "right" sensorial aesthetics that confirm and reinforce the marketing message is a key to sustaining product market share. In the same manner, selection of the fragrance for a skin care product is important and should be started early in the design process. This will allow for a more measured process to be taken for integration of the fragrance into the base, and matching the overall aroma to appeal to the target consumer. Even in

cleansing products like shampoos and body washes, scent provides significant psychological cues.

In an unpublished study conducted by Quest International, the influence of fragrance on consumer acceptance of skin care products was evaluated. Two skin cream formulations were selected; one deemed "heavy" when applied to skin and the other one considered "light" in feeling. Two fragrances for these formulations were selected, one that communicated a richness and heaviness, another which spoke of airiness. The four combinations were produced and tested by panelists to decide whether a particular formulation was heavy or light feeling. Panelists easily identified the light/light and heavy/heavy products, but when it came to the ones with contradictory feel and smell, by and large the respondents chose based on the character of the fragrance rather than the measured tactile aesthetics of the formulation when asked whether the product was light or heavy (see **Figure 1**.) The influence of fragrance is powerful. The formulation chemist and marketing professional need to select a fragrance that matches the product's premise.

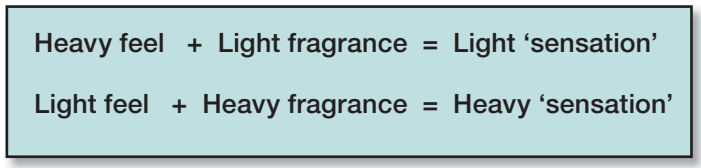

Figure 1. Fragrance dominates sensation

If a product can communicate a single unified message that combines both the promotional and aesthetic aspects, it has better likelihood of resonating with consumers. If the message is disjointed, even an excellent performing product may not succeed. For more detailed description on the effect and selection of fragrance in skin care products please refer to the appropriate chapter in this book.

Matching the Product to the Consumer

Horses for courses is a British racing idiom, meaning that what may be suitable for one person or occasion may not be suitable for another. This idea can be applied to the skin care aesthetic arena. The market is flooded with suppliers of ingredients which offer "good," "excellent," or even "outstanding" skin feel. This may be so for certain occasions, but possibly not for others. The "activity" of a certain compound is dependent on a variety of factors such as percentage use, pH, other ingredients and final form of vehicle. These claims therefore need to be reviewed carefully and understood in the context of the testing provided.

The aesthetic properties the product should be designed to fit the time of application, its intended use and the site on the skin. For example, the aesthetic properties of a night cream will normally be different than those of one that is applied

in the morning. A face cream may feel different than a hand cream; a body cream for dry skin should have different rub out and after feel characteristics than that of a sunscreen that is designed for the same area of the body but delivers different benefits. For facial products, the designer should know whether the product will typically be used underneath makeup or not, because the aesthetics will need to be quite different for either situation.

Understanding the target consumer in terms of the type, condition, and age of the skin is an important key for both the formulation chemist and the marketing professional. Facial treatment products designed to (cosmetically) address fine lines and wrinkles, even skin tone, or firm the skin are not necessarily applied to dry skin. The skin on various parts of the body is very different in terms of topography, thickness, and ability to perceive sensations.[2] The condition of older skin will be different when compared to younger skin, as well possibly in those with perceived sensitive skin.[3] Other variations in skin can be seen when one looks at gender, color/ethnicity, pregnancy, and levels of stress differences of the consumer.[4-7] In addition, the perception of appealing aesthetics may be different from one demographic area due to cultural implications. For example, Asian consumers may prefer lighter feeling products, while Europeans take to heavier products, and Americans fall somewhere in the middle, though this is a gross generalization. Products aimed to treat certain skin conditions such as acne or psoriasis, where the consumer's expectations are set more on the improvement of the condition, should bear different aesthetics than those that do not treat. Nevertheless, even if the main purpose is treating an undesired condition, the appearance and sensation of the product is extremely important for good patient/consumer compliance.

With regard to matching the ideal aesthetics for a particular application, there are some considerations the formulation chemist and the marketing professional should be aware of. Frequently, a tested formulation is applied to the skin on the back of the hand, but this site may not be the best one to reflect the sensation to the skin in other parts of the body. Ideally the product should be tested on the site of the body for which it is designed to be used. If for example the project objective is to develop a facial product, the product should be tested on the face. Even here, it may make a difference in sensation if the product is a general facial product or one that is aimed to be applied under the eyes. Appearance of the product on the skin during and after application is important as well—whether it is shiny or matte and whether it disappears quickly or slowly. If the product is being marketed to a specific subset of the population (i.e. based on age, condition, or ethnicity), panelists who represent that target population should be enrolled in the study. Better yet, conducting a preference study with target consumers, done via a series of questions answered on a survey or to an evaluator is an excellent way to narrow and refine the aesthetic options. The more samples that vary in tactile aesthetics that can be evaluated under real use conditions by a target consumer, the better.

Sustained Success

A considerable amount of resource is invested in the launch of a new skin care product. Scaling up and manufacturing, packaging, and distributing the product can be laborious and time-consuming. Establishing and maintaining distribution channels is an ongoing challenge. Advertising and promotion costs can dwarf the expense of development, production, and distribution.

All these resources are spent to increase the chance of a successful launch. It is doubtful, though, that a profit is turned on this effort during the initial launch phase, since the period after launch is usually aimed to earn a return on the initial investment. The profit is most likely to be generated in the repeat consumer purchase when the design and development stages are no longer required and the return on the development stage investment has been achieved. Having consumers return for more products on their own, with no cajoling or incentive, is where the profit is made. Furthermore, if consumers are excited enough to spread the word, this is the type of credible promotion that is so desired. Today, this communication is not done merely face-to-face, but more often and more widespread by use of information technology, whether in reviews or blogs or tweets. Some of the more popular sites are *The Beauty Brains*,[8] *Product Girl*,[9] and *Musings of a Muse*.[10]

An old marketing adage loosely states that if a customer has a good experience, he/she may tell one friend, but if the experience is bad, they'll tell ten. In the new information world, the numbers are more balanced, but are multiplied by factors of thousands. Word gets around quickly, easily, and efficiently. A sad reality is that many new product launches do fail. According to AccuPoll research, the failure rate for launch of personal care products is 8095%.[11] Considerable effort does need to be placed on making sure that a new product gets noticed and purchased for the first time. If long-term emphasis has to be placed on continually searching for new customers, it is likely that the product will not be a success from a profit standpoint. In this scenario, costs will eventually need to be shaved from the product, ultimately resulting in a product that disappoints loyal but discerning customers.

Formulating a product that excites the consumer so much that they buy it again *and* tell their now thousands of friends is the goal. Formulating a product that performs as expected *and* is aesthetically pleasing is the key to attaining this goal. Developing products that have a life beyond the launch can mean that whole companies can survive and thrive.

Developing products that generate sustained excitement with the consumer may mean doing things differently. This may be uncomfortable, and may mean offering a product that contains high quality and relatively highly priced raw materials. In the end, though, rewards will be reaped.

Research That Changed Everything

Research presented by Dr. Johann Wiechers at the December 2001 meeting of

the Society of Cosmetic Chemists in New York changed the way aesthetic design of emulsions is viewed. His project was titled *Impact in Different Phases of the Sensory Evaluation Process but How Does One Demonstrate the Absence of such an Influence?*[12] This work included sensory evaluations by Sensory Spectrum (New Providence, NJ), headed by Gail Vance Civille. This work demonstrated that the emulsifier, a functional compound that is responsible for an emulsion's physical stability is a dominant factor in determining the sensory aspects of emulsions. This study evaluated 24 emulsions using 4 emollients with measured statistical differences in skin feel and 6 different emulsifier systems. The emollient phase volume of these emulsions was held constant, and the emulsifiers used at the recommended use levels for stability. Sensory Spectrum, using the Spectrum Descriptive Analysis Method, evaluated the emulsions on 31 different aesthetic attributes within the following categories:

- Appearance (3 attributes)
- Pick-up (4 attributes)
- Rub-out (8 attributes)
- Immediate afterfeel (8 attributes)
- Afterfeel after 20 minutes (8 attributes)

Each expert evaluator provided an assessment as to the level of stickiness, spreadability, integrity of shape, and so on. The scale ran between 0 to 100, with 0 being the low point based on a defined standard and 100 being a high point based on a different standard control point product. A rigorous statistical analysis was performed running paired comparisons on each of the attributes.

The surprising result of the study was that the predominant contributor to variance in skin feel is the emulsifier and not the emollient, as was expected. Contribution to skin feel attributed to the emulsifier was pegged at 74%, whereas emollient selection controlled only 12% of the total variance. Large portions of the emulsifier skin feel control was observed as an important factor in the categories of appearance, pick-up, and rub-out. The afterfeel quantified numbers appeared to be more directly related to emollient selection when compared to the previously described skin feel attributes, but still a significant contribution from emulsifier selection was observed.

The conclusion of this study and the message it delivers is clear. In order to fundamentally change the aesthetic properties of a topically applied emulsion formulation, one should not focus on the choice of the emollient but on the choice of the emulsification system. This is not a surprising outcome since the formulation chemist is choosing the ingredients for the formulation according to their anticipated function, Therefore, the emollient is the component that is chosen for its feel and the emulsifier is merely there to ensure stability. Moreover, the emollient is normally incorporated at much higher percentages than the emulsifier. In retrospect, since the emulsifier is usually a surface active agent, it might be more active in its interaction with the upper layer of the skin, the stratum corneum, and thus be a more significant factor in contribution to feel.

The results of this study highlight the importance of the evaluation of a wide range of emulsifiers and combinations thereof in order to find the proper aesthetic properties for the particular application. Most formulation chemists mistakenly choose to focus on emollients, thinking that these will fundamentally change the way the product feels. Though this approach may be easier than changing emulsifiers, the desired end result is rarely reached.

The Challenge of Matching Sensorial Attributes

A common error in the development of a new skin care product is trying to match aesthetic attributes with those of an existing product. The assumption that matching aesthetics is the key to success is somewhat dogmatic, since the existing product may capture a significant market share because of heavy advertising and promotion, not just because of its performance. Adopting this approach may result in a launch of a product that feels like your competitor's, but if there is no marketing match it will most likely not enjoy similar market share and will not offer challenging, or successful, competition. A better practice is to chart a new aesthetic course that will match the original objective of your new product.

As we learned about the dominant role that emulsifiers play in the appearance, pick-up, rub-out, and afterfeel of a product, we can assume that when a manufacturer uses a standard emulsion stabilization system across a range of products it is likely to lead to very similar tactile aesthetics. Packaging and fragrance elements may be different, as well as ad copy and claims, but the skin feel of the products will be aligned.

If the goal of the product development is to match the aesthetic elements of a product in the marketplace because those elements are significant and sufficient to justify its success, then the idea of aesthetic match is valid. The formulation chemist should identify the emulsifier system used in the marketed product and look to match that system. Of secondary importance would be to study the emollient oils used, though these contribute less to the overall product aesthetics to the degree that if the aesthetic mimicking strategy is the goal, then the formulation chemist can match the emulsification system and use a different emollient system in an attempt to differentiate the formulation without appreciably altering its aesthetics. Next the fragrance and packaging can be selected independently to set the product apart from others in the marketplace.

When a product is not selling well in the marketplace, its tactile properties may not necessarily be to blame. Success may be strictly linked to consumer perception that is created by heavy advertising and promotion, appealing claims, or exciting packaging and fragrance. The team should therefore consider a point of differentiation for a new launch in their product's aesthetics. If the new launch can excite the senses and communicate the claims message to the target consumer, then the product has a chance to eclipse the success of the competition. Sampling a wide range of tactile aesthetic options early in the development process can assist in the decision-making process to create a better fit between the purpose of the product

use and the sensation it generates when interacting with senses. A call will need to be made as to whether matching a certain look and feel found in the marketplace is the best option for success, or whether blazing a different aesthetic trail will be the means for triumph. The key, as always, is to find a tactile aesthetic that excites the consumer and communicates the message of the product.

Selecting Ingredients for a Novel Approach

Based on the observation that highlights the importance of emulsifier selection, an approach to creating appealing topically applied formulations is to have an aesthetic vetting process via designing a series of emulsions using different types of emulsifiers, with the emollient phase concentration and chemistry being constant. Once the field is narrowed based on how closely the particular candidates are to the aesthetic ideal for maximum appeal, an assessment of other factors which may influence the final decision can be performed. These additional factors can include:

- Performance benefits attributes from a particular emulsifier system to the skin
- Ease and familiarity of formulation, scale-up, and manufacturing
- Cost and security of supply
- Compatibility with other formulation components

These factors while of high importance should not drive the product development plan but rather the first milestone should be the selection of emulsification system. Once selected, these factors should be considered as a second tier that allows breaking ties between formulations that are deemed to have identically high potential for maximum aesthetic appeal. This approach is recommended, since compromising aesthetics, which is the priority for consumer appeal, will lead to a product launch that will most likely not withstand the marketplace. Another important factor to consider is to refrain from adhering to one emulsification system only and to base a series of products on it. In the current environment of product diversity and global regulations, counting on specific selection may be risky. A secured way to approach this challenge is in the team's flexibility. A primary system can be selected and a backup emulsification system for development should be tested in conjunction to the original one. If supply, cost, or stability require the emulsification system to be revised, it will not require the team to go back to step one in the product development process. The selected first and second priority emulsification systems should be the top two choices based on the preferred aesthetics. Replacing the emollient system that is responsible for the afterfeel can be the second tier of product improvement. In that sense, the emulsifier is chosen for its contribution to the formulation's appearance, pick-up, and rub-out, as well as the moderate impact on afterfeel aesthetics described earlier. After that, the emollients can be mixed and matched to adjust and fine-tune the afterfeel. In addition, if there is a featured oil-soluble active ingredient or cosmetic functional material to be included, there is the opportunity to select an oil phase that will enhance the delivery to the stratum corneum and improve bio-availability. Knowing that the emollient is but a secondary contributor

to a formula's aesthetics can free the formulation chemist to choose an oil phase for its properties of interaction with the skin.[13]

Real Security

Since in principal an emulsification system is selected for its ability to maintain a coherent and stable formulation, company-based formulation chemists tend to adhere to a specific combination as a safety anchor that ensures stability. By doing so however they may miss creative opportunities to improve the aesthetics of the formulation.

Many skin care companies develop standard emulsion bases to serve as a system of formulative stability. This simplified approach can save time and resources in the development process, because the behavior of the base is known and established. If the same emulsifier is used for every product a company produces, manufacturing of these emulsions is easy; there is no need to re-learn and employ new techniques and methods of manufacture. In addition, purchasing a higher volume of fewer emulsifiers can allow for qualifying multiple suppliers, driving cost down and securing a supply chain. Adhering to standard emulsion systems with well-studied and predicted characteristics and limitations makes the manufacturing operations much easier. With a growing number of finished products for which companies are using the services of outside contract manufacturers for production, straightforward systems are preferred as their production trail and instructions are simple to communicate and implement. Nevertheless, this may be a false approach, since, in the end, it limits creativity in formulation design—and it is the creativity and innovation that yields differentiation and success.

The approach of adopting one prototype formulation may sometimes compromise the will to review new and different chemistries. Alternative systems may require new formulation methods and new production tactics. Often, change is not more difficult, requiring (initially) cognitive adaptation, though it may take time to assume and implement.

As a result of a speed-to-market approach and the need to re-invent every two to three years, development timelines have been shortened and staffing has been reduced, as well. Therefore, the time to explore alternative emulsion systems is almost nonexistent. The times when scientists and formulation chemists were provided with "blue sky brainstorming" is long gone, having been replaced with stressful timelines and demanded deliverables. Once a project brief is issued, formulation chemists can tend to be risk-averse, often for very good reasons, such as additional time required to understand and formulate with alternative emulsion stabilization systems and the risk of unpredictable emulsion stability issues. The understanding that the emulsifier is key to a formulation's elegancy needs to be the driving force for building a portfolio of emulsion alternatives, so that when a challenge arises, requiring a modification, a pool of alternatives is readily available.

Combining Elements of Development

The fragrance and the packaging may have a powerful influence on consumer's perception.[14] The package carries the visual appeal and can be a determining factor to the decision for the initial purchase. In many cases, the visual appeal of the package, along with what is communicated thereon, play a bigger role than advertising and promotion in garnering the first sale of a product. Therein reveals a question: *Should a product be built around the package, or the package around the product?*

Same as with the selection of a fragrance to be used in a product, the development of the package should be conducted very early in the product design process. In the initial consumer experience, and in all subsequent encounters, product and package are intimately tied. The package conveys a means by which its content is expected to deliver. Key parameters to consider in package development would be:

- Visual appearance of the package
- Feel to touch
- Appearance of the formulation in the package once opened to use
- The experience of dispensing from the package

One option by which to initiate product design is to define the purpose of the product, the message that it should convey, and identify the target consumer. When these milestones are clearly documented and agreed upon, the team should move to the evaluation of tactile aesthetic options, deciding upon a vehicle based on feedback from the marketing group and study data from the target market. This preliminary evaluation should be followed by refining the details *with* the emulsion base set; then, packaging and fragrance development can begin in earnest. Often the practice is to begin with stability testing and claims substantiation work before moving to packaging development; however, it is highly recommended to have an idea and direction on the package requirements at the early stages of development. Moreover, since the package material can potentially interact with the emulsion components and since the dose dispensed is highly linked to the design of the container, it is recommended to run the evaluation studies using the finished product container.

Determining the base formulation at the early stages of development followed by package design brings the following key advantages:

- Flexibility with adjustments to the product or the packaging to allow for proper dispensing of the product for greatest consumer appeal
- Testing for physical, chemical, and microbiological stability using the package and therefore eliminating risk factors of unpredicted interaction of package components with the formulation ingredients. This stability work should preferably be done with not only the package but also with the intended labeling. All packaging elements, including the ink used for printing on the label, can be troublesome, notably in products containing sunscreen agents. Again, forestalling issues before they hit the crisis stage is a better way to go.

Going through an initial sensory design process, then moving quickly into package design can be very helpful on many fronts. As with fragrance development, the longer the wait, the greater the risk and the less chance the product has of reaching full market potential (See **Figure 2**.)

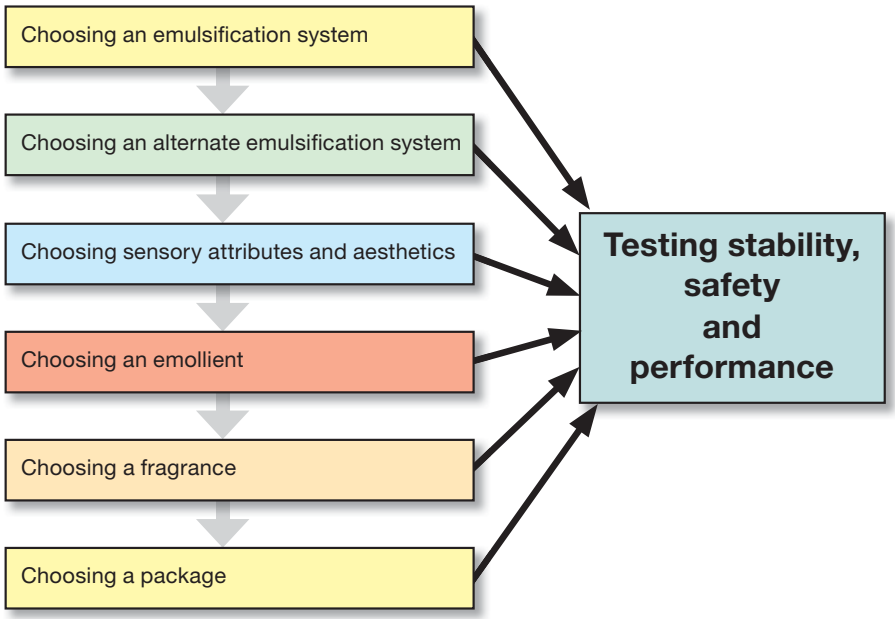

Figure 2. Optimum product development flow chart

Involving Scale-up and Manufacturing

In line with the tactics of orchestrating an aligned approach to product development and encouraging teamwork, manufacturing considerations should be brought into the process of development at an early stage. Why? With regard to scale-up, some variables ordinarily maintained in a laboratory setup are eliminated when production grows larger. In addition, equipment that may be available in production may be absent in the laboratory. Therefore, production specialists can advise as to the most efficient way to produce a formulation, especially if an emulsifier system that is not commonly used within the company is to be employed. They can look at a lab process and be able to advise on the feasibility of large-scale adaptation. If outside contract manufacturing companies are to be involved, this exercise is crucial, because it may determine which manufacturer is chosen. Bringing the manufacturing personnel into the team at the development phase rather than the implementation phase may save time and frustration.

This approach is even more important if a non-standard emulsifier type is to be used and the prediction of the scale-up outcome is not clear. Not only might

different equipment and conditions need to be used, but also completely different processes. These processes may not necessarily be more difficult, but can present challenges because they can often be radically different than normal procedures.

Most manufacturers are attuned to producing emulsions that are stabilized with nonionic emulsifiers for steric stabilization. Steric stabilization is achieved when physical repulsion around emulsion droplets is used in conjunction with osmotic effects. A small amount of anionic emulsifier (often a soap of fatty acid) is used for charge stabilization. Charge stabilization refers to building an ionic double layer around droplets so that they are electrically repulsed. In addition, a few tenths of a percent of hydrocolloid polymer is used for zero shear viscosity—building the thickness of a formulation at rest so that droplets are slowed from moving up, or together, and coalescing. Mixing at high temperature for droplet size reduction and adding waxy compounds to promote the creation of liquid crystalline phases are steps taken to enhance emulsion stability. These are generally produced by heating the water and oil phases to approximately 70°C, with the emulsifiers and waxy materials mixed into the oil phase, and the hydrocolloid into the water phase.

From a theoretical standpoint it would be advantageous to add the water phase to the oil phase under moderately high mixing. The practice of adding water would first create a solubilized system, then a water-in-oil (w/o) emulsion, and finally invert to create a standard oil-in-water (o/w) emulsion with uniform and small particle size. In practice, this exercise is not readily adopted since normally the main bulk of the emulsion is water. As such, since most operations do not have vessels with agitators that are situated low enough in the vessel to provide the crucial mixing energy for the smaller amount of oil and emulsifier phase before the bulk of the water phase is added, most operations are set up to add the oil and emulsifier phase to the water phase under propeller mixing, then have the emulsion go through a high shear homogenization phase when the emulsion has almost cooled to room temperature. An interesting sideline to this process is that had a clever manufacturing person been exposed to the fact that the inversion method, the one first described, is preferred technically, the engineer could have suggested a creative solution with the concept of carrying on the first addition of water until inversion in a smaller vessel, then transferring the emulsion to a larger vessel for the addition of the remainder of the water phase. (This skims the surface; see Kimball's chapter in this book on scale-up for a comprehensive look.)

Another emulsion type that may be desired is a liquid crystal phase stabilized emulsion. Liquid crystals are flat or lamellar phases present in the aqueous phase of the emulsion and partition the oils from the water. The preferred method of manufacturing this type of emulsion is radically different from the production of the standard emulsion described previously. The liquid crystal method begins by heating the water to 7580°C, adding a tenth of a percent of hydrocolloid polymer, and then adding the emulsifier and other wax components into the hot water with moderate mixing until melted and uniform. At this point the heat can be removed, and the liquid

oil phase can be added, even when the emulsion has reached room temperature, with medium propeller agitation. Homogenization is likely not necessary, or may only be needed for a limited time to assist providing the emulsion with additional gloss. If the method used to produce standard emulsions is used, often an emulsion will be created, but it will not be of the same physical consistency and character as intended and batch-to-batch variations will be common. In addition, if the manufacturing operation is in the habit of homogenizing emulsions for extended periods to make up for difficulties earlier in the emulsification process, they might be challenged if requested to create a liquid crystal phase stabilized emulsion. If these emulsions are homogenized for long periods of time, they will separate irreparably because the liquid crystalline matrix is likely to be destroyed.

It is therefore recommended to consider alternative emulsion forms that may provide the desired aesthetic aspects because of perceived manufacturing difficulties or the concern that scale-up will be a resource drain and source of risk for the formulation chemist. The formulation chemist should allow the manufacturing operation or contract manufacturer into the process at the design phase. This is good practice in any situation and can save time and aggravation in the long run.

Time Scale

After a project brief for a new skin care product is initiated, forces need to be summoned to generate a time scale that is linked to expectations. At this point, all the groups that are to be involved in the project should be taught the brief of the project and understand the timing the scope and expectations. The hope is that all develop a clear understanding of the relevance and the rationale of the work. During this introduction phase, the different parties flag real obstacles that will stand in the way of meeting the timing set forth for the project.

Building excitement for the project creates the drive for success. If there is no excitement, then the same effort is taken to erect walls. The thought that the marketing group and formulation chemist should stay together throughout the process, and that manufacturing, packaging, and fragrance professionals should be involved at early stages, might sound like a prescription for disaster. But it needn't be. The project initiation meeting should be run and led by the marketing group. Without leadership that follows a clear path, chaos is likely to be generated. Properly managed, the result can be much better and the timing decreased considerably.

It is crucial to assign a strong project leader with good communication skills. It is best if the project leader is not directly involved in a large portion of the activities. There have been very successful projects run by management trainees, with a more senior manager designated as a sponsor. When necessary, one of the major contributors in a project can be the leader. If the objectives are clearly communicated to the team and everyone is committed to the success of the launch, the project can be run with speed and efficiency. It may not make a difference whether the marketing or research groups lead the effort, but the leading entity must be clearly communicated and

should assume responsibility for project success or failure. The fun part about the skin care industry is that everyone involved in it is a consumer and therefore has a basic understanding of what is to be accomplished and can have an opinion. This can slow the process, but may encourage involvement. Shorter meetings with tight objectives are very important to the acceleration of the process. It should be clear whether the meeting is to update the status of the project, to make a decision or to seek input on a particular issue. With the advent of newer information technology, meetings can happen remotely with excellent success. These should be interspersed with tightly run physical meetings, if possible.

The ideal situation is when the marketing group provides a brief to the formulation group, who then quickly submits back a range of aesthetic options for evaluation by the marketing group. The options can be narrowed down to a few candidates. At this stage, the target audience should be engaged in order to refine the options. In addition, the research group should look at the options to determine whether one has an advantage in terms of efficacy on the skin and with a particular active or functional material. Manufacturing and purchasing groups should evaluate the options, but prime candidates should not be eliminated based on difficulty of manufacturing or cost. In almost every case, the company launching a new product cannot afford *not* to put forth the best option that will excite the customer the most. Too much is at stake and too much will be invested in the launch to skimp or limit options in product design.

Once an option is chosen, preferably with a back-up base, packaging and fragrance development should begin. This can be done while the formulation is being refined and claims work is being performed. Microbial challenge studies to ensure preservation studies efficacy should begin at this time, as well. (For more detailed information about this topic, see Malik's chapter on microbiological stability.) This is the stage when frequent communication is crucial. Working in concert rather than in the traditional linear fashion with the product handed from one group to the next, then often back again, can save considerable time, but if mismanaged can cause confusion. So, many of the aspects can start sooner than normal if an accelerated aesthetic design approach that gets the formulation closer to the ideal sooner is taken. By changing the correct variable, the emulsifier, up front, not only can the resulting formulation be closer to the ideal for the particular marketing brief, the process can be faster with less risk and overall cost.

Summary

The business of formulating topical skin care products is a high stakes one. The market is highly competitive but can be highly profitable. Many resources go into the development and launch of a new product. The key to gaining profitable repeat business in the skin care market is to offer products that have emotional appeal through aesthetics as well as performance. The primary determining variable for engineering the tactile aspects of a topically applied emulsion is the emulsifier choice.

Formulation chemists can help marketing professionals communicate aesthetic needs and desires by offering a wider array of emulsion options up front in the development process from which to choose. By using this information and changing the order in which the development process is sequenced, more aesthetically pleasing topical formulations that resonate with a target audience can be designed and scaled up in a fraction of the normal development cycle time.

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CHAPTER 15

The Use of Fragrance in Topically Applied Formulations

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Key Words

Fragrance, Aroma chemicals, Natural fragrance materials, Terpenes, Solubility parameters, Fragrance translation, Stability, Controlled release, Malodor, Regulations, RIFM, IFRA, Aromascience.

Introduction

Why we use fragrance

Almost every ingredient in a personal care product has a practical function: emulsifier, preservative, emollient, and so on. These compounds all play an essential role in the formulation. Fragrance is a rare exception, as its presence usually serves a purely aesthetic purpose. A fragrance or individual aroma chemical may be added merely to mask an undesirable base odor, but if not for odor-masking, the fragrance added beyond that to a topically applied formulation is intended to provide a valuable sensory identification to the product. Indeed, fragrance may be the most important product attribute at the point of sale. Consumers studying shelves of shampoos in a store are frequently seen sniffing them. No one can wash their hair in the store, but everyone can smell the different brands and make a selection based on odor preference. Fragrance has even been shown to influence consumer evaluation of foaming and cleansing performance, which is entirely a psychological effect.

A number of general references on fragrance technology have been published.[1-9] Additional information is available in industry journals and the trade press (*Perfumer & Flavorist* magazine being a uniquely valuable publication) and in the compendiums created by major fragrance and raw material suppliers. Moreover, books are available on other aspects of the subject, such as the psychological effects of odors, the history of fragrance, or detailed studies of aroma chemicals or essential oils. Guenther[10]

and Arctander[11,12] are the classics in the area of essential oils and aroma chemicals.

From a chemical viewpoint, fragrance is an important ingredient in a product, and it can significantly affect product attributes such as viscosity and stability. Yet far too often fragrance is an afterthought, the last few drops thrown into the base formulation when everything else in the development process is complete. Then, when instability is imparted, it provokes the false idea that the fragrance is the cause of the instability, as though not considering it an integral part of the formulation was not a fundamental oversight. It is important to consider the addition of the fragrance into the process as early as possible. It should be studied for its unique attributes, a blend of chemicals with diverse properties, and a formulation should perform well with the fragrance of choice at its proper use level.

While most of the ingredients used in a base formulation are usually selected by the formulation chemist, often the fragrance and color of the formulation are selected by the marketing department. Therefore, it is necessary to take whatever steps are necessary to prepare the base in such a way as to perform properly with the chosen fragrance. Knowledge of the chemical properties of the individual chemicals in the fragrance composition, often 50 to 100 ingredients, is essential to solve problems when they arise.

Yet a unique challenge exists for the formulation chemist using fragrance. Unlike every other ingredient, the exact composition of a fragrance is confidential,[13] and with rare exceptions the formulation chemist does not know the precise composition of the fragrance blend. The only labeling requirement for the finished product is the single word "fragrance," and there is thus no legal necessity for full disclosure. The best scenario is for the chemist to have an accurate knowledge of the effect individual fragrance materials can have on a product, so problems can be communicated to and rectified by the fragrance supplier. On the reverse side, detailed knowledge of the intended base can enable the fragrance supplier to submit the best possible functional and aesthetic fragrance oil.

Why products may develop unpleasant odor

Semi-solid topical bases may exhibit mildly unpleasant odors that result from the incorporation of surfactants, emulsifiers, and emollient oils. As the bases age, pH shifts and the oxidation of compounds with unsaturated double bonds increases the intensity and olfactory nature of the problem. In an extreme case, like a thioglycolate used in permanent hair wave lotions, the base odor is extremely noxious. For "unfragranced" emulsions, the solution for a masking odor is often the use of a musk-type aroma chemical, such as ethylene brassylate. For thioglycolates it may require a robust masking fragrance such as rose, which can soften the malodor impact and be stable at an extreme pH. In these cases the functionality of the fragrance is more important than any subtleties of the aroma profile.

In addition to intrinsic base odors, personal care products can contain ingredients that degrade over time into odorous components such as proteins, fatty acids and terpenoids. For example, certain lipids can degrade into short chain fatty acids

such as butyric acid, a classic malodor molecule. Only conducting comprehensive stability testing of the perfumed versus the unperfumed base can guarantee the creation of an appealing consumer product.

It is also necessary to test the odor of the formulation while packaged in its final, on-shelf container. Plastic manufacture can leave noticeable solvent odor in its wake, and many fragrance ingredients and solvents can react with plastic. Soft or porous plastic can be severely weakened by some fragrance ingredients or can allow the fragrance to migrate through the package resulting in significant odor loss. Caps and pumps can also cause odor problems. Labels are another component that can be affected by the solvent properties of fragrances. Testing the product in glass as a control is necessary to reveal the effects that derive from the base and fragrance from those derived from other components.

Fragrance creation and duplication

The majority of fragrances are created by trained perfumers to provide a unique and broadly appealing scent to satisfy a clearly defined customer profile. Most perfume companies manage a library of 1000 to 1500 aroma chemicals for the perfumer to draw on. It is necessary for a skilled perfumer to be acquainted with the odor profile of the majority of those ingredients, their rate of evaporation, and their performance and stability in a variety of media in order to successfully create appropriate fragrance compositions.

Other than its olfactive profile, the most important property of any molecule used in a fragrance composition is its volatility. Some materials such as those extracted from citrus fruit evaporate very quickly and are called the "top notes" of the composition. Materials of intermediate volatility such as many florals last for several hours and are called the "middle notes." Extremely tenacious molecules, often of high molecular weight, such as musks and woody and amber notes, create the "bottom note" and are the last materials left as a fragrance evaporates. When sprayed on the skin, the top note might last five or ten minutes, the middle notes an hour, bottom notes many hours, but the exact rate depends on the individual fragrance, the delivery system, and the substrate. A classic description of the fragrance creation process was provided by Jean Carles[14] in the 1960s.

Accords are simple mixes or fragrance materials that combine in a unique way, creating building blocks for more complex mixtures. Carles created fragrances from the bottom up, first making a very tenacious accord to anchor the composition, then adding a middle note accord of moderate volatility, and finally a sparkling top accord of very volatile materials. One the basic structure was in place, Carles would round out and elaborate the creation based on the aesthetic sense of the individual perfumer.

The fragrance triangle (**Figure 1**) is commonly used to show top, middle and bottom notes. When a fragrance is smelled out of the bottle, all the notes are included in the olfactive perception—the triangle is an indication of how the composition will evolve over time. After an hour the top note ingredients will be significantly reduced

if not totally absent. After a few hours the middle notes will vanish. The bottom notes can last for a long time, the exact time varying from fragrance to fragrance.

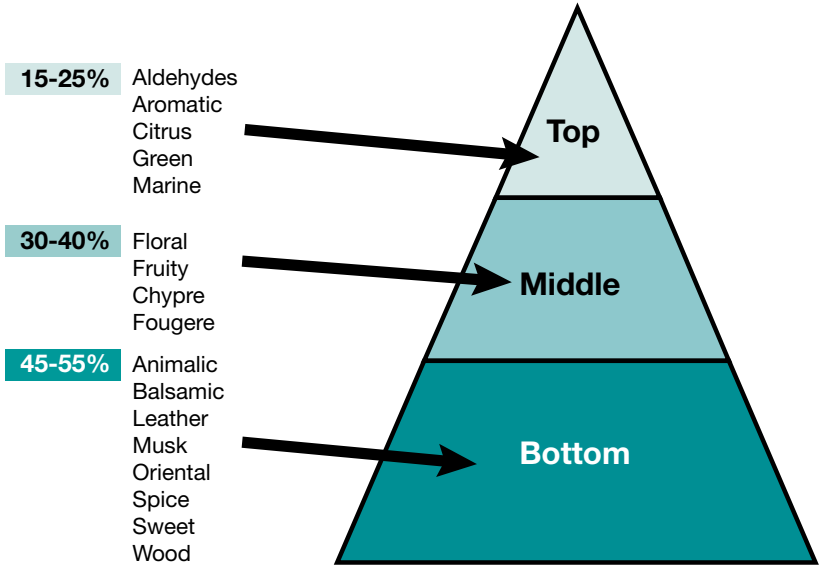


Figure 1. Fragrance triangle

Fragrances were historically created for use in hydroalcoholic systems, mixtures of alcohol and water. Hydroalcoholic fragrances, if successful, are usually translated into functional forms for line extensions such as shampoos or lotions. Now it is common for fragrance creations to be initially constructed for products such as candles or shower gels. It is important for the base to be considered when creating fragrances, as the partitioning of aroma chemicals in different media has a crucial effect on odor formation and perception.

With emerging high technology analytics, product odor duplication has been made much faster, easier, and more reliable. This is often done with laboratory equipment that linked computer software programs. A fragrance is a complex mixture of a large number of chemicals. The gas chromatograph (GC) separates these components by passing the mixture through a column packed with a material which interacts with the components in varying degrees. **Figure 2** shows an example output. The separate portions can then be placed in a mass spectrometer (MS) for the identification of the chemical structure. The GC/MS chromatogram alone is not sufficient in identifying the composition of a fragrance. A database of values of aroma chemicals is required to convert the raw data into the information needed to reconstruct the target oil.

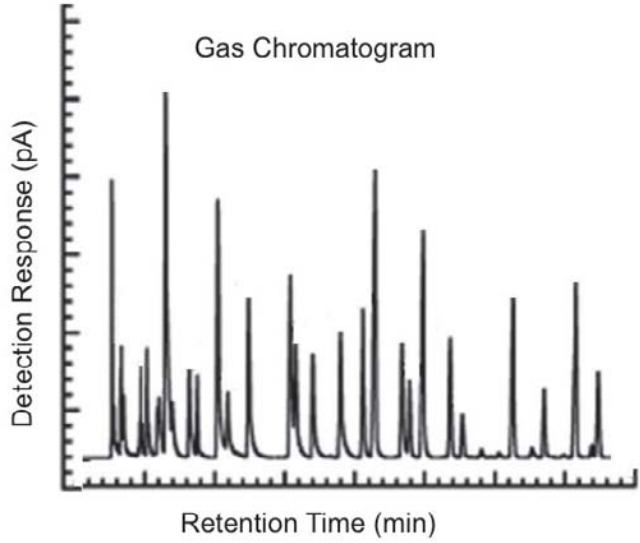


Figure 2. Example output

The vapors over a fragranced object or in the air can be identified by the addition of head space analysis. Solid phase micro-extraction (SPME) is a sophisticated version of this technology. A glass globe is placed over the object being analyzed, and a porous material absorbs the aroma chemicals. The quantity extracted can then be analyzed and is proportional to the concentration in the sample, so the odor can be quantitatively replicated. This has been used by fragrance companies to replicate many odors in the environment, from flowers and exotic woods to the canopy of the Amazon Rain Forest.

Aroma Chemicals

Aroma chemicals first entered the fragrance industry in the 1880s, and a steady stream of newly introduced molecules has since revolutionized the industry. From simple citrus, woody, and floral blends, modern perfumers have created a series of great fragrances from the famous *Chanel No. 5* (Chanel, France 1921) to *Angel* (Thierry Mugler, 1992) based on synthetic compounds that are not available in nature. Most of the essential fragrance ingredients are readily available to the industry, but the large companies that invent new molecules often keep their best new products proprietary. These proprietary compounds and blends that in most cases are protected intellectual property are coined "captives." Captives are developed for the creation of a combination of a distinct odor profile and impart extraordinary strength.

Ideally an aroma molecule is required to exhibit a unique odor profile. Strength is an important factor, since it allows low quantities to impart a strong influence on the finished composition. The molecule must not only perform well in isolation but integrate well within the composition and in finished products. Stability is another

major issue, both chemically with regard to integrity over a wide pH range, and physically with regard to photostability when exposed to UV radiation. Safety is critical, and no molecule without a clean safety profile can ever be commercialized. Environmental issues such as sustainability (if derived from nature and bio-accumulation) have, of late, become important as consumer required qualities for new and existing molecules. Cost is also important, primarily based on the starting materials and the complexity of the synthesis process.

Approximately 3,000 ingredients are currently available for the creation of fragrance compositions, and there is a wide diversity of chemical types represented. If broadly broken down into chemical families they can be classified as: 33% esters, 16% alcohols, 12% ketones, 10% aldehydes, 4% hydrocarbons, 0.3% musks, and 26% a variety of other types. Solvents and solubilizers may be frequently added to the fragrance compositions either to modify solubility properties or to lower costs. In addition to the specific chemicals used, natural extracts consisting of complex mixtures are used in many fragrances, making the total mixture extremely complex.

One example of how knowledge of chemistry can explain the behavior of aroma molecules in cosmetic bases is provided by vanillin. Phenols are very susceptible to reactions with bases such as sodium hydroxide, oxygen, high pH, elevated temperatures, and form highly colored complexes with metals such as iron and copper. The vanillin structure (**Figure 3**) contains a phenol group, and despite the presence of other functional groups on the aromatic ring, exhibits all the stability issues of a phenol. This means vanillin will rapidly discolor soaps and emulsions. The substitution of ethyl vanillin for vanillin can assist but not completely solve this problem.

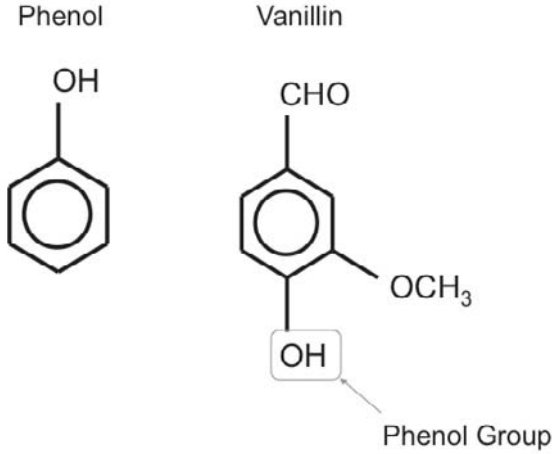


Figure 3. The vanillin structure

Natural Products

Before aroma chemicals were identified and then synthesized, followed by the synthesis of totally new materials, perfumery relied exclusively on naturally derived

compositions. Many parts of plants (and in increasingly rare instances, animals) were used. The earliest use of natural compounds for generating distinct odor involved burning aromatic wood and roots for religious rituals. Later, aromatic oils were concentrated by solvent extraction and distillation, maceration (extraction in warm fats) and enfleurage (extraction in cold fats).

Enfleurage was (and to an extremely limited sense still is) used for the extraction of some very delicate flowers, such as jasmine, tuberose, and violet. The flowers must be hand-picked at precise times; for example, tuberose blossoms just about to open in the early morning. The blossoms are spread on a sheet of glass coated with animal fat where they remain for 48 hours, after which they are removed and replaced with fresh blossoms. This process continues until the end of the flower harvest, at which time the aromatic oil is removed from the fat by alcohol. Vacuum distillation is then used to yield the pure aromatic oil. This procedure is far too labor intensive and expensive to be economically practical except in some very rare instances.

Around 1000 CE, steam distillation enabled the processing of aromatic materials into a concentrated liquid form (**Figure 4**). To date, steam and later solvent distillation are still the major methods applied to the processing of aroma chemicals from natural materials. The plant materials are placed in water and heated, or steam is directly applied. The vapor condenses. The essential oil is separated with yields typically 0.15.0%.

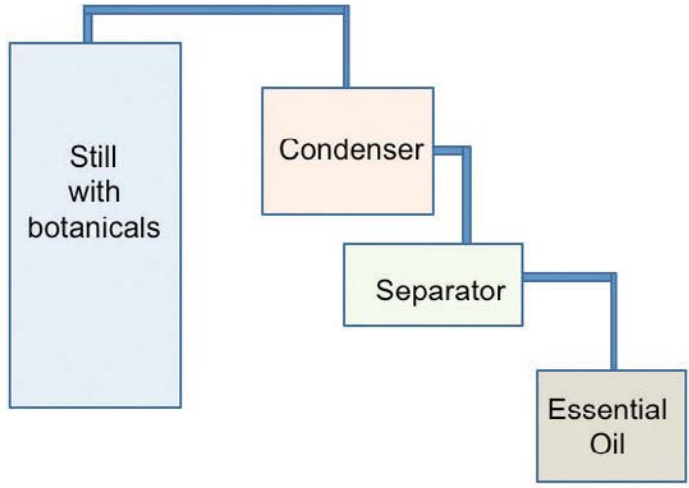


Figure 4. Steam distillation process

Another extraction method, common for citrus products, is expression or cold pressing. It is a mechanical process of squeezing the oil out of the fruit, and is closely related to food processing.

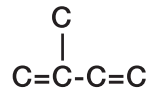
The most sophisticated modern extraction uses supercritical CO_2. This process exhibits the benefits of solvent extraction with no actual solvent use and no exposure to the degrading effects of heat, and therefore creates the finest materials currently

available. CO_2 is easily compressed to a supercritical liquid phase at ambient temperatures. It has lipophilic solvent properties and leaves no solvent residues. Solubility in supercritical liquids changes with temperature and pressure to allow the fine tuning of the extraction. Other solvents can be added for finer solubility adjustment.

Of course, natural products are composed of chemicals. For example, bergamot oil contains 35-40% linalyl acetate. Natural oils require specifications for key chemicals, which are necessary to achieve reasonably reproducible odor when using them. Because of the many variables in the growth and processing of naturally derived compounds, significant deviations between sources are inevitable, but there must be a clearly defined range of agreeable properties such as color, and the levels and nature of major chemical components.

Terpenes: Where Nature and Chemistry Collide

Terpenes are a large family of aroma chemicals whose study unites natural products and synthetic chemistry. They are formed from head to tail polymerization of isoprene, $(C_5H_8)_n$:



They are major components of resin, from which turpentine is produced—indeed, the name terpene derives from turpentine.

There are common names for the basic terpenes:

n	Name	Formula
2	Monoterpene	$C_{10}H_{16}$
3	Sesquiterpene	$C_{15}H_{24}$
4	Diterpene	$C_{20}H_{32}$
6	Triterpene	$C_{30}H_{48}$
8	Tetraterpene	$C_{40}H_{64}$

There are acyclic, monocyclic and bicyclic versions (**Figure 5**). Double bonds shift position easily, and in addition to the basic hydrocarbon backbones, oxidation products and alcohols are common, so a large family of molecules is created. The entire family is sometimes called the terpenoids. The historic nature of the nomenclature has led to terpenes and terpenoids being used interchangeably

Since molecules must be relatively small to be volatile, the low molecular weight terpenes have the highest potential to generate odor. Thus the monoterpenoids are the class that is used most frequently in perfumery, although larger molecules often contribute to the odor profiles as well.

On a negative note, some terpenes can cause problems. Limonene has very little

odor and makes up a large share of many citrus oils, 95% in the case of orange oil. Removing the limonene makes a much stronger concentrate. These are called "folded oils," starting with ten drums of orange oil and removing nine drums of limonene results in a "10X" oil. Also, limonene is safe as is, but easily oxidizes into harmful byproducts and thus must be used in combination with an antioxidant to ensure the integrity of the product.

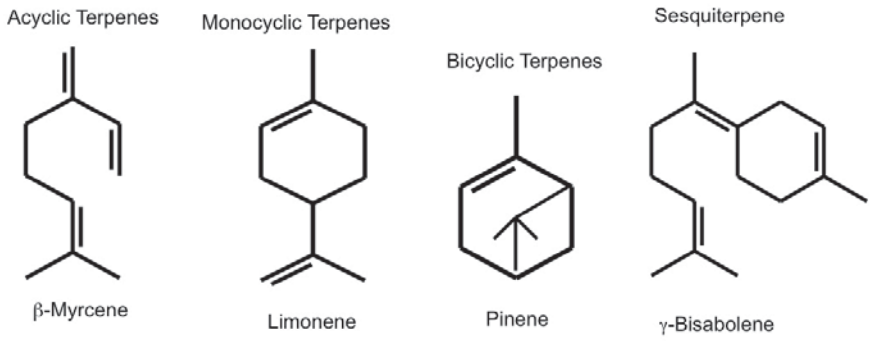


Figure 5. Terpene structures

Natural and Organic Fragrances

The pervasive use of synthetic chemicals in modern perfumery has opened the door for a countermovement, the promotion of natural and organic fragrances. The exact definition of *natural* is hazy, as some type of manipulation is necessary to make almost every product useable in a fragrance composition. For more detailed information on the definition of *natural* and *organic* in skin care products refer to the appropriate chapter in the book edited by Dayan and Kromidas.[15] Animal derived products have been almost entirely eliminated from the industry due to avocation of animal rights by activists groups and the fear from animal transmitted diseases such as Mad Cow Disease. Thus natural compounds can be essentially defined as products derived from plants via extraction, expression, or distillation without intentional chemical reaction or modification. Solvents have traditionally been used in many processes, but some regulatory groups limit their use exclusively to heat and water to allow maintaining their natural properties.

An interesting issue arises in the difference between the definitions of *natural* and *nature identical*. For example, phenyl ethyl alcohol exists in rose oil. It can also be synthesized. It is impossible to distinguish by chemical analysis between the naturally extracted and synthetic molecules, and the synthetic compound can be added to a naturally derived rose oil to "extend it." This creates a soft interface between natural and synthetic materials. Of course, it only exists with materials that can be found in nature, so it is possible to easily identify a material which can only be sourced synthetically as not derived from nature. Recent technology

utilizing isotopes identification has made it possible to identify the source of some compounds, but this is not in common use.

Creating fragrances exclusively with natural materials may pose challenges. They tend to be more expensive and despite the common perception linking "natural" with "safe", these may often cause skin irritation and sensitization reactions. In addition, the components of many natural products are prone to oxidation and decomposition as they frequently discolor and change odor. In addition to technical drawbacks, on the creative side being deprived of synthetics severely restricts the perfumer's palette.

To be certified as organic, a composition must comply with specific regulatory guidelines and create a precise paper trail. Organic certification is a legal process in the United States, created and monitored for food products by the United States Department of Agriculture (USDA) that was extended, rather uncomfortably, to personal care products and fragrances. Creating a formulation based exclusively or mainly on organic products is difficult; the availability of organic surfactants is limited, not to mention organic emulsifiers and preservatives. An organic fragrance is restricted to natural product compositions that are certified, which further reduces the raw material palette, elevates the price significantly, and can create raw material shortages.

There will always be an important niche market for natural and organic fragrances, but restrictions on creativity, the generation of high costs, and limited and uncertain supplies of raw ingredients will most likely not allow these forms of fragrance to become a major share of the overall market.

Hydroalcoholics

The simplest technical application of fragrance is by incorporation into a hydroalcoholic system, a simple mix of primarily ethanol and water. This form is often referred to simply as "perfume." Different names are loosely applied to hydroalcoholics based on fragrance level: Perfume (parfum), eau de parfum, cologne, toilet water, and aftershave being the most common. **Figure 6** shows some typical formulas.

Hydroalcoholic Compositions			
	Perfume	**Cologne**	**Aftershave**
Alcohol SDA 40 190 proof	80.0	80.0	65.0
Water	----	12.0	32.0
Propylene Glycol or Glycerin	----	----	2.0
Perfume Oil	20.0	8.00	1.0

Figure 6. Hydroalcoholic compositions

Specially Denatured Alcohol (SDA) is used, which is poisoned to eliminate the need to pay the customary taxes on alcoholic beverages. Example formulas of alcohol used in hydroalcoholics:

- SDA 39C: To every 100 gallons of alcohol add one gallon of diethyl phthalate
- SDA 40: To every 100 gallons of alcohol add one and one-half avoirdupois ounces of brucine or brucine sulfate or quassin; or one and one-half avoirdupois ounces of any combination of two or three of these denaturants and 1/8 gallon of tert-butyl alcohol
- SDA 40B: To every 100 gallons of alcohol add 1/16 avoirdupois ounce of denatonium benzoate (Bitrex) and 1/8 gallon of tert-butyl alcohol.

190 proof (95% alcohol by volume—actually 95.6% alcohol, 4.4% water) is used because it is the least expensive version, being the azeotrope (lowest boiling mixture) of alcohol and water. To produce an anhydrous alcohol, additional distillation is required and this added step in processing will add to the final cost.

High fragrance oil concentrations would cloud if more water were present, but as the fragrance level drops, increasing amounts of water can be added. Water not only lowers the cost but has the aesthetic advantage of reducing the biting solvent effect of alcohol. Aftershaves not only have a low fragrance level and thus a large percentage of water, but as functional products often include a humectant to improve afterfeel.

The solution must be aged, chilled, and filtered to ensure clarity over time. This is because waxes and resins in essential oils may not be alcohol-soluble. Color, if required in the finished product, must be added after filtering. The addition of UV stabilizers is often required.

The Importance of Weak Forces

To explore the fate of fragrance compounds as they are incorporated into a more complex media like surfactant and emulsion systems, it is useful to explore the consequences of weak chemical forces. Chemistry is usually concerned with the strong forces created by covalent or polar bonds. Solubility depends on weak forces often loosely described as van der Waals forces. Some other weak intermolecular forces are the London Dispersion, Keesom, and Debye forces. In elementary chemistry, we learn that compounds can be either water-soluble (hydrophilic) or oil-soluble (lipophilic), polar or nonpolar. It is useful to refine polarity on graduated scales, examples being kow, P, Clog P, or solubility parameters, both Hildebrand and Hanson versions.

The partition coefficient, P, is defined as the ratio of concentrations of a compound in a mixture of two immiscible phases at equilibrium. The immiscible phases are often two liquids. A special case that is universally recognized to evaluate the nature of a molecule is the water-octanol partition coefficient Ko/w. In this instance the material is placed in a tube containing water and oil (standardized as octanol) and shaken. Depending on its nature, some of the material will part into the water phase and some into the oil phase, and the ratio between these two concentrations is defined as Ko/w. Partition coefficients are more linear when the logarithm is used (logP), and computer programs can be used to estimate this value. The result

is ClogP, the calculated logarithm of the water-octanol partition coefficient. Many aroma chemical compendiums and data sheets provide the Clog P, and fragrance manufacturing companies use this parameter during internal product development to optimize performance in the end use. Examination of the primary P&G patent[16] for *Febreze* show a heavy reliance on Clog P to identify preferred fragrance attributes.

Solubility parameters were introduced by Hildebrand, whose key value is the square root of the cohesive energy density, which in turn is equal to the heat of vaporization divided by molar volume:

$$\delta = \sqrt{\frac{\Delta H_v - RT}{V_m}}$$

This was later refined by Hanson using a three-dimensional space utilizing the dispersion bonds, the energy from dipolar intermolecular force between molecules, and hydrogen bonds. The closer two molecules are in this space, the more miscible they will be, where:

$$\text{Distance}^2 = 4(\delta_{D2}-\delta_{D1})^2 + (\delta_{P2}-\delta_{P1})^2 + (\delta_{H2}-\delta_{H1})^2$$

Software has been developed,17 HSPiP (Hanson Solubility Parameters in Practice), to evaluate compatibilities in complex mixtures utilizing large chemical databases, including extensive data on aroma chemicals.

Figure 7 shows two molecules in the Hanson space. **Table 1** has solubility parameters of some common fragrance materials interspersed with some ubiquitous personal care formulation ingredients. It is clear that fragrance molecules range from very non-polar to moderately polar.

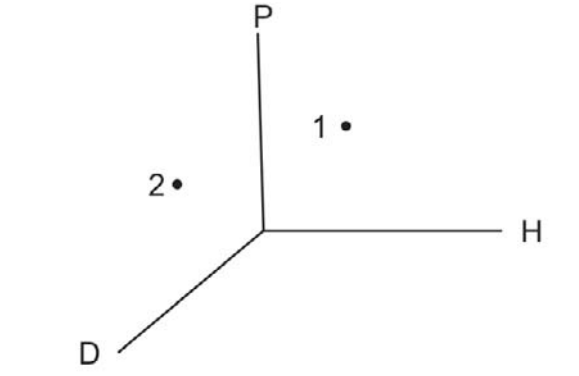


Figure 7. Hanson space

Table 1. HSP of some common aroma chemicals and cosmetic ingredients

White mineral oil	14
Stearic acid	15.86
β-pinene	16.43
Amyl acetate	17.27
Citronellal	18.07
Stearyl alcohol	18.21
Citral	19.12
Linalool	19.68
Amyl alcohol	22.18
Benzaldehyde	22.51
Eugenol	22.75
Dipropylene glycol	24.05
Phenylethyl alcohol	24.08
Benzyl alcohol	25.14
Vanillin	25.20
Propylene glycol	30.70
Water	48

Emulsion Systems

It is natural to perceive a bottled fragrance as a uniform material with a single property. The reality, however, is that fragrance is a complex mixture of chemicals. One important property of fragrance blends is the diversity of chemistry in the molecules used. One composition can contain hydrocarbons, alcohols, aldehydes and ketones, heterocyclics, nitriles, and more. The presence of different chemistries elevates the odds for the fragrance to react with skin care bases to impart instability issues such as in color and viscosity shifts, changes in odors, and reactions with packaging material. Only by understanding the potential interaction of each component with its environment can the effects of fragrance mixtures be fully understood, and solutions found to problems in a rational manner. When a fragrance compound is incorporated into an emulsion system, a variety of processes can occur. An emulsion being a non-continuous system that has water, oil, and interface compartments consists of different regions wherein individual fragrance materials can partition based on their chemical and physical properties. In a classic o/w emulsion that would include the external phase, usually water, and an internal phase, usually oil-based, and the interface between these two phases. This interphase is the layer of emulsifier coating the oil phase droplets, or, if in access, will create micelles in the bulk of the emulsion. The external phase usually contains areas of liquid crystal structures, often loosely organized regions of fatty acids. Considering the emulsion as such that is composed of different phases, one can distinguish between highly nonpolar areas in the micelles, surface active films, and a highly polar area as the external phase, and the air at the product- environment interface.

The fragrance is composed of molecules typically spanning the entire range from nonpolar to moderately polar, causing the fragrance mix to separate and migrate into different phases of the emulsion. Considering the solubility parameter and ClogP of each component, the formulation chemist can hypothesize which areas of the

emulsion the component will tend to migrate next. Very lipophilic materials such as pinene will concentrate in the interior of the micelles of an o/w emulsion, while relatively polar materials such as vanillin and phenylethyl alcohol will partition into the external phases This will change the balance of fragrance components in the air above the emulsion, consequently changing the fragrance character compared to the fragrance out of its bottle.

Another process of significant consideration occurs when the emulsion is applied to the skin. By applying external shear, the emulsion breaks, especially if it is an ionic system susceptible to salt—and the water and other volatiles will evaporate quickly. What is left on the skin after application is the oil phase, most of the fragrance, and the emulsifiers. This will re-emulsify the fragrance, retarding its evaporation and thus muting its character and impact. Many fragrance materials can discolor an emulsion system. The compounds indole and vanillin are classic examples, and pH plays an important role in their stability profiles. High levels of fragrance can break an emulsion. Therefore, it is important to conduct a full battery of stability tests including elevated temperatures, freeze-thaw, and UV radiation exposure comparing unfragranced to fragranced samples to ensure product integrity.

There is a systematic approach to counteract the effect of any substrate or carrier base on perfume quality. If the fragrance formula is known, and the headspace over the fragrance oil and over the perfumed base is analyzed, a ratio between the two headspaces can be used to reformulate in such a way that the modified fragrance in the headspace over the base will be the same as the headspace over the fragrance oil.

Figure 8, based on the work of Saunders,[18] show the effect of the substrate on the headspace of five aroma chemicals. Column A represents the headspace over the pure oil, and column B represents the headspace over the fragranced product. Column C is A:B, and column D is the original formula. Column E is a new formula using the ratio of A to B to rebalance so the original fragrance quality is maintained in the new substrate.

Place a fragrance mixture in a base or on a substrate. Analyze the compositon of the headspace.

a = headspace of fragrance
b = headspace over fragranced base or substrate
c = a/b
d = original fragrance formula
e = adjusted fragrance formula

	a	b	c	d	e
Limonene	31.9	15.9	2.0	2.0	4.0
Linalool	13.2	12.9	1.0	2.0	2.0
Linalyl acetate	12.3	7.7	1.6	2.0	3.3
PEA	6.2	22.6	0.3	3.5	1.1
Benzyl acetate	11.6	18.7	0.6	2.1	1.3

Figure 8. Substrate effect on aroma chemical headspace (5 ex.)[8]

Surfactant Systems

Surfactant systems such as shampoos and body washes pose yet another area for fragrance migration and interaction. This can cause significant changes in viscosity. Surfactant systems form micelles where the external liquid is water, the polar heads face the water, and the nonpolar tails face inward. The size and shape of the micelle structures is a decisive parameter for determining viscosity. The larger the micelle, the greater the resultant resistance to flow will result. If the fragrance partitions in such a way that these structures expand, the viscosity will increase (**Figure 9**). If the fragrance breaks these structures into smaller units, the viscosity will decrease. Thus it is possible for the addition of fragrance to either increase or decrease viscosity.

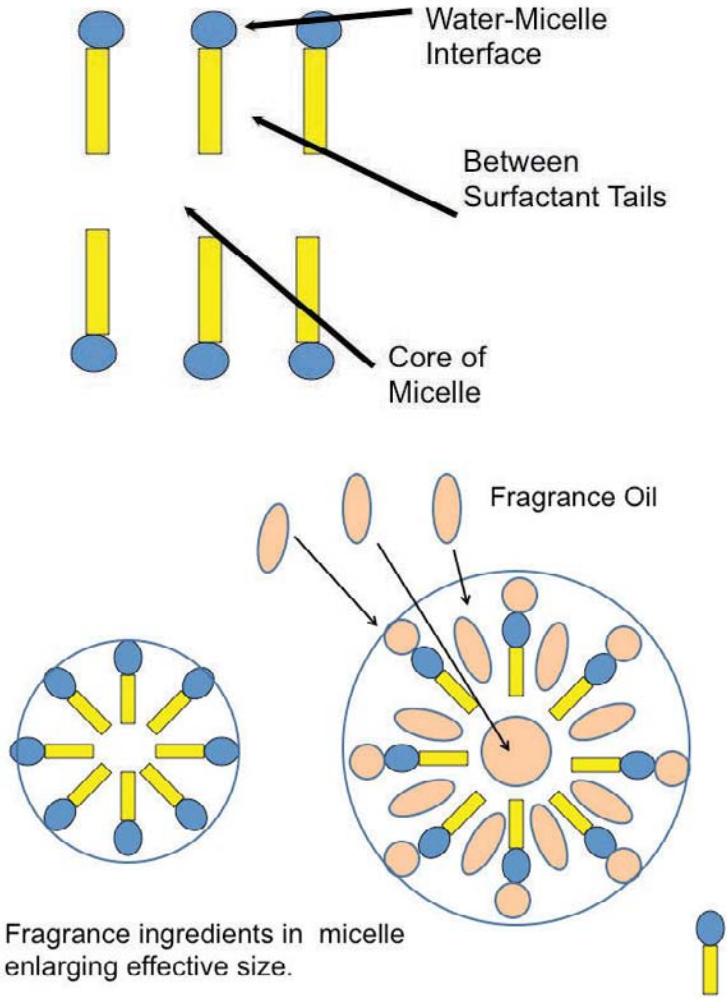


Figure 9. Fragrance effects on micelles

Surfactant system viscosity can be adjusted by the judicious selection of surface active materials. Many formulations can build viscosity with the addition of salt, which is a less expensive approach. Fragrance is easily solubilized by surfactants, but a low active formula with a high level of salt may become hazy when fragrance is added. In these cases, fragrances mixed with nonionic surfactants such as polysorbates may be needed to achieve clarity.

In addition, many surfactant systems such as bath gels are colored, creating light stability problems when fragrances are present. Cosmetic colors contain molecules that are chromophores; structures which emit light in the visible spectra thereby become visible colors. Examples of chromophores parts are conjugated double bonds and the azo group. A standard stability test involves exposure to UV light. Some aroma chemicals, such as benzaldehyde, create free radicals when exposed to UV (**Figure 10**). In the free radical state they can react with the color generating structures and cause pronounced discoloration.

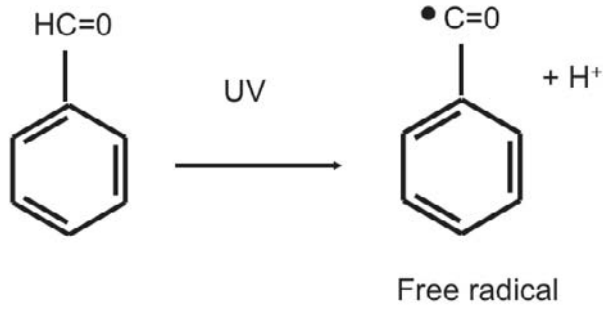


Figure 10. Benzaldehyde + UV

Hostile Environments

Many aroma chemicals are not stable in extreme environments such as high and low pH formulations. An example of a common aroma family with limited stability is esters, which readily hydrolyze at high and low pH. Since esters are the largest single family of aroma chemicals, this is a significant restriction on creativity. Many fruity notes are esters, and the hydrolysis of these molecules can result in a carboxylic acid with a distinctly rancid odor. Basic environments can similarly affect the stability of aroma chemicals, although the high pH will convert foul-smelling short fatty acids into salts, lessening their unpleasant impact.

Reactions of aroma chemicals with the functional base can also cause a pH shift in the total product that may put it above or below the acceptable specified range. This also creates an indication of product stability; monitoring the pH of fragranced samples will indicate a problem if a noticeable pH shift is observed.

Certain product types have clearly delineated fragrance challenges; soap, antiperspirants, hair dyes, depilatories, and alpha hydroxy acid containing creams are obvious examples. Ingredients such as proteins and quaternary salts can also

cause problems. While one can attempt to theoretically predict aroma ingredients that may or may not perform in these systems, none is more reliable than a raw material study.

A useful raw material study would start with a library of materials a perfumer would commonly use to create an aesthetically pleasing and stable product. Each material is tested separately in the base, and they are evaluated for color and odor changes as well as physical changes to the base formulation. A creation is then made with the materials that successfully passed all test criteria. It is very likely that a fragrance so constructed will have superior odor coverage and excellent stability.

Controlled Release

One way to protect sensitive ingredients or alternatively to provide a different rate of use is controlled delivery, typically but not always utilizing some form of encapsulation. The history of encapsulation started in 1927 when capsules were spray-dried with an oil-gum acacia coating. In 1955 the National Cash Register Company received a patent for encapsulation, using the technology to make carbon paper. The first major fragrance use was the "scratch and sniff" sampling of *Giorgio* fragrance in 1983, and this form of sampling has been a staple of the fragrance industry ever since.

Controlled release can provide fragrance when and where it is needed. It can also counteract loss of intensity during use. A practical use of encapsulation is to protect a fragrance chemical from a hostile environment. Common triggers of release are water, heat, or pH. Mechanical action can also function as a release mechanism, as in the "scratch and sniff" sampling system.

While controlled release has been around for many years, the contemporary formulation chemist may be using nanotechnology, where the first generation technologies such as liposomes are being replaced by newer structures such as solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC). Nanosized particles which have a shell and an interior space that can be used to load perfume are called nanocapsules. Polymers have been widely used to create nanocapsules which are then functionalized for various applications. The payload can be released by an external trigger or changes in the environment. Application of nano-encapsulation in fragrance products enables more efficient, prolonged, and time-controlled release of the scent. Materials can be engineered to be stable in aqueous solution, nontoxic, and biodegradable.

Malodor

Malodor control would seem outside the realm of fragrance applications and beyond the frequent use of fragrance materials as masking agents. But since fragrances and malodors are both essentially smells, fragrance companies are frequently called upon to provide remediation solutions to body generated odor problems.

Malodor chemistry is fundamentally different from most fragrance chemistry. Malodor molecules frequently contain nitrogen or sulfur. Sulfur imparts a skunk-like excretion as its distinctive aroma, and nitrogen creates the smell of a rotten egg or cigarette smoke.

Osmophores are functional groups often linked to odor, some common ones being:

CHO	Aldehydes
CH_2OH	Carbinols
C=O	Carbonyls
COOH	Carboxyls
OH	Hydroxyl compounds
SH	Sulphydryls

The replacement of oxygen by sulfur can convert an odorless molecule to a malodor.

Non-odorous compounds	
H_2O	Water
H_2O_2	Hydrogen Peroxide
CO_2	Carbon Dioxide
Become the malodors	
H_2S	Hydrogen Sulfide
H_2S_2	Hydrogen Persulfide
CS_2	Hydrogen Disulfide

To some extent all fragrances may assist in masking malodor, but some materials are much more effective than others. Aldehydes, orange oil, minty, fruity, and green notes are often useful. An example is IFF patent 5,683,979,[19] which indicates a combination of 260% musk, 3070% citrus, and 120% mint. An example of a fragrance specifically marketed for malodor control is Neutroleum, a sketch of which is shown in **Figure 11**.

Fragrance companies have also designed non-aroma chemicals targeting malodor. An example is Veilex, patented in 1980 by Bush Boake Allen (now part of IFF), the structure of which is shown in **Figure 12**.

Another patented approach from Robertet (patent no: 5,795,566[20]) specifies a blend of two aldehydes coming from specific lists as the active component. This was extended in patent no: 8,124,114[21] to "A malodor counteractant composition comprising beads of a water absorbent polymer and an aroma chemical comprising at least two aldehydes."

Perhaps the two most pervasive materials used in malodor products are zinc

ricinoleate (**Figure 13**) and cyclodextrin (**Figure 14**). They both capture malodor molecules but use very different mechanisms.

Neutroleum Type Fragrance	
Coumarin	2.30
Terpinyl Acetate	0.30
Clove Leaf Oil	4.65
Iso Bornyl Acetate	4.15
Anethole	1.55
Linalool	5.80
Eucalyptus 70/74	2.35
Benzaldehyde	0.10
Amyl Acetate	9.40
Cinnamic Aldehyde	11.15
Terpineol	13.50
Methyl Salicylate	18.15
Orange Oil Florida	24.30
	100.00

Figure 11. Neutroleum type fragrance

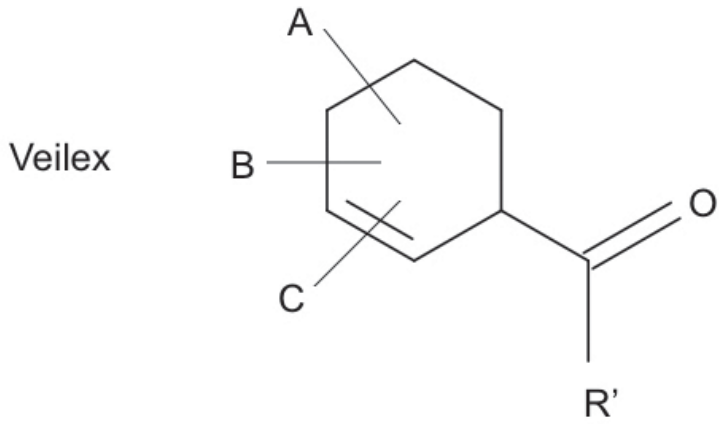


Figure 12. Veilex

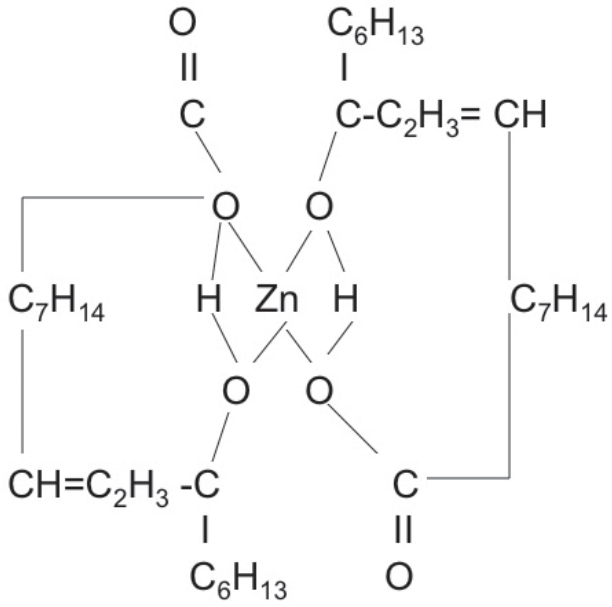
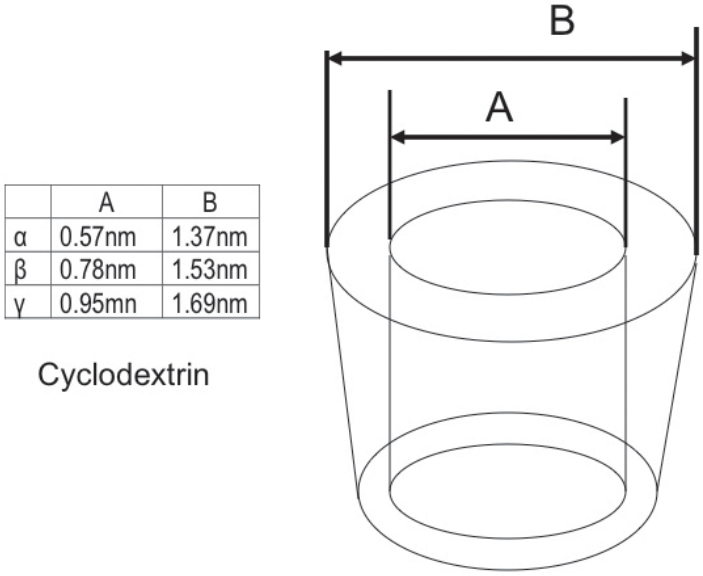


Figure 13. Zinc Ricinoleate



	A	B
α	0.57nm	1.37nm
β	0.78nm	1.53nm
γ	0.95mn	1.69nm

Figure 14. Cyclodestrin

Zinc binds very strongly to nitrogen and sulfur, both characteristically found in malodor molecules. The ricinoleic chains sometimes cover the zinc, and other times expose it. When exposed, a malodor molecule can bind to the zinc, and the chains

fold around it to totally encapsulate it. Since ricinoleic acid comes from castor oil, this material has been positioned as *natural*.

Cyclodextrin comes in three different forms (alpha, beta, gamma) and is shaped like a truncated cone. Cyclodextrin is relatively polar on the outside and nonpolar on the inside, so it can capture aroma chemicals or malodor molecules in its interior and be compatible with water-based delivery systems. This material is used extensively in P&G's *Febreze* line and is covered by many patents, such as 5,783,544.[22] In addition to cyclodextrin as an active material, this patent also specifies a preferred Clog P of three or less for fragrances, implying hydrophilic behavior, with the preferred embodiment using 75% or more of these materials.

Regulatory Essentials

Over the past two decades there has been steadily increasing global emphasis on safety and regulatory issues. There is a general notion in the Western world that chronic cumulative exposure of the human body and earth generates long-term and even second-generation toxicity and is affecting our health and quality of life. Regulatory bodies are therefore following these concerns by developing requirements for the industry to follow. It is not an exaggeration to say that from a practical perspective, safety and regulatory compliance is the single most important requirement for a fragrance. Even for industry professionals not directly responsible for regulatory affairs, a basic knowledge of the field is essential for formulating an acceptable consumer product.

Since 1966, with the creation of the Research Institute of Fragrance Materials (RIFM), the industry has aspired to self-regulation. There had been national trade groups before then: in the United States the first organization was the Essential Oil Association (EOA), renamed the Fragrance Materials Association (FMA), and renamed yet again IFRANA (the North American component of the International Fragrance Association (IFRA), which unites all the national trade organizations and transforms the data generated by RIFM into industry guidelines for the safe use of fragrance.

RIFM's mission hinges on the science of fragrance safety and through the intermediary role of REXPAN, RIFM's Expert Panel, publishes its results in peer review journals. RIFM divided its scientific endeavors into four key areas: risk assessment, Quantitative Risk Assessment (QRA, essentially the evaluation of skin safety), respiratory effects, and environmental impact. The key technical pillars of RIFM science are risk assessment, skin safety, respiratory safety, and environmental impact. Each of these areas is covered by a guidance document.[23-26] Since more than 3,000 chemicals are used by the fragrance industry, and the science of safety keeps evolving, a systematic approach is needed to ensure the best possible safety data and regulatory compliance.

In keeping with the need to continually refine its approach to safety, RIFM will release a new master guidance document in 2013 tentatively known as *Criteria 2*

combining all the components of RIFM's program into a unified process. RIFM's refined approach to safety will evaluate data coming from various approaches, human, animal, *in vitro*, and *in silico*. Also being considered is using the concept of Threshold of Toxicological Concern (TTC), and the validity of the widely accepted uncertainty factor of 100 is appropriate. Risk assessment assigns three numbers to a material, one based on structural alerts, one to volume of use, and one to dermal exposure. Structural alerts are found by looking at the molecular structure and identifying groups known to be in problematic materials. Materials with higher total number numbers merit further scrutiny, although a high number alone does not imply a material is harmful. The assessment is a guide to assigning resources to further test those materials most likely to exhibit safety issues.

The safety of fragrance on the skin has been a critical issue since the beginning of RIFM, and the approach to this area has continually evolved. Categorization was once divided between leave-on and rinse-off products on skin, and non-skin exposure products such as candles. But exposure is more complicated, and RIFM adopted 11 categories of use, each with different exposure levels (**Table 2**).

Table 2. IFRA Categories for Fragrance Use

Category 1	Lip Products, Toys, Insect Repellents
Category 2	Deodorants/Antiperspirants
Category 3	Hydroalcoholic Products for Shaved Skin, Eye Products, Men's Facial Creams & Balms, Tampons
Category 4	Hydroalcoholic Products for Unshaved Skin Hair Styling Aids & Sprays, Body Creams
Category 5	Women's Facial Cream/Facial Makeup, Hand Cream, Facial Masks, Wipes/Refreshing Tissue for Hands, Face, Neck, Body
Category 6	Mouthwash, Toothpaste
Category 7	Intimate Wipes, Baby Wipes
Category 8	Makeup remover, Hair Styling Aids (Non-spray), Nail Care
Category 9	Shampoo, Rinse-off Conditioners, Bar Soap, Feminine Hygiene Pads and liners
Category 10	Detergents, hard Surface Cleaners, Diapers
Category 11	All Non-skin or Incidental skin contact products

Skin safety is now guided by Quantitative Risk Assessment (QRA), and what looks like an algebraic equation:

$$\text{Acceptable Exposure Level (AEL)} = \frac{\text{WoE NESIL}}{\text{SAF}}$$

Where:

NESIL = No-Expected-Sensitization Induction Level
WoE = Weight of Evidence
SAF = Sensitization Assessment Factor

WoE of NESIL is essentially the conclusion of the Expert Panel regarding the level of a fragrance material that can be applied to skin with no sensitization induced. The SAF, usually but not always 100, is an additional factor routinely applied by toxicologists to give an extra level of assurance to the assessment. All available data available regarding the safety of a material is considered by the Expert Panel in reaching its conclusions.

Environmental safety can also be estimated by using a simple formula as guidance:

$$\frac{\text{PEC}}{\text{PNEC}} < 1$$

Where:

PEC = Predicted Environmental Concentration
PNEC = Predicted No-effect Concentration

This implies, quite reasonably that if a material is present in the environment at a lower level than that which has no effect, it is safe. Of course there is a more complicated process required to calculate the PNEC which RIFM has placed in a spreadsheet taking into account all the pertinent data for an individual material.

Respiratory safety has necessitated the creation of new methods and has not yet reached a stage where guidance is available. Testing to date has revealed no instances where fragrance has contributed negatively to respiratory organ safety. Models have been made available by RIFM to calculate exposure from fragrances in an indoor environment for a limited number of aroma chemicals.

IFRA translates the raw scientific date of RIFM into guidelines that impose quantitative limits on certain ingredients based on their concentration in products with different end uses; the guidelines are amended bi-yearly as additional data becomes available. All IFRA fragrance material restrictions are publicly available on its website, along with many other documents relating to the safe use of fragrance. The European Union has an important regulation involving labeling, which identifies 26 allergens which, though not banned or quantitatively limited, if present at significant levels must appear on the ingredient list on the package label (**Table 3**). A proposal to significantly expand this list and add selective quantitative limits is currently being debated.

Table 3. EU Allergens

Amylcinnamyl alcohol	Anisyl alcohol
Amyl cinnamal	Benzyl benzoate
Benzyl alcohol	Benzyl cinnamate
Benzyl salicylate	Citronellol
Cinnamyl alcohol	Farnesol
Cinnamyl	Hexylcinnamaldehyde
Citral	Lilial
Coumarin	D-Limonene
Eugenol	Methyl heptine carbonate
Geraniol	g-Methylionone
Hydroxycitronellal	Oak Moss
Hydroxymethylpentyl cyclohexenecarboxaldehyde	Tree Moss
Isoeugenol	

Aromascience

While developing topically applied formulations that contain fragrance poses a variety of challenges (as previously described in this chapter), one cannot ignore the mere fact that human response to odor presents an arc of emotional responses and is anchored to the fundamental perceptions, such as the link between a mother and her baby. The study of aromascience introduces the entry into an ethereal realm. Aromascience deals with the temporary effects of smell on our emotions, behavior, and physical performance. It is a real science with measurable consequences, and the scientific foundation for the emotional power of scent. Some of the most common aromascience effects concern odors that are stimulating or calming, enhance physical or mental performance, promote lingering in a space, or encourage appetite stimulation or suppression.

A related subject, aromatherapy, is often confused with aromascience, though the two have much in common. Aromatherapy is shaped by culture and therefore acquires different forms in different countries. It has different implications in France or England than in the United States. A key departure from aromascience is that aromatherapy commonly uses massage to help essential oils penetrate the skin and enter the circulatory system, a means of delivery from which the fragrance industry has chosen to distance itself.

There is scientific basis for aromascience—the direct connection of the olfactory bulb to the limbic system. In McLean's concept of the triune brain, as the human brain evolves, layers of different fundamental nature develop. A parallel process of evolution occurs as each individual human fetus develops in the womb, summarized in the phrase "ontogeny recapitulates phylogeny."[28] The Reptilian Cortex is the earliest part of the brain to evolve. It controls many essential physical functions such as breathing and heartbeat, and certain basic reactions such as fear. Next in development comes the limbic system, which is the seat of emotions and behavioral characteristics including sexual desire and playfulness. The last layer to evolve is the neocortex, where logical thought resides. Alone among the senses, the olfactory system leads directly to the limbic system. This is the essential physiological foundation for the emotive powers of aromas, and the keystone of aromascience. Common fragrance ingredients can trigger and impart an aromascience effect, a typical example being the stimulating effect of lemon. These ingredients can be used singly, as a blend of natural oils, or in a conventional fragrance composition. There is no solid scientific basis to the idea that natural products have more efficacy than synthetics. One common rule is that for a blend to be effective, the aroma must be pleasant to the subject. If the subject does not like the smell it is far less likely to stimulate an emotional or physiological response.

Another effect frequently encountered is fragrancing spaces such as retail stores, supermarkets, shopping malls, and casinos, in order to subtly influence behavior. Here, passive air fresheners are possible, but metered sprays are more effective. Every location from the slot machines in a casino to the outside of a burger restaurant has used the subliminal power of fragrance to drawn the attention of customers.

Requests are occasionally made to incorporate pheromones in fragrances or for fragrances to exhibit pheromonal characteristics. Technical support is often asked for an assessment of the effects of pheromones, most typically implying an element of sexual allure. For humans, pheromones are highly unlikely to affect behavior, while it works quite well for fruit flies. The human pheromone receptor, the VNO (Vvolmeronasal organ or Jacobson's organ) is almost universally considered vestigial, although there is some evidence that pheromonal effects can be mediated through the olfactory system. Pheromones are, by definition, chemical signals that influence behavior, but behavior extends far beyond sexual attraction and includes fear, sources of food, territorial marking, aggression, even death. The only universally accepted proof of pheromonal behavior in humans involved the synchronization of menstrual cycles of college women living in close proximity. A paper by McClintock, published in 1971,[27] was proof of a chemical signal altering human behavior, but one solid result followed by 40 years of silence is hardly a tidal wave of progress in this field. Humans are emphatically different from fruit flies or any other lower species of plant or animal, and our mate choices (and before that point, sexual partners) are not selected by a sniff of a chemical, although we can surely be negatively influenced by bad body odor. Humans seek stable families, and use visual, societal, and emotional

clues far more than pheromones. There may be a positive psychological effect for the user of products claiming pheromonal activity, and this positive mental attitude may transform itself into a more positive social encounter, but the magic of human pheromones is more in the mind than in the chemistry.

Summary

The science and technology of fragrance is broad and complex. For the formulation chemist there is one key fact: a fragrance is a mixture of chemicals. The volatility, polarity, and stability of the individual chemicals determine the performance of the fragrance in diverse media. Natural products present in fragrances must likewise be reduced to their individual chemical components. Beyond chemistry itself, safety and regulatory concerns are critical for any fragrance placed in commerce. After all the technical and regulatory issues are satisfied, fragrance remains an aesthetically pleasing and emotionally potent component of most personal care products, and its role is critical for product success.

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SECTION V:
Stability and Preservation

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CHAPTER 16

Stability Testing for Topical Formulation Development

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Key Words:

Accelerated Testing Conditions, Chemical Stability, Fit and Acceptable for Use, Kinetic Stability, Physical Stability, Shelf Life, Stability, Thermodynamic Stability.

Introduction

This chapter discusses approaches to estimate and evaluate the stability of semi-solid topical products. "Stability" is used as a comprehensive description of the ability of a product to resist changes in composition and consistency, and remain fit and acceptable for use over time. Such changes can adversely affect the performance of the product in providing its intended benefit or efficacy and its aesthetic properties. These will have a negative impact upon consumer acceptance and subsequent market success. A further potential consequence of changes in product composition and consistency is an adverse effect upon product safety.

The length of time a product remains fit and acceptable for use is termed its "shelf life." The shelf life of a product has important logistical and financial implications. It should be sufficient to provide adequate time for manufacture and distribution, the expected time duration in retail, and the probable length of time the product will be used by the consumer, all under the environmental conditions anticipated in each segment. A product with an inadequate shelf life will require special efforts to accelerate distribution and more frequent re-stocking in retail, and risks consumer dissatisfaction if it isn't stable for a reasonable period of time in the consumer's hands.

The nature of most topical consumer products renders them subject to changes in composition such as degradation of components including active agents, as well as attributes such as consistency over the expected shelf life of the formulation. These changes can be both chemical and physical and are often affected by environmental

conditions such as temperature, humidity, and sunlight exposure, as well as physical stresses such as those experienced in transport. The latter can substantially affect the rate at which the changes occur. In addition, topical products, especially those subject to repeated environmental or human contact during use, can be subjective to microbial contamination. Importantly, any of these alterations in the product composition and/or attributes can adversely impact the performance and efficacy of the product, its aesthetics (including in-use characteristics), and even the safety of the product, or in other words, its fitness and acceptability for use.

The definition of "fitness and acceptability for use" will vary with product type and the developing company. For many topical over-the-counter (OTC) drug products, "fitness and acceptability for use" depends upon the remaining level of the active drug and is usually defined as at least 90% of the labeled amount per dose.[1] Alternative measures of efficacy benefits such as levels of non-drug biological actives or measures of consumer acceptability may be the criteria for other types of topical products. The latter may be based upon either objective or subjective evaluations linked in some manner to consumer acceptance. Measures of product safety may also be included in the criteria defining a product's fitness for use.

The United States Food and Drug Administration (FDA), which has regulatory authority for topical cosmetics and drugs marketed in the United States, has established stability guidelines for topical drug products, but not for topical cosmetics.[2] Nonetheless, there is an implied warranty for "fitness for intended use" in US commerce, which in essence means that the consumer may expect that an item of commerce such as a topical product will be suitable for use at the time of purchase and a "reasonable" period of time thereafter.[3] Since an unstable product will not meet these requirements and expectations, it is important from a legal standpoint to determine the shelf life of a product prior to marketing.

The purposes of topical product stability testing are therefore manifold, depending upon the type of product and its stage of development. Given the importance of the type of product to the study of its stability, this chapter will begin with a brief review of the primary topical product types and their pertinent stability concerns followed by a discussion of the nature and mechanisms of product instability, particularly with regard to the primary formulation types used in topical products. Stability considerations with respect to the concepts of absolute and relative stability, the stage of product development, and product/package interactions will be covered along with both theoretical and pragmatic applications of accelerated conditions. The last sections of the chapter will discuss chemical and physical measurements pertinent to topical product stability. The objective of this chapter is to provide an overview of stability testing of topical semi-solid products and a discussion of many of the factors that should be considered in the evaluation of the stability of a product during its development. It is based primarily upon the author's 35 years of consumer and drug product development. It is not designed to provide proscriptive protocols, as these will be highly specific to a given situation.

Types of Topically Applied Products

Semi-solid topically applied personal care products encompass a broad range of consumer product categories including OTC drugs, color cosmetics, skin care products, and hair care products. However, all of these can be essentially categorized by their physical/chemical characteristics as either a solution or gel, suspension, emulsion, or aerosol. The first three terms describe a product formulation type/application, whereas the latter is a packaging form that incorporates several formulation types. Although product formulation/package interactions are important considerations for all products, the propellant inherent to an aerosol package can become an integral part of the product formulation and therefore this will be considered a separate formulation type for the purposes of this chapter. This section will provide an overview of these formulation types and associated stability concerns. More detail regarding the latter will be presented in the section on nature and mechanisms of instability.

Solutions and gels

A solution is a combination of two or more components to form a homogenous molecular dispersion. Essentially all topical personal care products that are solutions are liquid at ambient temperature and consistent of a vehicle or solvent which comprises the bulk of the solution and dissolved solutes. The former is typically water or a mixture of water and water-miscible components such as ethanol, isopropanol, and other polyhydric components such as glycerin, propylene glycol, and polyethylene glycols. A very few topical personal care products such as nail polish removers employ non-aqueous vehicles such as acetone and ethyl acetate. Solutes include "active" agents, surface active agents, components intended to modify the tactile properties of the product, aesthetic agents such as colors and perfumes, rheology modifying materials, and preservatives. Gels are solutions that exhibit non-Newtonian rheology at ambient temperature due to the presence of rheological modifying solutes. This means that shear stress must be applied to the product to induce flow. For more detailed information about rheology aspects of topically applied formulations please refer to Chapter 11.

The primary stability concerns of solutions include solute chemical degradation and precipitation of solutes due to temperature changes, loss of vehicle by evaporation, or introduction of contaminants that will change the solubility balance. The latter refers to situations in which the solvent (usually water) activity is lowered by contaminants, resulting in reduced solubility of the original solute. The former should be reversible when the product is returned to ambient temperature, but the kinetics of dissolution of the precipitated solute(s) may be such that this may not be complete prior to product use. Gel products are particularly affected by changes in the rheological modification system due to chemical degradation or precipitation or change in concentration of the rheological modifying components due to temperature or solvent loss. Packaging effects upon stability include vehicle loss and adsorption or absorption of solutes or vehicle components.

Suspensions

For the purposes of this chapter, a suspension will be defined as consisting of a solid dispersed in a liquid or semi-solid, often a solution, gel, or emulsion (see below). Unless the particle size of the dispersed solid is sufficiently small that the particles are suspended by Brownian motion, suspensions are inherently thermodynamically unstable in that the dispersed particles will tend to settle due to gravitational effects. However, most topical semi-solid products are viscous and therefore pseudo-stable with regard to settling. These include skin care products that contain particulates such as microderm abrasives, inorganic sunscreens, "fillers" for fine lines/wrinkles, and surface refractory particles, as well as anti-dandruff shampoos containing particulate zinc pyrithione, soft solid antiperspirants, and skin protectant ointments containing particulates such as zinc oxide. There are a few topical personal care products that are non-viscous such as silicone-based (vehicle) antiperspirant roll-ons in which the suspended particles typically settle between product uses. Re-dispersion of the settled particles is therefore required prior to each use.

In addition to the chemical stability concerns associated with solutions and gels, there are a number of physical stability concerns with suspensions. These include the rate of particulate settling, particulate re-dispersion as a function of time, and particulate size growth, which is dependent of the particulate solubility in the vehicle as a function of temperature variation during storage.

For non-viscous topical products, an additional concern is whether the nature of the bed of settled particles changes into a coherent mass over time. The preferred situation is the formulation of a system in which the suspended particles form loosely adherent aggregates in a process termed flocculation. Properly formulated, these aggregates settle in a non-viscous product into a non-coherent mass that can be readily re-dispersed. Non-flocculated particulates in a non-viscous product can form a coherent mass upon settling that doesn't re-disperse readily.

Emulsions

A large proportion of topical products are emulsions, which are thermodynamically unstable dispersions of immiscible liquids (and occasionally low melting solids). Therefore, a primary objective of emulsion formulation is to kinetically stabilize the emulsion in order to provide an adequate shelf life.

The immiscible liquids or phases are usually characterized as polar and nonpolar, one of which (usually, but not always, the one present in lesser amount) is dispersed as droplets in the other (**Figure 1**).

The latter is often termed the dispersed phase and the other the continuous phase. The

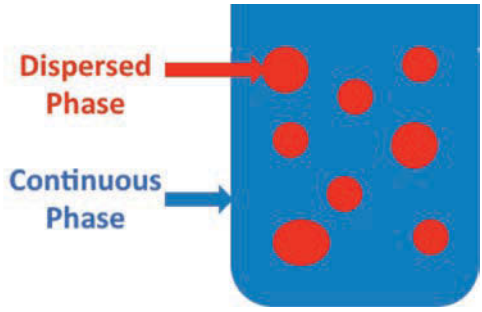

Figure 1. Emulsion structure

thermodynamic instability is a result of the increase in free energy of the system produced by surface tension between the two phases and the increased surface of the dispersed phase during its dispersion into droplets.[4] The primary exception is the so-called micro-emulsion, which differs from the typical emulsion in forming spontaneously and being thermodynamically stable.

Since typical emulsions are thermodynamically unstable, one of the principle stability concerns of this product type is the physical stability of the emulsion. Factors involved in the physical destabilization of emulsions are:[4]

1. The interfacial tension between the two immiscible liquid phases which makes the low energy state of the system one in which the surface area between the phases is minimized, or two bulk phases.
2. Creaming or sedimentation in which the dispersed phase droplets tend to migrate to the top (creaming) or bottom (sedimentation) of the emulsion due to density differences between the two phases and gravitational forces (**Figure 2**). The increased concentration of dispersed phase droplets at the top/bottom of the emulsion enhances the rates of droplet collision which can lead to coalescence and eventual phase separation (see below). Another factor that may accelerate creaming is the creation of larger dispersed phase droplets through Ostwald ripening, or disproportionation in which dispersed phase molecules can diffuse through the continuous phase from smaller to larger droplets, increasing the size of the latter.

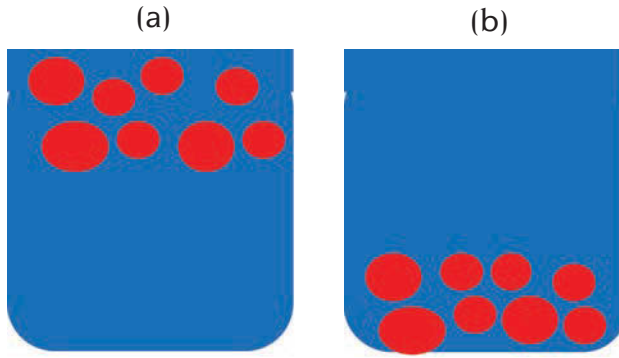

Figure 2. Emulsion (a) creaming and (b) sedimentation

3. Flocculation, as shown in **Figure 3**, a process in which the droplets aggregate into larger structures while retaining their individual integrities. These aggregates have a larger effective particle size, which is a primary determinant of the rate of creaming/sedimentation according to Stokes Law:

$$V = [(2 \bullet g \bullet r^2) \bullet (D-d)] / (9 \bullet \eta)$$

where: V = creaming/sedimentation rate

g = gravitation constant
r = effective dispersed phase particle (droplet) radius
D = density of continuous phase
d = density of dispersed phase
η = viscosity of continuous phase.

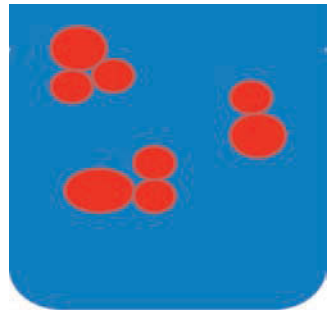

Figure 3. Emulsion flocculation

4. Coalescence (**Figure 4**), which occurs when the film of continuous phase liquid between droplets of the dispersed phase is ruptured, thereby permitting fusion of the droplets into a larger droplet. The ultimate result of continued coalescence is separation of a portion or all of the dispersed liquid from the bulk of the remaining emulsion or the continuous phase.

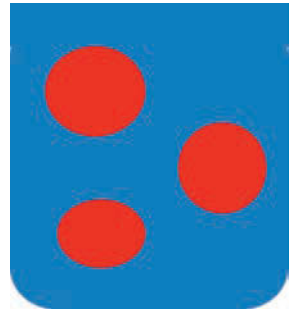

Figure 4. Emulsion coalescence

Although emulsions are thermodynamically unstable, topical product emulsions can be adequately stable for a suitable shelf life. This is often termed kinetic stabilization and can be achieved through a variety of formulation approaches. Perhaps the primary approach is the reduction of surface tension between the two liquid phases through the use of surface active components. According to Stokes law, sedimentation/creaming can be reduced through reduction of the dispersed phase droplet size and increasing the viscosity of the continuous phase. Flocculation and coalescence can be impeded by creating physical or electrical barriers at the interface as well as by the use of lamellar structures in the continuous phase that reduce dispersed phase droplet mobility. More detailed information on emulsion

formulation and stabilization is available in Chapter 6.

Therefore, monitoring and predicting the rates of change of the physical factors which affect emulsion kinetic stability are important to determining the shelf life an emulsion topical product. These include the viscosity of the continuous phase, droplet size of the dispersed phase, and homogeneity of the concentration of dispersed phase throughout the emulsion. In addition, the factors associated with the chemical stability of solutions and gels are also applicable to emulsions.

Aerosols

Aerosols are a packaging system that utilizes a gas under pressure (i.e., in excess of ambient pressure) or propellant to force the product contents out of the package through an orifice designed to disperse the product onto the skin. The expelled product may be applied directly to the skin (shaving creams, for example) or sprayed through the air to adhere to the targeted skin (i.e., deodorants, antiperspirants, perfumes). The propellant is either the vapor phase of a liquefied gas such as propane, butane, isobutene, and dimethyl ether, or a compressed gas such as nitrogen, carbon dioxide, or nitrous oxide. Liquefied gas propellants maintain a constant pressure within the aerosol package due to the equilibrium between the liquid and vapor phases of the propellant, whereas the pressure within the container of a compressed gas aerosol decreases continually with use as the amount of propellant decreases. The product within the container can be a solution or gel, suspension, or emulsion. The liquid phase of liquefied gas propellants is an intrinsic part of this type of aerosol.

Aerosol products are subject to all of the chemical and physical stability concerns of the above product types, although non-thermal environmental factors (light, moisture, oxygen) are essentially eliminated, since aerosol products are separated from them. In addition, homogenous dispensing of the product from aerosols is a primary stability concern. Non-uniform dispensing can result from the instability of the product itself (including the liquefied gas propellant liquid phase), or clogging of the orifice with dried or congealed product or product particulates. The declining pressure of compressed gas propellants with use can also affect the homogeneity of dispersed product with time. Finally, since aerosol containers are considerably more limited in composition and availability than other types of packaging, interactions between the product and container can be more of a concern, since there is limited flexibility in altering the container to improve product/package compatibility. This is particularly true for products such as antiperspirants, which are corrosive to tin plate aerosol containers.

Product Instability

Product instability can be manifested as a change in composition, which may be termed chemical instability, homogeneity, consistency/rheology (the latter two changes may be termed physical instability), or microbial contamination. Product/package interactions may also produce product instability. This section will discuss

chemical and physical product instability as well as product/package interactions. Microbial instability is covered in a separate section.

Chemical instability

Chemical instability is due to chemical reactions occurring within the topical product over time. These typically involve degradation of one or more components of a formulation into reaction products. Chemical reactions may be induced and/or accelerated by environmental factors such as temperature, light, oxygen, and humidity, as well as formulation factors such as pH and water activity. Chemical instability may also involve the reaction of two or more components of the formulation. It can be manifested in consumer observable changes in the topical product such as color, odor, and/or consistency or rheology in addition to changes in other product attributes such as pH. However, some chemical changes can only be detected by specific chemical assays of the specific product component(s). Chemical instability can result in a loss of product efficacy or function, adverse changes in product aesthetics, and can also negatively impact the safety of the product. Although all topical product types can be subject to chemical instability, those with high water content, particularly high or low product pH values, or that contain especially reactive components are of particular concern.

As indicated above, there are a number of environmental factors that can influence chemical reactions in a topical product. Increased temperature will accelerate the rate of chemical reactions. The effect of temperature upon chemical reaction rates is the basis of accelerated temperature testing, which is discussed later in this chapter. Accelerated temperature testing permits determination of changes in a shorter period of testing time and prediction of the rate of change at ambient temperature. However, products that may be subjected to high temperatures during distribution, storage, and use may undergo chemical changes that would not be observed at ambient temperatures (usually considered to be 20-25°C). Such changes are due to the increased rates of reactions that occur slowly at ambient temperature and the induction of reactions that do not occur at ambient temperature by exceeding their activation energy at higher temperatures.

Light is another factor that affects chemical reactions. Being a type of electromagnetic radiation, light is a source of energy and can therefore provide the necessary activation energy for a chemical reaction in a molecule capable of absorbing light. In addition, the absorption of a photon of light by a reactant molecule may also permit a reaction to occur by changing the symmetry of the molecule's electronic configuration to enable another reaction mechanism. Due to the nature of the influence of light upon susceptible chemical reactions, the effects of increases in light intensity can be predictive of the rates of changes at ambient light intensity.

Light can primarily be a factor in the stability of products stored in transparent packaging. However, it can also be a consideration for products intended for prolonged use on parts of the body exposed to light, particularly intense sunshine.

Many components of topical products are subject to oxidation reactions. Oxidation

can be defined broadly as the loss of electrons from a molecule (increase in oxidation number), which for organic molecules can be summarized as an increase in oxygen or decrease in hydrogen content.[5] One factor affecting the initiation and rate of oxidation reactions is the availability of oxygen, either dissolved in the product (especially those containing water) or in the packaging headspace. Therefore, for products containing components particularly subject to oxidation reactions, package permeability to atmospheric oxygen, and the amount of oxygen introduced into the product from raw materials and during processing are considerations in determining the stability of a product.

Atmospheric water content, or humidity, is primarily a factor in the stability of solid or non-aqueous topical products. Products containing appreciable amounts of water should not typically be affected by exposure to the relatively low amounts of atmospheric moisture, or humidity. Humidity can adversely affect solid products through adsorption or absorption onto or into the product and thereby altering product consistency, aesthetics, and application properties. Further, the absorbed/adsorbed water can facilitate chemical reactions that either do not occur in the solid state or proceed sufficiently slowly so as to not materially affect product stability. The water permeability of packaging and potential for water exposure during product use are considerations for such products.

Product formulation factors such as pH and water activity will also influence chemical stability. These effects can be component specific and the susceptibility of the components of a product to pH influenced chemical reactions should be specifically examined. However, since it is more difficult to remove an electron from a molecule when it is more positively charged, components susceptible to oxidation are generally more stable under lower pH conditions.[5] Product water activity can also influence the rate of chemical reactions with lower water activity generally associated with slower reaction rates.

As indicated above, chemical instability of a topical product can be manifested in a number of consumer observable ways. Color is produced by the absorption of certain wavelengths of visible light and refractions of others by the specific structure of the compound. These often involve conjugated double bonds in organic compounds and the electrons of the outer valence shells of atoms. Thus, change in the color of a product is indicative of a change in the chemical structure of one or more components and therefore of chemical instability. However, color changes are not necessarily specific to a single reaction or component. Additional investigations or testing such as specific chemical assays for a given component are usually needed to identify which product components are involved in the reactions producing the color change. Further, the lack of a change in color doesn't mean that chemical instability doesn't exist. Nonetheless, measuring color change is a practical method of monitoring chemical instability in addition to its obvious impact upon product aesthetics.

The odor of a product is a function of the interaction of volatile components

with olfactory organs. A change in odor (under given sampling conditions) indicates an alteration in the detectable concentration of specific volatile compounds from the product in the sampling atmosphere and/or the production of new volatile compounds. A change in the detectable concentration of specific volatile compounds is indicative of a reduction of the concentration of these compounds in the product through chemical reactions, or physical loss to the environment, adsorption/absorption onto/into packaging components, or other product components such as particulates. However, the detection of new volatile compounds in the sampling atmosphere is clearly indicative of a chemical change occurring in the product. A classic example is the degradation of lipids through hydrolytic, oxidative, and microbial reactions to product volatile compounds producing the typical rancid odor.

Changes in the consistency or rheology of a product are usually associated with physical instability phenomena (see below). However, these changes may also be the result of chemical instability. The rheology of a product is a complex function of the product components and processing as well as environmental factors such as temperature. Alterations in the structure of components that control product rheology due to chemical reactions such as degradation of polymeric thickeners will produce changes in product consistency. In addition, many components that control product rheology are sensitive to product pH so that chemical changes that alter product pH can affect consistency. Therefore, both chemical and physical instability sources should be considered when changes in product rheology/consistency are observed.

Changes in product pH are usually indicative of chemical changes although loss of acidic or basic components through evaporation or absorption/adsorption is also possible. However, in an adequately buffered product, a stable pH is not a guarantee of chemical stability. As noted above, pH instability can particularly affect product consistency and it can also influence color, odor, component solubility, performance, and safety.

Physical instability

Physical instability is a change in a product not typically associated with chemical reactions. It is usually manifested in a change in the homogeneity of a product or its consistency (i.e., rheology) and is a function of the topical product type. However, chemical reactions affecting components responsible for the rheology of a product such as polymeric thickeners may also produce this type of product instability. The source of an observed instability in product homogeneity or consistency should be determined during the course of stability evaluations, since approaches to correct it will vary depending upon whether it is of chemical or physical origin.

External factors that affect product physical stability include temperature, especially temperature cycling, and physical stress that introduces shear in the product. However, the proportionality of these effects upon the physical properties of topical products is not as well defined as those of external factors such as temperature and light upon chemical reactions. Increased temperatures and stress rates may increase the rate at which physical changes occur, but well-defined or accepted

relationships such as the Arrhenius (see the section on accelerated testing) for the effect of temperature upon First Order chemical reaction rates do not exist. Therefore, extrapolation of rates of physical changes occurring at accelerated conditions to ambient conditions is problematic at best.

As discussed above, most topical products consist of one of the following: solutions or gels, suspensions, emulsions, and aerosols. Solutions are thermodynamically stable and are rarely affected by physical stability issues except with regard to solute precipitation. In addition to solute precipitation, gels may be affected by changes in the physical interaction of the components impacting product rheology, producing alteration in consistency. Emulsions, with the exception of micro-emulsions, are thermodynamically instable combinations of two immiscible phases and will eventually physically separate, although an adequately kinetically stabilized emulsion should not separate with the time period encompassed by a typically adequate shelf life. Suspensions are also inherently physically instable. Aerosol products are primarily solutions, suspensions, and emulsions and are subject to the physical instability inherent to its formulation product type.

Physical stability of solutions and gels: The physical stability of solutions (and gels) is primarily affected by changes that reduce the solubility of solutes such as in temperature and loss of solvent, which can produce solute precipitation. With the primary exception of certain polymers and nonionic surfactants, the solubility of most solutes decreases with decreasing temperature. Therefore, assuming that the concentration of a solute doesn't exceed its solubility at ambient temperature (a condition of supersaturation that ideally will be eliminated during product formulation), exposure to low temperatures during transport and storage has the potential to produce precipitation of one or more solutes. A return of the product to ambient temperature will eventually permit re-solubilization of the precipitated solute(s). However, dissolution is a kinetic phenomenon that is dependent upon the concentration gradient (typically the difference between the solute saturation solubility at the product temperature and its bulk concentration in the product), dissolving surface area (primarily a function of the precipitate particle size), and agitation. Therefore, it is possible that re-solubilization may not occur before product use. Hence, it should be determined if precipitation of solutes occurs at low temperatures and the rate of re-solubilzation of any precipitate(s) at ambient temperature.

The rheology of gels may be subject to change with time. In addition to potential chemical degradation of polymeric components used to thicken the gels discussed previously, the physical interactions between dissolved polymers and/or colloidal particulates such as fumed silica that can contribute to the rheology of selected gel formulations may change with time. The kinetics of the formation (or re-formation after disruption due to physical stress including that encountered in dispensing) of these physical interactions may be such that the final rheology of the product is not attained before the first consumer use or re-use of the product.

Physical stability of suspensions: Suspensions are subject to two primary types of physical instability. The first is the particulate size of the suspended solid and the second is sedimentation, or settling of the suspended particulates.

If the solid has a finite solubility in the vehicle of the suspension, changes in temperature can affect the amount in solution—typically, increased solubility with higher temperatures and decreased solubility with lower temperatures. Therefore, an increase in temperature can decrease the size of suspended particulates due to enhanced solubilization of the suspended solid. This will be a function of both the increase in temperature and the initial particulate size, as smaller sizes will promote faster dissolution. Similarly, a decrease in temperature will tend to increase particulate size as the solubilized solid precipitates out of solution onto existing particulates that act as nucleation sites. The processes of solubilization and precipitation as a function of temperature may also affect the particulate size distribution that exists in most suspensions. Smaller particles will be disproportionally reduced in size during the dissolution process. During precipitation a number of scenarios can occur that may affect the particulate size distribution. Dissolved solids may precipitate as a larger number of very small particulates. Alternatively, dissolved solids may precipitate onto existing particulates increasing their size. Since the latter process may not be proportional to existing particulate size, the existing particulate size distribution may be affected.

Suspended particulate size may also be affected by the process of flocculation. Since the initial particulate size of most suspensions is relatively small, the resulting large surface area is associated with a surface free energy which makes the system thermodynamically unstable. Thus the particulates will tend to associate in order to reduce apparent surface area, producing conglomerates of particulates held together by weak Van der Waals forces.

Sedimentation is the process of migration of suspended particulates towards the lowest part of the product under the influence of gravity. This will adversely affect the homogeneity of the product. The rate of sedimentation is predicted by Stokes Law (discussed previously with regard to emulsions):

$$V = [(2 \bullet g \bullet r^2) \bullet (D\text{-}d)] \,/\, (9 \bullet \eta)$$

According to Stokes Law, the velocity of sedimentation is proportional to the square of the particle size and the density difference between the suspended particulate and the vehicle and inversely proportional to the viscosity of the vehicle. In addition, the concentration of suspended solids will affect the sedimentation rate. Most topical suspensions are creams and ointments that are sufficiently viscous, so sedimentation is not a major cause of physical instability. Exceptions are suspension aerosols and products such as calamine topical suspension, USP, and inorganic sunscreen lotions. If sedimentation does occur with time, it is important that the particulates settle as flocks and re-disperse readily with minimum agitation.

Physical stability of emulsions: As discussed previously, all emulsions except the so-called micro-emulsions are thermodynamically physically unstable. Emulsion

physical instability can be manifested in a number of ways, culminating in complete emulsion breakdown, or separation into essentially two bulk phases with the less dense phase, usually the non-polar phase, on top. Stokes Law describes the relationship among the factors affecting this process.

The creaming/sedimentation velocity, which drives emulsion physical instability, is directly proportional to the density difference between the two phases and the square of the dispersed phase droplet size, and inversely proportional to the viscosity of the continuous phase. Therefore, the primary physical changes that can lead to increases in the creaming/sedimentation velocity include increases in the size of the dispersed phase droplets and alterations in the rheology of the continuous phase that reduce the viscosity of the emulsion at the low shear rates experienced during storage.

Increases in dispersed phase droplet size that adversely affect emulsion physical stability involve not only increases in the absolute size of individual droplets, but also the creation of aggregate structures of dispersed phase which increase effective droplet size. Coalescence is induced by many factors and is difficult to predict, although it is potentiated by large differences in the density of the two phases.

Reductions in the viscosity of the continuous phase can be produced by chemical degradation of rheology modifying components such as polymers, and by physical changes in other structures producing the rheology properties of the continuous phase. The latter include lamellar gel and liquid crystalline phases created by surfactants and other fatty amphiphiles as well as "latex" type polymers. The physical change induced alterations are primarily the result of temperature increases and variable cooling rates, especially with regard to lamellar gel structures. Lamellar phases are created when amphiphilic molecules in water organize into sheet-like bilayer structures with the lipophilic portions of the molecule aligned towards each other and the polar portions of the molecule aligned outward towards the aqueous environment, and with a water channel between the two "sheets" of the bilayer structure (**Figure 5**). The bilayers can subsequently form various three-dimensional arrays that can affect the rheology of the water (polar) phase of the emulsion.

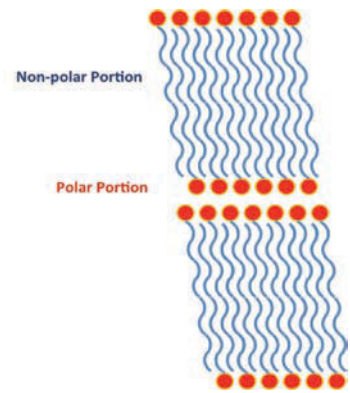

Figure 5. Lamellar bilayer structure

Stability of aerosols: Aerosol products may incorporate any of the preceding formulation types (solutions, gels, suspensions, emulsions) as concentrates in conjunction with the propellant. Liquefied gas propellants introduce an additional liquid to the concentrate, and both liquefied gas and compressed gas propellants introduce a vapor phase. There are, however, special aerosol containers that provide

for complete separation of the propellant from the concentrate.

A primary advantage of aerosol packaging with regard to product stability is the separation of the product from environmental light, oxygen, and moisture, which can greatly improve the chemical stability of product concentrates susceptible to these factors. Temperature effects upon both chemical and physical stability are usually unaffected by the use of aerosol packaging. Physical stability issues applicable to the various concentrate product types are also typically unaffected in aerosols. In addition, the potential of induced clogging of the dip tube, valve, or actuator is of particular concern in aerosol products.

Considerations

This section will discuss several aspects that should be considered in the evaluation of the stability of a topical product. These include the concepts of absolute and relative stability, the differing stability testing needs associated with the various stages of product development, packaging interactions, and, importantly, accelerated testing, which involves approaches to increase the rate at which chemical and physical changes occur in order to determine potential product instability in shorter periods of time that would be required under ambient conditions.

Absolute and relative stability

The ultimate goal of most stability programs, especially in the later stages of product development, is determination of the absolute or actual stability of the product over its projected commercial shelf life. This is pragmatically accomplished though testing of chemical and physical properties at ambient conditions throughout the length of time corresponding to the desired shelf life. Alternatively, for some product properties such as the chemical stability of various components of interest, data obtained at accelerated stress conditions such as temperature may be confidently extrapolated to ambient conditions through the use of well-established relationships such as the Arrhenius relationship of First Order chemical reaction rates and temperature (see section on accelerated testing).

The proportional relationships of other product properties, including most physical properties such as rheology, emulsion structure and droplet size, and suspension homogeneity and particulate size with accelerated stress conditions are not well established. There are other circumstances in which the use of accepted proportional relationships to extrapolate accelerated stress condition data is problematic due to the potential of induction of additional chemical reactions at very high temperatures which invalidates the basis of the Arrhenius relationship. Hence, data obtained under these accelerated stress conditions cannot be confidentially extrapolated to "absolute" values at ambient conditions. Therefore, the concept of relative stability is often employed with such data.

The premise of relative stability is that products of similar formulation types will correspondingly respond to accelerated conditions in similar manners. Therefore, comparison of accelerated stress data on a product with known stability properties

at ambient conditions, (termed a reference product) with that of a test product will provide perspective on the potential ambient stability of the latter. A test product exhibiting equivalent or less change in the measured chemical or physical property than the "stable" reference product may be expected to exhibit similar, or even better, ambient condition stability. It must, however, be recognized that whereas positive relative stability results provide evidence of the potential stability of the test product at ambient conditions, such results should not be considered indicative and that confirmatory data under ambient conditions should be obtained.

Stage of product development

The type and extent of stability testing will vary not only with product type, but with the stage of product development. For the purposes of this chapter, three general stages will be discussed: (1) Exploratory; (2) Developmental; and (3) Pre-Market. The terminology and exact number of stages can certainly vary with specific company practices, but these will provide an overview of the types of issues that should be considered over the course of the development of a product from conception to commercialization.

Exploratory: The Exploratory Phase comprises those activities involved in defining the product. These can include exploration of new formulation approaches and processes, or new excipients to meet new consumer needs in terms of product appearance, application or in-use characteristics/aesthetics, and efficacy benefit delivery. The latter may involve the incorporation of new benefit agents or improved delivery of existing agents to enhance efficacy or reduce adverse experiences. Often batch sizes are small and stability testing is designed to answer specific questions such as the chemical stability of new components, or the physical stability of new formulations including the impact of new excipients upon existing formulation approaches.

Specific chemical assays are usually not available in the Exploratory Phase, and surrogate evaluations may be required such as color, pH, and odor changes. Physical stability will most likely be determined using visual observation or simple viscosity measurements. The length/extent of stability testing is dictated by company procedures and/or personal experience with systems being investigated and the objective of the stability evaluation, but three months is often the longest duration required for exploratory tests to be conducted. Since determination of the absolute stability of a product cannot be expected from such testing, it can be helpful to evaluate its relative stability by comparing results to those obtained concurrently (ideally), or previously with similar products of known stability under the same testing conditions. Exaggerated temperature and physical conditions are probably most helpful in this phase of product development due to the typically shorter timeframe of stability testing and the potential use of relative (to known products) stability concepts.

Inert containers are typically used in Exploratory Phase stability testing, especially when the objective is to provide information as to whether a new formulation's

approach, its inclusion of a new excipient(s), or of a new benefit agent is sufficiently stable to proceed with further development. The length and design of such testing will vary depending upon the factors indicated above. If the stability test objective is to provide support for a human exposure test (efficacy, safety, or consumer acceptance), the human test package should be used and the length/design of the stability testing should be sufficient to permit extrapolation of suitable product stability over the proposed length of the human exposure as well as product preparation and release time.

Developmental: The Developmental Phase of product development incorporates all of the activities required to finalize a product for Pre-Market development. Such activities can include refinement and finalization of formulation components and levels, investigation of the impact of ingredient lot-to-lot variation, definition of process and scale-up (at least through pilot plant scale), selection of commercial package design and components, human evaluations to confirm consumer acceptance and product efficacy, and final safety clearance (which may involve additional human exposure testing). Stability testing during the Developmental Phase usually becomes progressively more refined in terms of time and extent of evaluations in order to permit increasingly enhanced predictions of product/package shelf life. However, some of the precepts of Exploratory Phase stability testing such as short-term, aggressive designs, use of surrogate measures of stability, and comparative instead of absolute stability determinations may be continued in the Development Phase to answer specific questions regarding the formulation, process, or product/package interactions.

Specific chemical assays for critical formulation ingredients such as efficacy benefit agents or fragrance components will often become available during the Developmental Phase, and should be used judiciously to augment more general surrogate measures. The time/temperature design of stability tests should permit Arrhenius relationship-based extrapolation of chemical reaction rates and the patterns of component loss with time evaluated to confirm that application of the Arrhenius relationship is appropriate (see below). Defined organoleptic evaluations of fragrance/odor are also typically introduced during the Development Phase.

Physical stability testing during the Development Phase is often expanded to include evaluations for precipitation of soluble formula components, particle and emulsion size droplet measurements, and shear stress/shear rate rheological measurements. In addition to normal accelerated temperatures, temperature cycling and accelerated physical testing such as centrifugation and vibration testing should be considered. If trained panels are available for evaluation of in-use/application aesthetics, use of these characteristics to determine stability can be added to augment laboratory measurements.

As the product composition nears finalization and the type of commercial package is selected, testing of product/package compatibility should be conducted with regard to product component loss, and if appropriate, with regard to impact

upon the package. Product application/dispensing should also be evaluated as described later in this section.

The work in the Developmental Phase can be iterative in nature. Hence, it is useful to try to design stability tests so that results can be used to improve further testing as well reduce re-testing as much as possible.

Pre-Market: The transition from the Developmental Phase of product to the Pre-Market Phase can vary considerably. Again, for the purposes of this chapter, it will be assumed that the formula, manufacturing process, and commercial package have been defined. Therefore, the activities in this phase will usually involve scale-up to the manufacturing facility, large-scale confirmatory consumer evaluations including market tests, transportation evaluations, and formalized stability testing to confirm product/package shelf-life. Stability testing will typically be an extension of that conducted during the Development Phase, but usually more formal in nature with more replicates per evaluation and less product/package variants.

Packaging interactions

The product package may be considered to have four principal aspects/functions: (1) compatibility of the packaging components with the product; (2) protection of the product from environmental stress; (3) facilitation of product application to the site of use; and (4) promotion of "shelf appeal" as well as enhancement of consumer delight during product use. All but the latter should be considered as part of the total stability program of the product/package combination.

Product/package compatibility: It is self-evident that the package should not adversely interact with the product. Most packaging components are selected on the basis of compatibility with the proposed product. Nonetheless, product interactions with the package can occur. These typically take the form of absorption of one or more product components into or adsorption on the surface of packaging components in contact with the product. Frequently this involves the adsorption or absorption of small organic or lipophilic molecules such as fragrance/perfume components onto/into plastic packaging surfaces. Less frequently this may involve the absorption of actives components, a process that may diminish the formulation efficacy. In very rare situations, a packaging component can act as a surface catalyst for a reaction involving a product component. The possibility of such interactions should be detected by loss of these components based upon organoleptic evaluations of fragrance intensity and character and/or direct assay of fragrance components and active components.

If reductions in the level(s) of a product component are detected in routine product/package stability testing, additional work may be required to ascertain whether such losses are the result of interactions between the product and the package. The most straight-forward approach is concurrent or supplemental stability evaluations of the product in a container presumed to be inert, such as glass. The absence or reduction of specific component losses in the inert container relative to the commercial package may be indicative of a product/package interaction. However,

differences in component losses between an inert container and commercial package may also be due to the putative ability of the former to provide a better barrier to environmental stresses such as moisture, oxygen, and light (although an opaque commercial package would be expected to be superior to transparent glass with regard to the latter).

An additional approach to confirm a product/package interaction is the introduction of packaging components into product stored within an inert container. If this increases product component loss relative to the absence of packaging components, it is a reasonable assumption that a product/packaging component interaction is occurring. Further, since the volume-to-surface area ratio in many product/package combinations is relatively high, the absorbing/adsorbing surface area may be rate-limiting and the kinetics of component loss in a the commercial package may not follow the chemical reaction rate order observed when the product is stored in an inert container.

Aerosol containers can present a singular product/package interaction with corrosion of the container by the product concentrate. This is of particular concern with three-piece tin plate containers and lower pH product concentrates such as antiperspirants containing aluminum salts. Preliminary compatibility tests should be conducted for such products involving exposure of the containing materials to bulk product concentrate under exaggerated conditions, and containers should be opened and examined for corrosion as part of normal stability testing.

Product protection: The selected commercial packaging should be constructed so as to provide requisite production to the product from environmental stresses such as moisture, oxygen, and light. Initial stability testing of product prototypes should ideally be designed to indicate the susceptibility of the product to these environmental stresses and the degree to which the commercial package should prevent water and oxygen diffusion as well as the degree of opacity required for product stability. Comparison of various potential commercial packaging materials alone and relative to an inert container may be required as part of the developmental stability program.

Another aspect of product protection by the commercial package is prevention of product component loss during storage. This typically involves loss of volatile components through the package closure, or, more rarely, by diffusion through the package walls. Silicone vehicles can migrate through package closures due to their very low surface tension with most packaging materials. Component loss can be monitored by weight loss evaluations during stability testing in the commercial package and by visual evaluations for product leakage/migration.

Product application/dispensing: A further aspect of the commercial aspect is facilitation of product application/dispensing during use. Therefore, the ability of the product/package combination to provide the desired dispensing characteristics such as amount, rate, and application pattern over the anticipated life of the product, after storage, and after exposure to anticipated environmental and physical stresses

during storage and transport should be evaluated during stability testing. This can be accomplished in a variety of ways, one of which is through the use of tests in which the product is dispensed to exhaustion in individual use amounts. The amount, rate, and pattern of the product dispensed in each individual use can be determined. In addition, the impact of residual product in or around packaging orifices upon dispensing performance and overall aesthetics can be determined. This type of testing can also be conducted on product that has been aged, exposed to various temperatures, and subjected to vibrational forces in order to determine the impact of these factors upon package performance.

Accelerated testing

The objective of accelerated stability testing is to obtain predictions of long-term product or product/package stability under ambient conditions in shorter periods of time. The definition of "long-term" will certainly vary with the stage of product development, the type of product, and developing company or organization. The final goal is typically the determination of the shelf life of the commercial product/package in a scientifically justifiable minimum period of time. As indicated previously, shelf life may be defined as the period of time the product/package remains suitable for use after manufacture under expected storage and use conditions.

Accelerated testing employs aggressive environment stress factors such as temperature, moisture or humidity, light, gravitational force, vibrational force, and, in less frequent situations, oxygen in an attempt to increase the rate at which product alterations produced by these factors occur or the frequency of occurrence of these alterations. The rates of chemical reactions are typically proportional to temperature, and often light, humidity, and oxygen will proportionally affect the reactions influenced by these factors. Therefore, it is often possible to extrapolate rates of changes from higher levels of the stress factor to ambient conditions.

Physical changes can be affected by temperature, especially temperature variations, but also by gravitational and vibrational forces. However, physical changes are not often proportional to the degree of stress and therefore extrapolations of changes occurring at higher levels to ambient levels are problematic. Approaches to dealing with this issue are discussed below.

Temperature—Chemical Stability; Chemical Reaction Rates: The rate at which a chemical reaction involving the loss of a component of interest occurs at a given temperature depends upon the concentrations, or more precisely, the chemical activity of the component of interest, and that of other components involved in the reaction. The number of components involved in the reaction determines the Reaction Order.[6]

A Zero Order reaction is one in which the rate at which the concentration of the component of interest [C_a] decreases with time [dC_a/dt] is independent of [C_a] or the concentrations of other components. The reaction rate is equal to a constant [k], termed the reaction rate constant, at a given temperature, or: $-dC_a/dt = k$

Note that [dC_a/dt] is negative to denote that the concentration of the component

of interest is decreasing with time. Integration of this equation with:

$$C_a = 100(\%) \text{ at } t \text{ (time)} = 0$$
$$\text{yields } C_a = 100 - k \bullet t$$

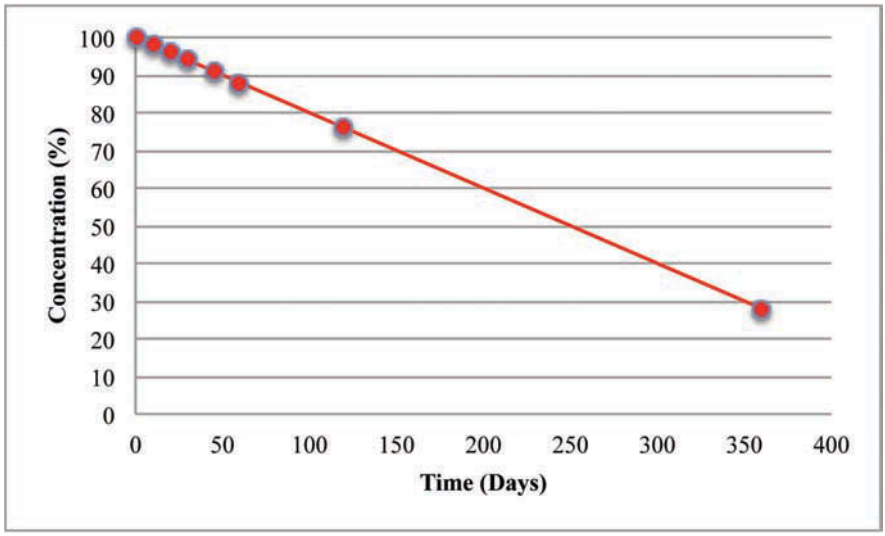

Figure 6. A graph of a Zero Order Reaction with an initial concentration of 100% and reaction rate constant of 0.2%/day.

A First Order reaction is one in which the rate of decrease of the component of interest, or its reaction rate [dC_a/dt] is proportional to its concentration [C_a]. Thus, the reaction rate is faster when [C_a] is high and decreases as [C_a] is reduced by the chemical reaction. A First Order reaction is expressed as:

$$-dC_a/dt = k \bullet C_a$$

where [k] is the reaction rate constant at a given temperature and with [dC_a/dt] again negative to denote that [C_a] is decreasing with time.

Integration of the First Order reaction rate equation with the same boundary conditions as used for the Zero Order rate equation above, yields:

$$C_a = (100) \bullet \exp^{-k \bullet t}$$

Taking the natural logarithm of both sides of this relationship produces the linear expression:

$$\text{Ln}(C_a) = \text{Ln}(100) + k \bullet t$$

Therefore, a graph of [C_a] *versus* time [t] will exhibit a curvilinear relationship (**Figure 7**), whereas a graph of the logarithm of [C_a] at a given temperature *versus* [t], also termed a log-linear or semi-log graph, will be linear with a slope of [k] (**Figure 8**) which may be estimated by linear regression.

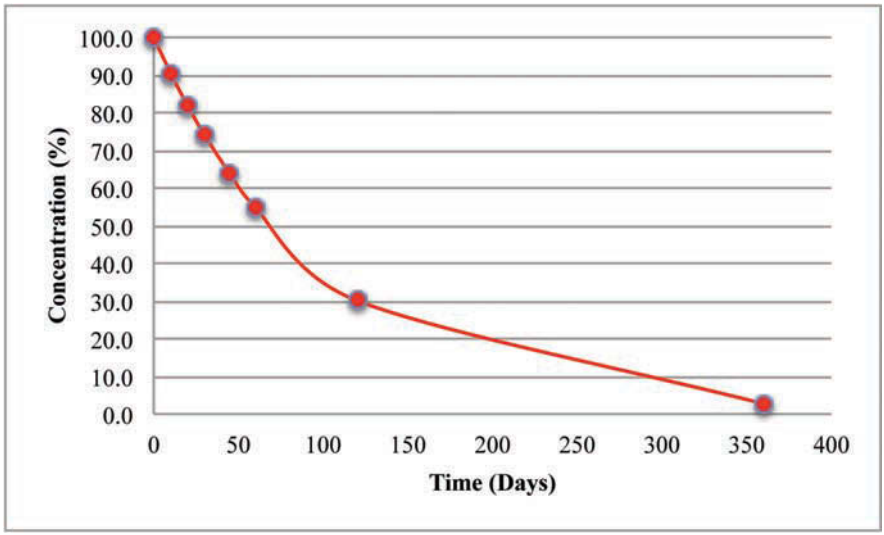

Figure 7. A linear graph of a First Order Reaction with an initial concentration of 100% and reaction rate constant of 0.1% Day^{1}.

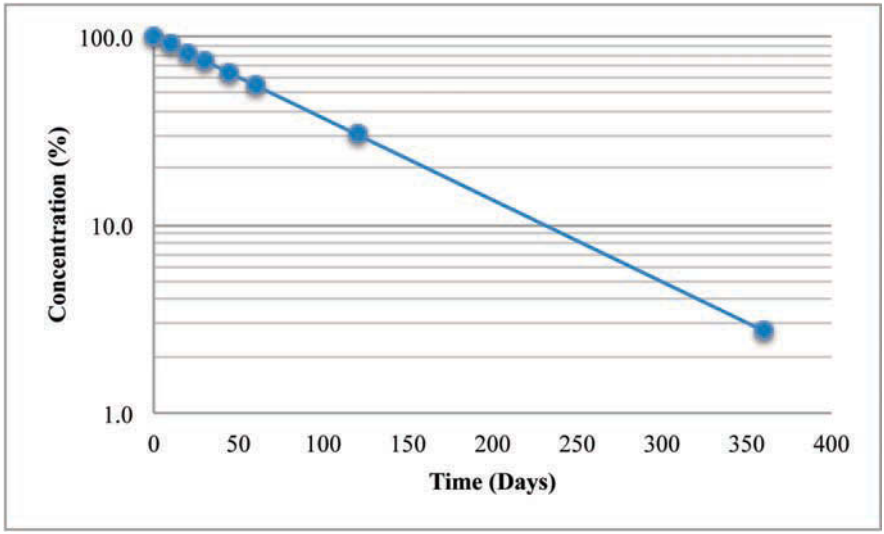

Figure 8. A semi-log graph of a First Order Reaction with an initial concentration of 100% and reaction rate constant of 0.1% Day^{1}.

Chemical reactions can also be Second Order in which the rate of decrease of the component of interest, or its reaction rate [dC_a/dt] is proportional to both its concentration [C_a] and that of a second component [C_b]. A Second Order reaction may be expressed as:

$$-dC_a/dt = k \bullet C_a \bullet C_b$$

In some Second Order reactions, the amount of decrease of the concentration of the second reacting component [C_b] is much lower than that of the component of interest and [C_b] may be considered essentially constant relative to [C_a]. In this situation, the true reaction rate [k] and [C_b] may be combined into a pseudo-reaction rate constant, as follows:

$$k' = k \bullet C_b$$

with the resulting expression:

$$-dC_a/dt = (k') \bullet C_a$$

Such reactions may be considered pseudo-first order and evaluated mathematically in the same manner as a true First Order reaction.

Zero Order reactions are relatively rare and typically observed when a material that is required for the reaction to proceed, such as a surface or a catalyst, is saturated by the reacting components. Hence, it is unlikely that chemical instability will be due to a Zero Order reaction.

Second Order chemical reactions are also relatively rare in topical products in this author's experience. When they do occur, the amount of the second reacting component is often present in excess over that of the component of interest, and the chemical instability of the latter may be treated as a pseudo-First Order reaction. In reality, it is typically difficult to distinguish pseudo-First Order reaction behavior from that of a true First Order reaction without extensive analytical evaluations. Therefore, the majority of reactions involved in topical products may be evaluated as First Order.

Arrhenius Relationship: The rate at which most chemical reactions occur will increase with temperature due to the potential for more frequent molecular collisions of the required orientation and energy to produce the reaction. This is simply because molecules move faster with increasing temperature. The impact of temperature upon First Order chemical reaction rates can be described mathematically using the Arrhenius relationship:[7]

$$k = A \bullet \exp[-E_A/(R \bullet T)]$$

where:

T = absolute temperature
k = chemical reaction rate constant at temperature [T]
A = frequency or pre-exponential factor
E_A = activation energy for the reaction
R = universal gas constant

Taking the natural logarithm of both sides of this relationship produces the linear expression:

$$\text{Ln}(k) = \text{Ln}(A) + (E_A/R) \bullet (1/T)$$

Therefore, a graph of the logarithm of [k] *versus* the reciprocal of absolute temperature [1/T] will be linear with a slope of [$-E_A/R$] (**Figure 9**) which may be estimated by linear regression.

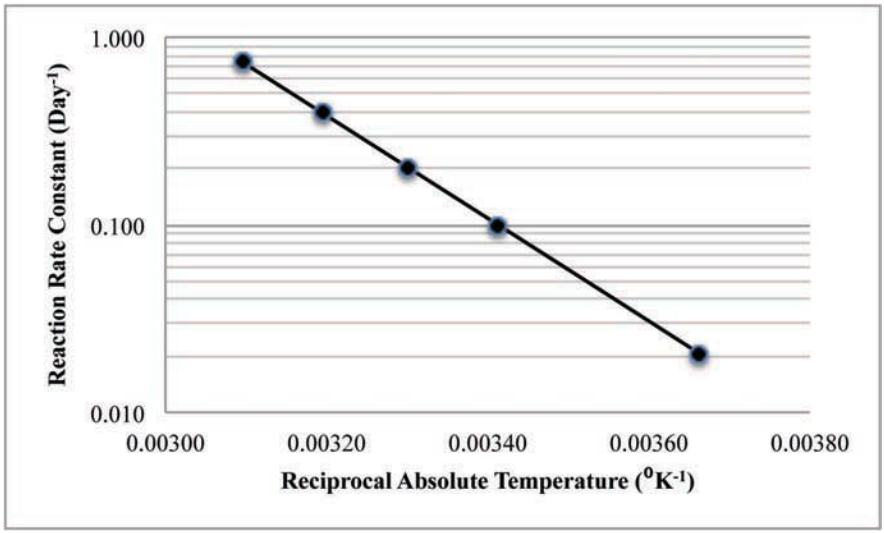

Figure 9. A semi-log graph the Arrhenius Relationship of First Order Reaction Rates and Reciprocal Absolute Temperature. E_A was selected as 1.5 kcal with a value of A of $2.1x10^8$ Day^{-1} which provides a reaction rate constant of 0.1% Day^{-1} at 20˚C.

Note that in Figure 9, the reaction rate constant of 0.01 Day^{-1} at 20°C (reciprocal absolute temperature of 0.0034°K^{-1}) doubles to about 0.2 Day^{-1} at 30°C (reciprocal absolute temperature of 0.0033°K^{-1}). First Order reaction rates approximately double for every 10°C increase in temperature for values of [E_A] and [A] typical of reactions occurring in topical personal care products such as those used to generate the data in the figure.

The Arrhenius relationship is used extensively to extrapolate chemical degradation data obtained at high temperatures to estimate the reaction rate at ambient temperature. However, it is only appropriately applied when the observed chemical degradation is monomolecular and First Order at all temperatures studied. The conditions under which a Second Order reaction exhibits pseudo-First Order behavior at a given temperature may not necessarily exist at a higher temperature. Similarly, the activation energy(s) of additional reaction(s) involving the component of interest which are not observed at lower temperatures may be exceeded at higher temperatures.

Traditional accelerated temperature stability testing: Typical accelerated temperatures do not usually exceed 40°C. Additional conditions will often include ambient (20-25°C), an intermediate temperature such as 30°C, and cold storage such as 0-4°C. The latter is suggested if freezing has a deleterious effect upon the product (i.e., physical properties) which could impart evaluation of chemical stability. It is often recommended that the highest temperature condition, i.e., 40°C, also incorporate

a higher relative humidity level such as 75% with a lower, but controlled relative humidity at the ambient and intermediate temperatures such as 50-60%. The exact temperatures (and relative humidities) and length of time at each temperature will vary with the objectives of the testing and stage of product development, but typical lengths of storage are two years, one year, and six months at 20°C, 30°C, and 40°C, respectively. Cold storage should be as long as the longest time at the next highest temperature, and it is often helpful to retain cold storage samples longer in order to provide reference data.

Chemical analysis schedules should vary with temperature and should be designed with regard to a number of factors. These include the estimated reaction rate at ambient temperature, the expected doubling of reaction rate per 10°C increase in storage temperature, the sensitivity of the assay used to monitor the concentration of the component of interest, and the need to obtain sufficient data points at each temperature to confirm First Order behavior in a minimum length of time, as well as minimizing analytical resource utilization.

If an *a priori* estimate of the ambient temperature reaction rate is not available, one approach to development of an analysis schedule is assay of the product stored at the highest temperature on a preset basis, such as weekly or biweekly. Product stored at the next lower temperature is not assayed until that stored at the highest temperature has reduced in concentration of the component of interest to ~10–20 %. This procedure is subsequently repeated until sufficient data points are available to evaluate the reaction order and estimate a reaction rate constant at each temperature.

Ideally, the chemical assay should be specific for the component of interest and sufficiently sensitive and precise to detect relevant changes to the concentration of this component. It is important that concentration changes employed in data evaluation are in excess of the error associated with the assay. Surrogate assays are often used in the absence of a specific assay, but it should be recognized that this approach can provide misleading results if the surrogate assay is differentially affected by temperature effects upon the product.

Once sufficient data points (minimum of three) are obtained at the highest storage temperatures, these data should be evaluated for First Order behavior as described above by determining if a semi-log graph of the percentage of remaining concentration of the component of interest exhibits a linear relationship. This should then be confirmed by linear regression which will provide an estimate of the reaction rate constant. If either visual inspection of the graph or linear regression does not confirm a linear relationship, the data at this temperature should not be used in an Arrhenius relationship. This procedure is subsequently repeated for the lower temperatures as sufficient data become available.

A minimum of three reaction rate constants (three temperatures) should be employed in using the Arrhenius relationship. If three temperatures above ambient are used in the testing plan, these can be used to estimate the reaction rate constant, and hence shelf life at ambient temperature. If ambient temperature is included in

the minimum three temperatures, the Arrhenius relationship will help confirm the reaction rate constant at ambient temperature estimated from the data obtained from product stored at that temperature. More sophisticated regression techniques may be used in the Arrhenius relationship evaluation to account for the inherent errors of reaction rate constant estimation at each temperature when deemed appropriate.

Rapid Accelerated Temperature Stability Testing: It was noted above that traditional accelerated temperature stability testing rarely uses temperatures in excess of about 40°C because of the potential of inducing additional reactions with higher activation energies that are not a factor at ambient temperature. Another issue with very high storage temperatures is their potential effect upon the physical properties of the product which may in turn affect chemical stability. However, what may be termed "rapid" accelerated temperature testing employing storage temperatures as high as 60°C or even higher may be of benefit early in the development process. Such temperatures will greatly increase the rate of chemical changes, permitting determinations of chemical changes in as little as two weeks. This is counterbalanced by the likelihood of such changes being produced by reactions that are not a factor at ambient temperature.

A typical "rapid" chemical stability test design will employ many small individual test- and reference product samples at temperatures ranging from cold storage through at least 60°C at about 5- or 10°C intervals. Samples of both products are pulled from each storage temperature at short time intervals such as three to four days, and arranged in ascending storage temperature order. A simple, surrogate assay such as color, determined either by visual observation or digital imaging and analysis, is used to note the degree of chemical change occurring. Evaluation of the results involves the use of subjective judgment. For example, if the test product shows no evidence of color changes at 60°C after two weeks or appears to exhibit less color change than the reference product at all temperatures, there is a high probability that it will be adequately chemically stable. Alternatively, a test product appearing to exhibit a greater degree of color change than the reference product is at risk of having insufficient chemical stability.

Results of "rapid" chemical stability testing are obviously not definitive, but can be quite useful in helping differentiate prototype products in the early phases of product development.

Temperature – Physical Stability: Storage of topical product at temperatures in excess of ambient can produce significant changes in physical characteristics such as rheology, particle size, solubility, and product structure. Similarly, storage at temperatures at or below the freezing point of the product vehicle can also produce significant changes in physical properties. The physical property changes may be due to effects upon component solubility, including rheology modifying agents, the nature of lamellar structures that are often used to stabilize emulsions, the size of particulates and emulsion droplets, and the disruptive effects of vehicle freezing. These changes can be reversible upon restoration of the product to ambient conditions,

but the rate at which the physical property changes revert at ambient temperature can vary. Alternatively, some physical changes produced by storage at non-ambient temperatures are irreversible.

An important consideration when physical property changes are evaluated at high (and low) storage temperatures is that these changes are rarely proportional to temperature in a manner similar to chemical reactions. Most often, changes such as alteration of lamellar structures in an emulsion will occur at a given temperature such as the melting point of the fatty amphiphiles creating the lamellar structures, with little alteration below that temperature. Therefore, results at higher temperatures cannot necessarily be extrapolated to lower temperatures in a manner analogous to the use of the Arrhenius relationship with First Order chemical reactions. Nonetheless, physical changes observed at temperatures other than ambient are useful in establishing the stability of a product in several ways.

These data will provide perspective as to potential physical changes the product could undergo when it is stored at various conditions. It is helpful to determine whether these physical changes are reversible when the product is returned to ambient conditions, and if so, the length of time required. If the latter is excessive, the impact upon consumer acceptance could be essentially the same as an irreversible change. This information can be used to determine whether a product can be expected to withstand expected storage conditions over its commercial life, and, alternatively, establish storage recommendations as appropriate.

Temperature effects upon physical properties can also provide perspective on the potential ambient stability of a product when used in the context of relative stability, rather than absolute stability. Comparison of data on test product with that from a reference product of similar formulation type with known ambient stability can provide indications that the test product is probably stable at ambient conditions if it matches or exceeds the stability of the reference product at alternate temperatures. Note, however, that the latter cannot be interpreted as confirming the ambient stability of the test product. Confirmation must necessarily be obtained with long-term testing at ambient conditions.

Photostability: Photostability testing of topical products is an area that is easy to overlook in the determination of product stability. Test products undergoing stability evaluations are not typically exposed to light in the majority of stability testing chambers. Although this is not a major issue for the many topical products that are packaged in opaque containers and are not exposed to light during storage, the impact of light upon the physical and chemical stability of products marketed in transparent or translucent packaging should be considered, and if appropriate, evaluated.

Photostability testing is typically conducted employing light chambers in which appropriate measurements of the chemical and physical stability of test product constantly exposed to light are compared to those obtained in dark storage. Such a comparison will permit estimation of the impact of anticipated light exposure during

commercial storage (whether constant or intermittent, with the latter a percentage of the former). Guidelines for light chamber conditions can be found in the FDA guidance for photostabilty testing of pharmaceuticals.[8]

The photostability of topical products during use is usually a topic addressed in the safety evaluation of these products and is beyond the scope of this chapter. This is because components included in the formulation that absorb at the UV or visible spectrum carry the potential to become phototoxic. However, it is important that this topic is indeed considered during product development, especially for products containing sunscreens.

Physical Stresses: Physical stresses such as the impact of gravitational forces, vibration during transport, and aspects of consumer use can affect the physical characteristics of topical consumer products. In particular, these include emulsion structure and droplet size, and suspension homogeneity and particulate size, as these product types are not thermodynamically stable. Consumer use can introduce contaminants into residual product, such as water into shampoos, which can affect product structure. Therefore, a number of approaches have been used to estimate the susceptibility of a product to these stresses under accelerated conditions.

Centrifugation is a common approach to accelerate the impact of gravitational stress upon product physical characteristics. This testing can be performed at ambient and/or higher temperatures at various centrifugation rates and lengths of time. There is a relatively large body of literature on this topic that provides specifics of various testing approaches. However, the key aspect is that impact of the increased stresses of centrifugation upon a product's physical properties cannot be assumed to be directly proportional to centrifugation rate or length of exposure to centrifugation. Therefore, extrapolation of results obtained at increasing centrifugation rates or lengths of time back to ambient gravitational stress is problematic at best. A more appropriate approach is comparison of results from evaluation of a test product with those from a reference product of similar formulation type with known stability.

Essentially the same considerations apply to the use of enhanced vibrational stress (for example, that provided by testing equipment designed to mimic the motions a product experiences in transport) in evaluation of the stability of a product to potential stresses that may be encountered in transport. However, vibrational testing is typically specialized and, if employed in a stability program, will utilize equipment particular to the developing company or a contract testing company.

Chemical Stability Measurements

There are four primary measures of chemical instability used in the stability evaluation of topical consumer products: specific component assays, pH, color, and odor. All can be estimated using instrumental techniques and, secondarily, the latter two may also be gauged by sensory subjective methods.

Specific component assays

Specific component assays are usually employed to monitor the product concentrations of components that are critical to the performance of products such as OTC drugs or cosmetic "actives." OTC drug stability monitoring is often required by FDA outline, but monitoring the stability of cosmetic actives is usually a company based decision as to whether the resulting information is sufficiently critical to the marketing of the product to justify the expenditure of the additional resources needed to develop an assay and conduct the requisite stability testing.

Specific assay methods are usually developed by analytical chemistry specialists apart from formulation specialists. The procedures used in the development of these methods are beyond the scope of this chapter and will not be discussed in detail. However, the assays typically initially involve physical separation of the component from the product, e.g. extraction into a suitable solvent. This is followed by means of separating the component from its degradents or other components with similar properties that could also be separated along with the component of interest, such as the use of high-pressure liquid chromatography (HPLC). Lastly, a means of detection of the separated component of interest such as UV absorption is needed to quantitate the amount. Development of the assay method also involves validation of the specificity and precision of each step in the method.

There are a large number of methods available for each of these steps, each with particular advantages and degrees of precision, sensitivity, and specificity. Selection of the appropriate method for each step involves consideration of the type of product, the physical and chemical properties of the component of interest, and its level in the product. Other factors include analytical equipment availability, familiarity with a given method(s), the complexity of the method(s), and the associated expense. Development and validation of a specific component assay may require up to several months and significant utilization of analytical resources. Hence, careful consideration should be given to whether monitoring the stability of a specific component is critical to determining overall product stability.

Due to the length of time and resources typically required for development, validation, and execution of a specific chemical assay, the use of surrogate approaches to monitor the chemical stability of components can be helpful. This is particularly true in the early phases of product development in which there may be several active components under consideration. The use of color change is the most common and will be discussed separately. However, simple systems can be monitored by changes in UV absorption without a need for separation methodology, in order to provide a quick determination as to the relative stability of various components. This can even be applied to product compositions if the liquid phase in which the component of interest is soluble and can be easily separated from the rest of the product using a simple procedure such as centrifugation. Such approaches can rapidly provide perspective on the probable relative chemical stability of some components. However, it should be noted that these are only a guide and must not be construed as providing

definitive information, because any changes detected may not be associated with the component of interest (lack of specificity) and the surrogate methods may not be sufficiently sensitive to detect changes that are occurring.

pH

The pH value of an aqueous solution is the negative logarithm of concentration of hydronium ions. The pH of pure water is 7, which corresponds to a hydronium ion concentration of $1x10^{-7}$ moles per liter. pH values below 7 are termed "acidic," and those above 7, "basic." Most topical products with a water phase are formulated within a desired pH range for reasons of safety, consumer acceptance, and the compatibility and performance of various product components. Since the pH of skin is around 5.5 and is this acid mantle is required for its healthy barrier properties, it is desired that formulations have a pH close to this value. Many actives included in topical formulations have optimum chemical stability within a given pH range, and a number of rheological modifying agents as well as other components have pH dependent solubility which affects their performance in the formulation. Hence, it is desirable that the measured pH of a product remain within a specified range for the shelf life of the product. The specified pH range can vary considerably among products, with some able to tolerate a relatively wide pH range and others only able to exist and perform within a narrow pH range. In addition, changes in pH can also be indicative of the chemical degradation of one or more components.

Essentially all pH measurements are conducted using instrumental methods. There are numerous types of instruments and probes available, and selection should be based upon product characteristics and requirements of a particular laboratory. Similarly, the specific protocol for measuring pH will depend upon the product composition and physical properties such as rheology. However, there are several factors that should be considered in developing a pH measurement protocol.

The first is product composition, as pH values are only applicable to aqueous systems. Another factor is the presence of significant quantities of water-miscible polar components such as alcohols and glycerin. These will affect the accuracy of the measured pH and, potentially, the precision of these measurements. It may be necessary to conduct serial dilutions of the product in order to obtain an accurate pH measurement. If an accurate measurement is not absolutely required to assure product safety, acceptance, and performance, it may be sufficient to confirm the stability of a relative pH measurement on the product "as is." However, the precision and reproducibility of such determinations should be confirmed, rather than assumed.

Another important consideration is temperature. Any pH determination is a function of temperature, and care should be taken to assure that all measurements are made at a specified temperature, or that temperature compensation, using an integrated temperature probe for example, is used. Products stored at accelerated temperatures should be allowed to reach ambient conditions prior to pH measurements.

The final general factor is product consistency. A highly viscous product may reduce the interaction of the aqueous phase with the probe and hence affect the accuracy and reproducibility of the pH measurement, as well as the response time of the probe. It may be appropriate with such products to consider the use of specially designed probes, and product dilution.

Color

The color of a topical consumer product can be an important component in consumer acceptance, and potentially indicate to the consumer whether product is safe or effective. Color change can be indicative of the chemical instability of one or more components and can sometimes be used as a surrogate measure of chemical stability, particularly in the early phases of development.

Product color can be evaluated visually or instrumentally. Visual assessment will typically involve comparison to a standard, either fresh or from product stored under cold conditions, or a "physical" color standard. The assessment can be a simple determination of a detectable change with no attempt to measure the extent of change. This permits a determination of the length of time required to attain a detectable color change at a given temperature. The assessment can involve a simple comparison of the test product with the reference, either product or physical standard. Alternatively, an odd product can be selected from a set of three products—two of either the test or standard.

A series of physical reference standards of varying established degrees of color change can be also used in visual assessments. The reference standard which best matches the color of the test product is determined, permitting estimation of the degree of color change.

Ideally, a panel of trained assessors should be used, whose ability to distinguish color changes is known, permitting appropriate statistical evaluations of its results. Where this is not practicable, more than one evaluator, preferably three or more, should be used.

There are a number of instrumental color measurement systems available that can provide rapid, quantitative color measurements tailored to specific needs, such as those offered by HunterLab (Reston, VA) and Konica Minolta (Ramsey, NJ). Most instruments use the L^*a^*b color space measurement system in which L is lightness, and a and b represent color opponent dimensions. The instrumental method will depend to a great extent upon equipment availability, product characteristics, the amount of product required for evaluation, and the accuracy and precision required. Further, it is important to design a measurement protocol that provides for a maximum of reproducibility. Another factor is interpretation of the color space measurement system results. The instrumental data will provide information relative to the extent of color change, but not regarding its relevance to consumer perception, consumer acceptability, or relationship to component chemical degradation. These will have to be established separately.

More recently, the widespread availability of digital photography provides an additional approach to color evaluation. Digital color photographs of stability samples of even relatively small amounts of product can be obtained; such photographs can be useful in the early stages of product development when batch sizes are typically small. The photographs can be evaluated by visually or via digital imaging to provide relative or quantitative assessments of color change. This approach is particularly useful in "rapid" stability testing of prototype products. The digital color photographs also provide a convenient means of recordkeeping.

Odor

There two primary aspects regarding the stability of product odor. The first is the critical part product fragrance plays in the consumer acceptability of the product. A decrease in fragrance intensity caused by loss of fragrance components to the package or environment can diminish product acceptability, as can changes in fragrance character produced by preferential loss of selected fragrance components or their chemical degradation. The products of fragrance component chemical degradation can also generate "off-notes" which detract from the fragrance character.

Secondly, a change in product odor may indicate a chemical degradation of one or more (non-fragrance) product components. Such changes may have a deleterious effect upon product acceptability (i.e. rancidity of fatty components).

Olfactory assessment is probably still the primary method of odor evaluation. Typical protocols are analogous with visual assessment of color. The test sample is compared to a reference sample (product or fragrance sample) for character and intensity. Triple comparisons (two references with one test, or two tests with one reference) with selection of the odd sample are often used with trained panelists. The primary determination is "different from reference," although attempts to estimate the degree of difference can be made.

Instrumental methods of odor evaluation, often termed "electronic noses," are also available. Electronic noses usually have three major components: sample delivery to the detectors, a method of detection, and a computing system. These instruments cannot replace human olfactory evaluation in the determination of consumer acceptability, but can readily detect differences in fragrance intensity through evaluation of the concentrations of pre-determined components and can indicate the presence of "new" components that are indicative of chemical instability.

Physical Stability Measurements

The primary measurements involved in evaluating physical stability are appearance/homogeneity, weight change (usually loss), rheology, particle or dispersed phase droplet size, and conductivity. Some of these are particular to a given formulation type and other measurements may be needed for certain situations. With the exception of appearance, essentially all physical measurements are instrument-based.

Appearance/homogeneity

Appearance is perhaps the oldest stability measurement and is still a valuable tool, as it is quite relevant to consumer acceptance and perception. Appearance measurements can vary from rather subjective descriptions to highly descriptive evaluations based upon visual scales of various attributes.

A primary attribute observed is the physical homogeneity of the product such as phase separation and creaming/sedimentation of dispersed phases (liquid or solid). Another attribute is visually apparent changes in product rheology. Visually observed color changes are discussed under chemical stability measurements. A visual observation of product leakage or migration from the package is indicative of instability. This is usually most important when prototype or commercial packages are used in stability testing conducted during the later stages of product development, as it is a function of the performance of the product/package combination. However, product migration from a tightly sealed inert container used in early product development is often indicative of potential stability issues and the need for special packaging.

Except when appearance observations are recorded as scaled evaluations or a degree of change from a reference product, visual appearance measurements typically provide a "time to observable change" result at a given condition of storage or exposure such as centrifugation. Unless the changes are due to a First Order chemical reaction, there is no scientific rationale for applying an Arrhenius "type" of evaluation to data from accelerated storage conditions. Nonetheless, various approaches to extrapolation of appearance (or other physical data) from accelerated conditions to ambient are often attempted, and some may provide a degree of predictability. It must be recognized, however, that these extrapolations cannot be extended beyond the time limits of the data with a high level of confidence.

Changes in product homogeneity may be observed visually, but can also be measured quantitatively. This will require taking product samples from various sections of the storage container such as top, middle, and bottom, and subsequently determining product density (weight of a specified sample volume) or the amount of a particular component in a specific sample volume. Comparison of results from various sections of the container will provide quantitative indications as to whether creaming/sedimentation is occurring and its rate at a given storage condition. Other physical measurements such as rheology, dispersed phase particle/droplet size, and conductivity (discussed below) can also be conducted on the container section samples to provide measures of product homogeneity.

Weight change

As with visual assessment of product leakage/migration (discussed above), measurement of product weight change is typically conducted in either prototype or commercial packages as it is an evaluation of the performance of the product/package combination. These measurements are typically determinations of total product/package mass (weight). A major consideration is selection of balance

equipment sufficiently sensitive to detect relatively small changes in a comparatively large total mass.

Since evaporation of volatile components is proportional to temperature, extrapolation of product loss at accelerated temperatures to ambient conditions may prove helpful in predicting the latter. However, the potential for step-function changes at a particular temperature due to effects upon product consistency (emulsion separation) or package function should be recognized.

Rheology

Measurements of rheology can range from single shear rate evaluations such as those obtained with penetrometers, texture analyzers, and Brookfield type or kinematic viscometers, to complete shear rate/shear stress rheograms. Selection of the appropriate measurement should be primarily based upon the type of rheological data needed to detect changes in product consistency relative to product performance and acceptance, or absolute rheological changes predictive of the latter. Availability of rheological testing equipment and testing resources are also factors. The latter factors usually dictate the use of single shear rate measurements for most stability testing with more detailed rheological evaluations reserved for early in product development, establishing rheological correlates with product performance or acceptance parameters, "trouble shooting," and special situations in which complete rheograms are required to monitor product rheological stability.

There are a large number of commercial rheology measurement instruments available. Apart from the type of rheological measurement desired, factors such as product consistency, initial cost, ease of use, data acquisition interfaces, and company experience and preferences will influence selection of the specific instrument. Pragmatically, the selection is often based upon available equipment.

There are a variety of factors that can affect product rheology, which makes extrapolation of the data obtained from a product exposed to various accelerated conditions to ambient conditions problematic at best. Typically, product samples stored or exposed to accelerated conditions are permitted to return to ambient conditions prior to the rheological measurement. However, it may be appropriate to also obtain a rheological measurement at the accelerated temperature for comparison with a product allowed to return to ambient temperature (separate samples). It should also be recognized that a rheological measurement can affect the product, and that repeated measurements of the same sample will not necessarily be replicates. However, repeated measurements can be instructive, particularly when using a single shear rate evaluation.

Particle/droplet size

Measures of the size and distribution of dispersed solid phase particulates in suspensions and dispersed phase droplets in emulsions are an important indication of the stability of these types of thermodynamically unstable product types. The primary types of particle size measurement techniques use laser diffraction,

dynamic light scattering, acoustic spectroscopy, sedimentation, or image analysis. While a discussion of the features of each is beyond the scope of this chapter, it is noted that particle size can be assessed using optical microscopy with calibrated slides and manual assessment of particle size and number. The latter is extremely time consuming and is probably rarely used given the large variety of commercial instruments available.

Each instrumental method of particle size analysis has advantages and disadvantages in terms of size limitations, suitable product types, precision, and sensitivity. Each factor should be considered when selecting the appropriate methodology. Pragmatically, instrument availability will often dictate method selection.

A principle purpose of particle size measurement in stability testing is the determination of any change, typically an increase, in mean particle size and distribution that would be indicative of incipient product instability. Therefore, it is important that the selected methodology provide reproducible results that can be compared over time and after exposure to accelerated conditions. Exact or accurate values may be of less value in these comparisons than those that are reproducible. Consistency of sample preparation and the degree of compatibility of the instrument with the product type are important factors in obtaining reproducible results.

Most measuring instruments will provide particle size distribution results from which statistical descriptors such as mean and medium size, and standard deviation can be obtained. The distributions can be presented as either number of particles at each particle size, or the total volume (also area) of particles at each particle size. Both types of distributions are informative. For example, it may be possible to have a bi-modal distribution, in which the numerical majority of particles are relatively small, but in which the minority of larger particles constitute the bulk of the total particulate volume, hence mass. It is important to develop an understanding of those aspects of the particle size characterization that are indicative of the stability of the product during the course of product development.

Although most particle size measurements will be made on product samples returned to ambient conditions after exposure to accelerated conditions, some instruments may have the capability to measure samples at higher temperatures. Comparison of these values with those obtained at ambient temperatures either from a reference product, or product previously stored at the higher temperature can be indicative of the recovery of the product after transient exposure to the higher temperatures.

Conductivity

Evaluation of product conductivity is most often used in product development and processing to ascertain the type of emulsion present. Only emulsions with an aqueous based continuous phase are conducting and will have a measurable conductivity value. Conductivity is typically measured with special probes in conjunction with a pH/Ion meter. However, conductivity measurements on stability test product may

be helpful to elucidate whether or not non-visually apparent changes in emulsion structure have occurred.

Summary

Topical product stability testing is an ongoing process that proceeds throughout the stages of product development, and into commercialization and post-marketing. The specific objectives of stability testing and subsequent protocols will vary with the nature of the product and stage of development as well as the reason for the development (i.e. prototype for evaluation, consumer acceptance or clinical testing product, or commercialization). However, a typical overall objective is determination of its shelf life, the length of time a product and package combination will remain fit or suitable for use. Other objectives include determination of various environmental conditions upon a product's fitness for use, the impact of alternative packaging, the impact of new components, alternative raw material sources or component replacements, alternative/new processing conditions and equipment or manufacturing sites, and resolution of specific stability issues.

Topical product stability involves both chemical and physical aspects, with the latter often associated with the nature of the product formulation. Exaggerated environmental conditions such as relatively high temperatures, high light intensities, and exposure to centrifugation, and vibration can be used to accelerate the rate at which chemical and physical changes occur. Certain of these, especially the effects of temperature upon First Order chemical reactions can be confidently extrapolated to predict rates at ambient conditions. Accelerated testing of other parameters such as physical changes may require comparison to similar products of known stability to estimate ambient condition stability.

This chapter provides an overview of the key factors that should be considered in the evaluation of topical product stability. This should serve as a reference to those new to the field and as refresher to those experienced in topical product development. No attempt has been made to provide example stability testing protocols since each should be specific and customized to the nature of the product, its developmental objective, stage of development, specific needs/objectives, and resource availability including financial and time constraints. The reader is encouraged to make use of the many examples in the literature, developing organization records, and the expertise of colleagues, along with his or her own experience in the design of stability testing protocols.

There are no precise stability testing requirements for cosmetic topical products in the United States. Therefore, each organization has the responsibility to establish specific criteria constituting fitness for use and determining the corresponding shelf life. This permits the use of both well-established testing techniques and the use of innovative new approaches.

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CHAPTER 17

Preservation of Topical Formulations: An Historical and Practical Overview

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Key Words

Good Manufacturing Practics (GMPs), pH, Water Activity, Microbiology, Preservation Systems

Historical Perspective on Microbiology and Preservation in Personal Products

Introduction

The history of microbiology can be compared to the history of another science that has evolved over the millennia: astronomy. In both cases, people had observed a natural phenomenon and drawn conclusions from it, without a true understanding of the detailed scientific validity and guiding principles behind their conclusions. The understanding began with simple cause and effect correlations. Without understanding what or how, people have enjoyed some of the benefits derived from microbiological processes, such as fermentation. Simultaneously, they knew that undesired occurrences happened to them, their crops, their livestock, or even other resources derived from organic matter, if not protected from these unknown elements. The idea, significance, and impact of "spoiling" was well understood, even though the underlying cause remained unknown.

It was not until the 1600s when Anton van Leeuwenhoek observed bacteria using a single-lens microscope of his own design and Robert Hooke made the first recorded microscopic observation of molds,[1] that the first concepts of microbiology began to emerge. However, the actual field of microbiology didn't really come to recognition until late 19th century, propelled by the pioneering work of Ferdinand Cohn, Louis Pasteur, and Robert Koch, now regarded as the fathers of microbiology.[1,2] Cohn, who studied algae and photosynthetic bacteria, was also the first to formulate a scheme

for the taxonomic classification of bacteria and discovered spores. Pasteur is most famous for his series of experiments designed to disprove the then-widely held theory of spontaneous generation. Koch is best known for his contributions to the infectious theory of disease, proving that specific diseases were caused by specific pathogenic microorganisms. Koch's contribution was particularly important, as he was one of the first scientists to focus on the isolation of bacteria in pure culture. And so at last came the understanding of what causes spoilage of materials and products as well as spread of infectious diseases, long after people were already using cosmetics, facial paints, and other beautification products.

The period in human evolution when an actual cosmetic use is noted can be traced to the time of first settlements and birth of human nomadic tribes.[3] Once humans mastered the art of cultivating plants during the Neolithic Age (~ 10,000 years ago), the creation of permanent settlements allowed humans the "luxury" of beautifying themselves. Once small nomadic groups settled into more permanent communities, evolving into a cultural identity, such as Sumerian and then Egyptian, different classes and castes of people started to emerge, for whom the basic biological need to survive was no longer the major daily concern, allowing opportunity, time, and energy to make themselves look attractive to members of the opposite sex, and reinforce their status in society.[4,5]

During these early times, any products applied as part of a beautification process were naturally derived, and had to be freshly prepared before actual application, or would need to otherwise be protected from spoilage. When the Industrial Revolution yielded mass production, storage, and distribution, the need to preserve freshness became crucial. In contemporary times, the fundamental issue of spoilage remains a challenge to which we should apply modern scientific rigor and engineering to overcome. Despite all that we have learned, our adversary is constantly adapting to our solutions, requiring us to adjust our approach simultaneously.

Microbes as Agents of Spoilage

It is currently accepted that life on earth began at a microbial level and evolved through more complex organisms, living in the primordial soup of our early planet.[6,7] The early microbes thrived in this extreme environment, and have advanced since that time to occupy nearly every environmental niche on our planet. We now understand how truly omnipresent microbes (bacteria and fungi) are, even more than was suspected as recently as 20 years ago. The latest research shows the presence of bacteria in the most hostile environments. Not only around the thermal vents on the surface of our planet, but even more extraordinarily, thousands of feet underwater or as far underground as two miles, where immense pressure and heat can melt rock, and where nothing is expected to be alive.[8-10]

The metabolic diversity and adaptability of microbes is extraordinary, and is a result of four billion years of evolution in the extreme habitats where selective pressure is often the greatest, coupled with a short generation time that allows relatively fast adaption to a new environment. Bacteria have evolved to actively maintain an ideal

internal environment despite the external habitat, and use a diverse range of food sources, both organic and inorganic, as growth media. At a very basic level, though, bacteria require water, a means to control the osmotic concentration of its aqueous environment, and a carbon source to thrive.

Although most bacteria require a balanced environment of water, pH, temperature, and nutrition to survive, water is particularly important to the industrial microbiologist and formulations chemist. Because the osmotic concentration of a habitat has such profound effects on microorganisms, it is useful to be able to express quantitatively the degree of bio-available water. Microbiologists developed the concept of **water activity (a_w)** for this purpose and an adequate explanation found for this concept is provided by David C. Steinberg in his book *Preservatives for Cosmetics*.[11] He points out that honey should be an ideal growth medium for microorganisms as it contains water and sugar; however, nobody has ever needed to preserve honey–the reason being that sugar ties up the water and makes it unavailable for microorganisms to grow. In technical terms, water activity is a ratio of the water vapor pressure of a formula compared to that of pure water at the same temperature. Water activity is measured by an instrument that displays a value between 0.000 (completely dry, absent of available water) to 1.000 (pure water) in a sealed chamber at a set temperature, and can be a powerful tool guiding the necessity for preservation.

In general, most microorganisms of industrial concern cannot grow below a certain a_w threshold. Molds cannot grow below 0.7, Gram-positive bacteria cannot thrive below 0.8, and 0.95 is the level ideal level to support the growth of most all bacteria. The significance of this fact is that most aqueous topical and consumer products (such as creams, shampoos, and syrups) are designed with aw far above the 0.7 minimum. However, in some instances it is possible to lower this value and thus limit the dependency on chemical preservation by incorporating low molecular weight, water-soluble compounds (such as salts or glycols).[12] Unfortunately, this solution is rarely feasible, as it may affect the aesthetics or stability of the formula. Additionally, given the breadth of carbon sources that can be metabolized by bacteria and fungi, this combination of water and nutrition source creates an ideal environment of microbial growth, and makes product preservation through the addition of biocides often mandatory.

The challenge to the formulation chemist is to create a formulation that cannot only withstand the introduction of microorganisms during the industrial process, but also survive repeated insult and "re-inoculation" by the consumer during routine use into a system that is almost perfectly suited for microbial growth and survival. Contamination of a product may originate from plant environment (air, water, personnel), the raw materials, or during use of the product. Strategies of prevention to all three of these facets involved in product development must be considered when creating a product that is primarily aqueous.

While it is important to understand that skin care products are typically not

designed to be sterile, they all need to adhere to appropriate regulatory criteria for safety with set limits. Most often, the presence of low levels of microorganisms is to be expected as long as they are inhibited from proliferation and are non-pathogenic. A product that adheres to such local regulatory qualifications is considered "clean" and safe.

Clearly, contamination of topically applied products can occur at any point and can originate from multiple sources. Even before production begins, the quality of raw materials, including the packaging components, their transportation, storage, and handling can contribute to a significant bio-burden. It is essential therefore to understand the importance of using clean, unadulterated raw materials, which is why so many companies have developed a comprehensive program of handling and screening incoming materials. One cannot rely on an introduced preservative as a solution to poor process, especially considering the fact that accumulation of bio-burden can be a compounding issue with each subsequent step.

Basic Principles of Preservation

As mentioned previously, preserving skin care products is a challenging task for a number of reasons. The control of bacteria introduction, proliferation, and pathogenicity should be considered at the following steps:

1. Raw materials and supply chain up to formulation
2. Formulation, production, filling, and storage/distribution
3. Consumer use

The first step is clearly to ensure that the raw materials to be used are not contaminated and ideally not subject to microbial proliferation, which in itself is a major challenge, considering that many of the ingredients are in fact an excellent source of nutrition for microbes. Assigning a risk level or "grade" to a material is a good and smart practice. If a material is of high risk, such that it has been derived from plants or other organic material through non-aggressive means and there is no treatment to eradicate or inhibit microbial growth, it may as well be assumed that it will contain a large amount of various microorganisms. Likewise, proper handling, treatment, and subsequent production and formulation demands will be much lower if all the incoming raw material were synthetic and hostile to the microbial growth by their very nature, such as very high/low pH, low water activity or content of solvents and residual antimicrobial agents such as alcohol or glycols.

One must be mindful of the original source of the material as well as the means by which the material was treated and its final form. Frequently, the same raw material is available in several different forms; for example sodium lauryl sulphate (SLS) is a popular detergent that can be supplied at various concentrations (30% solution, 60% concentrate gel). While the gel should not require any protection by preservation and should be in fact bactericidal, the diluted 30% version must be protected with the addition of preservative(s).

When assessing various raw materials, it is essential to keep in mind that contamination is not a phenomenon specific to a particular product or particular

organism, but rather it is proof of and example for evolutionary adaptation at work. It has been well documented that materials generally accepted as extremely hostile to microbial growth, such as alcohol, Povidone or Benzalkonium Chloride, can become a source of contamination in some rare instances when an adaptive bacteria strains were allowed to be persistently exposed to such materials.[13-15]

Water, the main component of the majority of topical formulations, is the media where bacteria prefer to live and grow. Because water is omnipresent in most manufacturing locations and if not added directly to a formula is often used in other steps such as cleaning of the equipment, as an additive to raw materials, or as a coolant for special equipment, there are many opportunities for contamination. Once the task of selecting and protecting the raw materials, including water, has been outlined and devised by internal controls, it is time to manufacture the formulation.

The challenges of large-scale production are much different from those at the laboratory bench. First and foremost, there must be a comprehensive hygiene plan outlining detailed procedures to clean all elements of the production chain, including disassembly of all valves, house connectors, mixers, tanks and the like. Cleaning on the surface will sooner or later lead to contamination. Even before a seal within a particular piece of equipment is replaced, it frequently becomes a major source of contamination due to the residual organic matter and water gathering around it and sticking to it. Eventually around that area of organic matter which is constantly exposed to water, the formation of a biofilm can be found. That is, a highly resistive matrix of live bacteria that are slowly growing under the protection of complex and thick layers formed from the dead cells, secretions from the live cells and the residual ingredients that didn't get completely washed off. Eventually such thick film will break, releasing a huge amount of bacteria that will cause a massive product contamination in several production campaigns.[16]

There have been several books written about proper cleaning and maintenance of industrial equipment to prevent microbial contamination during production.[17-19] Sufficient to say that production, if done on the cheap, in a poorly maintained facility with lackluster controls and sanitization procedures will be the single most challenging step in the production of clean products. However, once the production campaign is over, the task isn't quite done yet. Even after all units have been filled and tested, this does not ensure that the product is, in fact, clean. It is the domain of the quality department to understand that microbiological testing is a sampling procedure with certain statistical limitations, and since it is not practical and economic to test every single unit, it is assumed that a small fraction of the samples tested reflects the quality of the entire batch. While very rare, there are situations when a product that passed all the testing was released to the market only to be recalled several weeks later due to significant microbial growth which may manifest itself as sudden bulging of the packaging unit when small numbers of the bacteria introduced during production at the limits of detection are now growing and fermenting the final product.[20]

The third and final phase affecting contamination during the life of a product is in the hands of the consumer. In most developed countries, where levels of self-hygiene are high and people frequently clean their entire houses, notably their bathrooms, with products that contain antimicrobial agents, one would believe that consumer level contamination would be a rarity. However, many studies still show the bathroom to be a major source for contamination[21,22] and this is the typical storage and usage location for most topical products and cosmetics. Comparing to what was norm just in the late 1950s, currently we have greatly mastered the art of preservation.

An important aspect of designing much better products stemmed from the understanding of the potential contaminants in a typical bathroom environment. The way to chemically preserve a product and to package it is key, so that the possibility of introducing outside contaminants is minimized. Companies nowadays conduct and should strive to conduct more consumer in-use studies. Observing how people actually use and misuse products is key to successful product development. Thanks to those earlier studies it is now well known, for example, that a large portion of users frequently add water to their shampoo bottles when they are close to emptiness just to get that extra few uses.[23,24] Leading makeup producing companies have learned from consumer behavior studies that women frequently wet their blushes and powders with their saliva. These examples demonstrate the need for highly customized preservation approaches that include proper chemical preservation as well as protective packaging that considers consumer use patterns and behaviors.

Another important element of consumer use is understanding the potential duration of application for a particular product. Shampoo is aimed to come in contact with the body for a short duration and then to be washed off, while a typical makeup blush is aimed to be applied for many hours. Therefore, it is important to assess the other attributes of the preservative system, including potential for skin penetration and to understand how the entire system interacts with the skin, how frequently it may become diluted, mishandled, or exposed to contamination.

This relatively short and general introduction on preservation would have one believe that we already have all sort of choices for preservation; however, over the years the task of preserving cosmetic products has become particularly challenging due to the increased scrutiny and frequently uneducated view of their potential health and environmental impact.

Preservative Types and Their Usage in Personal Care Products

The preservatives used in consumer products can be categorized into several major groups, most often based on their common chemical structure. However, it is important to note that some of the individual chemistries within each group will differ in other important aspects that will be discussed, such as potential for negative public relations or sensitivity to pH changes within the formula. Regardless of the preservatives employed, one must acknowledge that preservatives are amongst the

most studied chemistries within the entire category of skin care ingredients. They have a long history of use, and extensive toxicological and clinical safety studies and reviews that are frequently scrutinized and re-evaluated. Preservatives are one of the few ingredient types actually regulated in some regions. Europe has its official list of preservatives approved by independent scientific review organizations. The list is frequently reviewed and updated based on the latest scientific data. It is called European Annex VI–European Commission Health and Consumers List of Preservatives Allowed in Cosmetic Products.

In the United States, the Cosmetic Ingredient Review (CIR), lead by a panel of medical experts including dermatologists, pathologists, oncologists, and toxicologists, collaborates with the US Food and Drug Administration (FDA) to provide a review and assessment of the safety of ingredients used in cosmetics.

This chapter will present various preservative groups. It is important to point out that the regulatory status of the various preservatives is purposely not included, because the current state of regulation is very dynamic and varies from region to region, even country to country. The reader is advised to check the regulatory status of the preservative intended for use relative to the time of product development, region of use, and other applicable considerations. It is critical for the proper application of the various technologies described here to verify the up-to-date regulatory status for the region in which the final formula will be marketed. The chapter will list preservatives by their chemical classification as well as by their relative popularity in the industry within the past few decades.

Formaldehyde and Formaldehyde Donors

Formaldehyde is one of the most controversial molecules. While it is no longer used in cosmetics, there is an entire class of molecules called formaldehyde donors whose mode of action is to gradually breakdown to yield molecules of formaldehyde.

Formaldehyde is a simple molecule of chemical structure HCOH. At room temperature, it is a gas that is highly reactive, and when mixed with water it immediately undergoes a reaction yielding a mixture of methylene glycol, short polymers of itself, water, and undisocciated formaldehyde commonly referred to as formalin. The molecule has been widely studied and is well understood, being that it is largely used as a precursor to many reactions in a multitude of industries. The main concern with gaseous formaldehyde is its reactivity and toxicity. The molecule is well recognized as an allergen and a potent carcinogen when inhaled.[25]

However, there are several issues that complicate the matter.

The first issue is that, in fact, a water-based "solution" of formaldehyde doesn't contain much of an actual formaldehyde molecule, as the equilibrium is strongly towards methylene glycol. Therefore, as such, formalin contains very little formaldehyde. Many would argue that the toxicology assessment and risk associated with formaldehyde (gas) should not apply to the water-based solution, as it is a different chemical entity. Nevertheless, formaldehyde is being slowly released over time, and especially with increased temperature or significant changes in pH, it

may be released more rapidly.

The second argument is the fact that formaldehyde is a part of metabolic reactions and it is actually formed in every living cell. Some therefore argue that it is a natural component, even though at the cellular level its half-life time is rather momentary and it is quickly metabolized into further compounds (such as acetic acid) so in reality the duration of cellular exposure is extremely minimal.

So while no formaldehyde is actually added to the formulation—but rather chemists can now add relatively inert compounds that only gradually break down what is already in an aqueous phase—they immediately release formaldehyde into the above mentioned system in equilibrium. This brings the debate on the safety of the formaldehyde or formaldehyde donors or methylene glycol to a question of point-of-view. One could argue both ways—as surely the levels of free formaldehyde that have been historically used in personal care and cosmetic products are significantly reduced and far below any levels that would be considered a significant risk. However, it is also true that high usage of formaldehyde is associated with certain health issues, such as dermatitis, allergic response, and sensitization.[26]

However, as mentioned above, all independent scientific reviews allow the use of formaldehyde donors and conclude that these donors, when used as instructed, are safe for general preservation in cosmetic products for the general populous.

Formaldehyde Donor Chemistries

If the formulation chemist decides to use these versatile and highly effective ingredients, there are several choices. They do share some common characteristics, such as good compatibility with other ingredients, good solubility in water, and relatively good stability; however, some minor differences do exist and are described below for each specific chemistry. While the list isn't all-encompassing, these are the most popular of formaldehyde donors currently is use. It is also important to note that a frequent inactivation of all these chemistries with proteins and avobenzone (popular organic UV-blocker) has been observed.

DMDM Hyndantoin

This is the most popular of all formaldehyde donors. It is relatively widely used, especially in rinse-off formulas and frequently with the addition of Thiazolinones (described later in this chapter). This particular molecule is rather stable in a wide range of pH from about 3 to 9 and can withstand temperatures up to 80°C. The ingredient is available in two forms: as a 100% solid powder and as a solution of approximately 55% of the active compound. The recommended use level is about 0.3%. As with any preservative, it is formula dependent and should always be verified by preservative efficacy testing per regional requirements.

Imidazolidinyl Urea and Diazolidinyl Urea

These two similar formaldehyde donors are frequently found in value propositions (store brands, non-branded products). Interestingly, they show relatively low activity against molds, which requires addition of potent antifungal agents such as parabens.

Both of these chemistries are also less heat-tolerant than DMDM and should not be heated above 60°C for extended periods of time (more than 24 hrs). Typically used at 0.3%.

Quaternium-15

This once popular formaldehyde donor seems to be on the decline and its usage is significantly lower in personal care products, especially since it has been studied by many dermatologists as the representative molecule for all formaldehyde donors.[27] Just like other formaldehyde donors, it is compatible in a wide pH range (~ 4–9); however, it is more sensitive to high temperatures and frequently reacts with other ingredients at temperatures just above 50°C, causing product discoloration. Based on previous studies, quaternium-15 has the highest potency to release free formaldehyde.[28] It is most efficacious at levels around 0.15%

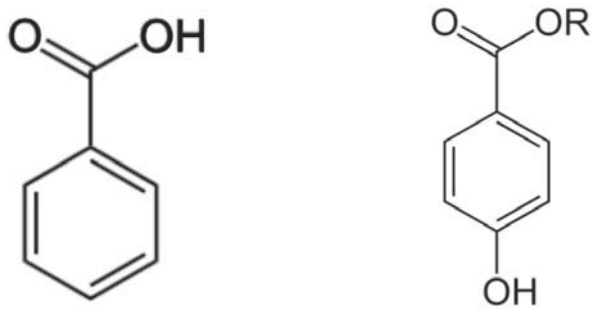
Sodium Hydroxymethylglycinate

Interestingly enough, despite the loud and clear opposition to any type of formaldehyde releasing chemistries in the new wave of natural, organic, or otherwise alternative products, this is one preservative that seems to appear frequently in such products that claim to be "nature-friendly" or "chemical-free." The possible explanation may be that out of all the formaldehyde donors, this chemistry is very difficult to analyze via current analytical methods and will frequently not show any free formaldehyde in the final product.[29] In addition, because it is synthesized from glycine (a simple amino acid that is widely present in nature), some suppliers have noted this fact while omitting the fact that it also requires a molecule of formaldehyde in the process of synthesis. The typical use level is 0.4%.

Parabens

Same as with formaldehyde donors, parabens are currently considered as one of the most controversial preservatives.

Chemically parabens are esters of parahydroxybenzoic acid, so structurally they somehow resemble the more popular and favored preservative; benzoic acid, as shown in **Figure 1**.



Benzoic acid Paraben (where R = methyl or ethyl)

Figure 1. Side-by-side comparison of the structures of benzoic acide and a common paraben

The most popular and still relatively widely used parabens include simple esters with non-branched chains, such as methyl-paraben, ethyl-paraben, and propyl-paraben. Previously, formulation chemists could also choose longer chains, such as butyl paraben or iso-parabens; however, their usage has been almost completely abandoned after recent assessment from the Scientific Committee on Consumer Safety (SCCS) which requested further safety review of long-chain and branched (iso) chained parabens.[30]

Paraben activity has been linked to side-chain lengths; the longer the chain, the more active the preservative; at the same time, longer chains impart reduced solubility in water, making the incorporation into formulations challenging. While all parabens are very difficult to dissolve in water, they have a good solubility in glycols and oils. As with other preservatives that have proved hard to work with, some suppliers, in an attempt to improve solubility, developed salts, such as sodium methylparaben. While these salts are easily dissolved, the active version is the ester and so if using salts, pH adjustment must be made to allow liberation of the free paraben ester. Of note is their ability to migrate into the oil phase, where they are not effective in preserving the product. Overall, the safest addition would be pre-dissolving parabens in glycols or adding them to the water phase at high temperature (above 70°C).

They are mostly effective against molds, and in fact they were the primary preservatives used for a long time to protect formulated products from potential mold contamination. Their low price, wide acceptance, and mostly non-irritating and non-sensitizing nature made them one of the most popular preservatives in the industry. Parabens also are well suited to preserve products that have relatively low risk of bacterial contamination due to their limited water content but that still might become contaminated by mold, which can spread even in products with little water, such as ointments or certain lotions.

The controversy around parabens came from the fact that while they have been widely used, greatly tolerated, and preferred by dermatologists as having fewer dermatological issues than other preservatives, a 2004 study was published which showed the presence of parabens in patients with breast cancer.[31,32] A link has been postulated that asserts a causative relationship between parabens and breast cancer. Further studies could not reproduce the link; however, media attention to the original study made this a matter of fact, forcing most companies to remove parabens and replace them with alternatives that were less studied and for which they possessed limited safety data.

While additional studies never confirmed the link between breast cancer and parabens, other studies revealed a possible estrogen-like activity. While *in-vivo* safety data shows that the activity is about 100,000 times lower than that of estradiol and it is also limited to the longer chain parabens (e.g. butylparaben), the damage is done, despite the frequent review and reassurance of safety by impartial scientific review boards (e.g. CIR and SCCS).[33]

Despite parabens' negative publicity and the many efforts to outright ban them, one can still find a large selection of products preserved with parabens. The typical level should be about 0.20–0.30% for methylparaben and 0.10–0.25% for ethylparaben and propylparaben. Usage of another, more bactericidal preservative (such as phenoxyethanol or benzyl alcohol) is almost always required. The recommended levels are based not only on regulatory restrictions (which should be checked frequently, due to ongoing regulatory discussions) but more so on their activity and solubility in water.

Organic Acids

Organic acids are considered to be some of the more friendly preservatives, used in many products that are positioned as "natural" or "chemical-free." While they are highly efficacious, this is only true when they are in their undissociated form at a relatively low pH—below 5.5 but dependent on the actual type of the organic acid. As the pH is increased, each of the organic acids will lose its activity based on pKa values, i.e. quantitative measure of the strength of an acid in solution. Unfortunately, the ones that have higher pKa values and so could potentially be still active closer to the neutral pH are also weaker preservatives overall. Their recommended usage levels, shown in **Table 1**, are highly dependent on formula composition and final pH. It is also important to verify the latest regulatory limitations, as various regions regulate usage and maximum allowable concentration for consumer products.

Table 1. Organic Acid comparison: pKa, pH, and use levels

	pKa	Ideal pH range	Recommended use level
Benzoic acid	4.20	Up to 4.5	0.2 to 0.5%
Sorbic acid	4.76	5.0	0.1 to 0.4%
Salicylic Acid	2.97	Below 4.0	*
Dehydroacetic Acid (DHA)	5.27	5.2 to 5.8	0.2 to 0.5%

Data derived from The Merck Index, 13th ed. (2001)[45]
*Salicylic acid is a monographed drug in the US; however, it can be used effectively from 0.2% up to 0.5% as a preservative providing the formula has low pH. At higher levels it is usually used as an active drug.

All organic acids exhibit low water solubility, but like all other preservatives they must be present in the water phase in order to provide the desired protection against microbial spoilage. It is generally recommended to add them in the form of a simple salt (such as sodium benzoate) and then covert to acid by gradually adjusting the formula's pH down to the optimal level for the particular organic acid. Another very effective approach is to use the combination of the salt and the corresponding acid (e.g. benzoic acid). This way it is possible to eliminate the need for another pH adjusting ingredient or acidic buffer system, such as (frequently used) citric acid.

The chemist should be mindful of appropriate ratio and overall concentration of the acid as to respect local regulatory requirements.

Benzoic acid

Benzoic acid (or sodium benzoate) is by far the most popular of the organic acids, despite its relatively low effective pH range. It is recognized as GRAS (Generally Regarded as Safe), frequently added for preservation in many foods, and has been found in nature.[34]

When used as a sole preservative system, its usage is mainly limited to rinse-off formulas, as it is rather undesirable in leave-on formulas of acidic pH (< 5.0). However, recently there have been several suppliers that incorporated this ingredient as a blend with other, more pH friendly preservatives for use in leave-on products and wipes. While the rules of basic chemistry would dictate almost complete inactivation of this acid at pH above 5.0, it seems there is a synergy in these systems, because the presence of benzoic acid provides additional benefits not realized when it is removed.

Final assessments should be made rather carefully, because potential shifts in pH over the shelf-life of a product may cause sudden inactivation of the organic acid. This author has noticed that sometimes the difference between a preserved product and inactivated preservative can be as narrow as 0.3 units on the pH scale.

Sorbic Acid

Much of what has been said above would apply to sorbic acid or its more popular salt, potassium sorbate. The important exception to note is the fact that sorbic acid seems to be more active against fungi and less effective against bacteria. While its pKa value is higher than that of benzoic acid, its activity and its solubility in water are lower. Since this behavior is typical for all organic acids, it is important to keep in mind when formulating with such chemistries. After all, even if the salts are highly soluble, the antimicrobial benefits are derived from the acid form and one must be mindful not to create an oversaturated solution. Additional limitation for the use of sorbic acid has to do with its tendency to discolor some formulas, the most probable mechanism being UV induced degradation but other pathways could possibly contribute to this discoloration phenomena.[35]

Just like with benzoic acid, there has been a recent influx of new blends that seem to provide a synergy between the various ingredients and thus allow the chemist to use them at higher pH; however, a careful assessment is required to ensure that the formula is indeed well-preserved, doesn't discolor, and that its pH stays stable over the shelf-life of the product.

Salicylic Acid

Salicylic acid is listed as a preservative in Europe; there it requires a label warning: *Not to be used for children under 3 years of age*; however, in the United States, it is classified as a monographed drug when used at levels above 0.5%. Its usage as a preservative is also limited by its very low pKa value, and so, in effect, any formula that relies on salicylic acid for preservation should be under a pH of 4.5, depending

on the concentration and other ingredients. Considering that benzoic acid doesn't present the same regulatory issues and maintains its activity over a wider pH spectrum, most formulas may as well be preserved with benzoic acid instead.

However, this shouldn't disqualify this chemistry altogether, as it is a well understood and potent antimicrobial agent with added activity related benefits, such as skin exfoliation.

Dehydroacetic Acid (DHA)

Preservation with DHA is very challenging. The main reason is its high instability in a variety of formulas, yielding degradation byproducts likely to discolor the formula from pale yellow to deep brown. Usage of antioxidants or other stabilizers provided little if any improvement. It is rather unfortunate, since this organic acid is effective at much higher pH when compared to other organic acids and could have been used effectively at pH as high as 6.5. Its major activity is against fungi, with some activity against bacteria. Supplementing with additional preservatives would be highly advisable; DHA ought not be used as a sole preservative.

Isothiazolinones

The two main chemistries in this group started as a single blend of methylisothiazolinone (MIT) and methylchloroisothiazolinone (MCT) marketed under the trade name Kathon CG by Rohm and Haas (currently Dow Chemical). The two chemistries are blended at an approximate ratio of 1 part MIT to 3 parts MCT (0.35% of MIT and 1.2% of MCT in a stabilized aqueous solution).[36] This combination became one of the most popular preservatives in the early 1980s due to its high efficacy, low required use level (used at ppm levels), broad spectrum, good compatibility, and ease of formulation. However, with unrestricted use in both leave-on and rinse-off formulas, a sudden increase in allergic reactions was reported soon afterward.[37] In an orchestrated effort to minimize the risk to the public while maintaining the usefulness of this preservative system, the manufacturing companies agreed to significantly limit the ratio's use to rinse-off formulas, concurrently lowering the maximum allowed concentration to 15 ppm. While the regulatory bodies allow the usage in leave-on formulas up to 7.5 ppm, such use is rare. Currently the combination is still widely used in rinse-off formulas, predominately where cost is of importance and where it is found to be compatible. There are only a few technical restrictions related to the use of this system; it should not be exposed to tempuratures above 50°C, and it shouldn't be mixed with bisulfites, secondary amines and thiols (e.g. cysteine and zinc pyrithione).[36]

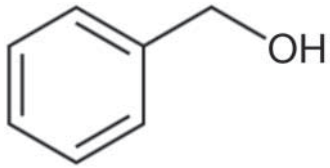
As previously mentioned, the use of this particular blend has been self-restricted over the years due to the complaints of sensitization. In the course of subsequent research, it has been postulated that the main culprit is the presence of the chlorinated isothiazolinone (MCT) and that MIT should, in fact, be tolerated much better on its own.

With that premise and after extensive safety studies, Rohm and Haas launched MIT as a single preservative in late 2006.[38,39] While MIT (up to 100 ppm) by itself doesn't quite deliver the same efficacy when compared to the combination of MIT/MCT at much lower concentration, the blend of MIT with other preservatives and certain glycols showed excellent broad spectrum activity. When used as recommended, most often in combination with caprylyl glycol (Neolone CapG) it is possible to preserve a very wide spectrum of formulations with relative ease. The preservative has been quickly adopted and incorporated into a wide variety of products (both rinse-off and leave-on). However, after some reports demonstrated reactivity for those allergic to MIT/MCT combination to MIT alone, additional epidemiological studies have shown that leave-on application of this preservative is not much better tolerated than the MIT/MCT combination with approximately 6% population reacting to MIT alone.[40] As of March 2013 MIT has been called an "Allergen of the Year" and its usage has been also self-restricted to rinse-off applications as a precautionary measure.[41]

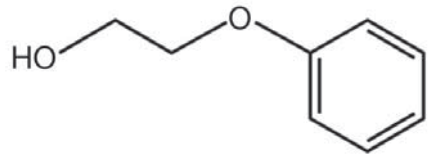
MIT and possibly future derivatives do pose some of the best attributes for preservatives, such as good compatibility, very low recommended use levels, good efficacy for most types of microorganisms, and good toxicity. It is only their clinical safety aspect, related to their potential to cause skin irritations/sensitizations among certain portions of the population that proves to be its Achilles' heel.

Phenolic Alcohols

The next group shares similar chemical structure and includes Phenoxyethanol and Benzyl Alcohol. Though both preservatives have been used for a long time, are popular and have relatively low PR "baggage" – they are by no means free of issues.



Benzyl Alcohol



Phenoxyethanol

Phenoxyethanol

This very popular preservative became an alternative to the formaldehyde donors and thiazolinones, though it doesn't deliver nearly the same broad spectrum efficacy. It is recommended to be used in the range of 0.5 to 0.9%. The upper limit being driven not just by the regulatory restrictions (the maximum allowed level being 1.0%) but rather by the fact that phenoxyethanol has been at times implemented in causing transient stinging, especially when the product containing it, is applied to the face. While it is a very easy chemistry to work with, with good solubility in water (as compared to many other preservatives), being excellent solvent, tolerant of high temperatures and relatively wide effective pH range, its activity is limited.

Phenoxyethanol is weakest against molds and often a poor choice for preservation of rinse-off formulas. It does perform relatively well in simple emulsions, though it can't fully protect formulas with organic or inorganic UV blockers, proteins, soy and plant extracts. Back when parabens were popular, the mixture of phenoxyethanol with various parabens was seen as one of the better options for preservation. While still a valuable option, due to the negative PR around parabens, this combination is not used as often anymore, especially in baby products or those that claim to be more "natural." When formulating with phenoxyethanol, the formulation chemist should be mindful of the purity of the ingredient. Depending on the grade (technical vs. pharmaceutical) there might be a varying levels of undesired impurities such as phenol and 1,4-Dioxane, a byproduct of ethoxylation step in the production of Phenoxyethanol.[42]

Because of its limitations, it is always necessary to combine it with other antimicrobials, and since the mid-2000s several suppliers have provided unique solutions based on phenoxyethanol. ISP (currently Ashland) was one of the first to launch a synergistic blend of phenoxyethanol with caprylyl glycol, under the trade name Optiphen, followed by a few other versions that combined it with added organic acids, such as sorbic acid (Optiphen Plus). Another offering came from Schulke as a blend of phenoxyethanol with Ethylhexylglycerin (Euxyl PE9010). All such technologies benefit from synergistic effect and do provide better activity against bacteria as well as improved performance against molds and yeast.

Benzyl Alcohol

Just like phenoxyethanol, Benzyl Alcohol is allowed at maximum 1% per regulation and shares many of the same attributes, including wide use as a fragrance component, solvent and popular preservative. Its use has been somehow negatively impacted since 1999 when the chemistry was identified by the SCCNFP (The European Scientific Committee on Cosmetic Products and Non-food products intended for Consumers (SCCNFP), a predecessor of the current Scientific Committee on Consumer Safety (SCCS)) as a fragrance allergen and required labeling warning for all products containing it (in EU market). Just like Phenoxyethanol, Benzyl Alcohol is mostly a bactericidal with weak activity against molds and yeast and would require additional antimicrobial agents, same as with phenoxyethanol. In addition it tends to oxidize and so any formula that depends on its activity should include an antioxidant.

It is of interest to note that both phenoxyethanol and Benzyl alcohol are found in nature,[43-44] however, as of 2012 it is not documented that any company would provide these raw materials as derived from plants and all sources are synthetic.

Halogenated Preservatives

The next group of preservatives is rather difficult to collate as they have rather varying success in the market place, ranging from highly controversial and almost banned molecules, such as iodopropynyl butylcarbamate (IPBC) and the more accepted and popular chlorphenesin. They also are quite different in their overall

safety or efficacy profiles; however, they all share the common halogenated element: chlorine, bromine, or iodine.

Chlorphenesin

Of all halogenated preservatives, chlorphenesin may be considered the most popular, even though comparing to the previously mentioned group of preservatives it is relatively underutilized. Its main activity is antifungal with very low activity against bacteria. The chemistry is relatively stable, though it has been noted to disrupt the stability of emulsions. It is recommended to be added to the water phase at temperatures around 50°C. It is important to note another property of this chemistry: as a muscle relaxant. This is particularly important to keep in mind, when designing products that may be accidently digested. A potential problem occurred when chlorphenesin was used with phenoxyethanol as a preservative in *Mommy's Bliss Nipple Cream*, a lotion designed to be used by nursing moms to help soothe and heal dry or cracked nipples. Accidental digestion by feeding infants was considered a risk and the product was recalled by the manufacturer upon recommendation from the FDA. Fortunately, no reports of injury have been reported.[45]

Iodopropynyl Butylcarbamate (IPBC)

Once considered a replacement for parabens, as it is a very potent antifungal agent, the chemistry had rather limited popularity due to health concerns. It is now considered a potent sensitizer and the EU has instituted several limitations to its use. It requires label warning; *Contains Iodine*. It is also forbidden in any products for children under the age of 3 except for rinse-off products. In addition, it is banned for all leave-on products that may be applied to the entire body. With so many restrictions in EU, the product use is now minimal, though it can still be found in some US formulations.

Other Preservatives

As with all other preservatives, care and disclosure is necessary for the following's use. Some of these preservatives belong, tangentially, to previously mentioned categories, but are listed here for their unique status or because they do not entirely fit into another given category.

Benzisothiazolinone – a member of the thiazolinone family. As with the other chemistries in this class, it is considered a sensitizer and currently is not approved in the EU as an official preservative for cosmetics. It is widely used in industrial applications (such as in paints and sealants).

Propionic acid – a member of the organic acids family. It is highly depended on pH of the final formula and active mostly against molds. The chemistry is difficult to work with due to its limited efficacy at tolerable pH and particularly strong unpleasant odor. Its use is mostly limited as a preservative for animal feed or baked goods.

Bronopol: 2-bromo-2-nitropropane-1,3-Diol – a halogenated compound that is allowed to be used at levels of up to 0.1% and provides broad spectrum efficacy.

Due to its instability and reactivity, however, its use has been limited. Not only does it break down under high pH and elevated temperatures but it also is known to catalyze reactions that yield nitrosamines (known toxins).

Chlorobutanol – another halogenated chemistry that in the EU requires a label disclaimer. It has limited activity and is also a monographed drug with sedative and hypnotic properties. Practically, it is not used in any cosmetic products at this point, though it still may be used in some eye drops, ear drops, or nose preparations.

Chloroxylenol – also member of the halogenated family. Mostly used as a topical antiseptic and disinfectant. As with most of the halogenated compounds it shows better activity against molds than bacteria. It is inactivated by nonionic and cationic ingredients.

Dichlorobenzyl alcohol – while accepted as a preservative for all topical and cosmetic products in the EU up to 0.15%, its use is mostly limited to some specialty products, such as mouthwashes. The chemistry is rather difficult to incorporate in typical cosmetic products due to the fact that both nonionic and anionic surfactants inactivate this chemistry, and also due to its very limited solubility in the water phase.

Benzalkonium chloride – belongs to a different class of chemistries called quaternary ammoniums. It is a strongly cationic surface acting agent and for that reason it is most popular as a hand sanitizer, especially in professional applications (such as in surgical scrubs or hygienic towelettes). The chemistry is relatively weak against molds and when misused (diluted) or used at less than bactericidal concentrations, it will actually allow for selection of resistant bacteria to thrive, causing contamination in the product.[46] It is very stable, however, due to its charge; it reacts and is neutralized by anionic surfactants, so careful attention to ingredients used is required.

Benzethonium chloride – another quaternia compound with very similar properties to benzalkonium chloride, mostly used in antiseptic applications as well as household disinfectants.

Polyaminopropyl biguanide – this cationic polymeric preservative shares some basic properties with the quaternia chemistries; however, it is less effective across the spectrum of microorganisms. While it is currently approved in the EU for use at levels of up to 0.3%, it is also under safety review and might be reclassified in the coming years. Currently, it is mostly used as a contact lens preservative with an excellent toxicity profile for this particular application. The technology, which combines it with borate buffer, is patented.[47] During formulation for cosmetic products it is necessary to avoid any anionic chemistry.

Non-classified Preservatives (non-regulated)

As the debate over the safety of various preservatives rages on, suppliers and skin care product manufacturers are seeking alternative solutions that will still provide adequate protection of their products when used by consumers. Up to this point, there hasn't been any major discovery that would allow everyone to fulfill

the obligation of providing safe products without the use of currently recognized preservatives. However, what many were able to accomplish is to blend classical preservatives at lower concentration with other ingredients that, while not officially recognized as preservatives, do possess certain level of antimicrobial efficacy. Among the most popular in this class are glycols; such as caprylyl glycol, pentylene glycol, decylene glycol, and ethylhexylglycerin. Their typical use levels vary from about 0.2% to 0.5%. A synergistic bactericidal effect can be obtained when used with other preservatives, such as phenoxyethanol. Based on the author's observations, the use of glycols in leave-on applications is preferred where they seem most appropriate, as they allow the levels of other preservatives to be minimized, while maintaining proper microbial robustness of the formula. They may be used in rinse-off products as well; however, in most cases, rinse-off formulas do not require the strategy of minimizing preservative levels due to potential sensitization, irritation or other transient skin reaction. Interestingly, while the preservatives are often blamed as the triggers for adverse effects, it is quite often other components in the formulations that are responsible for such reactions.

Another class of ingredients that can be used in order to increase the efficacy of classical preservatives is that of chelating agents. The most popular but also somehow controversial is ethylenediamine tetraacetic acid (EDTA) or rather its salts (disodium EDTA, trisodium EDTA and tetrasodium EDTA). Their effectiveness is limited and they should only be considered as enhancers for actual preservatives in the formula and not as sole protectants from microbial contamination.

The use level required for actual antimicrobial synergy with the preservatives occurs above 0.2% and it is most apparent in rinse-off formulas. The problem with EDTA salts is their persistence in environment and possible effect on aquatic life.[48]

The last two chemistries of interest are p-anisic acid and Biovert (an enzymatic system developed by Arch Personal Care, now part of Lonza). para-Anisic acid chemically is a 4-methoxybenzoic acid and currently is classified as a fragrance for use in cosmetics. The substance has very low solubility in water and can easily precipitate if the formula is oversaturated. This may occur if the initial pH of the formula was high enough to allow for much of the acid to be converted into a salt (soluble), but later adjusted toward lower level causing a free acid to precipitate. The ideal use level should be around 0.2% and the pH should be between 5.0 and 6.0 to ensure both solubility and activity.

Biovert is an unique two-component system comprised of lactoperoxidase with glucose oxidase and the second part being solution of glucose with thiocynate and iodide. The system has shown a lot of promise and is highly effective; however, its high price and the fact that as an enzymatic system, it is prone to degradation at high temperatures, made it rather difficult to launch in many mass products. If one chooses the system, particular attention should be paid to the direction of use, such as ratio of enzyme to substrate, temperature and phase of addition and product storage.[49]

Final Words

Recommending preservatives usage is something of a thankless job. No company advertises how they achieve the microbiological stability of their products and no consumer buys a product because there is a particular preservative in it. There is no claim of anti-aging or beautification thanks to a preservative, but no such claims could exist without the preservatives because any given product would most likely not last more than a week before becoming contaminated. One could say they are necessary evil; however, that would be a very misguided opinion, as they are anything but evil.

Considering the number of reports of infections caused by contaminated products,[50-52] it would be irresponsible to simply discard all preservatives and assume that products can somehow maintain their safety without this particular group of ingredients. Predicting how consumer use and effect on a product during the course of the product life cycle is difficult, and, as already illustrated in the introductory section of this chapter, microorganisms are not only ubiquitous but also resilient and adaptable. No half measures will suffice and nothing like this should be attempted at the risk of spreading infectious agents in topical products.

All the chemistries currently classified and allowed to be used as preservatives have been extensively tested and studied in great details, not only in clinical and toxicology laboratories but also via epidemiological means of recording use data of thousands of different products by hundreds of millions of consumers across all regions. Still, we continue to explore potential risks and gain deeper understanding, and as we learn we continue to provide safety assessment and appropriate regulatory guidance. There is no company that would intentionally endanger the public, risk its reputation and potentially ruin itself by using ingredients that are unsafe.

The so-called "natural" alternatives often provide inadequate preservation, are of dubious origin, are not well understood, or simply are the very chemistries listed above in disguise. This author has experimented with testing a multitude of various natural extracts, and even if their activity was comparable to the classical preservatives, they often turned out to contain formaldehyde, benzoic acid, or salicylic acid. Many others, which are proven to be free of such chemistries, will in turn contain at least a dozen of essential oils, known to be as irritating and having the same sensitizing potential as any other "harsh" chemicals. In times when it seems that everyone demands natural products, it is important to maintain consumer safety as paramount. It is our responsibility to verify the efficacy, safety, and purity of the new materials that are on offer by the suppliers. It is our responsibility to verify the story behind all new chemistries and ensure that the final product would be something one is comfortable to be exposed to himself and share with loved ones.

If chemical preservation cannot be incorporated for whatever reason, other means must then be considered, such as unique manufacturing (sterile or semi-sterile) using raw materials that are hostile to microbial proliferation and packaging that is fully protective and doesn't allow any exchange with the outside environment

(by use of a one-way valve, for example). Alternatively, we would have to resort to single use packaging or refrigeration in order to maintain the safety and stability of our products.

We all strive to develop and launch products that are as close to the chemistry of our bodies and as close to what is given us by nature as possible; however, we must also understand that not everything in nature is good and safe for human exposure. Some of the most potent poisons and toxins are nature-made. The mode of action of many naturally occurring chemicals is not understood. In addition the nature of complex chemistries that may be absorbed through skin and how they are metabolized or excreted remains vague. We will all continue to research new ways and means of protecting our products from contamination, as our first responsibility is that to our patients and consumers. While science keeps working to our benefit, we continue to improve our strategies to deliver safe, effective, and practical solutions to our customers. The ultimate assurance of safety and efficacy comes when all experts pull together to formulate and produce products that are thoroughly tested, esthetically pleasing, produced according to current GMP standards, packaged in protective and functional containers, and delivered to satisfied customers. Preservation is an integral part of the success, but it is still only a part and requires all other pieces to come together.

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CHAPTER 18

Microbiological Stability for Skin Care Formulations

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Key Words

Antimicrobial, Conventional Preservatives, HACCP, Nosocomial Infections, Objectionable Organisms, Preservatives, Preservative Efficacy Test

Introduction

Microbial contamination of topically applied formulations can be a consumer safety concern as well as it may adversely affect product stability. Preservatives are antimicrobial compounds that are added to topical formulations to protect both the product and the consumer from microbial contaminants that may be introduced during normal use. Although topically applied formulations are non-sterile, they should be free of pathogenic organisms and capable of preventing microbial growth. Composing an optimal preservative system for complex products can be a challenging task. In addition to preservative performance against microbial contamination, consideration must be given to consumer safety, regulatory requirements, and incompatibility with other ingredients in the formulation. Attributes of an optimal preservative system include:

- Broad spectrum antimicrobial activity at low concentration
- Efficacy over a wide range of pH and temperature
- Compatibility with other ingredients and with the packaging material
- High water solubility
- Safety for consumer use
- Relatively low cost (cost effectiveness)

Several key factors should be considered when designing a topically applied formulation with an optimal preservative system:

i. Type of formulation (lotion, gel or emulsion)

ii. Intended use (leave-on, rinse-off, eye area)
iii. Consumer safety (no or minimal risk for skin sensitization and irritation)
iv. Regulatory limitations (global acceptance, if possible)
v. Type of packaging (open jars or enclosed packaging)
vi. Manufacturing, storage and distribution conditions

The preservative efficacy test (PET) is performed routinely to determine that the product is adequately preserved against microorganisms. The preservative efficacy (or a "challenge") test is designed to mimic consumer use to predict the microbiological stability of the product during its intended use and shelf life. The design and execution of the challenge test is a complex process which requires expertise in microbiology for the interpretation of test results.

This chapter focuses on the critical elements that need to be taken into consideration during the formulation process to develop a microbiologically stable product.

Preservation Of Topical Formulations – Defining The Purpose

The US Food and Drug Administration (FDA) requires consumer-use products to be produced under sanitary conditions with adherence to Good Manufacturing Practices (GMP). Cosmetics and personal care products fall under the jurisdiction of the Federal Food, Drug, and Cosmetic Act, as amended (FD&C Act). As defined in the FD&C act, the articles considered cosmetics are those intended to be applied to any part of the human body for beautifying, cleansing, and/or promoting attractiveness.[1,2]

Topically applied products are not required to be sterile, however, under FD&C Act Section 601(a), the presence of specific infectious microorganisms, such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*, categorize them as adulterated products (**Figure 1**).[3] The FDA requires that consumer products be sold free of objectionable organisms. This is of critical concern for the cosmetic microbiologist, who plays a major role in establishing procedures and practices to prevent introduction and proliferation of both pathogenic and nonpathogenic microorganisms in these products.

The industry failed to focus on the importance of preventing microbiological contamination in the development of topically applied formulations until the 1960s and 1970s, when increased reports of nosocomial (hospital acquired) infections from contaminated lotions and creams accumulated and triggered an alertness.[2-6] Assignable causes for these contaminations were determined to be unsanitary manufacturing conditions, contaminated raw materials, and inadequate preservation.1 These sources of contamination resulted in an increased awareness of the importance of microbiological science in the preparation of topically applied formulations and led to the development of microbiologically safe products.[7]

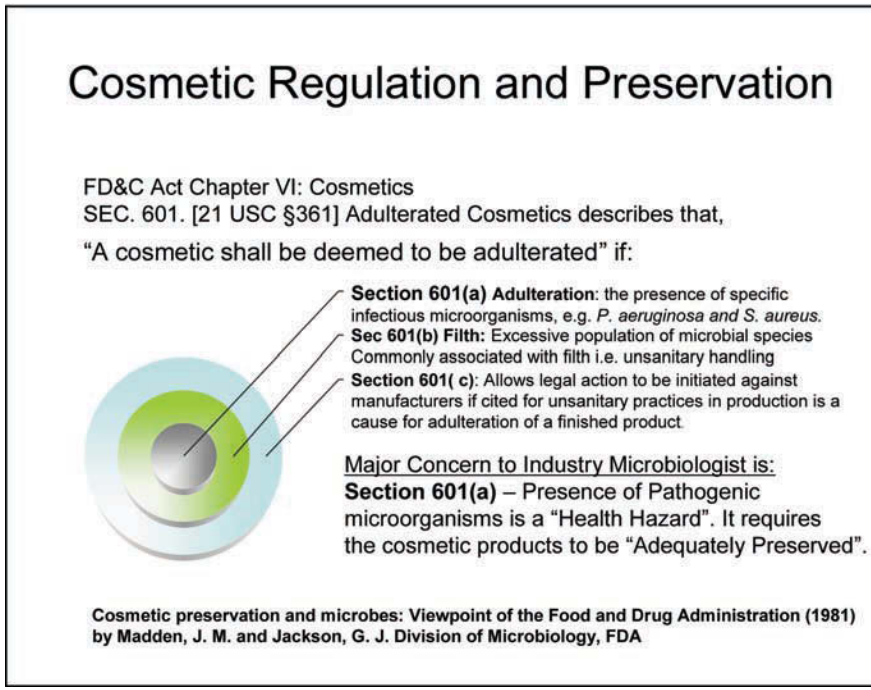

Figure 1. Cosmetic Regulations and Preservation – US Food, Drug & Cosmetic (FD&C) Act

FDA regulations existed pertaining to manufacture of drug products requiring the manufacturers to produce the drug products in accordance with current Good Manufacturing Practices (cGMPs). However, this requirement did not exist for cosmetic products. The FDA had a different legal authority over cosmetics[8] as compared to other regulated products such as drugs, biologics, and medical devices. The FDA may pursue enforcement action against manufacturers or individuals who violate the law and market adulterated products.[9] However, it was the Personal Care Product Council (PCPC, formally known as the Cosmetic Toiletry and Fragrance Association) initiative to published guidelines and procedures to ensure correct manufacturing conditions to prevent potential product contamination. Since the issuance and publication of these guidelines and procedures, the occurrence of contaminated cosmetics has dropped significantly.[10]

Microbial contaminations in a product can be introduced in the manufacturing process or during consumer use. These contaminants include bacteria, yeasts, and molds, which are ubiquitous in nature and thrive in aqueous environments. Therefore, a lack of controlled manufacturing processes can lead to significant problems in manufacturing plants. Introduction of microbiological contamination due to inadequate control of the manufacturing process is minimized with adherence to proper GMPs and implementation of a Hazard Analysis of Critical Control Point (HACCP) plan.[11] Application of an HACCP strategy is useful for the identification

of critical control points (CCP) where microbial contamination can potentially be introduced in a manufacturing process. The risk of potential product contamination can be reduced through establishment of control procedures and by continuous monitoring of each CCP.

Prevention of microbial growth in products during consumer use is achieved by developing adequately preserved formulations. The addition of preservatives is essential to protect products from spoilage and for consumer safety when protecting from microbial contaminants that may inadvertently be introduced during the period and practice of product use.

Most ingredients used in topically applied products, such as water, peptides, carbohydrates, proteins, and fatty acids, can create an environment conducive to survival and proliferation of microorganisms. Most of these ingredients are biodegradable and provide sufficient nutrients for microbial growth. In addition, water may contain sufficient amounts of trace nutrients to support the growth of bacteria, especially *Pseudomonades*.

Water-based formulations, especially those packaged in jars that are allowed to be open and exposed to air and applied by fingers, are subjected to the introduction of relatively small amounts of microbial contaminants during normal use, which increases the risk of product spoilage (**Figure 2**). Furthermore, since topically applied products are not expected to be sterile, microorganisms may be introduced via raw materials, packaging components, and processing equipment. The formulation ingredients (substrates) combined with storage conditions of high temperature and humidity (growth factors) may encourage microbial growth and become a potential consumer health hazard as a result.[12]

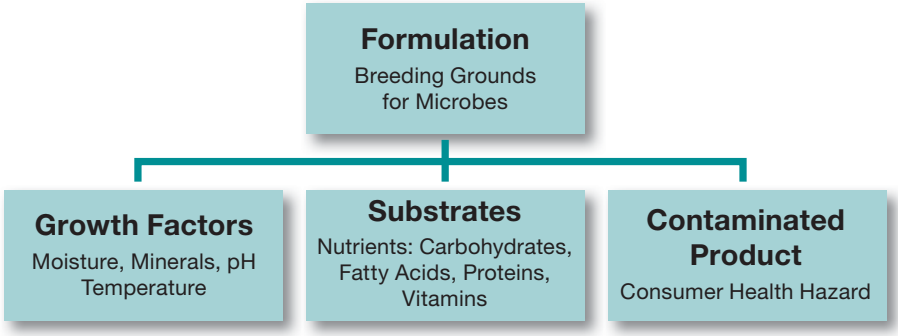

Figure 2. Topically Applied Formulations and Potential Sources of Contamination

Adherence to proper GMPs introduces control measures to the process and allows the prevention of microbial contamination from raw materials and manufacturing processes, whereas the addition of a preservative to a formulation minimizes the risk for microbial contamination during storage and use. The addition of preservatives being synthetic or natural into topically applied products ensures that the products

pose no microbiological hazard to consumers and maintains product integrity throughout its shelf life.

Preservatives are antimicrobial agents that protect the product from microbial proliferation in aqueous-based formulations and microbial survival in anhydrous products. Hence, antimicrobial ingredients or preservatives are added into a formulation for prevention of microbiological contamination from the time of production until expiration of product shelf life and/or its in-use. The addition of antimicrobial ingredients is not intended to control microbial contamination from raw materials, replace GMPs, or cover poor hygiene conditions in the plant. While the product is not intended to be sterile, the manufacturer should exercise reasonable efforts to minimize the introduction of microbial contamination during production to ensure its microbial quality remains unchanged during use and shelf life.

Microbiological spoilage of cosmetics, personal care, and topically applied pharmaceutical products is significantly important from both human health and economic viewpoints and should be prevented.[12] Therefore, these formulations contain preservatives to prevent consumer health hazards occurring from repeated product insult during normal use.

Types And Classes Of Preservatives

The frequency of preservative use in cosmetic formulations is documented from data supplied through voluntary registration of cosmetic formulations with the FDA from 1990–2010.[13-16] The data shows that parabens are the most frequently and widely used preservatives in cosmetics and personal care products. Similar findings have been noted in a Mintel report (2012)[17] showing that the parabens were the most commonly used preservative until 2008 (**Figure 3**).

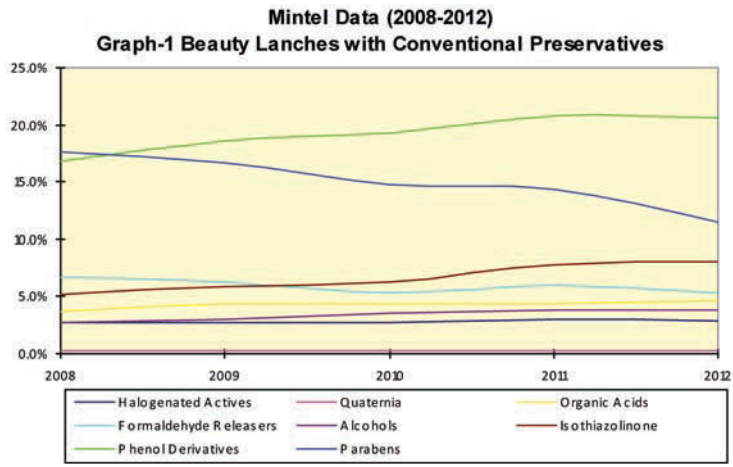

Figure 3.

The following list highlights the most desirable characteristics required for antimicrobial ingredients or preservatives to be used in topically applied formulations:[18]

i. Broad spectrum antimicrobial activity – effective against bacteria, yeast and mold and preferably, tolerant or adapted strains
ii. Colorless, odorless and safe at use concentrations
iii. High antimicrobial activity at low concentrations
iv. Effective at wide pH range
v. Temperature stable
vi. Water-soluble or liquid-soluble (highly soluble)
vii. Highly stable at extreme conditions
viii. Remains effective over product shelf life
ix. No effect on product aesthetic and feel—formulation compatibility
x. Chemically and physically compatible with other ingredients
xi. Compatible with packaging materials
xii. Globally acceptable
xiii. Safe for use—does not irritate, sensitize or inflame the skin
xiv. Cost effective

Conventional Preservatives

There may be more than a hundred known chemical preservatives and their blends to choose from, but only a few are commonly found in cosmetics and personal care products sold worldwide. Among those, parabens, phenol derivatives, quats, isothiazolinones, organic acids, formaldehyde donors, and alcohols (**Figure 4**) are considered conventional or commonly used preservatives. Conventional preservatives are chemical or synthetic compounds with known activity against microorganisms at a certain dose level. These preservatives are considered safe and effective when used as directed for recommended use.

Commonly Used Preservatives[19]

The use of phenol derivatives has been reported to be on the rise since 2008. Of all chemical preservatives, the most commonly used preservatives in cosmetic products are phenolic types (phenoxyethanol, benzyl alcohol, and phenethyl alcohol) followed by parabens (methyl, ethyl, propyl, and butyl) (**Figure 5**).[17]

Parabens: Parabens have been under a controversial position in the European Union (EU) until the recent Scientific Committee on Consumer Products (SCCP) formation of opinion on their safety.18 Despite the negative wave of public opinion against their use, parabens have been the most favored antimicrobial ingredient used in cosmetic and personal products because of their antimicrobial efficacy. In the United States, methylparaben and propylparaben have attained GRAS (Generally Recognized as Safe) status in foods.7 Among all types of parabens, methylparaben was most frequently added to topically applied products followed by propylparaben (**Figure 6**).[17]

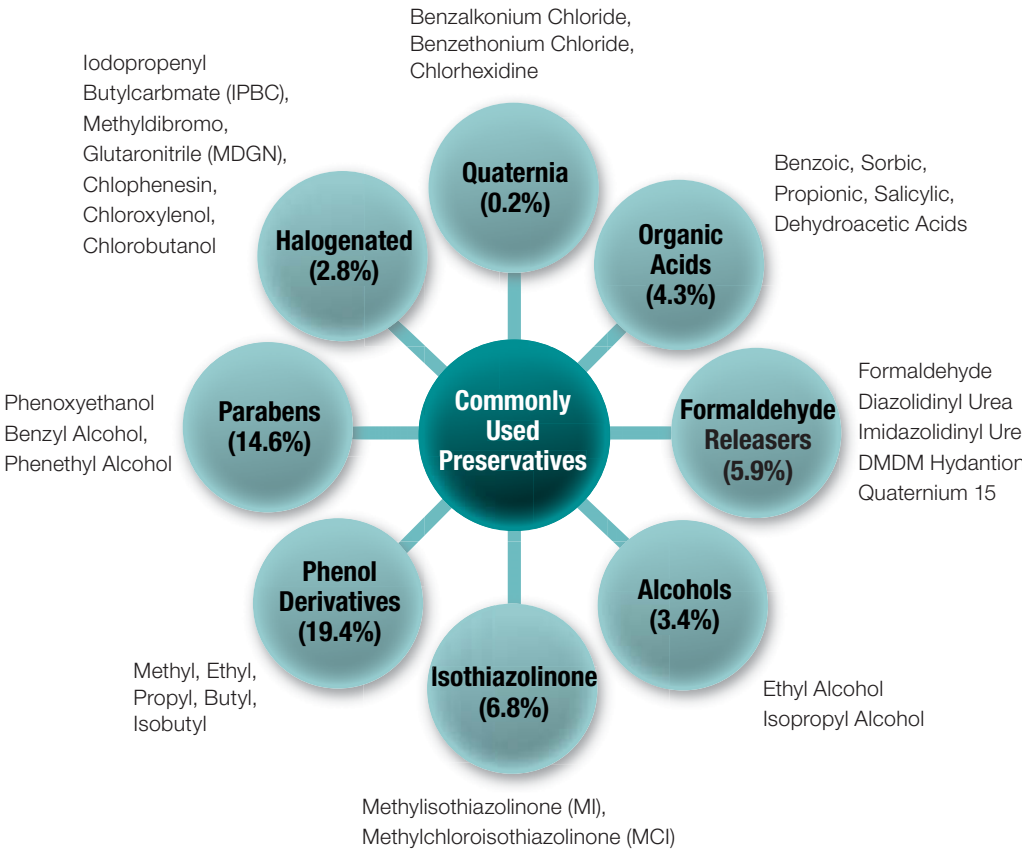

Figure 4. Conventional Cosmetic Preservatives

*(%) = taken from Beauty launches since Jan 2008 containing preservative type
Source Mintel report prepared for Amway (2012) [12]

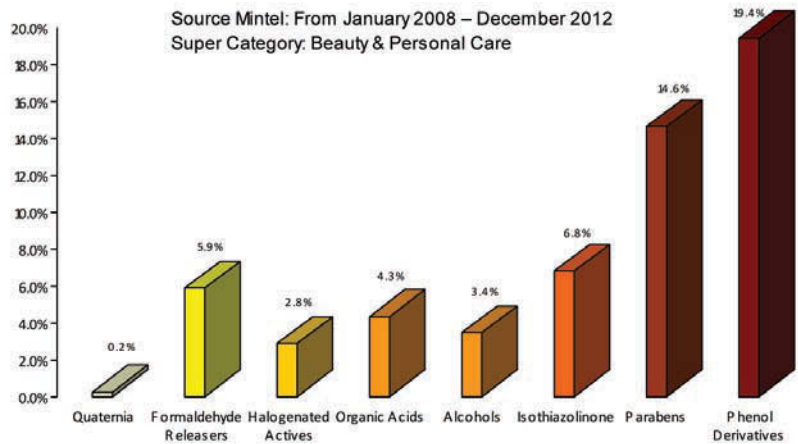

Figure 5. Percent of Beauty Launches since Jan 2008 with Preservatives

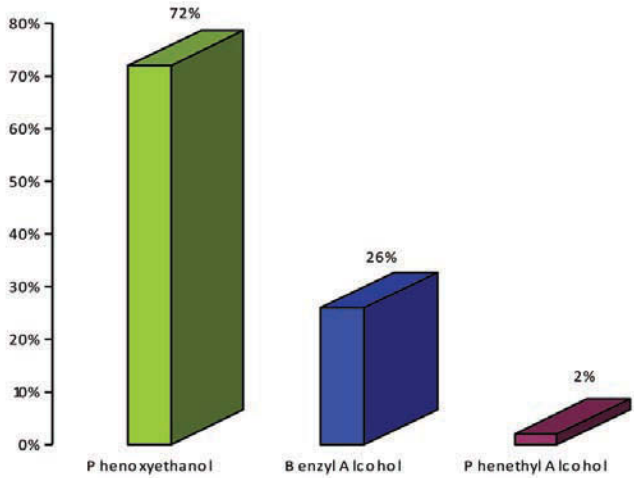

Figure 6. Percent of beauty launches since Jan 2008 – August 2012 Containing Phenol Derivatives as Preservative

Source: Mintel Data (2008 – 2012)
Ingredient: Phenoxyethanol, Benzyl Alcohol, and Phenethyl Alcohol
Super Category: Beauty & Personal Care

Chemically, parabens (methyl, ethyl, propyl, and butyl) are esters of parahydoxybenzoic acid, also known as PHB esters. They appear physically as white free-flowing or crystalline powders. Their water solubility is inversely proportional to the number of carbon atoms of the ester, i.e. the water solubility decreases with an increase in the chain length (water solubility: methyl > ethyl > propyl > butyl). Conversely, the antimicrobial activity and the solubility of paraben esters in ethanol, propylene glycol, and oils is increased with an increase in chain length (antimicrobial activity and ethanol, glycol, and oil solubility: butyl > propyl > ethyl > methyl). therefore, methyl and propyl esters are usually combined to attain good antimicrobial activity and solubility if both water and oil phases compose the formulation.[20]

Combinations of esters with different solubility properties are very effective in two-phase emulsions, where water-soluble methyl ester protects the water phase and oil-soluble propyl ester protects the oil phase. Parabens demonstrate good antimicrobial activity even at pH levels as high as 7-8; however, their optimum activity is achieved in acidic solutions (pH < 6). Paraben efficacy is best achieved when pre-dissolved in solvents (e.g., propylene glycol) and adjusting the pH to 6 or lower.

Parabens exhibit strong activity against yeast and mold and moderate activity against Gram positive bacteria as compared to their activity against Gram negative bacteria, where it is considered weak. Phenoxyethanol, which has strong activity against Gram negative bacteria, is an excellent solvent for parabens. A broad spectrum antimicrobial activity is achieved by combining parabens with phenoxyethanol.[21]

Paraben activity is greatly diminished by ethoxylated compounds such as polysorbates, proteins, and lecithin, and can be adsorbed by polyethylene packaging thereby partially losing availability for interaction with microbial contaminants.

Phenol Derivatives or Phenolic Types

Phenoxyethanol: Phenoxyethanol is the most widely used preservatives (Figure 5) among phenol derivatives, which is a phenolic compound derived from a reaction of 1 mole of ethylene oxide with 1 mole of phenol. It is considered a weak biocide, and is known to demonstrate strong activity against *Pseudomonas aeruginosa* when compared to other bacteria. When used as a solvent, phenoxyethanol exhibits high solvent properties for parabens and other preservatives, which is why it is usually blended with other preservatives to achieve enhanced activity against a wide range of microorganisms. Phenoxyethanol is stable over a wide pH range (3-10) and at high temperatures (up to 85o C). It is a free-flowing liquid and can be incorporated into most formulations. Similar to parabens, phenoxyethanol is also inactivated by highly ethoxylated compounds (polysorbates, proteins, and lecithin).

Benzyl Alcohol: Benzyl alcohol is a natural aromatic alcohol found in jasmine and other plants. It is heat-stable, with an optimum efficacy at pH 5. It is primarily active against Gram positive bacteria with some activity against Gram negative bacteria. It is soluble in water up to 3% and can be used as a solvent. Benzyl alcohol is oxidized when exposed to UV light and inactivated by nonionic surfactants.

Phenethyl Alcohol: Phenethyl alcohol is a natural colorless liquid with a rose or floral odor and is listed as GRAS by the FDA for foods. It is active against bacteria and exhibits weak activity against mold; it has an optimum efficacy at an acidic pH. Phenethyl alcohol is partially inactivated by polysorbate 80 and other nonionic surfactants. It is used in conjunction with benzalkonium chloride (BKC) to broaden its antimicrobial activity.

Isothiazolinones

Methylisothiazolinone: Methylisothiazolinone (MI) is available as a solution in water, phenoxyethanol, caprylyl glycols, or ethylhexylglycerin. It is highly stable over a wide pH range (pH 2-10) and can be heated up to 70°C while maintaining its stability. It is inactivated by the addition of sulfites. Methisothiazolinone shows a broad spectrum activity against bacteria, and is highly effective at low concentrations. Its recommended use levels are 0.053–0.10%. It is also compatible with other fungicides such as parabens.

Selection of Preservatives

When choosing an effective preservative system, several key factors should be taken into consideration:

- Broad spectrum activity at a low concentration (i.e. highly active against bacteria, yeast and mold) and cost effective.
- Type of formulation base (i.e. creams, lotion, anhydrous, and type of emulsions (oil-in-water [O/W] or water-in-oil [W/O]) it is to be used in.

- Type of product packaging, since the preservative may react with packaging material, a process that can lead to partial loss of activity
- Product application and intended use; whether it is intended for leave-on, rinse-off, applied in proximity to mucous membrane such as eyes or lips, as well as target population that might be at higher risk such as babies or the elderly.
- Stable over time and adverse storage conditions such as hot, humid, and cold temperatures.
- Compatible with most commonly used ingredients and exhibiting minimal interaction with formulation components; incompatibility can lead to breakdown and compromise efficacy.
- Causes no or minimal irritation or sensitization to the skin or area of application, i.e. non-toxic and safe to use.
- High solubility in water or oil is desired. Otherwise, solubilization in other solvents prior to addition to the formulation is highly recommended. If the preservative is amphiphilic, it will tend to partition into the water-oil interface, a process that may compromise its efficacy in interaction with microbial contamination.
- Optimal pH for the preservative should be within the pH range of the formulation. Typical pH for topically applied formulations can vary; however, most products exhibit pH in the range of 3.5 to 7.0, with the majority at a pH approximately 5.5 to match normal skin pH.
- Blending antibacterial and antifungal preservatives to achieve broad spectrum antimicrobial activity.
- Enhancement of antimicrobial activity by adding EDTA (ethylenediamine tetra-acetate), known to increase the sensitivity of microorganisms to antimicrobial agents.

The chemical and physical properties of a specific preservative should be viewed in consideration of the whole formulation since it acts as part of a complex system that includes other preservatives or preservation boosters (i.e, preservation system), physical and chemical composition of the finished product, formulation ingredients, protective packaging, and intended use. General consideration should be taken into account based on the formulation factors when selecting a preservative or preservative system (**Table 1**).

Formulation Design And Preservation

In the words of David K. Brannan, "The proper use of preservatives to prevent microbial contamination of cosmetics is often viewed as an art rather than a science."[22] The formulation of cosmetics has evolved from simply blending a few ingredients to formulating with a wider range and higher number of complex ingredients with multifunctional activity. With an increased consumer demand for natural and sustainable cosmetic products, effective preservation is especially important because

natural ingredients may serve as growth media for bacteria, yeast, and mold if not adequately preserved. Several critical factors require consideration when developing a preservative system for these complex products. The performance of a preservative system can be affected positively or negatively by the formulation composition and process conditions to which it is exposed (**Figure 7**).

Table 1. Examples of formulation factors and related general consideration

FORMULATION FACTORS	GENERAL CONSIDERATIONS
Formulation Susceptibility	Ingredients may act as a nutrient for bacteria or may be inherently hostile
Ingredient Compatibility	Percent of active ingredients, for example, proteins and highly ethoxylated compounds (type of surfactants) may deactivate the preservatives
Formulation Parameters	Chemical and Physico-chemical properties (pH, water activity, or alcohol may enhance the preservative efficacy)
Type of Formulation	O/W or W/O emulsion or anhydrous nature of a product impacts the solubility and availability of preservatives
Type of Packaging	Jar, pump, unidirectional pump to prevent backflow can influence the product exposure to contamination
Processing	Temperature of incorporation- hot or cold process temperature may improve solubility or be a deterrent to chemical compound
Order of addition	Addition at post emulsification or pre-emulsion, addition to the water phase, or pre-dissolving in glycols
GMP	Controlling the raw material microbial quality and hygiene practices in manufacturing

Effect of pH

The pH of the finished product may dictate the type of preservative selected. Most microorganisms are able to proliferate at a pH range of 4–10. The optimal pH range for most pathogens is 5.5–8 (neutral range).[24] A slight increase (alkaline) or decrease (acidic) in pH of a formulation can significantly enhance the efficacy of a preservative system. For example, organics acids are highly effective in their un-dissociated form which can be achieved when incorporated in a product at a pH range of 3–5. Therefore, the use of organic acids as preservatives is recommended

for low pH formulations. Normally, the pH of topically applied products is within the neutral range (pH 5.5–7). The antimicrobial activity of sorbic acid, benzoic acid, and dehydroacetic acid (DHA) is diminished if used in these types of products. Therefore, the use of organic acids is limited to products with low pH. In contrast to preservatives that are acids in their chemistry, quaternary ammonium compounds (QACs), such as benzylkonium chloride and benzylthonium chloride, function over a wider range of pH (pH 4–10),[25,26] with an effectiveness at pH 6 and above.[19]

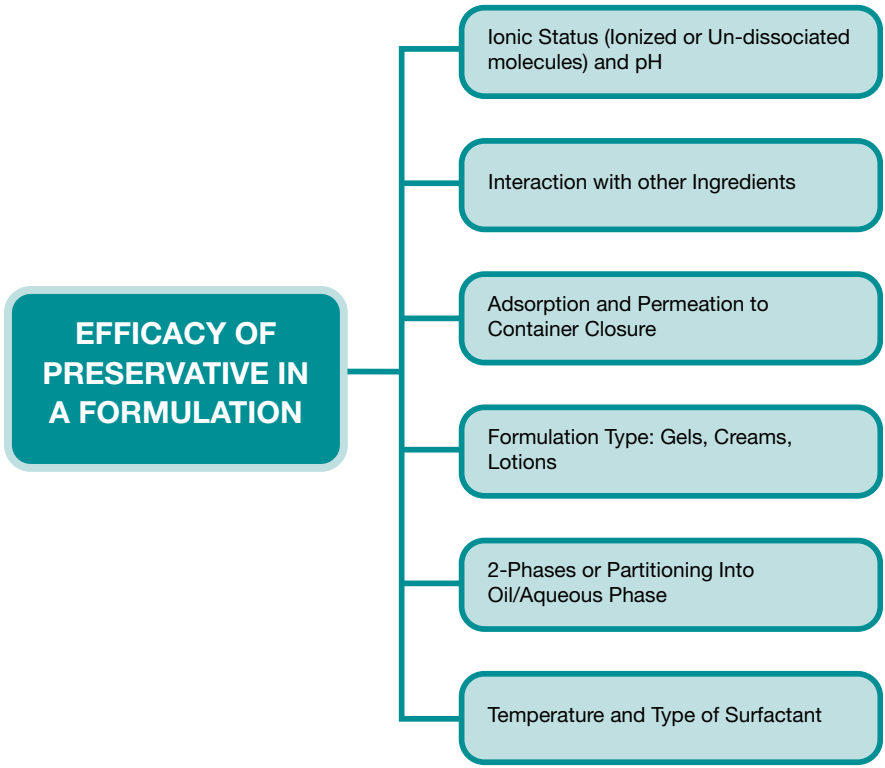

Figure 7. Conditions Affecting the Availability and Efficacy of Preservatives [23]

The Influence of Base Formulation Ingredients

Cosmetic and personal care formulations contain a variety of ingredients and each ingredient has its unique properties and purpose. During the formulation process, the ingredient properties adjust according to the continuous phase it is partitioning into, and the formulation will develop into a coherent single entity with its own physico-chemical properties. The most appropriate preservative system is one that is not or only minimally affected by the formulation ingredients and therefore exhibits no compromised efficacy. Some ingredients in a formulation may act as nutrients for bacteria, adsorbers, or inactivators of the preservatives,

thus adversely affecting the preservative activity (e.g. inactivation of parabens by certain nonionic surfactants). Adversely there are raw materials that enhance the antimicrobial activity of preservative ingredients, either by affecting their bio-availability in attacking the bacteria or by exhibiting bacteriostatic/ bactericidal activities. Examples of typically used formulation ingredients that may interact with preservatives are listed in **Table 2**.

Table 2. Key Examples of Interaction of Preservatives with Other Formulation Ingredients

Microbial Nutrients	Preservative Adsorbers	Preservative Inactivators	Preservative Enhancers
Vitamins	Talc	Lecithin	Chelating Agents (EDTA)
Plant Extracts	Titanium Dioxide Silicon Dioxide	Non-Ionic	Emollients
Carbohydrates	Kaolin	Cellulose & Xanthium Gum	Essential oils
Emulsifiers	Silica	Polysorbates	Humectants
Lipids, Proteins	Pigments	Over-heating Alkaline pH	Antioxidants
Negative Effect	**Negative Effect**	**Negative Effect**	**Positive Effect**

Compatibility of Preservatives with Other Formulation Ingredients

Compatibility between preservative agents and formulation components (such as surfactants and other active ingredients) is important to ensure the chemical stability of a preservative. It is highly recommended not to add anionic compounds to a formulation that is preserved with cationic preservatives to prevent their neutralization. For example, if a formulation contains quaternary ammonium salts (e.g., benzylkonium and benethonium chloride) or chlorhexidin as preservatives, both cationic in nature, the addition of anionic compounds (e.g., sodium lauryl sulfate) to the formulation will offset the antimicrobial activity and leave the formulation completely unpreserved as a result. Similarly, highly ethoxylated compounds such as polysorbates, lecithin, proteins, and cellulose derivatives inactivate the efficacy of parabens.[19]

Effect of Packaging

The type of packaging in which a formulation will be filled is another important consideration in the selection of an effective preservative system. The type of packaging may either increase the contamination risk (e.g., open lid jars) or lower the incidence of in-use introduction of contaminants by limiting exposure to

human and environmental contact during consumer use (e.g., tubes with narrow opening, pumps). Certain types of packaging (e.g., aerosol cans) create a hostile environment (anaerobic condition under pressurized gas) that prevent the survival of most microorganisms.[27,28] Protective packaging creates a barrier to a product's susceptibility to contamination.[29] Incompatibility of formulation ingredients with packaging components (e.g., plastic, metal, rubber liner, or caps) may also influence antimicrobial activity (**Table 3**).[30] In addition, dispensing closure design can impact the susceptibility of a formulation to contamination either by protecting (closure with no backflow) or by exposing (screw cap closures) the product during use. In certain cases, closure material may inactivate the preservative.[31] Therefore, a challenge test of the packaged product is recommended to determine that the packaging materials exhibit no adverse effect on performance of a preservative or preservative system.

Table 3. Examples of Adsorbents with Susceptible Preservatives

ADSORBENTS	PRESERVATIVES
Polyethylene	Parabens [19], Benzyl alcohol [32], Sorbic acid [33] Thiomersal [34], Chlorbutanol [35].
Kaolin	Benzoic acids [36]
Cellulose	Phenoxyethanol [37]
PVC Plastic	Phenoxyethanol [38], Sorbic acid [33]
Rubber	Thiomersal [39], Benzyl alcohol [32]

Additional aspects of interactions between the preservative and the package are related to its potential corrosiveness, or any other possible chemical or physical interaction, whether or not it affects the efficacy of the preservative. One should strive to create a system in which the preservative remains intact in the formulation in its packaged form.

Effect of Water

The term "water activity" defines the amount of free, unbound, or available water in a formulation. It is the ratio of the vapor pressure of a test material to the vapor pressure of pure water at an ambient temperature.

Water Activity (a_w) = Vapor Pressure of the Product / Vapor Pressure of Pure Water

The water activity of pure water is 1.00, therefore, the lower the water activity of a product, the lower the amount of free or available water. Low water activity value means that a portion of the total water content of a formulation is strongly bound to specific sites on certain chemicals contained in the product, making it unavailable to foster microbial growth. In other words, since microbial proliferation requires water, the water activity of a product is directly proportional to the rate of microbial proliferation. Therefore, microbial contamination of a formulation can be controlled by lowering its water activity. This is achieved by adding water binding ingredients

to the formulation thus creating an intrinsically hostile environment for microbial growth and reducing the risk of microbial contamination. In general, growth of most bacteria is inhibited if the water activity is < 0.90. Similarly, the growth of yeasts and molds, with the exception of osmotolerant species, is retarded if the water activity is < 0.70 and no microorganisms can grow when the water activity reaches a value below 0.60.[24] Humectants such as glycerin, glycols, and sorbitol may offer dual activities. In the formulation, these components will interact with water thereby reducing their availability to bacteria and when applied to the skin will minimize transepidermal water loss (TEWL) thus acting as moisturizers.[40]

Effect of Type of Formulation

The physical state of a formulation strongly affects its susceptibility to microbial contamination. Microorganisms multiply in the presence of water; therefore, preservatives are effective only when present in the aqueous phase. Aqueous-based products such as solutions, suspensions and gels, as well as o/w emulsions or hydrous gels, are highly susceptible to microbial contamination when compared to w/o emulsions, where oil is a continuous phase that hinders microbial penetration to the water phase.[41] However, w/o emulsions are generally more difficult to preserve despite the lower susceptibility to microbial contamination because of either limited solubility of the preservatives in the continuous phase or its limited efficacy in the oil phase. Some preservatives, especially amphiphilic compounds that exhibit both water and oil solubility, can partition between the aqueous and oil phase and, even if incorporated at the recommended efficacious percentage, still can be present at a sub-optimal concentration in the water phase. When formulating emulsions, it is advantageous to know the oil/water partition coefficient of a preservative, the ratio of the concentration of a compound adsorbed or dissolved by one phase to the concentration of the chemical compound in the other phase. The oil/water partition coefficients of the preservatives are a measure of their solubility in either phase. If the oil/water partition coefficient is low, the preservative concentration in the aqueous phase will be higher since it has a greater affinity for the water phase. In contrast, with an increase in partition coefficient, most preservatives tend to migrate to the oil phase, and therefore their activity may be partially lost.[42] Usually, higher amounts of preservative are required in vegetable oil/water systems where high partition coefficient values are noted when compared to mineral oil/water systems with a low partition coefficient value.[43]

Effect of Process Conditions

In addition to water solubility, other factors, temperature, pH stability, and order of addition of ingredients, may significantly affect the preservative activity. For example, in aqueous-based products, water-soluble preservatives should be added to the water phase or to the emulsified portion of the formulation late in the process when the formulation is cooled to a temperature of 45°C or below. Similarly, certain preservatives may lose their antimicrobial activity and physical stability at a higher or alkaline pH. In order to determine the order of addition and achieve

an effective preservative system, it is important to know the temperature and pH tolerance of the preservative and complement it with the process conditions. This will prevent the accidental decomposition of the preservative and, subsequently, leave the formulation unpreserved. A few examples of conditions, their effects on preservative performance, and recommendations for improvements are listed in **Table 4**.

Table 4. Conditions Affecting the Performance of a Preservative and Recommendations for Improvement

Conditions	Recommendations
Solubility	Pre-dissolve in solvent to achieve homogenous solution
pH	Optimize the pH of aqueous phase – a slight change in pH (acidic) can enhance the antimicrobial activity as a result.
Processing Conditions	Temperature of Incorporation - add at low temperature Order of Addition – Post emulsification
Water Activity (Aw)	Microorganisms grow only in the presence of water – Lower the amount of available water by adding glycols, glycerin or other water binding molecules to lower the Aw.
Partition Coefficient	Preservative are active in the aqueous phase - Lower the water partitioning to prevent migration of preservatives away from the aqueous phase.
Temperature	High temperature may inactivate preservative by accelerating hydrolysis (Formaldehyde donors, MI/MIT)
Active Ingredients	Some compounds such as Silicones and Solid particles may absorb preservatives on the surface (e.g., sunscreens, pigments)
Type of Surfactants	Micelle formation tends to capture or adsorb preservatives and limit or inhibit their activity
Preservative Blends	Enhance activity by combining preservatives (antibacterial & antifungal agents), Create synergy between two molecules to optimize the antimicrobial activity at lower concentrations.
Preservative Enhancers	EDTA increases microbial cell wall permeability

Preservative Blends

Blending preservatives that have complementing activities may lead to a synergistic effect and thus increase the spectrum of their activity against potential microbial contaminants, allowing a reduction in the use level of the individual preservatives.

For example, broad spectrum antimicrobial activity is obtained if imidazolidinyl urea (a preservative with a high activity against bacteria) is blended with an antifungal chemical such as parabens.

Blended preservative systems may demonstrate the following benefits:

- Broaden the spectrum of antimicrobial activity against various types of microorganisms (bacteria, yeasts, and molds).
- Prevent the potential development of resistance of an organism against one biocide.
- Reduce the potential skin adverse effect by lowering the concentration of the individual preservatives
- Broaden the options and applications to various types of formulations.
- Reduce the effects of formulation constraints such as solubility, pH, partition coefficient, and adsorption.
- Increase homogenous distribution of preservatives in complex formulations.
- The following are some examples of known preservative combinations that have been shown to create a synergistic preservative effect at relatively low concentrations:
- Chlorphenesin with phenoxyethanol
- Parabens with phenoxyethanol
- Chlorphenesin with ethylhexylglycerin in pentylene glycol

A list of commercially available preservative blends is presented in **Table 5**.

Table 5. Examples of Commercially Available Preservative Blends

Phenonip XB – *Phenoxyethanol, Methylparaben Ethylparaben, Propylparaben*	**Neolone PE –** *Phenoxyethanol, Methylisothiazolinone*
MicroKill COS – *Phenoxyethanol, Chlorphenesin, Caprylyl Glycol*	**Microcare – MTC/MTC2** *Methylisothiazolinone and Chlorphenesin*
Nipaguard PO 5 *Phenoxyethanol, Piroctone Olamine*	**Optiphen Plus –** *Phenoxyethanol, Caprylyl Glycol*
EUXYL PE 9010 *Phenoxyethanol, Ethylhexylglycerin*	**Symdiol –** *Caprylyl Glycol, Hexanediol*
Geoguard Ultra *Gluconolactone (and) Sodium Benzoate*	**Kathon CG –** (Rinse off Products only) *Methylisothiazolinone Methylchloroisothiazolinone*

In addition to creating a synergistic effect by combining preservatives, chelating agents (e.g., EDTA) and/or solubilizing agents (e.g., propylene glycols) can be incorporated to achieve optimal efficacy.

Natural Preservatives

In general, when comparing to conventional preservatives, natural preservatives may need to be added at higher concentrations to achieve equivalent efficacy. Formulation chemists may face some challenges regarding product aesthetics, stability, or consumer safety concerns when formulating with higher concentrations of natural ingredients. Preservatives in cosmetics must appear in the positive list of Annex VI of the European Economic Community (EEC) Cosmetic Directive 76/768/EEC.[44] However, there is no current legislation limiting the use of natural substances that are inherently hostile to bacterial growth as cosmetic ingredients to benefit skin. Therefore, formulations containing natural substances may require a lower amount of chemical preservative to yield optimal efficacy.

With the new trend toward the development of natural and sustainable products, certain natural peptides are currently under investigation or being marketed with antimicrobial claims, demonstrating many excellent properties such as functionality at a pH range of 3.5–7.5, mildness to skin, and compatibility with other cosmetic ingredients. Currently, the evaluation is being expanded to achieve broad spectrum activity as well as synergy with chemical preservatives and other cosmetic ingredients.

While there is no broad spectrum all-natural preservative, the addition of natural antimicrobial compounds could be effective when combined with other cosmetic ingredients or with very mild and safe synthetic preservatives. The addition of natural ingredients exhibiting multifunctional properties (e.g., antioxidant, antimicrobial, anti-aging, conditioning, moisturizing, and/or antiwrinkle) may make the formulation intrinsically hostile to certain organisms. In such formulations, other chemical or synthetic preservatives may be very effective at lower concentrations. Similarly, certain extracts with antimicrobial properties combined with natural peptides may demonstrate broad spectrum antimicrobial activity.

Formulating with biodegradable and natural antimicrobial systems requires a thorough understanding of the implications, as there may be some barriers in supporting such claims.

Preservative Efficacy Testing

As defined in the FD&C act, the articles considered as cosmetics are intended to be applied to the skin or hair for beautifying, cleaning, and/or promoting attractiveness.[2] Topically applied formulations are non-sterile products manufactured with adherence to GMPs. Preservatives are added to these products primarily as a safety measure to prevent inadvertent microbial contamination of the product during its normal use and to maintain product integrity post-manufacturing.

One of the important shortcomings of chemical preservation is the potential for adverse skin effects (typically an allergic reaction) on susceptible individuals that may lead to allergic contact dermatitis (ACD). Therefore, maintaining a balance between an effective and safe concentration is a key element in the selection of a preservative system for a given formulation. This balance is achieved by performing

the Preservative Efficacy Test (PET, also known as a Challenge Test), which measures the antimicrobial activity of a preservative (or preservative system) against the challenged or inoculated organisms in a test formulation.

The following are two critical methods designed to evaluate either the microbial quality of finished products and raw materials (Microbial Limit Test), or antimicrobial efficacy of preservatives against the challenged organisms (PET).

1. Microbial Limits Test (MLT) – This test is performed to evaluate raw materials and finished products for microbial content and to determine whether they meet the acceptance criteria as established by the manufacturer or marketing company. Finished products are tested prior to release of the product in the market, if required.
2. Preservative Efficacy Test (PET) – This test is performed to assure that the product is adequately preserved against potential pathogenic and spoilage organisms. It determines an appropriate preservative (or preservative system) at its optimum effective and safe concentration in a test formulation to remain safe during consumer use and product shelf life.

For preservative efficacy testing of non-sterile drugs, and cosmetics and personal care products, there are compendia tests (e.g., United States Pharmacopoeia (USP), chapter 51; European Pharmacopoeia (EP) section 5.1.3; and Japan Pharmacopoeia (JP), section 19),[45-47] and tests that are developed either in collaboration (AOAC, ASTM)[48,49] or with industry technical guidance (PCPC, COLIPA, JCIA, and ISO/TC-217).[50-53] These tests are designed to evaluate the preservative effectiveness of a formulation during its development and may assist in determining product shelf life.

Generally, during the initial stages of a product formulation, several prototype formulas are screened to select a suitable preservative system. In addition to physico-chemical properties, other factors should be taken into consideration in selecting a suitable preservative, such as, type of formulation (i.e. water-based or anhydrous), type of product application (leave-on or rinse-off), type of packaging (open or protective), compatibility or incompatibility with other ingredients, and regulatory limitations of the countries in which the product is intended to be marketed and sold. Ideally, the preservative efficacy test should be conducted for the formulation in its final container.

Preservative Efficacy Test (PET or "challenge test")

The PET measures the capacity of a formulation to control or withstand microbiological growth upon contamination that is inadvertently introduced during or subsequent to manufacturing. It is accomplished through inoculating a product with stock cultures of bacteria, yeast, and mold at a known relevant concentration (10^5–10^6cfu/g) and assessing its ability to inhibit their growth. An aliquot of inoculated sample is tested at predetermined time intervals for 28 days after inoculation.

Primarily, PET is intended to mimic the potential introduction of bacteria during consumer use of a product in a lab setting and predicts if the microbiological resistance will be maintained during its intended use practice and expected duration

(**Figure 8**). Most compendia and global requirements for the challenge test involve a minimum of 3 log (or 99.9%) reduction for bacteria and 1 log (or 90%) reduction for yeast and mold counts at day 7 after inoculation with no increase in their count (remain in stasis) thereafter until day 28.

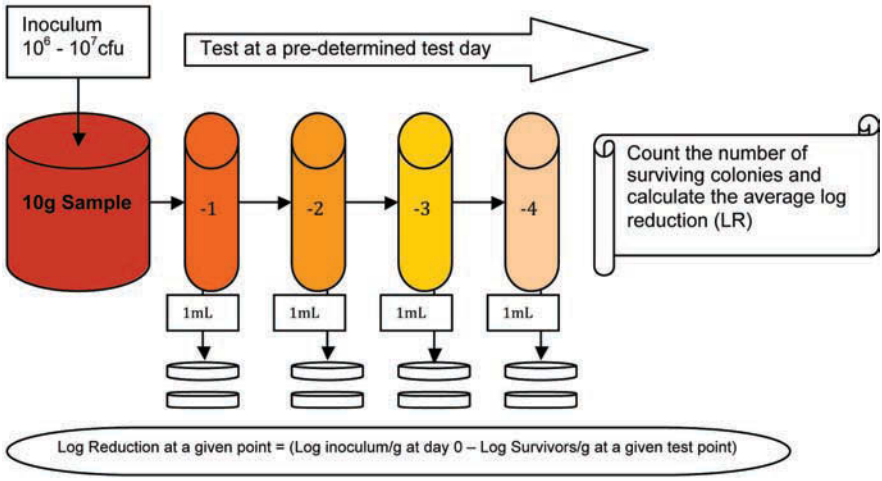

Figure 8. Example Flow Diagram of Preservative Efficacy Test

Ensuring Preservative Stability

Generally, the expected shelf life of cosmetic and personal care products is 30 months. Therefore, during their development, products are assured to be adequately preserved to withstand extreme exposure conditions such as temperature fluctuations and humidity during transit, storage and use. These adverse conditions can potentially lead to chemicals' partial or complete decomposition and hence to loss of activity. Chemical stability during adverse storage conditions is generally confirmed through packaged product stability testing.

Packaged product stability testing of cosmetics is intended to ensure that the product retains its physical, chemical, and microbiological quality as well as its functionality and aesthetics throughout its shelf life, when stored under appropriate conditions. In order to predict product integrity, the stability testing program (real time or accelerated) is designed to address the potential adverse effects due to incompatibility between container and contents under storage conditions.

Due to the inherent complexity of cosmetics made with multifunctional ingredients, remarkable new technologies, and state of the art packaging, following a standard stability testing format may not be adequate. Taking advantage of in-depth knowledge about formulation ingredients and type of packaging, it is important to design a scientifically sound and flexible stability program.

The PCPC/COLIPA guidelines on "Stability Testing of Cosmetic Products"

outline the critical parameters, and variables to be incorporated in a stability testing program.[54]

Regulatory And Safety Aspects Of Preservative Use In Cosmetics

Regulatory framework is the key driver in the selection of a preservative when developing a formulation for local and/or global markets. In most countries, regulations require that every cosmetic and personal care product sold to the end-consumer be safe for its intended use. The regulation of cosmetics in the United States is shared between different federal agencies: topically applied cosmetics and personal care products fall under the jurisdiction of FD&C Act, amendments to which are issued by the FDA and the US Department of Health and Human Services (USHHS).[55] A detailed review of regulatory requirements for the marketing of cosmetics in the United States is available.[56]

Likewise, the regulatory bodies in the EU and Japan include the Cosmetic Directive of the European Union (76/768/EEC)[57] and Ministry of Health, Labor and Welfare (MHLW),[58] respectively. Other regions such as Latin America[59] and ASEAN (Association of Southeast Asian Nations)[60] are also evolving from pre-market registration to post-market surveillance of cosmetic and personal care products.[61]

The US FDA Center for Food Safety and Applied Nutrition (CFSAN)[62] primarily monitors the cosmetic use and safety aspects of FDA policies and programs and is the authority to ban or restrict ingredients due to safety concerns and mandate the warning labels on products for restricted use. Unlike pharmaceutical products, cosmetic and personal care products do not require pre-market approval from the FDA. Although the FDA is the authority in regulation and safety management of cosmetic products, it is the manufacturer's responsibility to uphold the recommended regulatory requirements ensuring that their products remain safe and pose no harm to consumers during use. The FD&C Act mandates that the safety of a cosmetic product as well as each ingredient be substantiated before the product is marketed. In addition to regulatory agencies, industry trade associations such as the PCPC,[63] European Cosmetic Toiletry and Perfumery Association (COLIPA),[64] and Japan Cosmetic Industry Association (JCIA)[65] are vital sources of safety information on cosmetic ingredients, and issue guidance for the industry. In 1976, the FDA, Consumer Federation of America, and the PCPC (then CTFA) established the Cosmetic Ingredient Review (CIR),[66] an independent scientific body that assesses the safety of ingredients used in cosmetic products. After a thorough review and safety assessment by the CIR Expert Panel taking into account public comments on the ingredients, a final report was published in the *International Journal of Toxicology*.[67]

Similarly, the European Commission (EC) established the Scientific Committee on Consumer Products (SCCP),57 an organization responsible for the safety evaluation of cosmetic ingredients in the EU. Annex II through Annex VII list substances that are either prohibited for use in cosmetics or allowed in specific products according

to their intended use (i.e. leave-on, rinse-off, eye area) in limited concentrations.[68] Under EC No. 1223/2009, Annex V contains the list of permitted preservatives along with their limitations for use in cosmetic products marketed in the EU.[69] Another barrier in the EU is the REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals) requirements for the preservatives under the EU Environmental Chemical Policy.[19,70] Many other countries have composed lists of preservatives that are either prohibited or allowed for use in cosmetic and personal care products. These countries also regulate the maximum allowable concentration that is safe for the intended use of the product.

When selecting a preservative system for a cosmetic formulation, attention must be paid to the safety evaluation and risk assessment of the biocide. Most information regarding the chemical safety and use limitations can be obtained from the manufacturer or the Material Safety Data Sheet (MSDS) provided with the chemical. For an existing preservative system, in addition to a review of the safety data from suppliers and information readily available from public online databases (e.g., CIR, CDC, EPA, and EU directives), the history of use and post-marketing surveillance of current products containing the same preservative system should be taken into account.

Traditionally, in addition to the safety assessment of preservatives or individual ingredients, potential adverse reactions to skin are evaluated on the finished product. For example, the Human Repeated Insult Patch Test (HRIPT) is performed to detect potential irritation and type-4 sensitization, and photosensitization tests are used to assess potential photosensitivity, when applicable. In addition, *in vitro* skin irritation and photosensitivity assays are used for screening potential harm and ensure that there are no deleterious effects due to chemical interactions. Preservative interaction with other ingredients may reduce the preservative efficacy against microorganisms and adversely affect the skin. Knowledge of preservative chemical compatibility with other ingredients is critical for the development of a safe formulation. Product safety is assessed at different stages to identify potential chemical safety hazards and to alleviate any related risks.[61]

Summary

Adequate preservation of topically applied formulations is required to protect the consumer and the product during its normal intended use and shelf life. Cosmetic products contain multiple ingredients, each of which have different physico-chemical properties. Formulation science is the art of combining a variety of ingredients creating a single coherent physical form while maintaining balance among all ingredients. During the complex process of formulation, the combined ingredients interact with each other to create a consistent system and therefore lose their intrinsic identity while forming a united and stable entity. Any change in the product's chemistry may result in favorable or unfavorable changes in the properties of any individual ingredient.

Physical factors can also alter the performance of the preservatives. When formulating a product, pH, temperature, water activity, and order of addition of its ingredients are important factors to be taken into considerations. There is no "one size fits all" concept in selecting an effective preservative system.[71]

An essential aspect of stability of a formulation is establishing its microbiological safety, which is determined through performing a preservative efficacy test that measures the capacity of a formulation's preservative system against microbial contamination. Effective formulation is crucial to formulative success in process and at market.

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SECTION VI:

Color Cosmetics

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CHAPTER 19

Lip Care Product Formulation Strategies

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Key Words

Colorant, Organic Colorant, Inorganic Colorant, Surface Treated Pigment, Pearlescent Pigments, Film Former, Syneresis, Blooming/Crystallization, Ball Bearing Effect, Bleeding

Types of Lip Products

Let's eschew the standard introduction and instead jump right into it. In general, lip formulations can be classified to the following applications:

Lipsticks: Traditional lipsticks are complex systems consisting of mixtures of waxes and oils in which colorants are dispersed and suspended. The mixture is heated and melted before it can be poured into metal split molds **(Figure 1)** to form a bullet-shaped stick, which is then inserted into swivel components. This type of packaging allows the user to raise the product for application and lower the product for increased protection of the pomade. The edge of the bullet is usually flamed to give a smooth and shiny surface. Cosmetic companies recently started using silicone molds for shaping, a practice that eliminates the need for flaming, thus creating lipsticks with a shinier surface. This approach also allows companies more flexibility to create unique shapes and logos.

Figure 1. Melted lipstick being poured into metal split mold

The surface of a lipstick should appear smooth and attractive, exhibit even color, and be free of any imperfections such as dents, pinholes, and

striations. The structure should be somewhat firm and durable, yet it should apply easily and impart even coverage. If formulated and manufactured properly, a lipstick should not break during application or have any sweating, nor should it feel rough, gritty, dry, or possess a bad odor or taste. The color applied to lips should not migrate to the upper or lower lip area, feather or change over time. Lipsticks on the market are available in many different shapes and sizes. Coverage ranges from sheer to full in all types of finishes such as glossy, satin, frost, glittery, and matte.[1]

Lip Glosses are liquid variants of lipsticks and are more geared towards providing glossy lips. Most lip glosses contain tacky film-formers that have replaced and reduced the wax. These film-formers provide more transparency and fluid texture. The most commonly used film-former for lip glosses is polybutene. They also tend to be less intense in terms of color and usually flavored. Lip glosses are more popular with younger consumers who prefer sheer coverage and wet-looking lips versus an intense lipstick shade. The main difference in manufacturing a lip gloss versus a lipstick is the omission of the molding process. Lip glosses are directly poured into their package which is usually a vial, pot, or plastic squeeze-tube.

Lip Balms are primarily used to condition, protect or reduce the symptoms of chapped lips. Typically these products contain minimal to no colorant along with occlusive waxes, emollients, antioxidants, and sunscreens to provide additional benefits. Consumers of all ages and both genders use lip balms. They can provide soothing relief to dry, chapped lips and protect lips from exposure to harsh environmental conditions such as wind, sun, cold and dry weather. Lip balms are usually sold in sticks, squeezable tubes, pots, and jars.

Emulsion Lip Products: Almost every lip product on the market is an anhydrous formulation. This means that it is composed of one continuous oily phase that does not include water. Emulsion lip products such as water-based lipsticks are rarely launched to the market. Here, the water phase is added into the oil phase and emulsified. They offer unique aesthetics and their manufacturer may claim benefits that are related to the content of water, such as moisturization. Emulsion lipsticks are very challenging to formulate due to potential formulation and color instability and require the inclusion of a robust preservative system along with the proper surfactants.[2] The inclusion of preservatives and surfactants may be irritating to the lip tissue, which is more sensitive to insult since it lacks the upper layer of the skin, the stratum corneum.

Setting Specifications and Path of Development

Desired Aesthetics: Once the desired coverage (determined by the level and type of pigments used) is selected, the formulation chemist can begin choosing key ingredients which will assist in achieving the preferred aesthetic attributes such as smoothness on application, cushion, tack and length of wear, as well as other consumer desired benefits. The most commonly desired benefits for lip products are gloss, moisturization, creaminess, long-wear and transfer-resistance. Waxes

provide the structural integrity but can also cause tackiness, drag and reduced gloss. Oils and emollients provide slip and gloss, and assist in reducing the tackiness. Semi-solid emollients and gelling agents can provide different textures such as cushion. Adhesive film-formers typically come in different forms and exhibit a scale of softness-to-hardness characteristics that are usually denoted by their glass transition temperature. The glass transition temperature (denoted T_g) is defined as the critical temperature at which a substance changes from being soft, rubbery, and flexible to being hard, glassy, and brittle.[3] The more viscous liquids, which have a glass transition below room temperature, tend to provide enhanced gloss, better adhesion and wear but may be tacky and impart onto the product more drag on application. Solid film-formers have a T_g above room temperature and tend to be less tacky, less flexible, and with reduced gloss. Some products contain solid film-formers with volatile silicone liquids and hydrocarbons. These provide excellent transfer resistance due to their ability to evaporate after application, leaving a film on the lips. Finding the right balance of ingredients to create the desired texture, performance, and aesthetics is a continuous challenge for all formulators. Consumers also expect their product experience to remain constant across different temperature ranges.

Lipstick Shapes: Lipsticks come in all shapes and sizes but the most common is the full-size pomade which is a half-inch in diameter. They are usually referred to as "bullets" due to their molded shape. The most traditional lipstick shapes have always been fishtail, teardrop, and the wedge.[4] Pictures of these are shown in **Figure 2.** Some lipsticks even come in a slimline shape which are smaller in diameter and are fully supported by the package. Novel shapes continue to evolve offering lipstick users new types of application and style.

Figure 2. Different lipstick shapes and designs

Ingredients

As noted, in order to develop a lip care product that will meet market needs, the components of the formulation, their ratio, and production method need to be carefully planned. The formulation chemist must understand the role and appropriate use level of each component and the advantages and limitations of their carefully weighted use, respectively.

The main components used in lip care products, their properties and use, are described on the next page.

Waxes: Choosing an appropriate wax system is critical to the formulation development of a lipstick. Waxes provide the lipstick with body and structure which can be adjusted based on the desired coverage, aesthetics, and packaging. Waxes have the highest melting points of all ingredients in a lipstick and usually comprise about 15% of the formulation. A good blend of waxes will ensure that a lipstick provides a pleasant application experience and does not break or bend when applied. A lipstick needs to maintain its integrity at elevated temperatures, such as when left in a car or an un-cooled freight container or warehouse during summer months. Different waxes are typically used in combination at different ratios to adjust the physical characteristics of a lipstick. These characteristics may be hardness, fragility (resistance to breakage), texture, flexibility, stability and shrinkage. Lip glosses on the other hand, usually contain about 50% less wax and more oils or liquid film-formers, such as polybutene, to provide a shinier finish.

Waxes are derived from plants, seeds, petroleum, animal-derived fats, or fats manufactured synthetically. Formulation chemists tend to use a range of waxes to balance structural integrity, hardness, brittleness, mold release, and aesthetics such as drag and surface gloss. The most often used waxes in a lipstick are listed in **Table 1** along with their melting point ranges.[5]

Table 1. Melting point ranges for a variety of waxes

WAX	MELTING POINT RANGE IN DEGREE CELCIUS
Carnauba	80-86
Candelilla	69-73
Ozokerite	68-96
Ceresin	54-74
Microcrystalline	63-94
Beeswax	62-65

Because most lipsticks are made by pouring or injecting the molten formulation into a metal mold that is then cooled, the ease at which a formulation releases from the mold is an important consideration when choosing a wax or adjusting the wax levels. The coefficient of thermal expansion (sometimes called the coefficient of volume expansion) is a measure of the expansion of a wax with increasing temperature. Some of the waxes used in cosmetics that exhibit the highest coefficient of expansion are beeswax, microcrystalline, ozokerite and paraffin wax.[6,7] For microcrystalline and paraffin waxes which are commercially available with different melting points, the lower melting point variants tend to have the highest coefficients of thermo-expansion.

Vegetable wax: Two relatively hard texture plant derived waxes which have similar functions are carnauba and candelilla. These waxes are extracted from *Copernicia cerifera* and *Euphorbia cerifera*, respectively,[8] and like most plant derived compounds have complex chemical composition. They both provide good structure and surface

gloss to a lipstick. Carnauba wax, which is more brittle, has a higher melting point.

Mineral wax: Petroleum derived mineral waxes such as ozokerite, ceresin and microcrystalline exhibit a wider range of melting points. The use of ozokerite and ceresin, offers resistance to lipstick breakage because they form three-dimensional microstructures that enhance stability.[9] Microcrystalline waxes have higher degrees of branching when compared to most petroleum waxes[10] and because of this they are less likely to crystallize.[11,12] These attributes will reduce the likelihood of oil separation or blooming from the formulation over time. It also means that in most cosmetic oils higher levels of microcrystalline wax will be needed to obtain the same level of structuring when compared to more linear waxes with the same melting properties. The lower melting point variants of microcrystalline wax can generate tackiness if used at high levels, which will cause poor mold release.[9]

Animal wax: Beeswax is an animal (bee) produced wax that acts as a thickening agent, aids in preventing lipstick breakage, and provides good mold release because of its high coefficient of thermo expansion, but can impart tackiness and reduce shine if used at high levels in lip formulations.

Synthetic wax: Synthetically derived waxes such as silicone waxes offer increased slip and detackifying properties. Because of incompatibility with traditional lipsticks, which are mostly alkyl hydrocarbon-based formulations, alkyl modified silicones, such as stearyldimethicone are often used to increase compatibility. There are a plethora of substitution options available for alkyl modified silicones and the functional properties of these compounds can be tuned to meet a broad range of formulation needs.[13]

Other useful compounds that provide structure and improve stability of lipsticks at elevated temperatures are low molecular weight linear polyethylenes, conforming to the structure $(C_2H_4)_x$. These synthetic polymers have high melting points and limited room temperature solubility in most oils, making them ideal for hardening lipstick formulations.[14] Because linear polyethylenes have very low polarity, they are more compatible with nonpolar oils.[15,16]

Oils: The oils used in lip formulations can be vegetable-based emollients, silicones, polymers, or hydrocarbons. They provide a wide range of functions depending on their chemistry and viscosity. Other than being used as solvents, they wet and disperse pigments, provide moisture, slip, cushion, gloss, long-wear, transfer-resistance, and even thickening properties. Some of the most common oils used in lip products include the following:[17]

Hydrogenated Polyisobutene
Octyldodecanol
Ricinus communis Seed Oil (castor oil)
Diisostearyl Malate
Caprylic/Capric Triglyceride
Bis-diglyceryl Polyacyladipate-2
Pentaerythrityl Tetraisostearate

Simmondsia Chinensis Seed Oil (jojoba oil)
Ethylhexyl Palmitate
Squalane
Dimethicone
Methicone
Phenyl trimethicone

Table 2 shows a formulation for a traditional lipstick using castor oil—which is widely used because it is an effective pigment dispersant, may enhance moisturization, may impart shine, and is cost-effective. The formula has been offered by Lipo Chemicals Inc. and published in *Cosmetics & Toiletries* magazine.[18]

Table 2. Lipstick with Polyethylene	%
Ricinus communis (castor oil)	38.40
Tridecyl Trimellitate	9.00
Hydrogenated Vegetable Oil	7.00
Synthetic beeswax	7.00
Tridecyl stearate	11.00
Candelilla wax	4.00
Carnauba wax	5.00
Propylparaben	0.10
Tocopheryl acetate	0.50
Ricinus communis seed oil (and) iron oxide red (40% Grind in Castor Oil)	6.00
Ricinus communis seed oil (and) iron oxide black (40% Grind in Castor Oil)	2.00
Ricinus communis seed oil (and) titanium dioxide (50% Grind in Castor Oil)	3.00
Ricinus communis seed oil (and) iron oxide yellow (40% Grind in Castor Oil)	2.00
Ricinus communis seed oil (and) D&C Red No.7 (40% Grind in Castor Oil)	3.00
Polyethylene	2.00

Longer wearing lip products which can be transfer resistant tend to have a significant amount of volatile silicone or hydrocarbon. Cyclomethicone and isododecane are typically used to extend wear since they evaporate to leave a dry film on the lips. Lip formulations with volatile oils require air-tight packaging. They also tend to have a high amount of colorant which prolongs wear. The formulation shown in **Table 3** has been offered by Presperse Inc. and published in *Cosmetics & Toiletries* magazine.[18]

Table 3. Long-wearing Lipstick with Polyisobutene	%
Polyisobutene	2.00
Paraffin	2.80
Copernica cerifera (carnauba) wax	7.20
Euphorbia cerifera (candeilla) wax	2.40
Synthetic *Cera alba* (beeswax)	3.20
Tricontanyl PVP	8.00
Isononyl isononanoate	20.00
Tridecyl trimelliate	5.00
Titanium dioxide, 50% (and) *Ricinus communis* (castor) oil	4.40
D&C Red No.7 Calcium Lake, 33% (and) *Ricinus communis* (castor) oil	3.40
Brown Iron oxide, 50% (and) *Ricinus communis* (castor) oil	2.20
Red No.6 Barium Lake, 33% (and) *Ricinus communis* (castor) oil	9.80
Isododecane	29.60

During the last decade, many companies in the industry have offered long wearing lip glosses based on silicone resin technology. Silicone resins are combinations of monomers designated as M, D, T or Q. When the alkyl chain is methyl, M is Me_3SiO, D is Me_2SiO_2, T is $MeSiO_3$, and Q is SiO_4.[19] Long wearing lip formulations normally have an MQ (combinations of "M" and "Q") or MT (combinations of "M" and "T") silicone resin and include a high percentage (30-60%) of volatile organic or silicone solvents.[20,21] These long wearing products tend to be less glossy and less comfortable than a conventional lipstick. Commercial products are often sold as a two-step application with a top coat that provides increased shine and comfort.[22] An example of a long wearing formulation that contains silicone resin is given in **Table 4**.[23]

Table 4. Longwearing lip gloss with alkyl silicone resin	%
Alkylsilicone resin (MK resin WackerChemie)	22.0
1 centistoke dimethicone	57.0
Pentaerythrytyltetraoctanoate	5.0
Cetyldimethicone	2.0
Trilaurin	1.0
Cyclomethicone blend	5.0
D&C Red 7, Ca lake	0.8
Iron oxide red/methicone	0.4
Iron oxide black/methicone	0.2
Titanium dioxide/methicone	1.4
Mica	5.2

Lip gloss formulations contain more oil when compared to lipsticks and significantly lower amounts of waxes and colorants. They typically contain a high level of tacky film-formers such as polybutene, which improve color, adhesion and have a high refractive index for increased shine. The formulation shown in **Table 5** has been offered by Scher Chemicals and published in *Cosmetics & Toiletries* magazine.[18]

Table 5. Lip Gloss	%
Red No.6 Lake, 35% (and) *Ricinus communis* (castor) oil	0.10
Red No.7 Lake, 35% (and) *Ricinus communis* (castor) oil	0.05
Mica (and) Titanium dioxide (Flamenco Violet, Englehard)	5.00
C24-30 alcohol	1.75
Copernica cerifera (carnauba) wax	1.70
Microcrystalline wax	4.00
Triisostearoyl polyglyceryl-3 dimer dilinoleate	43.30
Triisostearyl citrate	38.40
PE/VA copolymer soy triglycerides	5.00
Methylparaben	0.20
Propylparaben	0.10
Tocopherol	0.10
Raspberry flavor	0.30

Colorants: All colorants used in cosmetic products sold in the United States are subject to regulation under the Federal Food, Drug and Cosmetics Act (FD&C Act).[24] The FDA classifies color additives into two general categories: those that require certification, and additives that are exempt from certification. Code of Federal Regulations (CFR) Title 21, Part 73 subpart C lists the color additives that are exempt from certification.[25] The regulatory definition of a colorant, taken from the CFR is:

"The term *colorant* means a dye, pigment, or other substance that is used to impart color to or to alter the color of a food-contact material, but that does not migrate to food in amounts that will contribute to that food any color apparent to the naked eye. For the purpose of this section, the term "colorant" includes substances such as optical brighteners and fluorescent whiteners, which may not themselves be colored, but whose use is intended to affect the color of a food-contact material."[26]

A very useful resource for information regarding colorants used in the cosmetics industry is the Society of Cosmetic Chemists' Monograph Number 9.[27] Organic colorants made synthetically need to be certified by the FDA, which requires colorant manufacturers to obtain certification for each batch.[28] Organic colorants used in lip formulations are mostly organic laked pigments. Organic laked pigments are usually made by precipitating a water-soluble acid dye onto a substrate, such as alumina, silica, or maltodextrin. They are either preceded by the letters FD&C which means it can be used in food (F), drugs (D) or cosmetics (C) or D&C which means it can only be used in drugs or cosmetics.[29] They provide clean and vibrant colors. Chemical structures examples of these are shown in **Figure 3.**

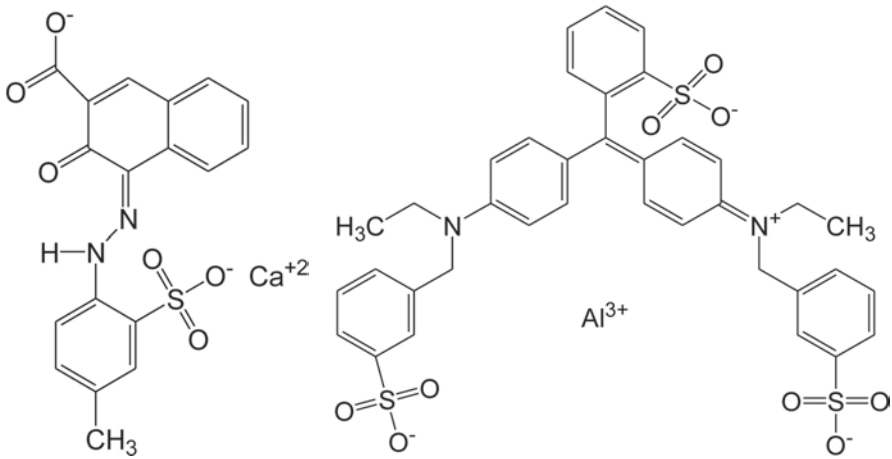

Figure 3. Illustration of D&C Red No.7 Ca.Lake and FD&C Blue No.1 Al. Lake

Natural organic colorants are exempt from FDA certification. The most common natural colorant in lip care products is carmine, which is a red colorant extracted

from female beetles that originate from Central and South America.[30]

The majority of inorganic colorants are natural pigments derived from minerals (such as iron oxides). They provide earth tones and lack the vibrancy of organic colorants. Unlike organic colorants, they are very stable to light and heat. Inorganic colorants are manufactured synthetically and are exempt from FDA certification. One of the most widely used inorganic pigments utilized to impart opacity and brightness due to its white color is titanium dioxide. Other inorganic pigments, such as iron oxides, provide the brown, black, russet and yellow colors. Black iron oxide is called magnetite in nature.[31]

Manganese violet on the other hand is a synthetic inorganic pigment that is very stable and provides a reddish violet shade. All pigments are in a physical form of dry powders that are insoluble in water and oil. The only colorants that are soluble in water or oil are dyes, which are used to stain the skin. A dye is a colorant that is soluble in the medium it is dispersed in. Dyes may be used in water-based formulations if they are soluble in water. Dyes such as D&C Red No.21 and D&C Red No.27, which are oil-soluble, can be used in anhydrous lip formulations if staining the lips is the desired outcome. Other colorants that are typically used to add a shimmer effect to lip products are pearlescent pigments. These are prepared by precipitating titanium dioxide and iron oxides on mica. The FDA restricted the particle size for mica to less than 150 μM.[32] This restriction is only on the upper particle size limit.

The very first step in shade matching is deciding which combination of colorants to use. There are numerous red pigments with different hues along with hundreds of pearlescent pigments to choose from. It can be challenging to select the exact colorants used to match the shade of an identified benchmark, especially if it is a competitive product. There are various methods in which a formulation chemist can achieve a desired shade based on the colorants available. Shade matching is a skill that combines art and knowledge and is acquired through experience. The best advice is to try and match the shade using the least amount of colorants, which will make it easier to manufacture. For red shades, Red 7 lake is the pigment of choice because it provides the most intense red color.

When color matching, using pigments in which the particles undergo surface treatments will result in different hues and intensities. For example, a shade obtained by formulating a product using 3.0% untreated titanium dioxide and 0.20% untreated Red 7 lake will result in a different hue and shade intensity when compared to the same product made with equivalent quantities of the fluorosilane treated pigments. The base color might also experience batch-to-batch variations because of small color changes in base raw materials. Therefore, each batch made in manufacturing is individually shade matched.

Surface treatment of the colorant particles can also aid in improving the aesthetics and performance of the product. Surface treated pigments are prepared by either physical absorption or by reacting a chemical additive onto the surface of an untreated pigment. This modification can offer many advantages over traditional

untreated pigments. It provides improved dispersion along with reduced tendency for agglomeration, leading to easier wetting which is required in order to achieve higher pigment loading. The effective dispersion improves lip coverage and allows for a smoother application. In addition, surface treatment can provide pigments with improved adhesion as a result of change in oil absorption/wetting properties. This can improve wear when applied to lips. Various surface treatments are commonly used in lip care formulations; examples include silicone, fluorosilane, amino acids, and titanate treatments such as isopropyl titanium triisostearate.

Before incorporating pigments into a lip care formulation, it is recommended that they are milled into a pigment grind to reduce the tendency for particle agglomeration and to improve dispersion. An oil for the lip product formulation with good pigment wetting properties is normally selected as the grind medium. Semi-polar esters, oils, or fatty alcohols such as castor oil, octyldodecanol, diisostearyl malate or ethyl palmitate are particularly effective grind agents. Allowing the pigment to absorb the liquid medium and spread around the particles surface is referred to as "wetting" the pigment. Wetting reduces the surface tension between the particle and the air, allowing for a more homogenous incorporation into the formulation media. Non-polar oils such as hydrogenated polyisobutene or squalane wet pigments poorly and are not ideal in aiding with the preparation of pigment grinds. The dispersion is then milled to ensure that pigment agglomerates are broken down and well dispersed. Milling is typically done with a three-roll mill but other mills such as a ball mill can be used. Following milling, a Hegman gauge **(Figure 4)** is used to determine the fineness of a pigment dispersion to ensure that all coarse particles have been reduced to the smallest possible particle size and agglomeration has been sufficiently reduced. This grind gauge is a steel block with two grooves along its length. A pigment grind mass is placed near the top where the groove is at its deepest and drawn down to the lower end where the groove becomes flat using a metal scraping bar. Indication of undispersed pigment or agglomerates will appear as streaks along the grooves closer to the flat end. For measurements, two types of units can be utilized: Hegman units on one side of the grooves and mils units on the other. Hegman units on the gauge range from zero to eight. The goal is to reach 7 or above, which indicates a good dispersion.[33] The opposite side of the gauge contains the mils units, which can be converted to microns. The mils scale on the gauge starts at 4 and descends to zero, since it correlates with the depth of the grooves. One mil is the equivalent of 25 microns.[34]

A shimmer effect can be added to lip products through the use of pearlescent pigments. They act as a prism, because the color they provide is derived from light reflection. They are usually mica based and coated with titanium dioxide or iron oxide ranging in size from 1 μM to 150 μM. They are added directly to a batch. Milling or homogenizing pearls may result in the loss of pearlescence, as pearlescence is related to particle size. Pearls range in a variety of shades and finishes depending on the amount of luster needed. Calcium sodium borosilicate pigments, which

are larger than most mica based pearls, can also be used to enhance the sparkling effect. One disadvantage of using high levels of large particle size pearls is adding grittiness to the application of lip products. Typically, particles of around 40 μM or larger can be sensed on the lips.[35]

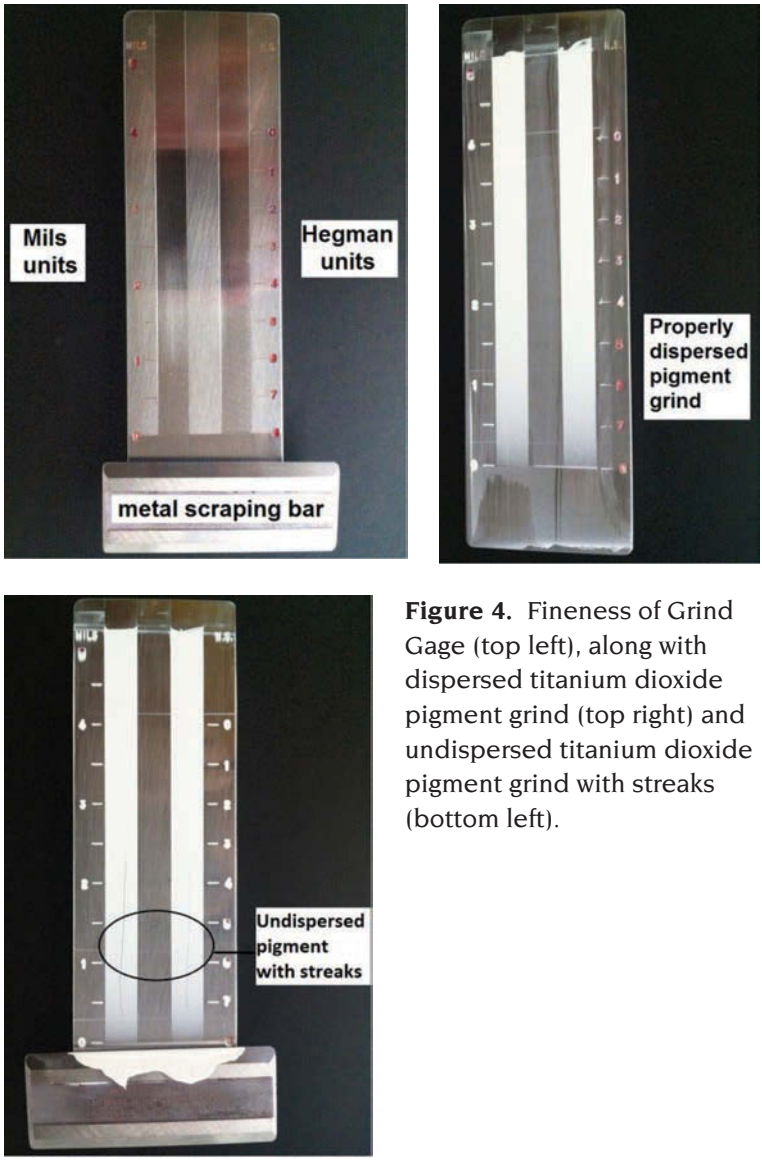

Figure 4. Fineness of Grind Gage (top left), along with dispersed titanium dioxide pigment grind (top right) and undispersed titanium dioxide pigment grind with streaks (bottom left).

In choosing a colorant, it is necessary to verify its regulatory status in the specific market/region in which the lip care products are intended to be sold, to determine

if there are any raw material inclusion restrictions. Restrictions for colorants can vary from one country to another and can be found in the literature.[36] For example, ultramarines which are inorganic colorants are restricted for use in lip care products in the United States but not in other countries. D&C Red No.6 Barium Lake along with D&C Red No.27 Aluminum Lake are permitted for use in the United States and Europe but not in Japan. Pearlescent pigments containing ferric ferrocyanide are not permitted for use in United States but are allowed in other countries. Pearlescent pigments and glitters also have particle size restrictions.

Pigment Dispersants/Emulsifiers

To achieve optimum color development and shade stability, an effective dispersion of pigments is necessary. Poor dispersion may result in pigment agglomeration which may lead to color streaking on application or with a Hegman gauge.[37] Pigment dispersion is impacted by solvent viscosity, surface tension, and mechanical energy (shear) that can be applied to the mixture. There is an abundance of literature in the pigment coating industry that discusses the theories for dispersant stabilization.[38] O'Lenick has classified a broad range of surfactants by function, including wetting agents and dispersants.[39] Examples of commonly used wetting agents for color products are:[17]

bis-diglyceryl Polyacyladipate-2
Tridecyl Trimellitate
Polyglyceryl-2 Diisostearate
Polyglyceryl-3 Polyricinoleate
Cetyl PEG/PPG-10/1 Dimethicone
Glyceryl Oleate
Glyceryl Behenate/Eicosadioate
Polyglyceryl-4 Isostearate
Stearyl/PPG-3 Myristyl Ether Dimer Dilinoleate
Polyglyceryl-2 Dipolyhydroxystearate

Some of the more effective wetting agents are nonionic surfactants, such as alcohol ethoxylates. Studies have shown that some nonionic surfactants are skin permeation enhancers, which could also lead to irritation. Permeation enhancers usually alter the stratum corneum structure and show a similar effect on the lips, which lack or have only few layers of corneocytes. Such irritation may be even more pronounced than when applied to intact skin in other areas of the body.[40,41] This may be one of the reasons consumers find some lipsticks to be drying and uncomfortable when compared to a lip balm.

Film-formers: Film-formers are substances that promote the formation of film on the lip surface. These are commonly polymers or other high molecular weight compounds that have a strong cohesive force, and may be either adhesive or non-adhesive. Polyethylene, polybutene, sucrose acetate isobutyrate, and polyvinyl

pyrolindones are a few examples of these. They are used in lip care products to promote longer and more even wear. Such compounds often require the use of a co-solvent, called a plasticizer, to be effective film-formers. Examples of these are silicone MQ resins (plasticized with dimethicone), polyvinylpyrolidones (plasticized with polyols) and certain polyacrylates. For the MQ resin, "M" stands for Me_3SiO and "Q" for SiO_4.[42] The glass transition temperature T_g, is one of the more important parameters to consider in the behavior analysis of film-formers. Below their T_g, film-formers tend to be in a solid state, non-flexible, and non-tacky. Above their T_g, these compounds are liquids in form, very flexible, and often extremely tacky. The goal of the formulation chemist is to create such balance in the selection of film-formers to obtain the expected end use aesthetics. Lip glosses, which are expected to be tacky, often contain polybutene (T_g = -24 °C)[43] as the major ingredient. Traditional lipsticks, which are expected to have 3 – 4 hours[44] of wear and not be tacky, generally contain only a small percentage of low T_g film-formers such as polybutene, sucrose acetate isobutyrate, or alkyl modified polyvinyl pyrolidones. Long wearing lipsticks contain film-forming systems that have a T_g that is greater than a typical lip surface temperature because this will result in good adhesion with low tack. A potential drawback of such applications may be the creation of a more rigid film. Examples of commonly used film-formers in lip products are:[17]

Polybutene
Polyethylene
Acrylates Copolymer
VP/Hexadecene Copolymer
VP/Eicosene Copolymer
Methyl Hydrogenated Rosinate
Sucrose Acetate Isobutyrate
Trimethylsiloxysilicate
Hydrogenated Styrene/Methyl Styrene/Indene Copolymer
Stearic Acid
Phenylpropyl-dimethylsiloxysilicate
Acrylic Acid/Isobutyl Acrylate/Isobornyl Acrylate Copolymer

Rheological modifiers: There are multiple reasons for including rheological modifiers in lip care products, primary of which is their aid in the suspension of pigments during production. In addition, these modifiers may change the aesthetics and structure of the product. Rheological modifiers are normally associative or non-associative thickening agents. Most of these compounds tend to be shear thinning, i.e. their viscosity decreases with increasing sheer rates. After the application of sheer has stopped, it is takes some time for the formulation to re-build its structure and hence its maximum viscosity. One of the major difficulties with identifying appropriate thickening agents for lipsticks is the right balance between consumer acceptability and stability. To add to the complexity, most of the available ingredients will exhibit a decrease in viscosity with increasing temperature. At temperatures

which lipsticks are typically processed, most rheological modifiers impart minimal impact on the viscosity, pigment suspension or emulsion stabilization capabilities. The most effective high temperature thickening agents are disteardimonium hectorite, fumed silica, and dimethicone/vinyl dimethicone crosspolymers. A limitation of the dimethicone crosspolymers is their partial solubility in many organic oils commonly used in lip products. Another major challenge associated with rheological modifiers is that many such compounds are particles that function by forming crystalline networks (similar to waxes) and as such have significant detrimental effects, reducing gloss. Examples of compounds that form transparent gels in oils are ethylene/propylene/styrene copolymer, butylene/ethylene/styrene copolymer, cholesterol. and 12-hydroxystearic acid.[45]

Rheological modifiers are used to adjust the aesthetics of formulations both in bulk and on application. Many long wearing lip care products contain isododecane, which is a very low viscosity solvent. In order to suspend the pigments and increase the volume of the product on application, clays such as disteardimonium hectorite or stearalkonium bentonite are usually added to these formulations. For lipsticks, when used in moderation, under 1.0%,[46] these thickeners increase the volume of product on application and impart a perceived increase in cushioning. A wide range of carboxylic acid derived rheological modifiers have been developed for the personal care industry. These products are sold under INCI names carbomer, acrylates crosspolymer, and many others. Almost all of these thickeners are water-dispersed and would be ineffective in oil-based formulations. For emulsion-based lip care formulations, the carboxylate will interact with metal oxide pigments resulting in unstable formulations. Examples of commonly used rheological modifiers in lip products are:[17]

- Disteardimonium Hectorite
- Ethylene/Propylene/Styrene Copolymer
- Butylene/Ethylene/Styrene Copolymer
- Dipentaerythrityl Hexahydroxystearate/Hexastearate/Hexarosinate
- Cetyl Alcohol
- Stearalkonium Hectorite
- Hydroxystearic Acid
- Cholesterol
- Palmitic Acid
- Stearalkonium Bentonite
- Trihydroxystearin
- Dipentaerythrityl Hexahydroxystearate
- Ethylcellulose
- Cellulose
- Dimethicone/Vinyl Dimethicone Crosspolymer
- Fumed silica

For more detailed information about rhelogical modifiers please refer to Chapter 11.

Sunscreen actives: One of the most desired benefits in lip products is UV protection. The FDA classifies lip products containing sunscreens as over-the-counter (OTC) drug products since they are intended to be used to reduce the incidence of cancer.[47] The FDA has established testing procedures as a requirement for making sunscreen claims for lip products.[48]

Lip care products can contain chemical or physical sunscreens. Two of the most commonly used chemical sunscreens which absorb UV light are octylmethoxycinnamate and benzophenone-3. Other chemical sunscreens that can be incorporated to boost the SPF number are octocrylene and octyl salicylate. Taste is an important factor in the selection of sunscreens to use. Octocrylene, for example, tends to impart the most negative impact on lipstick taste. For physical sunscreens, micronized titanium dioxide, which absorbs and reflects UV light, can be used. One of the advantages of using physical sunscreens is that they do not degrade with prolonged UV exposure like chemical sunscreens do. Each sunscreen active can be used at a maximum use level depending on its regulatory status in the market where the product is being sold.[49] In the US market, sunscreens need to be listed separately as active ingredients along with their use levels in the ingredient list on the product package.[50] For more detailed information on sunscreen products please refer to Chapters 21 and 22.

Spherical powders and fillers: Powders and fillers are added to lip care formulations for a variety of purposes. These powders are either spherical or flat in shape and vary in particle size and size distribution. Common spherical powders used in lip formulations include silica, nylon, and polymethylsilsesquioxane. Spherical powders assist in improving the aesthetics of lip formulations by providing a "ball bearing effect." This "effect" is imparted by their spherical shape, which reduces friction and provides a slippery smooth feel. They assist in improvement in slip, spreadability, creaminess, coverage, and uniform application. Silica can be used to improve structure and stability of lipsticks due to its high oil absorption which increases hardness and can help reduce syneresis. Syneresis is the separation of the oil(s) from the bulk of the lipstick formulation.

Common fillers that are non-spherical include mica, barium sulfate, and sericite. They also improve application but are typically used to keep the solid content constant in the formulations. Since the amount of colorant varies from shade to shade, to ensure stability and other properties, fillers are used in place of colorant. This ensures all shades have same amount of powders, oils, and waxes. Matte lipstick formulations contain higher amounts of powders and fillers when compared to traditional lipsticks. The excess powder absorbs more oil, providing a non-shiny finish and creamy feel.

Preservatives: Most lip care products are anhydrous and will not contain water. They are also filled at very high temperatures, ranging from 150°F to 200°F, are therefore likely not to contain preservatives. Bacteria will grow and survive in a water containing environment. In addition, the high filling temperature

thermally inactivates most microorganisms, which results in a low microbial count. Preservatives are not essential unless the formulation contains water or raw ingredients that could possibly contain traces of water such as emulsifiers, esters, glycerin, powders, botanical extracts, and alcohols. A preservative system can be used to protect against microbial contamination after the lip product has been opened and used. Common preservatives used are caprlyl glycol, parabens, phenoxyethanol, benzoic acid and disodium EDTA. Due to negative press regarding the safety of parabens, there are some lip care products on the marketplace claiming to be "paraben-free."[51,52]

Promotional (claim) active ingredients: Many lip care product sales are promoted based on new seasonal shades or new types of finishes, but these are usually short lived, fashion related marketing themes. As new trends emerge, marketers will introduce promotional ingredients to make new claims to draw consumer appeal. Components such as vitamins A and E along with botanicals such as aloe have always been popular and offer many benefits. In recent years, lip care products have been marketed with other ingredients that are claimed to provide health benefits such as plant extracts from pomegranate, jojoba, chamomile, and soy. Honey and various butters such as shea, mango and cocoa may also be added. Promotional ingredients tend to be used at very low levels which allow cosmetic companies to protect trade secrets. Ingredients used < 1% do not have to be in descending order in a lip product ingredient list. It is highly unlikely that such low levels actually provide any detected benefit. A more detailed description for labeling requirements can be found in the FDA's Cosmetic Labeling Manual.[53]

Fragrance, flavor, and sweetener: Lip care products typically impart a pleasant fragrance or flavor. They are used to mask the fatty base odor which certain ingredients such as waxes can produce. They can also improve the taste of the product when combined with sugar substitutes such as sucralose, saccharin, and aspartame, which are used as sweeteners. Fragrance oils and flavors need to be compatible with other ingredients in the formulation to ensure good stability. They are usually incorporated at the end of the manufacturing procedure because they are heat sensitive. Fragrance oils and flavors need to be safe both to the lips and for ingestion and non-irritating to the consumer. Since most adverse effects are directly linked to the dose applied, it is recommended that these compounds are used at low concentrations. Common fragrances used in lipsticks tend to be floral, fruity, minty. or sweet aromas like vanilla.

Common Formulation Challenges

Lip care product formulation design requires knowledge and expertise. The complexity of the formulation and its physical/chemical and aesthetic properties is achieved through a carefully designed process. Below is a description of key challenges that the formulation chemist might face when developing a lip care product.

Syneresis: Formulating a good lipstick requires the right balance of waxes, oils,

powders, and pigments. One of the most common challenges when formulating a lipstick is the occurrence of syneresis. This usually occurs at either room temperature or elevated temperature when droplets of oil appear on the surface of a lipstick. Syneresis which can also be referred to as "sweating" and is usually observed during the course of stability testing when the product is exposed to changes in temperature. The sweating can be reabsorbed back into the lipstick at lower temperatures. Syneresis is an indication of incompatibility among the oils and waxes. Substituting or reducing the oil or adding microcrystalline wax, silica powder, or high oil absorbing silica may assist in reducing the syneresis effect.

Crystallization/Blooming: The crystallization of waxes, fatty alcohols/triglicerides or other substances on the surface of a product is known as blooming. This crystal growth is dependent on several factors such as incompatibility between oils and solid ingredients in the formulation along with storage conditions. A good way to improve aesthetics and moisturization properties is adding semi-solid emollients which melt at skin temperature (around 32°C). Vegetable butters such as shea and cocoa are examples of wax-like emollients that can crystallize and cause blooming at the surface of lipsticks if used at high quantity. Vegetable butters are composed of triglyceride esters of fatty acids such as stearic acid which have a tendency to crystallize. Crystallization and blooming can sometimes take months to appear especially during storage at various temperatures. There are many factors to consider in avoiding blooming. Reducing the concentration of butters to < 1% can reduce the risk of blooming. Care must be taken to ensure that all the ingredients are compatible with one another, along with having good solubility of polar and non-polar ingredients. Using a liquid shea butter in place of a solid shea butter is also a good alternative since the liquid butters do not crystallize. Another ingredient that is notorious for crystallizing on the surface of lipsticks is the sunscreen benzophenone-3. This can occur over time in samples that undergo stability testing and indicate that the content of oily solvent in the lip product is limited and cannot fully solubilize the benzophenone. A very common solvent to be considered for benzophenone is alkylbenzoate.

Color fading: Organic colorants are not completely stable and can exhibit fading issues. Unlike inorganic pigments, they can be sensitive to light, heat and pH depending on their concentration and combination with certain ingredients such as chelating agents. For example, Red No. 7, which is a calcium lake, will undergo shade shifting in the presence of the chelator ethylenediaminetetraacetic acid or in more polar solvents.[54] Lower concentrations of organic colorants are more susceptible to fading over time than higher concentrations. Fading can also be accelerated when using a clear package because it allows sun radiation to penetrate through the package. UV absorbers are typically incorporated into clear package material to prevent fading issues.

Bleeding/Feathering: Lip care products need to provide even coverage and should not migrate beyond the lip area after application. "Bleeding" occurs when a lip care

product smears around the edges of the lip line and does not stay put. Another problem associated with wear is when color seeps into the lines and wrinkles of the lips and above it. This is known as "feathering." Both bleeding and feathering are caused by using relatively high percentages of low viscosity oils. Low molecular weight esters provide lip care products with slip and glide but can also cause bleeding if used in high percentages. Increasing the viscosity with waxes, fumed silica, semi-solids, and higher molecular weight oils will reduce the odds for bleeding.

Physical Stability Requirements

Visual: During lipstick base development, the formulation needs to undergo a series of stability tests to ensure that it can withstand changes in environment, climate, and temperature. Its surface should be smooth and have even distribution of color. The lipstick should not feel gritty when applied to lips. Grittiness could be an indication of undispersed solids, excessive use of large particle size pearlescent pigments, or particle agglomeration. For stability testing, lipsticks should be placed in stability chambers at different temperature conditions ranging from freezing to elevated temperatures up to 50°C for a minimum of one month, and should be observed and evaluated periodically. Successful stability results are essential prior to launching a lip care product onto the market to ensure the product will remain stable over time. Lip care products typically have a three-year shelf life which indicates they should no longer be used or purchased three years from the date they were manufactured. Lipsticks need to be evaluated for syneresis, blooming, fading and leaning which can occur when the lipstick tilts to one side most likely due to insufficient coherence.

Hardness: A lipstick needs to have good structural integrity. After a lipstick has been molded and has reached room temperature, it should not deform, crumble, or melt upon application. If it bends upon application or has poor mold release after being allowed to cool and solidify, adding wax may assist in correcting these attributes. Lipsticks typically reach their peak in hardness twenty-four hours after being molded at optimum conditions. The hardness can be measured using an instrument such as a Texture Analyzer (Texture Technologies Corporation Scarsdale, New York). This valuable device can evaluate and quantify the degree of hardness of the formulation as it probes the product at a specified distance and speed to measure the amount of force used to penetrate the product.

Breakage: One of the more common methods used to evaluate the structure of a lipstick is by measuring the amount of force the lipstick can withstand before it breaks. The peak force which is commonly referred to as "the breaking point of a lipstick" can be measured by using an instrument such as a Chatillon Force Measurement System (Ametek, Inc., Berwyn, PA). The lipstick in its lipstick case is swiveled up completely, inserted horizontally and secured into an orifice or platform. Once secured, a probe applies weight to the lipstick at a specified speed, usually a half inch from the base of the lipstick or top of the inner cup. The weight

is increased until the lipstick breaks and the breakage value is recorded by a force gauge which measures the weight in units of kilograms or grams. Multiple samples are generally tested in order to determine the average break value.

Processing

The processing of a lip care formulation may require specialized equipment and tools as well as unique ways of operation and care throughout the process. Below is a description of a few key instruments and their manner of use:

Mixers: Overhead stirrers are generally used in the research and development phase at the formulation laboratory to mix anhydrous lip care formulations. These may be used in adjustable speeds which make them ideal for formulations that increase in viscosity with the addition of ingredients. A propeller shaft is inserted to the base of the stirrer and can be adjusted for depth for optimum mixing of the entire batch.

Homogenizers: High shear homogenizers can be used in place of mixers when low viscosity liquids or ingredients that are not easily dispersed are incorporated. Homogenizers rotate the batch at very high speeds, providing extreme shear which greatly reduces the particle size of the ingredients to ensure the batch is homogenous. They provide excellent circulation which makes them ideal for emulsions. Some lip care formulations contain rheological additives such as stearalkonium hectorite which need to be dispersed with high shear mixing using a homogenizer.

Molding: Lipsticks are generally molded in the laboratory using metal split molds. The molds must be clean and dry prior to being filled. The filling temperature used to pour bulk into molds should slightly exceed the melting temperature of the highest melting point wax in the formulation. For example, if the formulation contains ozokerite wax with melting point of 88°C, the filling temperature should be around 89–90°C. Bulk should not be poured directly into the wells of the mold but rather from the end of the short side of the mold so that the bulk floods and flows into the wells one row at a time. This prevents air becoming trapped and forming a shrink hole. Such hole can be formed at the top center as the lipstick solidifies upside down. Cooling the lipstick after the molding process results in faster solidification, better structure, and better mold release. Cooling is conducted for up to ten minutes using either an air conditioned cooling tunnel or a cooling table. When using a cooling table, the lipstick mold is placed on top of its cold surface and the metal mold is cooled to freezing temperatures.[55]

After a lipstick has been molded and reaches ambient temperature, it can undergo flaming. In a laboratory set-up, a Bunsen burner is typically used to flame the lipstick surface and to provide a smoothness and gloss. The flame should be held at a distance from the lipstick so it provides just enough heat to melt its surface without further deforming it. If air is trapped in the lipstick, pinholes can form on the surface, which is why air is removed in the manufacturing process using high vacuum mixing kettles.

Packaging

Packages: Over the course of time, applying color to lips has evolved from painting lips with carmine powder to using lipsticks in stylish lipstick cases. Packaging suppliers are continuously providing the cosmetic industry with unique package designs which are appealing to consumers. Whether it's a new sleek lipstick package shape or a new lip gloss applicator, the product must still provide a pleasant experience along with good performance.

Lipsticks are typically sold in full-size packages made out of plastic or metal with a cylindrical shape. Plastic packages are more common due to their low cost and are usually made out of polypropylene, polystyrene, or polyethylene. Aluminum is the common metal employed for lipstick cases when a metal case is desired. Lipstick packages usually have a swivel mechanism which turns the lipstick up and down during application. The lipstick pomade is inserted into an inner cup which is located inside the shell of the package. It is about a half inch deep and contains splines which prevent the lipstick from moving during use along with slipping out (**Figure 5**).

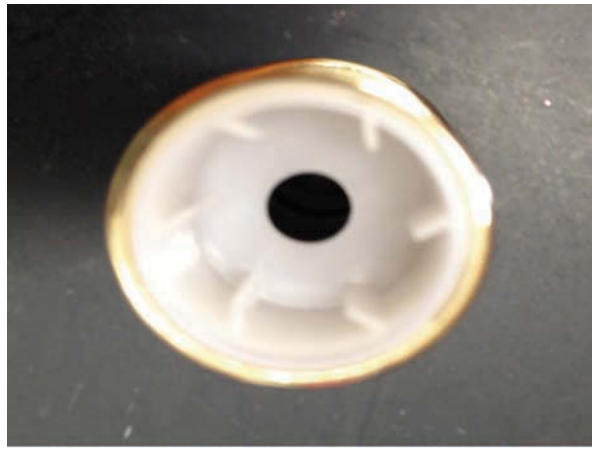

Figure 5. Inner cup of lipstick package with splines

There are some solid stick formulations that require no molding process. Many traditional lip balms with high levels of wax and emollients such as petrolatum are usually poured directly into their packages.

Lip glosses require a package that differs from that of lipsticks due to their lower viscosity. The most common are clear plastic vials with either doe-foot or brush applicators. Clear packaging allows consumers to observe the shade of the gloss to see if they find it appealing. Unlike lipstick packages which require a molding process prior to filling, here the bulk is poured directly into the vial. The top of the vial has a plastic wiper which is inserted after filling to prevent messy application. It wipes off excess bulk from the rod of the applicator as it dips in and out of the vial. Squeeze-tubes made out of soft flexible plastic like low density polyethylene

are also quite popular. Squeeze-tubes used for lip glosses usually have a slanted tip applicator for precise application. Tubes are supplied with an open end and sealed after filling using a tube sealer machine. This process crimps the end of the open tube using heat to melt the plastic to form a seal. Vials and tubes can be supplied with cheater bands which are solid lines printed across the top of the package to conceal the empty space at the top of the package after the product is filled.[56] Other types of packages that can be used for lip glosses include pots, compacts, twist pens, click pens, and roller-ball packages, any of which can be selected depending on the viscosity of the formulation.

Lip product formulations that contain volatile ingredients or water require airtight packaging to prevent weight loss which may affect the aesthetics of the product since it can dry out and possibly shrink. Polypropylene packaging is ideal in terms of helping to reduce weight loss.

Packages purchased by consumers are usually shrink-wrapped or cartoned. This outer package must list all the ingredients along with usage instructions and product claims. Packages also must contain a date lot code along with an expiration date to trace the product back to manufacturing in case any quality issues arise.

Summary and the Future Perspective of Lip Care Formulations

There are a variety of elements that should be taken into consideration when formulating a lip care product. The overall quality of the product is key to satisfying lip product users. As lip product sales continue to grow worldwide, marketers and formulation chemists will strive to come up with exciting new ideas and claims to attract consumers. The lip care market is highly competitive, with new trends emerging year after year. The opportunity to be innovative will never cease as long as suppliers continue to introduce new raw materials and packaging to the cosmetic industry.[57] Lip products are continuously being launched with ingredients that ordinarily have not been used before in color cosmetics. Years ago, the lip plumping trend emerged partly due to the incorporation of cooling ingredients such as menthol, which provides a cooling and tingling effect. Ingredients and technology from skin care are now being introduced to provide new moisturization and anti-aging benefits. Formulating lip care products is not an easy task. The ultimate inspiration and strategy behind most new product ideas is formulating a unique product. Figuring out how to raise the bar for creativity is the ultimate challenge when it comes to innovation.

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CHAPTER 20

Formulation of Nail Care Products

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Key Words

Additive, Bottle Tone, Cross-linking, Diluent, Drawdown, Dye, Explosion-Proof, Film-former (Primary and Secondary), Film Modifier, Lake, Molecular Weight, Monochromatic, Monomer, Nail Lacquer, Nail Tone, Nitrocellulose, Non-volatile, Oligomer, Organoclay, Personal Protective Equipment, Pigment, Polar Activator, Polymer, Rheology, Shade Matching, Solvent, Substrate, Thixotropy, Volatile Organic Compound

Introduction

Hands and fingernails may be regarded as an individual's "calling card." It is not uncommon to make implicit value judgments about someone based on the appearance of his or her hands and nails

This is understandable because hands and nails are used an integral part of a person's daily activities. The hands and nails of a young girl, a "soccer mom," and an elderly grandmother likely will have very different appearances and textures. The look and feel of the hands and nails of a concert pianist probably will differ from those of a construction worker. The same general comments extend to toenails and feet as well. Fingernails and toenails are important anatomical structures that require periodic maintenance for good overall hygiene and health. In addition to the need for nail trimming, there often is a desire to enhance the texture and appearance of nails, sometimes significantly. Nail cosmetics are used to make fingernails and toenails look and feel well groomed, attractive, and protected. These products are offered in a variety of formulation types, including emulsions, anhydrous preparations, and lacquers. In particular, lacquers represent the vast majority of nail products. Regardless of specific product form, all nail products must deliver the following key attributes:

- **Safety**: Nail products must be toxicologically innocuous.
- **Aesthetics**: Nail lacquers must be visually appealing initially and over time.

- **Viscosity**: Consistency must be acceptable during application and throughout the service life of the product.
- **Appearance:** Bulk color (bottle tone) and color on nails (nail tone) must be acceptable initially and throughout the shelf life of the product. Opacity on nails must be adequate. Gloss level must be acceptable on initial application and throughout the wear period.
- **Odor:** Odors are characteristic, but must not be noxious.
- **Application:** Product must glide smoothly across the nails with smooth, even film deposition.
- **Drying time:** Lacquers must dry to form durable, flexible films approximately 1-3 minutes following application.
- **Longevity of wear:** Lacquer films must adhere to the nails for an acceptably long period of time following application.
- **Ease of removal:** Product must be removed from nails using acceptable removal solvents such as acetone or ethyl acetate. Nails must not be stained or damaged after removal.
- **Stability:** Nail products shall not separate excessively or undergo unacceptable physical or chemical changes during transportation, storage, and use conditions.
- **Ease of manufacture:** Products must be manufactured and filled safely and efficiently under mass production conditions.
- **Cost:** Nail products must meet corporate cost objectives in order to be profitable, whether they be sold at mass-market or at prestige price points.

Most nail products use ingredient technologies that differ significantly from those typically used in other cosmetic products. This is especially true for lacquers, since they are classified as dangerous fire hazards and must be handled with extreme caution. Stringent safety practices always must be present. Specialized expertise and equipment, typically derived from non-cosmetic industries, are required to develop and manufacture lacquers safely and efficiently. As a consequence, most cosmetic marketers do not manufacture their own nail lacquer products, relying instead on the services of a select group of expert third-party manufacturers and fillers. Because of this requirement for special expertise, many veteran cosmetic chemists have little or no expertise in nail cosmetics. Nevertheless, such products have great commercial importance, especially in light of the recent proliferation of nail salons in the United States and other markets.

In order to explain the intricacies of nail cosmetics, it is useful to divide the nail category into two broad classes: *lacquers* and *non-lacquers*. The former class includes highly specialized products consisting of formulations that form durable films by evaporation of organic solvents, while the latter class includes products such as crèmes, lotions and anhydrous products which closely mirror those commonly used in mainstream skin care products. The scope of this chapter is shown below:

1. Nail Lacquer Chemistry and Formulation

2. Nail Lacquer Manufacture
3. Nail Lacquer Testing
4. Nail Lacquer Packaging
5. Non-Lacquer Nail Products
6. Summary

Nail Lacquer Chemistry and Formulation

Nail enamel, *nail polish*, and *nail varnish* are common and familiar terms, but they are technically inaccurate. These familiar products more correctly are described as *nail lacquers*. *Lacquers* contain one or more polymers and other non-volatile ingredients (called *solids*, *non-volatiles*, or *N.V.*) dissolved in a mixture of volatile organic solvents. They form hard, durable films at ambient temperature by evaporation of their volatile ingredients. Such films subsequently can be re-dissolved with solvents when re-application is desired.

Nail lacquers are liquids that are applied to nails with miniature brushes. They form hard, glossy films upon evaporation of their solvents. Other types of coatings form films by different means. "Enamels" are heated at high temperatures in order to form films; typically they are used on metal objects such as cookware. "Varnishes" undergo oxidation to form films; they typically are used as wood coatings. "Polishes" consist of waxes dispersed in organic solvents or emulsion vehicles. They often contain fine-particle abrasives to assist in surface cleaning. Like lacquers, polishes dry to form films, but these films are relatively soft and usually must be buffed to achieve smooth, high gloss finishes. Shoe polish and auto polish are prime examples of this type of coating. Still other industrial coatings are designed to undergo various chemical reactions immediately following application to enhance their durability and performance. Two-pack epoxy sealants, UV-cure inks, and powder coatings are examples of such robust coatings.

Examination of commercial nail lacquer formulations shows that these products contain numerous ingredients, many of which are industrial in nature and not typically used in other cosmetic formulations. In order to explain how nail lacquer formulations are constructed, it is convenient to classify their ingredients into five general categories, as outlined below:

- Film Formers
- Film Modifiers
- Solvents
- Additives
- Colorants

Film-formers: The ultimate goal of a nail lacquer is the deposition of robust films on the nails of the user, thus film formation is an extremely important subject in nail lacquer formulation chemistry. In common with nail lacquers, many cosmetic formulations are designed to form different types of films at various locations on the anatomy of the user. Lipstick, eye shadow, mascara, and liquid foundation makeup

products all deposit films on the lips, eyelids, eyelashes, and face, respectively. These films typically are relatively soft and flexible, and they normally are expected to remain intact for less than 24 hours following initial application. Most of these product films can be removed by mechanical wiping or by washing with soapy water; removal of more tenuous products is facilitated by use of oily or emulsified remover products. In contrast, nail lacquer films are quite hard, and must be sufficiently durable to remain substantially intact up to 7 days or longer following initial application. Unlike the lips, eyes, or face, fingernails are exposed constantly to a range of acute chemical, mechanical, and thermal attacks. Toenails suffer somewhat lesser degrees of insult, as shoes and hosiery usually protect them from the environmental shocks to which fingernails routinely are subjected. Regardless of where they are applied, nail lacquer films must be very robust chemically and physically to withstand harsh treatment for an extended period of time. Such robustness is extremely critical to the overall success of a nail lacquer: with the exception of oxidative hair dye, no other cosmetic product is expected to last longer on the body of the user. Removal of durable coatings invariably requires the use of *nail lacquer remover*, a liquid formulation that contains a high percentage of one or more organic solvents. Some specialty nail lacquers can be removed by means of peeling, but these products use films that are not designed for maximum film durability.

The heart of a nail lacquer is the *primary film-former,* a polymer that confers numerous important film properties, such as chemical, mechanical, and thermal resistance, as well as adhesion, ease of removal, toxicological safety, and regulatory compliance. Formulators of industrial coatings products routinely have at their disposal an enormous variety of primary film-formers from which to choose, since they are developing products intended for application on inanimate substrates. In stark contrast, nail lacquer chemists select their primary film-formers from a very short list of polymers, since they are creating products that must be safe enough for application on human nails. In addition to stringent requirements for toxicological safety and global regulatory compliance, nail lacquer chemists also must be concerned with ease of film removal. While many industrial coatings are designed for maximum service life without periodic removal (e.g. automobile finishes and paints used on the structural steelwork of bridges) nail lacquers are applied to a substrate that grows continuously and is attached to a living person. Periodic nail lacquer removal is a necessary requirement, and such removal cannot involve the use of extreme mechanical abrasion or highly toxic organic solvents. Fortunately, several acceptable nail film-formers do exist.

Nitrocellulose is the most common primary film-former used in nail lacquer formulations. It forms hard, glossy films that dry relatively quickly. It is known by several other names such as N/C, nitrocellulose nitrate gun cotton, pyroxylin, and collodion. Nitrocellulose is a naturally-derived polymer created by esterification of cellulose (in the form of cotton fibers or wood pulp) with nitric acid. Each 6-carbon ring unit of cellulose has three pendant hydroxyl groups that can be esterified by reaction with nitric acid under acidic conditions. Its structure is shown in **Figure 1**.

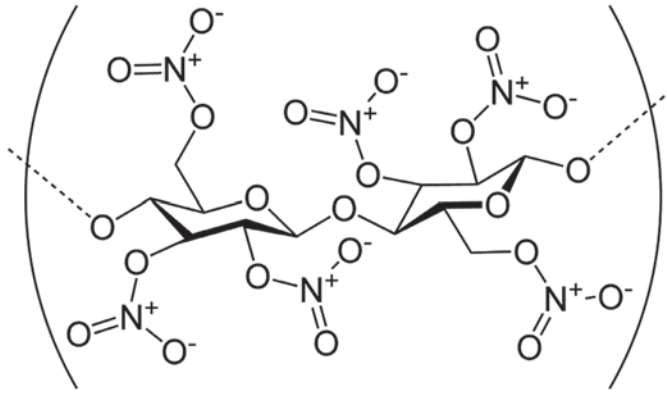

Figure 1. Chemical structure of Nitrocellulose repeat unit in a polymer

Tri-nitrated cellulose is an extreme explosion hazard, so in practice the degree of nitrate esterification is limited to the type of solvent system in which nitrocellulose will be dissolved. Lower degrees of nitration enhance solubility in solvent blends containing significant amounts of hydrocarbons and lower alcohols, while higher degrees of nitration require use of solvent mixtures containing alkyl esters, ketones, and glycol ethers. Because nitrocellulose with a high degree of nitration confers maximum water resistance, nail lacquers normally use the RS-type (RS = R Soluble, where R signifies an alkyl group). Less nitrated grades are called AS-type (**A**lcohol **S**oluble) or SS-type (**S**pirit **S**oluble), which are not typically used in mainstream nail lacquer formulations.

In addition to varying degrees of nitration and solubility, another important property of nitrocellulose is molecular weight. It is useful to depict the linear nitrocellulose polymer as a freight train, with each "car" consisting of a nitrated cellulose ring. Following this analogy, low molecular weight nitrocellulose is a short freight train with a few cars, while high molecular weight nitrocellulose is a long freight train with many cars. When dissolved in solvents, low molecular weight nitrocellulose produces solutions with low viscosity, and its films have relatively poor mechanical strength. Conversely, when dissolved in solvents, high molecular weight nitrocellulose produces viscous solutions, with films having good mechanical strength. Industrial lacquer formulation chemists can select from many viscosity grades, but nail lacquers typically use only four or five different molecular weights of nitrocellulose blended to achieve an optimum balance of viscosity and film strength properties.

A numerical viscosity-based nomenclature system is used to describe various molecular weight grades of nitrocellulose. Based on the falling ball method of viscosity measurement, each numerical designation refers to the time required for a steel ball of specified size and mass to travel the length of a glass tube filled with nitrocellulose dissolved in a specific solution. Test solutions prepared using lower

molecular weight grades of nitrocellulose are quite fluid, and the times required for the steel ball to transit the tube are very short, often less than 1 second. Conversely, the same test conducted with high molecular weight grades of nitrocellulose requires significantly greater time. Nitrocellulose is produced commercially in molecular weight grades ranging from 0.1 to 200 seconds; nail lacquers extensively use both the ¼-second and ½-second grades. The 5-6-second, 30-40 second, and 60-80-second grades are used primarily at low levels as viscosity builders. Viscosity range in centipoises is used to describe grades of very low molecular weight nitrocellulose (e.g. 18-25). On a side note, it is standard practice to abbreviate ¼-second as ¼", thus it is easy to spot novice lacquer chemists who sometimes speak about the properties of "¼-inch nitrocellulose."

Yet another descriptor of nitrocellulose involves a material called a wetting agent. This term has a very different meaning in other parts of the cosmetic and topical pharmaceutics formulations, such as in the preparation of emulsions and suspensions, but in the lacquer industry it refers not to a surfactant, but to an organic liquid that is added to nitrocellulose in a ratio of 70% dry nitrocellulose to 30% wetting agent. The resulting damp slurry sometimes is called *wet cotton*. The reason for this practice lies in the inherently explosive nature of organic nitrates, whose propensity for detonation increases dramatically when they become dry. Just as nitroglycerin and TNT (trinitrotoluene) are well-known explosives, nitrocellulose is a dangerous explosion and fire hazard, especially when dry. This property explains some of the early uses of nitrocellulose for the manufacture of gunpowder and other forms of ordnance. The addition of a suitable quantity of wetting agent reduces explosion hazards to the point where nitrocellulose may be transported and stored safely. Most wetting agents are capable of forming hydrogen bonds with the polar functional groups on nitrocellulose, thus helping to control the amount of extraneous water that nitrocellulose might otherwise absorb. The most common wetting agent is isopropyl alcohol, and nitrocellulose that contains isopropanol sometimes is termed "iso wet." Ethyl alcohol may be used instead, and nitrocellulose that is so dampened is called "ethyl wet." It is extremely important to keep containers of "wet cotton" sealed tightly when not in use. Samples of nitrocellulose that are believed to have become dry must be handled with extreme care to prevent detonation, and should be wet carefully with a sufficient quantity of water or alcohol prior to proper disposal as hazardous flammable waste. From a formulation standpoint, experienced lacquer chemists always take into consideration how much additional alcohol they automatically are adding along with "wet" nitrocellulose.

The foregoing discussion has provided clues necessary to decode the mysterious term "¼' RS N/C, 70:30 iso wet," and the serious fire and explosion hazards of nitrocellulose have been duly noted, yet there are other significant properties that also must be explained. Nitrocellulose is a reactive polymer that is sensitive to many common environmental factors. It is sensitive to various metals, particularly iron, and will rapidly turn yellow or brown even on minimal exposure to these

elements. Given that iron and steel are ubiquitous in the industrial world, this is a major inconvenience; nitrocellulose therefore must be handled in stainless steel or other non-ferrous containing metallic vessels. Nitrocellulose is exceptionally sensitive to alkaline materials, so much so that exposure to even small amounts of alkaline materials will darken nitrocellulose, and may even cause a fire or explosion. (Conversely, it is not especially sensitive to acids.) Nitrocellulose contains many polar moieties (i.e. ether, nitro, and hydroxyl groups) that are capable of forming hydrogen bonds with water, which can cause stability problems with organic colorants and rheological control additives in finished nail lacquer formulations unless the degree of residual moisture is controlled carefully during polymer manufacture. As mentioned earlier, wetting agents are useful in controlling undesired water contamination. Nitrocellulose is also sensitive to both sunlight and heat, and will turn progressively more yellow or brown upon prolonged exposure to these forms of energy. Mechanically, nitrocellulose films are hard, but brittle. The physical properties of nitrocellulose films vary in direct proportion to molecular weight. Generally, higher molecular weight nitrocellulose produces films having greater tensile strength and less brittleness as compared with films produced by grades of lower molecular weight.

Having read the dire hazard warnings and the long list of negative attributes of nitrocellulose, it is perfectly understandable to question why any intelligent chemist would want to use nitrocellulose in a lacquer formulation. Nail lacquer formulation chemists have tried for many years to find suitable replacements for this venerable film-former, but their efforts largely have been met with little success. Why is this so?

Strange as it may seem, for all its not-inconsiderable drawbacks, nitrocellulose actually is a toxicologically safe, cost-effective polymer that is manufactured from renewable plant-based resources. It contains no undesirable residual monomers or catalysts, and is innocuous to the skin and nails. It arguably is one of the earliest commercial "bio-polymers," because it is manufactured from sustainable, non-petroleum, plant-based feedstock (i.e. cotton or wood). The time-honored process technologies required to manufacture nitrocellulose are relatively straightforward, and can be performed even in developing countries worldwide. As a consequence, nitrocellulose is a very cost-effective raw ingredient for nail lacquer manufacture, and it is unlikely to be replaced at any time in the foreseeable future. In light of possible restrictions on the use of large amounts of volatile organic compounds (VOCs) in certain markets, it is likely that lower molecular weight grades of nitrocellulose will become more widely used to give acceptable film properties at reduced solvent levels.

Although nitrocellulose by far is the predominant primary film-former in nail lacquer formulations, alternative film formers sometimes are used for specific applications.

Cellulose contains free hydroxyl groups as shown **Figure 2**.

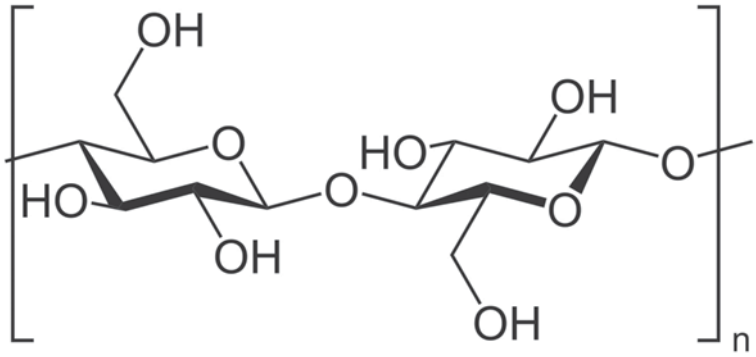

Figure 2. Chemical structure of cellulose repeating unit in a polymer

Cellulose ester polymers are chemically similar to nitrocellulose, except that the free hydroxyl groups are esterified with various low molecular weight carboxylic acids instead of nitric acid. Cellulose acetate butyrate (CAB) and cellulose acetate propionate (CAP) are manufactured in several different grades, based on molecular weight and degree of esterification with butyric and propionic acids, respectively. The molecular weight grades of CAB and CAP are described by the same falling ball method used for nitrocellulose, thus it is common to speak of ½" CAB or 20" CAP. They are soluble in the same types of organic solvents as nitrocellulose. Films produced by these polymers are clear and hard, but somewhat brittle. Because they do not present explosion hazards when dry, CAB and CAP do not require the use of wetting agents, and are sold commercially as 100% active powders. They are safer to handle and less chemically reactive than wet cotton, but they do not exhibit the same depth of gloss or film robustness as nitrocellulose. As a result, cellulose esters typically are used as primary film-formers in specialty lacquer applications where the color instability of nitrocellulose is unwelcome, such as non-yellowing topcoat formulations.

Acrylic and methacrylic acids and their esters are very commonly used to manufacture a wide range of "acrylic polymers". The structure of acrylic acid is shown in **Figure 3a**.The structure of methacrylic acid is similar to that of acrylic acid, except for the position of the C-C double bond, as shown in **Figure 3b**. Low molecular weight esters of acrylic and methacrylic acid are produced by reaction of these acids with low molecular weight alcohols, as illustrated by the structure of methyl methacrylate shown in **Figure 3c**.

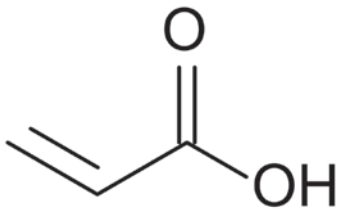

Figure 3a. Chemical structure of acrylic acid monomer

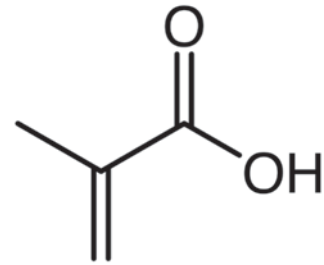

Figure 3b. Chemical structure of methacrylic acid monomer

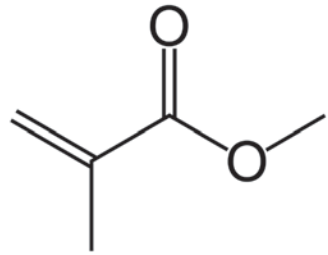

Figure 3c. Chemical structure of methyl methacrylate monomer

Acrylate and methacrylate polymers (generically classified as "acrylics") can be used as primary film-formers in nail lacquers. They are offered in a variety of grades, and are very widely used in industrial coatings. Many of these polymers have very good light stability and will not become yellow over time. Many acrylics are soluble in esters, ketones, and glycol ethers; some grades are compatible with nitrocellulose and other cellulosics. The chemical and physical properties of acrylics vary considerably and can be tailored to suit specific end applications. Some acrylate and methacrylate esters are regarded as sensitizers, and great care must be taken when selecting an acrylic polymer for use in nail lacquer formulations. Residual monomers are an important safety consideration and should be reviewed by a toxicologist prior to use of any polymer in a nail lacquer formulation. (Acrylic polymers will be discussed further in the section titled *Film Modifiers*.) It should be noted that acrylics are used extensively in specialty products intended for use in nail salons. Unlike conventional nail lacquers, such products use low molecular weight acrylic "oligomers" (literally a material with "few parts"). These oligomers are designed to undergo chemical reactions when applied to the nails of the customer. Such reactions typically involve cross-linking upon mixture with suitable catalysts, or by exposure to various forms of electromagnetic radiation, such as ultraviolet light. When cross-linked, these polymers grow into a high three-dimensional network of very high molecular weight. Resulting films are very hard, tough, and chemical-resistant. These

films are extremely resistant to acetone and other solvents typically used in nail lacquer removers, and require prolonged solvent exposure and intense abrasion (i.e. sanding) for removal. "Nail extensions" probably represent the largest application for acrylic polymers in nail salon products. As their name implies, extensions are used to create artificial nail surfaces. They often are used in conjunction with injection molded artificial nails or with various textile reinforcements (e.g. silk or fiberglass). A thorough analysis of nail extensions and the reactive acrylic chemistry needed to create them is beyond the scope of this discussion, but this subject is covered in great detail by Doug Schoon (*Nail Structure and Product Chemistry, Second Edition*; Independence KY: Cengage Learning, 2005).

Theoretically, many types of polymers might be used as primary film-formers in nail lacquer formulations, provided they meet important criteria such as toxicological safety, solubility in common organic solvents, strong adhesion to nails, high gloss, ease of removal, and acceptable cost. Practically, very few such polymers have been found, despite the tireless efforts of many dedicated nail lacquer chemists, and the search for improved primary film-formers continues unabated.

Film Modifiers: From the foregoing discussion, it can be inferred that few viable primary film-formers are available to nail lacquer formulators. Moreover, it also can be inferred that these film-formers have several inherent chemical and physical properties that are not optimal. It is not surprising that one or more *film modifiers* are required to offset some of the negative attributes of primary film formers and to improve overall lacquer performance. It is convenient to divide film modifiers into two sub-groups: *secondary film-formers* and *plasticizers*. The former sub-group typically includes various polymers that are blended with primary film-formers, while the latter sub-group normally includes non-polymeric fatty organic ingredients. It has been mentioned that nitrocellulose and related cellulosic polymers tend to form hard, brittle films. Polymer scientists quantitatively describe the hardness of polymers by means of a thermal measurement known as glass transition temperature (commonly abbreviated as Tg).[1] Analogous to melting point measurements for simple organic solids, Tg is defined as the temperature below which a polymer takes the physical form of a hard, brittle, glassy solid. Polymers with high Tg values form hard, brittle films, while polymers with low Tg values form soft films that also may be tacky at room temperature. From a formulation standpoint, polymers with high Tg values must be mixed with a relatively significant amount of film modifying ingredients in order to make them sufficiently flexible for use in nail lacquers. Conversely, polymers with low Tg values inherently are soft and flexible, and often are used to modify polymers having high Tg values. Tg values for nail lacquer polymers run from -20°C to +150°C. The Tg of nitrocellulose is 53°C, therefore its neat films are hard and brittle at room temperature (i.e. 20°C). Human nails may appear to be hard, unyielding objects, but in reality nails are constructed of layers of keratin that can be quite flexible, particularly when wet. In order to exhibit long wear properties, nail lacquer films ideally should exhibit approximately the same degree

of flexibility as the nails on which they are applied. Brittle nail lacquer films will chip, crack, and peel easily, and will not be durable in service. Flexible nail lacquer films will deflect in unison with their underlying substrates, and will exhibit greater longevity. Therefore, it can be seen that nitrocellulose must be mixed with one or more film modifiers in order to make its films sufficiently flexible for nail lacquer applications. *Secondary film-formers* are further classified as "modifying resins" if they dry to form solid films, or "polymeric plasticizers" if they remain as liquids. In pure form, these polymers produce films that are too soft or tacky to be used as primary film-formers, but they are very useful for softening ("plasticizing") hard primary film-formers such as nitrocellulose or cellulose esters. In certain instances, modifying resins also confer other beneficial properties such as enhanced water resistance and improved gloss. Seventy or more years ago, naturally derived resins often were used as modifiers for nitrocellulose. The most common of these natural resins is shellac, a secretion produced by certain species of Asian beetles.[2] Shellac is a complex mixture of organic compounds, including aleuritic and shelloic acids.[3] This resin is yellow in color and is very soluble in ethanol. In common with many naturally derived ingredients, properties of shellac vary according to seasonal climatic changes in the geographical regions in which the raw material is harvested. The performance of shellac is not particularly outstanding in nail product applications. When synthetic modifying resins became available on a widespread commercial basis, most nail lacquer formulation chemists abandoned use of shellac. Given the current interest in "green chemistry," it is not unrealistic to state that use of shellac might be revisited for nail coatings applications, especially since it is very soluble in ethanol (a solvent that can be manufactured readily from biological sources). In the late 1930s, nail lacquer chemists began using toluenesulfonamide/formaldehyde resin (sometimes abbreviated as tosylamide/formaldehyde resin or TSFR) as a film modifier in nitrocellulose-based nail lacquer formulations. TSFR is made by the polymerization of p-toluene sulfonamide (PTSA) and formaldehyde as shown in **Figure 4**.

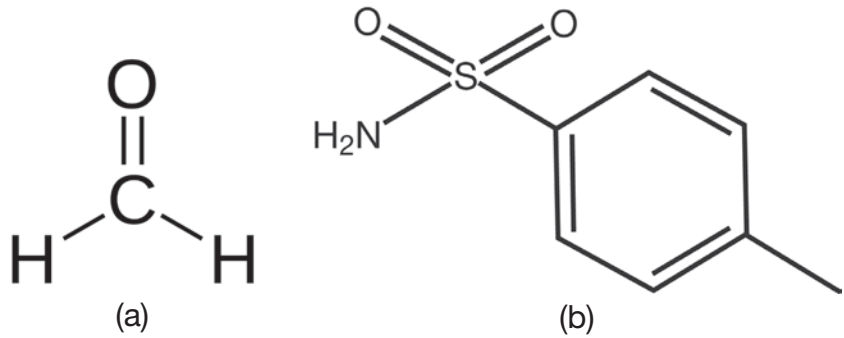

Figure 4. Chemical structures of formaldehyde (a) and toluenesulfonamide (b)

TSFR ultimately became the most commonly used secondary film-former in commercial nail lacquer formulations. Although soft and tacky when initially applied, neat TSFR films dry to eventually become hard, glossy, brittle films. Nitrocellulose blended with TSFR produces films with very good adhesion, gloss, detergent resistance, and water resistance properties. Films containing high levels of TSFR dry slowly and remain tacky for extended periods of time. Residual formaldehyde is found in such films only at very low levels (i.e. parts-per-million), but for a small portion of the population, formaldehyde is a potent allergen. As a consequence, "hypoallergenic nail lacquers" (formulations that are less likely to trigger an allergic reaction) use alternative secondary film-formers (e.g. polyester resins) in place of TSFR. In recent years, the safety of formaldehyde has come under increasing scrutiny, and by the late 1980s resin manufacturers began offering toluenesulfonamide/epoxy resin (abbreviated tosylamide/epoxy resin or TSER) as an alternative to TSFR in nail lacquer formulations. TSER has film properties similar to those of TSFR, with the exception of color; TSER tends to be darker than TSFR.

Polyester resins are polymers formed by the reaction of one or more polyhydric alcohols with one or more polycarboxylic acids or acid anhydrides. An example of this class of polymers is adipic acid/neopentyl glycol/trimellitic anhydride copolymer. Polyesters are highly versatile resins, and many different types and grades are sold commercially. Types and ratios of reactants can be varied, and a range of performance attributes typically can be achieved. Polyester resins have been used for many years in lieu of TSFR in hypoallergenic nail lacquers. Recently, they have become very popular film modifiers in mainstream nail lacquers as well. In comparison with certain other classes of polymers, polyesters often have a more favorable toxicological profile, possibly because the "monomers" used to create polyester resins are relatively mild fatty acids and alcohols, as opposed to more highly reactive monomers (e.g. acrylate and methacrylate esters) used to create other polymers.

Acrylics have been discussed earlier in the context of primary film-formers, but they historically have been used as film modifiers for nitrocellulose. The most common acrylics used in nail lacquers include copolymers of methyl methacryate and butyl methacrylate. Styrene (vinyl benzene) is an aromatic hydrocarbon that confers improved hardness and gloss on polymers into which it is polymerized; its structure is shown in **Figure 5**.

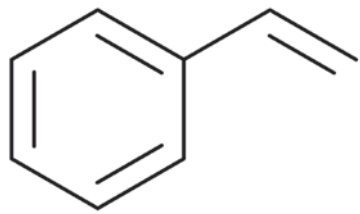

Figure 5. Chemical structure of styrene monomer

Copolymers of styrene and acrylate/methacrylate esters are also used frequently. These polymers are available in a variety of performance grades. Acrylics typically have favorable color stability, and often are used in clear lacquers where clarity and water white color are important. The monomers used to manufacture acrylic polymers are chemically reactive, and care must be taken to ensure that types and amounts of residual monomers are acceptable from a toxicological standpoint. Polyurethanes are formed by the reaction of isocyanates with hydroxy-functional organic compounds, according to the following general reaction (**Figure 6**).

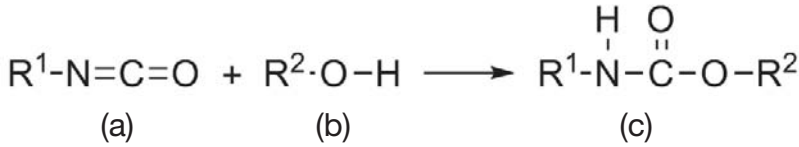

Figure 6. Reaction of isocyanate (a) and alcohol (b) to form a polyurethane (c)

They are known for flexibility and great chemical resistance, and are extensively used in a broad range of industrial coatings applications. These polymers have been used only to a limited extent in nail lacquers. One possible reason is the potential presence of residual amounts of toxic isocyanates, although most commercial polyurethanes are fully reacted and would not contain such compounds. Another possible reason is that although some polyurethanes exhibit excellent cohesive film strength, they may have less adhesive strength. Finally, some polyurethanes require the use of solvents that are not commonly used in nail lacquers (e.g. N-methylpyrollidone) or solvent blends that require high percentages of alcohols. Given that polyurethanes have exhibited high performance in many demanding industrial applications, including automobile finishes, it is likely that chemists will continue to investigate their use in nail lacquer applications.

Vinyl resins are used in various industrial applications, but only one member of this class of polymers is used to any degree in nail lacquers. Polyvinyl butyral (PVB) is the product of the reaction of polyvinyl alcohol with butyraldehyde, with the structure shown in **Figure 7**.

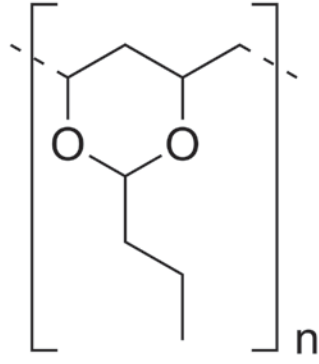

Figure 7. Chemical structure of vinyl butyral monomer

It forms clear, rubbery films of exceptional toughness. Industrially, it is sold in several different grades and is used in many diverse applications, most notably as an interlayer in laminated safety glass windshields. PVB requires alcohol-rich solvent systems, which is a significant drawback for mainstream nail lacquer applications. As a result, PVB is used mostly for specialty nail lacquers such

as basecoats, where its extreme toughness is greatly prized, and where unusual solvent requirements can be more easily accommodated.

As with primary film-formers, theoretically almost any polymer could be used as a secondary film-former, provided that it has an acceptable safety profile and good chemical compatibility with primary film-formers (typically nitrocellulose). Polymer science continues to evolve, and it is likely that as new polymers become available for industrial coatings applications, nail lacquer formulation chemists will evaluate their potential utility as secondary film-formers.

Plasticizers can be liquid or solid, and can be single compounds, mixtures of more than one compound, or polymers. The terms "solvent plasticizer," "monomeric plasticizer," or "chemical plasticizer" often are used interchangeably to refer to non-polymeric plasticizers. The role of plasticizers is straightforward yet critical: they make hard, brittle primary film-formers (and certain secondary film-formers) more flexible or plastic. By performing this critical function, plasticizers make nail lacquer films more flexible, resilient, and resistant to mechanical attack, which generally translates into good wear properties for nail lacquer formulations. Plasticizers must be soluble in the solvents and polymers with which they are mixed; otherwise they will migrate from dried films and lose their efficacy. They should exhibit low volatility in order to remain permanently in dried lacquer films. Ideally, they also will confer additional film benefits, such as clarity, acceptable color, good gloss, film smoothness, detergent and water resistance, and smooth application. As with all other lacquer ingredients, plasticizers should be toxicologically acceptable and cost effective. A 1:1 to 2:1 ratio of plasticizer to film-former(s) is very critical to the successful performance of a nail lacquer formulation. Insufficient levels of plasticizer will result in brittle films that chip, crack, and peel easily. Excessively high levels of plasticizer will result in soft films that dry too slowly and mar easily. The type and amount of plasticizer that should be added varies according to the type of primary and secondary film formers used in a specific nail lacquer formulation. Invariably, qualitative and quantitative selection of plasticizers must be determined experimentally. In some instances, a combination of several plasticizers may be required to achieve desired performance objectives. As a general recommendation, long wearing nail lacquers require flexible films, and they typically use a relatively high plasticizer-to-film-former ratio. Conversely, fast-drying nail lacquers normally produce hard films, and they use lesser amounts of plasticizer to achieve short drying times. Relative plasticizer efficacy varies according to the type of plasticizer and film-former type: a "strong" plasticizer achieves a high degree of film modification at a low concentration. It must be emphasized that each time a primary film-former or secondary film modifier is changed in a formulation, the plasticizer system of the formula must be reviewed for performance.

Given the stringent performance requirement for plasticizers in nail lacquer formulations, it should not be surprising that historically only a small number of ingredients have been used in this capacity. Very old nail lacquer formulations

sometimes used castor oil as a plasticizer for nitrocellulose (**Figure 8**).

Obtained from beans of the castor plant, castor oil mainly consists of glyceryl tri-ricinoleate. As the structure illustrates, castor oil contains multiple hydroxyl and ester groups (plus three double bonds) making it readily useful in nitrocellulose/solvent solutions. Camphor is another venerable plasticizer. This alicyclic ketone, having a cool, soothing odor, is obtained from *Cinnamomum camphora*, the camphor tree.[4] It is a solid material that sublimes readily at room temperature. Ready volatility is an unwelcome property for a plasticizer. Because the concentration of camphor gradually diminishes over time in a dried film, that film will become increasingly brittle due to a progressive loss of plasticizer. The structure of camphor appears in **Figure 9**.

Historically, the most common plasticizer in nail lacquer formulations has been dibutyl phthalate (DBP). Its structure appears in **Figure 10**.

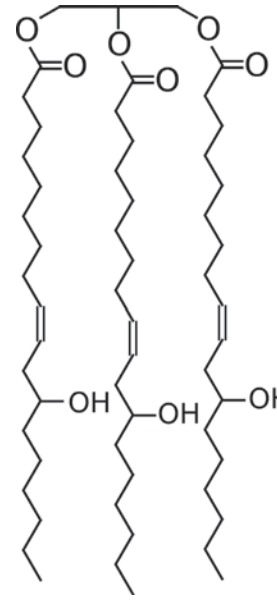

Figure 8. Chemical structure of castor oil (triricinolein)

Figure 9. Chemical structure of camphor

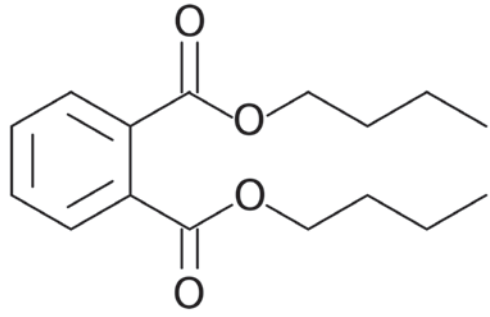

Figure 10. Chemical structure of dibutyl phthalate (DBP)

Related phthalates (e.g. butyl benzyl phthalate) also have been used as plasticizers in nail lacquers, but to a much lesser extent. DBP is an oily liquid ester that has a boiling point of 340°C.[5] It is very soluble in most film-formers and solvents, and is an effective plasticizer. During the past several years, the toxicological safety of DBP has come under intense attack, and this material has been banned from use in nail lacquers sold in the countries of the European Union.

Esters of citric acid (e.g. acetyl tri-n-butyl citrate) are used extensively as nail lacquer plasticizers. Similarly, esters of benzoic acid, triphenyl phosphate, dibutyl adipate, glyceryl triacetate, and trimethylpentanediol diisobutyrate also have been used as plasticizers in nail lacquer. The subject of nail lacquer plasticizers is an ever changing one, and this area is likely to see a great deal of experimental activity in the near future as traditional plasticizers become increasingly obsolete, either due to technological advancements, increased regulatory scrutiny or a desire to utilize "green" chemistry.

Solvents: Discussion of nail lacquer ingredients might seem a bit like a discussion of chickens and eggs. Which is more important to a nail lacquer: the film-former, or the solvent blend needed to dissolve it? Rightfully, the selection of a film-former must be prioritized, as this choice dictates the selection of an appropriate solvent system, along with film modifiers, plasticizers, and other components. Regardless of the exact priority in which components are chosen, decisions regarding solvents are always extremely important in nail lacquer formulation chemistry. To the uninitiated, solvents may appear to be inert, disposable "carrier" ingredients that evaporate quickly following product application. In fact, proper solvent selection ranks high among the more difficult challenges that a nail lacquer chemist must face during the product development process. Solvents impact product viscosity, ease of application, length of drying time, film smoothness, gloss, nail adhesion, use-up rate, formulation cost, product flammability, manufacturing safety, package selection, and long-term product stability. Considering that solvents have such a powerful effect on total product performance, it is ironic that their selection sometimes is treated as an afterthought.

Solvents are liquids at room temperature, but they all exert vapor pressure and evaporate readily. Atmospheric boiling point (BP_{760} or BP) is a convenient way to compare solvents. Solvents are classified as low, medium, or high boilers, based on a combination of factors including vapor pressure, boiling point, and ability to form hydrogen bonds with polymers and/or other ingredients. This latter property can be significant for nail lacquers, because nitrocellulose itself is a polymer that has polar functionalities. Solvents can be divided into two broad categories according to their general chemical structure. "Oxygenated solvents" have one or more oxygen-containing functional groups (i.e. carbonyl, ester, ether and/or hydroxyl); this class includes low molecular weight alcohols, esters, glycol ethers, and ketones. The time-honored adage of organic chemistry "Like dissolves like" is operative here; polar solvents are very effective for dissolving polar film formers and plasticizers.

Lacquer chemists refer to these materials as "active solvents." Lower alcohols (e.g. ethanol, isopropanol) cannot dissolve RS-type nitrocellulose. When mixed with stronger oxygenated solvents (i.e. esters, glycol ethers, ketones) alcohols enhance the solubility of these solvents. For this reason, lower alcohols often are termed "coupling solvents." Hydrocarbons are volatile non-polar aromatic and aliphatic liquid compounds that are not true solvents for most nail lacquer raw ingredients. Because they lack oxygen-containing functional groups contained in such "oxygenated solvents" as esters and ketones, hydrocarbons cannot dissolve polar polymers such as nitrocellulose. More accurately termed "diluents," hydrocarbons are less costly than their oxygenated counterparts and often are used to reduce formulation costs. Aromatic hydrocarbons (e.g. xylenes and toluene) and aliphatic hydrocarbons (e.g. n-heptane) have seen use in nail lacquer formulations. Structures of representative hydrocarbons appear in **Figures 11 through 13**.

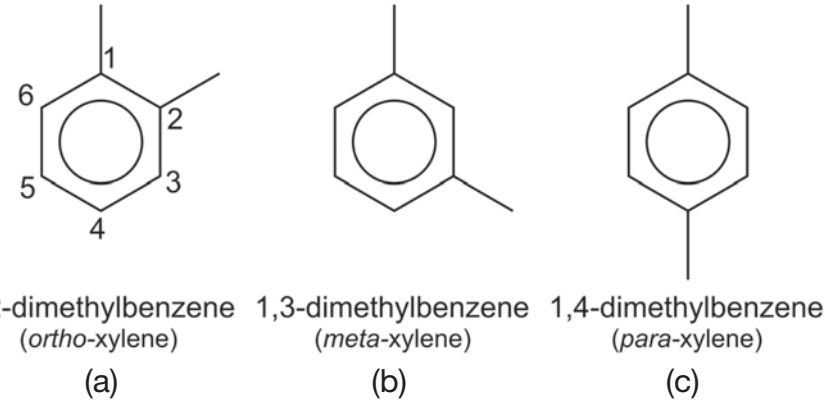

Figure 11. Chemical structures of o-xylene, m-xylene and p-xylene (a, b, c)

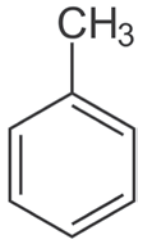

Figure 12. Chemical structure of toluene

Figure 13. Chemical structure of n-heptane

During the early 1990s, the California Air Resources Board (CARB) declared toluene an undesirable air pollutant and banned its use in retail nail lacquer products marketed in that state. Other jurisdictions in the United States and

elsewhere followed suit, and today toluene has all but disappeared from nail lacquer formulations. Xylenes are avoided for similar reasons. Although n-heptane is not prohibited to use, modern formulations tend to downplay the role formerly held by all diluents. The reason for this trend is not known, but perhaps it may be due to the desire to maximize levels of active solvents to achieve products that have high solids content (for better wear) and moderate viscosity (for easier application). Toluene had been widely used to disperse organoclay-type rheological additives in shaded nail lacquers, and early attempts to remove toluene sometimes resulted in shaded lacquers with poor stability. Nail lacquer manufacturers eventually learned how to disperse organoclays successfully in ester-type solvents (especially n-butyl acetate) and today the long-term stability of toluene-free shaded nail lacquers is as good as or better than that of their toluene-rich predecessors.

Due to their diverse molecular structures, solvents exhibit varying degrees of solvency power. Solvent power is described computationally by a numerical system known as "solubility parameter." Esters and ketones contain carbonyl groups, making them powerful solvents for dissolving polar polymers such as RS-type nitrocellulose. In contrast, alcohols are polar, oxygenated solvents, but they contain only hydroxyl groups, and do not dissolve RS-type nitrocellulose. Solvency power for hydrocarbons is determined by an empirical test method called "Kauri-Butanol (KB) value" (re: ASTM D 1133-04[6]). Aromatic hydrocarbons typically have greater solvency power than aliphatic solvents.

Generally, esters are the most common solvents in nail lacquer formulations. Most of these are the reaction products of acetic acid with lower aliphatic alcohols. Esters conform to the general structure described in **Figure 14**.

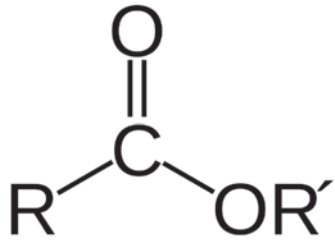

Figure 14. Chemical structure of an ester

In nail coatings applications, R is usually methyl, while R' is usually C1-C5. Common ester solvents include ethyl acetate (BP = 77°C[7]), n-propyl acetate (BP = 101.6°C[8]), and n-butyl acetate (BP = 126°C[9]). Structures for these solvents appear in **Figure 15**.

Older nail lacquer formulations sometimes had used primary amyl acetate (BP = 142°C[10]) with the structure describe in **Figure 16**.

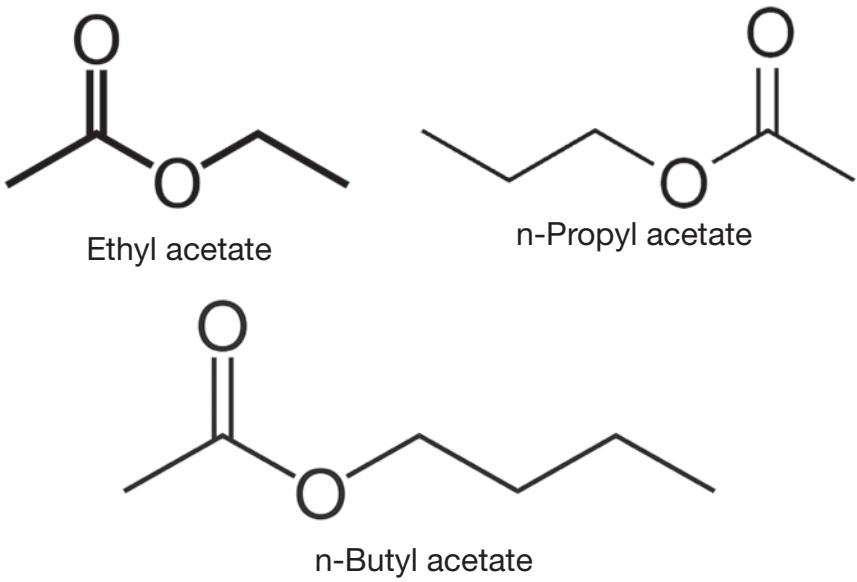

Figure 15. Chemical structures of ethyl acetate, n-propyl acetate and n-butyl acetate

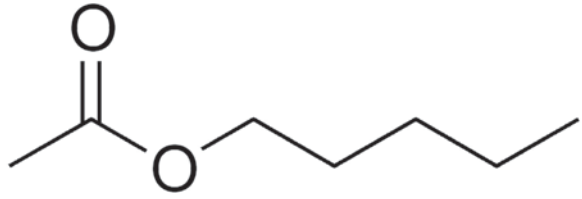

Figure 16. Chemical structure of primary amyl acetate

As illustrated in the foregoing series of esters, boiling point rises as the length of the alcohol portion of the ester increases. Increase in chain length of the acid portion of the ester would have a similar effect. In contemporary nail lacquers, esters of acids other than acetic acid are rarely used. The sole exception is ethyl lactate (BP = 154°C[11]) shown in **Figure 17**.

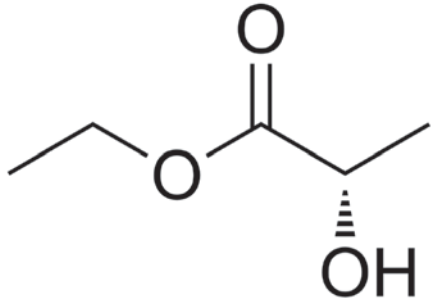

Figure 17. Chemical structure of ethyl lactate

Presence of chain branching in the alcohol portion of an ester will reduce the boiling point of that ester. Thus, linear n-butyl acetate boils at 126°C, isobutyl acetate boils at 118°C[12], sec-butyl acetate boils at 112°C[13], and highly branched tert-butyl acetate boils at 97.8°C.[14] The more "sterically hindered" a solvent is (i.e. the more highly branched its molecular structure) the lower its boiling point will be.

To better grasp this concept, compare the various degrees of chain branching in the alcohol portions of all four isomeric butyl acetates shown in **Figure 18**.

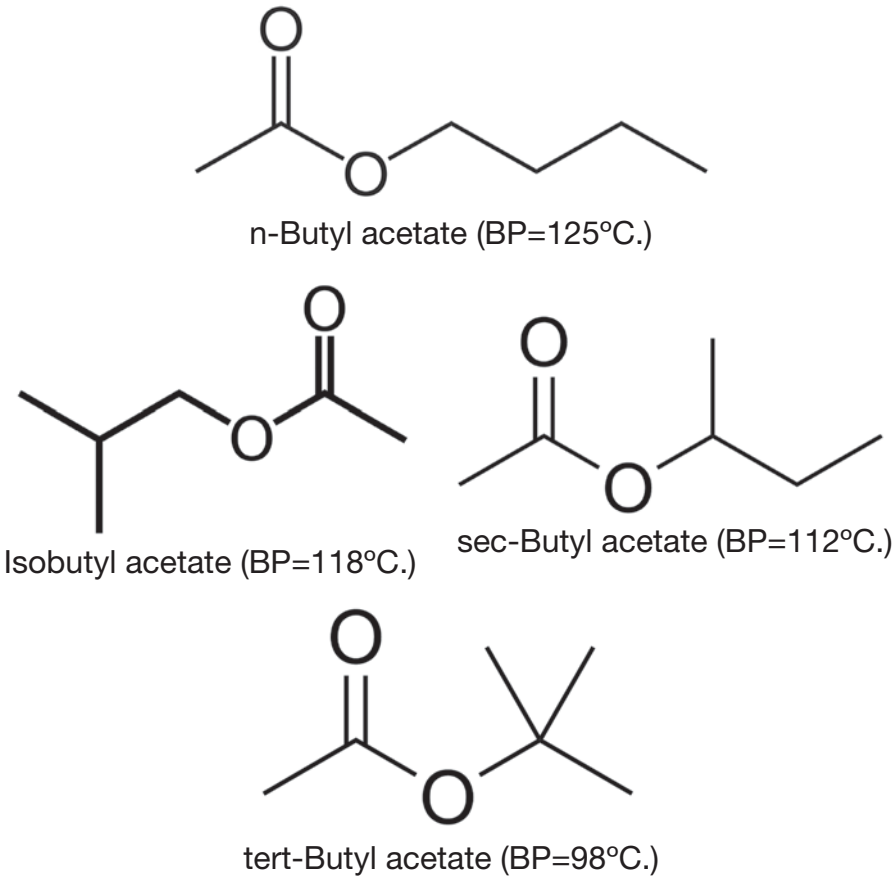

Figure 18. Chemical structures of four isomers of butyl acetate

Glycol ethers are widely used in many industrial coatings formulations, but they have been used much less widely in nail lacquers. The ethers of ethylene glycol (e.g. ethylene glycol monobutyl ether) generally are not permitted for use in cosmetics due to adverse toxicology. Ethers of propylene glycol have more favorable toxicological profiles, and propylene glycol monomethyl ether (methoxypropanol; BP = 118°C[15]) sometimes is used in nail lacquers. Its structure is described in **Figure 19**.

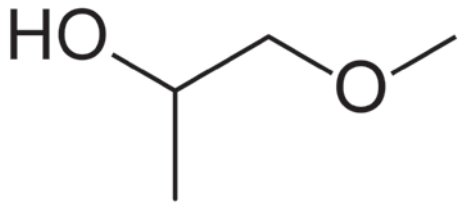

Figure 19. Chemical structure of methoxypropanol (propylene glycol monomethyl ether)

Surprisingly, ketones are seldom used in nail lacquers, most likely due to their strong odors and their relatively low boiling points. Only methyl ethyl ketone (MEK; BP = 80°C[16]) has seen limited use in nail lacquers in recent years. Acetone (BP = 56°C[17]) evaporates much too rapidly to be useful in nail lacquer formulations, but it is widely used as the principal solvent in nail lacquer removers, and as a cleaning agent in nail lacquer manufacturing and filling operations; its structure appears in **Figure 20**.

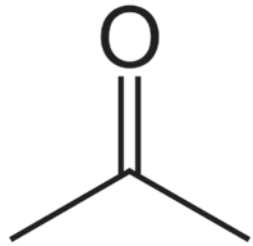

Figure 20. Chemical structure of acetone

Formulation chemists of certain high-performance industrial coatings (e.g. automotive finishes) are known to use computer models to select solvent combinations for their formulations. For nail lacquers, selection of a solvent system usually entails a great deal of experimental laboratory work. Generally, when developing a new nail lacquer formula it is advisable to use a 1:1 blend of ethyl acetate and n-butyl acetate as an initial solvent system. Some formulation chemists prefer to include n-propyl acetate in the mix as well. Once primary and secondary film-formers, plasticizers, and other ingredients have been dissolved, the overall suitability of the solvent system can be assessed for viscosity, ease of application, drying time, and film hardness. After the results of these preliminary studies have been evaluated, levels of individual solvents can be changed as required. Fast-drying formulations typically contain relatively higher levels of ethyl acetate, while long-wearing formulations often contain higher levels of n-butyl acetate. Some formulation chemists prefer to include small quantities of high-boiling solvents (e.g. methoxypropanol) to improve brushing. Historically, amyl acetate or n-butyl alcohol (BP = 117°C[21]) also had been used for the same purpose. Excessive amounts of high-boiling solvents

will retard drying time and may delay film hardening. Excessive amounts of low-boiling solvents may make brushing difficult, and may contribute to poor film properties and unacceptable viscosity increases with repeated product use. Use of acetone or other very low boiling solvents may cause an undesirable phenomenon called "blushing," defined as a clouding of the film caused by the condensation of humidity during drying. Each time a container of nail lacquer is opened portions of the solvent system evaporate immediately, thus changing the composition of the overall product. If the solvent system contains too much low-boiling solvent, the product eventually will become unacceptably viscous.

Additives: Up to this point, the basic ingredients needed to create a clear nail lacquer have been reviewed in detail. Having explored such critical subjects as film-formers, modifiers, and solvents, it is tempting to regard additives as unimportant or insignificant. Such thinking would be erroneous. Additives are to nail lacquers as seasoning is to food. These ingredients are incorporated into commercial nail lacquers to improve product stability, to extend shelf life, and to enhance performance. Rheological control additives are blended with clear lacquers to create suspension bases, which are used to produce shaded nail lacquers. Ultraviolet light absorbers (UV absorbers) protect nitrocellulose and colorants from degradation and color change due to prolonged light exposure. "Slip and mar additives" are used to improve application and to enhance film gloss. Promotional additives are used to pique consumer interest and to provide competitive marketing advantage. These include vitamins, botanicals, proteins and other raw ingredients normally used in "mainstream" cosmetic products.

Rheological control additives are organically modified clays ("organoclays") that are used to suspend colorants in shaded nail lacquers. They accomplish this important task by creating a three-dimensional gel-like network that prevents colorant particles from falling to the bottom of a nail lacquer container. Organoclays consist of montmorillonite clays called bentonites or hectorites that have particles surface-treated with a quaternary ammonium compound that makes these clays easier to disperse in an organic solvent system. Stearalkonium bentonite and stearalkonium hectorite are used very extensively in commercial shaded nail lacquers. Importantly, organoclays impart a rheological condition known as "thixotropy." Thixotropic nail products have flow properties similar to that of tomato ketchup: they are firm liquids when at rest, but become thinner liquids when shaken. This behavior is called "shear thinning" and is described in detail in Chapter 11.

What distinguishes thixotropic rheology is a combination of shear thinning, followed by time-dependent viscosity recovery. This behavior sometimes is called "reversible gel-sol-gel transition." This rheological condition affords both higher product viscosity during storage ("undisturbed viscosity") and low product viscosity during application ("disturbed viscosity"). The elevated undisturbed viscosity provides a robust gel structure that prevents dense colorants from settling due to the effects of gravity. The reduced disturbed viscosity affords ease of application.

Organoclays require careful high-shear dispersion prior to incorporation into nail lacquer formulations. Both under laboratory and manufacturing conditions, considerable skill is required to handle them successfully. This subject will be covered in greater detail later in this chapter. Alternative rheological control additives sometimes are used for specialized applications. Suspension lacquers that contain organoclays have an opaque appearance. Hydrophobic silica is used to produce transparent suspension lacquers, that contain specialized "glitter" pigments to create unusual aesthetic effects. Lacquers containing silica often have brushing characteristics significantly different from lacquers that contain organoclays.

Nitrocellulose is vulnerable to attack by many environmental agents, including sunlight and heat. Prolonged exposure to sunlight will make nitrocellulose turn yellow, then brown. Some colorants also will fade under similar conditions. Several UV absorbers are added to protect nail lacquers from the effects of ultraviolet light. These ingredients protect the formulation only, not the nails of the user, and should not be confused with *sunscreens*, which protect human skin from the harmful effects of UV light. Examples of common UV absorbers include benzophenone-1, etocrylene, and octocrylene; the two latter ingredients often are used in clear lacquer formulations. Nitrocellulose degradation due to prolonged exposure to heat is a significant problem, but thermal stabilizers are not used in nail lacquers.

Slip and mar additives reduce the coefficient of friction at the surface of a dried nail lacquer film, making such films appear smooth and glossy. Silicones, especially polydimethylsiloxane (dimethicone), are effective slip and mar additives. They are poorly soluble in nail lacquers, tending to orient toward the air-film interface as films dry. They must be used very sparingly to avoid creation of various surface defects caused by excess insoluble material in the dry film.

Promotional additives are used primarily to generate consumer interest. Members of this diverse category include vitamins, botanical extracts, proteins, and other ingredients. Because nail lacquer formulations contain a blend of powerful solvents, many different cosmetically acceptable materials can be added at low levels. Caution must be exercised to avoid adding pure metals (especially iron) or alkaline materials to nail lacquer formulations, as these ingredients can discolor and degrade nitrocellulose. Water and aqueous ingredients usually can be added at very low levels, but excessive amounts of water may cause stability problems, such as haziness in clear lacquers or suspension failures in shaded lacquers.

In contrast to most cosmetic products, conventional nail lacquers do not require addition of antimicrobial compounds. Nail lacquers contain minimal traces of water in a microbiologically hostile solvent system. Similarly, antioxidants are not used, because most nail lacquer ingredients do not contain unsaturated ingredients that might be prone to oxidation. Fragrances can be added to nail lacquers, but they are not used extensively because the strong odors of nail lacquer solvents are extremely difficult to mask. Fragrances are detectable only in dried nail lacquer films. Use of fragrance in nail lacquer must be planned carefully. Fragrance ingredients are

reactive organic compounds that may interact negatively with lacquer ingredients, producing discoloration and/or malodor development. Additionally, high-boiling point ingredients in fragrances may act as plasticizers for lacquer films, making dry films excessively soft, slowly-drying, and/or tacky. Fragrances are used extensively in nail lacquer removers and in non-lacquer nail products, such as drying oils, cuticle treatments, and hand crèmes.

Colorants: Clear lacquers represent a significant portion of the total nail cosmetics category, but shaded nail lacquers are considered to be more aesthetically appealing, and are more exciting to create. The nail color category offers a wider color palette than all other color cosmetic products. A casual look at any retail display of contemporary nail lacquers will illustrate this. Thanks to the artistic work of nail salons, elaborate *nail art* has become an increasingly popular means of creative expression.

Three general types of colorants are used in nail lacquer: dyes, pigments, and pearls (sometimes called "frosts" or "effect pigments"). Dyes are organic colorants that are soluble in solvents. Pigments and pearls are colorants that are insoluble in their dispersion vehicle. They must be dispersed properly to obtain maximum color impact in the final product formulation. Pigments may be organic or inorganic. Dyes and organic pigments originally were known as "coal tar colors" to indicate their origin, but today these colorants are synthesized from petrochemical sources. Carmine, a naturally derived red organic pigment, is occasionally used in nail lacquer. It is obtained from the shells of a specific species of beetle, but it exhibits poor light fastness and its use therefore is limited. Inorganic pigments are obtained from mineral sources. As mentioned previously, a lack of vehicle solubility distinguishes organic pigments from dyes. In contrast to pigments, which require dispersion to achieve proper base coloration, dyes first must be dissolved in one or more appropriate solvents in order to develop maximum color impact. Dyes can be used to give a dramatic bulk appearance to nail lacquers. When used at high concentrations, dyes can stain the nails objectionably. They are not used extensively in shaded nail lacquers, but they often are used to impart a pale tint in clear lacquers. D&C Violet #2 is an intense purple dye that often is added at very low levels to clear lacquers to reduce yellowness caused by the degradation of nitrocellulose. Lacquers tinted with this dye typically appear water white or slightly lilac in color. D&C Red #33 is a reddish violet water-soluble dye that sometimes is added to clears in small amounts. FD&C Yellow #5 is a yellow-orange water-soluble dye that sometimes is mixed with another water-soluble dye, FD&C Blue #1, to impart green tints. Dyes often are used to tint nail lacquer removers and other ancillary nail products.

The manufacture and use of synthetic colorants historically is steeped in legal and regulatory complexity. The U.S. Food and Drug Administration (FDA) has regulated colorants closely for many years. Relevant cosmetic legislation is covered in great detail in the 21st Section of The United States Code of Federal Regulations (commonly abbreviated as 21CFR22). A detailed study of global

cosmetic regulations is far beyond the scope of this discussion. Nevertheless, it is important to emphasize that *only* FDA-approved colorants may be used in nail products sold in the United States.[20]

Similar restrictions apply in other countries, and it is critical that nail lacquer formulation chemists are educated periodically with regulatory restrictions prior to starting any product development activities.

Organic pigments are named using FDA nomenclature, rather than by their actual chemical names. The designation "D&C" signifies "drug and cosmetic," while the term "FD&C" signifies "food, drug, and cosmetic." The prefix "Ext." indicates that a colorant is restricted to use only in externally applied cosmetic products. A generic color name and a numerical designation then follow. A good example of typical FDA colorant nomenclature is the water-soluble dye FD&C Yellow #5. For "lakes" (which will be defined shortly) the cationic portion of the inorganic lake substrate is used to describe the pigment. Thus, FD&C Yellow #5 Aluminum Lake is produced by reacting the dye with aluminum hydrate to render the dye less soluble in water. Pigments also are known by their Color Index (CI) numbers, numerical designations used in non-US markets to identify colorants used in cosmetics and other products. Additionally, colorants often have historical names: FD&C Yellow #5 is known as "tartrazine," while D&C Reds #'s 6 and 7 are called "lithol rubines." The decision to use abbreviated names for organic colorants undoubtedly was motivated by a desire for brevity. Organic colorants are not simple compounds, and their actual chemical names usually are several lines long. Their molecular architecture is characterized by the presence of a number of electronically active functional groups, such as double bonds and hetero groups. These functionalities and the aryl rings to which they are attached interact with visible light in energetically complex ways to produce a broad spectrum of colors. Such color producing groups sometimes are called "chromophores." The *azo* group (depicted as -N=N-) is the most common functional group present in the organic pigments that are used in nail lacquer. Pigments that contain aromatic rings joined together via a single azo linkage are termed "monoazo colors." These colorants contain two or more aromatic groups to which several additional functional groups are attached in highly specific configurations. Typically, one aromatic group consists of a single phenyl ring substituted with methyl, sulfonic acid, nitro, and/or chloro groups. The second aromatic group usually consists of a naphthyl group substituted with amino, carboxyl, hydroxyl, sulfonic acid groups. In some cases, a heterocyclic ring may be present between an azo link and an aromatic ring. Various functional substituents attached to aromatic rings change the shade of the compound. These groups are called "chromophores." The structure of D&C Red #6 is shown in **Figure 21**.

Closer examination of this structure shows important "architectural" elements, such as the single central azo group, a sodium carboxylate group at top left and a sodium sulfonate group at lower right.

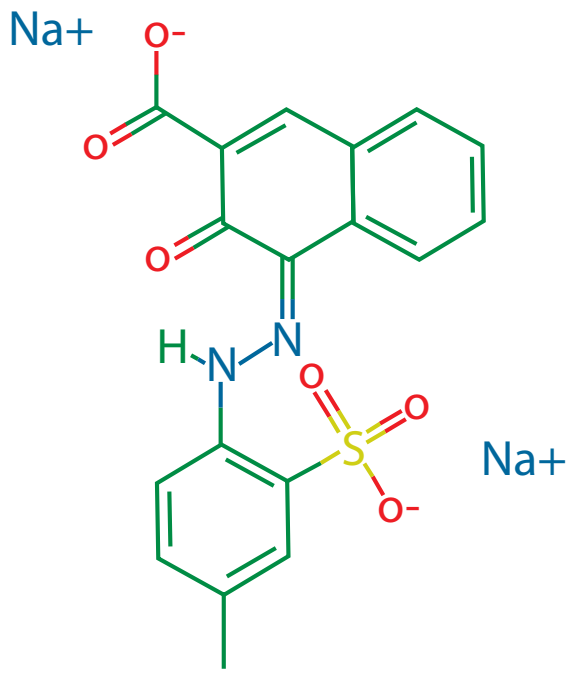

Figure 21. Chemical structure of D&C Red #6 dye

It must be noted that many organic pigments are synthesized from water-soluble organic dyes that have had their acidic functional groups neutralized by aluminum, barium, or calcium cations to render them insoluble in water or other solvents. Neutralization is conducted in the presence of an inorganic substrate material, such as barium sulfate, calcium sulfate, or aluminum hydroxide (sometimes known as aluminum hydrate). The resulting colorant is insoluble in water because the acid groups that facilitate water solubility have been neutralized. This type of organic pigment is known as a "lake." Most azo pigments used in nail lacquer are lakes, such as D&C Red #6 Barium Lake, D&C Red #7 Calcium Lake, D&C Red #34 Calcium Lake, and FD&C Yellow #5 Aluminum Lake. The type of substrate affects the color of the lake. FD&C lakes must use aluminum hydrate as a substrate; some D&C lakes also use this substrate. Other types of organic pigments also are used in lip products, although they are not used to the same extent as azo lakes. D&C Red #30 is a yellow-toned red pigment that is a member of the indigoid class of organic pigments. This colorant does not contain any acid functionalities, is insoluble in water, and actually is a "toner," defined as an organic colorant inherently insoluble in various solvents. It is a costly pigment, and very often is replaced by less-costly D&C Red #6 Barium Lake. FD&C Blue #1 is a bright blue dye that is a member of the triphenylmethane class of colorants. Its structure is shown in **Figure 22**.

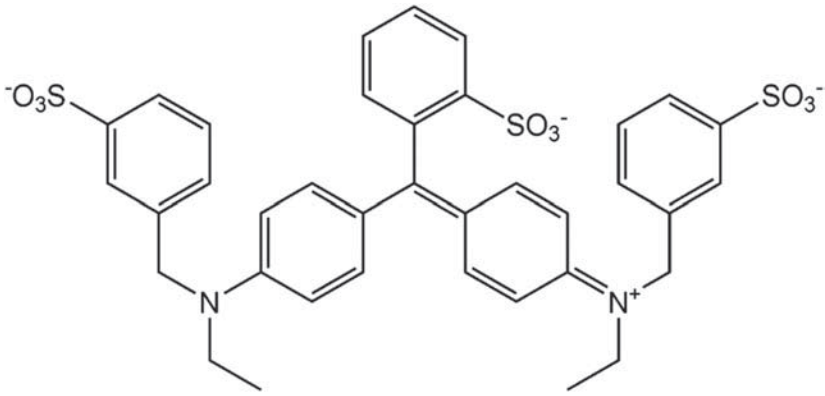

Figure 22. Chemical structure of FD&C Blue #1 dye

It is used very sparingly as FD&C Blue #1 Lake, either as a minor ingredient in blue shades of nail lacquer or in specialty nail products. The sole naturally derived organic colorant available for nail lacquer use is carmine. The principal constituent of carmine is carminic acid, a complex molecule with the structure shown in **Figure 23**.

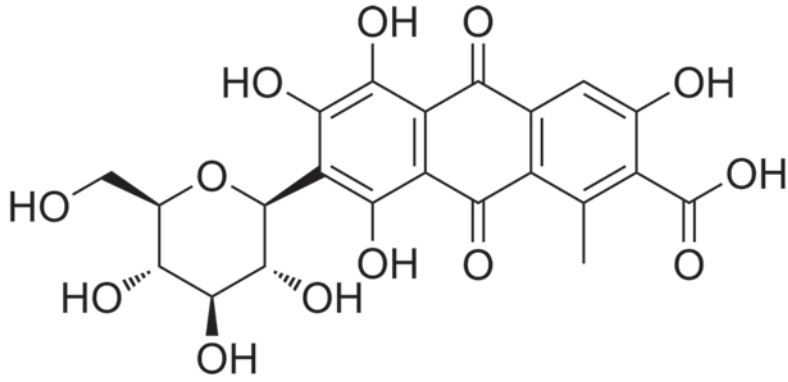

Figure 23. Chemical structure of carmine

Organic pigments can be challenging to disperse into nail lacquers. Pigment particles must be "de-agglomerated "(i.e. mechanically broken into the smallest possible particles) and thoroughly "wetted" under high shear mechanical mixing into a nitrocellulose lacquer base. This process involves a special, often hazardous dispersion technique called "chipping," covered in greater detail in the section of this chapter titled Nail Lacquer Manufacture and Quality Control. Generally, lakes having greater residual dye content tend to be more difficult to handle than their lower dye counterparts. Some pigment manufacturers incorporate various proprietary treatments to facilitate dispersion. Organic colorants are not simple materials in any sense of the term. Such complex materials occasionally may exhibit batch-to-batch

variations in shade and other parameters, however slight. Skilled color matching is needed to ensure consistent quality in shaded nail lacquers.

Inorganic pigments are considerably less complex than organic colorants. They invariably are of mineral origin, and usually consist of single chemical composition of compounds. They sometimes undergo a considerable amount of processing to make them suitable for use in cosmetic products. As a general rule, inorganic pigments often have high opacity, but they are not nearly as vivid as organic colorants. Inorganic colorants usually are quite stable to light, heat, and many chemicals. The majority of inorganic pigments are metal oxides, such as titanium dioxide and various iron oxides. Titanium dioxide is a brilliant white pigment that is very widely used in many cosmetic products, as well as in numerous industrial applications. It is available in two different crystal forms, "anatase" and "rutile", and is produced in conventional and "micro-fine" particle sizes. The anatase form traditionally had been the most popular form of titanium dioxide used in the cosmetic industry. During the 1990s, cosmetic grades of the rutile form became available on a commercial basis. It has greater opacity than its anatase counterpart, and therefore it is possible to use less titanium in a formulation if rutile is used. Conventional titanium normally is used for shaded nail lacquers. "Micro-fine" titanium is used occasionally to impart whiteness to the bottle appearance without increasing film opacity. Iron oxides are manufactured in a wide variety of earth tone shades, such as red, brown, yellow, black, and maroon. These pigments have high opacity, but they appear to be "muddy" as compared with organic colorants. Certain inorganic pigments are made more dispersible in nail lacquers by means of surface treatments of various types. Untreated pigments sometimes are difficult to disperse, most likely due to the surface charges that occur on pigment particles. Using cosmetically acceptable chemical treatments, treated inorganic pigments become more hydrophobic, making them easier to disperse in various emollients and more resistant to attack by water. One type of surface treatment uses reactive silicones called "silanes" to bind chemically to pigment surfaces, while dimethicone treatment is deposited on particle surfaces in more superficial, less robust fashion.

Arguably, the most attractive type of inorganic colorants are pearlescent pigments or "pearls." These shimmering materials are also known as "frosts" and shaded nail lacquers that contain them are referred to as "frosted shades." Pearlescent pigments sometimes are called "effect pigments," and for a very good reason: pearls create attractive, often spectacular light effects in nail lacquers. They achieve this light display by reflection and/or refraction and/or absorption of incident light. They can be used in nail lacquers alone or in combination with other colorants. In order to understand the optical properties of pearls, it may be helpful to think of "reflectance pearls" as tiny little mirrors that capture and reflect incident light. As with a flat mirror, light is not bent as it strikes the surface of a particle of a reflecting pearl, and the perceived color of the reflected light does not vary according to the position of the observer relative to the pearl particle. Silver reflecting pearls behave exactly in

the manner thus described. Next, imagine that the glass used to create the original mirror has been changed to a specific color, perhaps blue. Once again, as incident light strikes the mirror, it is reflected as blue light, regardless of the position of the observer relative to the mirror. Note that a blue mirror absorbs light of all colors *except* blue. Colored reflecting pearls exhibit this type of optical behavior. Whether they are gold, russet, brown or some other color, these pearls absorb light of many different wavelengths, and reflect light of a specific wavelength. They do not bend light. Bending of light is called "refraction" or "interference," and is accomplished by using a prism. As a ray of light travels through the prism, it is bent ("refracted") and emerges as a multi-colored rainbow, depicted in the diagram shown in **Figure 24**.

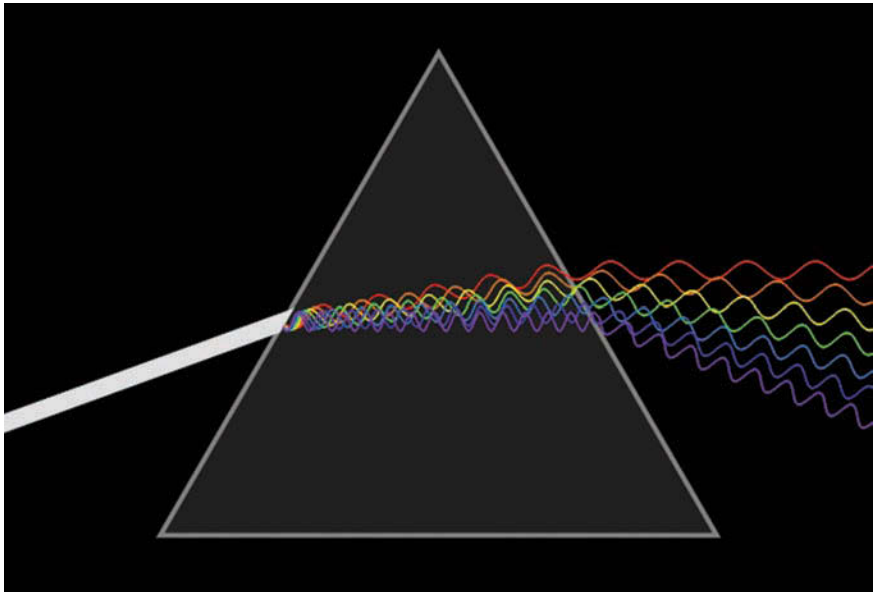

Figure 24. Refraction of white light by a prism

"Interference pearls" function in a prism-like manner. They reflect and refract light. The perceived color of these pearls varies according to the position of the observer relative to the pearl particle. When observed directly, interference pearl appears to be a white powder because it reflects light, but when viewed at an angle, a distinct interference color can be observed. Interference pearls have multi-layered particles. The thickness of the outermost layer determines the exact shade of interference color that will be produced. Some interference pearls are also colored with various pigments, and are capable of producing very attractive dual-toned optical effects. The terms "color travel," "flip," "flop," and "goniochromaticity" (i.e. a phenomenon whereby a pigment appears to change color as viewed through a range of angles) are used interchangeably to describe dramatic shifts in color appearance caused by changes in angles of observation.

A vast majority of pearls used in nail products are categorized as "titanated micas." These ingredients consist of particles of mica (a white, flaky silicate mineral) on which thin layers of titanium have been deposited. Some pearls use substrates other than mica, such as fluorphlogopite (a form of synthetic mica) or calcium borosilicate (a type of glass). Thickness of the titanium layer determines whether the pearl will be a reflectance or interference pearl. For the latter, precise changes in very thin titanium layers dictate the specific interference color produced. Silica occasionally is incorporated into certain pearls to produce dramatic interference effects. Size and shape of the particle determines whether the pearlescent effect will be subtle (fine particles) or glittery (large particles). Additional colorants such as iron oxides or carmine are added to create colored pearls. Caution is advised when using pearls that contain carmine. This colorant is not light stable nor is it stable in acidic environments, of which nail lacquer is an example. It is important to emphasize that large pearl particles can make nail films feel rough and appear less glossy, so lacquer chemists must take care to avoid excessive amounts of such colorants in their formulations. Additionally, excessive levels of any type of pearl may cause suspension instability due to settling; pearls are dense, and gravity will pull them to the bottom of a container. Shaded lacquers that contain high pearl levels often require additional amounts of rheological control agents to ensure good long-term pigment suspension properties.

Bismuth oxychloride (BiOCl) often is used in nail products. It is a metal oxide pigment that exhibits a silver luster. Some grades of BiOCl have very finely sized particles, and are used to create a metallic look. Other metal pigments are used to achieve similarly brilliant shade effects, including aluminum powder which is used to create the appearance of polished chrome. Bronze and copper powders also are available, but they may be used only if they have been surface treated to isolate their surfaces from acidic vehicles, or they may become discolored or liberate gases. Powdered metal dust is a dangerous explosion hazard, and extreme caution must be used when handling metallic pearls, especially in the presence of flammable solvent vapors.

Although pearls are attractive colorants that can produce very beautiful aesthetic effects, some practical caveats must be observed. Pearls must not be subjected to excessive levels of shear during mixing, otherwise their particles may be destroyed. Pearls tend to be relatively dense particles and are prone to settling in shaded nail lacquers unless sufficient rheological control additives are present. Pearls typically cost more than many other colorants, and certain specialty pearls are very costly. Use of too many different types of pearls in a single formulation also complicates shade matching during production. Generally, it is advisable to use a combination of pigments and pearls to achieve lacquer shades, in order to give shade matchers a degree of flexibility during manufacture.

Formulation of nail lacquer products is relatively straightforward. A comparison of ingredient labeling statements on commercial nail lacquers reveals an unusually

high degree of common ingredient usage across many brands and product types. This commonality holds true for lacquer products of all retail price points, across all global markets, and in both the professional and home use classes of trade. Successful nail lacquers require high performance coupled with safety and economy. The principal reason is that lacquer formulations are driven mostly by functional performance attributes, such as quality of wear and speed of drying. Aesthetic properties (i.e. gloss, film smoothness, shade) are important product characteristics. In common with other cosmetic products, intended product usage dictates formulation strategies. Nail lacquer formulations tend to differ from each other quantitatively more than qualitatively. The overall concentrations of ingredients and the relative ratios at which they are combined will drive key formulation properties. Lacquer chemists refer to non-volatile ingredients as "solids" or "N.V." Solids content (commonly abbreviated % N.V.). This is an important parameter that affects film robustness, bulk viscosity, ease of application, gloss, drying time, ease of removal, and cost.

High solids formulations tend to be more viscous, slower drying, longer wearing, and more costly to manufacture than their lower solids counterparts. Low solids formulations exhibit opposite behavior. Long-wearing products usually require high level of solids, while fast drying products usually have lower levels of solids. The relative ratios of lacquer ingredients play a very important role in overall product performance, and critical parameters such as quality of wear and speed of drying are impacted directly and significantly by these ratios. The length of wear versus drying speed conundrum has vexed nail lacquer chemists for many decades without any simple reconciliation. Using conventional ingredient technologies, these two highly important attributes exhibit mutually exclusive properties. As a result, most commercial nail lacquers represent varying degrees of design compromise, and formulation chemists must prioritize which attribute is more critical within a specific formulation. Long-wearing nail lacquers require flexible films that resist chipping, cracking, and peeling for up to one week or longer. These formulations usually contain high levels of film modifiers relative to the amount of primary film-former. This combination produces softer, more slowly drying films as a consequence. Fast-drying nail lacquers need hard films that dry very quickly after application. These formulations usually contain higher levels of primary film-former relative to the amount of film modifiers. They produce hard films that dry quickly, but have less chip and crack resistance. Fast-drying lacquers usually are marketed as convenience-oriented, home-use products. Long-wearing lacquers are marketed as high performance products, and are especially favored in nail salon applications, where manicure appearance and longevity are important "advertisements" for salon quality. Conventional manicuring practice involves application of two coats of shaded lacquer. Sheer lacquers may require a third coat to achieve suitable nail coverage. Specialized one-coat nail lacquers also have been marketed as convenience products. While conventional shaded nail lacquer formulations typically contain a total of approximately 1% dry non-pearlescent pigment, one-coat formulations

may contain more than twice this amount of pigment. A single coat of a one-coat nail lacquer delivers approximately the same opacity as that of two coats of a conventional product. One-coat lacquers contain higher levels of solids, and usually exhibit higher viscosity as compared to conventional lacquers. The development of one-coat formulations requires that many design compromises be made regarding application quality, drying time, duration of wear, and long-term pigment suspension stability at point of sale.

When developing shaded nail lacquer formulations, it is customary to begin by creating an unpigmented "suspension base" that contains film-former, film modifiers, solvents, and additives. Various colorants are mixed with the suspension base to create shaded nail lacquers. The performance characteristics of the suspension base (i.e. film hardness, drying time, film adhesion, gloss, viscosity) determine the overall performance of the shaded products manufactured using that base. Examples of shaded and unshaded long-wearing and fast-drying nail lacquer formulations are provided in the examples of formulations below:

Suspension Base (Long Wear)

Ingredient:	Weight %:
n-Butyl Acetate	36.00-39.00
Ethyl Acetate	23.00-26.00
Tosylamide/Epoxy Resin (100% N.V.)	8.00-11.00
Trimethylpentanediol Diisobutyrate	7.00-9.00
½" RS-type Nitrocellulose (70% N.V. in Isopropyl Alcohol)	8.00-10.00
¼ " RS-type Nitrocellulose (70% N.V. in Isopropyl Alcohol)	8.00-10.00
Stearalkonium Bentonite (100 % N.V.)	1.00-1.25
Isopropyl Alcohol	0.15-0.35
Benzophenone-1	0.10

Nail Lacquer (Long Wear, Mauve Crème Shade)

Ingredient:	Weight %:
Suspension Base (Long Wear)	87.50
Ethyl Acetate	5.00
Titanium Dioxide (Lacquer Dispersion)	3.00
D&C Red #6 Barium Lake (Lacquer Dispersion)	2.00
FD&C Yellow #5 Aluminum Lake (Lacquer Dispersion)	1.00
Red Iron Oxide (Lacquer Dispersion)	1.00
Black Iron Oxide (Lacquer Dispersion)	0.50

Suspension Base (Fast Dry)

Ingredient:	Weight %:
Ethyl Acetate	35.00-39.00
¼ " RS-type Nitrocellulose (70% N.V. in Isopropyl Alcohol)	15.00-20.00
n-Propyl Acetate	12.00-16.00
n-Butyl Acetate	12.00-16.00
Styrene/Acrylate Copolymer (100% N.V.)	7.00-10.00
Acetyl Tributyl Citrate	4.00-6.00
Stearalkonium Bentonite (100 % N.V.)	1.00-1.25
Isopropyl Alcohol	0.25
Benzophenone-1	0.10

Nail Lacquer (Fast Dry, Coral Frost Shade)

Ingredient:	Weight %:
Suspension Base (Fast Dry)	91.00
Titanium Dioxide/Mica	5.00
Titanium Dioxide/Iron Oxides/Mica	2.40
D&C Red #6 Barium Lake (Lacquer Dispersion)	1.00
FD&C Yellow #5 Aluminum Lake (Lacquer Dispersion)	0.50
Dimethicone (100 cSt)	0.10

Many different types of clear lacquers are sold commercially. At first glance such products may appear to be nearly identical. Perhaps surprisingly, clears are formulated in a variety of ways to satisfy very specific performance requirements. Some clears are sold as transparent versions of shaded nail lacquers. These products must be formulated in identical fashion as shaded products, except that rheological control agents must be eliminated to maintain transparency in the bottle. Because these clears are applied in direct contact with bare nails, they must be developed as long wearing products. A typical general purpose clear lacquer formulation appears below:

Clear Lacquer (General Purpose)

Ingredient:	Weight %:
Ethyl Acetate	30.00-35.00
n-Butyl Acetate	30.00-35.00
½" RS-type Nitrocellulose (70% N.V. in Isopropyl Alcohol)	15.00-20.00
Acetyl Tributyl Citrate	6.00-9.00
Acrylates Copolymer (100% N.V.)	6.00-9.00
Benzophenone-1	0.05-0.10
D&C Violet #2, 0.1% in n-Butyl Acetate	0.01-0.05
Tocopheryl Acetate	0.01-0.05

Many clear lacquers are marketed under a broad classification known as "nail care." The term "care" may refer to manicure care (i.e. enhancement of shaded lacquer performance). "Basecoats" (applied directly to bare nails prior to application of nail color to improve product adhesion and wear quality) and "topcoats" (applied over nail color to improve gloss and wear quality) fall into this category. This term also may refer to "biological care" for protection and improvement of the appearance of nails, cuticles, and surrounding tissues of the hands or feet. Nail hardeners, cuticle oils, and hand and foot crèmes fall into this category. Some products claim to provide both manicure and biological enhancement. Nail care products are an integral part of a traditional manicuring regimen, particularly in nail salons. A "full manicure" in the nail salon context customarily includes application of at least four coats of nail lacquer: a single coat of basecoat, two coat of shaded nail lacquer, and a single coat of topcoat.

Basecoats are the nail lacquer equivalent of primers in the industrial coatings environment. As their name implies, they are the first lacquer product applied directly to bare nails. Their function is to improve adhesion of overlying coats of nail lacquer to improve wear quality. They also provide important secondary benefits such as smoothing of the nail surface (i.e. "ridge-filling", defined as filling in low spots in the nail surface) and reduction of nail staining caused by certain pigments. Any lacquer coating that has direct contact with the bare nail surface must have flexible and robust film properties. The ingredient ratios of basecoat formulations must reflect this requirement. Basecoats may be clears, or they may be suspension lacquers containing pigments (e.g. titanium dioxide) and one or more inorganic powders (e.g. hydrated silica, talc) to fill nail ridges. Formulations containing such powdered raw ingredients are termed "ridge-fillers" as they tend to make ridged nail surfaces appear smoother. Many suspension basecoats have opaque films that also are semi-matte or totally matte in appearance. Examples of clear and ridge-filling basecoats are as follows:

Basecoat (Clear)

Ingredient:	Weight %:
n-Butyl Acetate	38.00-45.00
Ethyl Acetate	20.00-25.00
Acetyl Tributyl Citrate	7.00-10.00
½" RS-type Nitrocellulose (70% N.V. in Isopropyl Alcohol)	7.00-10.00
¼ " RS-type Nitrocellulose (70% N.V. in Isopropyl Alcohol)	7.00-10.00
Ethanol (SD Alcohol 40-B)	7.00-10.00
Polyvinyl Butyral	1.50-2.50
Octocrylene	0.1-0.30
Panthenol	0.01-0.10

Basecoat (Ridge-filling)

Ingredient:	Weight %:
Suspension Base (Long Wear)	96.70
Titanium Dioxide (Lacquer Dispersion)	1.00
D&C Red #6 Barium Lake (Lacquer Dispersion)	0.10
FD&C Yellow #5 Aluminum Lake (Lacquer Dispersion)	0.10
Red Iron Oxide (Lacquer Dispersion)	0.10
Hydrated silica	2.00

Carmine is susceptible to attack by water and is not light stable. Given these considerable drawbacks, it is not used extensively in nail products. Carbon black (D&C Black #2) is a common industrial pigment that recently has been approved by the FDA for cosmetic use. It produces very deep, "jet" black shades, a property that is particularly valuable in cosmetic formulations such mascara and eyeliners.

Topcoats provide glossy, protective films when applied over nail color films. Because they are applied directly onto dried lacquer films and not directly on bare nails, topcoats usually are formulated to produce hard films. High gloss is a critical performance requirement for topcoats, as is ease of application and speed of drying. Many topcoats are formulated to low viscosities for ease of brushing and rapid drying times. An example of a typical topcoat is shown in the following formula:

Topcoat

Ingredient:	Weight %:
Ethyl Acetate	40.00-45.00
n-Butyl Acetate	25.00-30.00
¼ " RS-type Nitrocellulose (70% N.V. in Isopropyl Alcohol)	15.00-20.00
Acetyl Tributyl Citrate	3.00-6.00
Acrylates Copolymer (100% N.V.)	5.00-9.00
Etocrylene	0.1-0.30

Clear lacquers may be used either as basecoats or topcoats. Because topcoats have hard films, they may crack or peel when applied directly on bare nails. Conversely, basecoats usually have films that are too soft or matte for use as topcoats. This is particularly true for ridge-fillers. Some clears are marketed under various names such as "nail builders," "nail strengtheners," "nail thickeners," or "nail hardeners." Most of these products are medium to high viscosity clears containing small quantities (i.e. < 0.5%) of various promotional ingredients such as vitamins, botanical extracts, proteins, etc. A truly functional nail additive is formaldehyde. The nail hardening efficacy of formaldehyde is well known, but its use in cosmetic formulations

has been the subject of ongoing controversy because of potential toxicity.[21] Formaldehyde-free nail hardeners produce tough lacquer films that make nails feel stronger and harder simply due to mechanical reinforcement (much as a cast supports a fractured bone). "Nail menders" usually are high viscosity clears. Such products do not replicate the rapid, aggressive bonding action of cyanoacrylate adhesives (e.g. "super glue") but they are far more forgiving if applied incorrectly and are much easier to remove.

Emulsion paints are very common industrial coatings products extremely popular with both professional and do-it-yourself painters. This begs the question as to why similar emulsion nail coatings have not enjoyed similar widespread popularity. Simply put, industrial coatings formulations are not intended for application on the human body, thus they can exploit aggressive chemistry that would not be appropriate for use in cosmetic product formulations. Emulsion coatings formulations are stabilized dispersions of acrylate or polyurethane polymers in an aqueous vehicle. Unlike traditional lacquers, emulsion coatings dry by means of a mechanism termed "coalescence." This is a multi-step process whereby water evaporates from a freshly applied film while the chains of the primary film-forming polymer move progressively into close physical contact until they fuse together into a durable continuous film. It is important to note that the final film usually is water-insoluble, even though it was produced by a water-rich emulsion formulation. Polymer coalescence is facilitated by certain types of polar organic solvents known as "coalescing solvents" or "coalescents." The most commonly used coalescing solvents are "glycol ethers". A glycol (i.e. a di-hydroxy alcohol) is used as the starting material, as exemplified by propylene glycol, the structure of which is shown in **Figure 25**. Glycols can be reacted with one or more lower molecular weight alcohols to produce glycol ethers. These compounds generally conform to the structure of propylene glycol mono methyl ether (methoxypropanol), shown in **Figure 26**.

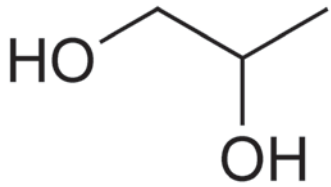

Figure 25. Chemical structure of propylene glycol

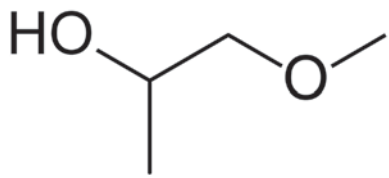

Figure 26. Chemical structure of methoxypropanol (propylene glycol monomethyl ether)

Note that in glycol ethers, the hydroxyl hydrogen is replaced by the alkyl group of the alcohol with which the parent glycol is reacted. As the chain size of the alcohol increases, the resulting glycol ether becomes less water-soluble. The presence of multiple oxygen atoms is important, and not surprisingly glycol ethers are capable of forming hydrogen bonds with water and with polar polymers. This hydrogen

bonding capability effectively prevents water from evaporating too rapidly from the wet film, thus giving more time for the film-forming polymer chains to associate closely. It must be noted that ethylene glycol ethers formerly were workhorse coalescing solvents in emulsion coatings formulations for many years, but their adverse toxicology has made them unwelcome for use in personal care products. They have been supplemented by ethers of propylene glycol, di-proplyene glycol and tri-propylene glycol. Although the majority of emulsion coatings ingredients are not suitable for use in nail coatings, certain polymer emulsions used in cosmetic formulations such as mascara and eyeliner also can be used to formulate emulsion nail products. Unpigmented emulsion products can be used as basecoats. Formulation of pigmented emulsion nail coatings is a far more challenging task. Organic cosmetic colorants have dye residues soluble in aqueous media. Presence of solubilized free dyes can cause significant nail staining. As opposed to conventional nail lacquers rich in microbially hostile organic solvents, water-rich emulsion nail formulations require use of one or more anti-microbiological agents to prevent microbial growth. Long-term product stability may be problematic, especially with regard to freeze-thaw stability. Although pigmented emulsion nail coatings are available on a widespread basis in certain global markets (primarily Japan), to date their popularity has been very limited in other markets. Most current emulsion nail formulations sold in the North America are specialty products that address the specific requirements of certain market segments such as young children, wherein water-washable and peelable nail coatings are preferred for their ease of removal. As emulsion polymer technologies targeted for cosmetic applications become increasingly sophisticated, it is likely that high-performance pigmented emulsion nail coatings will become a reality in the future.

Nail Lacquer Testing

Numerous tests have been devised to evaluate the performance of nail lacquers. These tests fall into two broad categories: *in vitro* and *in vivo*. Both types of testing are used extensively in the development of nail lacquer formulations, but each class of tests must be used at the appropriate point in the development and manufacturing cycle for any given formulation.

From the Latin phrase "on glass," *in vitro* studies are conducted by depositing films of nail product formulations directly on various artificial testing surfaces. Commonly used testing substrates include glass plates, metal panels, paper cardstock, injection-molded polymeric artificial nails, and other substrates. These studies rely heavily on test methods routinely used in the paint, ink, and industrial coatings industries. Certain studies require specialized coatings test equipment available from specialty equipment distributors. Chemical tests (e.g. ash, solids level, solvent blend, and water) must be performed by an analytical chemistry laboratory to establish product specifications and to ensure batch to batch consistency in the manufacturing environment. Multiple *in vitro* studies normally are used to pre-qualify experimental

formulations prior to the onset of consumer testing. Importantly, they also are used to develop performance specifications for product scale-up and commercial manufacturing. Some *in vitro* tests are conducted solely in the R&D lab environment during the initial stages of new product development. Quality assurance personnel also conduct a battery of in-process tests on manufactured bulk lacquers to evaluate critical parameters such as viscosity, drying time, film hardness, solids level, solvent composition, and other properties. These tests are outlined in **Table 1**; **Figures 27a through 27e** show images of several lacquer testing devices.

Table 1: Nail Lacquer Test Methods & Equipment

Test	Testing Equipment	Substrate
Abrasion Resistance	Taber Abraser	Metal Panel
Adhesion	Cross Hatch Test Kit	Glass Panel
Ash	Muffle Furnace	Clay Crucible
Drying Time	Digital Dry Time Recorder	Opacity Chart[1]
Fade Resistance	UV Test Chamber	Sealed Glass Bottle
Flexibility	Cylindrical Mandrel	Metal Panel
Gloss	60° Digital Glossmeter	Opacity Chart[1, 2]
Hardness	Digital Sward Rocker	Glass Panel
Hardness	Pendulum Hardness Tester	Glass Panel
Heat Stability	Test Ovens	Sealed Glass Bottle
Scrub Resistance	Wash Tester	Glass or Metal Panel
Shade/Opacity	Bird Film Applicator	Opacity Chart[1]
Solids Content	Test Oven	Aluminum Dish
Solvent Blend	Gas Chromatograph	N/A
Viscosity	Brookfield LVF Viscometer	Sealed Glass Jar
Water Content	Karl Fischer	N/A

Note 1: Leneta 5 DX or equivalent. Note 2: Black glass panel may be used in place of opacity chart.

Many *in vitro* tests are conducted to assess the performance properties of dried lacquer films. These tests require use of a Bird Film Applicator or equivalent device. Most studies are conducted using wet films of 0.006 inch thickness. Some tests (most notably drying time) require application of a wet film of 0.003 inch thickness. Films for adhesion and hardness tests usually are cast onto clean glass plates. Certain tests (e.g. abrasion resistance and film flexibility) require deposition of a film onto metal panels, while other tests (e.g. drying time, gloss, opacity, and shade) are conducted on paper opacity charts. An encyclopedic presentation of coatings testing devices and discussions of relevant standardized test methods are available.[22,23]

Much as a physician orders a comprehensive blood test for a patient, so the nail lacquer chemist also can order a range of tests for his or her product. Typically,

both the chemist and the physician consider the entire spectrum of test results and their implications before making a prognosis. Skilled practitioners of either discipline usually analyze all known available facts prior to deciding on a suitable course of action. When it becomes apparent that a product is out of specification and requires a remedial adjustment, the chemist must act carefully yet decisively. High viscosity is the most common problem likely to be encountered, and usually it is resolved by addition of solvent. Low viscosity is not common in shaded lacquers, but it occasionally is seen in clears. The remedial measure for this condition in most lacquer formulations is addition of small quantities of high molecular weight wet cotton. Film performance occasionally deviates from the norm. Films with low hardness require additional quantities of primary film-former (usually nitrocellulose) while films with elevated hardness readings require additional amounts of primary film-former (usually nitrocellulose), while films with elevated hardness readings require additional amounts of plasticizer(s). Shaded lacquers may exhibit varying degrees of separation during heat stability tests. These tests involve placing samples of test product in sealed bottles or jars, conditioning them for two to 28 days at 25°C (room temperature control samples), 45°C, and/or 50°C, then periodically observing the overall appearance of the test samples. During each observation interval, it is necessary to determine if any aesthetic defects become noticeable. *Syneresis* (also called *supertanancy*) is defined as the formation of a liquid layer at the top of a test sample. *Settling* is defined as the formation of a layer of pigment at the bottom of a test sample. The exact mechanisms by which syneresis occurs are not completely understood. Although liquid residing in the syneresis layer has low viscosity and can be re-dispersed easily while shaking the sample by hand, such a layer may be conspicuously colored and is unsightly. Settling may be indicative of either excessive colorant loading and/or a weak rheological control system, and is seen more frequently in heavily frosted shades. Unlike syneresis, settling usually is a less conspicuous defect, yet it can be much more difficult to re-disperse heavily settled pigments without the use of a paint shaker. Curiously, the same remedial measure sometimes can be used to mitigate both syneresis and settling: stepwise addition of small quantities of rheological control pre-gel usually will improve overall in-package stability. Examples of settling and syneresis appear in **Figure 28**.

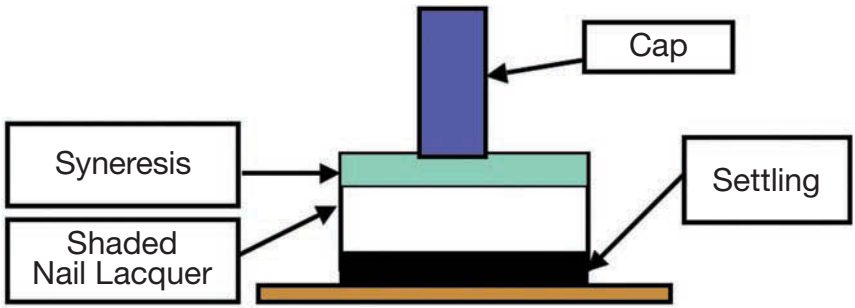

Figure 28. Nail Lacquer Pigment Suspension Defects

Only the most commonly used *in vitro* test methods have been described in this chapter. Lacquer testing is limited only by the imagination and equipment budget of the chemist. Nearly any type of test may be valid and helpful provided that such tests are well defined, carefully conducted, and repeated with consistency.

Translated from Latin as "in life," *in vivo* tests involve application of nail product films on the nails of human volunteers. Not surprisingly, tests conducted on persons under "real world" usage conditions yield valuable performance information about a product. Results of *in vivo* studies represent the ultimate "report card" for a lacquer formulation. These test results often are used to substantiate product advertising claims. As with *in vitro* test methods, the type of possible *in vivo* test protocols largely is limited by the imagination and budget of the testing administrator. Personnel who conduct *in vivo* tests must be well trained in the fields of sensory evaluation and statistical analytical methodology. In contrast to the synthetic substrates universally employed during *in vitro* testing, human nails on living test subjects exhibit subtle inherent biological variability and the specific environmental and lifestyle factors that influence the results of *in vivo* wear tests sometimes are very significant. Given this situation, it is prudent to conduct small-scale preliminary *in vivo* tests (i.e. tests conducted on panels of five to 20 persons) prior to conducting large-scale *in vivo* tests. Two types of *in vivo* tests are in common use: "monadic tests" and "paired comparison tests." In a monadic test, one test product is applied to all ten nails of all panelists; a reference product ("control") is not used in such a study. Monadic tests are useful when it is necessary to obtain the maximum number of data points for a test product within the shortest amount of time. A significant drawback to monadic testing is the absence of a benchmark product. Regardless of the results obtained in a monadic test, an inevitable question is raised: how does performance of the new product compare with that of a benchmark product? In a paired comparison test, Product A (the experimental product) is tested directly versus Product B (another experimental product or a benchmark product). Standard protocol in paired comparison tests requires Products A and B to be applied on alternate nails. This test method is useful when trying to determine the better of two experimental formulas within a compressed timeframe. Paired comparison testing definitely is required when it is necessary to compare performance of an experimental product simultaneously against that of an established benchmark product.

Nail Lacquer Manufacture and Quality Control

Manufacture of nail lacquer is relatively straightforward, but the hazardous nature of this product requires specialized equipment, training, and strict attention to safety. Nail lacquers, their main raw ingredients and waste are dangerous fire and explosion hazards, and must be handled with extreme caution at all times. Nitrocellulose reacts with ferrous metals and will degrade on contact. All mixers and manufacturing tanks therefore must be fabricated of stainless steel. Small-scale mixing may be conducted directly in metal drums or pails, provided that their

interiors are coated with chemically impervious coatings (e.g. epoxy or double-baked phenolic linings). Polyethylene bags or liners may be used to line drums, but care must be exercised to avoid puncturing such items with mixer blades. To prevent ignition of hazardous atmospheres, all wiring and electrical equipment must be "explosion-proof" ("XP") in accordance with local fire codes. All standard devices (e.g. including balances, viscometers, clocks, telephones, thermostats, fans, etc.) must be "XP rated."

Figure 27a. Digital Drying Time Recorder
Photo courtesy of Paul N. Gardner Co.

Figure 27b. Cross Hatch Test Kit
Photo courtesy of Paul N. Gardner Co.

Figure 27c. Digital Sward Hardness Rocker Photo courtesy of Paul N. Gardner Co.

Figure 27d. Pendulum Film Hardness Tester Photo courtesy of Paul N. Gardner Co.

Figure 27e. Brookfield LVF Viscometer Photo courtesy of Brookfield Engineering

Pneumatic mixers and other devices are sometimes used in lieu of XP electrical equipment. In addition to specially sealed switch gear and motor housings, all mixing stations must be equipped with suitable grounding cables to conduct static discharges safely to ground. All mixing and storage vessels must be equipped with covers that prevent solvent evaporation when not in active use. Adequate ventilation of manufacturing areas is very important to minimize concentrations of flammable solvent vapors. Fire suppression equipment (i.e. fire extinguishers, building sprinklers, etc.) must be adequately installed and maintained, as per local fire code requirements. Appropriate personal protective equipment (PPE) must be worn by all personnel engaged in handling lacquers. Such items as safety goggles, face shields, and chemical-resistant gloves and aprons are necessary when working with lacquers and their ingredients. Safety shoes with non-skid soles are very important in any industrial environment, especially where drums and heavy equipment are handled regularly. Forklifts must be specially equipped for operation in hazardous environments.

Typically, manufacture of nail lacquer begins with manufacture of a suitably sized batch of clear. This is carried out in a grounded stainless steel kettle that has been cleaned thoroughly with acetone or ethyl acetate. Solvents normally are charged first via pumping. Large lacquer manufacturing plants often are equipped with complex internal piping systems that may be controlled via computer from a central control console within the facility. Each pipeline carries an individual solvent to a specific manufacturing vessel, thus eliminating the need to use numerous drums of solvent at each mixing station. Agitation is conducted at low RPM while wet nitrocellulose or another primary film-former is loaded into the tank using non-sparking, non-ferrous hand tools. This process is sometimes referred to as "cutting" wet cotton. When the film-former has been charged fully, the tank is closed and agitation speed is increased moderately to facilitate dissolution. During mixing, it is always good practice to discharge several one-gallon aliquots from the bottom of the manufacturing vessel, and then re-charge them back into the tank via the top hatch. Complete clarity of bulk indicates that the film-former has been dissolved fully. At this point, various film modifiers may be added. Typically, solid or high viscosity liquid modifiers are charged ahead of low viscosity liquids (e.g. most plasticizers). As before, aliquots of product are withdrawn from the batch to check for continued bulk clarity. At this point, various low-level additives (e.g. UV absorbers) are added under continued agitation.

When all ingredients have been added and the bulk is homogeneous and clear, if the desired end product is a clear lacquer, the batch will be checked for conformance to specifications. If the batch is on specification, it is filtered through a nylon filter screen and discharged into suitable sealed containers (i.e. lined containers of 5-, 10-, 30-, or 55-gallon capacity). If the desired end product is a suspension base, then the all-important rheological control additive must be charged. Because these additives are sold as dry powders, these materials require pre-dispersion using

high-shear mixing equipment. This pre-gel manufacture normally is accomplished in a separate manufacturing loop prior to manufacture of batches of suspension base. This process begins with charging solvents into a grounded stainless steel tank, beginning agitation, and slowly adding dry organoclay under continuous agitation. A slurry will result, at which time a small amount of a *polar activator* (usually a mixture of water and either isopropanol or ethanol) is added slowly. This activation step causes the rheological additive to swell. The viscosity of the slurry will increase noticeably and often is signaled by an audible drop in mixer speed. At this point, nitrocellulose solution can be added slowly. When mixed completely, the batch is pumped through a high-shear homogenizer several times in order to achieve maximum viscosity development in the batch of pre-gel. Aliquots of the in-process pre-gel are withdrawn and checked for viscosity and film clarity versus an established standard. Given the rigorous demands of pre-gel manufacture, it is customary for lacquer manufacturers to prepare and stockpile relatively sizable quantities of pre-gel in advance of suspension base manufacture.

Once the pre-gel has been deemed acceptable for use, it can be added to the in-process batch of suspension base. After the pre-gel has been charged the suspension base is transformed visually from a transparent, medium-viscosity liquid into an opaque, higher-viscosity liquid. The batch is mixed until it is homogeneous, and aliquots of base periodically are withdrawn to check for conformance to established specifications. Given the steps required to manufacture and evaluate suspension bases, it is standard practice for lacquer manufacturers to prepare and store large quantities of base in advance of immediate need.

Once an adequate supply of suspension base has been manufactured, shaded nail lacquer bulk can be manufactured. Simply put, shaded nail lacquers consist of a mixture of suspension base and colorants. Manufacture of shaded lacquer is conducted in a clean, grounded stainless steel mixing tank equipped with a variable speed XP mixer. Suspension base is charged first, agitation is commenced, and colorants then are charged. Pigments normally are supplied to nail lacquer manufacturers in the form of viscous liquid color dispersions. These dispersions consist of dry pigments that have been mixed under high shear with nitrocellulose and a plasticizer to form dry, solid color chips. This process is termed *chipping*, a very hazardous activity typically performed by a small group of specialized manufacturers. Chips are dissolved into a suitable mixture of solvents and nitrocellulose to form *monochromatic* (i.e. single pigment) color dispersions. A separate dispersion is furnished for each pigment that will be used in shaded lacquer manufacture. Color dispersion manufacture for nail lacquer applications is demanding and dangerous. "Wet grind dispersions" sometimes are used instead of chipped colorants. Dry colorants are dispersed directly into a lacquer base under high shear agitation. These dispersions do not involve the hazardous color chipping process and are far less hazardous to produce, but they may not have the same degree of color intensity and transparency as chipped pigments. Addition of liquid color dispersions is accomplished by charging them

into a batch of suspension base under moderate agitation.

Pearls do not require high shear dispersion, and can be added directly to the batch, also using moderate agitation. When all colorants have been added, the batch is turned over several times, and aliquots are withdrawn periodically to evaluate the appearance of the shade of the batch relative to a standard batch.

If the shade of the in-process batch does not match the standard, small quantities of monochromatic color dispersions are added as necessary to adjust the shade. This procedure (termed *shade matching*) is conducted until the shade of the batch matches that of the standard. While shade matching is in progress, aliquots of bulk are withdrawn for measurement of in-process viscosity. It is not unusual for viscosity readings to be slightly out of specification on the high side due to solvent evaporation during manufacturing, and appropriate quantities of solvent are added to reduce viscosity. Solvents (usually ethyl or n-butyl acetates) typically are added in an amount not exceeding 3% of total batch weight. Each time a solvent addition is performed, it is necessary to agitate the batch sufficiently prior to withdrawing a fresh aliquot for viscosity measurement. Excessive amounts of adjustment solvent should not be added, as this may compromise lacquer performance, especially long-term colorant suspension properties. If the batch is deemed acceptable for shade and viscosity, it is filtered through a nylon filter screen and discharged into suitable sealed containers (i.e. lined containers of 5-, 10-, 30-, or 55-gallon capacity). Care must be exercised when filtering shades containing large particle pearls, and a larger screen size must be used to avoid removal of frosts.

Numerous quality control tests are performed on bulk nail lacquers prior to filling. These tests closely mirror the battery of *in vitro* tests used in the laboratory during initial product development. Some tests are performed directly on bulk samples, such as viscosity determination. Many tests are performed on glass plates, metal panels, or specially treated paper cards. Evaluations of shade, opacity, gloss, drying time, film hardness, and film adhesion all are performed on various artificial testing substrates. Shade quality is evaluated visually using three different methods. The appearance of the product viewed in a transparent jar or glass bottle is termed *bottle tone*. The appearance of two coats of the product applied to one or more nail of the evaluator is called *nail tone*. The appearance of a test swatch of product applied to a paper opacity chart is termed a *drawdown*. The test swatch is applied to the opacity chart using a Bird Film Applicator. It is standard practice to perform all three types of shade evaluations versus an established standard. It is desirable to match a shade as closely as possible for nail tone, bottle tone, and drawdown. Practically, nail and bottle tones take priority over drawdowns. The latter evaluation is extremely critical, and will show very minor shade differences that average nail lacquer users are not likely to detect. Care must be taken when making color observations, especially with frosted shades that produce complex interplays of light. A good source of neutral lighting (natural northern daylight or color-corrected fluorescent lighting) is necessary when shade matching.

When bulk lacquer manufacture has been completed, it is necessary to fill the product into small bottles for consumer use. It is customary to manufacture bulk in advance of filling runs, and bulk typically is stored in lined, tightly sealed metal containers until filling is required. During transport and storage, nail lacquer bulk must not be subjected to ambient temperatures in excess of 35°C, otherwise shade degradation may occur. Due to the hazardous nature of bulk nail lacquer, its transportation over public highways and other facilities is subject to regulation by numerous governmental agencies, including the US Department of Transportation.[24] Among the items regulated by this agency are specifications for containers suitable for transportation of bulk nail lacquer in interstate commerce.

Prior to filling, it is highly advisable to agitate bulk using an XP propeller mixer or drum roller. Lacquers normally are filled using automated filling equipment. All such equipment must be equipped with XP electrical apparatus. Before and after filling runs, all piping must be cleaned using acetone or ethyl acetate to prevent cross contamination of batches. A fully loaded 55-gallon drum of nail lacquer bulk typically yields > 10,000 filled pieces. Given that some automatic filling machines are capable of producing thousands of finished pieces per shift with minimal labor, nail lacquer filling typically is a very cost-effective operation.

A process map for the manufacture of typical nail lacquer formulations appears in **Figure 29**.

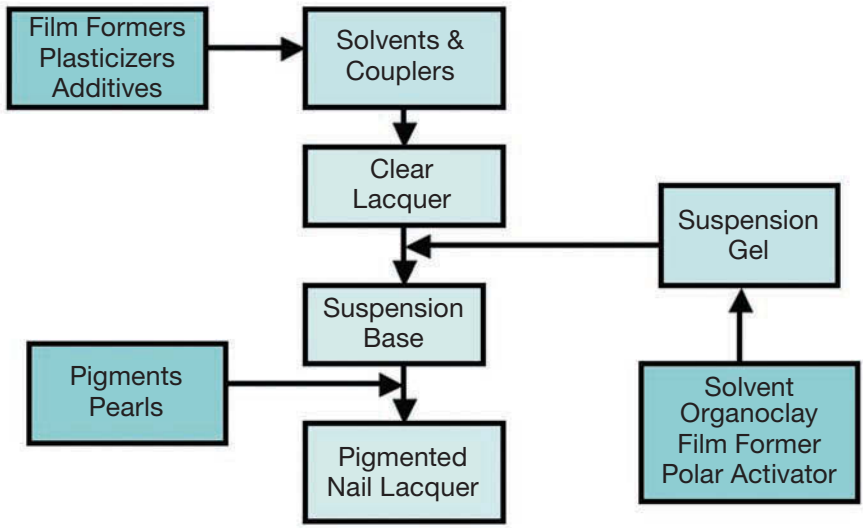

Figure 29. Process map for nail lacquer manufacturing

Nail Lacquer Packages

A brief word about nail lacquer packages is in order. The primary mission of a nail lacquer package is to protect the chemical and physical integrity

of the product during transportation, storage, retail sale, and end use. Nail lacquers contain large quantities of chemically aggressive, volatile organic solvents that evaporate very readily at and above room temperature from poorly sealed containers. Solvent evaporation occurs as a result of insufficient sealing (i.e. evaporation around or through a deficient package closure) or due to infiltration through packaging materials that are vulnerable to solvent attack. The net result eventually will be either an excessively viscous nail lacquer, or a totally dried product. The secondary mission of a nail lacquer package is to showcase the visual aesthetics of the product. Pigmented nail lacquers often have complex and beautiful appearances, thus it is advantageous to use packaging that facilitates visual observation at and after point of sale. Despite the overwhelming use of polymeric packaging in most modern color cosmetic products, glass packaging still is the most preferred material of construction for nail lacquer packages. The archetypal nail lacquer bottle is constructed of transparent flint glass, with a threaded neck and a nominal fill weight of 0.5 fluid ounces (15 mL). In recent years, smaller bottles (i.e. capacities of 8-10 mL) have become increasingly popular. Nail lacquer bottles universally employ threaded plastic caps that contain a plastic rod to which a brush tuft has been affixed with a stainless steel staple. Such caps must be dimensionally precise and resistant to solvent perfusion. They also must be mechanically robust to withstand the rigors of repeated applications of torque, otherwise they will "back off" and allow solvents to escape. A stainless steel shaker bead often is included to provide a convenient means of agitating the product immediately before application. The principal reason for shaking lacquer prior to use is not for mixing as much as it is for shearing the thixotropic lacquer down to a minimal viscosity. As has been mentioned previously, this *shear-thinning* phenomenon facilitates ease of brushing.

All metallic packaging components that have direct contact with lacquer must be constructed of stainless steel to prevent corrosion due to exposure to acidic nitrocellulose lacquers. Similarly, all plastic packaging must be sufficiently robust to withstand continuous immersion in powerful organic solvents. Rods and inner caps usually are injection molded from high-density polyethylene (HDPE). Brush tufts are constructed from a small bundle of hundreds of nylon filaments. They usually are coated with a stiffening material called "sizing" to prevent tuft damage during handling. Lacquer brush tufts normally are sized with low-solids nitrocellulose solutions. Alternative lacquer packages also are available in the form of plastic vials (usually blow molded of acrylonitrile/methyl acrylate copolymer) or various flow-through pens, but these components are more costly than standard glass bottles and sometimes can be more difficult to use.

The manufacture of nail lacquer requires special equipment and considerable expertise. Significant fire and explosion hazards are involved in

this type of work. Constant attention to safety is mandatory, and regulatory oversight is very stringent. In deference to these issues, most marketers of nail cosmetics do not manufacture or fill their own lacquers, relying instead on third-party manufacturers that specialize in the manufacture and filling of bulk nail lacquer.

Non-lacquer Nail Products

Lacquers represent the vast majority of nail products, but they are supplemented by a variety of other types of nail care formulations. These products use several different vehicles to accomplish their tasks. Many of these vehicles are used extensively in mainstream cosmetic products, such as aqueous solutions, *anhydrous* preparations (e.g. oils and ointments), and emulsions.

Not surprisingly, the most common ancillary nail product is nail lacquer remover. It uses a volatile organic solvent to dissolve dried lacquer films and remove them from the nails. Dried nail lacquer films can be very difficult to dissolve, especially when four or more lacquer films products may be present. Acetone is the most common solvent used to remove nail lacquer. It is freely miscible with water and is relatively inexpensive. Most removers contain at least 70% acetone plus water (to mitigate cost), fragrance, dyes, and small amounts of oils for conditioning the nails and cuticles. Such products are manufactured in large stainless steel tanks equipped with XP electrical devices. No special mixing procedures are required. The following formula illustrates a typical acetone-based remover formulation:

Ingredient:	Weight %:
Acetone	70.00-80.00
Water (deionized) (aqua)	20.00-30.00
Octyl Palmitate	0.25-1.50
Fragrance (parfum)	0.25-1.00
D&C Yellow #10	0.05-0.50

Ethyl acetate formerly had been used as a remover solvent in products marketed as acetone-free removers, but new air pollution control regulations in California in 2004 effectively terminated the use of non-acetone remover solvents. (Additional information on solvents permitted for use in consumer products in the State of California is available at *www.arb.ca.gov/consprod/regs/2009/regs-all-nov2010.pdf.*) Ethyl acetate is more hydrophobic than acetone and does not mix readily with water. In order promote water miscibility, isopropanol is used as a coupling agent. Ester-type solvents are prone to hydrolytic degradation, and use of an appropriate buffer (e.g. sodium acetate) is advised when formulating mixtures of ethyl acetate and water. Most removers are packaged in injection molded plastic bottles constructed

of high-density polyethylene (HDPE). Filled packages must be tested for at least 8 weeks at 50°C to ensure that remover formulations will not cause weight loss or stress crack formation.

Various oil-based formulations are used for nail care products such as cuticle oils and "quick dry" products. Cuticle oils moisturize and protect cuticles and surrounding tissues. They consist of several liquid emollients blended with low levels of promotional ingredients and fragrance; an example of typical cuticle oil is shown below:

Cuticle Oil

Ingredient:	Weight %:
Octyl Palmitate	85.00
Tridecyl Trimellitate	13.30
Caprylyl Glycol	1.00
Fragrance	0.50
Tocopheryl Acetate	0.10
Ascorbyl Palmitate	0.10

Quick dry oils are applied as a final step before completion of a manicure. These products do not actually accelerate the drying time of a nail lacquer, but they provide a perception of drying by nullifying the sensation of tackiness characteristic of a partially dried lacquer. Such products may be completely non-volatile, or they may contain a high percentage of volatile non-solvent liquid ingredients (e.g. cyclopentasiloxane, isododecane) that evaporate rapidly after application. Quick dry products usually improve gloss temporarily and protect new nail lacquer films from minor smudges. A representative product is shown below:

Quick Drying Oil

Ingredient:	Weight %:
Cyclopentasiloxane	98.00-99.00
Dimethicone (100 cSt)	1.00-2.00

Cuticle oils and quick dry products may be packaged in a variety of containers. Some quick dry products are packaged in aerosol or pump spray containers. Conventional lacquer bottles and brushes frequently are used as well, with the important exception of brush sizing. Conventional brushes are sized with nitrocellulose sizing, which will not dissolve in products that do not contain lacquer solvents. Brushes designed for use in anhydrous nail products usually are sized with a hydrocarbon wax, such as paraffin.

Aqueous solution and emulsion products also are used for nail care formulations. Hand, nail, and foot creams and lotions are the most common forms of water-based

nail care products. They contain water and oils, and may also contain waxes and miscellaneous ingredients, including *emulsifiers* to promote homogeneity. They are formulated, manufactured, and packaged in exactly the same manner as mainstream skin care cosmetics. A detailed discussion of emulsion technology is beyond the scope of this chapter and is discussed in details in a separate chapter in this book.

A special type of emulsified nail care product is *cuticle remover cream*. Formulated in the same manner as conventional skin care creams, this product typically has an alkaline pH to soften cuticles and render them easier to remove. The pH of such cuticle remover crèmes often is quite high, and care must be taken to avoid contact with nitrocellulose-based nail products, which will degrade and discolor significantly on exposure to alkaline materials.

Summary

The nail cosmetics category has enjoyed growth in recent years, primarily due to a thriving professional nail salon market. As consumers become increasingly aware of the biological and psychological benefits of nail grooming, it is reasonable to expect that such growth will continue in the foreseeable future. Adhering to business and geopolitical trends (e.g. increased regulatory and environmental pressures, the demands of a highly competitive global economy, escalating energy costs, a desire to implement "green chemistry, conservation of resources, etc.) already have impacted the industrial coatings industry in many ways. In response to such trends, manufacturers of coatings ingredients offer a steady stream of innovative polymers and other raw materials to help paint and ink formulation chemists meet new product development challenges. Similar trends have impacted the cosmetic industry. In a dynamic modern environment, nail lacquer chemists must not only be well informed about polymers and solvents; they also need to be sensitive to global environmental, safety, and regulatory issues. It is incumbent upon nail product formulation chemists to keep abreast of current developments both in the coatings industry and the cosmetic industry. Through a combination of technical acumen and a spirit of innovation, the handiwork of present and future generations of formulators will help to keep the nail cosmetics category vibrant and viable.

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Handbook of Formulating Dermal Applications: A Definitive Practical Guide.
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SECTION VII:

Sunscreens

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CHAPTER 21

Formulation of Sunscreens in the United States

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Key Words:
Sunscreen, UV filter, FDA, Ultraviolet radiation, Photoaging, SPF, UVA, Photostability, Daily- wear, Beach-wear

Introduction

The predominant physical forms of sunscreens currently on the market are emulsion-based lotions and alcohol-based continuous sprays. Solid sticks and oily formulations are also available. The basic formulation type for sunscreen lotions is quite similar to those of other cosmetic and personal care products. The major difference lies in regulatory status, since sunscreens in the United States are considered an over-the-counter (OTC) drug by the Federal Food and Drug Administration (FDA) due to the fact that a health benefit claim, namely prevention of sunburn, as measured by Sun Protection Factor (SPF), or cancer prevention, is made. This means that the active ingredients, which are UV filters, must be present on the sunscreen filter list that the FDA has approved based on their safety and effectiveness. This list is more restrictive than other globally approved UV filters for sunscreens. Global regulation of sunscreen products is not harmonized. In some regions, sunscreens are considered cosmetic products and in others they are considered drugs or quasi-drugs. Furthermore, the permitted ingredient lists are determined by various, disparate regulatory agencies and differ from one region to the other. The active ingredients in the United States must have a US Pharmacopeia (USP) monograph, and the USP or drug name, which is reported on the label, may be different from the International Nomenclature of Cosmetic Ingredients (INCI) name of the compound.

The formulation of sunscreens for the US market, whether designed for beachwear or daily wear, is guided by the FDA Sunscreen Monograph. This document is still in

the final approval process by the FDA after several changes were proposed in 2007. The major challenge to the sunscreen formulation chemist is complying with the monograph guidelines for UV filter types, use levels, and combinations permitted to achieve the claims conforming to the monograph substantiation criteria as outlined, while satisfying a consumer need that is analyzed and communicated by marketing professionals. The most up-to-date monograph can be found on the FDA website for OTC products.[1]

Nowadays sunscreen products are expected to provide a high level of broad spectrum (UVA and UVB) protection, water resistance (for beach/sport use), and the filters and filter combinations need to be photostable. There are also many daily wear products designed for general UV protection for everyday use, and these have less stringent requirements since their potential user is generally exposed to intermittent sun with no exposure to water, thus the formulation need not require water resistant properties. However, since an SPF claim is made, these products still must be formulated in adherence with FDA guidelines.

The sunscreen formulation chemist therefore has a major challenge to create an acceptable product. In addition to conforming to the regulatory requirements, the product needs to have overall stability (chemical, physical, and photochemical), which can be more difficult with beach products, as they are often exposed to high temperatures over short periods of time, compared with general daily wear products. Hence, packaging considerations are very important as the package can play a key role in maintaining the stability of the formulation. Acceptable aesthetics can be especially challenging to achieve for beach/sport products given the high levels of active sunscreen ingredients and water resistance agents used. The ease of application and overall comfort when on the skin during the period of use are probably the most important factors to the consumer, after efficacy. The consumer expectation for ever higher SPF and UVA protection increases the difficulty of formulation substantially. Finally, the consumer perception of product safety is constantly changing, as reports emerge about possible harm that may be associated with certain ingredients. Products marketed to target segmented populations such as babies and children and those with sensitive skin require special consideration.

Fortunately, there are many formulation strategies that have been developed over the years that can be exploited by the sunscreen formulation chemist to overcome these hurdles. This chapter describes the means for evaluating and communicating the effectiveness of a sunscreen product and reviews the active ingredients chosen for the claim. Various *in vitro* techniques for estimating SPF and levels of UVA protection can be used during development to optimize performance prior to *in vivo* testing for labeling. In addition, important attributes such as aesthetics, photostability, and water resistance, are addressed by ingredient combinations. Finally, this chapter describes some of the new UV filters which are expected to become available to the formulation chemist in the future. As the title stipulates, in effort to examine this topic with some good measure of detail, the discussion will focus primarily on formulation for the US market regulatory strictures.

SPF and UVA Protection in Sunscreen

The SPF reported on the label of a commercial sunscreen product informs the consumer of the level of protection against potential sunburn caused predominately by UVB radiation. When formulating a sunscreen with a specified degree of skin protection, generally broad spectrum, one needs to understand the definitions of UVA and UVB. Ultraviolet (UV) radiation is a type of electromagnetic energy, differentiated by its wavelength. It comprises a very small proportion of the entire solar spectrum reaching the surface of the earth, with short wavelength and therefore high frequency and energy. The vast majority of incoming radiation is visible and infrared, characterized by increasingly longer wavelengths over 400 nm and therefore relatively lower energy.[2] **Figure 1** illustrates the ranges of wavelength defining UV radiation.

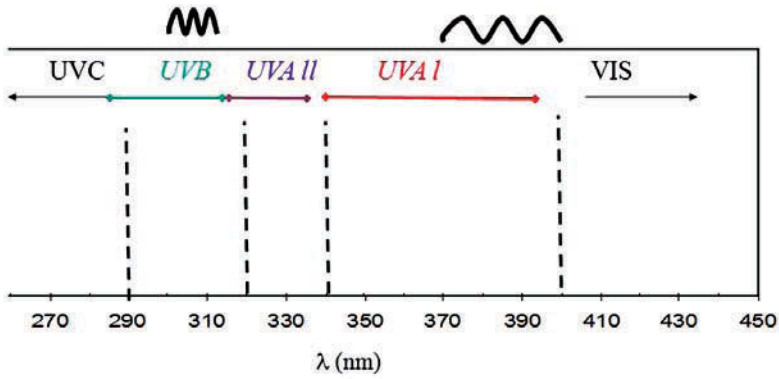

Figure 1. Solar UV spectrum ranges; UVB = 290–320 nm; UVA II (short UVA) = 320–340 nm; UVA I (long UVA) = 340–400 nm

UVC radiation exhibits extremely high energy and is considered toxic; however, for the most part, it is filtered by the atmospheric ozone layer and therefore does not reach the surface of the earth in any significant amount. Of the UV radiation between wavelength 290–400 nm that does reach the surface, most is UVA, with UVB varying somewhat depending on the time of day.[2] UVB radiation, spanning 290–320 nm, has the highest energy and is the major contributor to sunburn. Typical UVB filters, including octinoxate, octocrylene, octylsalate, and homosalate, absorb almost exclusively in this range and provide most of the SPF in a sunscreen. Radiation in the UVA spectrum (320–400 nm) is also known to contribute to sunburn, making filters covering this range important as well. While the contribution of UVA to sunburn is lower when compared to UVB, it is still significant. In addition, UVA has been shown to generate high amounts of free radicals in the skin and to play a significant role in skin cancer generation via secondary mechanisms that are affecting the DNA.[3,4]

It is well known that long-term exposure to the sun without protection, particularly prolonged and/or frequent episodes of sunburn that can result from such exposure, contributes significantly to the development of skin cancer, notably in light-skinned individuals. Another result of long-term exposure, although of course not nearly as life-threatening as cancer, is the premature aging of the skin, also known as photoaging or actinic aging.[5] It has not been clearly defined to what extent UVB and UVA are responsible for cancer and accelerated skin aging, but the general consensus is that both are responsible; with UVB being a greater factor in the development of cancer and UVA contributing more to photoaging. Regardless, it is necessary for an effective sunscreen to filter both UVA and UVB for the fullest possible protection. The ratio of desirable SPF against UVB to UVA can vary in different formulations and the degree from high to low conveyed to the consumer in regions outside the United States on the label. In the United States, this is addressed in the FDA Sunscreen Monograph, with sunscreens labeled as "broad spectrum" requiring a set ratio of UVA to UVB screening.[1]

Determination of SPF

SPF for label claim on a marketed sunscreen in the United States is measured by a specified *in vivo* method.1 Basically, individuals of light- to medium-toned skin are exposed to increasing amounts of UVB radiation from a solar simulator to determine at which level visible perceivable sunburn or reddening occurs. The value that is determined subjectively is called the Minimal Erythemal Dose (MED). The tested sunscreen formulation is then applied to the skin at a specified dose of 2 mg/cm2 and the treated skin is exposed to the solar simulator to determine the amount of radiation that will result in visually perceivable sunburn. The ratio of energy dosage required to induce erythema on sunscreen protected skin relative to unprotected skin determines the SPF value. The SPF value is equivalent to:

SPF = MED of skin protected with sunscreen / MED of skin without protection.

Higher SPF values provide better protection from UVB and thus from sunburn. There are a great number of standardizations and specifications for the FDA method that are outlined in the monograph with respect to application, test subjects, equipment, and other conditions that must be followed to qualify as a claim that can be listed on the product label.

Additionally, there are instrumental *in vitro* techniques that can be used to prescreen and estimate the SPF of a particular formulation.[6-8] The SPF values generated by using these methods cannot be used to market a sunscreen to the public, since they are not recognized by regulatory authorities. They are used during formulation development to optimize UV filter combinations in the system and can greatly reduce the number of *in vivo* tests needed, as well as improve the overall process of formulation design. Accuracy can vary with the substrate onto which the

product is applied (such as quartz, polyacrylate, or plastic) and the formulation type (e.g. difficulties routinely encountered when using inorganic particulate filters). In spite of the expected error margin of these screening methods, they are helpful in refining the formulation before a costly *in vivo* procedure is conducted. In addition, lowering the number of human studies in which panelists are exposed to radiation is an important ethical consideration. The approximate SPF that an individual UV filter contributes to the formulation at specific concentration is known; however, combining these compounds does not necessarily generate an additive effect and often there are synergistic effects between UV filters as well as with other formulation ingredients that can affect the magnitude of the SPF.[9]

Computer simulated methods, also known as *in silico*, can be an effective tool in evaluating the efficacy of the UV filter combinations.[10,11] The online Sunscreen Simulator[10] is a type of calculation program that estimates SPF and UVA protection values based on the types and levels of UV filters for all global regions. This calculation allows one to determine a reasonable starting point within minutes by screening a number of combinations of approved UV filters in a specific region of the world before beginning any laboratory bench work. Like the *in vitro* SPF measurement method mentioned, the results generated *in silico* cannot be used for the commercial SPF product claims, but may assist in overall development by providing variable estimates applicable during formulation.

High SPF

Commercially marketed sunscreen products, most notably beachwear, are available with increasingly greater SPF values—up to 100 and even higher. Whether these extremely high SPF values are actually more effective in the prevention of sunburn is debatable. Since higher levels of sunscreen ingredients are used to achieve high SPF values in these products, there is increased exposure to topically applied chemicals. The final ruling of the FDA monograph published in 2007 caps the maximum SPF claim at 50+. This does not mean that a particular sunscreen cannot have a higher SPF; just that it will be labeled and marketed as "50+" rather than at its specific higher value, i.e. 80 or 100. In review of this ruling, several points of consideration have been raised both for and against. One very valid argument in defense for labeling with values exceeding 50 is that the SPF is determined *in vivo* applying a specified level of the sunscreen, 2 mg/cm2, to the test subject. In actual practice, however, most consumers apply far less than this tested amount, depending mainly on the degree of spreadability on the skin. An SPF 30 for example that is applied at a lower level than the tested dose provides less protection than its listed 30 value. In addition, particularly with beachwear products, the sunscreen can be removed by rubbing or toweling, both activities that will reduce the amount applied, resulting in lower protection. If the sunscreen is not applied at the tested amount or is not reapplied, a SPF value that is higher than 50 can compensate for loss by abrasion and wash-off and provide the adequate protection. On the other hand,

neither the FDA nor any other research body has determined that an SPF higher than 50 offers significantly more protection and is needed under normal exposure to sun radiation. In fact, if the sunscreen is properly applied, SPF 50 should provide more than adequate protection. Higher levels of UV filters may cause irritation to individuals with sensitive skin, notably children, or to the eyes if applied on the face.[9] Another matter to consider is that UVA protection needs be in proportion to that provided for UVB in order to be labeled as "Broad Spectrum." It is technically challenging to achieve even moderate proportional UVA protection for extremely high SPF sunscreens.

The issue of high SPF is much less of a concern for daily wear products which generally range from SPF 15–45. Due to the aesthetic requirements of very easy spreading on the skin for a very light film for such products, it may be even more likely that less will be applied than the tested dose of 2 mg / cm2; however, due to their intended use for protection from intermittent sun exposure, this is generally deemed adequate.

UVA Protection

Effective protection from damaging solar radiation requires a product to be broad spectrum, that is to contain filters that absorb across much of the UVB/UVA spectrum. Compared to the long history of reporting SPF for protection against sunburn, UVA protection has become a major concern in the United States over the past couple of decades, when the two UVA filters, avobenzone and zinc oxide, were added to the FDA list of approved actives. More recently, ecamsule (trade name: Mexoryl SX) was approved by a New Drug Application (NDA) submitted to the FDA by L'Oreal; however, this compound has restricted general use due to its NDA status and the company's patent protections.

The determination of UVA protection *in vivo* is more complicated compared to the determination of SPF (UVB). The *in vivo* method is similar to that for SPF, but rather than a clear-cut visual endpoint of erythema, UVA produces a clinical tanning response which may be more difficult to accurately assess and is defined as Persistent Pigment Darkening (PPD). The latest FDA ruling for UVA testing for the broad spectrum claim requires a much easier *in vitro* technique called "critical wavelength."[1] This technique assesses the degree of UVA protection relative to UVB or SPF of the formulation. It is therefore a representation of the ratio between UVA and UVB. This ratio is determined instrumentally by integrating the area under the UV absorption curve of a film of a sunscreen formulation. The wavelength at which 90% of the area of the spectrum falls below and 10% above is the termed the "critical wavelength" shown in **Figure 2**.

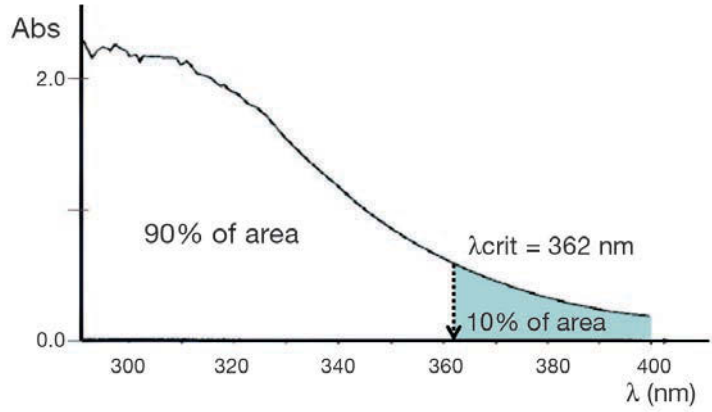

Figure 2. A typical *in vitro* absorbance vs. wavelength curve for TiO2. The critical wavelength (λcrit) is the dividing point of the area under the absorbance curve (90% : 10%)

A minimum value of 370 nm is considered adequate as a sufficient ratio between UVA to UVB protection. In the figure, the critical wavelength of 362 nm would not meet this requirement. While other global regions generally report the degree of UVA protection from low to high, the critical wavelength is a "Pass / Fail" for the broad spectrum label claim in the US market.[1]

Broad Spectrum Protection and Prevention of Skin Damage

The structure of the skin breaks down to three basic layers: the stratum corneum, which is a thin but highly resilient surface layer; the thicker epidermis beneath it containing melanocytes that regulate pigmentation; and a much thicker vasculated dermis, which contains the structural framework consisting of mainly collagen and elastin proteins that provide the skin its overall shape and elasticity. **Figure 3** depicts an approximation of these layers and how UV radiation penetrates the skin. UVB radiation penetrates to the epidermis, while UVA can reach much deeper, into the dermis.

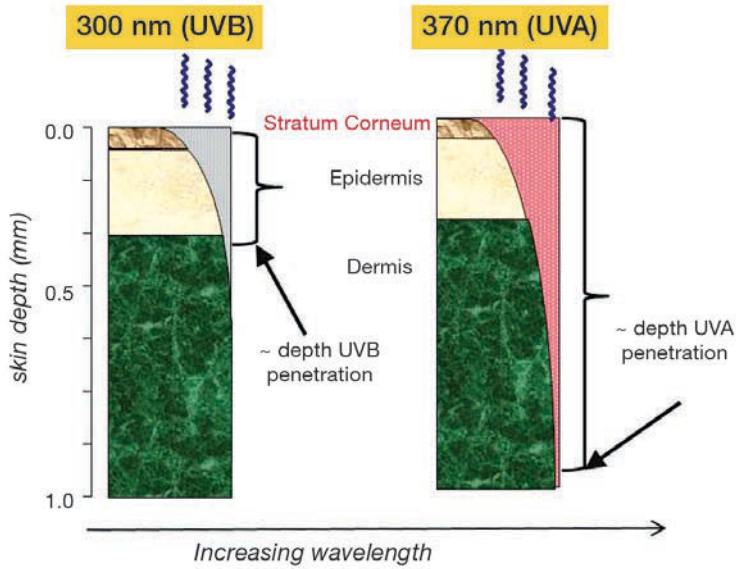

Figure 3. Degree of UVB/UVA penetration into the layers of the skin: UVB: mainly penetrates and interacts with epidermal components; UVA: penetrates deeper, reaching the dermis where the structural components (elastin and collagen) as well as blood vessels reside.

As mentioned, electromagnetic UV radiation delivers energy inversely proportional to its wavelength. The high energy short wavelengths of UVB radiation can directly damage and degrade DNA within the skin, causing mutations that eventually may lead to the development of skin cancer. In addition, other photochemical transformations are known to cause immuno-suppression, or weakening of the skin immune system, another factor that plays a role in cancerous cell formation.[12] UVA radiation is less energetic compared to UVB and causes damage in a different way when it interacts with the skin.[5,13-15] Rather than directly altering biological molecules within the skin, it can interact with chromophores, such as various nucleic acids, proteins, quinnones, and other molecules, causing an excited state. These chromophores are colored compounds that reside in the skin and can specifically absorb certain wavelengths of radiation according to their molecular structure. From the chromophore, energy transfer to cellular or surrounding environment components such as water, oxygen, and nitrogen generates what is known as Reactive Oxygen Species (ROS), often commonly popularized by the term "free radicals." ROS have an unpaired electron which makes them highly reactive with nearby susceptible molecules or cellular components. ROS cause inflammation, interfere with the function of the mitochondria, and damage enzymes, DNA, and lipids. One destructive mechanism in particular involves alterations in the structural

elastic dermal fibers by increasing the activity of matrix metallo-proteinases (MMPs). This class of enzymes degrades collagen and elastin present in the dermis and this process is thought to be associated with the premature aging of the skin when exposed to radiation.[13-15] These enzymes are essential for maintaining the normal turnover in healthy skin, but when expressed in higher amounts (up-regulated) they cause accelerated degradation. This is followed by repeated repair, which over time creates small imperfections within the dermal matrix. It is hypothesized that the resulting visual effects of this cascade are the deep wrinkles, excessive and uneven permanent pigmentation, abnormal spots and growths associated with photoaging.[5] The incorporation of an adequate level of UVA filters has shown to reduce the formation of ROS and so to assist in prevention of such damage.[16-18] Clearly, broad spectrum sunscreens are advantages in the prevention of the biological changes associated with excessive sun exposure that can severely impact skin health and appearance.

Ingredients and Formulation Strategies

UV filters function as protective agents, because they are able to absorb radiation in a particular wavelength range either as conjugated chromophores, in the case of those based on organic chemistry (**Figure 4**), or because they scatter, reflect, increase path-length, and absorb radiation, as is the case of inorganic particulate filters (**Figure 5**).

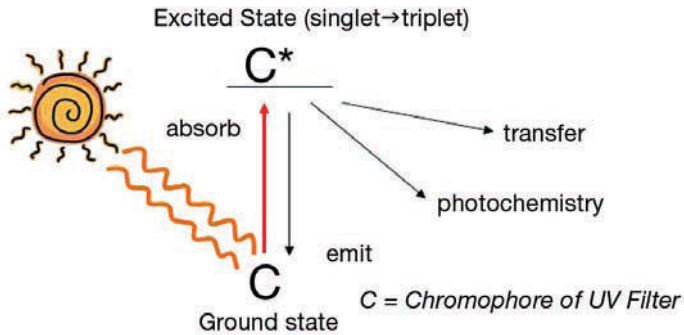

Figure 4. Organic Sunscreens: Chromophores absorb UV radiation

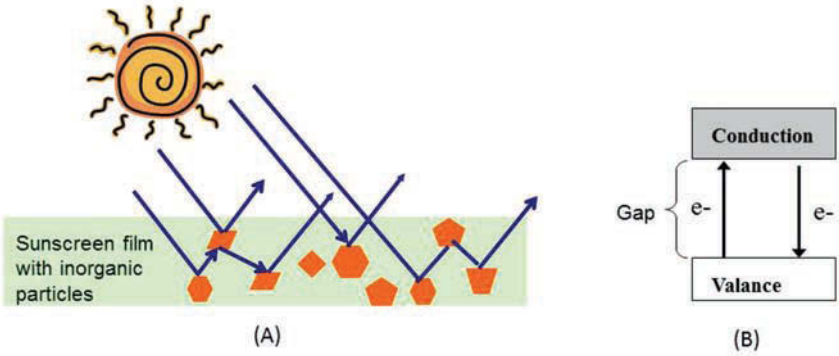

Figure 5. Inorganic Sunscreens: Particles reflect, scatter, and increase the path-length of UV radiation (A) and absorb UV radiation (B)

The majority of UV filters are organic compounds that are soluble in oils, a few are anionic organic-based salts soluble in water, and two are inorganic particulates—titanium dioxide and zinc oxide—which are dispersible but not soluble in liquids. A variety of grades of these powders are available; many are treated with either hydrophobic or hydrophilic coatings to enhance their stability in the formulation. In addition, there are a number of zinc oxide and titanium dioxide products commercially available that are pre-dispersed in various liquids. These may be stabilized with dispersants and pre-sheared, and are therefore relatively easy to incorporate into the formulation, sometimes allowing for the elimination of the milling step, thereby reducing production time, energy, and cost. Regardless of the type of particulate coating, according to the USP the active ingredient listed is zinc oxide or titanium dioxide.

One of the main challenges a sunscreen formulation chemist faces is to be able to create a product with the desired broad spectrum protection within the constraints of the current FDA approved UV filter list and the maximum allowed levels of each. Not all UV filters perform equally; each has its own extinction coefficient, which determines the amount of radiation it can absorb.[2] In addition, there are often positive synergies between filters that can produce higher SPF than would be expected based on the individual absorption curves.[9] Of the list of 17 filters in **Table 1**, over half have fallen out of general use for a number of reasons, and one, ecamsule, is not readily available for use outside of its parent company's NDA and patents (the aforementioned L'Oreal). Some combinations, most notably avobenzone with octinoxate, will degrade upon UV exposure, and therefore require special stabilization techniques. In addition, there are particular combinations of ingredients that are not allowed to be combined together in a formulation according to the FDA monograph, due to the potential of chemical interaction between them. An example of such a combination is avobenzone with titanium dioxide.

Table 1. FDA approved UV filters.[1,2] *Ecamsule is used only under NDA.

	USP name	Max % allowed
1	Aminobenzoic Acid	15
2	Avobenzone	3
3	Cinoxate	3
4	Dioxybenzone	3
5	Ensulizole	4
6	Homosalicylate	15
7	Meradimate	5
8	Octocrylene	10
9	Octinoxate	7.5
10	Octisalate	5
11	Oxybenzone	6
12	Padimate O	8
13	Sulisobenzone	10
14	Titanium Dioxide	25 (min 2)
15	Trolamine Salicylate	12
16	Zinc Oxide	25 (min 2)
17*	Ecamsule	3

Avobenzone, zinc oxide, meradimate, and ecamsule are UVA filters. There are several more ingredients that are currently used in other regions, but as of this writing, they are not yet approved in the United States. A number of filters absorb primarily in the UVB region and also extend beyond 320 nm into the short and mid-UVA wavelengths and can contribute to achieving broad spectrum protection.

As previously mentioned, an efficient way to get to a starting point for selecting a UV filter combination to reach the desired SPF and UVA protection level is to first employ the online Sunscreen Simulator.[10,11] This calculation of the theoretical levels and types of sunscreens to use is recommended as a starting point as laboratory work begins. The program of the Sunscreen Simulator contains a database of UV spectra for all filters approved anywhere in the world. A region is selected and levels of UV filters approved for that region are entered. The resulting calculation then provides the expected SPF/Filter Efficiency, UVA Metrics, and estimation of the real-life SPF. This value is calculated using a standard solar spectrum which has a greater UVA spectrum than an irradiation lamp. Results are given with allowed filters and levels for the individual region chosen. A complete description of this *in silico* system is described in Herzog and Osterwalder.[10]

Product Forms

The two most popular product forms of sunscreens in the United States are lotions and sprays. Lotions or creams are based on oil- and water-based emulsions for both beachwear and daily wear. Continuous sprays are based on a volatile alcohol and are generally used as beach/sport products. Sunscreen sticks are also used for spot application, although to a lesser extent.

Continuous sprays are comprised of a mixture of oil-soluble UV filters dissolved in an ethanol base and are fairly straightforward to formulate. In addition, they may contain a polymeric film former to increase water resistance, additional emollient, and fragrance. In such formulations where the composition is hostile for microbial growth, there is no need to include preservatives since these do not contain an aqueous phase that will encourage bacterial growth. Particulate inorganic UV filters are generally not used in such formulations, as they do not suspend well in the media and can clog the spray valve. The packaging of such products is more complex; the sunscreen is contained in a flexible sack surrounded by compressed air in a can with a spray valve. This system does not require the use of hydrocarbon propellants that are typically used in conventional aerosol sprays, and the product is dispensed continuously when the nozzle is compressed. When applied, an even coat of the alcoholic solution covers the skin with little or no need for rubbing in. When the alcohol vehicle evaporates, a film of the UV filter is left on the skin. Due to the hydrophobic nature of these organic filters, some water resistance is imparted and can be greatly enhanced to meet the criteria for FDA labeling by the addition of specific hydrophobic copolymers often based on substituted acrylate or polyvinyl pyrrolidone (PVP) chemistry. These sprays are highly popular with consumers as they are much easier and faster to apply compared with lotions or creams and do not impart a greasy feel. Sprays of this type also do not contain surfactants that are incorporated into emulsion-based lotions and therefore are not easily washed off in water.

One drawback of sprays, however, is that during application a fair amount of product can be wasted because it is dispensed in a fine mist, and some formulations are reported to have a tight film-like feel after drying. In addition, when applying the product the consumer needs to be careful not to inhale it or spray it in proximity to eyes. Safety measures should be taken not to apply alcohol-based spray in the vicinity of fire; they are flammable.

Emulsion-based lotions and creams are widely used as well. For these types of products packaging is simple, generally in plastic bottles or tubes; however, formulation design and production is generally more complex compared to the continuous spays. The viscosity of such formulations can range from thin lotions to creams. Both water-in-oil (w/o) and oil-in-water (o/w) emulsion formulations are used, although the vast majorities are o/w due to their preferable aesthetics. For a more detailed explanation on these types of emulsions please refer to the chapter on emulsions in this book, as well as Reference 9 of this chapter. The emulsion

is prepared from an oil phase containing hydrophobic organic and/or dispersed inorganic particulate UV filters, a water phase which may contain water-soluble or -dispersible UV filters. In addition, an emulsifier system, thickeners, water-resistant film formers, and other incidental ingredients are added as needed for the application.

Key Formulation Considerations

The aesthetics of wear and in particular the ease of application of lotions is of high importance to the consumer for both beachwear and daily wear. Formulating to achieve acceptable rub-in and after-feel requires special consideration of the combination of oil phase ingredients (emollients, UV filters), the emulsifier system, and especially the thickener system, along with water-resistant polymeric film formers included in beachwear designed formulation.[9] The efficacy of UV protection is determined mainly by the combination and level of the filters incorporated. The solubility of organic UV filters that are in solid form must be maximized, and with some, oxybenzone in particular, this can be difficult. These actives may become partially ineffective if significant crystallization occurs in the formulation phase. Typical oil phases are emollients comprising a wide array of fatty esters and hydrocarbons, silicones, and fatty alcohols (which can also contribute to the viscosity and stability of the system). The choice of solvent have an effect on the SPF value due to the degree of solubilization of the UV filter and/or interactions with the excited state

Protecting the skin from the destructive nature of solar induced free-radicals induced by UVR exposure is generally not achieved by solely using UV filters. Therefore, a variety of antioxidants are frequently incorporated into the formulation. These complement the UV filters by potentially reducing the inflammation caused by UV irradiation and neutralizing free radicals that form during sun exposure. Commonly used antioxidants include esters of vitamin E and vitamin C, as well as a number of botanically derived ingredients. While broad spectrum UV filters assist in preventing the formation of free radicals in the skin, they most likely cannot entirely block radiation and its effects. This is the reason for the incorporation of antioxidants into sunscreen formulations, as they have been shown to be effective at reducing the level of ROS when compared with UV filters alone.[9,18]

The use of zinc oxide and/or titanium dioxide, which are dispersed rather than dissolved or solubilized in the sunscreen formulation, may be more complicated. For stability and performance, the particles need to be well suspended in the medium. To achieve this, mechanical shear needs to be applied to break apart agglomerates and the particles must be stabilized to minimize re-agglomeration. Since these small size particles exhibit high surface energy they will tend to re-agglomerate, a process that may reduce their efficacy, lower the SPF and UVA protection values and potentially generate white color when applied to skin. There are many commercially available grades of titanium dioxide and zinc oxide for sunscreen applications, coated with hydrophobic polymers to increase their ease of dispersion in oil and stability

in the emulsion. In addition, there are grades with hydrophilic surface treatments for dispersion in water. Dispersing agents that reduce the surface energy and wet the particles are often used to produce and stabilize the suspension.[9] In addition, there are a great number of commercially available pre-dispersed zinc oxide and titanium dioxide products in various mediums (organic or aqueous) for optimized stability and ease of incorporation of the particles into the emulsion. Elimination of the initial wetting and milling step reduces production time, energy, and cost.

Zinc oxide and titanium dioxide have been used traditionally in color cosmetic formulations as pigments to provide opacity. However, when used in sunscreens, transparency is desired; to achieve this, zinc oxide and titanium oxide for sunscreen use are available in very small particle size, known as *attenuation grade*. With average primary particle diameters in the range of up to 100 nm for titanium dioxide and up to 200 nm for zinc oxide, light scattering is avoided in the visible range above 400 nm and only UV radiation is affected. Particles ranging up to 100 nm are considered nanoparticles, by definition. However, when they are dispersed in a formulation, even high shear does not allow for the primary particle to exist without some degree of aggregation, so in reality most sunscreen emulsions will contain a very small number of particles under the nano-scale limit. As long as the particles do not form large agglomerations, they will be stable against precipitation and function efficiently as UV filters.

The public perception of nanoparticles can be negative at times. Concerns have been raised by consumer advocate groups about the potential for skin penetration leading to adverse health effects.[19] There are a number of published scientific studies that show that attenuation grade UV filters do not penetrate the stratum corneum or cause specific harmful effects if accidently introduced through compromised skin.[20-22] If the intent is to market a sunscreen formulation based on inorganic UV filters that does not contain particles at the nano-scale, there are commercially available grades of inorganic UV filters that are larger and do not contain any particles below 100 nm. Although sized above 100 nm, these systems are specifically designed not to cause whitening when applied to skin due to their unique physical structure and manufacturing methods.

There are specific formulation and stability challenges associated with using inorganic filters; however, these are outweighed by their benefits. Due to their particulate nature, such filters have very low potential for penetrating beyond an intact stratum corneum and therefore their potential of triggering skin irritation is likewise low. This makes them especially suited for infant and children's products, as well as products targeted at individuals with sensitive skin. They are also used extensively in daily wear products to provide a lighter, drier feel (less greasy) when compared to some of the organic filters. The appropriate amount of UV filters can be incorporated into the optimal solvent system; however, UV protection will not be maximized unless the product is applied to skin in a manner that creates an even film.[23] The incorporation of film-forming polymers and/or careful control of

rheological properties enhances skin coverage and protection.

The overall stability of the emulsion over time is achieved by optimizing the mix of oil and water phases with the appropriate surfactant system and using viscosity enhancing agents in the same way as in any other topical emulsion. Guidelines for generating emulsion stability are well known and published in a number of texts and reviews as well as in this book's chapter on emulsions. The incorporation of film formers into beachwear sunscreens may present additional stability challenges. It is recommended, notably with sunscreens, that the emulsifying system be as hydrophobic as possible to reduce wash-off when the skin comes in contact with water or with sweat. Since sunscreens can be exposed to relatively high temperatures over a short term by the consumer during use and storage, they need to be stable at higher temperatures, up to at least 100°F

Photostability of UV filters during use is of crucial importance to any type of sunscreen regardless of its product form.[24-26] Avobenzone is particularly susceptible to degradation when exposed to sunlight, and this propensity is enhanced in the presence of octinoxate, where the two compounds will mutually and rapidly lose efficacy over a period of a couple of hours, so that both SPF and UVA protection are depleted. Referring back to Figure 4, a properly functioning, photostable UV filter will act in a cycle of absorbing energy and achieving an excited state, and then return to a ground state where it releases only thermal energy as it prepares to absorb solar energy again. In the case of avobenzone, another photochemical path occurs, changing the molecule and rendering it less efficient over time. When octinoxate is present along with avobenzone, energy transfer also takes place, accelerating the process and significantly degrading both molecules within a few hours.[26]

To evaluate the degradation potential of UV filters in formulated products when exposed to sunlight, pre-irradiation with a solar simulator of the substrate after sunscreen application prior to testing can be done. There are ways to stabilize avobenzone and octinoxate against degradation.[27] One way in particular is the inclusion of the UV filter octocrylene, which prevents both UVA and UVB protection from being lost. In addition to octocrylene, some UV filters from regions other than the United States—which it should be noted are *not* presently FDA approved—including bemotrizinol, bisoctrizole, and enzacamene, can offer excellent photoprotection for avobenzone.[28] Encapsulation of UV filters can also enhance photostability by minimizing interactions between the components. Some other photostabilizing agents which are not UV filters include diethylhexyl 2,6-naphthalate, polysilicone-15, and salicylate derivatives and particular esters/polyesters optimized to prevent or slow degradation.[25] Some of these compounds and their effective combinations with UV filters are protected under patent rights, so careful evaluation of the legality of their use should be conducted before consideration. Inorganic particulate UV filters (zinc oxide and titanium dioxide) are quite stable against photo-degradation, and the potential for free-radical generation is virtually eliminated by the polymeric coating used for most of these commercial products.

As far as specific prototypes for sunscreens for beach/sport products and for daily wear is concerned, there are many formulation guidelines published mainly by the UV filter suppliers. These vary considerably with respect to claims, UV filter combinations, and use of innovative ingredients for special effects, so it would make little sense to attempt to reproduce a representative selection in this chapter. An excellent resource for an up-to-the date catalogue of stable formulations can be found in *Cosmetics & Toiletries* magazine's *Sun Care Formulary* which is published periodically.[29-32]

New Active Ingredients on the Horizon

The list of FDA approved UV filters available to the formulation chemist working in the United States is currently limited to 16 ingredients (plus ecamsule by NDA). As mentioned above, many of these have fallen out of general use due to low effectiveness and/or negative public perception. In addition, only avobenzone and zinc oxide are highly effective in screening the long UVA wavelengths. Each of these has formulation challenges: Avobenzone is allowed to be incorporated only up to 3%, and is not inherently photostable. Some stabilization techniques are under patent protection, but at present it can stain clothing. Zinc oxide needs to be dispersed in such a way that it does not agglomerate to reduce SPF or cause undesirable skin whitening.

With the FDA Sunscreen Monograph requirement that a broad spectrum sunscreen should provide an appropriate ratio of UVA and UVB protection, it becomes increasingly difficult to formulate effective photostable SPF 50+ products with the existing approved ingredients. There are several filters approved for use in regions outside the United States that have been shown to be highly effective and safe for use. These include UVB, UVA, and broad spectrum UVB/UVA absorbers. The FDA allows new active ingredients to be used when approved as an NDA and by TEA (Time and Extent Application). In theory, the TEA process should be more rapid and less expensive when compared with the traditional NDA because it allows previous data compiled from historical use in other regions to be used instead of generating new data (minimum of 5 years in 5 countries). As of this writing, TEA proposals for seven new UV filters have been submitted to the FDA of the process in 2002, but they have not yet added to the monograph (**Table 2**).

Table 2. New UV filters currently under TEA evaluation with the FDA1

Ingredient submitted for TEA	Date
Amiloxate	2003
Bemotrizole	2005
Bisoctrizole	2005
Diethylhexyl butamidao triazone	2006
Ecamsule (has NDA)	2008
Enzacamene	2003
Octyl Triazone	2003

In addition to new ingredients, new physical forms of currently approved ingredients are being introduced. One example is zinc oxide with larger particle sizes that offer the same transparency and protection of the skin as nano-particles. Sunscreens of this nature are marketed to segments of the public that may have concerns about the application of small particles to the skin and prefer the product to be free of nano-sized ingredients (diameter < 100 nm). In addition, some encapsulated forms of organic UV filters can offer increased efficacy and photostability.

With respect to evaluation of the health benefits of a sunscreen, in addition to SPF and UVA values, there are newer rating systems based on *in vitro* methods. These more specifically address and quantify the metabolic and physiological responses to sun exposure, and, in addition to conventional SPF and UVA ratings, they quantify the level of protection a UV filter or a sunscreen formulation offers. One of these is the Radical Skin/Sun Protection Factor (RSF) which determines the degree to which individual UV filters prevent the formation of solar-induced ROS within the skin. Strong protection is seen in particular with filters that provide protection in the UVA spectrum as radiation in this range penetrates deep into the dermis promoting the formation of ROS. This is further evidence that broad spectrum protection is essential for truly effective sunscreen products.[16,17,33] Another system is the Immune Balance Rating (IBR) which evaluates the negative potential for allergic or toxic reactions from UV filters along with the positive impact of the degree of protection from solar-induced immunosuppression. An optimal rating would be for a sunscreen to induce minimal or no allergic or toxic reactions while affording the maximum level of immunoprotection.[34,35]

Summary

Formulating effective sunscreens requires a number of considerations beginning with the selection and combination of approved UV filters for desired SPF and UVA protection. Since sunscreens are considered OTC drugs, all associated claims need to comply with the FDA Monograph. *In vitro* and *in silico* methods can be very

useful during development to estimate the right balance of filters within the FDA Monograph. The formulation itself needs to be stable and the UV filters should be resistant to photodegradation. Aesthetics for application and wear are key factors in the marketability of any product and sunscreens are no exception. The most recent formularies from various UV filter suppliers can be found in the trade publication, *Cosmetics & Toiletries* magazine, updated yearly.

There are a great many issues and changes in the regulation of sunscreen products taking place at present. There is anticipation that newer, more effective UV filters will be approved by the FDA through the TEA process, thus greatly expanding formulation capabilities. Harmonization of efficacy testing methods is ongoing as well. Implementation of the final FDA Sunscreen Monograph will ensure that products on the market provide the end-consumer with adequate protection and clear label information describing the health benefits they can expect.

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CHAPTER 22

Formulating a Day Cream with SPF: A Case Study

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Sunscreen, Sunblock, Physical and chemical filters, UVA and UVB radiation, Sun protection.

Introduction

One of the more challenging products to formulate is one that exhibits a Sun Protection Factor (SPF) in addition to other skin care benefits. Key reasons include:

1. The need to be well-versed in sunscreen technology and regulatory limitations;
2. The physical characteristics of sunscreen ingredients make it challenging to create a sensorially pleasing product;
3. The packaging presents challenges in terms of preserving the integrity and stability of the sunscreen ingredients; and
4. There are tight regulations that differ globally.

The following illustrates a case study of a brand going through the effort of formulating a facial moisturizer with SPF.

Background

Alchimie Forever is a small skin care company that develops products based on combinations of plant extracts that have been demonstrated to have antioxidant effects, acting either in neutralizing free radicals, preventing their formation, or supporting the up-regulation of the body's natural antioxidant defenses. The plant derived compounds used in this skin care line are typically combinations of small molecular weight molecules. As such, they have the potential to penetrate through

the stratum corneum into the viable parts of the epidermis where they can exert their intended effects. Generally, molecules with a molecular weight that is below 500Da penetrate through various routes to passively diffuse through the skin: intercellular, transcellular, intrafollicular, and the polar pores.[1] It should be noted that the vehicle carrying the active ingredients can also facilitate penetration through the stratum corneum by reversibly compromising the skin barrier. Vehicles may have a range of molecular interactions with the proteins and lipids of the stratum corneum: to modify the properties of the barrier and therefore allow permeation, and to improve dermal delivery.[2]

UV Damage

Ultraviolet radiation (UV) exposure (180–400 nm) leads to multiple cellular damages, some facilitated by the generation of Reactive Oxygen Species (ROS). UVB rays (290–320 nm) are absorbed by epidermal chromophores such as melanin and urocanic acid and lead to direct molecular damages while also generating ROS. In the presence of hydrogen peroxide, UVB radiation leads to the formation of the hydroxyl radical,[3] which causes DNA damages. UVA rays (320–400 nm) penetrate more deeply in the dermis, increase the production of ROS, and contribute to long-term actinic damage. Both UVA and UVB induce the activation of a wide range of transcription factors in skin cells, including NF-κB (transcription factor involved in inflammation and cellular stress responses),[4] which in turn may increase the production of Matrix Metallo Proteinases (MMP), a family of enzymes that degrade collagen and elastin.

The skin is continuously affected by environmental factors and notably UV radiation.[5] In the skin, free radicals induced by UV radiation cause damage to DNA and proteins, and destabilize the membranes of living cells, leading to premature aging of the skin cells. In that sense, the equation *oxidation = facilitated aging* may be applicable to all body organs, skin included. When exposed to UV radiation, the skin undergoes alterations resulting in inflammation, photoaging, and various skin disorders.[6] Skin photoaging is clinically expressed by wrinkling, loss of elasticity, increased skin fragility, and slower wound healing.

Chemical and physical sunscreens play today a critical role in UV protection. But despite the importance of use of the sunscreens they may not be sufficient for protection from damage.[7] Indeed, even with the proper use of the best screens, some UV rays penetrate the skin and induce oxidative stress; hence the rationale of utilizing antioxidants in addition to sunscreens.

Antioxidants inhibit the production of ROS by direct scavenging, decrease the amount of oxidants in and around cells, prevent ROS from reaching their biological targets, limit the propagation of oxidants such as occurs during lipid peroxidation, and thwart oxidative stress, thereby preventing the aging phenomenon.

While antioxidant molecules, in order to act, are required to penetrate beyond the stratum corneum to the living epidermis as the site of action, it is preferred that

sunscreen molecules stay on top of the skin for effective radiation absorption and scattering. Therefore, it is desired that a sunscreen product be applied separately, as sunscreen molecules tend to be larger in size or particulate in nature when compared to some components of natural extracts, and may impede the penetration of the smaller plant extracts. However, our market analysis revealed a need by customers for a combination of the two functions in one product, i.e. a moisturizing formulation with Sun Protection Factor (SPF). This is a challenge, because the base of the formulation should have properties that on one hand will enhance penetration of the active antioxidants and on the other retard penetration of sunscreens. This market need is the drive for the exploration of various options of creating the "ideal anti-aging moisturizer with SPF." This effort will serve as a case study that will be described in this chapter.

Sunscreens: An Overview

Sunscreen compounds can be classified into three main categories: physical blocks that reflect UV light (for example, by using titanium dioxide molecules of a size of 200–400 μm), physical (mineral) filters that absorb UV light (for example, by using titanium dioxide in nanoparticle size), and chemical filters that absorb UV light (for example, octyl methoxy cinnamate). **Table 1** outlines these types of sunscreens and their properties.

Table 1. Comparison between physical blocks, physical filters, and chemical filters.

Type of sunscreens	Structure	Function	Advantages	Limitations	Examples
Physical blocks	Mineral molecule of 200-400 μm	Reflect solar radiation	well tolerated effective on UVA and partially UVB	opaque leave a white deposit on skin	titanium dioxide zinc oxide
Physical filters	Mineral molecule at the nano scale 15-100 nm	Absorb solar radiation	no white deposit effective on UVA and UVB	difficult dispersion dryness of skin controversy of nanoparticles	titanium dioxide zinc oxide
Chemical filters	Chemical substance	Absorb one type of wavelength	stable each filter has its own absorption coefficient	can cause allergic reactions can cause photosensitivity combinations of chemical filters may be required	benzophenones PABA Mexoryl (trade name)

Physical blocks

Physical blocks are substances with a particle size of about 200–400 μm that act by reflecting solar radiation. The most commonly used blocks are titanium oxide, zinc oxide, iron oxide, mica, and silica. The last three mentioned are not sunscreens but soft-focus effect powders. When incorporated into a semi-solid formulation at such size, titanium and zinc oxides may generate an opaque appearance on the skin and typically leave an unsightly white deposit. On the other hand, these compounds are very well tolerated by most skin types, since they do not penetrate the skin, and the adverse effects they generate are therefore minimal.

Iron oxide, mica and silica are not sunscreen ingredients. From a regulatory perspective, they are considered cosmetic ingredients or excipients that provide skin coloration or assist in formulation elegancy. However, given their particle size, these compounds act as particulate matters that may reflect and scatter UV radiation[8] although they are not regulatory accepted as active sunscreen ingredients. **Table 2** lists properties of titanium dioxide and zinc oxide.

Table 2. Zinc oxide and Titanium oxide status as sunscreens

International Nomenclature of Cosmetic Ingredient (INCI) name	UVB	UVA	The highest % allowed to use in Europe	The highest % allowed to use in the United States	The highest % allowed to use in Japan	Comments
Titanium dioxide	++	++	25	25	No limit of concentration	In the US, titanium dioxide cannot be mixed with avobenzone. No authorization in Japan as sunscreen use, but as cosmetic ingredient use.
Zinc oxide	++	++	No limit of concentration	25	No limit of concentration	No authorization in Europe and Japan as sunscreen use, but as cosmetic ingredient use.

Physical filters

The most common example of a physical (mineral) filter is titanium oxide, which appears in particle sizes ranging 15–80 nm. These particles absorb both in the UVB and UVA radiation regions. Due to their small size, they do not leave a white deposit upon skin application, an advantage that is appealing to consumers. However, the

small particle size has a large surface area and when incorporated into a formulation, an agglomeration is thermodynamically favored. Dispersing and maintaining the small particle size in the formulation is therefore challenging. Pre-dispersion of the particles to reduce surface tension is generally carried out in liquids that are called "wetting agents" at levels of 40% or 60% to ease the generation of a paste or a suspension. Even when well-dispersed during the manufacturing process, the particles tend to agglomerate over time, creating unevenness of the protective film and thus may dramatically decrease the filter's protection capacity. Furthermore, when agglomerated, a sensation of dryness may occur on the skin.

Chemical filters

Chemical filters are compounds that have one or more aromatic rings which are fixed on the carbonyl groups associated with a substituent donor of electrons and/or unsaturated carbon chains. The chromophore is the part of the molecule that is responsible for the absorption of the radiation energy at certain wavelengths. The absorbed energy moves the molecule from the ground state to an excited state. What follows is either photodegradation or deactivation by emission of radiation of lower energy. The emission can be in the infrared region with generation of heat, in the visible wavelength with appearance of fluorescence, or in the ultraviolet range by isomerization *cis-trans* phenomenon. Then the molecule returns to the energetic ground state. However, the excited state is highly unstable and can generate ROS in the skin by interaction with biological molecules. For this reason the photostability of these filters is of high importance. Chemical filters are characterized by the wavelength at the absorption maximum, and by their absorption coefficient, which is a unit measure of a chemical filter layer's ability to absorb the light radiant energy.

Chemical filters are known to be the cause of allergic contact dermatitis, irritative dermatitis, and photo-sensitivity.[9] Repeated applications may amplify these risks. The filters that most commonly cause such skin reactions include: benzophenones (benzophenone-3 or oxybenzone), butylmethoxydibenzoylmethane, methoxycinnamate, methylbenzylidene-camphre, and aminobenzoic acid. When selecting a sunscreen, not only its effectiveness and safety should be taken into consideration, its regulatory status in the region of marketing interest is also essential. **Table 3** lists the variety of chemical filters and their regulatory status, while **Table 4** lists their advantages and limitations.

Table 3. Overview of chemical filters authorized to use in Europe and/or in the United States and/or in Japan.

INCI name	Example of commercial names	UVB	Short-wave UVA	Long-wave UVA	Max (nm)	EU %	USA %	Japan %
Aminobenzoic acid (PABA)	PABA	++++	+	0	283	5	15	5
Ethylhexyldimethyl PABA	Escalol 507	++++	+	0	311	8	X	10
PEG-25 PABA	Uvinul P 25	++++	+	0	308	10	X	10
Octyl methoxy cinnamate	Parsol MCX	++++	+	0	308	10	7.5	10
Isoamyl p-methoxy cinnamate	Neoheliopan E 1000	++++	+	+/-	308	10	X	10
Homosalate	Filtrasol A	++++	+	0	308	10	15	10
Ethylhexylsalicylate	Escalol 587	++++	+	0	310	5	X	5
Benzylidene camphor		++++	+	0	295	2	X	2
4-methyl benzylidene camphor	Eusolex 6300	++++	+	0	295	4	X	4
Camphor benzalkonium methosulfate	Mexoryl SO	++++	+	0	283	6	X	6
Benzylidene camphor sulfonic acid	Mexoryl SL	++++	+	0	293	6	X	6
Polyacrylomethyl benzylidene camphor	Mexoryl SW	++++	+	0	295	6	X	6
Teraphtalylidene dicamphor sulfonic acid	Mexoryl SX	+	++++	++	345	10	X	10
Phenylbenzimidazole sulfonic acid	Eusolex 232	++++	+	0	310	8	4	8
Bisymidazylate	Neo Heliopan AO	+	++++	+/-	335	10	X	10
Octocrylene	Octocrylene	++++	+	0	303	10	10	10
Butyl methoxydibenzoylmethane	Parsol 1789	0	++	++++	358	5	3	5
Dimethicodiethyl benzalmalonate	Parsol SLX	++++	+	0	310	10	X	10

Benzophenone-3 or oxybenzone	Eusolex 4360 Uvinul M40	+++	+++	0	288 and 329	6	6	10
Benzophenone-4	Uvinul MS40	+++	+++	0	286 and 324	5	10	10
Drometrizole trisiloxane	Mexoryl XL	++++	++++	++	303 and 344	15	X	15
Methylene bis-benzotriazolyl tetramethylbutylphenol	Tinasorb M	++++	++++	++	306 and 348	10	X	10
Ethylhexyl triazone	Uvinul T 150	++++	++	0	312	5	X	X
Diethylhexyl butamido triazone	Uvasorb HEB	++++	++	0	312	10	X	10
Anisotriazine	Tinosorb S	++++	++++	++	310 and 340	10	X	X
Cinoxate		++++	+	0	290	X	3	X
Dioxybenzone		++++	++++	0	284 and 327	X	3	X
Menthyl anthranilate	Neo Heliopan	0	++++	0	336	X	5	5
Octyl dimethyl PABA	Escalol 507	++++	+	0	283	8	8	8
Octyl salicylate		++++	+	0	307	8	5	10
Octyl triazone	Uvinul T-150	++++	+	0	314	X	X	5
Trolamine salicylate		++++	+	0	298	X	12	X

Table 4. Overview of the advantages and limitations of key chemical filters.[10-12]

Note: In the US, FDA regulations state that avobenzone can only be used with cinoxate, dioxybenzone, homosalate, octinoxate, octisalate, octocrylene, oxybenzone, sulisobenzone, and trolamine salicylate.

INCI name	Example of commercial name	Advantages	Limitations
Aminobenzoic acid (PABA)	PABA	excellent absorption coefficient satisfactory stability	maximum of absorption varies with the pH doubtful tolerance allergenic potential
Ethylhexyldimethyl PABA	Escalol 507	excellent absorption coefficient satisfactory stability	not used
PEG-25 PABA	Uvinul P 25	excellent absorption coefficient satisfactory stability hydrosoluble	not used
Octyl methoxy cinnamate	Parsol MCX	high absorption coefficient	imperfect photostability sensitization problems
Isoamyl p-methoxy cinnamate	Neoheliopan E 1000	high absorption coefficient	imperfect photostability sensitization problems
Homosalate	Filtrasol A	very stable well tolerated	low absorption coefficient
Ethylhexylsalicylate	Escalol 587	very stable well tolerated	low absorption coefficient
Benzylidene camphor		table to radiation well tolerated	no UVA protection

4-methyl benzylidene camphor	Eusolex 6300	stable to radiation well tolerated	no UVA protection
Camphor benzalkonium methosulfate	Mexoryl SO	stable to radiation well tolerated	no UVA protection
Benzylidene camphor sulfonic acid	Mexoryl SL	stable to radiation well tolerated	no UVA protection
Polyacrylomethyl benzylidene camphor	Mexoryl SW	stable to radiation well tolerated	no UVA protection
Teraphtalylidene dicamphor sulfonic acid	Mexoryl SX	stable to radiation well tolerated UVA	
Phenylbenzimidazole sulfonic acid	Eusolex 232	hydrosoluble potentiates the action of soluble filters introduced into the oily phase	difficult dissolution
Bisymidazylate	Neo Heliopan AO	UVA low skin penetration	
Octocrylene	Octocrylene	UVB short-wave UVA photostable non-allergenic	low absorption coefficient but is mainly used as a stabilizer
Butyl methoxydibenzoylmethane	Parsol 1789	long-wave UVA high absorption coefficient	very bad stability

Table 4 (Continued). Overview of the advantages and limitations of key chemical filters.[10-12]

Note: In the US, FDA regulations state that avobenzone can only be used with cinoxate, dioxybenzone, homosalate, octinoxate, octisalate, octocrylene, oxybenzone, sulisobenzone, and trolamine salicylate.

INCI name	Example of commercial name	Advantages	Limitations
Dimethicodiethyl benzalmalonate	Parsol SLX	photostable non-allergenic low skin penetration	low absorption coefficient
Benzophenone-3 or oxybenzone	Eusolex 4360 Uvinul M40	UVB short-wave UVA	poor skin tolerance allergenic low absorption coefficient
Benzophenone-4	Uvinul MS40	UVB short-wave UVA	poor skin tolerance low absorption coefficient
Drometrizole trisiloxane	Mexoryl XL	UVB UVA photostable low skin penetration	

Methylene bis-benzotriazolyl tetramethylbutylphenol	Tinasorb M	UVB UVA photostable low skin penetration	
Ethylhexyl triazone	Uvinul T 150	photostable	no UVA protection
Diethylhexyl butamido triazone	Uvasorb HEB	photostable	no UVA protection
Anisotriazine	Tinosorb S	UVB UVA photostable low skin penetration	
Cinoxate		UVB	allergenic
Dioxybenzone		UVB UVA	imperfect photostability
Menthyl anthranilate	Neo Heliopan	short UVA	weak UVB
Octyl dimethyl PABA	Escalol 507	high absorption coefficient stable well tolerated	binds strongly on the skin
Octyl salicylate		UVB	low absorption coefficient
Octyl triazone	Uvinul T-150	UVB	no UVA protection
Trolamine salicylate		UVB	no UVA protection

Formulation Considerations

The formulation of a sunscreen is challenging since it requires tailoring for maximal efficiency, stability, and safety. It must allow the filters to be maintained on the surface of the skin by providing a suitable persistence and effectiveness of protection. For efficacy, several filters of different absorption wavelengths are combined to generate a synergistic effect, thereby decreasing the concentration of each filter. This is done in order to generate spectrum recoveries to obtain sufficient coverage against harmful radiations, and to increase the protection capacity by combining lipophilic filters mixed into the oily phase of the emulsion together with hydrophilic filters mixed into the aqueous phase.[13] This approach leads to a two-phase formulation that offers continuous coverage when applied to skin. For a sunscreen to be effective against erythema, it must contain filters that absorb UVB radiation. Furthermore, protection against UVA radiation is also very important. UVA radiation is responsible for the occurrence of photodermatoses, photoaging,[14] and skin appearance of actinic keratosis,[15] as well as some forms of skin cancer. The FDA requirements are such that a sunscreen that carries the label "broad spectrum" ultimately must provide protection against UVA and UVB radiation alike.[16]

The term "water-resistant" describes a formulation that is not easily washed off by contact with water, which may be achieved by the incorporation of silicone oils, dimethicones, and/or cyclomethicones.

Skin penetration

The penetration of chemical filters beyond the surface of the skin can be enhanced and was shown to be multiplied by a factor of 3 in the presence of erythema for specific compounds and by a factor of 7 on skin affected by strong sunburn. The penetration is multiplied by 1.7 in children and 2.7 by infant.[17] This facilitated penetration in infant and children is due to the fact that the stratum corneum of an infant may not be as strong in its innate immunity when compared to that of an adult. Moreover, since the circulation of infants is lower when compared to that of an adult, any compound that penetrates the blood may exhibit higher toxicity.

The lipophilic character of most of the filters and the size of their chemical structure may allow the adherence to the stratum corneum, but some molecules such as benzophenone-3, octyl-methoxycinnamate and benzylidene camphor are small enough that they can penetrate between corneocytes and then diffuse throughout the different layers of the epidermis.[18,19]

It is of great advantage if a sunscreen remains on the surface of the stratum corneum to ensure its efficacy against UV radiation and safety. Thus, the vehicle should be formulated in a manner that limits penetration of filters as much as possible.

Photostability

Photostability is a property of a single or of a mix of UV filters and is an important factor in ensuring the efficacy of a sunscreen so it is unaltered during sun exposure. If a UV filter is not stable, it may lose its efficacy during UV exposure

and therefore the sunscreen may only partially protect against UV radiation, or lose its effectiveness completely. In 2003, the final draft version about the method for the *in vitro* determination of photostability of UV filters in cosmetic products was approved and published by the European Cosmetic, Toiletry, and Perfumery Association (COLIPA). This method utilizes a simple and reliable *in vitro* model to determine analytically the concentration of UV filters before and after exposure to controlled doses of UV radiation.[20]

Photostability is important because it allows the sunscreen to continue working on the skin for a longer period of time. Most sunscreen users do not reapply the product every two hours as directed, hence increased sunscreen filter longevity is important. A photostable chromophore is one that is not deactivated when exposed to radiation and thus repeatedly available to absorb more photons from the sun. The fundamental goal in maintaining photostability, therefore, is to prevent the excited molecule from acquiring sufficient activation energy during its lifetime to react at a rate competitive with other modes of excited-state deactivation. This goal is accomplished by prompting the excited molecule to deactivate quickly and nondestructively.

Upon UVA exposure, ROS can quickly overload the skin's defense system. In particular, photo-unstable filters may generate exogenous UVA sensitizers. These may contribute to overload of ROS-inducing intermediates that are produced during the photolysis of photo-unstable filters.[21] For example, aminobenzoic acid, octylmethoxycinnamate, butylmethoxydibenzoylmethane (avobenzone) are relatively photo-unstable filters.[22] Octocrylene, for example, may assist in stabilizing avobenzone. For this reason, the combination of sunscreens in the formulation should be evaluated to ensure photostability as well as efficacy of absorbing radiation.

Galenic forms

Sunscreen products can exist in a few galenic forms: sticks, oils, oil-in-water (o/w) emulsions, water-in-oil (w/o) emulsions, creamy gels, and oily sprays. These different forms all have advantages and limitations.

Lipsticks provide protection of the lips. Sticks are one-phase formulations that are composed of a mix of waxes and oily esters combined with photoprotective filters and sunscreens against UVA and UVB. Oily formulations may be based on paraffin oil, synthetic oily esters and/or natural oils (olive, coconut, and sesame). They are lipophilic in nature and are resistant to water. They tend to spread well on the skin's surface due to their fluidity and form very thin protective films. To obtain an SPF of 15, these oils must contain up to 10% chemical filters.

O/W emulsions, such as milks, foams, or creams, impart a reduced oily sensation when applied to skin when compared to oily or w/o formulations. Most of these emulsions contain cationic polymers (such as polyquaternium 35 or polyquaternium 40), which do not impart oily feel. In absence of these polymers, this type of emulsion can be removed with bathing, sweat, and/or friction. The addition of polymers therefore may enhance water resistance of such formulations.[23]

Because of the lipophilic nature of the outer phase of the w/o emulsions that allows even spread of the oily sunscreens, they may have a high power of protection against UV radiation as compared to o/w preparations. Such formulations may also contribute to moisturization due to reduction in transepidermal water loss (TEWL). W/O emulsions are more effective with a higher SPF for the same percentage of sunscreen. In addition, w/o emulsions are preferred in sunscreen products since they are more water-resistant than o/w emulsions. The most commonly used emulsifiers are silicone derivatives or polyglycerols, which yield a stable fluid form; however, they may be less appealing to consumers because they may feel greasy.

Creamy gels are galenic forms that combine gel and fluid emulsion. They are obtained by mixing a small quantity of fatty substances (around 3%) (such as paraffin oil or candelilla wax) with an emulsifier. The presence of these oily compounds slows the natural evaporation of water from the skin and minimizes the drying effect imparted by conventional gels. **Table 5** below summarizes the different galenic forms, their advantages and limitations.

Table 5. Overview of the advantages and limitations of galenic forms.

Galenic forms	Advantages	Limitations	Ideal use
Sticks	against UVA and UVB	some parts of body	for lips
Oils	resistant to water thin protective films	need of high quantity of filters	product of low protection
Oil-in-water emulsions	no greasy feel	can be removed with bathing, sweat, friction	product for face
Water-in-oil emulsions	high power of protection against UV reduction in TEWL	greasy feel	product for body product of high protection
Creamy gels	slows the natural evaporation of water minimizes the drying effect	may be removed with bathing, sweat, friction	product for face product for body

Nanoparticles

Titanium dioxide and zinc oxide in nano size (i.e. 100 nm or less) are often used as UV filters. Their particle size distribution can range 10–100 nm in diameter. When incorporated into sunscreens, these nanoparticles avoid the formation of white and shiny residue typically left on the skin that may be generated when the particles are larger. However, in recent years, there has been a public concern regarding the ability of nanoparticles to penetrate into and through the skin and potentially cause harmful effects. Studies have demonstrated that these particles in most cases remain on the outer layer of the stratum corneum.[24] Whereas the

intercellular penetration of particles seems to be unlikely, the transfollicular route of the skin penetration of nanoparticles may be of significance. In a study observing the penetration of nanoparticles into the hair follicle, it (the follicle) has been shown to act as an important potential long-term reservoir for these particles.[25] The nanoparticles were deposited in the hair follicles for up to 10 days, while the larger particles could be detected only up to 4 days. The movement of the hairs may act as a pumping mechanism pushing the nanoparticles deep into the hair follicles according to the study of Lademann's team.[24] Bronaugh from the FDA claims that selected nanomaterials under certain conditions can penetrate into the hair follicle.[26]

Despite the benefits of sunscreens containing nanomaterials, such as titanium dioxide and zinc oxide, which are said to have a high level of efficacy, there is continuing debate whether they could pose health risks to consumers. The European Union requires that from 2013 onwards, the use of nanoparticles in cosmetic products be explicitly declared on product packaging and listed as a part of the ingredients. In the list of ingredients, the substances will be followed by the word "nano" in brackets—e.g. *titanium dioxide (nano)*. Preclinical toxicological evaluations in humans have shown that nanoparticles of titanium dioxide are nontoxic, non-irritating, non-sensitizing, non-photo-sensitizing, and do not cause side effects after repeated applications on the skin of both animals and humans.[27,28] Still, there might be a potential risk if nanoparticles penetrate the body barriers resulting in their ability to modify the immune system (may act as a hapten and facilitate autoimmune diseases), their ability to form complexes with proteins, and especially their ability to create, under irradiation, free radicals that can lead to DNA damage.[29]

The potential risks of dermal absorption, oral absorption (lipstick), and respiratory intake cannot be overlooked in the use of sprays. In addition, the penetration may be accelerated when applied to irritated, wounded, or broken skin. Further studies are necessary to assess the potential penetration in damaged skin, the effect of sun exposure on the penetration, and the future of ROS formed in the stratum corneum from these nanoparticles exposed to UV.

Incorporation of antioxidants

As the largest outer organ of the body, the skin is constantly insulted by environmental challenges, notably UV radiation.[5] Within the skin, production of free radicals is induced by UV radiation and causes damage to DNA and proteins. This damage destabilizes the membranes of skin cells, leading to premature aging. When free radicals are generated, natural antioxidants in the skin are activated to combat and attenuate the damage. Antioxidants inhibit the production of free radicals by direct scavenging or by decreasing the amount of oxidants in and around the cells. This prevents free radicals from reaching their biological targets, and thwarts oxidative stress, thereby slowing the advancement of aging.[30]

Vitamin E is the most powerful known lipo-soluble antioxidant. It inhibits the peroxidation of lipid components in the cellular membrane. It reacts with free radicals

to form the radical tocopheryl, a stable substance that attenuates the oxidative chain reaction of membrane lipids. It acts in conjunction with the hydrophilic vitamin C. Vitamin C is a water-soluble vitamin and has a strong antioxidant activity that protects cells against free radical damage.

Plants contain multiple antioxidants (named phyto-antioxidants), components which act effectively in synergy within the plant. These combinations are capable of protecting both the plant cells and the extracellular matrix against oxidative stress induced by UV radiation. For example, green tea contains four major flavonoids that exhibit the ability to scavenge free radicals. Katiyar et al. have shown that epigallocatechin from green tea leaves applied topically on mouse skin exposed to UVB inhibits the production of hydrogen peroxide both in the dermis and in the epidermis.[31] Another example is blueberries, which contain antioxidants and are even claimed to be "the most powerful antioxidants of all."[32] Quercetin and myricetin, two flavonoids found in blueberries, exhibit iron chelating properties, meaning that they minimize the formation of free radicals stimulated by excess free iron and UV radiation.[21]

Furthermore, the use of antioxidants contributes significantly to the photostability of chemical filters, and may act as "SPF boosters," elevating the SPF value of the formulation by mitigating redress. When first introduced into the industry, SPF boosters were emollients that effectively dissolved ultraviolet filters that were crystalline rather than liquid. These compounds also affected the UV absorbing patterns and provided better skin coverage, which was translated into improved SPF numbers. These SPF boosters improve the photostability of UVA filters in the same manner as octinoxate improves the photostability of avobenzone.

Plants, due to the nature of their habitats, are challenged by oxidative stress induced by UV radiation, but cannot protect themselves as humans do by exogenous artificial means such as clothing or screens. They have therefore developed multiple strategies and highly effective molecules such as phyto-antioxidants and detoxifying enzymes to defend themselves against environmental stress. For example, the edelweiss plant has developed a layer of filamentary hair which covers the bracts surrounding the flowerheads and the entire aerial part of the plant. This fleece prevents dehydration and shields the plant against cold, but also shields the covered living cells from harmful UV radiation. This protection is not obtained by reflection but rather by absorption within the protective layer.[33] Another example is the Antarctic lichen plant, which contains natural filters called usnic acid for protection against UVB radiation.[34]

Review of market available facial moisturizers with SPF

An essential aspect of any successful formulation development is market research of the competition. Reviewing the competing products, competitor price points, as well as overall competitor messaging and branding surrounding specific products is always enlightening. **Table 6** lists some examples of leading industry facial moisturizers with SPF, looking specifically at their properties and compositions.

Table 6. Example of facial moisturizers with SPF.

Brand	Name of moisturizer with SPF	Image	SPF	Physical blocks	Chemical filters
Avon	Anew platinum day cream		25	X	Octinoxate 7.5% Octisalate 4.75% Oxybenzone 4% Avobenzone 2.85%
Benefit	Triple performing facial emulsion		15	X	Octinoxate 7.5% Avobenzone 3% Octocrylene 2% Benzophenone-4 1.5%
Clinique	Age defense moisturizer-Superdefense – Combination oily to oily		25	X	Octisalate 8% Oxybenzone 5% Avobenzone 3%-Octocrylene 1.3%
Clinique	Youth surge – age decelerating moisturizer – dry combination		15	Titanium dioxide 1.2%	Octinoxate 7.5% Octisalate 3.5%
Elizabeth Arden	Time complex moisture cream - Ceramide		15	X	Octylmethoxycinnamate 6%

Table 6 (Continued). Example of facial moisturizers with SPF.

Brand	Name of moisturizer with SPF	Image	SPF	Physical blocks	Chemical filters
Estée Lauder	Advanced multi-protection antioxidant crème oil free		25	X	Octisalate 5% Avobenzone 3% Octocrylene 2.7%
Estée Lauder	Sheer Tint Release Advanced multi-protection antioxidant moisturizer		15	X	Octisalate 5%
Juice Beauty	Mineral Sheer Moisturizer		30	Titanium dioxide 10%	X
Kinerase	Cream		15	X	Avobenzone 3% Octocrylene 8% Oxybenzone 4%

La Prairie	Anti-aging day cream		30	X	Avobenzone 3% Octinoxate 7.5% Octisalate 5% Octocrylene 2.5%
Murad	Oil-control mattifier		15	Zinc oxide 3%	Phenylbenzimidazole sulfonic acid 1% Octinoxate 7.5%
Nu Skin	Radiant Day - Ageloc		22	Titanium dioxide	Avobenzone 3% Homosalate 5% Octisalate 4% Octocrylene 2%
Olay	All day moisture cream		15	Zinc oxide 3%	Octinoxate 6%
Paula's Choice	Daily Moisturizing Lotion – Skin recovery		15	Titanium dioxide 3.85% Zinc oxide 3%	X

Table 6 (Continued). Example of facial moisturizers with SPF.

Brand	Name of moisturizer with SPF	Image	SPF	Physical blocks	Chemical filters
Paula's Choice	Daily Restoring Complex – Moisture Boost		20	Titanium dioxide	Homosalate 4% Octisalate 4% Oxybenzone 3% Avobenzone 3% Octocrylene 2%
Sephora	Perfecting Tinted Moisturizer		20	X	Octinoxate 7.5% Octisalate 5% Avobenzone 3%
Stila	Tinted moisturizer		15	X	Octinoxate 4% Avobenzone 2%
Stila	Oil-free sheer color tinted moisturizer		30	Zinc oxide 5%	Octinoxate 7.5% Oxybezone 4%

Table 6 shows that many combinations are possible to obtain protection ranging from SPF 15 to SPF 30 (medium to high protection). Generally, these day creams contain either chemical filters or physical screens, rarely both. This fact is due to FDA regulations that do not allow certain combinations of chemical and physical filters in the same sunscreen, such as titanium dioxide and avobenzone, for example, per 21 CFR Part 352.

Summary: Our Final Formulation

This chapter outlines the steps taken into consideration in the development of an anti-aging moisturizer with SPF to meet the expectations and needs of our consumers and regulatory agencies.[35] Feedback from consumers revealed a need for a light cream that will not stick to the skin, will moisturize without leaving a greasy residue, and absorb quickly, thus making it easy to layer makeup. This cream should also attenuate the appearance of wrinkles and provide protection against environmental stress, including UV radiation. Daily sunscreen use has been demonstrated to prevent squamous cell skin carcinoma in a community-based randomized controlled trial.[36]

As we put the final touches on this chapter, our formulation is in its final stages of production. Our formulation is designed to provide protection with an SPF of 20–25 to allow the use of modest amounts of filters to prevent potential adverse effects. Consumers will be instructed to apply the cream several times a day rather than applying a cream with a higher SPF once per day. Indeed, a study by Dupuy et al. showed that consumers use more cream when the cream has a medium protection when compared to a high protection formulation. In this study, the amount of sunscreen of SPF 12 applied actually approached 2 mg/cm2, namely the quantity used to define the SPF labeled on the packaging, whereas the amount of sunscreen of SPF 40 did not.[37]

We had initially chosen to formulate our cream with a combination of physical blocks of microparticular size (to avoid controversial nanoparticles) and chemical filters, to provide protection against both UVA and UVB. The choice of combination rather than an exclusive use of a physical screen at high concentration are driven by the elegance of the formulation. Indeed, for a cosmetic product to be effective, it needs to be used and applied. Customer feedback indicates that if the cream leaves an unsightly white deposit, it will not be used.

Initially the following combination was selected:

- Titanium dioxide, of microparticular size for UVA and UVB protection
- Avobenzone, for UVA protection
- Homosalate, for UVB protection, better tolerated and more stable than octinoxate
- Octocrylene to stabilize avobenzone.

This is where the market for distribution becomes a key consideration in the development. Indeed, this product will be launched in two continents: the United States and Europe, and as such needs to comply with the regulations of both. In the United States, titanium dioxide and avobenzone cannot be combined, per 21 CFR Part 352. We thus had to rethink our formulation, and replaced titanium dioxide with octylmethoxycinnamate as the ingredient to protect against UVB.

To promote anti-aging skin benefits and ensure the stability of the formulation, we added antioxidants that exhibit known synergistic activity to the formulation. Vitamins C and E protect against the oxidation of chemical filters and are among the best synthetic antioxidants on the market. We also added a plant extract containing a multitude of antioxidant molecules that exhibit a variety of actions to protect the skin: bilberry extract in glycerin. Bilberry also has anti-redness properties that are ideal for sensitive skin. Plant extraction with glycerin further contributes to microbial stability due to the bacteriostatic effect of glycerin, and can be easily incorporated into the formulation due to its miscibility with water. To complete antioxidant protection and protection against UV radiation, we incorporated the leaf extract of edelweiss, which naturally reflects UV radiation.

To promote skin moisturization, the formulation contains compounds that create a film on the stratum corneum and reduce TEWL. Glycerin in normal conditions of relative humidity is an excellent humectant that is able to bind spontaneously to 10% water and impart smoothing effects to the skin surface that may persist for at least 24 hours.[38] Hyaluronic acid, a Natural Moisturizing Factor (NMF) found in the extracellular matrix of the dermis, has a high water retention capacity similar to that of another NMF, chondroitin sulfates.

The pH for this formulation is 5.0–6.0, thus preservatives effective at this pH range were incorporated.

In its final form, our moisturizing day cream with sun protection is light on the skin, absorbs quickly, and will not leave a white residue. In addition to providing a combination of chemical filter protections against UVA and UVB, antioxidants such as Vitamins C and E as well as bilberry and edelweiss extracts enable this day cream with SPF to provide protection to the interior of the stratum corneum. Customers will appreciate the cream's light feel and mix of protection against UV rays. This, in combination with the cream's pleasant scent, will provide an effective solution to UV protection while working to prevent and repair signs of skin aging.

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GLOSSARY OF TERMS, BY CHAPTER

The following glossary of terms is offered as a reflection of the key words as noted in the respective chapters of this book. Note that the terms are defined as they are applied/discussed in the chapters, and therefore any potential redundancy or disparity is noted and has been allowed for the sake of completeness.

Chapter 1

Emulsion Oil-in-Water: A mixture of two or more liquids that are normally immiscible (non-mixable or un-blendable), should be used when both the dispersed and the continuous phase are liquids. In an emulsion, one liquid (the dispersed phase) is dispersed in the other (the continuous phase). Two liquids can form different types of emulsions. As an example, oil and water can form, firstly, an oil-in-water emulsion, where the oil is the dispersed phase, and water is the dispersion medium.

Emulsion Water-in-Oil: Water is the dispersed phase and oil is the external phase.

Emulsifiers Quaternary: Emulsifying agents that carry a positive charge on their molecule. They are frequently used as conditioning agents and in fabric softeners.

Formulation Design: An organized pre-formulation plan. It is a strategy that describes the rationale for a new product, how it will be created, and describes the benefits it will provide to the person who will purchase the product.

Global Intellectual Property: A group of laws that protect innovative products through patents, copyrights, and trademarks. Intellectual property is intended to protect creative expression and permit inventors the ability to benefit from their innovation. The laws protecting intellectual property may differ depending upon the region of the world.

Marker Compounds: Single well-characterized chemical components in botanicals that may be used as potency standards and to assist in identification of the botanical.

Oil-in-Water (octanol) Partition Coefficient: A pure substance may distribute between two solvent partially miscible phases. The equilibrium ratio of solute concentrations in the two phases is known as the partition coefficient. The biological activity of simple organic compounds was found to correlate with their oil-in-water partition coefficient.

Over The Counter (OTC) Drugs: Medicines that may be sold directly to a consumer without a prescription from a health care professional.

Surfactant (Amphoteric): A surface active agent where the charge on the hydrophilic part is controlled by the pH of the solution.

Surfactant (Anionic): A surface active agent where the hydrophilic part of the surfactant consists of a negatively charged group

Surfactant (Cationic): A surface active agent where the hydrophilic part is positively charged group.

Tyrosinase: A rate limiting enzyme for controlling the production of melanin that is responsible for skin pigmentation.

Chapter 2:

Hydrated: Chemically combined with water in its molecular form.

Hydrophilic: Having an affinity for water; readily absorbing or dissolving in water.

Hydrophobic: Repelling, tending not to combine with, or incapable of dissolving in water.

Lipophilic: Refers to the ability of a chemical compound to dissolve in fats, oils, lipids, and non-polar solvents.

pH: A measure of the activity of the (solvated) hydrogen ion.

Sensory: Of, or pertaining to, the senses or sensation. Tactile properties of touch and impulse of nerve endings in the skin and touch of hand.

Surface active: Polymer which demonstrates enhanced surface activity and performance properties

Stabilize: To make or hold stable, firm, or steadfast. To maintain at a given level or quantity, keep in equilibrium.

Translucent: Permitting light to pass through, but diffusing it so that objects on the opposite side are not clearly visible.

Chapter 3

Acne vulgaris: An inflammatory disease of the sebaceous glands characterized by pimples and comedones.

Comedones: A plug of keratin and sebum within the hair follicle that is blackened at the surface.

Cytokine: A class of immunoregulatory proteins secreted by cells especially of the immune system.

Delivery systems: A means to transport the functional ingredient to its site of action.

Exfoliator: A process of removing a layer of skin.

Follicular-sebaceous unit: A three-dimensional block of skin comprised of the tubular cavity that contains the root of hair and microscopic glands that secrete sebum.

Functional ingredient: A substance that provides a benefit.

Inflammation: A biological response to initiate healing and remove injurious stimuli characterized by swelling, heat, redness and pain.

Nodules: A severe form of acne characterized by numerous, deep inflamed bumps on skin.

Papule: A solid, raised skin lesion up to 0.5 cm width.

Pustule: An inflamed acne lesion presenting as a red bump with whitehead consisting of pus, oil, and cell debris.

Sebum: An oily secretion of sebaceous glands that keeps the skin and hair moisturized.

Sub-micron spheres: Three-dimensional particles with dimensions (diameter) smaller that 1 micron.

Topical: Directly applicable to the skin or mucous membranes.

Chapter 4

Alkylmethylsiloxane: A siloxane polymer where the organic groups are a mixture of methyl groups and longer chain alkyl (hydrocarbon) groups.

Cyclomethicone: A family of volatile cyclic dimethyl siloxanes where the number of dimethyl siloxane units in the ring range from four to six. Each particular cyclomethicone also has been assigned a specific INCI name. **Cyclotetrasiloxane** has four dimethyl siloxane units in the ring, **Cyclopentasiloxane** has five dimethyl siloxane unts, and **Cyclohexasiloxane** has six.

INCI Name: International Nomenclature for Cosmetic Ingredients (INCI) names are names for cosmetic ingredients that were created for the purpose of labeling on cosmetic packaging.

Polydimethylsiloxane (PDMS): A siloxane polymer that has the general formula $-[(CH_3)_2SiO]_x-$. The ends of the polymer can be capped with various groups. When the end-capping groups are methyl, the silicone polymers are called **Dimethicone** in the INCI nomenclature system. Then the ends of the PDMS polymer are hydroxyl groups, the polymers have the INCI name **Dimethiconol**.

Silicone: A generic term for siloxane polymers, a large class of synthetic materials that are based on a backbone of alternating silicon and oxygen atoms. The most common type of silicones are based on dimethyl polysiloxanes, where each silicon atom has two methyl substituents.

Silicone Elastomer: A cross-linked siloxane polymer. Silicone elastomers used in skin care applications are dimethyl siloxane polymers that have been cross-linked by the reaction of vinyl groups with silicon hydride groups. Silicone elastomers are solids where the hardness depends upon the degree of cross-linking.

Silicone Polyether: A siloxane polymer, typically a dimethyl siloxane polymer, where some of the methyl groups have been replaced by polyethylene glycol (PEG) or polypropylene glycol (PPG) chains. An example of a silicone polyether is **PEG-12 Dimethicone,** which has PEG side chains with an average of 12 PEG units.

Siloxane: Siloxanes are a class of chemical compounds based on silicon and oxygen in alternating sequence. Each silicon atom also has from one to three organic substituents. Common substituents are methyl, phenyl, aminopropyl, and polyether (polyalkylene oxides). Siloxanes are often linear polymers that have the general formula $-(R_2SiO)_x-$.

Silsesquioxane: A type of siloxane that has a complex three-dimensional structure and is often referred to as a silicone resin. Silsesquioxanes have the general formula $(RSiO_{3/2})_x$ where R is an organic substituent such as methyl or phenyl. The "3/2" or 1.5 designation on the oxygen in the general formula indicates that each silicon atom has three oxygen atoms that are shared with another silicon atom in the silsesquioxane.

Chapter 5

Corn wet-milling process: Continuous process that separates the corn kernel into its many components

Hydrolyzed corn starch: Corn starch that has undergone enzymatic or chemical hydrolysis, resulting in shorter chained saccharides.

Modified corn starch: Corn starch that has either been physically, chemically or enzymatically altered for a specific functionality

***Zea mays* (corn) starch:** Unmodified corn starch derived from the corn wet-milling process

Chapter 6

Emulsion: A heterogenous system in which two or more immiscible liquids or semi-solid materials are dispersed in another liquid in discrete droplets. The dispersed materials represent the dispersed or internal phase, while the remaining components for the continuous or external phase.

Sensorial analysis: The organoleptic properties of a skin care product as they are sensed by a consumer. Normally, comprehensive consumer studies and panel tests are carried out to determine the acceptance of a product based on its sensorial appeal.

Textural attributes: Properties of a skin care product dealing with its structure, which includes firmness, compressibility, shape, tackiness, spreadability, cohesiveness, resilience, and elasticity.

Texture profile analysis: A method to quantitatively describe the textural properties of foods and skin care products.

Chapter 7

Elastic Solids: A feature of compressed emulsions.

High Internal Phase Water in Oil Emulsions (HIPEs): A water-in-oil emulsion that contains in excess of 70% water in the internal phase.

Polyhedral: Each flat surface (or "face") is a polygon.

Chapter 8

Body of Knowledge: The sum of technical and practical information acquired by past experience with similar products.

Control Strategy: The collection of critical quality attributes identified by process risk assessment and the analytical methodology employed to monitor them.

Critical Process Parameter (CPP): A process parameter that is known to or expected to affect the critical quality attributes of a process intermediate or finished product.

Critical Material Parameter (CMP): A raw material attribute that is known or expected to affect the critical quality attributes of a process intermediate or finished product.

Critical Quality Attribute (CQA): A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

cGMP: Current Good Manufacturing Practices, as defined by 21 CFR 210 and 211: cGMP in Manufacturing, Processing, Packing, or Holding of Drugs and Finished Pharmaceuticals.

Design of Experiments (DoE): Statistically based design of process trials or experiments intended to efficiently and clearly elucidate the effects of selected process inputs on measured or observed outputs.

Design Space: The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

FMECA: Failure Modes Effects and Criticality Analysis. An extension of FMEA, FMECA is a product development methodology of analyzing failure modes including their severity and probability; criticality element charts the severity of consequences versus probability of occurrence for each failure mode, allowing risk mitigation resources to be focused in areas with the greatest return.

Passivation: Chemical surface treatment typically applied to a metal surface such as stainless steel to provide a corrosion resistant layer.

Pharmaceutical Inspection Convention: Also known as called "The Convention for the Mutual Recognition of Inspections in Respect of the Manufacture of Pharmaceutical Products," this multinational organization was formed to streamline and harmonize the compliance inspection process across different markets and countries.

Process Characterization: General term describing the sum total of all techniques used to gain knowledge of a process, including but not limited to prior body of knowledge, process experimentation, and theoretical modeling.

Process Map: A graphical representation of a manufacturing process subdivided by unit operation in order to create manageable areas of focus; includes process parameters and boundaries to ensure risk assessment and control strategy is comprehensive and appropriate.

Process Validation: Data-driven demonstration through repetition that a process is robust and consistently produces product with the desired critical quality attributes.

Quality by Design (QbD): A systematic approach to process development which starts with a set of predetermined objectives (QTPP) and emphasizes product and process understanding as well as process control, based on good science and appropriate risk management.

Quality Target Product Profile (QTPP): A prospective summary of critical quality attributes which define a safe and effective finished product. The QTPP can be viewed as a subset of the more high-level and qualitative TPP.

Risk Management: The identification, analysis, assessment of risk, followed by control strategy involving mitigation or acceptance or a combination thereof. Applies to process design by providing a framework within which a control strategy is developed to ensure critical quality attributes are satisfied.

Scale-up: Scale-up is generally defined as increasing the size of a batch of product. For mixing steps, this generally involves a larger vessel with a greater mass of product; for a filling operation, such as with tubes or pumps, scale-up may simply mean an increase in throughput by faster and/or more efficient filling and packaging equipment and processes.

Target Product Profile (TPP): Not to be confused with Quality Target Product Profile, the Target Product Profile is the embodiment of the desired use, effectiveness, and safety of the product, or essentially the desired content of the product labeling; sometimes viewed as the "user interface" of a product. The TPP is generally driven top-down by strategic, marketing forces which have identified a business need or opportunity.

Technology Transfer: The transfer of the entire body of technical knowledge associated with the development of a product, to another entity which requires that knowledge. May involve transfer of a manufacturing process from one scale to another, or may involve transfer of an established process from one manufacturing site to another.

Chapter 9

Aqueous Foam: A foam wherein the primary component of the PFF is water.

Foam: In the context of topical treatment, a foamed formulation which comprises a mass of bubbles of air or gas in a matrix of foamable semisolid or liquid PFF.

Foam adjuvant: An agent which assist the surfactants in stabilizing the emulsion and forming a stable foam. Foam adjuvants are selected from the variety of fatty alcohols and fatty acids.

Hydroethanolic Foam: A foam wherein the primary components of the PFF are water and ethanol.

Hydrophilic Emulsion Foam: A foam wherein the PFF is an oil in water (o/w) emulsion.

Hydrophilic Ointment Foam: A foam, wherein the primary components of the PFF are hydrophilic organic solvents.

Humectant: A substance that promotes retention of moisture in the skin and retains skin hydration.

Lipophilic Emulsion Foam: A foam wherein the PFF is a water in oil (w/o) emulsion.

Nanoemulsion Foam: A foam wherein the PFF is a nanoemulsion or a microemulsion.

Oil Foam: A foam wherein the primary component of the PFF is liquid oil.

Ointment Foam: A foam wherein the primary component of the PFF is petrolatum.

PFF (pre-foam formulation): A foamable formulation which is prepared prior to filling into an aerosol can and pressurizing with a propellant.

Potent-Solvent Foam: A foam wherein the primary component of the PFF are solvents, having high solubilization capacity.

Propellant: A liquefied or compressed gas, intended to pressurize an aerosol product. Common propellants comprise hydrocarbon mixtures, e.g., n-butane, isobutane, and n-propane. Additional propellants are fluorocarbon propellants, such as 1,1,1,2 tetrafluorethane and 1,1,1,2,3,3,3 heptafluoropropane.

Saccharide Foam: A foam wherein the primary component of the PFF is a saccharide.

Suspension Foam: A foam wherein the PFF comprises a suspended active agent.

Chapter 10

Alias: When the estimate of an effect also includes the influence of one or more other effects (usually high order interactions) the effects are said to be *aliased* (see *confounding*). For example, if the estimate of effect D in a four factor experiment actually estimates (D + ABC), then the main effect D is aliased with the 3-way interaction ABC.

Analysis of Variance (ANOVA): A mathematical process for separating the variability of a group of observations into assignable causes and setting up various significance tests.

Blocking: A schedule for conducting treatment combinations in an experimental study such that any effects on the experimental results due to a known change in raw materials, operators, or machines become concentrated in the levels of the blocking variable. Note: The reason for blocking is to isolate a systematic effect and prevent it from obscuring the main effects. Blocking is achieved by restricting randomization.

Center Points: Points at the center value of all factor ranges.

Coding Factor Levels: Transforming the scale of measurement for a factor so that the high value becomes +1 and the low value becomes -1 (see *scaling*). After coding all factors in a 2-level full factorial experiment, the design matrix has all orthogonal columns.

Comparative Designs: A design aimed at making conclusions about one a priori important factor, possibly in the presence of one or more other "nuisance" factors.

Confounding: A confounding design is one where some treatment effects (main or interactions) are estimated by the same linear combination of the experimental observations as some blocking effects. In this case, the treatment effect and the blocking effect are said to be *confounded*. Confounding is also used as a general term to indicate that the value of a main effect estimate comes from both the main effect itself and also contamination or bias from higher order interactions. Note: Confounding designs naturally arise when full factorial designs have to be

run in blocks and the block size is smaller than the number of different treatment combinations. They also occur whenever a fractional factorial design is chosen instead of a full factorial design.

Design: A set of experimental runs which allows you to fit a particular model and estimate your desired effects.

Effect: How changing the setting of a factor changes the response. The effect of a single factor is also called a *main effect*. **Note:** For a factor A with two levels, scaled so that low = -1 and high = +1, the effect of A is estimated by subtracting the average response when A is -1 from the average response when A = +1 and dividing the result by 2 (division by 2 is needed because the -1 level is 2 scaled units away from the +1 level).

Error: Unexplained variation in a collection of observations. Note: DOEs typically require understanding of both random error and lack of fit error.

Factors: *Process inputs* an investigator manipulates to cause a change in the output. Some factors cannot be controlled by the experimenter but may effect the responses. If their effect is significant, these *uncontrolled factors* should be measured and used in the data analysis. Note: The inputs can be discrete or continuous.

Fixed Effect: An effect associated with an input variable that has a limited number of levels or in which only a limited number of levels are of interest to the experimenter.

Interactions: Occurs when the effect of one factor on a response depends on the level of another factor(s).

Lack of Fit Error: Error that occurs when the analysis omits one or more important terms or factors from the process model. Note: Including replication in a DOE allows separation of experimental error into its components: lack of fit and random (pure) error.

Model: Mathematical relationship which relates changes in a given response to changes in one or more factors.

Orthogonality: Two vectors of the same length are orthogonal if the sum of the products of their corresponding elements is 0. Note: An experimental design is orthogonal if the effects of any factor balance out (sum to zero) across the effects of the other factors.

Random Effect: An effect associated with input variables chosen at random from a population having a large or infinite number of possible values.

Random Error: Error that occurs due to natural variation in the process. Note: Random error is typically assumed to be normally distributed with zero mean and a constant variance. Random error is also called experimental error.

Randomization: A schedule for allocating treatment material and for conducting treatment combinations in a DOE such that the conditions in one run neither depend on the conditions of the previous run nor predict the conditions in the subsequent runs. Note: The importance of randomization cannot be over stressed. Randomization is necessary for conclusions drawn from the experiment to be correct, unambiguous and defensible.

Replication: Performing the same treatment combination more than once. Note: Including replication allows an estimate of the random error independent of any lack of fit error.

Resolution: A term which describes the degree to which estimated main effects are aliased (or confounded) with estimated two-level interactions, three-level interactions, etc. In general, the resolution of a design is one more than the smallest order interaction that some main effect is confounded (aliased) with. If some main effects are confounded with some two-level interactions, the resolution is 3. Note: Full factorial designs have no confounding and are said to have resolution infinity. For most practical purposes, a resolution 5 design is excellent and a resolution 4 design may be adequate. Resolution 3 designs are useful as economical screening designs.

Responses: The output(s) of a process. Sometimes called dependent variable(s).

Response Surface Designs: A DOE that fully explores the process window and models the responses. Note: These designs are most effective when there are less than 5 factors. Quadratic models are used for response surface designs and at least three levels of every factor are needed in the design.

Scaling Factor Levels: Transforming factor levels so that the high value becomes +1 and the low value becomes -1.

Screening Designs: A DOE that identifies which of many factors have a significant effect on the response. Note: Typically screening designs have more than 5 factors.

Treatment: A treatment is a specific combination of factor levels whose effect is to be compared with other treatments.

Treatment Combination: The combination of the settings of several factors in a given experimental trial. Also known as a *run*.

Chapter 11

Complex Modulus: The mathematical representation of the sum of the elastic part (Storage Modulus) and the flow part (Loss Modulus) of the viscoelastic behavior of the system

Compliance: The strain divided by the stress.

Creep/Recovery: The deformation of a fluid system under an external force, usually under a constant stress, as a function of time, followed by the removal of the external force and monitoring the recovery as a function of time.

Dilatant Flow: A flow showing an increase in viscosity as a function of shear rate; shear thickening.

Dynamic viscosity: Generally describes the absolute viscosity as the stress over shear rate at any given shear rate. In rheology terms, it is the part of the viscosity calculated from the viscoelastic properties of the system (loss modulus over the frequency).

Flow: The deformation of the material under an external force, in which at least part of the energy is lost.

Flow curve: A curve showing the rheological profile of the system, relating shear stress to shear rate or viscosity to shear rate

Flow models: Mathematical equations describing the flow of the system and the elements that contribute to the flow

Frequency sweep: A test measuring the dynamic properties of the system (loss Modulus, storage modulus, dynamic viscosity) as a function of frequency at a constant strain.

Kinematic Viscosity: The viscosity of Newtonian fluids divided by the density of the fluid

Loss Modulus (G"): The imaginary part of the complex modulus representing the flow part of the viscoelastic behavior of the system

Modulus: The stress divided by the strain. A measure of the "stiffness" of the system.

Newtonian Fluid: A fluid in which the ratio between the shear stress and the shear rate is constant (i.e., the viscosity is independent of the shear rate).

Non-Newtonian Fluid: A fluid in which the ratio between the shear stress and the shear rate changes with changes in the shear rate (i.e., the viscosity is dependent on the shear rate).

Oscillatory mode: Operation of a rheometer while the fixture is oscillating at a pre-determined strain or frequency.

Pseudoplastic Flow: A flow showing a decrease in viscosity as a function of shear rate; shear thinning.

Plastic Flow: A flow showing a decrease in viscosity as a function of shear rate while retaining its shape for a period of time until a certain stress (yield value) is achieved; shear thinning with a yield value.

Rheological Additive (Thickener): Also known as rheology modifier, the material that changes the rheological behavior of the system, usually used in small quantities.

Rheology: The scientific field that studies how materials flow and deform under the influence of external forces.

Rheometer: An instrument that measures the rheological properties of the system.

Rotational mode: Operation of a rheometer while the fixture is rotating at a pre-determined stress or shear rate.

Shear Rate: The change in the shear strain as a function of time.

Shear Stress: The force applied on the system per unit area.

Shear thickening: The increase in viscosity as a function of increasing shear stress.

Shear thinning: The decrease in viscosity as a function of increasing shear stress.

Storage Modulus (G'): The real part of the complex modulus representing the elastic part of the viscoelastic behavior of the system.

Strain sweep: A test measuring the dynamic properties of the system as a function of strain at a pre-determined frequency.

Thickening mechanism: The mechanism describing the interactions of the rheological additive(s) and the other ingredients in the formulation as they build the three-dimensional structure.

Thixotropy: The ability of the system to exhibit lower viscosity as a function of increasing shear rate and to recover its structure over a period of time when the external force is removed.

Viscoelasticity: The combination of both viscous (flowing) and elastic characteristics of the material.

Viscometer: An instrument measuring the viscosity of the material.

Viscosity: The resistance of the material to flow. The shear stress divided by the shear rate. The viscosity is constant for Non-Newtonian fluids.

Yield Value: The minimum stress that is required to induce flow.

Chapter 12

Flow curve: Curve showing the viscosity at different shear rates.

Kinematic viscosity: Ratio of viscosity to fluid density.

Newtonian fluid: Fluid for which the viscosity does not change with applied shear rate.

Non-Newtonian fluid: Fluid for which the viscosity is not independent of shear rate.

Pascal (Pa): Units of stress.

Poise (P): Units of viscosity.

Rheology: Science that describes the flow and deformation of materials.

Shear strain: Ratio of deformation to the gap between two parallel planes sliding across each other.

Shear rate: Rate of change of shear strain.

Shear stress: Ratio of shear force applied to the area of the plate.

Shear thinning: Decrease in viscosity as shear rate increases.

Spindle: Rods supplied by Brookfield for the measurement of viscosity.

Stoke (St): Units of kinematic viscosity.

Thixotropy: Change in viscosity with time under shear.

Viscometer: Instrument used to measure viscosity.

Viscosity: Resistance to flow, defined as the ratio of shear stress to shear rate.

Yield value: Stress below which no flow occurs.

Chapter 13

Active Distribution: The spatial distribution of a specific chemical species within a formulation.

Fourier Transform Infrared Spectroscopy (FTIR): Refers to the fact that a Fourier transform is required to convert the raw data into a spectrum.

Formulation: A mixture of specific materials combined together according to a specific procedure.

Imaging: A visual image off the distribution of components generated from the simultaneous measurement of spectra and spatial information.

Spectroscopy: The study of the interaction between matter and light.

Chapter 14

Aesthetics: An artistically beautiful or pleasing appearance.

Consumer appeal: Possessing qualities which generate interest and excitement with potential purchasers.

Cosmetic formulations: Topical preparations made up of a complex combination of cosmetic ingredients and (typically) water.

Creams: A viscous skin treatment, generally an emulsion.

Emollients: A generally water-insoluble agent that softens or smoothes the skin.

Emulsifiers: A chemical agent allowing insoluble liquid materials, such as oils and water, to peacefully coexist.

Facial care: Creams and lotions intended for the face, usually imparting benefits in appearance and protection to the skin.

Lotions: A fluid skin treatment, generally an emulsion.

Skin care: The application of topical products to the face, hands, or body for beautification and therapeutic effect, often also eliciting an emotional response.

Skin feel: Tactile aspect of a topical formulation, pertaining to the initial touch, application, and post-application sensation of the formulation and the skin.

Topical formulations: Product applied to the skin, whether a cosmetic or drug.

Chapter 15

Aroma chemicals: Chemicals used in fragrance creation that are made synthetically.

Aromascience: The study of temporary effects on emotions via olfactory pathways.

Controlled release: Methods to capture, protect, and release fragrance.

Fragrance: A combination of natural and synthetic products designed to have a pleasant scent.

Fragrance translation: Modifying a fragrance to maintain its olfactive character in different functional products

Malodor: An unpleasant or offensive smell.

Natural fragrance material: Materials usually of plant origin used in fragrance creation.

Regulations: Laws which govern the safety of fragrances in commerce.

Stability: Maintaining product integrity over time under typical storage and use conditions.

Terpenes: A large family of natural fragrance materials created by head to tail polymerization of isoprene.

Chapter 16

Accelerated Testing Conditions: Accelerated testing employs aggressive environment stress factors such as temperature, moisture or humidity, light, gravitational force, vibrational force, and in less frequent situations, oxygen in an

attempt to increase the rate at which product alterations produced by these factors occur or the frequency of occurrence of these alterations.

Chemical Stability: Chemical instability is due to chemical reactions occurring within the product over time which typically involve degradation of one or more components of a formulation into reaction products.

Fit and Acceptable for Use: A condition in which a product provides the intended efficacy benefits, aesthetics, in-use experience, and safety to the consumer.

Kinetic Stability: The ability of a product to remain fit and acceptable for use over a defined period of time and under defined conditions, but not indefinitely. Primarily used with regard to those products such as emulsions which are thermodynamically unstable, but which can be kinetically stabilized through proper formulation to remain fit and acceptable for use for an adequate period of time.

Physical Stability: Physical instability is a change in the product not typically associated with chemical reactions and is usually manifested in a change in the homogeneity of a product or its consistency (i.e., rheology) and is a function of the topical product type.

Shelf Life: The length of time a product remains fit and acceptable for use under expected storage conditions.

Stability: Comprehensive description of the ability of a product to resist changes in composition and consistency and remain fit and acceptable for use over time.

Thermodynamic Stability: A term indicating that a product is at its minimum free energy state and will not tend to change unless acted upon by external forces.

Chapter 17

Good Manufacturing Practices (GMPs): A set of guidelines, production and testing practices that helps to ensure a quality product. In the United States, the Food and Drug Administration issues and enforces GMP guidelines.

pH: The decimal logarithm of the reciprocal of the hydrogen ion activity in a solution.

pKa: An acid dissociation constant is a quantitative measure of the strength of an acid in solution.

Water Activity (a_w): Ratio of the water vapor pressure of the product compared to pure water at the same temperature. A key measurement indicating potential for support of microbial proliferation

Chapter 18

Antimicrobial: A chemical agent, produced either in a plant, by microorganism or by synthetic means, which is capable of killing or suppressing the growth of microorganisms.

Conventional Preservatives: Synthetic compounds that are exhibit antimicrobial activity against microorganisms at a certain dose level.

Hazard Analysis of Critical Control Point (HACCP): A management system in which food safety is addressed through the analysis and control of biological, chemical, and physical hazards from raw material production, procurement, and handling, to manufacturing, distribution, and consumption of the finished product.

Nosocomial (hospital acquired) infections: Infections that originate or occur in a hospital or hospital-like setting, primarily caused by opportunistic pathogens (such as *Enterococcus spp., Escherichia coli, Pseudomonas spp.* and *Staphylococcus aureus*).

Objectionable organism: An organism that is present in a product and can be harmful to the user based upon the nature of the product, its intended use, or its potential hazard, or an organism that is able to compromise the physical integrity or appearance of the product.

Preservative: A chemical agent that kills microorganism or prevents microbial growth.

Preservative Efficacy Test (or a Challenge Test): A method in which a material is inoculated with selected microorganisms to determine the antimicrobial effectiveness of preserved or unpreserved formulations.

Chapter 19

Ball-bearing effect: An effect that is imparted by the spherical shape of the particles in powders which reduces friction and provides a slippery smooth feel.

Bleeding: Occurs when a lip care product smears around the edges of the lip line and does not stay put. It may be caused by using relatively high percentages of low viscosity oils.

Blooming/crystallization: The formation of crystals on the surface of a product which is dependent on several factors such as incompatibility between ingredients along with inappropriate storage conditions.

Colorant: A dye, pigment, or other substance derived from a vegetable, mineral, animal, or other source that is capable of imparting color

Inorganic colorant: A natural or synthetic pigment derived from minerals such as iron oxides. These provide earth tones and lack the vibrancy of organic colorants. Unlike organic colorants, they are very stable to light and heat. Inorganic colorants must also be manufactured synthetically and are exempt from FDA certification. Most widely used inorganic pigments include titanium dioxide along with iron oxides such as brown, black, russet and yellow color.

Organic colorant: Pigment that is subjected to certification by the FDA. The majority of these colorants are made by precipitating a water-soluble acid dye onto a substrate, such as alumina, silica or maltodextrin. Either preceded by the letters FD&C which means it can be used in food (F), drugs (D) or cosmetics (C) or D&C which means it can only be used in drugs or cosmetics. They provide clean and vibrant colors such as red, orange, yellow, blue, and violet.

Pearlescent pigments: Used to add a shimmer effect to color cosmetic products. They act as a prism since the color they provide is achieved from light reflection. They are usually prepared by precipitating titanium dioxide and iron oxides on mica.

Surface treated pigment: Untreated pigment coated with a chemical additive that is prepared by either physical absorption or a chemical reaction. This can offer many advantages over traditional untreated pigments. They provide better dispersion along with less agglomeration, which leads to better wetting needed to achieve higher pigment loading. Surface treatments can provide pigments with better adhesion or change oil absorption/wetting properties which can improve wear and increase coverage.

Syneresis: A phenomenon of appearance of oil beads on the surface of a lip product. It is usually observed during the course of stability testing when the product is exposed to changes in temperature. Syneresis can also be referred to as "sweating." It is an indication of incompatibility between the oils and waxes used in the formulation.

Chapter 20

Additive: Raw ingredient added at a very low level (e.g. < 0.50%) to a nail product formulation to impart a specific functional and/or market-related benefit.

Bottle Tone: Appearance of a pigmented nail lacquer as viewed through a transparent glass bottle.

Cross-linking: A chemical reaction involving chemical compounds and/or electromagnetic radiation and one or more functional groups present on one or more polymers. The chemical and physical properties of the end product become significantly more robust as compared to the reactants.

Diluent: A liquid volatile organic compound added to a nail lacquer formulation as a means of reducing bulk cost.

Drawdown: A small test swatch of nail lacquer applied to a glass, metal or paper substrate; wet film thickness customarily is controlled to 0.003" or 0.006".

Dye: An organic colorant that achieves its coloration strength by dissolving in one or more solvents.

Explosion-proof: Specially constructed electrical and process equipment installations used in laboratory and manufacturing areas wherein high concentrations of flammable vapors are present.

Film-former: Polymer that can form a continuous film when dissolved in one or more volatile solvents, then deposited on a substrate.

Film Modifier: Chemical compound intended to be mixed with a polymer so as to improve one or more performance characteristics of that polymer.

in vitro: Literally "in glass"; refers to test methods wherein a test product is evaluated on a non-living substrate (e.g. glass, paper, metal, plastic or wood).

in vivo: Literally "in life"; refers to test methods wherein a test product is evaluated on a living substrate (most typically the fingernails or toenails of human test subjects).

Lacquer: An organic coating consisting of one or more film-formers and modifiers dissolved in one or more volatile organic solvents. A coating is formed when all solvents have evaporated from the film.

Lake: An organic pigment produced by the precipitation of a water-soluble dye onto an inorganic substrate.

Molecular Weight: Literally the weight of a molecule or polymer; as understood in a coatings context, the chemical and physical properties of a polymer generally increase in direct proportion with its molecular weight.

Monochromatic: Literally "one color"; commonly used to describe a color dispersion or solution consisting solely of a single pigment or dye, respectively.

Monomer: Literally "one part"; describes an organic compound containing one or more reactive functional groups that can serve as "attachment points" for other monomers.

Nail Cosmetics: Various products intended for application to and enhancement of human fingernails, toenails, and immediately contiguous tissues.

Nail Lacquer: An organic coating consisting of one or more film-formers and modifiers dissolved in one or more volatile organic solvents. A coating is formed on the nails when all solvents have evaporated from the film.

Nail Tone: Appearance of a dried pigmented nail lacquer film applied to the nails of the user.

Nitrocellulose: Synthetic polymer prepared by reacting nitric acid with cellulose; the most common primary film-former used in nail lacquer formulations.

Non-volatile (NV): The portion of a liquid organic coating formulation that remains after all solvents have evaporated completely.

Oligomer: Literally "few parts"; describes a material consisting of a small number of monomers linked together.

Organoclay: Specific types of clay (usually montmorillonites) onto the surfaces of which specific organic compounds (usually fatty quaternary ammonium compounds) have been deposited.

Personal Protective Equipment (PPE): Clothing and accessories designed to protect the body of the wearer from the potentially harmful effects of exposures to hostile working environments.

Pigment: An organic colorant that achieves its coloration strength by dispersion in one or more vehicles. In contrast to a dye, a pigment is insoluble in its vehicle.

Plasticizer: Chemical compound added to a polymer to improve its flexibility. Plasticizers can be mono-molecular ("chemical plasticizers" or "solvent plasticizers") or polymenc ("polymeric plasticizers").

Polar Activator: Low molecular weight organic compound and/or water, added to an organoclay to cause gel formation under high-shear dispersion.

Polymer: Literally "many parts"; describes a material consisting of many monomers linked together to form a very long chain or other geometric structure.

Primary Film-former: The main polymer that forms the continuous film in a nail lacquer formulation; most typically this is nitrocellulose (q.v., above).

Rheology: Literally "study of currents"; the science related to the structure and flow of materials at rest and under application of mechanical stresses.

Secondary Film-former: Ancillary polymer(s) that supplements the primary film-former in a nail lacquer formulation; most typically this is a polyester resin and/or an acrylic polymer and/or tosylamide/epoxy resin.

Shade Matching: Also known as "color matching," this is the process by which the color appearance of one product is duplicated in a second product.

Solvent: As used in a nail lacquer context, a volatile organic compound capable of dissolving film formers, plasticizers and various additives, then evaporating spontaneously at room temperature.

Substrate: The surface to which a coating is applied.

Thixotropy: Literally "change of touch"; describes a thinning and time-dependent re-thickening of a formulation in response to application and cessation of mechanical energy.

Volatile Organic Compound (VOC): An organic compound capable of evaporating spontaneously at or below a specific temperature (the precise definition of which often has specific legal/regulatory implications).

Chapter 21

Beach wear: A topical product that contains UV protection which is designed to provide protection against sunburn in a setting where water wash-off must be reduced and high SPF is required since the exposure is generally over a period of several hours. These products contain film-forming polymers and must generally be re-applied. They are also referred to sport products as they are often used when sweating occurs.

Daily wear: A topical product that contains UV protection in addition to other benefits such as moisturizing, which is intended to protect the wearer from incidental exposure during the day and thus help to reduce premature aging. These typically have lower SPF than beach products and do not require water-resistance.

Photoaging: Premature aging of the skin due to excessive sun exposure. UV radiation causes physiological changes over time that result in wrinkling, discoloration, growths, and loss of elasticity and structure.

Photostability: The ability of UV filters to resist decomposing when exposed to solar radiation. Some organic chromophores are sensitive and can break down or initiate the breakdown of other UV filters, leading to a loss of SPF and UVA protection. UV filters that do not decompose readily over the course of several hours are considered photostable. To prevent loss of activity of sensitive combinations of UV filters, chemicals known as photostabilizers can be incorporated.

SPF: Abbreviation for Sunburn Protection Factor. This is a direct numerical measure of the degree of protection a sunscreen provides against sunburn. UVB (wavelength 290–320 nm) is the primary contributor to sunburn, which is known to be a significant factor in the development of skin cancer. The number correlates directly to the ability of the sunscreen to prevent erythema compared to untreated skin. The FDA monograph in the United States defines the *in vivo* protocol for

determining SPF for a consumer product. For sunscreen development work, *in vitro* methods or *in silico* methods can be used to estimate the SPF from various UV filter combinations

Sunscreen: A topically applied product that prevents solar radiation in the ultraviolet spectra from penetrating the skin. Sunscreens are regulated as over-the-counter drugs in the United States because they claim to prevent sunburn

US FDA: United States Food and Drug Administration. This is a United States government agency that regulates food stuffs, prescription and OTC drugs, and medical devices. Sunscreens are an OTC drug and guidelines that must be followed for formulation, testing, and labeling are listed in the FDA Sunscreen Monograph

UVA: Ultraviolet A radiation covers the wavelength range from 320–400 nm. It has lower energy than UVB due to its longer wavelength; however, it penetrates deeply into the skin and initiates free radicals that cause accelerated breakdown of the structural proteins within the skin.

Ultraviolet radiation (UV): Electromagnetic energy from the sun with wavelength between 290–400 nm are classified as ultraviolet radiation A and B.

UV filter: An active ingredient incorporated into sunscreen that absorbs and/or scatters UVA and UVB radiation. Filters can be organic molecules containing UV absorbing chromaphores or inorganic oxides of titanium or zinc that absorb and scatter/reflect UV radiation. UV filters that are approved for use in sunscreens sold in the United States are listed along with their allowed concentration limits in the FDA Sunscreen Monograph.

Chapter 22

Absorption coefficient: A unit measure of a chemical filter layer's ability to absorb light's radiant energy.

Chemical filters: A chemical substance that absorb UV light.

International Nomenclature of Cosmetic Ingredients (INCI) Dictionary: The official dictionary for cosmetic ingredients which has been established in the early 1970s by the Personal Care Products Council (formerly CTFA).

Physical blocks: Mineral molecules of 200-400 μm that reflect UV light.

Physical filters: Mineral molecules at the nano-scale (15-100 nm) that absorb UV light.

Photostability: The property of a single or mix of UV filters indicating the efficacy of a sunscreen product to keep unaltered its power during sun exposure.

Sun Protection Factor (SPF): A measure, expressed numerically, of the degree to which a preparation containing sunscreen protects the skin from ultraviolet (UV) rays. The SPF value is defined as the ratio of the UV energy required to produce normal erythema on protected skin to that required to produce the same erythema on unprotected skin in the same individual. The higher the value, the greater the level of protection from sun damage to the skin.

Transepidermal water loss (TEWL): The outward diffusion of water through skin. TEWL measurements are used to gauge skin water barrier function. An increase in TEWL reflects impairment of the water barrier.

Handbook of Formulating Dermal Applications: A Definitive Practical Guide.
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Joe Albanese is currently technical marketing manager of personal care at 3V Inc. During his career in the personal care industry, Albanese has worked for Avon, Shulton, and Colgate-Palmolive in both process and product development groups. His employment on the supply side of the industry included more than 12 years at GAF/ISP where he went from formulation chemist to manager of the hair care applications/tech service lab. He is a graduate of the FDU Cosmetic Science Masters Program. He joined the Society of Cosmetic Chemists in 1984, and in 2010 sat as chair of the New York chapter. He is currently Area I Director of the SCC.

Rachel Ametsitsi interned at Alchimie Forever as a scientific assistant. With research experience and a master's in scientific international business, she worked closely with Anne Pouillot on the conception and formulation of the brand's products.

Daphne Benderly is a senior applications scientist at Presperse, where she applies her more than 20 years' experience in R&D in the personal care, specialties chemicals, and plastics industries. Benderly holds a PhD in materials engineering from Technion–Israel Institute of Technology, an MS in macromolecular science from Case Western Reserve University, and a BS in mechanical engineering from MIT.

David Binder received his PhD in physical chemistry from the University of Minnesota, with post-doctoral research in enzymology at Albert Einstein College of Medicine. His industrial career includes positions with Unilever in innovation and product development for the laundry business unit, and with Avon Products in the innovation center, developing skin and lip products. He is currently employed by Lonza as a research scientist and is also an adjunct professor of chemistry at Ramapo College.

Slawomir Cebulski was born Krakow, Poland, and there began his studies in organic chemistries before immigrating to the United States. Cebulski earned his degree in medical laboratory technology and molecular biology from Montclair State University and started his professional career as a microbiologist at Reckitt Benckiser, where he evaluated disinfecting agents and preservative systems for household products and researched the effectiveness of infection control and prevention of communicable diseases by means of chemical disinfection and sanitization. In 2005, he joined the R&D microbiology team at Johnson and Johnson Consumer Products Worldwide, where he is responsible for management

of evaluation and qualification of antimicrobial and preservative chemistries for a global portfolio of products.

Mark Chandler is president of ACT Solutions Corp, a consultancy focusing on adaptive aesthetic design, emulsion technology, and formulating for efficacy. Chandler has been in the industry since 1984, most recently as skin care applications manager for Croda Inc. For 15 years he has taught the SCC cosmetic formulation course, in addition to instructing on emulsions for the Center for Professional Advancement and Cosmetic Raw Materials for the SCC. He lectures for the cosmetic science program and serves on the board of the pharmaceutical sciences department at the University of Toledo.

Susan Chen received a BS in fiber chemistry engineering from South China University of Technology (Guangzhou, China). She later pursued her graduate studies at Rutgers University where she earned an MS in chemistry. Chen has worked at Ashland Specialty Ingredients for the past 15 years, mostly in the area of personal care. She is also a certified teacher in the New York City school system where she has worked for 21 years at Manhattan Center High School for Science and Mathematics.

Dr. Joel Coret has a doctorate from Universite Fourier in Grenoble for research on the effects of surfactants on active delivery across bio-membranes.

Howard Epstein is director of technical services for EMD Chemicals, an affiliate of Merck KGaA. He was a scholar in residence at the University of Cincinnati's Department of Dermatology and received his PhD in pharmacognasy from the Union Institute & University in Cincinnati, Ohio during that time. He has been in the cosmetics industry for many years since he began his career formulating cosmetics for Estee Lauder, Maybelline, Max Factor, Bausch & Lomb and Kao Brands. In addition to his interest in botanicals Howard recently served as Editor of the Journal of the Society of Cosmetic Science and is a member of the International Academy of Dermatology. He is on the editorial board of the dermatological journals Clinics in Dermatology and SKINmed representing the cosmetics industry to dermatologists. Howard has authored chapters in various cosmetic technology textbooks, holds eight patents and two patent applications.

Mihaela Gorcea received a PhD in pharmacy/skin biophysics from the University College of London, School of Pharmacy, an MS in pharmacy from the University of Medicine and Pharmacy, Bucharest, and an MA in cosmetic chemistry from Fairleigh Dickinson University. She has over 15 years of experience in the personal care industry with emphasis on developing biophysical methods, measurements and models to investigate stratum corneum barrier structure, organization and function, as well as developing new technologies and formulation strategies to target various skin conditions. Mihaela is currently a research scientist in the materials science department at Ashland Specialty Ingredients where she conducts skin care biophysical studies.

Dr. Samuel Gourion-Arsiquaud has a doctorate in biotechnology and biophysics from the University of the Mediterranean for research on the FTIR spectroscopy of proteins.

Bryan Grossman holds a degree in biology from Rutgers University, where he received a Henry Rutgers scholar award. He joined Salvona in 2004 as a production manager, gained experience with technical sales and marketing, and now has combined these skills in technology and custom product development. Mr. Grossman manages new product development and serves as a liaison with customers searching for custom product development. He is also engaged in earning an MBA, to be completed in 2014.

Steve Herman is president of Diffusion LLC and a principal in PJS Partners. He is an adjunct professor in the FDU cosmetic science program. Steve is a regular columnist for *GCI* Magazine and has written a book, *Fragrance Applications: A Survival Guide*. His SCC activities include service as chairman of the New York chapter in 1992 and 2013.

Gary Kelm received his PhD in biopharmaceutics and MS in pharmaceutical science from the University of Cincinnati, College of Pharmacy, and a BS in chemical engineering from the Rose-Hulman Institute of Technology. In 2009, he retired from Procter & Gamble after 36 years during which he worked in formulation and drug/active delivery research and development on personal care, OTC drugs, and pharmaceutical products. He is currently director of the online graduate program in cosmetic science at the James L. Winkle College of Pharmacy, at the University of Cincinnati. Dr. Kelm has 22 issued US patents and over forty published articles and abstracts.

Michael Kimball is executive director, transdermal development at Actavis plc. Kimball's 20 years of experience include work in pharmaceutical product formulation, development, and manufacturing involving various dosage forms. He is the inventor on several approved and pending patents related to transdermal drug delivery. Kimball holds a BS in mechanical engineering from the University of Utah and an MS in the same from the University of California, Berkeley, where he attended as a fellow of Tau Beta Pi, the Engineering Honor Society.

Kausar Malik is principle research scientist (microbiologist) at Amway Corporation, where she leads discovery efforts in cosmetic microbiology and supports product development in preservation of cosmetic, personal care and oral care formulations. She is also responsible for development of cosmetic microbiology standards including validation of traditional and rapid microbiology methods. Malik earned MS and M. Phil degrees in mycology/microbiology from the University of the Punjab and Quaid-e-Azam University, in Islamabad, Pakistan, respectively. In 2004, she earned her MBA from the University of Phoenix. An active member of the Personal Care Products Council Microbiology Committee since 1993, Malik also chairs the annual seminar committee for PCPC and the SCC's Michigan chapter.

Bart Maxon is a senior industry specialist for Dow Corning Corporation. Maxon's 30-year career has included a 17-year stint with Dow Corning in a variety of roles within their beauty care and health care businesses. He has a bachelor of science in biology from Central Michigan University and a bachelor of science in chemistry from Northeastern Illinois University. Maxon is a very active member of the Society of Cosmetic Chemists and presently holds 11 patents.

Roger L. McMullen graduated with a BS degree in chemistry from Saint Vincent College, later studying at Seton Hall University, where he obtained an MS in chemistry and a PhD in biophysical chemistry. McMullen is an adjunct professor at Fairleigh Dickinson University's masters program where he teaches biochemistry. Author of the recently published *Antioxidants and the Skin*, his primary interests are in imaging and imaging analysis techniques related to both skin and hair care technologies. McMullen is currently a principal scientist in the materials science department at Ashland Specialty Ingredients where he leads a group of scientists who conduct biophysical studies of hair and skin care.

Dr. David J. Moore has a doctorate in biophysical chemistry from Rutgers University for spectroscopy studies of cell membranes.

Dr. Hemi Naé received his BS in chemistry from Tel-Aviv University and his MSc and PhD from the Weizmann Institute of Science in Israel. His postdoctoral studies were at the department of macromolecular science of Case Western Reserve University and at the department of chemical engineering of Princeton University. He then returned to the department of materials research at the Weizmann Institute of Science as a senior scientist. Currently, he is president of Hydan Technologies, Inc., providing consulting, research and development services and training in rheology and product development. Dr. Naé is the author of 16 patents and 34 technical publications.

Ada S. Polla is co-creator of the Swiss antioxidant skin care line Alchimie Forever, which launched in the United States in 2004. She holds an MBA from Georgetown University, and majored in art history and political science at Harvard University where she earned her BA magna cum laude in 1999.

Anne Pouillot joined Alchimie Forever in 2006 after obtaining a master's in biochemistry with a specialization in plant molecules. She is involved in product conception and formulation, working closely with chemists, and label and raw materials suppliers. She also leads the commercial development of the brand throughout Europe.

Jed Riemer has a PhD in synthetic organic chemistry. He has fourteen years' experience in the development of new personal care ingredients, including optical effect powders, sensory agents, skin actives, and functional polymers.

Thomas R. Russo is formulations lab manager/technical service at Lipo Chemicals Inc. Russo's 36 years in the personal care industry have grown his expertise in color cosmetics, OTC antiperspirants and deodorants, OTC SPF sunscreens, sunless self-tanning products, after-sun treatment products, and emulsion technology, and produced numerous patents on innovative product applications. Russo earned his bachelor's in chemistry from Rutgers University in 1977.

Robert Sandewicz's 33-year career has been devoted to the creation of new lip and nail products. He currently is director of nail technology and beauty tools at the Revlon Research Center. Sandewicz holds a BS in biology from Fordham University and a MS in cosmetic Science from St. John's University. A long-time member of the SCC, he has taught several continuing education courses on formulations for lip and nail cosmetics. He has authored chapters for two recent textbooks on cosmetic science, and has co-authored an SCC monograph on nail enamel technology.

Daniel Sango is a program manager in color cosmetics for Avon Products, Inc. He holds a MS in cosmetic science from Fairleigh Dickinson University and a BS in biology from Seton Hall University. Sango's has more than 16 years experience developing a vast array of lip product launches with unique consumer benefit driven claims. He began his career at AM Cosmetics, Inc., as a chemist working with color cosmetics before joining Avon Products in 2000.

Nripen S. Sharma holds a PhD in chemical and biochemical engineering from Rutgers University and was as a postdoctoral research fellow at Harvard Medical School. His research has focused on stem cells, biomaterials, and tissue engineering in relation to dermatological applications. Sharma manages the department of new product development at Salvona, where he is charged with developing new delivery systems for dermatological and consumer care products.

Sam Shefer holds a BS and an MS in biochemistry from Ben Gurion University, Israel, as well as a PhD in biochemical and chemical engineering from the same. His postdoctoral experience in biomedical engineering took place at MIT. Shefer has more than 20 years of experience in developing commercial products based on nano- and microspheres for pharmaceutical, personal care, and industrial applications. He has published multiple papers and has been granted over 100 US and worldwide patents. Shefer is a co-founder of Salvona Technologies, LLC.

Michael S. Starch's 33 years of experience in the personal care industry include work in research, development, and commercialization of ingredients and skin care products. Starch tenure at Dow Corning lasted 26 years, prior to which he spent seven years at the Andrew Jergens division of Kao Corporation. He currently works as a consultant in the personal care industry through Wintermute Consulting Services.

Dr. Dov Tamarkin is the CEO of Foamix Ltd and co-inventor of the Foamix Foam and OilGel technologies. He has more than 25 years' experience in the direction of preclinical, clinical and regulatory phases of drug development. He has

held positions of senior R&D section manager at Teva Pharmaceuticals and served as VP of R&D at Portman Pharmaceuticals, a company that develops immunologic therapies for Type I diabetes and other autoimmune diseases. He holds a PhD in chemistry from the Hebrew University of Jerusalem, and is the author of several papers on topical drug delivery, as well as the inventor of more than 100 patents in the field of pharmaceutical chemistry.

Paul Thau's 50-year career in the cosmetic industry included serving as assistant vice president of cosmetic product development and then as senior research fellow at Cosmair (now L'Oreal USA), the latter a post he held until his retirement in 1998. Thau was the recipient of the SCC Maison de Navarre Award in 2005. He is presently a consultant specializing in technology surveillance, technology acquisition, and innovations related to cosmetics and dermatology.

Cindy Yu is the business and applications specialist for personal care, fabric and home care at Ingredion Inc. She has been in the personal care industry for five years and has experience in method development, marketing, applications testing, and skin and hair care formulation.

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