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Antibacterial Agents and Preservatives

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INTRODUCTION

The term ''antibacterial agent'' is largely used to qualify chemical agents that are included in cosmetics or household products to provide them either with a specific bactericidal or bacteriostatic activity during usage. The second function of antibacterial chemicals is to protect the product during its life by providing a preservative efficacy against microbial insults. A particular chemical agent can be used as an active ingredient in antibacterial product or as a preservative to protect the formula from microbial contamination. Taking into account that not only bacteria but also fungi or yeast can be concerned, to cover all germs simultaneously the word ''antimicrobial'' will be used.

Historically, the first antibacterial products developed were skinwash products such as soap bars, derived from deodorant soap bars. The purpose was not only to clean the skin but also to reduce its microbial flora [1]. During the last 20 years, many different antibacterial or antimicrobial products were marketed. They include toothpastes and mouthwashes, liquid antibacterial soaps, deodorants, and even antibacterial products for dishwashing.

The first part of this chapter will review the different kinds of antibacterial products and the methods to show their efficacy.

The purpose of preservation is to protect all aspects of a product against microbial attack before and during consumer use. Integrity of products in terms of efficacy, fragrance, appearance, and stability must be maintained. The second part of this chapter will review the preservative systems and how to build a well-preserved formula. The test methods for preservative efficacy can be found in Chapter 64 of this book.

ANTIBACTERIAL PRODUCTS

Topical Antimicrobial Products

Most antibacterial soap bars contain triclocarban (TCC) as the active ingredient. In the past, antibacterial soap bars were also formulated with formaldehyde. These were very

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effective for hospital use, but skin toxicity and irritation were very high. Currently, liquid soaps are formulated with triclosan up to 1% maximum. Safety of the regular use of triclocarban and triclosan in hand-washing products was extensively discussed by the Food and Drug Administration (FDA) [1]. The agency prepared a tentative final monograph in 1994 in which topical antimicrobial products were classified in the following categories: 1) antiseptic handwash or healthcare personnel handwash, 2) patient presurgical skin preparation, and 3) surgical hand scrub. But this meant that products intended to be used in homecare would have to meet the requirements of products for healthcare. In response, two industrial associations, The Cosmetics, Toiletry, and Fragrance Association (CTFA) and the Soap and Detergent Association (SDA), proposed another classification, based on a healthcare continuum model (HCCM) in which the antimicrobial products were related to six categories; two to be used by the general population (antimicrobial handwashes and bodywashes), three for use by healthcare professionals (presurgical preparation, surgical scrubs, and healthcare personnel handwashes), and one category for food handlers. Since then, industry has submitted data to the FDA showing the efficacy of active ingredients used in the six categories; among these ingredients are triclosan, triclocarban, chloroxylenol (PCMX), povidone-iodine, surfactant iodophor, alcohol, and quaternary ammonium compounds [2].

Extensive studies have also been carried out with essential oils as antibacterial agents in soaps. Unfortunately, the data showed that the minimal inhibitory concentration (MIC) for antimicrobial soaps formulated with different essential oils were more than 100 times higher that the MIC obtained on TCC-based soaps when tested against *Staphylococcus aureus* [3].

Deodorants and Antiperspirants

The first antiperspirants appeared on the market at the beginning of the 20th century. They were based on aluminium chloride, which induced skin irritation and fabric damage because of the low pH of the solutions [4]. Several years later, Shelley and colleagues showed that underarm odor was provoked by the growth of the axillae bacterial flora which degraded the apocrine secretions [5]. These bacteria are mainly staphylococci (*S. epidermidis*) and diphteroids from the Corynebacteriaceae family. Antiperspirants can prevent the growth of these degrading bacteria by reducing the available moisture of the axillaries among other mechanisms (see Chap. 56). Some products used the hexaclorophene as an active but its use was discontinued because of its neurotoxic properties [6]. Currently, many contain aluminium salts, or zirconium-aluminium combinations such as Al-Zi-Tri-/tetra-chlorydrex glycinate as active ingredients. Their low pH (4.0) also helps the antibacterial activity. Antiperspirants are deodorants because they suppress the odor source by reducing perspiration and bacterial growth. Deodorants may or may not have an antimicrobial action; either they are masking products—in this case they contain perfumes or essential oils that hide the odor—or they can contain antibacterial agents which are mainly alcohols and triclosan [6].

Oral Care Products

These are mainly toothpastes and mouthrinses. In general, dental creams serve to clean the teeth, to remove dental stains, and most recently to reduce and/or to prevent gingivitis and to kill the germs responsible for bad mouth odor. Mouthrinses, whether their recommended use is before or after brushing, are also claimed to sanitize the mouth.

Active ingredients used in dental cream are mainly triclosan and chlorexhidine. Other ingredients such as the natural sanguinarine extract also claim a sanitizing effect on the oral flora. The same ingredients can be used in mouthrinses, but most also contain alcohol to ensure a good antiseptic effect of the product. It is interesting to observe that fluorinated dental creams without any specific active ingredient also exhibit antimicrobial activity [7]. This could be related to their fluoride content which, in association with the surfactant system in the formula, release antibacterial active cationic systems.

Dishwashing Products

Among the antibacterial household products that have recently appeared on the market, antibacterial hand dishwashing liquids have become increasingly popular. Even if these products are not true cosmetics, during the dishwashing, they are in direct contact with the skin for a certain time. From a safety point of view, they can be considered as rinse-off cosmetics.

Furthermore, some products on the market have a double claim: ''dishwashing liquid and antibacterial liquid soap.'' They are classical dish liquids based on anionic and non-ionic surfactants, to which one or more antibacterial agents have been introduced. Some of these formula have been optimized to maintain their cleaning/degreasing performance on dishes and to fight bacteria on the hands, in the washing solution, and on washing implements. Ingredients used can be Triclosan, essential oils, or others. The use levels are chosen to ensure a good balance between a maximum efficacy, a low skin toxicity, and keeping good cleaning performances.

Methods to Show Antimicrobial Product Efficacy

In vitro and in vivo tests can be used to show the efficacy of antimicrobial products. Only the in vitro tests will be considered here because they are applicable to all antibacterial products. A detailed review of the in vivo tests, useful for topical antibacterials, can be found in Ref. 1.

—*The minimal inhibitory concentration (MIC) test* principle is to determine the MIC of the test product by performing serial dilutions of the latter in growth medium and inoculating each dilution with the test strain. Products are generally tested at twofold serial dilutions. After suitable incubation, the first tube not exhibiting bacterial growth gives the MIC level, generally expressed in ppm (part per million) of product. The test can be carried out using either 2 mL of broth in tubes or 0.5 to 0.1 mL, in microtiter plates [8] or on agar plates. Control samples without any antimicrobials must be included in the test. This test is very useful to compare activities of different products, products from the same category (e.g., soaps) with different actives, or the active ingredients themselves. However, MIC data obtained on formulated products are very subjective and should be interpreted carefully. Usually, test organisms are *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Escherichia coli*, for topical antimicrobial. *Pseudomonas aeruginosa* and *Salmonella typhimurium* are added for the dishwashing products; for specific claims in the kitchen, *Aspergillus niger* and *Candida albicans* can be used as test strains. To test oral care products, the chosen organisms are *Actynomyces viscosus*, *Streptococcus mutans*, and *Streptococcus sanguis*, representatives of the oral flora [7].

—*The zone inhibition test* method is largely used to test the resistance of bacteria to antibiotics [9]. Antibacterial agents or products at different concentrations are applied

to a substrate, a paper disk, or directly to the surface of an agar plate previously seeded with the test bacteria. During the incubation, the test product will diffuse into the agar layer and produce a zone of growth inhibition of the micro-organism. The larger the inhibition zone, the higher the efficacy of the product. However, the data are influenced by the diffusion capacity of the product or the active into the agar; oily products will not diffuse at the same rate as aqueous-based products. It is thus very important to use negative and positive controls. The data will be expressed in millimeters of inhibition zone around the disk. The strains used for this test are usually the same that those used for the MIC test. These two methods give a good idea of the bacteriostatic concentrations of the tested product or ingredient.

The requirements from the FDA monograph of 1994 [10] are the MIC test on the active ingredient, the vehicle, and the final formula, associated with a time-kill test methodology to be carried out at several time points over a period of 30 minutes.

—*The time-kill test* determines both the killing kinetics and the activity spectrum of antibacterial formulations. This test is generally performed in suspension. The principle is to place in contact a dilution of the product or the antibacterial agent and a specified bacterial inoculum during a defined period of time. At the end of the contact time, the antibacterial in the mixture is inactivated by dilution into neutralizing broth. Serial dilutions in appropriate broth are performed and the number of survival bacteria enumerated on solid culture media. This method can use different concentrations of test agents and bacterial inocula, and different contact times. In general, the concentrations are chosen so that the final organism/test solution concentration is representative of the use concentration of the product.

In the United States, there is no detailed standardized time-kill test, even if the U.S. Food and Drug Administration (FDA) requested a standard procedure [10]. In response, the American Society For Testing and Materials (ASTM) subcommittee of antimicrobial agents has prepared a draft to standardize the organism inocula, media, neutralizers, and contact times [11].

In Europe, the situation is different: to test the antimicrobial efficacy of products and/or agents, standards exist since more than 20 years in France [12], Holland, Germany, and the United Kingdom. Recently, the Council of Europe has installed a Commission for the Normalization of European Norms [13], which is writing and publishing the European Norms (EN) for testing disinfectants and antiseptics. The requirements for disinfection are 99.99% to 99.999% of killing (4 to 5 log reductions) of the initial inoculum, depending on the test.

These norms are also used by the industry to prove the efficacy of their antibacterial products, but the requirements are less strict: 99 to 99.9% killing (2–3 log reduction). Detailed review of the ENs can be found in Ref. 14.

PRESERVATION AND PRESERVATIVE SYSTEMS

Concept of Active Preservation and Self-Preserving Formula

To ensure effective preservation, the method of choice is to add one or more active antimicrobial ingredients to the product. These ingredients must be compatible with the other ingredients of the formula and must retain efficacy for an extended period of time. They also have to be nontoxic for the consumer.

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To choose an active antimicrobial molecule as preservative is not so easy; this molecule must have a good oil-water partition coefficient because the contaminating microbes are living in the aqueous phase of the formula. It must not be inactivated by external factors such as the pH and the manufacturing process [15]. Other factors also have to be considered; such as the packaging, which could affect the preservative activity, the adsorption rate on some components of the formula, the solubility of the preservative molecule and its volatility [15].

Furthermore, the inactivation of the micro-organisms by the preservative should be sufficiently fast to prevent any adaptation or resistance to the preservative system [16]. So, the ideal preservative system must be selected for each formula, taking into account the possible inactivating ingredients or the potentiation capacity of other ingredients. Among these, ethylenediaminetetra-acetic acid (EDTA) is well known to act in synergy with many other chemical preservatives. This potentiation is delivered through the permeation of the cell membrane of gram-negative bacteria. EDTA is a chelating agent and disrupts the outer lipid layer where stability is calcium and magnesium ion dependent. As such, it increases the penetration of the other antimicrobial chemical into the bacterial cell [17,18]. In general, liquid- and emulsion-based cosmetic products are the most susceptible to the development of micro-organisms. Powdered products, such as talc, are also susceptible to contamination and need to be preserved [19].

Another way to preserve a product is to build a ''self-preserved'' formula by using raw materials that are not supporting germ growing and optimizing their relative content. The use of humectants such as glycerin or sorbitol at a sufficient level increases the formula resistance. In a dental cream, a mixture of sorbitol and glycerine, at respective levels of 10% and 12%, is often enough to protect the formula. This is linked to the decrease of the water activity in the formula because of the presence of these humectants [20]. Other ingredients, such as alcohols, cationic detergents, fragrance components, and lipophilic acids (lauric and myristic acids) used as emulsifiers, which have intrinsically antibacterial properties, can contribute to the self-preservation of a cosmetic. This is also true for essential oils like tea tree oil or geraniol or eucalyptol, often used as cosmetic ingredients.

Some physical factors, such as the pH and the formula water activity, can also contribute to build a self-preserved product. Micro-organisms are essentially living at pH of around 5 to 8, and any pH outside this range induces difficult life conditions for bacteria. The water activity or availability is an important factor as the water is a necessary ingredient for bacterial growth. The water availability concept is detailed in Chapter 64 of this book.

Most Commonly Used Preservatives

Table 1 lists the most commonly used chemicals to preserve cosmetic products. Attention must be paid to the regulations; in Europe, the Annex VI of the Cosmetic Directive 79/768 lists the chemicals, permanently and provisionally allowed to be used as preservatives in the cosmetic products. For each of them, there is an upper concentration use limit, and for several of them, restrictions are mentioned [21]. In the United States, the use of preservative molecules is regulated by the FDA. The chemical preservatives are too numerous to be listed here; details on preservatives can be found in Ref. 22. These molecules can be used in synergistic mixtures to improve the activity spectrum. For example, the parabens can be used with the imidazolydinil urea, the formaldehyde can be used with

TABLE 1 Most Commonly Used Preservatives

Preservative name	Activity spectrum	Compatible with:	Inactivated by:	Optimum pH
Parabens: esters of benzoic acid	fungi, gram+	cationic	anionic, nonionic, proteins	<7
Imidazolydinil urea Diazolydinil urea	broad, weak against fungi	anionic, nonionic cationic, proteins		4–9
Isothiazolones	broad	anionic, nonionic cationic	bleach, high pH	4–8
Formaldehyde DMDM hydantoin	broad	anionic, nonionic cationic	T° > 60°C	4–9
Benzalkonium Cl	gram+, gram−, weak against molds	nonionic, cationic	anionic, proteins, soaps	4–9
2-bromo-2-nitropropanel, 3-diol	broad	anionic, nonionic cationic	heat, high pH, cysteine, aluminum	<6

Abbreviation: DMDM, dimethyloldimethylhydantoin.

the EDTA, and so on. Most of the preservative manufacturers have developed their own synergistic mixtures of chemicals; this allows them to use lower levels of each chemical and thus decrease the toxicity potential with increased preservative efficacy.

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General Concepts of Skin Irritancy and Anti-irritant Products

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INTRODUCTION

In the past, some hazardous materials were used in cosmetics such as lead carbonate, bismuth, and mercurials. Serious adverse reactions to cosmetic ingredients and preparations are actually infrequent. However, side effects do occur and are by no means rare. The unwanted effects of cosmetics can be classified in the following categories [1–4]:

1. Irritation and contact urticaria
2. Contact allergy
3. Photosensitive reaction (photoallergy and photoirritation)
4. Acnegenesis and comedogenesis
5. Color changes of the skin and appendages
6. Systemic side effects
7. Other local side effects

When considering skin-irritation symptoms, we are dealing with nonimmunological mediated inflammation of the skin induced by external agents. Chemical irritants are the major cause, but mechanical, thermal, climatic, and UV and IR light are also important factors or cofactors of irritancy [5]. This nonimmunological skin irritancy reaction comprises two forms: the acute irritant reaction with a monofactorial cause (detergent, acid, oxidant, etc.) and the chronic multifactorial form. The symptoms of skin irritation are well known: erythema, dryness, scaling, itching, burning, and tingling. The clinical symptoms are described by some investigators as objective irritation [1–4]. Because these symptoms are clearly perceptible, in vivo testing in humans can easily and reliably detect strong and moderate irritants for cosmetic ingredients and eliminate these potential hazards. However, most cosmetic-use ingredients do not produce acute irritation from a single exposure because they are mild or very mild and consequently difficult to detect. However, they may produce inflammation after repeated application on the same area of the skin, which is referred to as cumulative irritation.

Application of a cosmetic causing symptoms of burning, stinging, or itching without detectable visible or microscopic changes is designated as a subjective irritation or subclin-

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ical irritation [2–4]. This reaction is common in certain susceptible individuals, occurring most frequently on the face. These persons are identified as ''stingers.'' Some of the ingredients that cause this reaction are not generally considered as typical irritants, and will not cause abnormal responses in nonsusceptible individuals. Typically about 10 to 20% of the subjects exposed to a 5% aqueous lactic acid develop a stinging response when applied to the face. Generally, all stingers have reported a history of adverse reactions to facial cosmetics, soaps, and similar products. Prior skin damage caused by UV sunburn, pretreatment with surfactants, and tape stripping increase the intensity of the response in ''stingers.'' Attempts to identify reactive subjects by association with other skin problems such as atopy or with phototype or skin dryness have not been very fruitful [6].

Among the potential adverse reactions of cosmetic ingredients and products such as irritant contact dermatitis, immediate contact reaction (urticaria), allergic contact dermatitis, and acnegenesis and comedogenesis, we will consider particularly adverse reactions of irritancy. It is the purpose of this chapter to 1) describe shortly the different symptoms of irritancy and how to evaluate skin irritants by clinical visual and tactile assessments, by noninvasive bioengineering measurements and by self-perception of skin irritation; 2) to give a short overview of the different chemical ingredients, which are potential cosmetic and occupational skin irritants; 3) to give a description of the different in vivo tests for measuring skin irritation and to test the efficiency of specific anti-irritant products and ingredients, and 4) to give an overview of the different possibilities to conceive anti-irritant cosmetics and treatments.

IRRITANCY AND SKIN IRRITANT EVALUATION AND SYMPTOMS

Methods to evaluate skin alterations induced by topical products can be classified in three categories [7]:

1. Clinical visual and tactile assessments
2. Instrumental noninvasive bioengineering measurements
3. Self-perception by the subjects themselves

Clinical Visual and Tactile Assessments

Several skin modifications induced by irritants can be easily evaluated visually and tactilely, e.g., by skin redness (erythema), skin dryness with increased desquamation, scaliness, and flakiness, and skin roughness or edema. Moderate to very intense signs of skin redness/erythema are the visual manifestations of a skin inflammatory process with vasodilatation of the capillary system and increase of the blood flow. After contact with an irritant (particularly with soaps and detergents), symptoms of skin dryness appear after a certain time with a whitish appearance, flakiness, scaliness, and roughness. In the most severe cases of irritation, fissuring, and cracking can also appear. Edema is the result of an accumulation of fluid from the blood vessels in the upper dermis. It appears only in very severe cases of irritancy, which happens very rarely unless in experimental conditions. The visual and tactile assessments of irritancy are made by dermatologists or trained evaluators. These observations always remain subjective in nature even with trained observers, with well-standardized clinical and experimental protocols and with well-established scoring grades. However, the clinical assessments are precise and very reproducible.

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Instrumental Noninvasive Bioengineering Measurements

Many changes in skin properties induced by irritant cosmetic ingredients can be evaluated quantitatively in a noninvasive manner by instrumental techniques. In this section the following techniques will be described: 1) skin redness by reflectance skin colorimetry and by Laser Doppler flowmetry; 2) alterations in the integrity of the barrier function by transepidermal water loss; 3) skin hydration measurements using electrical impedance and skin surface alterations using squamometry; and 4) other bioengineering methods such as elasticity and microrelief.

Skin Redness/Erythema by Measuring Skin Color

Most color measurements of the skin surface are based on reflectance colorimetry instruments, such as tristumulus color analysis, Chromameter Minolta, erythema index, Erythemameter Diastron, Mexameter Courage-Khazaka, and Dermaspectrometer Cortex [8–10].

The Minolta chromameter CR-200, considered by many investigators as a sort of reference instrument, quantifies skin surface color using the three-dimensional CIE color representation with the L*a*b* system. Skin redness is readily evaluated by means of the a* values; erythema is always characterized by an increase of the a* skin color parameter. Different, more simple, reflectance meters (Erythemameter Diastron, Mexameter Courage-Khazaka, and Dermaspectrometer Cortex) are also used [9,11]. These instruments are based on the same optical principle, namely, measurements of light absorption and reflection of respectively the melanin and hemoglobin components of the skin. The specific absorption of melanin and hemoglobin in the visible (green and red) and in the near infrared is determined and these instruments quantify redness by a relative erythema index. The erythema index is proportional to the hemoglobin content of the upper layers of the dermis.

Excellent correlations have been shown between visual clinical scoring and erythema and Chromameter measurements of the a* color parameter [12]. Furthermore, reasonably good correlations were noticed between the a* Chromameter parameter and the erythema index of the simple reflectance meters (Mexameter Courage-Khazaka and Dermaspectrometer Cortex) [9,13].

Measurement of Superficial Blood Flux by Laser Doppler Flowmetry

The hemoglobin of the red blood cells of the upper dermis microcirculation system partially absorbs the light of a helium laser beam. The laser Doppler method measures the shift in frequency of the reflected light of this laser beam. This small frequency shift is proportional to the number and the speed of red blood cells present in the superficial blood microcirculation system. An inflammatory reaction with vasodilatation of the capillaries will produce a marked increase in blood flow [14]. There two types of laser Doppler instruments: the first generation flowmeters, which measure the blood flux of a small spot area of the skin (2–3 mm^2) (Servomed, Sweden, Lisca, Sweden and Moor, United Kingdom), and more recently the development of laser Doppler imaging instruments, which has enabled the two dimensional quantitative measurement of blood microcirculation of a much larger skin area (maximum 10 cm^2) [15]. Good correlations were found between clinical assessments of irritancy and noninvasive bioengineering methods, such as skin color and laser Doppler flowmetry, respectively [16].

Alterations in the Integrity of the Barrier Function

When some irritant cosmetic ingredient comes in contact with the skin, the earliest modifications in the skin structure is an alteration of the lipidic barrier structure of the stratum corneum [17]. The physiological function of this barrier is to protect the skin from the penetration of irritants and to ensure low insensible perspiration of the skin [transepidermal water loss (TEWL)]. When the barrier function of the skin is altered by an irritant, the amount of water vapor passing through the stratum corneum is increased, which is characterized by an increase in TEWL. The two most widely used TEWL instruments are the Evaporimeter (ServoMed, Sweden) and the Tewameter (Courage-Khazaka, Germany). Both TEWL instruments are very sensitive, and the slightest alterations of the barrier function can be measured with this technique (''nonvisible'' subclinical irritation). This happens mostly when extremely mild cosmetic ingredients are tested or when normal-use application protocols are considered [18].

Alterations in the Skin Surface Hydration

The assessment of the hydration status of the superficial layers of the epidermis is an important parameter with which to characterize the skin. The hydration level of the stratum corneum remains more or less constant, taking in consideration the following mechanisms: 1) hydration coming from the deeper layers of the fully hydrated viable epidermis and retarded from evaporation in the stratum corneum by the lipids from the hydrolipidic barrier, 2) hydration due to equilibrium with the external ambient humidity, and 3) the presence of entrapped water bound to the natural moisturing factors (NMF) present in the layers of the stratum corneum. When an irritant cosmetic ingredient, such as a surfactant, interacts with the skin surface, it partially or completely removes the lipidic film coating the surface of these and extracts some NMF components altering the equilibrium mechanism of the hydration of the skin surface. Such a dehydration of the horny layer will have many different consequences, such as 1) increase of the desquamation rate of the corneocytes giving the skin a scaly aspect, 2) a modification of the relief of the skin with a rough and wrinkled appearance, and 3) modifications in the viscoelastic properties of the stratum corneum. The modifications in the hydration level of the stratum corneum have been extensively investigated using bioengineering methods based on the electrical impedance to the skin to an alternating current [19]. Many commercial instruments measure the electrical properties of the skin, such as capacitance, impedance, and conductance methods. The measured electrical properties of the superficial layers of the epidermis (impedance units or arbitrary electrical units) are indirectly related to the amount of water present in the horny layer. When used under standard conditions and in thermostatized experimental rooms, all the instruments are able to provide highly accurate and reproducible hydration values. Excellent correlations were obtained between the visual scoring of skin dryness induced by surfactants in a soap chamber test and instrumental readings [20].

Skin-Surface Stripping Tests

The investigation of skin-surface alterations has made great progress by the development and use of skin-surface stripping systems. The superficial layers of the stratum corneum can be easily collected, and without any damage for the viable epidermis, simply by pressing a sticky tape on the skin (D-Squames). When removing the sticky tape after a few seconds, several layers of corneocytes are collected and can be analyzed. The level of desquamation can be quantified by squamometry, which is the staining of the corneocytes

and measuring the amount of color [21]. The degree of cohesion between the corneocytes can be measured by visual scoring under the microscope and by image analysis. With some surfactants, no clinical irritation could be observed; however, they induce significant changes at the surface of the stratum corneum as shown by an increase of the amount of corneocytes and a deorganization/loss of the intercorneocyte cohesion [21,22].

Other Noninvasive Bioengineering Methods

Other methods are available to measure some symptoms of skin irritancy, but will not be described in this chapter. Skin dryness and roughness as induced by some irritants can be evaluated by the following techniques: (1) measurement of the viscoelastic properties of the upper layers of the epidermis [23], and (2) skin surface microrelief [24–26].

Self-Perception of Skin Irritations

Generally when a finished cosmetic product comes into contact with the skin of potential consumers, it is very unlikely that observable signs of irritation are noticed in normal use. However, the overall perception of the finished product by the consumer is an important criterion for accepting its cosmetic use. In this global perception many different parameters may play a role, some independant of the potential irritancy of ingredients, such as feeling of aesthetic nature, ease of spreading on the skin, viscosity, perfume, and color. However, the subjective perception of skin feel is closely related to the composition of the cosmetic product. Skin feel attributes, such as self-perception of dryness (feels tight, rough, and dry), or irritation (itching and burning), softness, and smoothness are easily perceived by the subjects. In most cases, the subjects are able to perceive very early on the effects of some cosmetics on the skin well before they become clinically observable or measurable by bioengineering techniques. The assessment of the self-perception of the interaction between some cosmetic ingredients with the stratum corneum is performed by means of questionnaires where several skin attributes are evaluated. Some questionnaires are designed to receive an answer Yes or No to each of the attributes, or the subject will have to rate each of the attributes on a 0 to 10 point scale.

FACTORS THAT INFLUENCE SKIN RESPONSIVENESS TO IRRITANTS

Many factors can influence the responsiveness of a consumer's skin to a potential irritant. Some factors are intrinsic, inherent to the subjects themselves (e.g., sensitive skin, atopic skin), the body site, and previous traumas to the considered skin area. Other factors are external, such as composition of product, conditions of exposure, occupation of the subject, and climatic factors [4,5,7]. The reason why these factors are covered in this chapter are evident. Some cosmetics with anti-irritant ingredients are designed for some specific skin sites, such as the face, or considered as seasonal products, such as cosmetics against winter dryness of the skin.

Factors inherent to the constitution of the skin of the subjects that may influence skin responsiveness are numerous. A marked interindividual variability in response to irritants have been reported and ascribed to host-related factors. Considering the interindividual variability of subjects to skin irritants, one must mention here the concept of ''sensitive skin.'' The term sensitive skin clearly has a different meaning for consumers than for cosmetic scientists and dermatologists [4,6]. Consumers use the term *sensitive skin* to indicate that their skin readily experiences adverse reactions or unwanted changes to

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external factors, such as the use of personal care products. Subjects with sensitive skin tend to more readily develop skin reactions to cosmetics and other topical drugs than do normal persons. Many attempts have been made by cosmetic scientists and dermatologists to describe and demonstrate in a scientific way what sensitive skin is. Visible effects, such as erythema and skin dryness, are noticed. However, half of adverse reactions are purely sensory perceptions, subjective symptoms of stinging, itching, burning, and feelings of dryness with or without visible effects.

Regional Differences in the Sensitivity of Normal Skin

It has been clearly demonstrated that when measuring the potential irritancy of cosmetic ingredients, great regional differences in the sensitivity of normal skin are observed [27,28]. Several factors must be considered in order to explain the observed regional differences in skin sensitivity, such as differences in total skin thickness, skin permeability, the amount and composition of epidermal and sebaceous lipids, blood microcirculation, hydration level of the horny layer, thickness of the horny layer, and desquamation rate and local daily exposure to irritant products. Most skin-irritation phenomena are noticed in the face.

Influence of Gender, Age, and Ethnic Group

Contradictory data are presented in the scientific literature about the influence of ethnic group on skin sensitivity [29]. It has been demonstrated that the irritant response may be higher in babies and children and decrease with age [30]. Concerning skin sensibility to irritants related to gender, many studies show that women are more reactive than men [31,32]. However, this difference could be attributable to the fact that women are more exposed to household chemicals and more frequently use face care cosmetics, rather than related to real physiological differences. Other factors are external to the subject, such as composition of their usual products, conditions of exposure, occupation of the subject, and climatic factors.

Mode of Exposure of the Product on the Skin

Acute skin exposures of a very irritant chemical cosmetic ingredient are very rare and attributable to accidents, inadequate use, or problems in the manufacturing of the cosmetic product. The list of very irritant products are known and must be totally avoided or used at very low concentrations; we will be dealing mostly with subacute and chronic exposure of the skin. Subacute exposure will provoke an immediate impairment of the skin barrier. Repeated exposures to certain cosmetic products with very limited impairment of the skin barrier can induce, after a certain time, significant cutaneous reactions.

Climatic Factors

There is clearly a seasonal or climatic effect on the amplitude of the skin irritation reaction. Generally, much higher irritation reactions are observed in winter than in summer. This difference is related to a dehydration factor: a situation of dryness of the horny layer provoked by ambient air with very low relative humidity. This situation is particulary present on the lower legs and more frequent in older subjects; typical symptoms include winter xerosis, extreme dryness, scaling, and rough skin surface. Furthermore, in the win-

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ter the epidermis is more aggressed by extreme temperature changes between the inside and outside world. In the summer period, the upper layers of the epidermis are well hydrated, and the skin is smooth unless excessively exposed to sun damage. Actinic aging of the skin is characterized by various clinical symptoms, including dryness of the skin.

COSMETIC AND OCCUPATIONAL SKIN IRRITANTS

Occupational Skin Irritants

A broad definition of occupational contact irritant dermatitis is contact dermatitis caused wholly or partially by the occupation of the subject. Occupational irritants may cause an acute response that may take from 1 hour to 1 day to appear, and is usually traceable to a single factor. Chronic irritant contact dermatitis may take months or years to appear and is often multifactorial [33]. Hands are involved in 80 to 90% of all cases of occupational contact dermatitis, and in the minority of cases the wrist, forearm, lower leg, or face is the primary site.

The clinical features are described as follows. Many cases of occupational irritant contact dermatitis start as erythema and scaling on the back of joints and adjacent parts of the back of the fingers, as well as in the web spaces between the fingers. A generalized, rather shiny, superficially fissured, scaly fingertip dermatitis is also characteristic of certain forms of irritancy. Exclusive or more severe involvement of the thumb, index finger, and/or middle finger of the dominant hand (or of the nails) is generally an indication of possible occupational causation [33]. The principal occupational irritants are listed in Table 1.

Cosmetic Skin Irritants

Cosmetics are complex mixtures of chemical compounds. The abundance of commercially available ingredients has created endless variety in cosmetic formulation. The cosmetic substances used in cosmetic products may be arbitrarily divided in great categories of product and/or function. The principal categories of cosmetic irritants are listed in Table 2.

Intolerance to some ingredients is related to symptoms of contact dermatitis and allergic dermatitis. There is not always a clear distinction between these problems. Some cosmetic ingredients present both an irritant character with the additional possibility of allergic reaction (e.g., cinnamic acid derivates). An overview of cosmetic categories causing irritant side effects in descending importance has been given by A. C. de Groot and coworkers [1–3] and are summarized briefly in Table 3. It has clearly been shown that certain categories of cosmetics, taking into account their composition, frequency of use, mode of application on the skin, and skin area to be treated, are more specific candidates for causing symptoms of skin irritation.

A short overview will be given of the potential irritant character of each category of cosmetic ingredients. Some chemicals are used in industry (occupational irritants) as well as in the cosmetic world (cosmetic irritants). Chapter 37 describes the irritancy of the most frequent emulgators and detergents used primarily in cleansing products.

Preservatives/antimicrobials, antioxidants, fragrances, colors, and UV filters are potentially irritant components. However, these components are often present in cosmetic preparations at low concentrations and are consequently not affecting the overall irritation potential of the final product. These substances are more often incriminated for their allergic reactions.

TABLE 1 Common Irritants in Occupational Dermatitis

Skin cleansers	Soaps, detergents, specific cleansers
Industrial cleaning agents	Detergents, emulsifiers, solubilizers, wetting agents, enzymes
Organic solvents	Alkanes, alkenes, halogenalkanes and alkenes, alcohols, ketones, aldehydes, esthers, ethers, toluene, carbon sulfide, petroleum derivates, silicones
Oils	Cutting oils, metal working fluids, lubrificating oils, braking oils
Acids	Severe irritants are sulfuric, chromic, nitric chlorhydric, hyperchloric, fluorhydric and trichloroacetic acids; milder irritants are formic, acetic, propionic, oxalic, and salycilic acids
Alkaline substances	Soaps, soda, ammonia, sodium, potassium and calcium hydroxides, various amines
Oxidizing agents	Hydrogen peroxide and peroxides, benzoyl peroxide, sodium (hypo) chlorate and bromate
Reducing agents	Phenols, aldehydes (formaldehyde), thioglycolates, hydrazines
Plants	Various plants are potentially irritant, especially the *Euphorbiaceae*, *Brassicaceae*, *Ranunculeae* families
Products of animal, food proteins, plant, and bacterial origin	Proteolytic enzymes such as pepsine, papaine, trypsine, subtilisine
Physical factors	

Source: Ref. 5.

TABLE 2 Common Potential Cosmetic Irritant Ingredients

Conservatives/antimicrobials
Antioxidants
Fragrance
Colors
UV filters
Lipids
Organic solvents
Emulgators, surfactants, and rheological agents
Humectants and emollients
Specific cosmetic ingredients such as keratolytic agents, tanning and whitening agents

Source: From Refs. 2 and 4.

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TABLE 3 Cosmetic Categories Causing Irritant Side Effects*

Soap
Deodorant/antiperspirant
Moisturizing/emollient
Aftershave
Shampoo
Lipstick
Hair dye
Perfume

* In descending importance.
Source: Refs. 2 and 3.

Lipids/Emollients

Most oils and fats are relatively mild. However, some oils from plant origin are incriminated for their allergic reactions. Emulgators, surfactants and rheological agents. Some surfactants are known to be rather irritant. These substances are usually classsified as follows, going from the most irritating to the mildest:

cationics
anionics
amphoterics
nonionics

In shampoos and body and shower gels or creams anionic detergents are rarely used alone but rather in combination with amphoterics and nonionic surfactants. In creams and milks nonionic and amphoteric emulgators are essentially used for their mildness.

Humectants

The classical humectants such as NMF are nonirritant. The other humectants such as proteins, hyaluronic acid, chitosan, proteoglycans, and polysaccharides are very rarely irritant components.

Specific cosmetic ingredients, such as keratolytic agents, tanning and whitening agents, etc., can be more irritant.

In the use of AHAs, irritancy increases with concentration and with a decrease in pH, which is controlled by the proportion of free acid to AHA salts. Classic alkaline soaps were potentially irritant because of the rise in skin pH and induction of skin dryness. Modern soaps are actually very mild because they are buffered to neutral or slightly acidic pH and contain lipids such as emollients and humectants.

Solvents in Aftershave Products

The irritancy of these products is easily related to the very high alcohol content (usually more than 50%) of this category of cosmetics. Alcohol dehydrates the skin and the skin that has been predamaged by the wet or dry shaving process.

TESTS FOR MEASURING SKIN IRRITATION

Tests for evaluating the irritation potential of a cosmetic ingredient or a finished product are considered in a progressive approach to the problem [7].

First, a minimum of toxicological information must be obtained from the general available scientific literature and from information derived from in vitro testing and testing on animals. Starting with the premises that the considered ingredient or product is not toxic or very irritant, testing on humans will be envisaged. A short overview of the different published test method will be given in this chapter. Supplementary information concerning the test methods can be found in Chapter 12 and in a recent review article by Paye [7].

Open Epicutaneous Applications

In a second phase of testing, single and eventual repetitive open application tests are normally used for studying new chemicals with a safety purpose in order to determine if this ingredient is likely to cause serious skin irritation [34].

Occlusive Patch Testing

If the product is not irritant in such open epicutaneous applications, it can be considered to use occlusive patch tests in a further phase. The objective of the clinical study is to compare the mildness or irritation potential of a certain cosmetic ingredient with other similar products. For this purpose some level of cutaneous irritation has to be induced. Generally we are dealing with very mild cosmetic products and it is necessary to include in the comparative testing some more irritating products as a positive reference. By using occlusive conditions one induces a better percutaneous diffusion of the test solution through the horny layer. Occlusion increases the hydration of this layer (increase in percutaneous penetration) and slight increase of skin temperature under the occlusive dressing.

Many variants of occlusive patch tests have been described in the literature [7], some of the most used tests are:

- The single 24-hour occlusive test [35,36]
- Successive occlusive applications, such as the Frosch-Kligman soap chamber test [37], the modified soap chamber test [18]
- The 21-day cumulative irritation test [37]
- The 4-hour occlusive test [38]

Skin irritation is evaluated clinically (visual and tactile) for erythema, dryness, scaling, roughness, and edema, and/or by bioengineering methods.

The Exaggerated Use Tests

The occlusive patch tests were developed as a rapid screening test for evaluating the relative irritation potential of cosmetic products and ingredients. However, these conditions do not simulate the normal usage of the test materials, and other test procedures were developed to be closer to realistic use conditions of the product by the consumer [39]. These exaggerated use tests combine the application of the product to its normal way but still in an exaggerated way: the number of applications per day and the total duration and temperature of application is exaggerated in order to induce more skin irritation reactions than expected in normal use. Several protocols have been published, differing in terms of sort of application, number of applications, skin sites, and so on [7]. Most of these exaggerated in-use tests are concerned with soaps and detergents, but can,

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with the necessary experimental adaptations, be used for other cosmetic preparations, such as the following:

- The forearm wash test [39]
- The flex wash test [40]
- The hand/forearm immersion test [41]

One advantage of these testing methods is the fact that they are carried out on a relatively small number of subjects [12–25].

Home-Use Testing

Even if the exaggerated in-use tests predict with good confidence the skin tolerance of a certain ingredient or product, it is necessary and safer for the manufacturer to run an extended study with a large number of subjects using the product in normal way and in their usual environment, so it is called a ''home-use test'' or ''in-use test.''

The panel will be selected among the population of potential users, e.g., for the target group and for the type of treatment. The duration of the testing is generally for a much longer period (weeks and sometimes months). Any unwanted effects of the product on the skin are recorded, such as visible signs of intolerance (redness, dryness, roughness,) as well as nonvisible perceptions such as itching, burning and tightness. Evaluations of these signs are made very regularly (most cases daily) by the subjects themselves and once a week by an expert evaluator. Usually clinical ratings by visual and tactile assessment are made using numerical grades. They can be completed by instrumental noninvasive bioengineering measurements.

STRATEGY OF MAKING ANTI-IRRITANT COSMETICS

Strictly by definition, an anti-irritant is an agent which, by its presence, minimizes the irritating effect of a cosmetic preparation on the skin. The anti-irritant could reflect all mechanisms that have an opposed effect to an irritant insult. Hence, the term could reflect actions such as skin calming, soothing, and healing, and assisting in the recovery of the skin from an irritation provoked by, e.g., contact with soaps and household cleaning products. As has been demonstrated earlier, very often irritant reactions are associated with inflammation, the so-called anti-irritant effect could eventually also mean alleviation from the inflammatory symptoms that arise shortly after the impairment of the skin barrier. The concept of anti-irritant activity also includes skin protection with barrier creams, which decrease irritant potential of some harmful substances encountered in occupational dermatitis [33]. Despite the numerous claims of skincare products for anti-irritant or protective activity, some lack of scientific data is present to substantiate these claims. There is also a lack of suitable standardized clinical protocols to quantify these anti-irritant properties.

The basic principle of development of general anti-irritant cosmetics or cosmetics for sensitive skin is to avoid as much as possible any risk of irritation [4, 42]. The safest way is to use well-tolerated, chemical compounds for the vehicle and active ingredients without history of ''skin problems.'' Allergic reactions and skin irritancy are generally provoked by known specific ingredients, mostly fragrances, colors, and preservatives. The easy task is to remove fragrances and coloring agents; hypoallergenic cosmetics minimize

the use of or do not contain these ingredients. Actually, a modern trend in cosmetics is to develop specific cosmetics without preservatives. This challenge can be partially answered in cosmetic preparations with none or low water content: oils, fats, water/oil emulsions, and lipogels using some synthetic lipids and/or essential oils with bactericidal properties as preservatives. With aqueous solutions, hydrogels, and oil/water emulsions, this goal is very difficult to achieve and presently not realized; consequently, these types of cosmetics still contain preservatives.

In order to elaborate an anti-irritant cosmetic preparation or a cosmetic preparation for sensitive skin, we have a choice from the following possibilities:

1. The vehicle must respect the natural, slightly acidic pH of the skin (pH around 5.3) or be neutral, avoiding alkaline preparations.
2. Strengthen or restore the hydrolipidic barrier function of the skin. As described earlier in this chapter, irritancy reactions are often accompanied by modifications of the structure of the intercellular lipids and water binding capacity resulting in an increase of TEWL and consequently higher penetration rate of irritants. Therefore, anti-irritant preparations should restore the disturbed barrier function by providing the appropriate lipids to the lipidic film. Modern skin care products contain endogeneous components of epidermal lipids such as ceramides and gamma linoleic acid. In a general way, lipids are emollients with soothing capacities.
3. Soothing effect by filmogen compounds. The skin surface is anionic in character. Quaternized derivatives of plant proteins or emollients that are positively charged will smooth the skin surface by a filmogen effect.
4. Irritated skin is very often partially dehydrated skin. In order to alleviate the symptoms of dehydration, water is brought back to the horny layer by humectants (NMF) or by occlusive effect of water/oil emulsions, lipogels, or silicone oils.
5. Use of very mild surfactants and emulgators in cosmetic preparations. General use of amphoteric and nonionic emulgators in creams/milks and cleansing products. In the preparation of shampoos and shower gels, use of anionic emulsifiers with an adequate carbon chain length and sufficient degree of ethoxylation in order to reduce irritancy. Another possibility is to use an adequate mixture of several surfactants. A strong antagonism effect occurs when combining the potential irritant anionic surfactants with amphoterics, nonionic, or even other anionic surfactants with resultant decreased skin irritation [7].
6. Use of specific anti-irritant ingredients. There are a lot of soothing ingredients in dermatological treatments mainly from plant origin, such as hamamelis, algae, chamomile, and aloe vera. Polysaccharides, proteoglycans, and glycoproteins with filmogen and hydrating properties can provide a feel of less or nonirritated skin. Polymers, when used at high concentrations, have also been demonstrated as reducing the irritation potential of anionic surfactants, essentially by entrapping high quantities of surfactants into micelles in solution (see Chap. 23).
7. Sun exposure without UV filters can induce or increase irritant reactions of the skin and accelerate actinic aging. The cosmetic industry has developed suncare products with very high sun protection factors that are waterproof and with reasonably good cosmetic acceptance. There are sun protection products with

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active UV filters with the lowest allergenic potential, especially developed for sensitive skin with a minimum amount of emulgators and are fragrance free.

IN VIVO STUDIES OF THE ANTI-IRRITATION PROPERTIES OF SOME COSMETIC INGREDIENTS

In vivo evaluation of the anti-irritant and/or anti-inflammatory effect of dermatocosmetic formulations on human skin is usually based on the quantification of the inhibition presented by these products against an artificially induced contact dermatitis [42]. The model irritant for this purpose can be selected out of a wide range of skin-aggravating factors. Irritation of the skin can be provoked after topical application of Peru balsam [43], solutions of anionic surfactants [44,45], nicotinates [46,47], after exposure to UV-B radiation [48,49], skin abrasion [50], or tape stripping [51,52]. There is clearly a difficulty in identifying the conditions under which these various irritants can be used for inducing a ''suitable'' irritation. The induced irritation should be great enough to be measurable with good reproducibility and to allow quantification of its inhibition by the tested products. The anionic surfactant sodium lauryl sulphate (SLS) has lately become the model irritant of choice, used widely for inducing experimental contact dermatitis in anti-irritation protocols [45,53–55] or as a reference irritant in safety tests ranking the skin irritation potential of soaps and detergents [56–58]. The irritant character of SLS is attributable to the following factors:

1. Modification of the protein and lipid structure of the stratum corneum. Impairment of the highly ordered bilayers and changes in the fluidity of the lipids [59]. Swelling of the horny layer occurs because of protein denaturation and exposure of new water-binding sites of the keratins [54].
2. Alterations in skin permeability [60]. This surfactant is often used as a pretreatment in order to enhance the penetration of topically applied products [45].
3. SLS causes a vascular inflammatory response [61–62]. SLS is not a sensitizer or carcinogenic agent; it causes no systemic toxicity or permanent cosmetic inconvenience to the skin [45]. The great sensitivity of TEWL parameter in quantifying the impairment of the barrier caused by SLS [63] and the property as a primary irritant have led to the large use of this surfactant in studies of experimental irritant contact dermatitis. However, as for other irritants, the induced cutaneous irritation is not completely reproducible. A marked interindividual variability in response has been reported for this irritant and is ascribed to several host-related factors [42, 45, 64]. Furthermore, intraindividual variability within anatomical regions of skin site have been reported [65]. In the experimental study of the anti-irritant properties of a cosmetic ingredient, three different types of clinical protocol are generally used: postirritation treatment protocols, pretreatment protocols, and treatment with the combined introduction of the anti-irritant into the irritant product.

In the postirritation treatment protocol, the considered skin regions are irritated by treatment with SLS during a certain time and with a certain frequency. After the SLS irritation challenge the skin areas are treated with the anti-irritant ingredient or finished product during a certain time and frequency. One irritated area remains untreated and serves as

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a control and the irritated areas are respectively treated with the vehicle alone and with the vehicle containing the active anti-irritant ingredient. This last site should heal significantly quicker than the vehicle-treated site. In the pretreatment protocol, the considered skin areas are pretreated during a certain time and frequency with either the vehicle alone or the vehicle with the anti-irritant component. A nonpretreated skin area serves as a control. Following this pretreatment the different skin areas are irritated with a SLS solution.

The typical clinical signs of skin irritancy (redness and dryness) are visually assessed by trained evaluators. Furthermore, redness is quantified by skin color (reflectance colorimetry) and microcirculation of the bloof flux by Laser Doppler flowmetry. Alterations in the barrier function are measured by TEWL and hydration is measured by electrical impedance of the skin. In order to obtain a significant measurable irritancy, the SLS challenge is carried under occlusive dressing. It can also be treated by repetitive open applications with the SLS solution. Different anti-irritant experimental protocols are described in the scientific literature [42].

As found in the literature, these studies are often concerned with the anti-irritant properties of plant extracts. Here follows a short overview of the anti-inflammatory/anti-irritant studies described in the literature:

- Anti-inflammatory properties of the active ingredients α-bisabolol and azulene of chamomile oil [66–69]
- Anti-inflammatory and healing effect of a cream containing glycolic extract of six plants (calendula, Roman and German chamomile, linden, cornflower, and millepertuis) [70]
- Anti-inflammatory effect of the active ingredient namely esculoside extracted from horse chestnut [71]
- Anti-inflammatory properties of the active ingredient, namely ursolic acid extracted from rosemary [72]
- Anti-irritant properties of a preparation containing licorice and chamomile against a wide range of daily life skin irritations (aftershave, depilation, solar erythema, and insect stings) [73]

All these studies differ with respect to the irritation challenge and with respect to the anti-irritant treatment. In both type of protocols, namely postirritation treatment and pretreatment with the anti-irritant cosmetic ingredients, significant anti-irritant effects were observed between the treated skin sites and the untreated skin sites used as a reference. With more discriminative protocols (double-blind vehicle-controlled), where the anti-irritancy efficiency of an anti-irritant ingredient solubilized or dispersed in suitable vehicles (water/oil or oil/water) is compared with the efficiency of the vehicle alone, one generally expects that the specific effect of the anti-irritant alone will be very small and not very often significantly different from that of the vehicle alone. To illustrate this statement, we refer to recent work on plant anti-irritants [42]. Manou [42] has studied, in a double-blind vehicle-controlled way, the potential anti-irritant properties of essential oils and glycolic extracts obtained from different plants such as chamomile, sage, clary sage, peppermint, and hyssop. The essential oils were solubilized at a concentration of 3 to 5% in oil/water and water/oil vehicles. The anti-irritant properties were examined according to the postirritation treatment protocols and pretreatment protocols using visual clinical assessments of redness and dryness and bioengineering methods (skin color, laser Doppler flowmetry, TEWL, and hydration). The results do not support the existence of a significant anti-irritant effect of the essential oils tested under these very strict conditions. In general, the

treated skin was found to have benefited from the treatment with the vehicle with or without the essential oils, compared with the irritated but untreated skin. These results could be explained taking in account the following points. First, the concentration range of the active anti-irritant ingredients used in these experiments is rather low (3–5%), and are concentrations that can be found in commercial cosmetic preparations. Probably at higher concentrations (5–10%) a significant specific anti-irritant effect will be observed, but because of the problems of high cost of these plant extracts and the possibility of increasing the risk for allergic contact dermatitis, these higher concentrations are rarely used in commercial cosmetic preparations. Secondly, there is always a significant anti-irritant, anti-inflammatory effect on the skin of the lipids and emollients present in the vehicle.

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Anti-irritants for Surfactant-Based Products

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In the scientific literature, sodium lauryl sulfate (SLS) is regularly used as the ''gold'' model to induce skin irritation [1]. This is for several reasons:

1. SLS is classified as a skin irritant, Xi-R38 [2],
2. SLS can be obtained in a very pure form, which allows different laboratories to work on the same material,
3. SLS can be easily formulated in various vehicles,
4. Although a few cases were reported [3], allergic reactions to SLS are not frequent, and
5. The level of induced irritation can be more or less controlled by adjusting the concentration [4,5], and any skin damage is rapidly reversible.

However, SLS is not the only surfactant to be an irritant to the skin, and even if some surfactants are not classified as such by the Dangerous Substances Directive [2], in certain conditions and concentrations all surfactants can be regarded as potential irritants to different degrees. This paragraph will, however, mainly focus on anionic surfactants, as they are mostly used in toiletries and require the most attention in order to optimize their skin compatibility in finished products.

Fortunately, nowadays many systems have been developed to minimize the risks of intolerance in hygiene cosmetics or surfactant-based products. This is extremely important because hygiene habits have strongly evolved over the years. Not so long ago, people came into contact with surfactants only once a day maximum with the only objective being to clean themselves; today it is not unusual to see people having several showers a day not only for cleaning themselves but also for pleasure and relaxation. So far, toilet products must be as mild as possible for the skin. Not only are the mildest ingredients used, but finished hygiene products also have to contain one or more of the following anti-irritant systems.

ANTI-IRRITATION BY AN APPROPRIATE COMBINATION OF SURFACTANTS

Although rarely described as an anti-irritation system, this approach, in my view, should be regarded as the most potent one to get a very mild surfactant-based product. The best

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counterirritants for surfactants are other surfactants. Several investigators have clearly shown such a positive interaction between various surfactants both in vitro [6,7] and in vivo [8–10], as well as with diluted [6–8] and highly concentrated solutions [9,10]. Amphoteric surfactants are probably best known to decrease the irritation potential of anionic ones [11], but nonionic surfactant can have the same effect as well when used at a sufficiently high concentration. More suprisingly, a well-selected anionic surfactant can also reduce the irritation potential of another anionic surfactant, instead of cumulating their effects [9].

The suspected mechanism occurring in this system is linked to the formation of larger and mainly more stable micelles of surfactants when several surfactants are present in the same solution. It has been described in Chapter 36 [12] that surfactants in aqueous solutions tend to assemble by their hydrophobic tail and form micelles. The totality of surfactants is, however, not entrapped into the micelles and the micelles are not static structures. They form and dissociate constantly at a rate depending on the type of surfactants entering into their composition. Importantly, even if micelles are capable of permeabilizing the skin barrier by interacting with the lipids [10], they do not irritate skin by themselves; only the monomers of surfactant can directly interact with the skin proteins and cause irritation. Forming larger and more stable micelles by an appropriate combination of surfactants can thus decrease the relative amount of monomers available to irritate the skin. Such a mechanism is well acccepted, but it would be too simplistic to consider that it is the only one. For instance, the addition of a secondary surfactant milder than the primary one could decrease the binding to skin surface of this latter by occupying and competing for the same binding site. Although such a mechanism has not been clearly shown yet as being a cause for anti-irritation, it looks quite realistic and possible when using two anionic surfactants in view of surfactant binding studies showing that various anionic surfactants saturate the skin surface from a very similar concentration (personal data). Furthermore, a decrease of binding of anionic surfactants to skin surface has been shown by attenuated total reflectance—Fourier transformed infrared spectroscopy (ATR—FTIR) in presence of a secondary surfactant of any type (personal data). However, this could be the consequence of the bulk effect previously described and not a direct cause of anti-irritation.

ANTI-IRRITATION BY POLYMERS OR PROTEINS/PEPTIDES

The counterirritant capability of polymers or proteins on surfactants has been known from literature data for a long time [13–16]. The mechanism by which they function is similar to the one previously described above for surfactant mixtures, being incorporated into the micelles to decrease the relative amount of free monomers into the solutions. Their usual skin substantivity can also involve some hiding of binding site at the surface of the skin for the surfactants.

All polymers are not equally effective to be incorporated into the micelles or to interact with the skin surface; when selecting a polymer/protein, the following parameters should be considered:

1. A better interaction with the micelles is obtained when the hydrophobicity increases [13]
2. A better substantivity with the skin is obtained when the hydrophobicity increases, such as when the polymer is quaternized or cationic or when the net charge or the size of the polymer/protein increases [14–16]

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In view of these properties, more hydrophobic and/or larger polymers/proteins are much more effective to depress the skin irritation potential of surfactants. However, in the literature the anti-irritant effect of proteins/polymers onto surfactants has usually been shown in a single surfactant solution, and at a high polymer-surfactant ratio that is often incompatible with a finished product for stickiness, formulation, foaming, or cost reasons. From my experience, many polymers or proteins, described as depressors of irritation, do not bring any additional benefit on the clinical mildness of the product when they are formulated into a finished product that has already been optimized for skin compatibility through an appropriate combination of surfactants. In some cases, however, those polymers have been shown to reduce the penetration of the surfactants into the stratum corneum in conditions where nonexaggerated application tests are run, but not in occlusive patch tests that would enforce such a penetration whether in the presence or absence of a polymer (personal data).

ANTI-IRRITATION BY REFATTENING AGENTS

One of the effects of surfactants on skin is the alteration of its permeability barrier, which can be easily assessed by measuring the transepidermal water loss [17,18]. Using refattening ingredients or skin barrier repairing ingredients in the surfactant-based product can lead to a reduction of irritation if appropriately delivered to the skin surface. Such ingredients are often the basis for barrier cream effect when topically applied before or after contact with an irritant. Some of these ingredients can, however, be formulated into a surfactant system to act directly as anti-irritants in the mixture. The occlusive effect they bring at the surface of the skin delays the water loss and maintains the skin in a less dehydrated state. Furthermore, they can introduce a barrier that can protect the skin against surfactants when running repetitive applications. Several types of refattening ingredients are available and can be formulated in surfactant systems, such as ethoxylated mono-, di-, and triglycerides, fatty alcohols and ethoxylated fatty alcohols, fatty acid esters, lanolin derivatives, or silicone derivatives. A few products containing a high percentage of oil also exist on the market and can possibly play such a role.

ANTI-INFLAMMATORY EFFECT

Ingredients with an anti-inflammatory effect are not specific for surfactants and are described in the other sections of this chapter. Such ingredients act directly at the skin level and it is obvious that they have no anti-inflammatory effect in solution. In order to be effective, they must be delivered to the skin in a bioavailable form and in sufficient amount.

ANTISENSORY IRRITATION

Although much less discussed than the clinical irritation that is characterized by observable or functional alterations, subjective irritation also exists. It does not have great interest for the dermatologists, but for cosmetologists it can be the reason for the success or rejection of their product. Two types of sensory irritation can be observed by the consumer: itching, stinging, or burning sensations, and unpleasant rough, dry tight sensations. Anti-irritant systems for the former sensations are described in Chapter 25 [19]. Regarding the latter sensations, the irritation perception can be addressed in two ways: by reformulating the surfactant system or by introducing ''good'' skin feel additives. Each surfactant pro-

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vides in itself a specific perception on the skin of the consumer, going from smooth (perception of nonirritated skin) to dry/tight (perception of irritated skin) skin feel. Adapting a combination of surfactants can allow formulators to provide the expected feel. However, if constraints in the choice of surfactants does not allow moving away from an ''irritated'' feel, it is still possible to add skin feel additives into the product in order for the product to be perceived as smoothing or hydrating the surface of the skin. Skin feel additives have been reviewed in Chapter 35 [20]. In the consumer view, this will often be considered as a milder product.

MAGNESIUM AND DIVALENT CATIONS ARE NOT ANTI-IRRITANTS FOR SURFACTANTS

Magnesium is frequently described as a depressor of skin irritation [21]. Such a false idea is essentially arising from in vitro data based on protein denaturation tests. In those tests, the more a surfactant solution denatures a protein, the more it is predicted to be an irritant for the skin, and magnesium clearly depresses surfactant-induced protein denaturation in vitro [22]. However, when well-controlled in vivo tests are performed to investigate the effect of magnesium directly on human volunteers, it comes out unambiguously that magnesium does not decrease the skin irritation potential of surfactants or surfactant-based products [21]. The in vivo studies included both acute irritation by occlusive patch tests and chronic irritation by repetitive short-term applications of the products. The study compared sodium and magnesium salts of surfactants (e.g., magnesium and sodium lauryl sulfate) in single solutions or incorporated into finished products, and investigated the effect of adding magnesium sulfate to a solution of surfactant. Some preliminary studies with calcium showed a similar behavior as magnesium (personal data) both in vitro and in vivo.

CONCLUSION

This chapter briefly reviews several systems by which it is now possible to control the skin irritation potential of surfactant-based products. This can be done

1. Through a modification of their behavior in solution,
2. Through a modification of their interaction with the surface of the skin,
3. Through a protection of the skin surface via the solution, and
4. Through an action onto the inflammatory process.

This last mechanism is, however, not specific at all to surfactant systems and has been reviewed in other parts of this chapter.

These anti-irritant systems, combined with a selection of mild surfactants, allow the cosmetic formulator to design very mild hygiene products. In the synthesis or chemical transformation of surfactants, it is also possible to modify the surfactant molecule to make it less irritating for the skin. This can be done by modifying the carbon chain length, by grafting fatty chains to the surfactant, or by increasing the ethoxylation level of the surfactant. Such modifications are, however, not directly considered anti-irritant systems, even if their goal and consequence is usually a decrease of the overall irritation potential.

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The Case of Alpha-Bisabolol

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INTRODUCTION

In the inflammatory process, monocytes leave the blood and enter the tissue at the site of inflammation as part of the cellular infiltrate. The tissue endothelial cells in inflammation express adhesion molecules to which monocytes adhere, then they penetrate through the endothelium into the tissue along a gradient of inflammation signals. The metabolites of the arachidonic acid cascade (Fig. 1), like leukotriene, prostaglandin, as well as oxygen radicals, play an important role.

Chamomile is one of the most popular plants in medicine as well as in cosmetics. Its active ingredients are essential oils with a blue color coming from chamazulen—yellow flavonoids as well as some coumarins and mucilage among others.

The essential oil has an excellent anti-inflammatory effect according to its chamazulene, (−)-α-bisabolol, -oxides, and enindicycloether content [1]. This is the reason why we have chosen chamomile ingredients, and especially Bisabolol, as an example of anti-irritants and how these ingredients actually work.

The major constituents of chamomile are: Matricin, (−)-α-bisabolol, bisabololoxides A and B, flavonoids (apigenin, apigenin-7-glucosides), and cis-trans-en-in-dicycloether. Chamazulen is formed from matricin. Matricin will be transferred by steam distillation into chamazulencarbonacid and further to chamazulen during extraction of the essential oil (Fig. 2).

Alpha-bisabolol is a sesquiterpene component (Fig. 3), which was detected by Isaac et al. [2] The antiphlogistic property was demonstrated in several animal tests [3–5]. In an in vitro study, Ammon et al. [6] described the mechanism of the activity of chamomile ingredients. (−)-α-Bisabolol works by inhibiting 5-lipoxygenase and cyclooxygenase. There is no inhibition of the 12-lipoxygenase and (−)-α-bisabolol does not have any antioxidant properties. The author found that bisabolol is effective at a concentration level of about 30 to 80 micromoles to inhibit 50% of the enzyme activity.

In 1983, Guillot et al. [7] compared the anti-irritant properties of various ingredients used in cosmetic products (Table 1). In this study, he made an emulsion irritating by the

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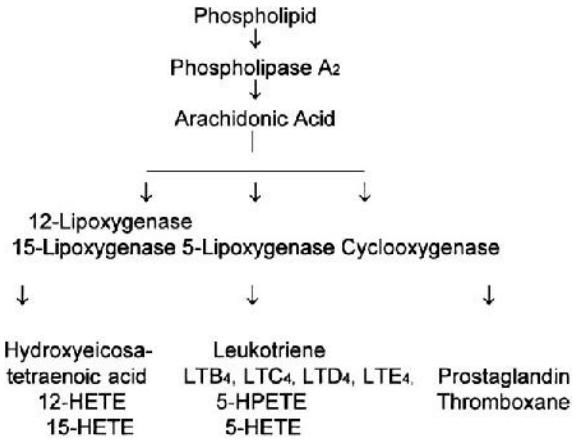


FIGURE 1 Arachidonic acid cascade.

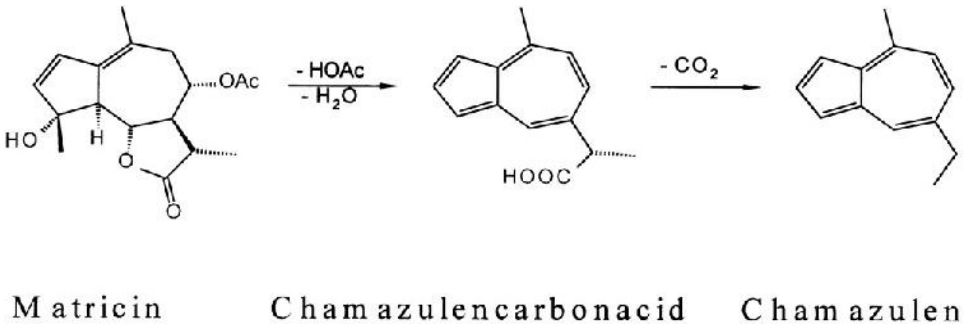
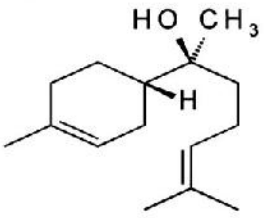


FIGURE 2 Transfer of matricin via steam distillation into chamazulen.

IUPAC-name:
(2S)-6-Methyl-2-((1S)-4-methyl-3-cyclohexenyl)-5-hepten-2-ol



(-)-α-
Bisabolol

FIGURE 3 Chemical structure of (−)-α-bisabolol.

TABLE 1 Anti-irritant Properties of Ingredients Used in Cosmetic Products

Product	% used	Irritation index
Glycyrrhetinic acid	1.0%	−0.42
Lidocaine	0.5%	−0.79
Phenylsalicylate	0.5%	−0.62
Bisabolol	1.0%	−0.55
Bisabolol	3.0%	−0.25
Azulene	0.2%	−0.21
Guaiazulene	0.1%	−0.13
Panthenol	3.0%	0/−0.13

addition of croton oil in sufficient quantities to provoke a clearly adverse reaction. The primary cutaneous irritation index was close to 2 according to the French method. The smaller the number, the more active the product. Interestingly, he found that bisabolol at 1% was more effective than bisabolol at 3%. Unfortunately, he did not mention what type of bisabolol he tested, because in a study conducted by Jakovlev [8], this investigator demonstrated that the various isomers of bisabolol show different activities. He found that (−) alpha-bisabolol was the most effective isomer. He set the efficacy of (−) alpha-bisabolol as 1,000 and compared the efficacy of the other substances to (−) alpha.

(−) alpha-bisabolol	1,000
(+) alpha-bisabolol	595
(+/−) bisabolol nat.	419
(+/−) bisabolol synth.	493

We conducted a clinical study to demonstrate in vivo the anti-inflammatory effects of natural (−)-α-bisabolol and synthetic bisabolol, which contains four stereoisomeric molecules (Fig. 4). The aim of this study was to find the concentration at which these ingredients are most active. A second test was designed to prove that the synthetic bisabolol also has protective properties against sodium hydroxide–induced irritation.

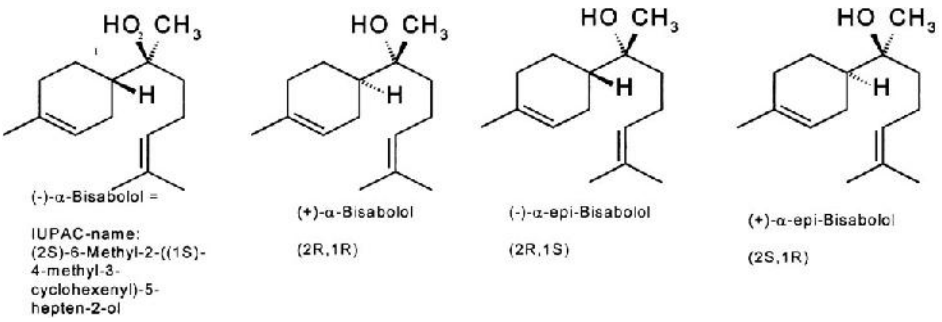


FIGURE 4 Molecular structure of bisabolol isomers.

STUDY OF THE EFFECTIVENESS OF FIVE PRODUCTS CONTAINING BISABOLOL OR SYNTHETIC BISABOLOL ON SLS-INDUCED SKIN IRRITATION: TEST METHOD

Thirty female volunteers at the age of 18 to 63 years with healthy skin were included in the test. The participants were briefed on the study procedures and each gave written informed consent. Measurements were carried out at a temperature of 22 ± 1°C and relative humidity of 60 ± 10%. The test was carried out on the volar forearms. Skin irritation was induced in the test sites by applying sodium lauryl sulphate (SLS) 2% in distilled water under aluminum chamber occlusion. After 24 hours, occlusion was removed, and 2 hours later skin redness and TEWL were recorded. After the initial measurement the five test products were applied, and one area remained untreated. The dose of application was about 2 mg/cm^2. In the following 5 days, the subjects applied the test samples in the morning and in the evening. Measurements were done during the treatment period on days 1, 3, and 5, 2 hours after the last daily application. No use of other cosmetics was allowed on the test sites during the whole test.

EVALUATION OF THE PROTECTIVE EFFICACY OF SYNTHETIC BISABOLOL AGAINST SODIUM HYDROXIDE–INDUCED IRRITATION

Fifteen volunteers between the age of 25 and 44 years with healthy skin were entered into the study. The participants were briefed on the study procedures and gave written informed consent. Measurements were carried out at a temperature of 22 ± 1°C and relative humidity of 60 ± 10%. The test was carried out on the volar forearms. The dose of application was about 2 mg/cm^2. Two products were tested. One contained 0.56% synthetic bisabolol in mineral oil, the other pure mineral oil. Two hours after the application, 50 μL 0.1 M sodium hydroxide (NaOH) was applied to the volar forearms with occlusive aluminum chambers for 12 hours. At the end of exposure, the skin was wiped with a soft paper towel to remove remaining solution, rinsed with distilled water and gently dried with a soft paper towel. Measurements were performed after 15 minutes.

Chromametry

Skin color was assessed with the Minolta Chromameter CR 300 (Minolta, Japan) in compliance with the Commission International de I'Eclairage (CIE) system. A color is expressed in a three-dimensional coordinate system with greed-red (a*), yellow-blue (b*), and L* axes (brightness). In inflamed skin, a positive change on the a* axis is observed. Each value was the average of three recordings.

TEWL

Measurements of TEWL were performed with the Tewameter TM 210 (Courage & Khazaka, Cologne, Germany). Each value was the average of three recordings.

Statistics

Summary statistics procedure was used to determine the center, spread, and shape of the data. Statistical analysis was performed using Wilcoxon matched pairs signed rank test. A p-value of less than 0.05 was taken to indicate a significant difference.

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717:		mineral oil
498:	0.5%	synthetic Bisabolol in mineral oil
984:	0.1%	synthetic Bisabolol in mineral oil
973:	0.05%	synthetic Bisabolol in mineral oil
251:	0.1125%	(-)-α-Bisabolol in mineral oil

FIGURE 5 Test products to determine the beneficial effect of synthetic bisabolol and (−)-α-bisabolol.

RESULTS OF STUDY 1 (HEALING POWER OF SYNTHETIC BISABOLOL)

Figure 8 shows the result of the TEWL measurements. The application of five test products (Fig. 5) after SLS exposure reduced TEWL in shorter time (after 24 h and 48 h) in comparison with the untreated area ($p < 0.05$). After 120 hours there was no difference between the six test areas. Neither synthetic bisabolol nor natural (−)-α-bisabolol influenced the repair of skin barrier. The measurement of the redness values shows (Fig. 7) that the inflammation was reduced faster (72 h and 120 h) in a dose-dependent manner with the products containing the actives compared with the mineral oil treatment (area 717) and the untreated area. Mineral oil delays the healing process.

RESULTS OF STUDY 2 (PROTECTIVE PROPERTIES OF SYNTHETIC BISABOLOL)

There was an increase of the a*-values in the untreated area after 4 hours indicating that a solution of 0,1 M NaOH–induced strong skin irritation. The redness in the test area with the synthetic bisabolol treatment increased only slightly after NaOH treatment. The Chromameter value a* after NaOH treatment was significantly lower for the test area with

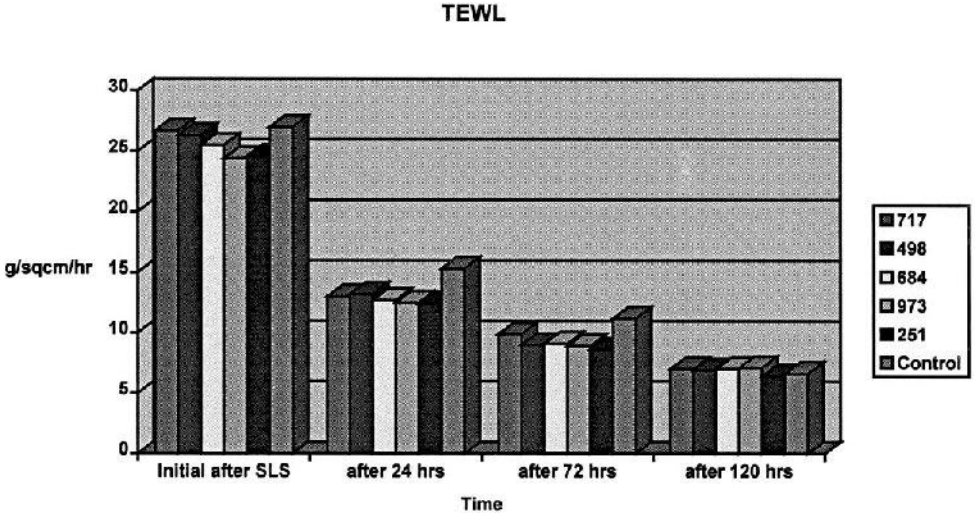

FIGURE 6 TEWL Measurements of five products containing different amounts of synthetic bisabolol/(−)-α-bisabolol.

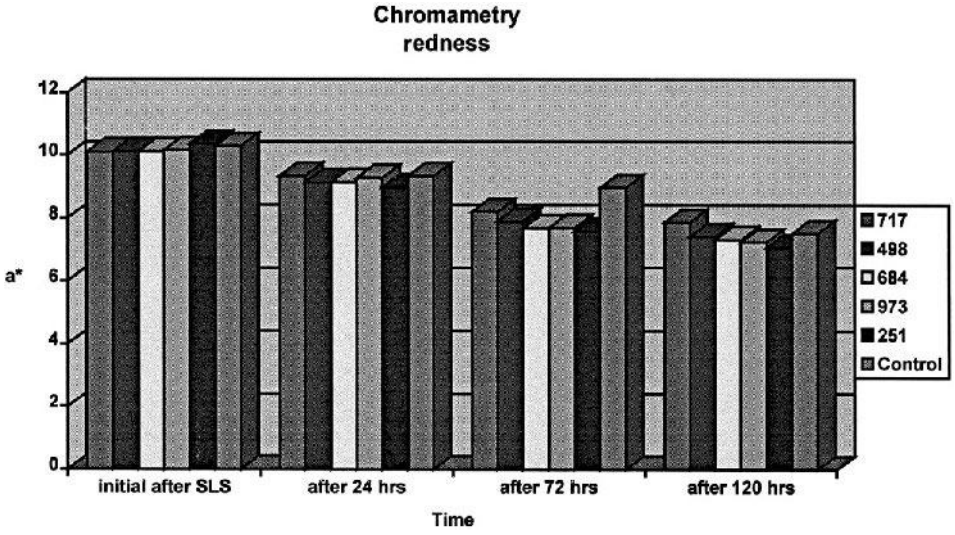

FIGURE 7 Redness assessment of five products containing different amounts of synthetic bisabolol/(−)-α-bisabolol.

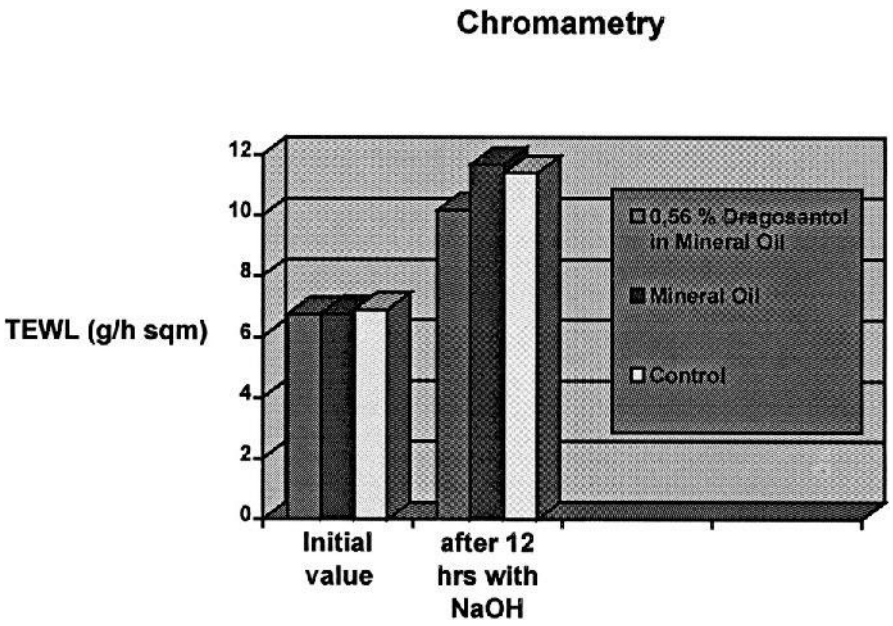

FIGURE 8 Redness assessment of a product with 0.56% synthetic bisabolol in mineral oil in comparison to the untreated area and the mineral oil–treated area.

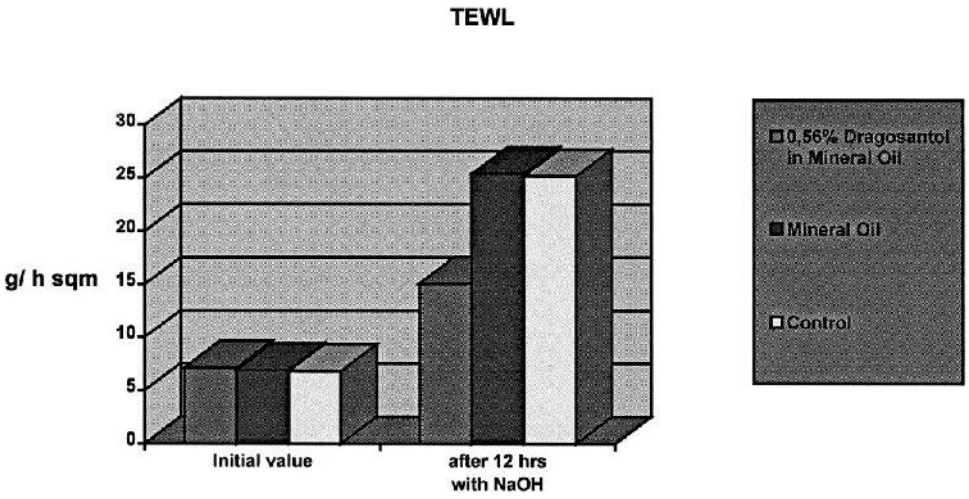

FIGURE 9 TEWL Measurements of a product containing 0.56% synthetic bisabolol in mineral oil compared with mineral oil and the untreated site.

the product, containing synthetic bisabolol, compared with the untreated site. The areas treated with pure mineral oil showed the highest increase in skin redness (Fig. 8). There was an increase in TEWL in all test areas after NaOH treatment. The TEWL values after exposure to NaOH were significantly higher for the untreated area in comparison to the pretreated sites (Fig. 9).

SUMMARY

Synthetic bisabolol and natural (−)-α-bisabolol have protective and beneficial effects, which were demonstrated by two new clinical studies. The grade of inflammation was measured with the help of a Minolta Chromameter and the a*-value was used to determine the grade of inflammation. The transepidermal water loss was used to reflect the damage of the skin barrier.

The studies proved that (−)-α-bisabolol and synthetic bisabolol reduces the development of an erythema and reduce erythema set by sodium lauryl sulfate. The damage of the skin barrier was also reduced by both products. It is important to mention that the concentration of the synthetic bisabolol and natural (−)-α-bisabolol is very essential for the efficacy of the cosmetic product. There is a maximum concentration level for both ingredients. An increase of the concentration beyond this point leads to a reduction in efficacy. For leave-on products, the maximum concentration depending on the base formula is between 0.05% and 0.2%.

Synthetic bisabolol and natural (−)-α-bisabolol show a significant substantivity to skin out of a rinse-off product. Therefore, both ingredients can add value to a body wash or shampoo by reducing the well-known irritation effect of certain surfactants. In this case, the maximum concentration level is approximately 0.3%.

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Anti-irritants for Sensory Irritation

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INTRODUCTION

Many chemicals found in cosmetics, personal-care products, pharmaceuticals, and in industrial processes can irritate the skin and mucous membranes of the eye and the respiratory and gastrointestinal tracts. Perhaps the most effective early-warning system that responds to these chemicals is sensory irritation—the rapid-onset stinging, burning, and itching sensations that alert an organism to their exposure to foreign, and potentially injurious, substances. These sensations, even when intense, may occur in the absence of visible signs of irritation or skin damage or, alternatively, may be accompanied by erythema and/or edema [1].

Sensory irritation occurs when thin, unmyelinated, chemically sensitive type-C nociceptors (from the Latin *nocere*, to injure) are activated and transmit a depolarizing signal via the dorsal root ganglia (DRG) in the spinal cord to the brain where stinging, burning, itching, and poorly localized burning pain is appreciated [2]. These sensations are neurologically distinct from the highly localized sharp pain caused by cutting or puncturing the skin that is transmitted by the thinly myelinated A-delta class of nerve fibers [3]. Type-C nociceptors are present throughout the dermis and extend to the outermost layer of the viable epidermis, thus acting as one of the skin's earliest warning systems [4]. When the intensity of the irritant stimulus is sufficiently high, interneurons in the DRG and/or depolarizing signals within the terminal aborization of a single nerve fiber trigger retrograde depolarization down the activated fiber, resulting in the exocytosis of inflammatory mediators at the site of the irritant stimulus [5,6]. The principal mediators in humans include substance P, calcitonin gene-related peptide (CGRP), and neurokinin-A, a member of the substance P family. These mediators, coupled with the neurogenically mediated vasodilatory erythematous ''flare'' surrounding the irritated site, produce erythema, edema, and activation of immune cells, including mast cells, that contribute to the clinical response of neurogenic inflammation.

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THE IDEAL ANTISENSORY ANTI-IRRITANT

The idea antisensory anti-irritant would effectively inhibit stinging, burning, and itching caused by a broad range of acidic, neutral, and basic chemical irritants by reducing the sensitivity of type-C nociceptors. In contrast, it would not inhibit the warning symptom of pain mediated by A-delta nerves, nor would it affect other nerve sensors that mediate tactile, temperature, or vibratory sensations. Since most cosmetic-induced sensory irritation occurs within several minutes after application, the ideal anti-irritant should work within seconds when formulated with the irritant. For broad product use, it should also work when applied as a pretreatment before the irritating formulation and it should work when applied after irritation has occurred. Because cosmetics use a wide range of chemicals, the anti-irritant should be stable in many chemical environments and inexpensive enough to be used in low-cost products. With repeated daily use, the ideal anti-irritant should provide the same effective level of anti-irritant protection (no tachyphylaxis) and, most importantly, it must be safe for broad, unsupervised use.

With the exception of local anesthetics that are regulated as drugs in most countries and may have undesirable side effects and safety concerns, no compounds have been described that are able to broadly inhibit sensory irritation from cosmetics and pharmaceuticals. Because a safe compound capable of blocking sensory irritation and inflammation would provide considerable benefit, I sought to identify compounds that could effectively block sensory irritant reactions. Simple water-soluble strontium salts have proved to be potent and selective inhibitors of chemically induced sensory irritation and neurogenic inflammation in humans and do not produce numbness or loss of other tactile sensations [7–10].

THE FIRST EFFECTIVE ANTISENSORY ANTI-IRRITANTS: STRONTIUM SALTS

Clinical Evaluation of Sensory Irritation

A variety of chemical irritants used in cosmetics were used to induce sensory irritation. All clinical studies were conducted according to double-blind, vehicle-controlled, random treatment assignment protocols in which each subject served as her own control. Test subjects were healthy women, aged 18 to 65, who self-reported a history of sensitive skin and were sensitive to lactic acid facial challenge. Treated skin sites were first washed with Ivory bar soap, followed by sequential application of test materials and sensory irritation evaluation. Statistical analysis of the mean sensory irritation differences between vehicle and strontium-treated groups was conducted using the Wilcoxon Signed Ranks Test for paired comparisons. All subjects provided informed consent and all protocols were reviewed by a safety committee.

Sensory Irritation Scale

Each minute for 10 to 60 minutes, depending on the study, subjects reported the magnitude of sensory irritation (stinging, burning, and itching) according to the following scale:

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0 = none	
1 = slight	Transient, barely perceptible irritation
	Does not bother them
2 = mild	Definite and continuous irritation
	Bothers them
3 = moderate	Distinctly uncomfortable irritation
	Bothers them and interferes with concentration
4 = severe	Continuous, intensely uncomfortable irritation
	Intolerable and would interfere with daily routine

ACIDIC IRRITANTS

Lactic Acid (7.5%, pH = 1.9) Sensory Irritation on the Face

Alpha-hydroxyacids (AHAs) including lactic and glycolic acids are used in cosmetics and in professionally applied chemical peels to reduce the visible signs of skin aging. To maximize AHA efficacy, the formulation must be acidic, which increases the active ''free acid'' form of the AHA molecule and, unfortunately, directly contributes to their irritation potential [11,12]. To evaluate the ability of strontium salts to reduce lactic acid sensory irritation, either lactic acid alone (7.5% in 10% ethanol/water vehicle, pH = 1.9), or an identical vehicle at the same pH containing various concentrations of strontium nitrate or strontium chloride was applied (0.1 g) to cheek sites using cotton swabs (6 swipes) extending from the nasolabial fold to the outer cheek. Test materials were applied to the right or left side of subjects' faces sequentially followed by sensory irritation assessment on each side for 10 minutes. A typical time-response curve for lactic acid (7.5%, pH = 1.9) on the face is presented in Figure 1. When the areas under both irritation curves are compared, strontium nitrate inhibited sensory irritation by 68% ($p < 0.01$). Both strontium nitrate and strontium chloride produced dose-dependent inhibition of sensory irritation when mixed with lactic acid (Table 1) [7]. In separate studies, the local anesthetic lidocaine (4%) was used as a positive control. When applied at the same time as the lactic acid, lidocaine did not produce significant inhibition (<10%), presumably because it requires time to be absorbed. When lidocaine (4%) was applied 5 minutes before the lactic acid, lidocaine inhibited by 51% ($p < 0.05$, n = 10).

Strontium Pretreatment on the Face

Many cosmetics such as toners and skin conditioners, are applied immediately before application of potentially irritating products. Incorporation of strontium salts into such a pretreatment product from 1 minute to 15 minutes before the same lactic acid facial challenge produced a substantial level of sensory irritation inhibition (Table 1). In other studies, substantial anti-irritancy was also observed when strontium nitrate was applied several minutes after lactic acid was applied.

When the same lactic acid challenge was used in conjunction with ''conventional'' anti-irritants used in cosmetics such as green tea (3%), alpha-bisabolol (1%), and glycyrrhizic acid (1%), no significant inhibition was observed (<10% difference from vehicle control).

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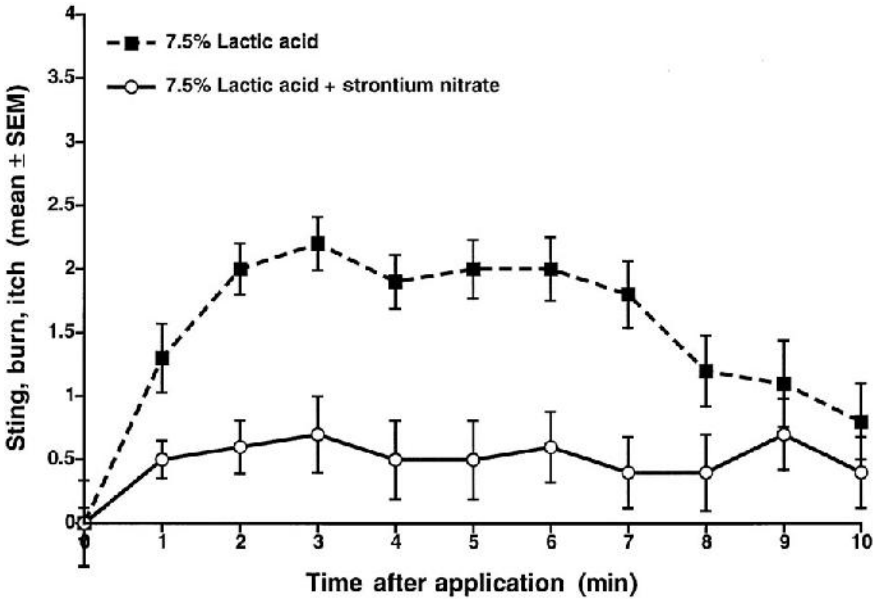

FIGURE 1 Lactic acid alone (closed squares) or with strontium nitrate (250 mM) was applied to the faces of 23 subjects and sensory irritation was assessed every minute for 10 minutes (see text for scale). Each data point represents the mean ±SEM irritation at each minute for all subjects. Total cumulative irritation (area under the curve) was inhibited by 68% ($p < 0.01$).

To determine whether the strontium cation was necessary for the observed antiirritant activity, sodium chloride (250 mM) and sodium nitrate (250 mM) were mixed with the lactic acid and compared with strontium nitrate (250 mM) or strontium chloride (250 mM). In both instances, sodium nitrate or sodium chloride produced insignificant (<10%) inhibition of sensory irritation proving that the nitrate or chloride anions did not produce the observed anti-irritant activity.

Lactic Acid (15%, pH = 3.0) Sensory Irritation on the Face

The anti-irritant activity of strontium salts is also evident for less acidic AHA irritants similar to what could be used in high-potency over-the-counter cosmetic products. When lactic acid (15% in a hydroxyethyl cellulose hydrogel, pH = 3.0) with or without 250 mM (5.3%) strontium nitrate was applied to the faces of 33 subjects, the cumulative irritation inhibition by the strontium-containing solutions was 66% ($p = 0.003$) (Table 2). The incidence of each of the four scores of lactic acid only versus lactic acid plus strontium was: severe: 25 vs. 1 = 96% inhibition; moderate: 59 vs. 2 = 97% inhibition; mild: 48 vs. 5 = 90% inhibition; slight: 22 vs. 48 = 118% increase; and none: 44 vs. 142 = 223% increase.

Glycolic Acid (70%, pH = 0.6) Sensory Irritation on the Arms

High-concentration, low-pH glycolic acid formulations are used by physicians to reduce the visible signs of skin photoaging and to treat moderately severe acne. To maximize

TABLE 1 Inhibition of Sensory Irritation Scores from 7.5% Lactic Acid (pH = 1.9)

Strontium salt (mM)	Strontium chloride* Inhibition† % ± SEM	Strontium chloride* Inhibition† (# subjects, p)	Strontium nitrate* Inhibition % ± SEM	Strontium nitrate* Inhibition (# subjects, p)	15-Minute pretreatment strontium nitrate* Inhibition % ± SEM	15-Minute pretreatment strontium nitrate* Inhibition (# subjects, p)
500	75 ± 7	(n = 16, $p < 0.005$)	68 ± 6	(n = 24, $p < 0.01$)	58 ± 12	(n = 16, $p < 0.01$)
250	65 ± 12	(n = 17, $p < 0.01$)	74 ± 7	(n = 23, $p < 0.01$)	48 ± 11	(n = 18, $p < 0.01$)
125	64 ± 5	(n = 15, $p < 0.01$)	42 ± 14	(n = 15, $p < 0.01$)	28 ± 16	(n = 15, $p < 0.01$)
63	30 ± 6	(n = 8, $p < 0.01$)	34 ± 8	(n = 16, $p < 0.01$)	17 ± 10	(n = 18, $p < 0.01$)

* Strontium nitrate or strontium chloride hexahydrate was either mixed with the lactic acid vehicle (7.5%, pH = 1.9, 10% ethanol/water) or preapplied to the face in a 10% ethanol/water vehicle 15 minutes before the application of the lactic acid vehicle.

† The total cumulative irritation in each study (scores of 1 + 2 + 3 + 4) for the lactic acid–treated side of the face was compared with the lactic acid + strontium-treated side of the face (areas under the curves) and irritation inhibition was calculated as a percent difference.

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TABLE 2 Inhibition of Sensory Irritation Scores by Strontium Nitrate

		% Inhibition of sensory irritation scores*				
	Irritation score	Lactic acid (15%, pH = 3.0)	Glycolic acid (70%, pH = 0.6)	Capryloyl salicylic acid (1%, pH = 3.5)	Ascorbic acid (30%, pH = 1.7)	Calcium thioglycolate (4%, pH = 12)
Subjects (#)		33	19	24	20	23
Total scores		363	209	312	110	506
None	(0)	−223†	−381	−74	−260	−65
Slight	(1)	−118	−6	−8	63	40
Mild	(2)	90	43	71	91	76
Moderate	(3)	97	92	31	100	71
Severe	(4)	96	100	58	100	—

* Sensory irritation was induced by lactic acid (15%, pH = 3.0) application to the face, glycolic acid (70%, pH = 0.6) application to arms, capryloyl salicylic acid (1%, pH = 3.5) application to face, ascorbic acid (30%, pH = 1.7) application to the face, and calcium thioglycolate (4%, pH = 12) depilatory application to the legs. For each study, the incidence of each of the four sensory irritation scores (0–4) for the irritant alone and the irritant plus strontium nitrate treatment was compared. Each number represents the percent inhibition of each irritation score incidence induced by strontium nitrate.

† Negative inhibition values represent an increase in the score incidence.

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potency, unneutralized glycolic acid solutions are used (e.g., 20%, pH = 1.5 to 70%, pH = 0.6) but all produce potentially severe irritation. For this reason, most patients are exposed to increased concentrations and exposure times over a multimonth period until they reach a ''maintenance'' exposure (e.g., 70% glycolic acid, pH = 0.6 for 4–6 min) [13]. With strontium nitrate added to such formulations, patients can immediately obtain the benefits of the most potent glycolic acid formulations with very little or no irritation.

To demonstrate the anti-irritant efficacy of strontium in glycolic acid peel solutions, 70% glycolic acid (pH = 0.6) with or without strontium nitrate (20% [945 mM]) was applied to the forearms of 19 subjects on 2 inch by 4 inch rectangular sites and sensory irritation was evaluated every minute for 10 minutes, followed by neutralization with sodium bicarbonate. Within seconds after glycolic acid application (time 0 in Fig. 2), sensory irritation differences were apparent between the two groups (mean ± SEM = 0.53 ± 0.16 for glycolic only vs. 0.16 ± 0.09 for glycolic plus strontium) indicating that strontium had an immediate onset of action. Throughout the remainder of the exposure, strontium strongly inhibited irritation at all time points, and cumulative irritation was inhibited by 75% ($p = 0.005$). The data in Table 2 presents the percent inhibition of each of the four sensory irritation scores induced by strontium nitrate. During the study, the 19 subjects reported 209 irritation scores. The incidence of each of the four scores of the glycolic acid only versus the glycolic acid plus strontium was: severe: 41 vs. 0 = 100% inhibition; moderate: 50 vs. 4 = 92% inhibition; mild: 44 vs. 25 = 43% inhibition; slight: 47 vs. 50 = 6% increase; none: 27 vs. 130 = 381% increase. In other studies, measurement of skin turnover using the dansyl chloride technique [14] showed that strontium nitrate did not affect the stimulatory effect of glycolic acid on skin turnover.

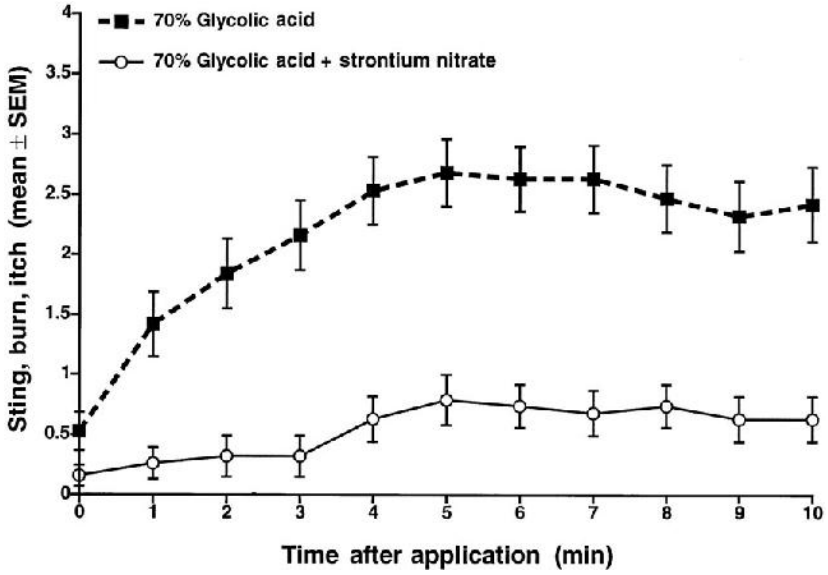

FIGURE 2 Glycolic acid (70%, pH = 0.6) only (closed squares) or with strontium nitrate (20%) (open circles) was applied to the forearms of 19 subjects and sensory irritation was measured every minute for 10 minutes. Each data point represents the mean ±SEM irritation at each minute for 19 subjects. Total cumulative irritation (areas under the curve) was inhibited by 75% ($p < 0.005$).

Clinical studies of a 70% glycolic acid (pH = 0.6) chemical peel solution with strontium nitrate applied to the whole face in over 150 human subjects demonstrated substantially reduced sensory irritation and erythema without reducing the expected benefits of the peel as judged by clinical response [15,16]. Histological analysis of punch biopsies from skin exposed to AHA formulations containing strontium nitrate (70% glycolic acid, pH = 0.6) every 2 weeks for 8 weeks and 15% lactic acid lotion (pH = 3.2) twice daily at the same facial sites) demonstrated that there was slightly *less* inflammation in the AHA and strontium-treated sites compared with untreated skin in the same individuals [16], thus demonstrating that strontium not only reduced irritation symptoms, but also protected the skin from cryptic damage.

Capryloyl Salicylic Acid–Induced Sensory Irritation

Capryloyl salicylic acid is a covalently modified derivative of salicylic acid with enhanced lipophylicity attributable to the 8 carbon caprylic acid moiety. It is used as a cosmetic exfoliant and is reported to have utility as an acne therapeutic [17]. A cream emulsion base containing capryloyl salicylic acid (1%) with or without strontium nitrate (500 mM) was applied to cheek sites 2 inches by 4 inches extending from the nasolabial fold to the outer cheek of 24 female subjects and sensory irritation was evaluated every 5 minutes for 60 minutes. The data in Table 2 presents the percent inhibition of each of the four sensory irritation scores induced by strontium nitrate. During the entire study, subjects reported 312 sensory irritation scores. The incidence of each of the four scores of the capryloyl salicylic acid versus the capryloyl plus strontium was: severe: 19 vs. 8; moderate: 13 vs. 9; mild: 35 vs. 10; slight: 39 vs. 42; and none: 50 vs. 87. The mean sensory irritation score of the capryloyl salicylic acid reached approximately 0.8 5 minutes after application, peaked at approximately 1.0 from 20 minutes to 35 minutes, and remained at approximately 0.8 until 45 minutes, after which it declined to 0.4 at 60 minutes. Total irritation, calculated as the percent difference of the areas under the 60-minute irritation curves, was inhibited by 46% ($p = 0.002$).

Ascorbic Acid (30%, pH = 1.7) Sensory Irritation on the Face

Ascorbic acid (Vitamin C) is used in many cosmetic products because it is a potent water-soluble antioxidant and can protect the skin against damage from ultraviolet radiation [18]. In vitro studies also show that ascorbic acid can also stimulate collagen synthesis [19]. Because ascorbic acid is most stable and bioavailable in aqueous formulations at a highly acidic pH (e.g., pH < 3) a 30% aqueous solution of ascorbic acid (pH = 1.7) was evaluated for sensory irritation with or without strontium nitrate (250 mM). After application to the face of 20 subjects, the cumulative irritation inhibition by the strontium-containing solutions was 84% ($p < 0.005$) (Table 2). The incidence of each of the four scores of the ascorbic acid only versus the ascorbic acid plus strontium was: severe: 1 vs. 0 = 100% inhibition; moderate: 13 vs. 0 = 100% inhibition; mild: 23 vs. 2 = 91% inhibition; slight: 48 vs. 18 = 63% inhibition; plus none: 25 vs. 90 = 260% increase).

Aluminum Chloride Antiperspirant Application to Axilla

Antiperspirants use aluminum salts alone or in combination with other agents to reduce perspiration. In the moist environment of the axilla, aluminum salts can cause sensory irritation and inflammation [20]. The axilla of 16 subjects was pretreated with 1.0 mL of

a strontium nitrate solution (500 mM, pH = 7.3 in 50% ethanol/water vehicle) followed 2 minutes later by a 1 mL application of the aluminum chloride (20%) antiperspirant solution. Sensory irritation was evaluated every 2 minutes for 20 minutes. The incidence of each of the four scores of the aluminum chloride versus the aluminum chloride plus strontium was: severe: 12 vs. 2; moderate: 22 vs. 9; mild: 30 vs. 13; slight: 60 vs. 41; and none: 52 vs. 111. Upon application, sensory irritation reached a mean score of 1 within the first minute and a plateau at approximately 1.5 from minutes 6 to 10, then gradually declined to a score of approximately 1 at 20 minutes. During the study, the 16 subjects reported 352 irritation scores. Total irritation caused by the aluminum chloride calculated as the percent difference of the areas under the 20-minute irritation curves was reduced by 56% when the areas under the irritation curves were compared ($p < 0.005$).

Aluminum/Zirconium Salt Erythema on the Arms

Aluminum salts, with or without zirconium salts, are FDA-approved antiperspirant ingredients and frequently cause both sensory irritation and inflammation [20]. Aluminum/zirconium salt solution (25%) with or without strontium nitrate (500 mM) or strontium chloride (500 mM) was applied to the arms of 29 subjects using occluded patches for 21 days and the magnitude of visible inflammation was evaluated every day. Inflammation was visually measured according to the following scale:

0 =	No evidence of erythema
1 =	Minimal erythema
2 =	Definite erythema
3 =	Erythema and papules

Both stronium nitrate (500 mM) or strontium chloride (500 mM) caused nearly complete inhibition of erythema development during the first week and substantially inhibited erythema during the second and third weeks (Fig. 3). Total erythema caused by the aluminum/zirconium salts, calculated as the percent difference of the areas under the 21 day irritation curves, was reduced by 64% ($p < 0.0001$) by strontium nitrate and by 66% ($p < 0.0001$) by strontium chloride.

BASIC IRRITANTS

Calcium Thioglycolate Sensory Irritation on the Legs

Chemical depilatories typically use calcium thioglycolate formulated at a basic pH (e.g., 9–12) to dissolve hair keratin [21]. Twenty-three subjects shaved their legs with a safety razor to enhance irritation, then strontium nitrate pretreatment solution (10% w/v, in 10% ethanol/water) or vehicle was applied to 2 inch by 4 inch sites on the lateral portions of the legs. After 2 minutes, 5 grams of depilatory lotion was applied to each leg followed by irritation evaluation every minute for 10 minutes. During the study, the 23 subjects reported 506 irritation scores (Table 2). The incidence of each of the four scores of the depilatory versus the depilatory plus strontium was: severe: 0 vs. 0; moderate: 7 vs. 2 = 71% inhibition; mild: 45 vs. 11 = 76% inhibition; slight: 88 vs. 53 = 40% inhibition; and none: 113 vs. 187 = 65% increase. Total irritation caused by the depilatory, calculated

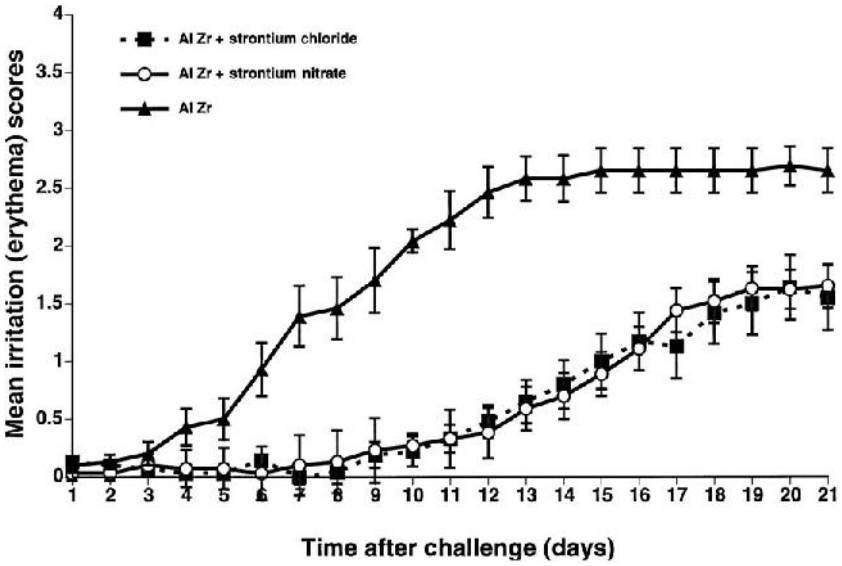

FIGURE 3 Strontium nitrate (500 mM, open circles) or strontium chloride (500 mM, closed squares) was formulated with the aluminum/zirconium salt solution each day when a new patch was applied. Each data point represents the mean ±SEM for 29 subjects. Total cumulative irritation (areas under the curve) was inhibited by 64% ($p < 0.0001$) for strontium nitrate and 66% for strontium chloride ($p < 0.0001$).

as the percent difference of the areas under the 20-minute irritation curves, was reduced by 59% ($p < 0.01$).

NEUTRAL IRRITANTS (HISTAMINE)

Histamine is a potent itch-inducing chemical contained in mast cells and basophils and is released in response to many inflammatory stimuli, including substance P during the neurogenic inflammatory process. It directly activates type-C nociceptors by binding to H1 histamine receptors [22,23]. Strontium nitrate (20%) in water or water alone were used to pretreat 4 by 6 cm sites on the volar forearms of 8 subjects 30 minutes and 5 minutes before intradermal injection of histamine (100 μg in normal saline). Itch was assessed using a visual analog scale for 20 minutes. The mean itch magnitude each minute for all subjects was always less for the strontium-treated sites and reached statistical significance ($p < 0.05$) from minute 12 to the end of the study. The mean difference between the two groups continued to increase until it reached the maximum difference at 20 minutes at which time itch was reduced 52% by strontium ($p < 0.05$) [24].

OCULAR IRRITANTS

The eye is perhaps the most sensitive organ of the body, especially to chemical irritants. When cosmetics, sunscreens, or other topical products are used on the face, they frequently contact the eye and can produce substantial sensory irritation. Preliminary studies of stron-

tium nitrate applied to the human eye indicate that it is a safe and effective anti-irritant. Studies of strontium nitrate in aqueous solution instilled into the eye of humans show that up to 2% strontium nitrate was well tolerated and safe for ocular instillation. Because alpha-hydroxy acids are used in cosmetics around the eye, lactic acid (1%, pH = 4.0) was used as an ocular irritant with or without strontium nitrate (1%) or sodium chloride (1%). In a study of seven subjects, strontium inhibited total cumulative sensory irritation by 63%. In contrast, strontium did not alter the eye's sensitivity to foreign bodies, thus preserving the protective senses of the eye.

STRONTIUM SAFETY

Strontium is the eighth most abundant element in sea water and is found in many foods, especially green leafy vegetables. Average human consumption of strontium in food is estimated to be 0.8 mg to 5 mg a day. Studies in animals and humans show that it is remarkably nontoxic, and in some studies it is estimated to be as safe as calcium. Percutaneous absorption studies of strontium salts indicate that predicted absorption of topically applied strontium salts is far less than would be typically consumed in the diet.

STRONTIUM MECHANISM OF ACTION

Simple salts of the element strontium can effectively suppress sensory irritation caused by chemically and biologically unrelated chemical irritants over a pH range of 0.6 to 12. Because strontium acts within seconds after application, it is likely that it is acting directly on the type-C chemical sensors that transmit stinging, burning, and itching. In animal studies, strontium salts have been reported to directly suppress neuronal depolarization [25,26]. In vivo, strontium is a divalent ion with an ionic radius similar to the divalent calcium ion (1.13 Å vs. 0.99 Å, respectively) [27]. Strontium also resembles calcium's ability to traverse calcium-selective ion channels and trigger neurotransmitter release from nerve endings. In many systems strontium is, however, less potent than calcium and thus can act as an inhibitor of calcium-dependent depolarization [26,28–31]. Strontium may act to block calcium-dependent pathways that lead to neuronal depolarization. Neurons are also known to be sensitive to compounds that alter the electrostatic field surrounding their plasma membrane and ion channels [32]. Because strontium can alter the electrostatic field of ion channels and reduce ion permeation through them [33,34], strontium may suppress irritant-induced depolarization of unmyelinated sensory neurons. Strontium salts may also directly act on non-neuronal cells such as keratinocytes or immunoregulatory inflammatory cells. For example, strontium salts can suppress keratinocyte-derived TNF-α, IL-1α, and IL-6 in in vitro cultures [35].

The fact that strontium can block the rapid intense irritation caused by a 70% (pH = 0.6) glycolic acid chemical peel without causing numbness or other detectable changes in cutaneous sensations suggests that strontium is highly selective in its ability to regulate type-C nociceptors (Fig. 4). In contrast, local anesthetics like lidocaine or procaine not only block irritant sensations, but also block tactile sensations that produce numbness [36]. Recent studies support the concept that strontium is highly selective for only nociceptive subsets of sensory neurons because strontium nitrate (20%) applied to normal skin did not alter sensory thresholds for cold sensations, warmth sensations, or pain caused by cold or heat [24].

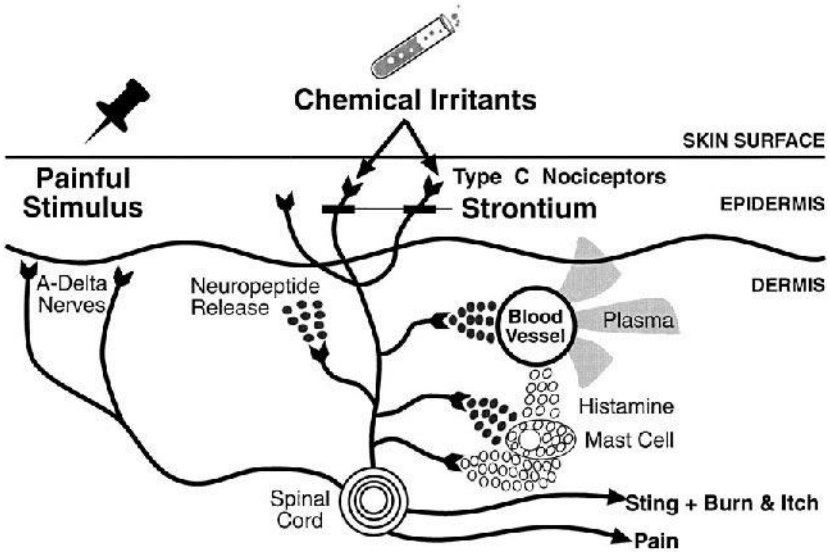

FIGURE 4 Chemical irritants activate unmyelinated type-C nociceptors and trigger their depolarization. Type-C nociceptors then synapse in the dorsal root ganglia (DRG) of the spinal cord and the signal travels to the brain where it is sensed as sting, burn, or itch. If the stimulation is of sufficient magnitude, interneurons in the DRG send a retrograde signal down the same type-C fibers, which triggers the release of inflammatory substances including substance P, neurokinin A, calcitonin gene-related peptide (CGRP), and other mediators. These substances trigger vasodilation, vascular permeability, and activate inflammatory cells, including mast cells that, in turn, release another set of inflammatory mediators, including histamine, which further activate nociceptive sensory signals and inflammation. Strontium reduces the sensitivity of type-C nociceptors to chemical irritants while not affecting the A-delta nerves that transmit the ability to detect pain.

PRODUCT APPLICATIONS

Burning, stinging, and especially itching sensations are among the most common consumer complaints from cosmetics and topical drugs. The rapid-onset and high-level anti-irritant potency of strontium salts suggest that they will have broad applications in topical products. Throughout the world, cosmetic products are used daily to cleanse and beautify the skin. With the discovery of new, potent, biologically active ingredients, formulators can provide consumers with increased benefit that may resemble that obtained from pharmaceutical products. Unfortunately, irritation frequently accompanies the use of higher concentrations of active ingredients or more potent skin-delivery systems. For people with sensitive skin attributable to inherently dry skin or other causes, the problem is further compounded. In addition to products intentionally applied to the skin, many workers are exposed to chemical irritants in the workplace that can result in considerable occupational disability [37–39].

Strontium salts, particularly strontium nitrate, has proven to be highly effective in reducing irritation, erythema, and inflammation from many irritating ingredients used in topical products and found in the workplace. The first strontium-containing cosmetic products were introduced in the United States, and made available internationally in October

1999. The safety of strontium salts, coupled with their ability to inhibit both sensory irritation and neurogenic inflammation, suggests that they may have therapeutic utility in the treatment of many dermatological conditions. Because the neurogenic inflammation syndrome is believed to be pathogenically important in many other conditions, including allergic contact dermatitis, psoriasis, atopic dermatitis, ocular irritation and inflammation, allergic rhinitis, asthma, rheumatoid arthritis, inflammatory bowel disease and other gastrointestinal disorders [40], strontium salts may have additional therapeutic utility. Strontium salts represent a new class of selective inhibitors of sensory irritation and irritant contact dermatitis without local anesthetic side effects.

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Antioxidants

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INTRODUCTION

In the field of dermatology, antioxidants are widely used and innovative ingredients in topical applications. This chapter is intended to provide an overview of the current state of research on the use of antioxidants in cosmeceutical applications. The most important antioxidants, vitamin E, vitamin C, thiols, and flavonoids will be introduced and their intriguing cooperation as well as their role in signal transduction events will be discussed.

The body is continuously exposed to oxidants. Endogenous sources arise as a consequence of normal metabolic pathways. For example, mitochondrial respiration produces superoxide and hydrogen peroxide, whilst enzymes such as lipoxygenases, xanthine oxidase, and NADPH oxidase produce hydroperoxides and superoxide respectively. Exogenous oxidants arise from environmental pollutants such as smoke, smog, UV radiation, and the diet. In response to these oxidants, a number of systemic antioxidants are available whose functions are to scavenge reactive oxygen species preventing damage to macromolecules such as lipids, DNA, and proteins. Antioxidant protection arises from molecules synthesized as part of metabolism, e.g., GSH and uric acid; essential vitamins which must be taken in from the diet, e.g., vitamin E and C; and enzymes which decompose reactive oxygen species, e.g., superoxide dismutases, catalase, and the glutathione peroxidases. These systems provide protection in various intra- and intercellular compartments. Usually there is a tight balance between oxidants produced and antioxidant scavenging, however under certain conditions the balance can be tipped in favor of the oxidants, a condition called oxidative stress. Potentially oxidative stress can be caused either by an increase in the number of oxidants, for example as a result of cigarette smoking or UV irradiation, or by a deficiency in antioxidants. This is of major concern since oxidative stress has been implicated in a number of conditions including atherosclerosis, skin cancer, and photoaging.

VITAMIN E

Vitamin is the major lipophilic antioxidant in skin, and it is the most commonly used natural antioxidant in topical formulations. It is found in all parts of the skin, the dermis,

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and epidermis, as well as in the stratum corneum, and is believed to play an essential role in the protection of biomolecules from oxidative stress.

Vitamin E is a family of 8 naturally occurring isoforms: four tocopherols (α-, β-, γ-, δ-form) and four tocotrienols (α-, β-, γ-, δ-form) (Fig. 1) [1]. All forms consist of a chromanol nucleus that carries the redox-active phenolic hydroxyl group, and a lipophilic tail. While tocopherols contain a phytil side chain, the isoprenoid tail of the tocotrienols is polyunsaturated, making the chain more rigid. The side chain is anchored in lipid membranes while the nucleus is located at the lipid/aqueous interface. Even though the radical scavenging activity of the different isoforms is essentially identical, their biological activity after oral administration differs dramatically [2]. This phenomenon can be explained by the existence of an α-tocopherol transfer protein in the liver that positively selects RRR-α-tocopherol and incorporates it into VLDL which leads to recirculation of the α-tocopherol pool, while this transfer protein does not recognize the other forms, which are therefore excreted more rapidly [3].

In skin, as in the other human organs, α-tocopherol is the predominant form of vitamin E with 5 to 10 higher concentrations than γ-tocopherol. Delivery of vitamin E to the SC occurs in two different modes. On the one hand it stored into differentiating keratinocytes and moves up into the newly formed SC, which leads to a gradient-type distribution of α-tocopherol with decreasing concentrations towards the skin surface [4]. On the other hand, vitamin E is secreted by sebaceous glands and reaches the SC from the outside. In sebaceous gland–rich regions like the face, this delivery mechanism is responsible for the enrichment of the outer SC with vitamin E [5].

Various oxidative stressors have been shown to deplete vitamin E, among other antioxidants. In the epidermis, a dose of at least four minimal erythemal doses (MED) of solar simulated UV radiation (SSUV) is needed to deplete vitamin E [6], while doses as low as 0.75 MED are capable of destroying vitamin E in the human SC [4]. Mouse experiments have shown that a dose of 1 ppm × 2h of ozone (O_3) depletes SC vitamin E [7]. Since this concentration of O_3 is higher than the naturally occuring levels of tropospheric O_3 the biological relevance of these findings for the skin of humans is not yet clear. A one time application of benzoyl peroxide BPO (10% w/v), a concentration commonly used in the treatment of acne, depleted most of the SC vitamin E in human volunteers [8].

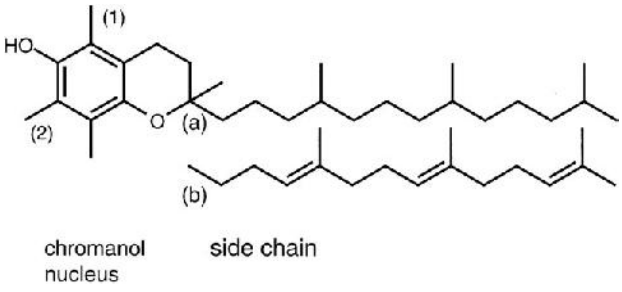

FIGURE 1 Naturally occurring forms of vitamin E. Tocopherols contain a saturated side chain (a), whereas the isoprenoid side chain of tocotrienols is polyunsaturated (b). The α-forms contain both methyl groups on the chromanol nucleus (1,2), whereas the β-forms contain only methyl group (1), the γ-forms only (2), and the δ-forms none.

α-Tocopherol is widely used as an active ingredient in topical formulations. After topical application, it penetrates readily into skin [9]. Since the free form of vitamin E is quite unstable and light-sensitive (it absorbs in the UV-B range), the active hydroxyl group is usually protected by esterification with acetate. This increases the stability but renders the compound redox inactive. When administered orally, vitamin E-acetate is hydrolyzed quantitatively in the intestines [10]. There is some controversy however as to whether α-tocopherol acetate can by hydrolyzed in human skin. Chronic application of α-tocopherol acetate leads to an increase in free vitamin E in both the rat [11] and the mouse [12], where it was recently shown that UV-B increases the hydrolysis of α-tocopherol acetate by induction of nonspecific esterases up to 10 to 30 fold [13]. While one study suggested that bioconversion of α-tocopherol acetate does not occur in human skin [14], significant hydrolysis was demonstrated in recent studies using a human epidermis–tissue culture model [15].

The availability of the free form of vitamin E needs to be considered when analyzing possible health benefits. The majority of studies have been carried out in animal models, while only limited data exists for human studies. Lipid peroxidation is inhibited after topical application of α-tocopherol [16]. Several studies indicate that topically applied α-tocopherol inhibits UVB-induced photodamage of DNA in a mouse model [17] and keratinocyte cultures (trolox) [18]. Protection against Langerhans cell depletion by UV light was observed after topical application of α-tocopherol in a mouse model [19]. α-Tocopherol and its sorbate ester were studied in a mouse model of skin aging. Both antioxidants were found to be effective, sorbate even more so than α-tocopherol [20]. Systemic administration of vitamin E in humans (only in combination with vitamin C) increased the MED and reduced changes in skin blood flow after UV-irradiation [21,22]. Yet several studies indicate that α-tocopherol acetate is not as effective as free vitamin E when applied topically. Inhibition of DNA mutation in mice was 5 to 10 times less effective [18]. Also, in a mouse model, unlike free vitamin E, the acetate form seemed to be ineffective [23]. In summary, even though some health benefits of vitamin E supplementation have been shown, there is still a need for controlled studies in humans under physiological conditions.

Recently, the tocotrienol forms of vitamin E have become a focus of interest, since they have been found to be more efficient antioxidants in some model systems than tocopherols [24]. Even if they are not bioavailable after oral supplementation, topical application circumvents the exclusion by α-TTP in the liver. In fact, free tocotrienols readily penetrate into mouse skin [9], and tocotrienyl acetate is hydrolyzed in skin homogenates and in murine skin in vivo [25]. Topical application of a tocotrienol-rich fraction has been demonstrated to protect mouse skin from UV- and O_3-induced oxidative stress [26,27]. In conclusion, tocotrienols bear a potential that yet remains to be explored.

VITAMIN C

Ascorbic acid or vitamin C is one of the most important water soluble antioxidants and present in high amounts in the skin. While most species are able to produce ascorbic acid, humans lack the enzymes necessary for its synthesis. Deficiency in ascorbic acid causes scurvy, a disease already described in the ancient writings of the Greeks [28]. Apart from the pure antioxidant function ascorbic acid is an essential co-factor for different enzymes. The antioxidant capacity of vitamin C is related to its unique structure (Fig. 2). Due to its pKa1 of 4.25 it is present as a monoanion at physiological pH, which can undergo a

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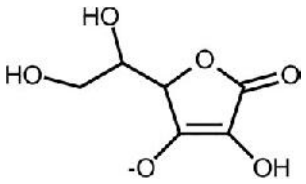

FIGURE 2 Structural formula of vitamin C as the monoanion ascorbate.

one electron donation to form the ascorbyl radical with a delocalized electron and can be further oxidized to result in dehydroascorbic acid. Dehydroascorbic acid is relatively unstable and breaks down if it is not regenerated (see antioxidant network). In vitro ascorbic acid can scavenge many types of radicals including the hydroxyl- ($OH^{\bullet}$), the superoxide- ($O_2^{\bullet -}$) and water soluble peroxyl- ($ROO^{\bullet}$) radicals as well as other reactive oxygen species such as O_3, and quenches singlet oxygen. Due to their relative reduction potentials, ascorbate can reduce Fe(III) to Fe(II), which in turn can decompose hydrogen peroxide (H_2O_2) to the dangerous hydroxyl radical. Therefore, vitamin C can exert pro-oxidant effects in the presence of unbound iron (fenton chemistry).

In the skin, vitamin C is found in all layers. In SC it forms a similar gradient as vitamin E with decreasing concentrations towards the outside. Vitamin C is depleted by O_3, UV radiation, and BPO. One of the earliest discoveries of vitamin C benefits in the skin was the observation that it stimulates collagen synthesis in dermal fibroblasts [29]. Recently a pretranscriptional role of vitamin C had been described [30]. Also, vitamin C is essential in the formation of competent barrier lipids in reconstructed human epidermis [31].

Several studies have investigated protective effects of vitamin C against oxidative stress. UVB-induced immunotolerance, as a marker of damage to the immune system, could be abrogated by topical application of vitamin C to murine skin [32]. UVB-induced sunburn cell formation was mitigated by vitamin C in porcine skin [33]. While one study reported a postadministrative protective effect of vitamin C-phosphate against UV-induced damage in mice [34], another study found no such effect in humans [35]. Systemic application of vitamin C in combination with vitamin E protected against UV-induced erythema in humans [21]. In a keratinocyte cell culture system vitamin C reduced UVB-induced DNA damage [18]. In mice, an anticarcinogenic effect of vitamin C was described [36]. However, no data regarding such benefits exists in humans.

Since vitamin C is not very stable, it is difficult to incorporate it into topical formulations. Esterification with phosphate is used to circumvent this limitation. In vitro experiments demonstrated that Mg-ascorbyl-2-phosphate penetrates the murine skin barrier and is bioconverted into free ascorbate [37].

THIOL ANTIOXIDANTS

Thiols share an oxidizable sulphhydryl (SH) group. Glutathione (GSH) is a tripeptide (Fig. 3) whose SH group at the cysteine can be oxidized, forming a disulphide (GSSG) with another GSH molecule. Physiologically, more than 90% of the GSH is in the reduced form. Glutathione peroxidases use GSH oxidation to reduce H_2O_2 and other water soluble peroxides. The synthesis of GSH by the human cell is stimulated by N-acetyl-cysteine (NAC), which is hydrolyzed to cysteine intracellularly. Moreover NAC acts as an antioxi-

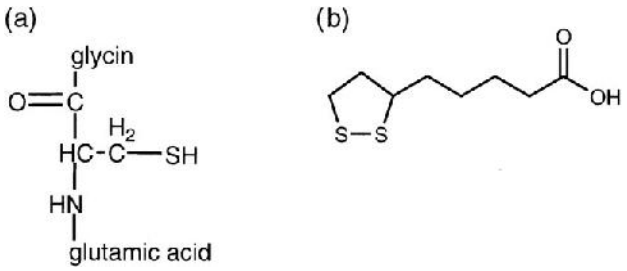

FIGURE 3 Chemical structures of thiols: (a) GSH consisting of glycine, cysteine, and glutamic acid; (b) lipoic acid as in its oxidized form as a disulphide.

dant itself. Lipoic acid (1,2-dithiolane-3-pentanonic acid or thioctic acid, LA) is a cofactor of multienzyme complexes in the decarboxylation of α-keto acids. Applied as the oxidized dithiol dehydrolipoic acid (DHLA) it is taken up by cells and is reduced by mitochondrial and cytosolic enzymes (NAD(P)H dependent). It thereby forms an efficient cycle, since it can in turn regenerate GSSG to GSH and stimulate the GSH synthesis by improving cysteine utilization [38].

General provisos in the use of thiols in skin applications are the typical smell and the poor solubility of LA in aqueous solutions below pH 7. Yet, several thiol agents have been tested for protective effects in the skin. For oral as well as topical application in mouse models, GSH-ethylesters and GSH-isopropylesters proved to be more efficient than free GSH. Oral supplementation decreased the formation of UV-induced tumors [39] and the formation of sunburn cells [40]. Topical treatment partially inhibited UV-induced immunosupression [41]. NAC was able to reduce UVA-induced DNA damage in fibroblasts [42] and protected mice against UVB-induced immunosuppression after topical application [43] in a mode that did not involve de novo GSH synthesis [44]. Lipoic acid was demonstrated to penetrate into mouse skin [45], while oral supplementation of lipoic acid has actually been shown to have an anti-inflammatory effect in mice [46], to prevent symptoms of vitamin E deficiency in vitamin E–deficient mice [47], and vitamin C and E deficiency in guinea pigs [48].

POLYPHENOLS

Flavonoids are widely distributed plant pigments and tannins occurring in barks, roots, leaves, flowers, and fruits. Their roles in plants include photoprotection and contributing to the plant color. Consequently, our diet contains flavonoids which can be found in a variety of foods from green vegetables to red wine [49].

Despite the fact that flavonoids have been used in traditional medicine for several centuries, it was not until 1936 that their first biological activity, the vitamin C–sparing action, was described by Rusznyak and Szent-Györgyi [50]. As a result, they received the name of ''vitamin P.'' Flavonoids, also referred to as plant polyphenols, have been recognized as potent antioxidants. Their free radical-scavenging and metal-chelating activities have been extensively studied. Nonetheless, given their polyphenolic structure (Fig. 4), the electron- and hydrogen-donating abilities constitute the major feature of their antioxidant properties [51]. By opposition to the antioxidants previously described, flavonoids

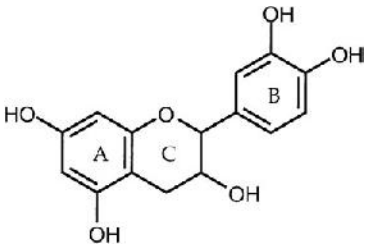

FIGURE 4 Chemical structure of catechin, a flavane, as an example of a flavonoid. Flavanes share a common base structure (rings A, B, C) that is hydroxylated in different patterns.

are not part of the endogenous antioxidant system but still interact with it through the antioxidant network (see the following paragraph).

Among the applications found in traditional medicine, flavonoids account for anti-inflammatory, antiphlogistic, and wound-healing functions [52]. Their effect on skin inflammation has been thought, for a long time, to be limited to the inhibition of the activity of 5-lipoxygenase and cyclo-oxygenase [49]. However, recent studies suggest a more subtle mode of regulation of the inflammatory reaction by flavonoids. In fact, flavonoids such as silymarin, quercetin, genistein, and apigenin are effective inhibitors of NF-κB, a proinflammatory transcription factor, thereby reducing the transcription of proinflammatory genes and preventing inflammation [53–55].

Oral supplementation and topical application of green and black tea polyphenols show beneficial effects against UVR-induced skin carcinogenesis in mice [56–58]. In addition, these flavonoids and silymarin were found to prevent UVR-induced inflammation as well as ornithine decarboxylase expression and activity [59], all of these events being potential contributors to carcinogenesis [60].

Procyanidins, also named condensed tannins, are flavonoids found in, e.g., pine bark (Pycnogenol), grape seeds, and fruits. By direct protein interaction, they were shown to protect collagen and elastin, two dermal matrix proteins, against their degradation [61]. Furthermore, some of these procyanidins exhibit a remarkable effect on follicle hair proliferation [62] thus extending the therapeutic applications of flavonoids to alopecia. Although the flavonoids are not part of our endogenous antioxidant defenses, they display a broad spectrum of properties particularly helpful in preventing UVR-caused deleterious effects in human skin.

THE ANTIOXIDANT NETWORK

When an antioxidant reacts with an oxidant, it is converted to a form that no longer functions as an antioxidant, and is said to be consumed. In order for the oxidized product to function again, it needs to be recycled to its native form. The antioxidant network describes the ability of the antioxidants to recycle and regenerate oxidized forms of each other thereby providing extra levels of protection (Fig. 5). Thus the process is synergistic; the net antioxidant protection is always greater than the sum of the individual effects.

The major systemic antioxidants vitamin E, vitamin C, and glutathione are present in different cellular compartments, and all have the ability to interact with one another. Typically the radicals formed on the antioxidants are more stable and longer lived than the damaging radicals produced in vivo, which is mostly attributable to delocalization of the unpaired electron. Thus they have more chance to interact with each other and be

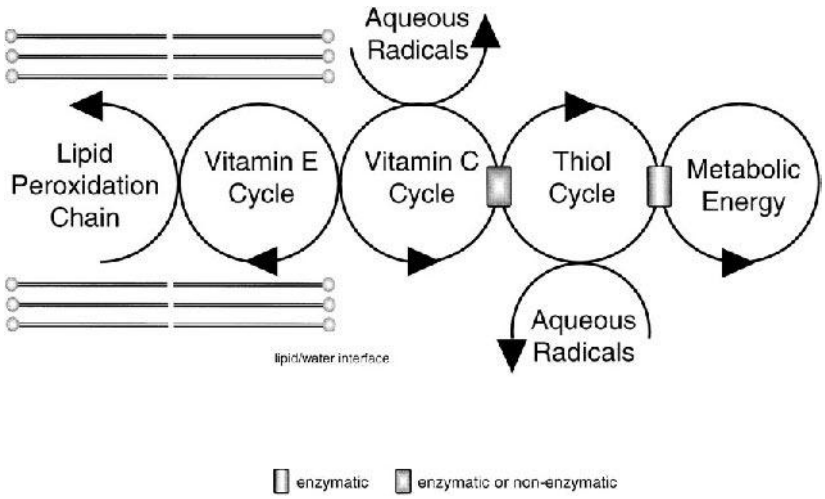

FIGURE 5 Schematics of the intertwined action of the antioxidant network. An ascorbate molecule can either recycle the vitamin E radical arising from breaking the lipid peroxidation chain, or scavenge an aqueous radical. Glutathione can either regenerate ascorbate or scavenge a radical enzymatically. Glutathione itself can then be regenerated by the cellular metabolism.

reduced than to react with macromolecules. Vitamin E is the major chain-breaking antioxidant, protecting biological membranes from lipid peroxidation [63], which is a difficult task considering the ratio of phospholipids molecules to vitamin E is about 1500 : 1. However, vitamin E is never depleted because it is constantly being recycled. When vitamin E becomes oxidized, a radical on vitamin E is formed (chromanoxyl radical). In the absence of networking antioxidants this radical can either become pro-oxidant by abstracting a hydrogen from lipids [64], or react to form nonradical products (consumed). However, a number of antioxidants are known to be able to reduce the chromanoxyl radical and regenerate vitamin E [65]. These include vitamin C [66], ubiquinol, and glutathione (GSH) [67]. Vitamin C, the most abundant plasma antioxidant and first line of defense, can reduce the tocopheroxyl radical, forming the ascorbyl radical. Interactions between vitamins E and C have been shown in various systems both in vivo (reviewed in Ref. 68) and in vitro [69] (reviewed in Ref. 70). The ascorbyl radical is practically inert and oxidizes further to form dehydroascorbic acid. This can be reduced back to native vitamin C by GSH. This process is known to occur both chemically [71] and enzymatically [72] in both erythrocytes [73] and neutrophils induced by bacteria [74]; the latter may relate to a host defense mechanism. Glutathione is the major intracellular antioxidant. Oxidized GSSG is constantly recycled to GSH enzymatically by glutathione reductase, thus providing a constant pool of GSH. Glutathione recycling relies on NAD(P)H as the electron donor. Thus metabolic pathways involved in energy production provide the ultimate electron donors for the antioxidant network. It is also known that GSH can directly recycle vitamin E [65,75], as can ubiquinol [76], another lipophilic antioxidant which itself is recycled in mitochondria as part of the electron transport chain.

Certain supplements are also known to contribute to the network by recycling antioxidants. Lipoic acid is a prime example since this potent antioxidant can recycle ascorbate, GSH, and ubiquinol in vitro (reviewed in Ref. 77). Recently it has been demonstrated that flavonoids may also play a networking role since they are also able to recycle the

ascorbyl radical [78]. Thus there exists a very organized defense system against free radical attack, which ultimately serves to protect and recycle antioxidants in various cellular compartments.

REGULATION OF GENE TRANSCRIPTION BY ANTIOXIDANTS

The skin is the largest human organ and permanently exposed to a variety of stresses. Among those, oxidative insults such as ultraviolet radiation and ozone exposure account for the cause of many skin disorders. However, oxidative damage are not responsible for all biological effects engendered by these stressors in the skin. Indeed, ultraviolet radiation (UVR) causes changes in the expression of genes encoding, e.g., proinflammatory cytokines, growth factors, stress response proteins, oncoproteins, and matrix metalloproteinases [79]. Although the immediate target(s) of UVR is/are still unknown, certain kinases and transcription factors can be activated by UVR thereby increasing gene transcription [80]. One transcription factor, NF-κB, appears of particular interest for the skin since the lack of its inhibitory protein, IκBα, is associated with the development of a widespread dermititis in knockout mice [81,82]. Furthermore, reactive oxygen species, such as the ones produced after UVR, are suspected to play an important role in the activation of NF-κB [83]. Consequently, antioxidants have been found to be among the most potent NF-κB inhibitors. However, clinical studies are required in order to assess the effectiveness of these antioxidants, including the flavonoid silymarin, α-lipoic acid and the glutathione precursor *N*-acetyl-*L*-cysteine, on skin inflammatory disorders. Using high-throughput procedures such as the cDNA arrays, for instance [84], the evaluation of the antioxidants on the whole genome is henceforth possible. These studies will only confirm the hypothesis that antioxidants are responsible for a much broader action spectrum than their antioxidant functions per se and extend their role on more subtle regulatory mechanisms of the gene expression.

PERSPECTIVES

The general role of antioxidants in the protection against oxidative stress is well established. In skin applications antioxidants are a promising tool to mitigate oxidative injury. Even though a growing amount of literature deals with skin protection by antioxidants, there is still a need for investigation. In particular, clinical human studies need to be carried out to show the efficacy of antioxidants in topical formulations.

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Alpha Hydroxy Acids

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Alpha hydroxy acids (AHAs) constitute a class of compounds that exert specific and unique effects on skin structures. The therapeutic utility of these acids continues to expand; when applied to the skin in higher concentrations they cause detachment of keratinocytes and epidermolysis while application in lower concentration reduces intercorneocyte cohesion and visible stratum corneum desquamation.

The smallest AHA is glycolic acid, which is constituted by two carbons ($H_2C(OH)$-COOH); lactic acid contains three carbons and converts to its keto form, pyruvic acid, and vice versa. Malic acid and tartaric acid consists of four carbon chains, while citric and gluconic acid have six carbon chains [1].

AHAs are found in nature in a variety of species including foods and plants (citric, malic, tartaric, glycolic), animals (cells and body fluids), and microorganisms such as bacteria, fungi, viruses, and algae. AHA are involved in many metabolic processes and participate in essential cellular pathways such as Krebs cycle, glycolysis, and serine biosynthesis. Furthermore, they promote collagen maturation and formation of glucosaminoglycans. Their mechanism of action can be hypothesized via multiple effects [2]:

1. On stratum corneum: low concentration of AHAs diminish corneocyte cohesion. The effect occurs at the lower levels of the stratum corneum and may involve a dynamic process, operative at a particular step of keratinization, like the modification of ionic bonding. The effect is clinically evident as a sheetlike separation of the stratum corneum [3]. Indeed, intercorneocyte bonds are mostly noncovalent. In noncovalent bonds, the bonding force may be ionic or nonionic. AHAs reduce corneocyte cohesion by influencing ionic bonds via three mechanisms: (a) the distance between charges, (b) the number of charges, and (c) the medium between charges. When the stratum corneum becomes hydrated, the distance between corneocytes is increased and therefore cohesion is decreased. Another mechanism involved is the enzymatic inhibition, induced by AHAs, of the reactions of sulphate transferase, phosphototransferase, and kinases which leads to fewer electronegative sulphate and phosphate groups on the outer wall of corneocytes resulting in diminishment of cohesion forces. On the contrary, retinoids reduce intercorneocyte cohesion by breaking down already formed sulphate and phosphate bonds via induction or activation of sulphatase or phosphatase.

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2. On keratinocytes: AHAs stimulate epidermal proliferation possibly by improving energy and redox status of keratinocytes. Changes detected on normal skin after treatment with AHAs [4] are similar to those noted during wound healing [5], in the rebound period after steroid-induced atrophy [6], and in retinoic acid–treated skin [7]. Increase in the overall thickness of viable epidermis as well as in the number of granular layers suggest a stimulation of epidermal turnover. The appearance of Hale's stainable material (GAG-like) in intercellular spaces between spinous and granular cells after treatment with an AHA like ammonium lactate has been reported also in retinoic acid treated skin [7,8].

3. On fibroblasts: at high concentration and in an appropriate vehicle, AHA induces epidermolysis, epidermal separation, and impact on the papillary dermis and reticular dermis that can lead to dermal changes including the synthesis of new collagen [1]. AHAs might turn on the biosynthesis of dermal glycosaminoglycans and other intercellular substances that could be responsible for eradication of fine wrinkles [9]. It has also been speculated that AHAs might promote collagen synthesis in human skin [9]. Ascorbic acid (an AHA in the lactone form) has been shown to stimulate procollagen synthesis in cultured human fibroblasts [10].

Because of these mechanisms, the cosmetic effects of AHAs on stratum corneum include an increase of plasticization and a decreased formation of dry flaky scales on skin surface. Indeed, a thinner stratum corneum is more flexible and compact; the increased flexibility obtained after topical application of AHAs is not related to an increased water content of the stratum corneum and is maintained even at low relative humidity [11]; this effect is also related to the free acid concentration of the formulation and is not dependent on transcutaneous penetration or sorption of the molecule [12]. The enhanced release of surface corneocytes is not equal for all AHAs and might lead in the long term to a stimulation of epidermal proliferation which increases thickness and metabolic activity of epidermis. The final cosmetic result of this process is an improvement of skin texture associated with increased skin firmness and elasticity.

Optimization of the formulation allows improvement of efficacy: pH is of great importance for achieving good therapeutical results. The suggested range is between 3.0 and 5.0, but lower pH values seem to be also very effective. The lower acid pH level reached in the stratum corneum after application of AHAs helps in dissolving desmosomes

TABLE 1 Mean Values (±SE) of CBF (Perfusion Units), TEWL (gm^2/h), and Erythema (a* Value)

	CBF		TEWL		Erythema	
	Glycolic	Betameth	Glycolic	Betameth	Glycolic	Betameth
Baseline	109.9 ± 14.9	101.9 ± 12.7	19.6 ± 3.4	18.5 ± 3.7	17.1 ± 1.0	17.7 ± 0.9
Day 5	78.3 ± 9.9*	52.6 ± 7.5	11.1 ± 1.5	10.8 ± 1.6	15.9 ± 0.7	16.3 ± 0.8
Day 10	82.1 ± 13.9*	38.4 ± 5.4	12.2 ± 1.6	8.8 ± 1.7	16.9 ± 1.1	15.2 ± 0.9
Day 15	57.6 ± 6.5*	35.3 ± 8.6	9.6 ± 1.6	8.6 ± 2.3	14.8 ± 0.8	14.5 ± 0.8

* Significant differences in CBF are recorded between glycolic acid–and betamethasone-treated sites during the study [17]. No significant differences appear concerning TEWL and erythema. All treatments induced a significant decrease of the parameters investigated during the study (TEWL, $p < 0.01$ glycolic, $p < 0.005$ betamethasone; CBF, glycolic $p < 0.001$, betamethasone $p < 0.0001$; erythema, glycolic $p < 0.01$, betamethasone $p < 0.009$).

Abbreviations: CBF, cutaneous blood flow; TEWL, transepidermal water loss; SE, standard error.

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and/or other linkages between cells increasing therefore cell shedding and AHA activity [13]. Chronic treatment with low pH formula is likely to induce changes in the pH of living epidermis. Several enzymes (e.g., phosphatases, lipases, transforming growth factor beta) have maximum activity at pH 5 or lower and is possible that an acid environment may activate these mechanisms. Other important factors in the development of the product are free acid concentration (the higher the better) [12], the presence of an appropriate delivery system capable to increase penetration of AHA molecule, and the association between AHA and their salts.

Retinoic acid, a well-known and accepted drug for treating photoaging, shows benefits similar to AHAs after long term application. The mechanism of action is different and, even though clinical results may be similar, more complex. Retinoic acid has specific receptors (CRABP) on keratinocytes and fibroblasts; it binds to cell membranes and causes directly or indirectly stimulation of cell metabolism [14]. AHAs are hydrophilic (and diffuse freely throughout the intercellular phase) whereas retinoids are hydrophobic and thus require certain proteins in plasma and skin to act as carriers [14,15]. Retinoids have several side effects including photosensitivity, erythema, irritant dermatitis, and potential teratogenicity. Furthermore, from a cosmetic viewpoint, it takes several months to induce clinically evident cosmetic improvements [16]; AHAs are generally safer, less irritant, nonphotosensitizing, and give cosmetic results after 8 to 10 weeks.

Alpha hydroxy acids have been recently used to treat some skin diseases. Vignoli et al. [17] showed a reduction in psoriasis severity after treatment with glycolic acid as measured by visual scoring and noninvasive instruments (Table 1); in this study, a signifi-

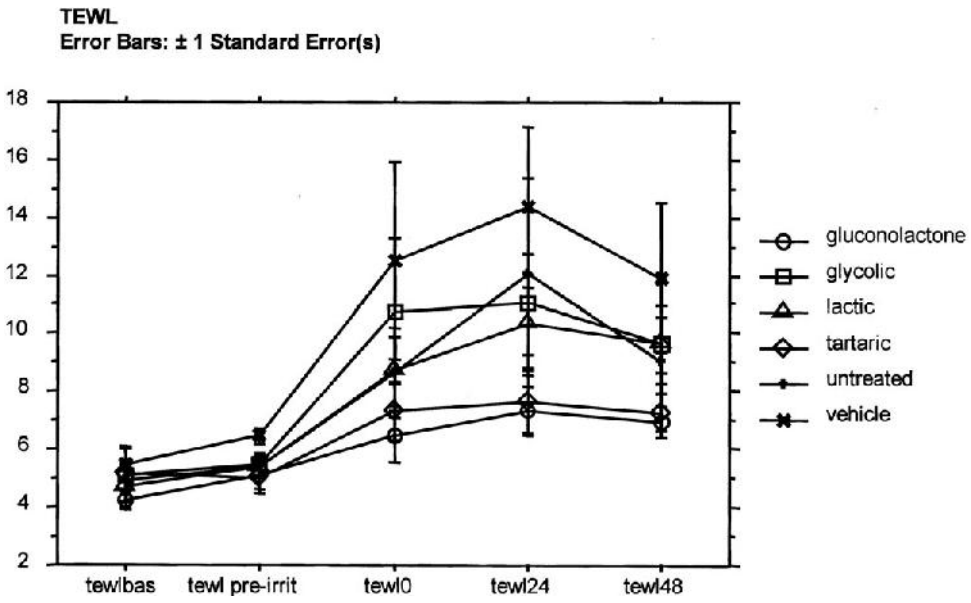

FIGURE 1 Transepidermal water loss (±SE) after SLS challenge (g/m²/h). Lower barrier damage is detected in AHA-treated sites compared to vehicle and untreated areas. ($p < 0.006$). Gluconolactone is significantly lower than glycolic acid at each time point. (hour0 = $p < 0.01$, hour24 = $p < 0.03$, hour48 $p < 0.04$) and than lactic acid at hour 48 ($p < 0.04$). (From Ref. 18.)

cant improvement of transepidermal water loss (TEWL), erythema (a* value), and cutaneous blood flow after treatment with either 15% glycolic acid or betamethasone 0.05%. No significant differences appear in TEWL and erythema between glycolic acid and betamethasone; on the other hand, a significantly decreased CBF is recorded in the sites treated with betamethasone confirming the higher effect of corticosteroid in terms of vasoconstriction and reduction of inflammation.

Prolonged treatment with AHAs can also lead to stratum corneum barrier fortification and increased resistance to chemical irritation; sodium lauryl sulphate (SLS) irritation has been shown to be reduced in AHA-treated sites; a recent study [18] shows that AHAs can modulate stratum corneum barrier function and prevent skin irritation; and the effect is not equal for all AHAs, being more marked for the molecules characterized by antioxidant properties (Fig. 1). This effect has been shown by other keratolytic compounds such as urea [19] and can be related to the increased production of stratum corneum lipids such as ceramides induced by the treatment [20].

Over the years a number of cosmetic or dermatological compounds have gained attention for the capability to treat skin disorders and in particularly skin aging. AHAs are certainly the most intriguing class of compounds that are beginning to be incorporated into the new generation of cosmetic products. Even though many mechanisms are still far from being completely understood and much work remains to be done, the future is promising for these simple molecules.

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28

Colorants

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The use of coloring agents for decorative purposes is one of the earliest cultural accomplishments of humankind. Even in prehistoric times, colorants could be found not only for art—the famous cave paintings in southern Europe, for example—but also especially for body painting, tattooing, or, to use the modern phrase, for decorative cosmetics. Although there were several historical periods in which those who wore cosmetics were scorned or condemned, its use has nevertheless remained a constant among cultures throughout history. In more recent times, decorative cosmetics have been joined by other cosmetic products whose colors are not intended to conceal or change the appearance of something; instead, these colorants must conform to the statement that a given product makes about itself. While it is true that many first-time purchases are heavily influenced by the way the consumer feels about the color of the product and the attractiveness of its packaging, we nevertheless have some very definite associations between certain products and the colors they should have. Blue would certainly be inappropriate for a soap perfumed with sandalwood; the only color that would do for a pine-scented bubble bath is green; and it is logical to give citrus scents psychological reinforcement by coloring them yellow or yellow-green.

Although the use of colorants* has a long history, a great deal of time passed before their role in cosmetics was legally established. This happened in Germany in 1887 with the enactment of the so-called Color Law, which banned the use of hazardous colorants. The issue of concern that led to this law was primarily pigments containing heavy metals; products of the then-developing color industry were not a genuine consideration. In 1906 a color law was passed in Austria that included various purity specifications and made the use of some coal-tar dyes illegal. In 1907 the use of the first certified food colorants were legalized in the United States, and at the same time purity specifications were also

* *Colorants*: general term for all materials that can be used to color. There are three kinds: (1) colorants that are soluble in the medium being colored (in the case of cosmetics, usually water- or oil-soluble), (2) pigments and color lakes that are not soluble in the medium being colored (the latter are usually aluminum hydroxide lakes of water-soluble colorants), and (3) water-dispersible pigments (pigments that yield stable dispersions in water when excipients are added; they can then be processed like soluble colorants).

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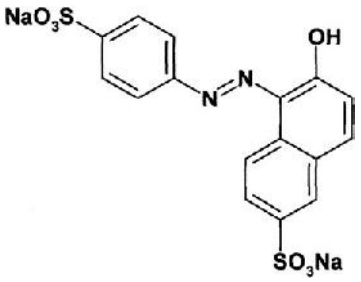

FIGURE 1 Azo colorant yellow-orange S (FD&C Yellow No. 6), C.I. 15985.

determined. The Federal Food, Drug and Cosmetic Act of 1938 first outlined the use of colorants in food, drugs and cosmetics.

The dramatic boom in the development of the color industry led to numerous new colorants and pigments. Because it had become clear that it was not only heavy metals that were dangerous, but the colorants themselves or their initial products could pose a threat as well, after World War II scientific organizations [2] increased their systematic efforts to compile and publish [3] the results of toxicological and dermatological research and encourage further studies. Unfortunately, international cooperation was less intense then than it is today. That means that there are significant differences between the approved colorants for cosmetics in the European Union (EU), the United States, and Japan, for example. An illustration of this is the colorant patent blue V (C.I. 42051), [4] which is approved in the EU for all cosmetic products, [5] but not in the United States or Japan. The same is true of fast yellow (C.I. 13015) and many other European cosmetic colorants. Furthermore, to some extent even approved colorants have different restrictions on their use,* especially for use in the area around the eyes. Table 1 shows the cosmetic colorants in the EU that are also approved for use in the United States and/or Japan. Because they lack fastness, natural colorants (e.g., carotenoids, anthocyans, chlorophylls) play only a minor role in the process of coloring cosmetics. Carmine is an exception (C.I. 75470); the classic red pigment for lipstick is also the only red pigment in the United States that can be used for the eyes.

By comparison, inorganic pigments are used in large quantities. In coloring decorative cosmetics, several products are of vital importance: titanium dioxide (C.I. 77891) in particular—the most important white pigment—the iron oxides and iron hydroxides for the colors yellow (C.I. 77492), and red (C.I. 77491) and black (C.I. 77499), ultramarine (C.I. 77007)—especially in blue and violet—Prussian blue (C.I. 77510), manganese violet (C.I. 77742), coal black (C.I. 77268:1), pearlescent pigments (mica C.I. 77019), and bismuth oxychloride (C.I. 77163). By combining iron oxides, including the addition of titanium dioxide, various brown tones can be created in makeup and toning cremes. The most significant colorant, however, is composed of the organic colorants and pigments which belong to different chemical classes. Mainly these are azo, triarylmethane, anthraquinone, xanthene or phthalocyanine colorants or pigments; occasionally they include indigo derivatives (Figs. 1–6; and Table 1).

* In the EU there are four areas of applications: (1) approved for all cosmetic products; (2) not for use around the eyes; (3) not for use near the mucous membranes; and (4) only for brief contact with the skin.

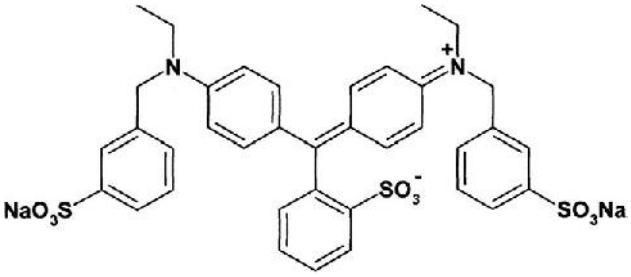

FIGURE 2 Triarylmethane colorant brilliant blue FCF (FD&C Blue No. 1), C.I. 42090.

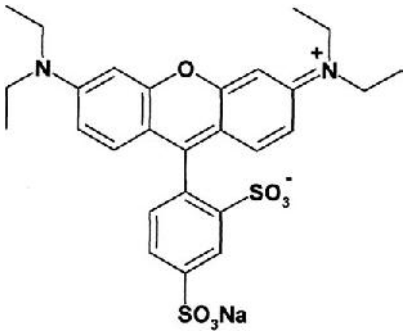

FIGURE 3 Xanthene colorant sulforhodamine B, C.I. 45100.

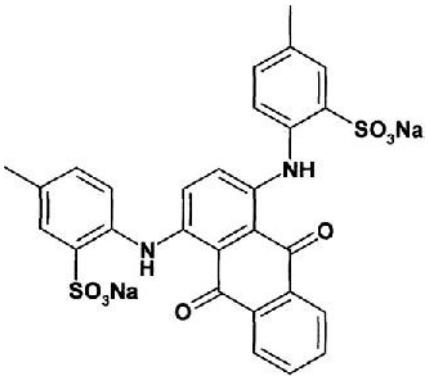

FIGURE 4 Anthraquinone colorant alizarin cyanine green (D&C Green No. 5), C.I. 61570.

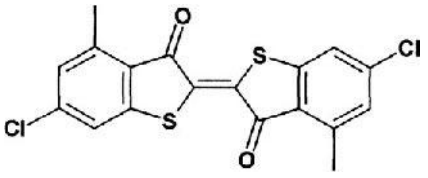

FIGURE 5 Indigo pigment indanthrene brilliant pink R (D&C Red No. 30), C.I. 73360.

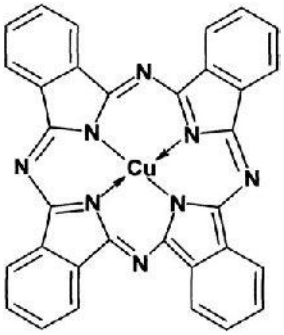

FIGURE 6 Phthalocyanine pigment heliogen blue B (phthalocyanine blue), C.I. 74160.

Regardless of their chemical class, cosmetic colorants are sorted into three groups; this classification is based on their solubility, which determines how they are used: (1) colorants that are soluble in the medium being colored (usually water- or oil-soluble), (2) pigments and color lakes that are not soluble in the medium being colored, and (3) water-dispersible pigments.

Because of the extensive differences in national laws, two major factors must be considered in the development of colored cosmetics: one is technical, and the other is a legal matter. There are three phases to the procedure:

1. After the formulation of the uncolored product has been developed, the decision must be made about the countries in which the product will be marketed.
2. Because not all colorant groups are appropriate for all cosmetics, some are selected (Table 2) and then examined to see which colorant of the respective category is approved in all of the countries where the cosmetic product will be marketed.
3. At this point, the product is colored, and stability tests are then conducted (original packaging, light, heat, etc.). Changing the formulation after successful completion of these tests is strongly discouraged. The testing must be repeated if the risk of unpleasant surprises is to be ruled out.

Although there are approximately 160 approved cosmetic colorants in the EU—many more than in the United States, for example—only a limited number of them is really used. Table 3 shows selected cosmetic product and the colorants that are often and usually added in industry.

Hair-toning and hair-coloring products have a special status among the cosmetics in the EU because the EU guidelines for cosmetics do not apply to these products, especially because common cosmetic colorants have little or no affinity to hair.

Two different kinds of colorants are used to color hair:

1. Oxidation hair colors, which permanently color the hair.
2. Substantive colorants, which only affect the outside of the hair and can be washed out again (semipermanent coloring).

In oxidation hair colors, a colorless initial product penetrates the hair, where a reaction takes place with the aid of hydrogen peroxide (hence the term oxidation hair colors) and

TABLE 1 Cosmetic Colorants in the EU That Are Also Approved in the United States and/or Japan* (as of July 1998)

Color Index Number or name, color, colorant category, solubility	Japan*	U.S.†	Application area in the EU, examples of use
10020 green, water-soluble nitrosonaphthol colorant	Green No. 401 approved (Category III)	Not approved	EU: 3 tenside products
10316 yellow, water-soluble nitro colorant	Yellow No. 403 approved (Category III)	Ext.-D&C Yellow No. 7 not for eyes and lips	EU: 2 soap, tenside products
11680 yellow, azo pigment (also water dispersible)	Yellow No. 401 approved (Category III)	Not approved	EU: 3 soap
11725 orange, azo pigment	Orange No. 401 approved (Category III)	Not approved	EU: 4 soap
12085 red, azo pigment	Red No. 228 approved (Category III)	D&C Red No. 36 not for use near eyes	EU: 1 lipstick (max. 3%)
12120 red, azo pigment	Red No. 221 approved (Category III)	Not approved	EU: 4
14700 red water-soluble azo colorant	Red No. 504 approved (Category III)	FD&C Red No. 4 not for eyes and lips	EU: 1 soap, alcohol-based perfume products
15510 orange, water-soluble azo colorant	Orange No. 205 approved (Category II)	D&C Orange No. 4 not for eyes and lips	EU: 2 tenside products, soap
15620 red, water-soluble azo colorant	Red No. 506 approved (Category III)	Not approved	EU: 4
15630 red (sodium salt), not easily water-soluble azo colorant	Red No. 205 approved (Category II)	Not approved	EU: 1 (max. 3%)
15630: 1 red (barium salt) azo pigment	Red No. 207 approved (Category II)	Not approved	EU: 1 (max. 3%) soap, lipstick, makeup
15630: 2 red (calcium salt) azo pigment	Red No. 206 approved (Category II)	Not approved	EU: 1 (max. 3%) soap, lipstick, makeup
15630: 3 (strontium salt) azo pigment	Red No. 208 approved (Category II)	Not approved	EU: 1 (max. 3%) soap, lipstick, makeup
15800: 1 red (calcium salt) azo pigment	Red No. 219 approved (Category II)	D&C Red No. 31 not for eyes	EU: 3

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TABLE 1 Continued

Color Index Number or name, color, colorant category, solubility	Japan*	U.S.†	Application area in the EU, examples of use
15850 red (sodium salt) not easily water-soluble azo colorant	Red No. 201 approved (Category II)	D&C Red No. 6 not for eyes	EU: 1
15850: 1 red (calcium salt) azo pigment	Red No. 202 approved (Category II)	D&C Red No. 7 not for eyes	EU: 1 soap, lipstick, makeup
15865: 2 red (calcium salt) azo pigment	Red No. 405 approved (Category III)	Not approved	EU: 1 soap, lipstick, makeup
15880: 1 red (calcium salt) azo pigment	Red No. 220 approved (Category II)	D&C Red No. 34 not for eyes	EU: 1 soap, lipstick, makeup
15985 orange, water-soluble azo colorant, also as aluminum lake	Yellow No. 5 approved (Category I)	FD&C Yellow No. 6 not for eyes	EU: 1 (food colorant E 110) alcohol-based perfume products
16035 red, water-soluble azo colorant, also as aluminum lake	Not approved	FD&C Red No. 40 also approved for eyes	EU: 1 (food colorant E 129) tenside products, alcohol-based perfume products, mouthwash
16185 red, water-soluble azo colorant, also as aluminum lake	Red No. 2 approved (Category I)	Not approved	EU: 1 (food colorant E 123) tenside products
16255 red, water-soluble azo colorant, also as aluminum lake	Red No. 102 approved (Category I)	Not approved	EU: 1 (food colorant E 124) tenside products, alcohol-based perfume products
17200 blue-red, water-soluble azo colorant, also as aluminum lake	Red No. 227 approved (Category II)	D&C Red No. 33 not for eyes	EU: 1 mouthwash, alcohol-based perfume products, tenside products
18820 yellow, water-soluble azo colorant	Yellow No. 407 approved (Category III)	Not approved	EU: 4
19140 yellow, water-soluble azo colorant, also as aluminum lake	Yellow No. 4 approved (Category I)	FD&C Yellow No. 5 also approved for eyes	EU: 1 (food colorant E 102) tenside products
20170 yellow-brown, water-soluble azo colorant	Brown No. 201 approved, also as aluminum lake (Category II)	D&C Brown No. 1 not for eyes and lips	EU: 3 tenside products
20470 blue-black, water-soluble azo colorant	Black No. 401 approved (Category III)	Not approved	EU: 4 tenside products, soap

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26100 red, soil-soluble azo colorant	Red No. 225 approved (Category II)	D&C Red No. 17 not for eyes and lips	EU: 3 oil products
40800 yellow-orange, oil-soluble (also water-dispersible)	Beta-carotene approved (Category I)	Beta-carotene (no FDA certificate) also approved for eyes	EU: 1 (food colorant E 160a) cremes
42053 blue-green, water-soluble triarylmethane colorant, also as aluminum lake	Green No. 3 approved (Category I)	FD&C Green No. 3 not for eyes	EU: 1 mouthwash
42090 blue (sodium salt), water-soluble triarylmethane colorant, also as aluminum lake	Blue No. 1 approved (Category I)	FD&C Blue No. 1 also approved for eyes	EU: 1 (food colorant E 133) tenside products, oral and dental care products
42090 blue (ammonia salt), water-soluble triarylmethane colorant, also as aluminum lake	Blue No. 205 approved (Category II)	D&C Blue No. 4 not for eyes and lips	EU: this ammonia salt is not approved
45100 red, fluorescent water-soluble xanthene colorant, also as aluminum lake	Red No. 106 approved (Category I)	Not approved	EU: 4 tenside products
45190 red-violet, water-soluble xanthene colorant, also as aluminum lake	Red No. 401 approved (Category III)	Not approved	EU: 4 tenside products, soap
45350 yellow, xanthene colorant fluorescent, water-soluble salts, also as aluminum lake; free acid oil-soluble	Yellow No. 201 free acid, Yellow No. 202 (1) sodium salt, Yellow No. 202(2) potassium salt, all approved (Category II)	D&C Yellow No. 7 free acid, D&C Yellow No. 8 sodium salt, both not approved for eyes and lips	EU: 1 (max. 6%) basically only the sodium salt is used: tenside products
45370 orange, xanthene colorant, fluorescent, as sodium salt and free acid (45370:1), water-soluble, also as aluminum lake	Orange No. 201 free acid, approved (Category II)	D&C Orange No. 5 free acid, not for eyes, in lipstick max. 5%	EU: 1 lipstick
45380 red, xanthene colorant, fluorescent, salts and free acid (45380:2) water-soluble, also as aluminum lake	Red No. 223 free acid, Red No. 230(12) sodium salt, Red No. 230(2) potassium salt, all approved (Category II)	D&C Red No. 21 free acid, D&C Red No. 22 sodium salt; sodium salt also approved as color lake; none approved for eyes	EU: 1 lipstick

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TABLE 1 Continued

Color Index Number or name, color, colorant category, solubility	Japan*	U.S.†	Application area in the EU, examples of use
45410 red, xanthene colorant, fluorescent, water-soluble salts, also as barium lake and aluminum lake, free acid (45410:1) soluble in ethanol and oils	Red No. 218 free acid, Red No. 231 potassium salt, both approved (Category II); Red. No. 104(1) sodium salt approved (Category I)	D&C Red No. 27 free acid, D&C Red No. 28 sodium salt, both not for eyes	EU: 1 lipstick
45425 red, xanthene colorant, fluorescent, sodium salt water-soluble, free acid (45425:1) soluble in ethanol and oils, also as aluminum lake	Orange No. 206 free acid, Orange No. 207 sodium salt, both approved (Category II), No. 206 not approved as aluminum lake	D&C Orange No. 10 free acid, D&C Orange No. 11 sodium salt, both also approved as color lakes, but not for eyes and lips	EU: 1 lipstick
45430 red, water-soluble xanthene colorant, also as aluminum lake	Red No. 3 approved, also as aluminum lake (Category I)	FD&C Red No. 3 not approved for cosmetics	EU: 1 (food colorant E 127) aluminum lake in lipstick
47000 yellow, oil-soluble quinophthalone colorant	Yellow No. 204 approved (Category I)	D&C Yellow No. 11 not for eyes and lips	EU: 3
47005 yellow, water-soluble quinophthalone colorant, also as aluminum lake	Yellow No. 203 approved also as aluminum lake, barium lake and zirconium lake (Category II)	D&C Yellow No. 10‡ not for eyes	EU: 1 (food colorant E 104) tenside products, soap, permanent and semi-permanent hair products
59040 green, fluorescent, water-soluble pyrene colorant, also as aluminum lake	Green No. 204 approved also as aluminum lake (Category II)	D&C Green No. 8, max. 0.01%, not for eyes and lips	EU: 3 tenside products, soap
60725 blue-violet, oil-soluble anthraquinone colorant	Purple (Violet) No. 201 approved (Category II)	D&C Violet No. 2 not for eyes and lips	EU: 1 oil products
60730 violet, water-soluble anthraquinone colorant	Purple (Violet) No. 401 approved (Category III)	Ext. D&C Violet No. 2 not for eyes and lips	EU: 3 hair, alcohol-based perfume products
61565 green, oil-soluble anthraquinone colorant	Green No. 202 approved (Category II)	D&C Green No. 6 not for eyes and lips	EU: 1 oil products
61570 green, water-soluble anthraquinone colorant, also as aluminum lake	Green No. 201 approved (Category II)	D&C Green No. 5 approved for eyes as well	EU: 1 tenside products, soap

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73000 blue, pigment (indigo, vat-blue colorant)	Blue No. 201 approved (Category II)	Not approved	EU: 1
73015 blue, water-soluble indigo colorant	Blue No. 2 approved, also as aluminum lake (Category I)	FD&C Blue No. 2 not approved for cosmetics	EU: 1 (food colorant E 132) aluminum lake for eye makeup
73360 red, indigo pigment	Red No. 226 approved (Category II)	D&C Red No. 30 not for eyes	EU: 1 toothpaste, lipstick
74160 blue, phthalocyanine pigment (also water dispersible)	Blue No. 404 approved (Category III)	Not approved	EU: 1 eye makeup, toothpaste, soap, tenside products
75120 yellow to orange, oil-soluble carotenoid (also water-dispersible)	Annatto, approved (Category I)	Annatto (no FDA certificate) for eyes as well	EU: 1 (food colorant E 160b) oil products, creams
75130 see 40800			
75170 white, natural organic pigment	Guanine, approved (Category I)	Guanine (no FDA certificate) for eyes also	EU: 1 decorative cosmetics
75470 red, natural anthraquinone pigment, also water-soluble	Carmine, approved (Category I)	Carmine (no FDA certificate) for eyes also	EU: 1 (food colorant E 120) makeup, lipstick
75810 see 75815			
75815 green, water-soluble porphyrine colorant	Sodium copper chlorophylline, approved (Category I)	Potassium sodium copper chlorophylline, (no FDA certificate) max. 0.1%, only approved for oral and dental care products	EU (listed as C.I. 75810) (food colorant E 141): 1, oral and dental care
77000 silver-colored, inorganic pigment	Aluminum powder approved (Category I)	Aluminum powder (no FDA certificate) external application, also for eyes (limitation of the particle size)	EU: 1 (food colorant E 173)
77004 white, pigment	Kaolin approved (Category I)	Kaolin (no FDA certificate), considered cosmetic raw material and not colorant	EU: 1 No known use as a colorant
77007 blue, violet, pink, red and green inorganic pigments	Ultramarine approved (Category I)	Ultramarine (no FDA certificate), also for eyes, but not in products for mouth and lips	EU: 1 makeup, eye cosmetics, lipstick, soap
77019 white to opaque, inorganic pearlescent pigment (mica)	Mica, approved (Category I)	Mica (no FDA certificate), also for eyes	EU (summarized in the EC Guideline with CL 77891): decorative cosmetics

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TABLE 1 Continued

Color Index Number or name, color, colorant category, solubility	Japan*	U.S.†	Application area in the EU, examples of use
77120 white, inorganic pigment	Barium sulfate considered cosmetic raw material and not colorant	Barium sulfate considered cosmetic raw material and not colorant	EU: 1 no known use as a colorant
77163 white inorganic pearlescent pigment	Bismuth oxychloride approved (Category I)	Bismuth oxychloride (no FDA certificate) also for eyes	EU: 1 decorative cosmetics
77220 white, pigment	Calcium carbonate considered cosmetic raw material and not colorant	Calcium carbonate considered cosmetic raw material and not colorant	EU: 1 no known use as a colorant
77231 white, inorganic pigment	Calcium sulfate considered cosmetic raw material and not colorant	Calcium sulfate considered cosmetic raw material and not colorant	EU: 1 no known use as a colorant
77266 black, inorganic pigment	Carbon black approved (Category I)	Not approved	EU: 1 decorative cosmetics
77288 green, inorganic pigment	Chromium oxide green, approved for eyes as well, but not around mouth and lips	Chromium oxide greens (no FDA certificate), also for yes, but not around mouth and lips	EU: 1 decorative cosmetics, soap
77289 green, inorganic pigment	Hydrated chromium oxide, approved for eyes as well, but not around mouth and lips	Chromium hydroxide green (no FDA certificate), also approved for eyes, but not around mouth and lips	EU: 1 decorative cosmetics, soap
77400 copper-colored, inorganic pigment	Not approved	Copper powder (no FDA certificate), for external application and also for eyes	EU: 1 decorative cosmetics
77491 red-brown, inorganic pigment	Red oxide of iron approved (Category I)	Synthetic iron oxide (no FDA certificate) also for eyes	EU: 1 (all food colorant E 172) creams, makeup, lipstick, soap
77492 yellow, inorganic pigment	Yellow oxide of iron approved (Category I)		
77499 black, inorganic pigment	Black oxide of iron approved (Category I)		

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77510 blue, inorganic pigment	Ferric ferrocyanide approved (Category I)	Ferric ferrocyanide (no FDA certificate), also for eyes, but not around mouth and lips	EU: 1 decorative cosmetics especially eye makeup
77713 white, inorganic pigment	Magnesium carbonate approved (Category I)	Magnesium carbonate considered cosmetic raw material and not colorant	EU: 1 powder
77742 violet, inorganic pigment	Manganese Violet approved for eyes but not around mouth and lips	Manganese Violet (no FDA certificate) also for eyes	EU: 1 decorative cosmetics
77820 silver-colored inorganic pigment	Not approved	Silver (no FDA certificate), max. 1% only for use on nails	EU: 1 (food colorant E 174) no known use as a cosmetic colorant
77891 white, inorganic pigment	Titanium dioxide approved (Category I)	Titanium dioxide (no FDA certificate) also for eyes	EU: 1 (food colorant E 171) creams, makeup, lipstick, powder, soap, toothpaste
77947 white, inorganic pigment	Zinc oxide approved (Category I)	Zinc oxide (no FDA certificate) for external application and also for eyes	EU: 1 no known use as a colorant
Aluminum stearate, calcium stearate, and magnesium stearate white, oil-soluble	Considered cosmetic raw material and not colorant	Considered cosmetic raw material and not colorant	EU: 1 no known use as a cosmetic colorant
Lactoflavin (riboflavin, vitamin B2) yellow, water soluble	Riboflavin approved (Category I)	Not approved	EU: 1 (food colorant E 101) no known use as a cosmetic colorant
Caramel sugar brown, water-soluble	Caramel approved (Category I)	Caramel (no FDA certificate) also used for eyes	EU: 1 (food colorant E 150a–d) rarely also in creams

* Japan: Category I—approved for all cosmetic products, Category II—for external use, Category III—not for use on mucous membranes.

† Unless otherwise indicated and if chemically possible, the corresponding aluminum color lake is also approved.

‡ Because of its perceptual composition of mono-, di-, and trisulfonic acid, D&C Yellow No. 10 does not correspond to the specification of EU-approved food colorant E 104, which is also listed under CI 47005.

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TABLE 2

Colorant group	Cosmetic products
Water-soluble colorants	e.g., bath products (shampoo, shower gel, and bubble bath), creams, soap, toothpaste gel, mouthwash
Oil-soluble colorants	e.g., oil products, soap
Pigments	e.g., makeup, powder, lipstick, toothpaste, soap
Color lakes	e.g., eye makeup, lipstick
Water dispersible pigments	soap

TABLE 3

Cosmetic products (selection)	Color	Recommended colorant
	blue	
Bubble bath	yellow	C.I. 42045, 42051, 42090
	green	C.I. 13015, 19140, 47005, 45350 (fluorescent)
	orange	C.I. 61570, 59040 (fluorescent) as well as by mixing blue and yellow colorings
	pink/red	C.I. 16255, 15985 as well as by mixing yellow and red colorants
	brown	C.I. 16255, 16035, 16185
	violet	can be created by mixing red and yellow or orange and blue colorants
		by mixing red and blue, especially C.I. 42090 and 16185.
Recommended dose		0.05–0.3%
Shampoo, shower gel, liquid soap	colors as for bubble bath and also	
	blue	C.I. 61585 and
	pink	C.I. 45100
Recommended dose		0.01–0.05%
Bath salts	blue	C.I. 42090, 42051
	yellow	C.I. 47005, 45350 (fluorescent)
	green	C.I. 61570, also as mixture of blue and yellow colorants
	pink	C.I. 45430
Recommended dose		0.005–0.01%
Oil products	blue	C.I. 60725
	yellow	C.I. 40800
	green	C.I. 75810
	orange	C.I. 75120
	turquoise	C.I. 61565
	red-orange	C.I. 12150
Recommended dose		0.01–0.05%

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TABLE 3 Continued

Cosmetic products (selection)	Color	Recommended colorant
Soap	blue	C.I. 61585, 74160, 77007
	yellow	C.I. 10316, 11680, 11710, 21108, 47005, 77492
	green	C.I. 10006, 10020, 59040 (fluorescent), 61570, 74260
	orange	by mixing red and yellow
	red	C.I. 12490, 77491
	black	C.I. 77499, 77268:1
	violet	C.I. 51319 and by mixing blue and red
	white	C.I. 77891
Recommended dose		water-soluble colorants or water dispersible pigments 0.01–0.05%
		pigments 0.05–0.5%
Toothpaste	blue	C.I. 74160
	green	C.I. 74260
	red	C.I. 73360
	white	C.I. 77891
Recommended dose		0.02–0.05%
Toothpaste gels	blue	C.I. 42051, 42090
Recommended dose		C.I. 0.02–0.05%
Mouthwash	blue	C.I. 42090
	green	C.I. 61570 or a mixture of C.I. 42090 and C.I. 47005
	red	C.I. 16035
Recommended dose		5–20 ppm
Alcoholic perfume products	blue	C.I. 42051, 42090
	yellow	C.I. 47005, 13015, 19140
	orange	C.I. 15985
	red	C.I. 16035, 17200
Recommended dose		5–20 ppm
Lipstick	all pigments (cosmetic application area 1 in the EU)	
Recommended dose		1–10%
Makeup, powder	brown	mixtures of C.I. 77491, 77492, 77499, 77891
Recommended dose		2–10%
Eye makeup	blue	C.I. 77510, 77007
	yellow	C.I. 77492
	red	C.I. 77491, 75470
	violet	C.I. 77742
	black	C.I. 77266, 77268:1, 77499
Recommended dose		5–30%

another colorless initial product. No colorants are used; the color is first created on the inside of the hair.

Substantive colorants are largely cationic and cannot penetrate the hair because their molecules are too large; therefore they only adhere on the outside and can be removed again comparatively easily.

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Hair Conditioners

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INTRODUCTION

Despite myriad claimed benefits, the primary purpose of a hair conditioner is to reduce the magnitude of the forces associated with combing or brushing hair [1], especially when wet [2,3]. This is generally accomplished by the deposition of conditioning agents that lubricate the hair fiber, diminishing surface friction and, therefore, combing forces [4].

In general, deposition of a conditioning agent also causes the hair to feel softer and more moisturized. Another secondary benefit is the reduction or prevention of flyaway hair [5], especially by cationic conditioners [6]. Increasing ease of combing also makes the hair more manageable, while improving the ability to align the hair fibers in a more parallel configuration can increase hair shine, even if the shine of individual fibers is not increased [7].

A number of other benefits have sometimes been claimed or implied for conditioners including, e.g., repair of damaged hair, strengthening of hair, repair of split ends, and vitamin therapy. Most of these are marketing hype or are based on laboratory conditions or concentrations not found under actual usage conditions. In this chapter, we will confine ourselves to a discussion of only the observable conditioner benefits presented above. The chapter will begin with a discussion of the relationship between hair damage, conditioning and the state of the hair surface. This will be followed by a discussion of the major classes of conditioning agents currently in use. Finally, we will end with a brief discussion of the auxiliary ingredients necessary for the production of a commercial conditioning product.

CONDITIONING AND THE HAIR FIBER SURFACE

Hair Damage

In previous chapters, it has been shown that hair fibers consist of a central cortex that comprises the major portion of the fiber, surrounded by 8 to 10 layers of overlapping cells termed the cuticle. The cortex is responsible for the tensile properties of the hair [8,9], while the state of the cuticle affects a variety of consumer perceivable properties including, e.g., hair feel, shine, and combability.

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A major function of conditioners is to protect the hair's structural elements, especially the cuticle, from grooming damage. This type of stress, characterized by chipping, fragmenting, and wearing away of cuticle cells, is probably the single most important source of damage to the hair surface [10–12].

A rather extreme example of combing damage can be seen in Figure 1, which shows the results of an experiment in which a tress of virgin hair was washed with a cleaning shampoo and then combed 700 times while wet. Since hair is more fragile when wet [3] and combing forces are higher [2], combing under these conditions insures maximum damage. It can be seen that damage to the cuticle was extensive with many cuticle cells lifted from the surface, while others were completely torn away by the combing process.

The ability of conditioning agents to protect the hair from this type of damage can be seen in Figure 2, which shows the results of an experiment in which a tress was washed with a high-conditioning ''2-in-1'' shampoo and then combed 700 times while wet. In this case, because the conditioning agents in the shampoo reduced combing forces, the hair surface is seen to be intact with evidence of only minor chipping and fragmenting of cuticle cells. This demonstrates the important role conditioners can play in maintaining the integrity of the hair fiber.

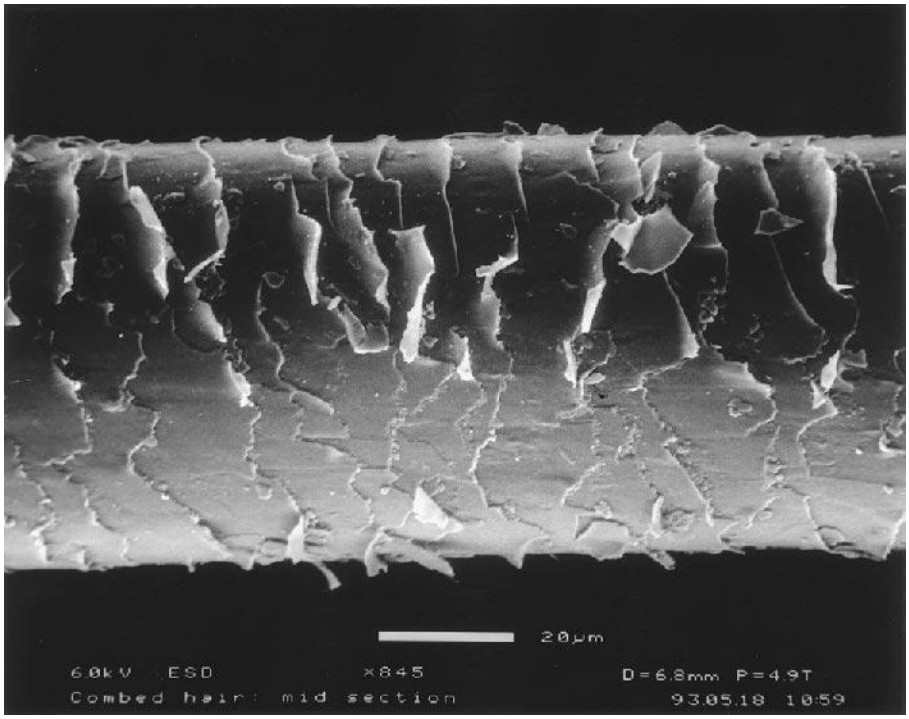


FIGURE 1 Typical scanning electron micrograph (SEM) of hair taken from a tress washed with a cleaning shampoo and then combed 700 times while wet. Note raised and chipped cuticle cells, and areas where cells have been completely torn away.

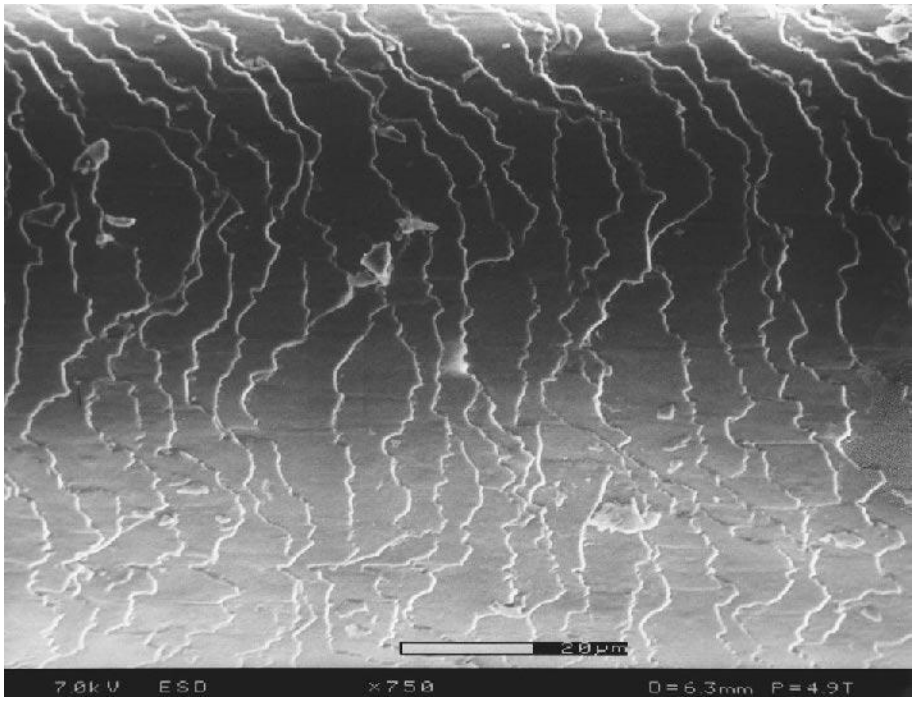


FIGURE 2 Typical SEM photo of hair taken from a tress washed with a high-conditioning 2-in-1 shampoo and then combed 700 times while wet. Note the minimal damage compared with Figure 1.

Hair Damage and the Cuticle Surface

The susceptibility of a hair fiber to grooming damage and the type of conditioner most effective in preventing this damage is affected to a large degree by the nature and state of the hair surface. It is therefore helpful to precede a discussion of conditioning agents with a presentation on the hair surface and how it affects conditioner requirements and deposition.

Virgin Hair Surfaces

Hair that has not been chemically treated is termed virgin hair. The cuticle surface of virgin hair in good condition is hydrophobic [13,14], in large part as a result of a layer of fatty acids covalently bound to the outermost surface of the cuticle (epicuticle) [15,16]. As a result of its protein structure, however, the hair surface has an isoelectric point near 3.67 [17], which insures that the surface will contain negatively charged hydrophilic sites at the ordinary pH levels of haircare products. This mix of hydrophobicity and hydrophilicity affects, of course, the types of conditioning agents that will bind to the virgin hair surface.

The situation is further complicated by the fact that the negative charge density on virgin hair increases from root to tip. This is primarily a result of oxidation of cystine in the hair to cystine S-sulfonate and cysteic acid as a result of exposure to UV radiation in

sunlight [18,19]. The tip portions of the hair, being older than the root portions, will have been exposed to damaging [10] UV radiation for a longer period of time and will therefore be more hydrophilic, again affecting the nature of species that can bind to these sites.

In addition to greater UV damage, the tips of hair are also subject to greater combing damage. One reason for this is simply that, being older, the tip portions will have been exposed to more combing. In addition, the surface friction of hair tips is higher (C. Reich, unpublished data) so that combing forces increase as one moves from root to tip. Finally, the ends of hair are subject to unusually high combing stress as a result of entangling during the combing process [2]. This eventually results in destruction of the covalently bound lipid layer and a feeling of dryness at the tips. Because of this, the tip ends of hair require more conditioning than the rest of the fiber. Without sufficient conditioning, the cuticle layer is eventually lost, resulting in a split end. An example is seen in Figure 3, which clearly shows the exposed cortical cells.

Chemically Treated Hair Surfaces

Chemical treatments, perming, bleaching, and permanent dyeing, can all cause significant damage to the hair fiber [3,10,20–22]. In addition to causing tensile damage, all of these treatments, which include oxidative steps, modify the surface of the hair, introducing negative charges as a result of oxidation of cystine to cysteic acid [3,10,20,21,23]. This can result in transformation of the entire fiber surface from a hydrophobic to a hydrophilic character.

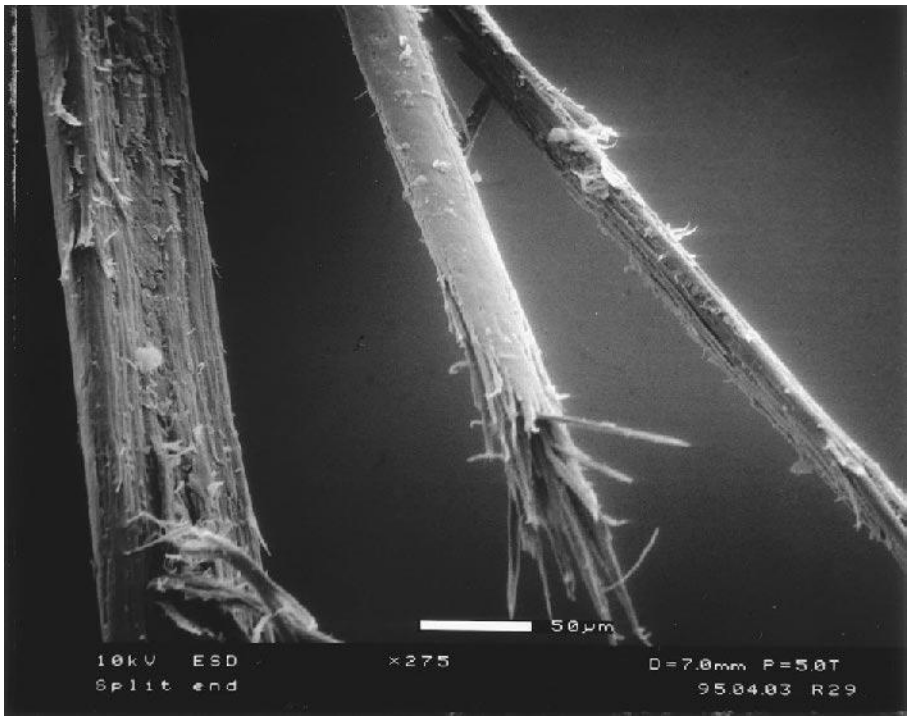


FIGURE 3 SEM photograph of a split end. Note the exposed cortex and the complete loss of cuticle cells on the fiber surface.

All of these treatments also increase surface friction considerably [3,4,24,25] resulting in a significant increase in combing forces. The result is hair that feels rough and dry and is subject to extensive grooming damage. Because of this, treated hair generally requires significantly more conditioning than does virgin hair.

COMMERCIAL CONDITIONERS

The commercial hair conditioners produced to deal with the aforementioned problems have appeared in almost every conceivable form, including thick vaseline pomades; thick, clear, water-soluble gels; spray mists of volatile substances; mousses; lotions; and creams. Conditioners have been marketed as leave-in or rinse-off products. They have also been positioned as pre-shampoo or post-shampoo formulations.

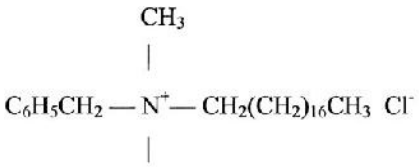
Despite the wide variety of forms available, most commercial conditioners are oil-in-water emulsions in lotion form, having viscosities somewhere between 3000 and 12,000 centipoise. The great majority of these products are of the rinse-off type. In addition, despite different forms and positionings, most commercial conditioners contain the same general classes of conditioning agents with differences mainly in concentrations, numbers of different agents, and the particular members of a conditioning class employed.

The major classes of conditioning agents used in commercial products are surveyed in the following sections.

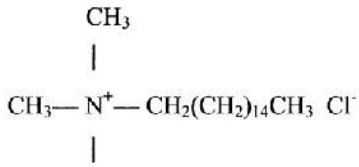
Cationic Surfactants

Cationic surfactants, in the form of quaternary ammonium compounds, are the most widely used conditioning agents in commercial products [26–28]. Among the reasons for this are their effectiveness, versatility, availability, and low cost.

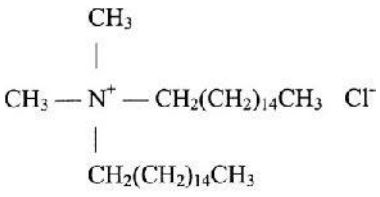
Important examples of these quats include stearalkonium chloride, cetrimonium chloride, and dicetyldimonium chloride.



Stearalkonium Chloride



Cetrimonium Chloride



Dicetyldimonium Chloride

Because of the positive charge on quaternary ammonium compounds such as the above, they are substantive to hair, binding to negative sites on the hair surface. Treatment

with these quats, therefore, results in a hydrophobic coating on the fiber that renders the hair softer and easier to comb [29]. Build-up of static charge (flyaway) is also greatly reduced as a result of this surface modification [6].

Another consequence of the positive charge on quats is that deposition increases with increasing negative charge on the hair surface. This is seen in Table 1, which shows the results of an experiment in which hair tresses were treated with 1% stearalkonium chloride and then rinsed. Compared with the roots, 22% more quat was found to bind to the tips of virgin hair, while deposition of stearalkonium chloride on bleached hair was found to be more than twice that on untreated fibers.

This result is important because, as previously discussed, damaged portions of the hair, which generally carry a greater amount of negative charge, require a greater amount of conditioning. The fact that cationic surfactants can supply this increased conditioning, makes them effective on a wide variety of hair surfaces. This is a major factor in the widespread use of these types of conditioning agents.

Conditioner Properties and Hydrophobicity

Many important properties of quaternary ammonium conditioners are related to the degree of hydrophobicity of the lipophilic portion of the surfactant. Thus, increasing the length of the alkyl chain of a monoalkyl quat, and therefore making it more hydrophobic, leads to increased deposition [31–36] on hair. Cetrimonium chloride, as a result, deposits on hair to a greater extent than does laurtrimonium chloride. Increasing the number of alkyl chains also increases deposition, so that tricetylmonium chloride exhibits greater deposition than does dicetyldimonium chloride, which, in turn, is more substantive than the monocetyl quat.

This dependence of deposition on degree of hydrophobicity indicates that van der Waals forces play an important role in deposition of quaternary ammonium conditioners [36]. This conclusion is consistent with the entropy-driven deposition demonstrated by Ohbu et al. [37] and Stapleton [38] for a monoalkyl quat and a protonated long-chain amine.

Increased hydrophobicity also correlates with increased conditioning by quaternary ammonium compounds [31–34,39]. Thus, cetrimonium chloride provides light to medium conditioning, while dicetyldimonium and tricetylmonium chlorides provide heavier conditioning. Detangling and wet combing, in particular, improve significantly from monocetyl to dicetyl to tricetyl quats; differences in dry combing and static charge among these compounds are not as significant.

Increased conditioning with increased hydrophobicity is probably due, in part, simply to increased deposition of quat on hair. Data from Garcia and Diaz [40], however, indicate greater improvements in wet combing from heavier conditioning quats even when present on the hair in much lower amounts than less hydrophobic species. The degree of

TABLE 1 Binding of Stearalkonium Chloride to Human Hair

Type of hair	Quat deposition at roots (mg/g hair)	Quat deposition at tips (mg/g hair)
Virgin hair	0.649	0.789
Bleached hair	1.62	1.83

Source: Ref. 30.

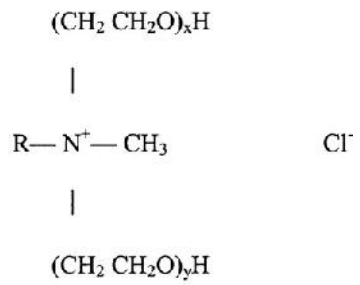
hydrophobicity of a quat must therefore play a direct role in the conditioning efficacy of these compounds [29].

Note that on some types of hair, the greater substantivity of higher conditioning quats can lead to build-up and result in limp, unmanageable hair with repeated use. This is especially true, e.g., for untreated, fine hair. Different quats, or mixtures of conditioning agents, are therefore suitable for different uses or different types of hair. A tricetyl quat might be used, e.g., in an intensive conditioner meant only for occasional use.

The length and number of alkyl chains of quats also determines water solubility of these compounds. Monoalkyl quaternaries up to cetrimonium chloride are water soluble, e.g., distearyldimonium chloride is water dispersible, while tricetylmonium chloride is insoluble in water [34].

Compatibility with Anionics

The quaternium compounds normally used in commercial conditioners are not generally found in shampoos because of incompatibility with common anionic detergents [41]. Introducing hydrophilic groups into the quat can increase compatibility with anionics. An example is the class of ethoxylated quaternaries, termed ethoquats. Typical members of this class are PEG-2 cocomonium chloride, where x + y equals 2 and R is a C12 alkyl chain, and PEG-15 stearmonium chloride where x + y equals 15 and R is a C18 chain.



Ethoxylated Quaternary

Both of these quats are compatible with typical anionic detergents. As would be expected from this discussion, however, introducing hydrophilic groups decreases the conditioning efficacy of these materials [31,34]. They are therefore suitable only in light-conditioning formulations. Furthermore, conditioning shampoos based on ethoquats would not be expected to be very effective as a result of low deposition of the detergent-soluble ethoquat complex.

Other detergent-soluble quats have been produced. These include alkylamidopropyl dihydroxypropyl dimonium chlorides [42], lauryl methyl gluceth-10 hydroxypropyl dimonium chloride [43], and even a hydrolyzed ginseng-saponin quaternary derived from Korean ginseng saponin [44]. Although certain advantages have been claimed for these surfactants, particularly low irritation, they all suffer from much the same conditioning limitations as the ethoquats.

Other Cationic Surfactants

In addition to the aforementioned examples, numerous other cationic surfactants are in use or have been proposed for commercial products. One example of a compound that has been receiving increasing use recently is the behentrimonium (C22) quat. This quat

exhibits significantly reduced eye and skin irritation compared with the corresponding C18 conditioner. In addition, superior conditioning and thickening properties have been claimed [45].

Another interesting example is hydrogenated tallow octyl dimonium chloride [46]. This material is quite substantive and provides high conditioning as a result of its two hydrophobic chains. Unlike conventional dialkyl quats, however, this particular conditioner is soluble in water as a result of branching (2-ethylhexyl) in the octyl moiety. This makes the compound much easier to formulate into a commercial product.

Stearamidopropyl dimethylamine is another conditioning agent that is found in many commercial conditioners. This material is cationic at the pHs normally used in conditioning products and therefore acts as a cationic emulsifier and, also, as a secondary conditioning agent.

Concern for the environment has led to the synthesis of ester quats that exhibit increased biodegradability and environmental safety. One such example is dipalmitoylethyl hydroxyethylmonium methosulfate, an ester quat based on a partially hydrogenated palm radical [47].

Other cationic surfactants used in conditioners include quats derived from Guerbet alcohols [39] (low to high conditioning depending on length of the main and side alkyl chains), distearyldimonium chloride (high conditioning), and the quaternized ammonium compounds of hydrolyzed milk protein, soy and wheat protein, and hydrolyzed keratin (varying conditioning efficacy depending on alkyl chain length).

Lipophilic Conditioners

Quaternary ammonium surfactants in commercial products are almost never used alone. Instead they are used in combination with long-chain fatty conditioners, especially cetyl and stearyl alcohols [28]. These fatty materials are added to boost the conditioning effects of the quaternary compounds [43]. In one study, e.g., addition of cetyl alcohol to cetrimonium bromide nearly doubled the observed reduction in wet combing forces on hair [48]. In another study, using a novel hydrodynamic technique, Fukuchi et al. [49] found that the addition of cetyl alcohol to a behentrimonium chloride formulation resulted in significantly reduced surface friction.

Several investigators have studied combinations of cationic surfactants and fatty alcohols. Under the right conditions, these mixtures have been found to form liquid crystal mesophases and gel networks [50–54] that can greatly increase viscosity and, at the same time, confer stability upon emulsions. As a result of reduced repulsion between cationic head groups when long chain alcohols are interposed, liquid crystal formation has been observed even at low concentrations [53,54]. The ready formation of these extended structures between quats and cetyl and stearyl alcohols, along with the low cost, stability, and compatibility with cosmetic ingredients of the latter are important reasons why these alcohols are so ubiquitous in conditioning formulations.

Other lipids found in commercial products include, e.g., glycol distearate, triglycerides, fatty esters, waxes of triglycerides, and liquid paraffin.

Cationic Polymers

There are numerous cationic polymers that provide conditioning benefits, especially improved wet combing and reduced static charge. Important examples of these polymers are Polyquaternium-10, a quaternized hydroxyethylcellulose polymer; Polyquaternium-7, a

copolymer of diallyldimethylammonium chloride and acrylamide; Polyquaternium-11, a copolymer of vinylpyrrolidone and dimethylaminoethyl methacrylate quaternized with dimethyl sulfate; Polyquaternium-16, a copolymer of vinylpyrrolidone and quaternized vinylimidazole; and Polyquaternium-6, a homopolymer of diallyldimethylammonium chloride.

By virtue of their cationic nature, these polymers are substantive to hair. The particular conditioning effectiveness of any of these materials depends on the polymer structure. In one set of studies, deposition on hair was found to be inversely proportional, roughly, to cationic charge density [55,56]. This has been explained by the observation that the higher the charge density, the lower the weight of polymer needed to neutralize all of the negative charge on the hair. Once deposited, however, multiple points of electrostatic attachment makes these polymers harder to remove, especially if charge density is high [30,57]. Care must be taken, therefore, in formulating conditioners containing these materials to avoid overconditioning as a result of build-up with continued use.

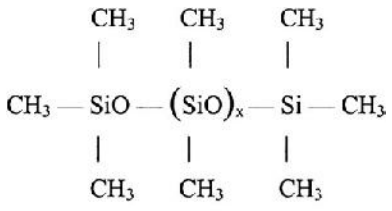
As with the preceding monofunctional cationics, deposition of polyquaterniums increases on treated, or damaged, hair [30,57,58]. Unlike common monofunctional quats, however, the first four of these polymers are compatible, to varying degrees, with anionic surfactants [57–61]. As a result, they are used more often in shampoos than in stand-alone conditioners, although they find some use in leave-in conditioners.

Polyquaternium-10 (PQ-10) and Polyquaternium-7 (PQ-7) are two of the most frequently used polymers in commercial shampoos. Both of these polymers form negatively charged complexes [57,59] with excess anionic surfactant, resulting in reduced deposition because of repulsion by the negatively charged hair surface. The magnitude of this effect depends on the particular anionic used, and on the anionic surfactant/polymer ratio. In all cases, however, conditioning from shampoos is significantly less than from stand-alone conditioners.

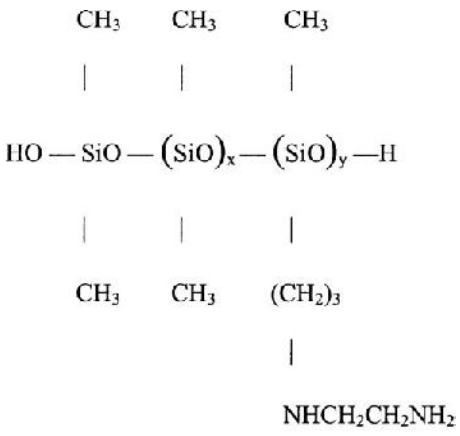
Despite reduced deposition, Hannah [62] has reported that polyquaternium association complexes formed with SLS resist removal from hair. Build-up and a heavy, coated feel on the hair can therefore result from conditioning shampoos containing polyquats unless they are carefully formulated.

Silicones

The use of silicones in haircare products has increased considerably in the past two decades, although their first incorporation into commercial products dates back to the 1950s. Different types of silicones find use as conditioning agents in a wide variety of products, including conditioners, shampoos, hair sprays, mousses, and gels [63]. One of the most widely used silicones is dimethicone, which is a polydimethylsiloxane. Other important silicones are dimethiconol, which is a dimethylsiloxane terminated with hydroxyl groups, and amodimethicone, which is an amino-substituted silicone.



Dimethicone



Amodimethicone

Most silicones used in haircare products, including those previously mentioned, are insoluble and must therefore be emulsified. To increase ease of product manufacture, many suppliers offer silicones as preformed emulsions, in addition to the pure material. The factors affecting deposition of silicones from such emulsions have been reported by Jachowicz and Berthiaume [64,65].

Conditioning Properties of Silicones

Silicones used in haircare products possess a range of unique properties including lubricity, low intermolecular forces, water insolubility, and low surface tension. These properties permit the silicones to spread easily on the hair surface, forming a hydrophobic film that provides ease of combing, and imparts a smooth, soft feel to the hair without greasiness.

The relative conditioning efficacy of silicones compared to other conditioners was demonstrated by Yahagi [66], who found that dimethicone lowered frictional coefficients and surface energy of virgin hair to a greater extent than did a series of cationic surfactants, including distearyldimonium chloride, a very effective conditioning agent. Dimethicones with molecular weights greater than 20,000 were found to be most effective in reducing surface tension.

Nanavati and Hami [67] measured conditioning on slightly bleached European hair treated with dimethicone fluids and dimethiconol gums. Both types of silicones were found to significantly reduce combing forces on hair. Ease of wet combing was roughly the same for the two silicone treatments, while dimethiconol was found to be more effective in reducing dry combing forces.

Interestingly, under the treatment conditions used (exposure to silicone solutions for 30 sec followed by drying without rinsing), deposition of all silicones studied was found to nearly double if tricetyldimonium chloride was present in the treatment solution. Reduction in combing forces was also doubled, roughly, when silicones were deposited in the presence of quat. This latter effect was found to be synergistic, i.e., it depended on deposition of both silicone and quat, and its magnitude was greater than the sum of the individual conditioner contributions.

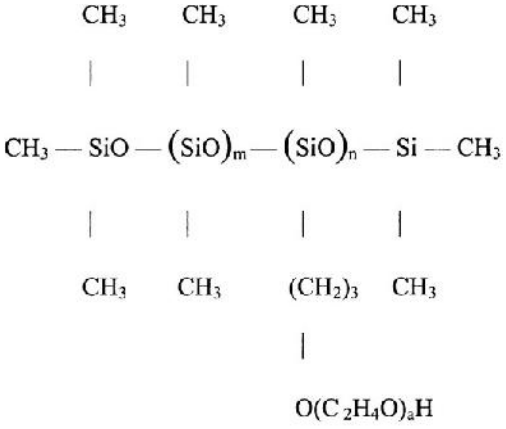
Wendel et al. [68] used electron spectroscopy for chemical analysis (ESCA) to demonstrate that the presence of amino groups in silicones considerably increases substantivity of these materials. This is a result of the positive charge developed by these groups at the pHs commonly found in commercial products.

Comparison of conditioning effects of a series of silicone emulsions on bleached and virgin hair was carried out by Hoag et al. [69]. Most of the silicones were dimethicones or amodimethicones, while emulsions were anionic, neutral, or cationic in nature. Diluted emulsions were applied directly to the hair and combing forces measured both before and after rinsing. Prior to rinsing, reduction of combing forces by most emulsions was greater than 80%. This number was decreased after rinsing as a result of partial removal of deposited silicone. Unsurprisingly, the least change in ease of combing was found for cationic emulsions, especially those containing amodimethicone. Combing forces on virgin hair increased less than on bleached hair after rinsing, indicating that the silicones were more substantive to this type of hair. This is also unsurprising considering the hydrophobic nature of these conditioning agents.

Further effects of amodimethicones can be seen in work reported by Berthiaume et al. [70], who studied a series of amodimethicone emulsions in a prototype conditioner formulation. Deposition on hair from the conditioner was found to increase with increasing amine content in the silicone. This increased deposition was found, in half-head tests, to correlate with conditioning efficacy, including wet and dry combing, softness, and detangling. A microemulsion in the test series that provided high conditioning was also shown to significantly reduce the color fading caused by shampooing of temporarily dyed hair.

Other Silicones

Two important silicones not covered in the preceding section are dimethicone copolyol, which is a dimethylsiloxane containing polyoxyethylene and/or propylene side chains, and cyclomethicone, which refers to a class of cyclic dimethyl polysiloxanes ranging from trimer to hexamer. The most commonly used variant is the pentamer.



Dimethicone Copolyol

Most commercial dimethicone copolyols are soluble in water and are therefore not very effective in rinse-off products. These silicones find important application, however, in leave-on products, including hair sprays, styling mousses, and gels.

Cyclomethicone is volatile and would not remain on dry hair, especially after blow-drying. It helps other conditioning agents disperse, however, and form films on hair. It also helps improve wet combing and provides transient shine.

2-in-1 Shampoos

Silicones find important application as the primary conditioning agents in 2-in-1 conditioning shampoos. These shampoos, upon their introduction in the latter part of the 1980s, represented a major advance in haircare technology, providing a significantly higher degree of conditioning than was then the norm for conditioning shampoos and, at the same time, leaving a desirable, soft, smooth feel on the hair.

Conditioning from 2-in-1 shampoos is expected to occur primarily at the rinsing stage during which time the shampoo emulsion breaks, releasing the silicone for deposition on hair. This separation of cleaning and conditioning stages permits the shampoo to perform both functions efficiently.

The conditioning agent used most frequently in 2-in-1 shampoos is dimethicone. This silicone can provide good performance in shampoo formulations without building-up excessively on the hair [71]. The level of conditioning from these types of shampoos is lower than that from stand-alone conditioners. This is especially true for treated hair because the greater the degree of negative charge on the hair surface, the lower the substantivity of a hydrophobic material like dimethicone. Many 2-in-1s contain polyquats, which might be expected to increase conditioning on damaged hair. In shampoos with high levels of anionic detergent, however, polyquat performance on treated hair may be no better than dimethicone as a result of formation of the negatively charged polymer complexes discussed in the section on cationic polymers (see p. 338).

Yahagi [66] studied the performance of dimethicone, amodimethicone, and dimethicone copolyols in 2-in-1 shampoos. Ease of combing was found to be similar on hair treated with shampoos containing dimethicone or amodimethicone. Unsurprisingly, soluble dimethicone copolyols did not perform well; insolubility, or at least dispersibility, was required for adequate silicone deposition. In the latter case, dimethicone copolyols were found to provide a somewhat lower level of conditioning than the other two silicones studied, especially once blowdrying was begun. Yahagi also studied silicone effects on foam volume. In these studies dimethicone was found to significantly reduce foam volume in a model shampoo formulation, while amodimethicone and dimethicone copolyol had a minimal effect on foam.

Auxiliary Ingredients

A number of ingredients besides conditioning actives are added to commercial conditioners for functional, aesthetic, and marketing purposes [72]. These include fragrances, dyes, preservatives, thickeners, emulsifying agents, pearlizers, herbal extracts, humectants, and vitamins. Some of these are discussed in the following sections; the literature also contains many examples [28,73–77].

Preservatives

Preservatives are necessary to insure the microbiological integrity of a conditioning product. If the product contains high concentrations of ethyl alcohol (generally 20% or above), additional preservatives are not needed and the product is described as self-preserving.

For other products, a wide variety of preservatives are available; in general, combinations of different preservatives provide the broadest possible protection. Every commercial product that is not self-preserving must be carefully tested over time for adequacy of preservation. Most of the preservatives used in personal-care products are described in the Cosmetic Preservatives Encyclopedia [75].

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Thickeners

The section on lipophilic conditioners described thickening as a result of liquid crystal formation in those products containing common quaternary ammonium compounds and fatty alcohols. Cationic conditioning polymers (see p. 338) can also act as thickeners. Many formulations may require additional thickening agents. Hydroxyethylcellulose, a nonionic cellulose ether compatible with cationic surfactants and stable over a wide pH range, is the most common thickening agent added to conditioning products [28]. In addition to providing increased viscosity, this material stabilizes viscosity over time.

Polyamides may also be used to thicken formulations. A commercial product, Sepigel, which contains polyamide, laureth-7, and isoparaffin, can be used to emulsify and thicken lotion or cream conditioners. Other thickeners are described in Ref. 76.

Humectants

Many conditioners contain humectants, which are used to attract moisture. Examples are propylene glycol, glycerine, honey, chitosan, and hyaluronic acid. These materials are not expected to be very effective in rinse-off products.

Emulsifiers

As previously discussed, the fatty alcohol, quat combinations found in common conditioners confer stability on product emulsions. If necessary, other emulsifiers may be added to improve stability. Information on emulsions and emulsifiers may be found in the literature [77,78], as well as from manufacturers' technical bulletins. Most emulsifiers used in conditioners are nonionic, including ethoxylated fatty alcohols, ethoxylated fatty esters, and ethoxylated sorbitan fatty esters.

CONCLUSION

The foregoing sections have surveyed the action and properties of a diverse assortment of commercially available conditioning agents. The availability of a large selection of conditioning materials enables the formulator to tailor products for a wide variety of people having differing conditioning needs and preferences. Thus, a person having short, straight hair in good condition might desire a conditioner primarily to control fly-away. Such a need could be satisfied by one of the ethoquats, which provide light-conditioning benefits together with very good static control. A person having long, heavily bleached hair, on the other hand, would require improved hair feel, ease-of-combing, and manageability. These benefits could best be provided by a trialkyl quat.

Those people sensitive to the feel of their hair might prefer a product containing a silicone as a secondary conditioner. Other people might prefer the convenience of a 2-in-1 shampoo. In many cases, both 2-in-1 shampoos and stand-alone conditioners are used to condition the hair.

There are a number of ways in which one might satisfy the conditioning needs of a target population. It is anticipated that the information in this chapter will help the formulator to quickly choose the best conditioning system for a given purpose. It is also hoped that the material in this chapter will help the formulator to effectively evaluate new conditioning agents and even to work with synthetic chemists as well as suppliers to design new conditioning compounds to solve particular problems.

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Hydrating Substances

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INTRODUCTION

Hydrating substances are used in cosmetic products to retard moisture loss from the product during use and to increase the moisture content in material in contact with the product. This function is generally performed by hygroscopic substances, or humectants. In the International Cosmetic Ingredient Dictionary 66 substances are listed as humectants and 76 hygroscopic materials are used to increase the water content of the skin [1]. The resulting effect of the substances depends on their inherent hygroscopicity at different humidity, as well as their volatility and penetration characteristics. Some factors to consider during product development are highlighted in Table 1.

Target body areas for treatment with humectants are dry hair and dry skin. Sometimes mucous membranes also benefit from application of humectants. Dry hair is brittle, rough, has a tendency to tangle, and has hardly any luster. Humidity of the atmosphere is the only source of moisture to hair, except shampooing, and addition of humectants to the hair will therefore facilitate its retention of water. The same is true for the skin, although it is constantly supplied with water from inside of the body. In the stratum corneum a special blend of humectants can be found, which is called natural moisturizing factor (NMF) [2]. NMF can make up about 10% of the dry weight of the stratum corneum cells [2]. Substances belonging to this group are amino acids, pyrrolidone carboxylic acid (PCA), lactates, and urea (Table 2) [2]. NMF is formed from the protein filaggrin and this formation is regulated by the moisture content in the stratum corneum (3). The water held by the hygroscopic substances in the stratum corneum is a controlling factor in maintaining skin flexibility and desquamation (Table 3) [3,4]. This chapter will provide basic information about some commonly used humectants, primarily used for treatment of the skin. Moreover, some safety information will be given.

BUTYLENE GLYCOL

Description

Butylene glycol is a viscous, colorless liquid with a sweet flavor and bitter aftertaste [5,6]. It is soluble in water, acetone, and castor oil, but practically insoluble in aliphatic hydrocarbon [5].

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TABLE 1 Parameters to Consider During Product Development

Formulation related	Effect on the target area
Price and purity?	Product claim?
Chemical stability during production and shelf life?	Substantivity in rinse-off products?
Sensitive to heat? UV light? pH?	Penetration characteristics?
Incompatibilities with other ingredients?	Hygroscopicity?
Adsorption to the packaging material?	Adverse effects?
Effects on the preservation system?	

General Use

Butylene glycol is used as humectant for cellophane and tobacco [5]. It is also used in topical products and as solvents for injectable products [6]. Butylene glycol is claimed to be most resistant to high humidity and it is often used in hair sprays and setting lotions [7]. The alcohol also retards loss of aromas and preserves cosmetics against spoilage by micro-organisms [7].

Safety

Human skin patch test on undiluted butylene glycol produced a very low order of primary skin irritation and a repeated patch test produced no evidence of skin sensitization [8]. The substance is reported to be less irritating than propylene glycol [9,10]. Few reports of contact allergy exist, but the substance does not seem to cross-react with propylene glycol [9]. As presently used in cosmetics the alcohol is considered as safe by the Cosmetic Ingredient Review (CIR) Expert Panel [8].

GLYCERIN

Description

In 1779, the Swedish scientist, C. W. Scheele, discovered that glycerin could be made from a hydrolysate of olive oil. The alcohol is a clear, colorless, odorless, syrupy, and hygroscopic liquid [5], that is, about 0.6 times as sweet as cane sugar [5]. It is miscible with water and alcohol, slightly soluble in acetone, and practically insoluble in chloroform and ether.

General Use

Glycerin can be used as a solvent, plasticizer, sweetener, lubricant, and preservative [11]. The substance has also been given intravenously or by mouth in a variety of clinical conditions in order to benefit from its osmotic dehydrating properties [12]. This effect can also be used topically for the short-term reduction of vitreous volume an intraocular pressure of the eye [12]. Concentrated solutions of glycerin is also used to soften ear wax [13]. Suppositories with glycerin (1–3 g) can also promote fecal evacuation [12,13].

TABLE 2 Chemistry of Hygroscopic Substances

Name	CAS No.	MW	Other names	Natural source
Butylene glycol	107-88-0	90.1	1,3-butanediol, 1,3-butylene glycol	
Glycerin	56-81-5	92.1	Glycerol, 1,2,3-propanetriol	Hydrolysis of oils and fats
Lactic acid	50-21-5	90.1	2-hydroxypropanoic acid	Sour milk, tomato juice
Panthenol	81-13-0	205.3	Dexpanthenol, pantothenol	Plants, animals, bacteria
PCA	98-79-3	129.11	L-pyroglutamic acid, DL-pyrrolidonecarboxylic acid, 2-pyrrolidone-5-carboxylic acid	Vegetables, molasses
Propylene glycol	57-55-6	76.1	1,2-propanediol	
Sodium hyaluronate	9067-32-7	5×10^4–8×10^6		Cock's combs, biofermentation
Sorbitol	50-70-4	182.17	D-glucitol	Berries, fruits
Urea	57-13-6	60.08	Carbamide, carbonyl diamide	Urine

Abbreviations: MW, molecular weight; PCA, pyrrolidone carboxylic acid.
Source: Refs. 5, 6, 12.

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TABLE 3 Moisture-Binding Ability of Humectants at Various Humidities

Humectant	31%	50%	52%	58–60%	76%	81%
Butylene glycol						38[e]
Dipropylene glycol		12[a]				
Glycerin	13[c]	25[a]	26[b]	35–38[c,f]	67[b]	
	11[b]					
Na-PCA	20[c]	44[a]	45[b]	61–63[c,f]	210[b]	
	17[b]					
Na-lactate	19[b]	56[a]	40[b]	66[f]	104[b]	
Panthenol	3[d]		11[d]		33[d]	
PCA	<1[c]			<1[c]		
Propylene glycol				32[f]		
Sorbitol		1[a]		10[f]		

Abbreviation: PCA, pyrrolidone carboxylic acid.
[a] *Source*: Ref. 28.
[b] *Source*: Ref. 72.
[c] *Source*: Ref. 40.
[d] *Source*: Ref. 35.
[e] *Source*: Ref. 5.
[f] *Source*: Ref. 73.

Effects on the Skin

The importance of glycerin in skincare products is well established. To explain its benefits, early studies have focused on its humectant and the protecting properties. More recently, glycerin has been shown to modulate the phase behavior of stratum corneum lipids and to prevent crystallization of their lamellar structures in vitro at low, relative humidity [14]. Incorporation of glycerin into a stratum corneum model lipid mixture enables the lipids to maintain the liquid crystal state at low humidity [14]. The biochemical consequences of these properties may be to influence the activity of hydrolytic enzymes crucial to the desquamatory process in vivo. Thereby, the rate of corneocyte loss from the superficial surface of human skin increases, probably because of an enhanced desmosome degradation [3].

Repeated tape strippings taken from skin treated with 15% glycerin cream indicates that glycerin diffuses into the stratum corneum to form a reservoir [15]. During some hours after application a decrease in TEWL has been noted [15–18], followed in animal skin by increased values after some hours [18]. Moreover, in human skin its surface profile, electrical impedance, and increase in the coefficient of friction were found to accompany an improvement in the skin condition, as assessed by an expert [16].

Safety

Very large oral or parenteral doses can exert systemic effects, due to the increase in the plasma osmolality resulting in the movement of water by osmosis from the extravascular spaces into the plasma [12]. Glycerin dropped on the human eye causes a strong stinging and burning sensation, with tearing and dilatation on the conjunctival vessels [19]. There is no obvious injury [19], but studies have indicated that glycerin can damage the endothe-

lial cells of the cornea [12]. Before application of glycerin to the cornea, a local anesthetic may be administered to reduce the likelihood of a painful response [12].

HYALURONIC ACID

Description

Hyaluronic acid is a member of the class of amino sugar containing polysaccharides known as the glycosaminoglycans widely distributed in body tissues. Molecular weight is within the range of 50,000 to 8×10^6 depending on source, methods of preparation, and determination [5]. Hyaluronic acid binds water and functions as a lubricant between the collagen and elastic fiber networks in dermis during skin movement. Sodium hyaluronate is a white odorless powder, which forms viscous solutions in water [6]. A 2% aqueous solution of pure hyaluronic acid holds the remaining 98% water so tightly that it can be picked up as though it were a gel [20].

During manufacturing, the large, unbranched, non–cross-linked, water-containing molecule is easily broken by shear forces [20]. The carbohydrate chain is also very sensitive to breakdown by free radicals, UV radiation, and oxidative agents [20]. The manufacturers state that solutions of sodium hyaluronate for injection are stable for 3 years when stored in refrigerator and for 4 weeks when stored at room temperature [12].

General Use

A viscous solution of the sodium salt is used during surgical procedures on the eye and intra-articular injections have been tried in the treatment of osteoarthritis [12]. Topical application of 0.1% solution in patients with dry eye increased tear-film stability and alleviated symptoms of burning and grittiness [12].

Effects on the Skin

High–molecular weight hyaluronic acid solutions form hydrated viscoelastic films on the skin [20]. The larger the molecular size, the greater the aggregation and entanglement of the molecules, and hence, the more substantial and functional the viscoelastic film associated with the skin surface [20]. Because of the high molecular weight, hyaluronic acid will not penetrate deeper than the crevices between the desquamating cells.

Safety

Sodium hyaluronate is essentially nontoxic [6]. When the substance is used as an ophthalmic surgical aid, transient inflammatory ocular response has been described [19].

LACTIC ACID

Description

Lactic acid is colorless to yellowish crystals or syrupy liquid, miscible with water, alcohol, glycerol, but insoluble in chloroform [5,6]. Lactic acid is an α-hydroxy acid (AHA), i.e., an organic carboxylic acid in which there is a hydroxy group at the two, or alpha (α), position of the carbon chain. Lactic acid can exist in a DL, D, or L form. The L and the D forms are enantiomorphic isomers (mirror images). Lactic acid is miscible with water,

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alcohol, and ether and practically insoluble in chloroform [12]. Lactate is also a component of the natural hygroscopic material of the stratum corneum and constitutes about 12% of this material [2]. Formulations containing lactic acid have an acidic pH in the absence of any inorganic alkali or organic base. pH is increased in several formulations by partial neutralization.

General Use

Lactic acid has been used in topical preparations for several decades because of its buffering properties and water binding capacity [21]. Lactic acid and its salts have been used for douching and to help maintain the normal, acidic atmosphere of the vagina. Lactic acid has also been used for correction of disorders associated with hyperplasia and/or retention of the stratum corneum, such as dandruff, callus, keratosis, and verrucae (viral warts) [12]. It has also been suggested that lactic acid may be effective for adjuvant therapy of mild acne [22]. Also, ethyl lactate has been suggested to be effective in the treatment of acne, because of its penetration into the sebaceous follicle ducts with subsequent lowering of pH and decrease in the formation of fatty acids [23].

Investigators have also reported increases in the thickness of viable epidermis [24,25] as well as improvement in photoaging changes [24,26]. Lactic acid in combination with other peeling agents is used to produce a controlled partial-thickness injury to the skin which is believed to improve the clinical appearance of the skin [27].

Effects on the Skin

In guinea pig footpad corneum, it has been shown that both lactic acid and sodium lactate increase the water holding capacity and skin extensibility [21]. When the pH increases, the adsorption of lactic acid decreases, because of the ionization of the acid [21]. In another study on strips of stratum corneum from human abdominal skin, the uptake of water by sodium lactate was greater than that by lactic acid, but the stratum corneum was plasticized markedly by lactic acid and not by sodium lactate [28].

The concentrations used for treatment of ichthyosis and dry skin have ranged up to 12% [29]. One formulation of 12% ammonium lactate has been approved by the Food and Drug Administration (FDA, 1988) for treatment of ichthyosis vulgaris and dry, scaly skin (xerosis) and for the temporary relief of itching associated with these conditions.

Safety

Lactic acid is caustic to the skin, eyes, and mucous membranes in concentrated form [19]. Compared with other acids, lactic acid has no unusual capacity to penetrate the cornea, so its injurious effect is presumably attributable to its acidity [19].

Immediately after application of an AHA, stinging and smarting may be noticed; this is closely related to the pH of the preparations and the substances in themselves [30–32]. In normal skin, irritation and scaling may be induced when the acids are applied in high concentrations and at low pH [30,33].

PANTHENOL

Description

D-panthenol is a clear, almost colorless, odorless, viscous hygroscopic liquid that may crystallize on prolonged storage [12]. Panthenol is an alcohol that is rapidly converted to

D-pantothenic acid in the body. Panthothenic acid is a water-soluble vitamin, subsequently called vitamin B_5. The substance can be isolated from various living creatures, which gave the reason for its name (panthoten is Greek for ''every-where'') (Table 2) [34]. Panthenol is very soluble in water; freely soluble in alcohol and glycerol, but insoluble in fats and oils [35]. The substance is fairly stable to air and light if protected from humidity, but it is sensitive to acids and bases and also to heat [35]. The rate of hydrolysis is lowest at pH 4 to 6 [35].

General Use

Panthenol is widely used in the pharmaceutical and cosmetic industry for its moisturizing, soothing, and sedative properties [36]. It is also found in topical treatments for rhinitis, conjunctivitis, sunburn, and for wound healing (ulcers, burns, bed sores, and excoriations) [36]. Usually 2% is used [12]. It can further be used to prevent crystallization at the spray nozzles of aerosols [35].

Effects on the Skin and Hair

Topically applied panthenol is reported to penetrate the skin and hairs and to be transformed into panthothenic acid [35,37]. Pantothenic acid can be found in normal hair [35]. Soaking of hair in 2% aqueous solution of panthenol has been reported to increase the hair diameter up to 10% [38].

Safety

Panthenol has very low toxicity. Panthenol and products containing panthenol (0.5–2%) administered to rabbits caused reactions ranging from no skin irritation to moderate-to-severe erythema and well-defined edema [39]. Low concentrations have also been tested on humans, and those formulations did not induce sensitization or significant skin irritation. Contact sensitization to panthenol present in cosmetics, sunscreens, and hair lotion has been reported, although allergy to panthenol among patients attending for patch testing is uncommon [34,36].

PCA AND SALTS OF PCA

Description

PCA is the cosmetic ingredient term used for the cyclic organic compound known as 2-pyrrolidone-5-carboxylic acid (Table 2). The sodium salt is a naturally occurring humectant in the stratum corneum at levels about 12% of the NMF [2] corresponding to about 2% by weight in the stratum corneum [40]. The sodium salts of PCA are among the most powerful humectants (Table 3). PCA is also combined with a variety of other substances, like arginine, lysine, chitosan, and triethanolamine [1].

Effects on the Skin

The ''L'' form is a naturally occurring component of mammalian tissue and absorption from cosmetics is in addition to PCA already present in the skin (41). A significant relationship has been found between the moisture-binding ability and the PCA content of samples of stratum corneum [40]. Treatment of solvent-damaged guinea pig footpad cor-

neum with humectant solutions shows that the water held by the corneum decreases in the following order: sodium PCA > sodium lactate > glycerin > sorbitol [21]. Treatment with a cream containing 5% sodium-PCA also increased the water-holding capacity of isolated corneum compared with the cream base [42]. The same cream was also more effective than a control product containing no humectant, and equally effective as a similar established product with urea as humectant, in reducing the skin dryness and flakiness [42].

Safety

In animal studies, no irritation to the eye and skin was noted at concentrations up to 50% and no evidence of phototoxicity, sensitization, or comedogenicity was found [41]. Minimal, transient ocular irritation has been produced by 50% PCA [41]. Immediate visible contact reactions in back skin have also been noted after application of 6.25% to 50% aqueous solutions of sodium PCA [43]. The response appeared within 5 minutes and disappeared within 30 minutes after application. CIR states that the ingredient should not be used in cosmetic products in which N-nitroso compounds could be formed [41].

PROPYLENE GLYCOL

Description

Propylene glycol is a clear, colorless, viscous, and practically odorless liquid having a sweet, slightly acrid taste resembling glycerol [11]. Under ordinary conditions it is stable in well-closed containers and it is also chemically stable when mixed with glycerin, water, or alcohol [5,11].

General Use

Propylene glycol is widely used in cosmetic and pharmaceutical manufacturing as a solvent and vehicle especially for substances unstable or insoluble in water [12,44]. It is also often used in foods as antifreeze and emulsifier [5,12]. Propylene glycol is also used as inhibitor of fermentation and mold growth [5].

Effects on the Skin

Propylene glycol has been tried in the treatment of a number of skin disorders, including ichthyosis [45,46], tinea versicolor [47], and seborrheic dermatitis [48], because of its humectant, keratolytic, antibacterial, and antifungal properties [12,44].

Safety

The estimated acceptable daily intake of propylene glycol is up to 25 mg/kg body weight (WHO) [12]. It is considered a harmless ingredient for pharmaceutical products [11] and safe for use in cosmetic products at concentrations up to 50% [49]. However, clinical data have showed skin irritation and sensitization reactions to propylene glycol in normal subjects at concentrations as low as 10% under occlusive conditions and dermatitis patients as low as 2% [10,49]. The nature of the cutaneous response remains obscure and, therefore, the skin reactions have been classified into four mechanisms: (1) irritant contact dermatitis, (2) allergic contact dermatitis, (3) nonimmunological contact urticaria, and (4) subjective

or sensory irritation [50]. This concept allows a partial explanation of effects observed by different investigators [50].

PROTEINS

Description

Proteins and amino acids for cosmetics are based on a variety of natural sources. Collagen is the traditional protein used in cosmetics. Collagen has a complex triple helical structure, which is responsible for its high–moisture-retention properties. Vegetable-based proteins have, in recent years, grown in importance as an alternative to using animal by-products. Suitable sources include wheat, rice, soybean, and oat.

In cosmetics native proteins can be used, but perhaps the most widely used protein types are hydrolyzed proteins of intermediate molecular weight with higher solubility. An increased substantivity is obtained by binding fatty alkyl quarternary groups to the protein. Improved film-forming properties can be obtained by combining the protein and polyvinylpyrrolidone into a copolymer. Such modifications may increase the moisture absorption compared with the parent compound. Potential problems with proteins are their odor and change in color with time. Furthermore, as they are nutrients their inclusion in cosmetics may require stronger preservatives.

Efficacy and Safety

Amino acids belong to the NMF and account for 40% of its dry weight [2]. Because of their relatively low molecular weight, they are capable of penetrating the skin and cuticle of the hair more effectively than the higher–molecular-weight protein hydrolysates.

Salts of the condensation product of coconut acid and hydrolyzed animal protein [51] and wheat flour and wheat starch [52] are considered safe as cosmetic ingredients by CIR. The most frequent clinical presentation of protein contact dermatitis is a chronic or recurrent dermatitis [53]. Sometimes an urticarial or vesicular exacerbation has been noted a few minutes after contact with the causative substance [53,54]. Hair conditioners containing quaternary hydrolyzed protein or hydrolyzed bovine collagen have induced contact urticaria and respiratory symptoms [54]. Atopic constitution seems to be a predisposing factor in the development of protein contact dermatitis [53].

SORBITOL

Description

Sorbitol is a hexahydric alcohol appearing as a white crystalline powder, odorless and of fresh and sweet taste [11,12]. Sorbitol is most commonly available as 70% aqueous solution, which is clear, colorless, and viscous. It occurs naturally in fruits and is easily dissolved in water, but not so well in alcohol. It is practically insoluble in organic solvents.

Sorbitol is relatively chemically inert and compatible with most excipients, but it may react with iron oxide and become discolored [11].

General Use

Sorbitol is used in pharmaceutical tablets and in candies when noncariogenic properties are desired. It is also used as sweetener in diabetic foods and in toothpastes. Sorbitol is

also used as a laxative intrarectally and believed to produce less troublesome side effects than glycerin [13]. Its hygroscopic properties are reported to be inferior to that of glycerin (Table 3) [21,55].

Safety

When ingested in large amounts (30 g/day) it produces a laxative effect and according to WHO the acceptable daily intake in humans should not exceed 9 grams/day [11].

UREA

Description

Urea is colorless, transparent, slightly hygroscopic, odorless or almost odorless, prismatic crystals, or white crystalline powder or pellets. Urea is freely soluble in water, slightly soluble in alcohol, and practically insoluble in ether [12]. The extraction of pure urea from urine was first accomplished by Proust in 1821 and pure urea was first synthesized by Wöhler in 1828 [56]. Urea in solution hydrolyzes slowly to ammonia and carbon dioxide [12].

General Use

Urea is used as a 10% cream for the treatment of ichthyosis and hyperkeratotic skin disorders [12,56], and in lower concentrations for the treatment of dry skin. In the treatment of onychomycosis, urea is added to a medicinal formulation at 40% as a keratoplastic agent to increase the bioavailability of the drug [57].

Effects on the Skin

An increased water-holding capacity of scales from psoriatic and ichthyotic patients has been observed after treatment with urea-containing creams [58,59].

Concern has been expressed about the use of urea in moisturizers, with reference to the risk of reducing the chemical barrier function of the skin to toxic substances [60]. That urea can increase skin permeability has been shown in several studies, where it has been found to be an efficient accelerant for the penetration of different substances [61–63]. Not all studies, however, support the belief that urea is an effective penetration promoter [64,65], and treatment of normal skin with moisturizers containing 5% to 10% urea has been found to reduce transepidermal water loss (TEWL) and also to diminish the irritative response to the surfactant sodium lauryl sulphate [66,67].

Safety

Urea is a naturally occurring substance in the body, as the main nitrogen containing degradation product of protein metabolism [68]. Urea is an osmotic diuretic and has been used in the past for treatment of acute increase in intracranial pressure due to cerebral edema [12]. No evidence of acute or cumulative irritation has been noted in previous studies on urea-containing moisturizers, but several patients [12–22%] have reported stinging after treatment with 10% urea creams [69,70]. Urea has also shown to give burning reactions on lesioned forearm skin at concentrations used in moisturizers [71].

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CONCLUSIONS

A number of interesting humectants are available as cosmetic ingredients. Most of them have a long and safe history of use, and several are also accepted as food additives. A potential drawback of the low–molecular weight substances are their stinging potential, since they may be absorbed into the skin. The high–molecular weight substances usually do not penetrate the skin; instead they are suggested to reduce the irritation potential of surfactants. However, case reports of urticarial reactions have been reported after exposure to modified proteins [54].

The advantage with the larger and chemically modified materials are that they have an increased substantivity to target areas, whereas it is apparent that small amounts of several low–molecular-weight hygroscopic substances have a questionable contribution to the water content of hair and stratum corneum in rinse-off products. Another issue to bear in mind is whether the obtained humectancy is the only mode of action. Some humectants may modify the surface properties and increase the extensibility of stratum corneum without influencing the water content. Furthermore, humectants may also affect specific metabolic process in the skin. One should also keep in mind that humectants can improve the cosmetic properties of the formulation and some of them also facilitate marketing of the product just because of their names.

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Ceramides and Lipids

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HISTORICAL PERSPECTIVES

Many published accounts of the composition of lipids from human stratum corneum have been complicated by the almost inevitable presence of sebaceous lipids as well as exogenous contaminants. When stratum corneum samples are obtained from excised skin, there is almost always massive contamination with subcutaneous triglycerides as well as fatty acids derived from the subcutaneous fat. In addition, precautions must be taken to avoid contamination with environmental contaminants such as alkanes and cosmetic components. As a result of these complications, much work has been done with pig skin as a model [1–6].

Young pigs, if properly housed and tended, can be kept clean, and the sebaceous glands are not active. By direct heat separation of epidermis from an intact carcass, it is possible to avoid subcutaneous fat. In terms of general structure, composition, and permeability barrier function, the pig appears to provide a good model for the human. An alternative approach is to use the contents of epidermal cysts [7,8]. This material represents exfoliated stratum corneum lipid that is free of sebaceous and environmental contaminants. If the contents are carefully expressed from the capsule, a contaminant-free sample of stratum corneum lipid can be obtained. Cholesterol sulfate is partially hydrolyzed during the desquamation process; however, this is only a minor stratum corneum component. In either the pig or cyst model, the major lipid components are ceramides, cholesterol, and fatty acids, which represent approximately 45, 27, and 12% of the total lipid, respectively [9]. Other minor components include cholesterol sulfate and cholesterol esters. The fatty acids in either model are predominantly straight-chain saturated species ranging from either 14 (cyst) or 16 (pig) carbons through 28 carbons in length with the 22 and 24 carbon species being the most abundant. The main focus in the rest of this chapter will be on the stratum corneum ceramides.

The first analysis of stratum corneum lipids was performed in 1932 by Kooyman [10], who showed a dramatic reduction in the proportion of phospholipid in stratum corneum compared with the inner portion of the epidermis. Subsequently, Long [11], using

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the very thick epidermis from cow snout as a model, analyzed lipids from horizontal slices of epithelial tissue. He observed a gradual accumulation of cholesterol and fatty acids in progressing from the basal region toward the surface. Phospholipids initially accumulated, but were degraded as the stratum corneum was approached. In 1965, Nicolaides [12] identified ceramides as a polar lipid component of stratum corneum. This fact was included in a footnote and was largely ignored until the pioneering work of Gray and Yardley in the mid to late 1970s [1,2,13,14]. Among other things, these investigators showed that the ceramides are structurally heterogeneous and contain normal fatty acids, α-hydroxyacids, sphingosines, and phytosphingosines as components. However, individual ceramide types were not well resolved and no definitive structures could be proposed. The first attempt to isolate individual ceramide types and to determine the identities of the individual fatty acid and long-chain base components was conducted in 1979 using neonatal mouse epidermis as a source of lipids [15]. Eight putative ceramide fractions were isolated, and six of these were analyzed. The remaining two were too minor for any analysis. Unfortunately, only normal fatty acids, sphingosines, and dihydrosphingosines were reported for each fraction analyzed. This suggests extensive cross-contamination sufficient to preclude recognition of the actual structural diversity. In 1983, the detailed structures of the ceramides from porcine epidermis were published [3]. Six structurally different types of ceramides were identified, and these included sphingosines, dihydrosphingosines, and phytosphingosines as the base components; normal, α-hydroxyacids, and ω-hydroxyacids as the amide-linked fatty acids; and one ceramide type included an ester-linked fatty acid. Subsequently, it was shown that the same ceramide structural types are present in human stratum corneum, although the proportions are somewhat different [8,15]. More recently it has been shown that in addition to the standard phytosphingosine present in porcine ceramides, the human ceramides also include a variant phytosphingosine, 6-hydroxysphingosine [16].

In 1987 it was discovered that porcine epidermal stratum corneum contains significant levels of covalently bound lipid, the major component of which is an ω-hydroxyceramide [4]. Small amounts of saturated fatty acid and ω-hydroxyacid are also present. A similar situation was shown for human stratum corneum; however, in this case there was a second hydroxyceramide that was shown to contain a variant phytosphingosine [17]. This subsequently proved to be 6-hydroxysphingosine [16]. The free and covalently bound ceramides are discussed in detail in the following section.

CERAMIDES FROM EPIDERMIS

As previously noted, the first comprehensive study of epidermal ceramide structures was directed at the porcine ceramides, which were separated into six chromatographically distinct fractions [3]. Each fraction was analyzed by a combination of chemical, chromatographic and spectroscopic methods, and representative structures are included in Figure 1.

The least polar of the porcine ceramides, ceramide fraction 1, consists of 30- through 34-carbon ω-hydroxyacids amide-linked to a mixture of sphingosines and dihydrosphingosines. The long-chain base component of this ceramide ranges from 16 through 22 carbons in length with 18:1, 20:1, and 22:1 being the most abundant. There is also a fatty acid ester-linked to the ω-hydroxyl group, 75% of which consists of linoleic acid. This species has often been referred to as ceramide 1 or acylceramide, but in the more systematic nomenclature system proposed by Motta et al. [18] this becomes Cer[OSE]. (In this system, the amide-linked fatty acid is designated as N, A, or O to indicate normal, α-hydroxy, or ω-hydroxy, respectively. The base component is designated S or P for sphingosine or

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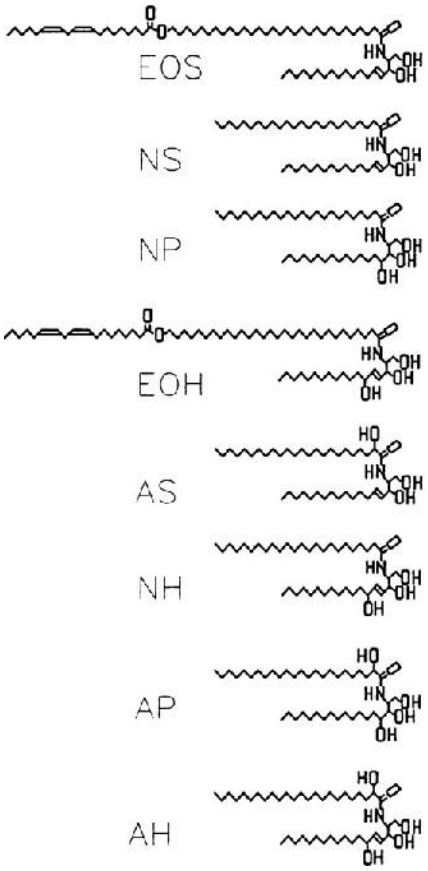

FIGURE 1 Representative structures of the free ceramides from human stratum corneum.

phytosphingosine, respectively. It is understood that sphingosines are generally accompanied by dihydrosphingosines in the ceramides.) Cer[OSE] is unusual in two respects: (1) the very long ω-hydroxyacyl portion of the molecule is long enough to completely span a typical bilayer; and (2) a high proportion of the ester-linked fatty acid is linoleic acid. It is thought that this ceramide along with an analogous glucosylated Cer[OSE] in the living layers of the epidermis account for the essential role of linoleic acid in formation and maintenance of the barrier function of the skin [3,19,20]. Specific roles for Cer[OSE] have been proposed in organization of the intercellular lipid lamellae of epidermal stratum corneum [20–22]. In formation of the intercellular lamellae of the stratum corneum, flattened lipid vesicles are initially extruded from the lamellar granules into the intercellular space [23]. These flattened vesicles fuse in an edge-to-edge manner to produce paired bilayers. Cer[OSE] is associated with each of the paired lamellae with both possible orientations.

Approximately half of the Cer[OSE] is oriented with the polar head groups in the outer polar regions of the paired bilayers, whereas the other half of the Cer[OSE] molecules are oriented with the polar head groups in the polar regions in the center of the pair of lamellae. For the Cer[OSE] in the former orientation the ω-hydroxyacyl portion of the

molecule will span the bilayer while the linoleate inserts into the other bilayer, thus linking the pair of bilayers together. For Cer[OSE] in the second orientation the linoleate tail is thought to participate in the formation of narrow interdigitated layers that intervene between the paired bilayers. This action of the Cer[OSE] results in the formation of broad-narrow-broad lamellar patterns that are seen in transmission electron micrographs when ruthenium tetroxide is used as a postfixative and which give rise to a 13 nm repeat unit in radiograph diffraction studies [5,6,22].

Porcine ceramide fraction 2 has proven to be Cer[NS]. The fatty acid component is saturated and straight-chained and ranges from 16- through 32-carbons in length. C20:0, C22:0, C24:0, C26:0, and C28:0 are the most abundant, constituting from 9% to 19% of the total fatty acid mass each. The long-chain bases again consist of a mixture of sphingosines and dihydrosphingosines ranging from 16- through 22-carbons in length. The most abundant bases are 18:0, 18:1, 20:0, and 20:1.

Porcine ceramide fraction 3, Cer[NP], contains the same range of fatty acids found in Cer[NS], but the long-chain base component is now a phytosphingosine with no double bond and a third hydroxyl group on carbon 4. The phytosphingosines found here range from 16- through 24-carbons long, and the most abundant are 20:0 and 22:0.

Porcine ceramide fractions 4 and 5 both proved to be Cer[AS], but they differed in terms of the chain length distributions of the α-hydroxyacid component. The chromatographically more mobile fraction 4 contained 24- through 28-carbon α-hydroxyacids amide-linked to sphingosines and dihydrosphingosines, whereas ceramide fraction 5 contains α-hydroxypalmitic acid amide-linked to sphingosines and dihydrosphingosines. Ceramide fraction 4 also contains somewhat longer bases with major amounts of 20:0 and 20:1, whereas ceramide fraction 5 contains mainly 16- through 18-carbon bases. This difference in carbon content results in chromatographic separation into two fractions, even though the basic structural type is the same in each.

Finally, the most polar of the pig ceramide fractions consists of α-hydroxyacids amide-linked to phytosphingosine, Cer[AP]. The α-hydroxyacids present in Cer[AP] range from 16- through 28-carbons in length, but the 24- and 26-carbon entities account for approximately 70% of the total fatty acid mass. The phytosphingosines have a chain-length distribution similar to that already described for Cer[NP].

Subsequently, the human stratum corneum ceramides were investigated and were shown to produce a similar, though not identical, pattern on thin-layer chromatograms [15]. Notably, the human fraction most closely matching porcine ceramide fraction 3 is somewhat broader and less symmetrical. The material most closely matching porcine ceramide fractions 4 and 5 merged into one broad peak, and was designated ceramide 4/5. This was shown to reflect a more continuous chain-length distribution among the α-hydroxyacid component of Cer[AS] as opposed to the bipolar distribution found in the pig. The most polar human fraction similar to porcine ceramide fraction 6 appeared as an incompletely resolved doublet. These two components were designated ceramides 6I and 6II. Subsequently it has been shown the ceramide fraction 6II contains the variant phytosphingosine—6-hydroxysphingosine [16]. The Motta system of nomenclature has been extended to include this new long-chain base as H [16]. So ceramide 6I is Cer[AP], and ceramide 6II becomes Cer[AH]. Human ceramide fraction 3 has been shown to contain a minor amount of a 6-hydroxysphingosine-containing acylceramide, Cer[OHE] [16], in addition to Cer[NH]. Likewise, ceramide fraction 4/5 contains Cer[NH] [24] in addition to Cer[AS] [15]. These additional ceramides containing 6-hydroxysphingosine can be resolved on thin-layer chromatography by use of multiple development regimens.

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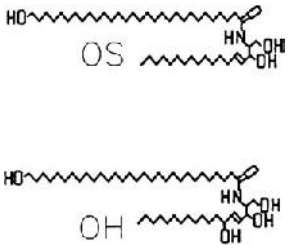

FIGURE 2 Representative structures of the covalently bound ceramides from human stratum corneum.

In addition to the extractable lipids, there are covalently bound lipids coating the outer surface of the cornified envelope in epidermal stratum corneum. This consists mainly of ceramides. In porcine stratum corneum the principal covalently bound lipid is Cer[OS] derived from Cer[OSE] [4]. In human stratum corneum, in addition to covalently bound Cer[OS], a second more polar covalently bound ceramide was found [17]. This was later shown to be Cer[OH] [16]. Representative structures of Cer[OS] and Cer[OH] are presented in Figure 2.

LIPIDS FROM OTHER KERATINIZED TISSUES

The hair and nails contain cholesterol sulfate and ceramides generally similar to those in the stratum corneum as their principal polar lipid components [25]. Unfortunately, the ceramides from these epidermal appendages have not been characterized in detail.

Hair contains 18-methyleicosanoic acid covalently bound to the outer surface of the cuticle cells in human as well as other mammalian hair [21]. The attachment is apparently through thioester linkages. This covalently bound lipid layer provides a hydrophobic outer surface for the hair shaft.

In the oral cavity, the regions of the hard palate and gingiva are covered by a keratinizing epithelium that closely resembles the epidermis in many ways [5]. The stratum corneum in these regions, like epidermal stratum corneum, contains ceramides, cholesterol and fatty acids as major lipid components; however, unlike epidermal stratum corneum, the oral stratum corneum also contains relatively high proportions of phospholipids and glycosylceramides. The ceramides in the oral stratum corneum include the same structural types found in epidermal stratum corneum in similar relative proportions, except that in the oral tissue the proportion of Cer[OSE], the acylceramide, is much lower. It is thought that this lowered proportion of Cer[OSE] accounts for the fact that the broad-narrow-broad lamellar pattern that is characteristic of the intercellular lipids of epidermal stratum corneum is never seen in oral stratum corneum.

COMMERCIALLY AVAILABLE CERAMIDES

There are presently no commercial sources of the ceramides based on 6-hydroxysphingosine.

A variety of ceramides based on phytosphingosine produced by a fermentation technique are commercially available from Cosmoferm, a group company of Gist-brocades based in Delft, the Netherlands. These include an acylceramide, Cer[EOP], which consists

of a 27-carbon ω-hydroxyacid amide-linked to phytosphingosine and bearing ester-linked stearic acid on the ω-hydroxyl group. There are also two ceramides of the type Cer[NP]. One of these contains stearic acid and the other oleic acid amide-linked to phytosphingosine. Finally, this supplier also produces N-2-hydroxystearoyl-phytosphingosine, Cer[AP]. These specific ceramides are routinely available; however, it is also possible to customize any of these general structural types to include different fatty acids.

There are several commercial sources of ceramides or ceramide analogues similar to the ceramide type Cer[NS]. For example, SEDERMA of Parsippany, New Jersey produces a synthetic ceramide consisting of N-stearoyl-dihydrosphingosine and sold as ceramide 2. This synthetic ceramide is partially racemic at carbon-3 of the base component; however, the stereochemical configuration at this carbon is at least 70% R, which is the configuration in natural dihydrosphingosine.

FUTURE DIRECTIONS

Presently, ceramides are being used in skin moisturizers and at least one line of hair care products. It has been documented that ceramides are important in the permeability barrier of the skin and the water-holding properties of the stratum corneum [26,27]. It seems likely that the interest in ceramides for incorporation into cosmetic products will result in the introduction of additional, novel ceramide formulations for use in skin and hair care. In addition, it can be anticipated that ceramides will eventually be incorporated into other personal care products, such as stick deodorants, or cosmetic products, such as lipstick. This will likely lead to commercial availability of additional ceramide structural variants that more closely resemble all of the ceramide types that have been identified in human stratum corneum.

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Natural Extracts

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INTRODUCTION

Natural extracts have played an important role since ancient times. Egyptian hieroglyphs over 3000 years old [1] offer formulas showing how treatment products were prepared with extracts from plants. For quite some time natural materials were the only possible raw materials available in cosmetic formulations. The very prosperous development of synthetic chemistry and manufacturing, which started around the beginning of the century, has led to a dramatic increase in materials of synthetic origin and with highly targeted functionality.

Up until the late 1960s, cosmetic formulators and consumers still did not perceive the benefits of traditional, plant-based therapies. This all changed starting in the early 1970s when consumers quickly returned ''back to nature.'' The dramatic changes in consumer perceptions that started some 30 years ago are still strong as ever. This evolutionary change in the society is reflected in a strong interest by the consumer in cosmetic care formulations having a ''natural'' benefit. The trend toward ''nature'' is paralleled by a fast-growing scientific knowledge about plant constituents, human molecular biology, and cell physiology.

Identification and commercialization of new efficacious materials are nowadays stronger than ever, and guided by looking at active principles found in native plant species. Using natural plant extracts in a cosmetic product offers the potential for improved product performance in addition to an appealing marketing story. The success of many mass and prestige products based largely on plant materials is testimony to this fact.

It is important to note however, that not everything that originates from nature can automatically be considered beneficial or safe. Expertise is needed in the selection and application of natural extracts.

DEFINITION

By definition, an extract is the product of a purification procedure that is able to be isolated from a given matrix. One might think of using the entire plant, e.g., dried leaves or ground plant material, for a given cosmetic application. The disadvantages of doing so might be poor application properties attributable to solid particles in the formulation, potential

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microbiological problems, and/or the requirement of a significantly elevated level of plant material to deliver the same active constituents as an extract would. Using purified extracts for cosmetic formulations is therefore much more convenient and safe.

CATEGORIZING EXTRACTS

There are several ways to categorize plant extracts. Some of the most common methods of differentiation are as follows:

1. Application area (e.g., anti-inflammatory, antimicrobial, moisturizing)
2. Botanical name and family together with origin
3. Extraction method used (e.g., infusion, percolation, maceration, solvents used, steam distillation)

KEY STEPS IN PRODUCTION AND INFLUENCES ON QUALITY

A number of sophisticated approaches exist on how to isolate a specific extract from herbs. However, there are some common steps.

Plant Cultivation, Harvesting, and Collecting

The process begins simply with the growing plant itself. This happens at random out in the fields or by cultivation. Although ''wild crafting'' is still a method used for some species, cultivated plants can be harvested much more easily. Wild crafting additionally leaves the risk of collecting the wrong species and getting impure plant material for extraction. By using analytical methods, one is able to identify the purity of the herb. To minimize contamination, the collectors should be well educated about their work. One of the major factors that must always be considered is the concern of overharvesting. The major concerns of farmers as well as commercial customers is the continued availability of raw material. Proper cultivation of plants in a controlled environment offers greater security that plant species can be made available. Today many plants are also available that are ''organically grown.'' Because no pesticides, chemical fertilizers, or chemical growing aids are used, there is a greater assurance that a minimum of such residues will be found in the extract. However, because analytical methods have become increasingly sensitive (concentration in the parts per trillion range can now routinely be detected), even some traces might be detected in those qualities as well.

Both of these methods, wild crafting and cultivating, are sensitive to seasonal changes and may produce different levels of active constituents depending on the time of year as well as the quality of the soil conditions. However, one of the most important points is the time of harvest. It should be at the peak of the activity level of the plant. Analytical techniques are available today that offer the farmer accurate information on when the right time for harvesting is.

Drying

In most cases plants are dried before extraction. The drying process results in a loss of between 60% to 80% of its weight as moisture and the plant actives are being concentrated by up to three to four times based on weight. Generally, mild conditions are used, usually between 100 and 140°F (38–60°C). In some cases, fresh plant material might be required

for extraction (usually whenever sensitive constituents could be totally damaged by drying). Specific examples are extracts with a special sensory profile for perfumery or flavor compositions, as well as extracts showing enzymatic activity. In those cases, fresh plant material has to be used. This requires a well-organized infrastructure for a ''just in time'' processing in order to avoid breakdown by micro-organisms. Generally, fresh plant extraction takes place during the harvest period of the plant and results in unused extraction capacity during the rest of the year, which might increase production costs.

Drug Preparation for Extraction

Whenever an active is found in only one part of a plant, garbling has to be performed to rid those parts of the plant that should not enter the extraction. For a high-yield extraction, most often the dried drug particles have to be prechopped or minced and then put into a grinding system. Thermal stress during the process should be avoided. Therefore, some mills use liquid nitrogen.

Extraction

Water Extraction

Usually the process is performed with cold (maceration) or hot (infusion) water on dried and broken plant material. This method delivers polar, water-soluble molecules from the source. Hot-water extraction offers the advantage of sterilization, as well as a potential disadvantage of heat-accelerated chemical reactions, which can induce breakdown or transformation of active constituents.

Solvent Extraction

A variety of solvents can be used, e.g., ethanol, isopropanol, acetone, or hexane. Generally, less polar components are extracted than with water. Hexane is particularly well suited to dissolve unpolar components like oils and waxes. The extraction of polar constituents with alcohols or mixtures of alcohol and water is often more selective than the extraction with pure water. However, in some cases a certain degree of oils and waxes are also extracted, which leads to difficult application properties. Solvent residues are a concern to be checked in these types of extracts. A special case to consider is the extraction using supercritical CO_2. Its polarity could be varied via changing temperature and pressure between hexane and ether. Because it is a gas it does not leave solvent residues. Unpolar substrates and smaller molecules, e.g., essential oils, could be extracted very selectively and commonly show only a minimum of color. The high-pressure jacketed extraction vessels and longer process times usually make this technology more expensive.

Steam Distillation

This method easily separates volatile compounds from all others. It has been used since ancient times to gain essential oils from plants. The process is started with the plant being placed into boiling water; steam is feted directly into the flask and the condensate with all the volatiles is collected. The process usually takes several hours and requires heating up to 100°C. This might lead to chemical changes as, e.g., seen for the steam distillation of chamomile by the formation of the blue azulene from a colorless precursor (matricin).

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Extract Concentration and Drying of Extracts

If necessary, solvents could be removed from the extract by, e.g., thin-layer distillation or spray drying. Both technologies place only minimal thermal stress on the extract. Thin-layer distillation even allows the removal of traces of organic solvents from a liquid formulation to yield the required level of extract. Liquid extracts with a suitable water activity usually require the addition of a preservative to prevent bacterial growth. Chemical reactions, e.g., polycondensation, may occur in the liquid phase. Solid-spray dried extracts offer good microbiological and chemical stability compared with liquid extracts, but in some cases there are difficulties in incorporating these powders into clear cosmetic systems. If there are no stability concerns, liquid extracts might offer a cost benefit because they spare the process step of concentration.

ANALYTICAL TECHNIQUES

Analytical techniques, such as high-performance liquid chromatography (HPLC) and to some extent gas chromatography (GC), provide a very useful tool to check quality as well as to make certain the presence of a plant constituent in a consumer product. HPLC is usually the preferred method, because it is very sensitive and provides reliable and quantitative data on the content of a certain compound. Thin-layer chromatography (TLC or HPTLC) is sometimes suitable as well if the mixture is not too complex and only a rough semiquantative identity of the active is needed. A very powerful analytical device is the combination of HPLC with mass spectrometry (HPLC-MS). This approach allows a fast, highly selective detection and quantification. This system is also able to separate complicated molecular structures in complex mixtures.

CONSTITUENTS TO AVOID

Undesired constituents, which might have entered the process chain at some stage, can be pesticides, fungicides (agrochemical treatment), polycondensated aromatic compounds (flame drying), heavy metals, aflatoxins (microbiological, carcinogenic metabolites), and specific plant constituents with known toxic side effects. The manufacturer of an extract should specify the absence of such impurities, respectively, toxic compounds, and guarantee certain legal limits for them.

STANDARDIZATION

If the beneficial constituents of an extract are known, establishing specific quality standards is not difficult. It has to be assured by a suitable analytical technique that the extract contains a certain level of these active constituents. By way of an example, the anti-inflammatory constituents of oat extract (*Avena sativa*) have recently been discovered [2]. This was a difficult task because the chemistry of oat is quite complex. The active in oat belongs to a group of compounds called avenanthramides [3]. Only a few parts per million (ppm) are necessary to achieve a significant redness reduction of a UV-induced erythema [2]. Knowing now the active principle, it is possible to drive the extraction process in a way of receiving the highest quality extract in regard to its activity level as well as giving a minimum guarantee on the amount of active in the extract. Standardization provides the cosmetic formulator a better guarantee of consistent raw material and ultimately product performance.

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Sometimes there is more than one active in an extract. Chamomile, e.g., contains several anti-inflammatory constituents [4]. The two major compounds are bisabolol and apigenin-7-glucoside. Standardization of a chamomile product could include either all compounds that have a similar level of activity or only the most active.

Not all discussions regarding standardization are as clear as with the previous examples. In some cases, the cause for activity (as well as the active constituent) has yet to be proven. One example of a substance that continues to cause controversy concerns a common plant: *Aloe barbadensis.* Its efficacy is well documented in various in vivo studies, whereas the active principle has not yet been fully elucidated [5]. Standardization and analysis are therefore less easy to perform [6], and a well-defined production process is important here to always receive the same quality.

In some cases where the active is currently unknown, it might be possible to standardize on another constituent. This substance could be typical for the particular species but not necessarily responsible for the plant extract's activity. The logic behind that is if there are variations regarding the level for the typical standard, the unknown active may vary with the same magnitude. This might not always be correct but is a reasonable working basis. At least this gives a rough tool to check the amount of plant used to produce the extract by comparing the level in the crude drug with that of the extract. It has to be in line with the drug/extract ratio, which should be specified by the manufacturing company. Moreover, it is one very helpful criterion to assure detection of a plant in a consumer product as well. To give an example, willowherb (*Epilobium angustifolium* [7]) is known for its anti-inflammatory efficacy, although the exact reason for its activity is uncertain [8,8a]. However, the plant contains a very typical constituent, called oenothein B [9]. This specific tannin could serve as a monitor for the quality of the extract as well as an identification tool.

There also exists a group of plant extracts for which it is hard to find characteristic constituents suitable for analysis. An example is cucumber extract. It contains mucilaginous polysaccharides, which are difficult to analyze. The minimum requirements for documentation of consistency of extracts with unknown active or lead compound(s) should include the botanical name of the species extracted, location of growth, process used for extraction, drug/extract ratio, stability data, data on impurities, safety data, and legal status.

EFFICACY TESTING

With the large variety of natural extracts it is possible to cover the full spectrum of cosmetic benefits. For details on claim substantiation see Chapter 65 of this book. An insight of possible claims can be offered only by in vivo studies. However, with the help of in vitro test data, prediction of in vivo activities could be made. Therefore, in vitro testing is of particular interest for research on previously undiscovered activities in plant extracts as well as for substantiation of previously described ones. Many physiological processes in human skin could meanwhile be modeled and monitored. Examples include the inflammation cascade by messenger molecules (IL-1α, PGE_2, LTB_4), collagen/elastin production from fibroblasts (ELISA for procollagen), collagen matrix degradation (MMP activity), antioxidant potential, or melanin formation.

INFORMATION SOURCES

Quite informative sources for cosmetic chemists are the sections in pharmacopoeial or medicinal plant handbooks [10] dealing with plant extracts and preparations. Botanical

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handbooks might give useful general information about the plant used for the extract. Another useful source is the Internet, either in searching for information on a particular species with the available search engines or by using free databases [11].*

FINAL REMARKS

Considering natural extracts for consumer products requires an inspiring relationship with nature and science. Specific know-how is required to ensure the safe incorporation of a substance in a cosmetic formulation. Natural extract suppliers should be called on to offer guidance of proper concentrations as well as regulatory status of the material they offer. The ultimate goal of the use of a natural extract is to provide the basis for a better cosmetic product that can benefit the consumer.

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Rheological Additives and Stabilizers

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INTRODUCTION

The use of rheological additives such as clays, plant exudates, and natural polymers, to formulate personal-care products dates back to ancient times. These rheological additives are used to thicken the fluid, suspend dispersions of additives in the fluid, and improve the stability of the ensuing dispersion or emulsion as a function of temperature and shear history. An attempt will be made in this chapter to classify the wide array of rheological additives with respect to the actual function they serve in the final product.

THICKENERS

Water and oils form the base fluids in which most personal-care and cosmetic products are formulated. These base fluids are generally classed as viscous or Newtonian fluids in that they possess a characteristic viscosity that is independent of the imposed rate of deformation. Newtonian fluids are also viewed as ideal fluids, in that they flow readily when subjected to very low deformations.

Non-Newtonian fluids on the other hand possess viscosities that are dependent on the rate of deformation and may exhibit other properties such as elasticity, yield stress, and thixotropy not seen in Newtonian fluids.

Newtonian Fluids

A schematic of the viscosity profiles of Newtonian and non-Newtonian fluids is shown in Figure 1. Fluid (a) represents a typical viscosity of the base fluid, which might be water, oils or other low molecular weight solvents. The viscosity of these fluids can be modified by addition of particulates that may strictly change the viscosity index as illustrated by the higher viscosity for fluid (b). When non-interacting buoyant particles are used in these fluids, the viscosity of the dispersion can be predicted using the Einstein relation [1].

$$\mu = \mu_o(1 + 2.5\phi + \ldots) \tag{1}$$

where μ and μ_o are viscosities of the dispersion and medium respectively and ϕ is the volume fraction of the particles. Examples of such rheology-modifying substances include

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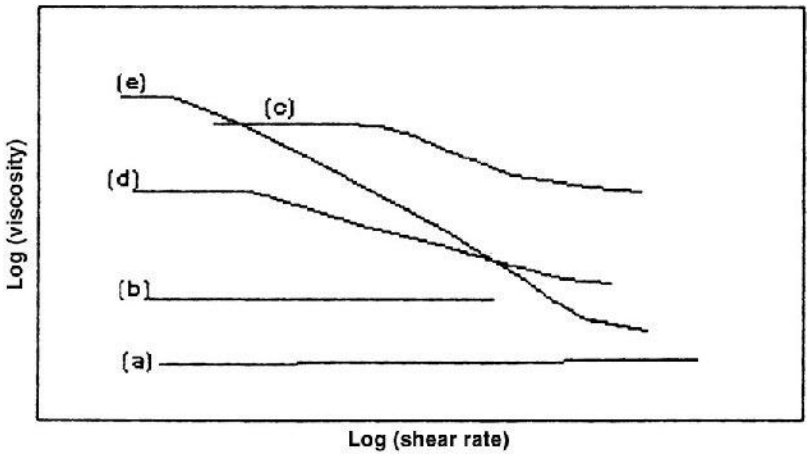

FIGURE 1 Schematic of flow properties of Newtonian and non-Newtonian fluids.

silica gels, fumed silica, carbon black, titanium dioxide and aluminum-magnesium-stearates when used at very small concentrations. Low molecular weight polymers also fit in this category and may be preferred if a smooth or fluid like formulation is desired. Their typical flow curve can also be represented by fluid (b) in Figure 1.

Non-Newtonian Fluids

Unlike Newtonian fluids, non-Newtonian fluids possess shear-rate dependent viscosities. Fluids (c), (d), and (e) in Figure 1 illustrates a range of non-Newtonian profiles observed in personal care formulations. In addition to shear-rate dependent viscosities, non-Newtonian fluids also exhibit elastic stresses when subjected to high shear rates. The usefulness of the elastic response varies with application, as will be illustrated in a later section.

The performance value of rheological additives that impart non-Newtonian characteristics to personal care formulations is demonstrated by the curve in Figure 2. On close

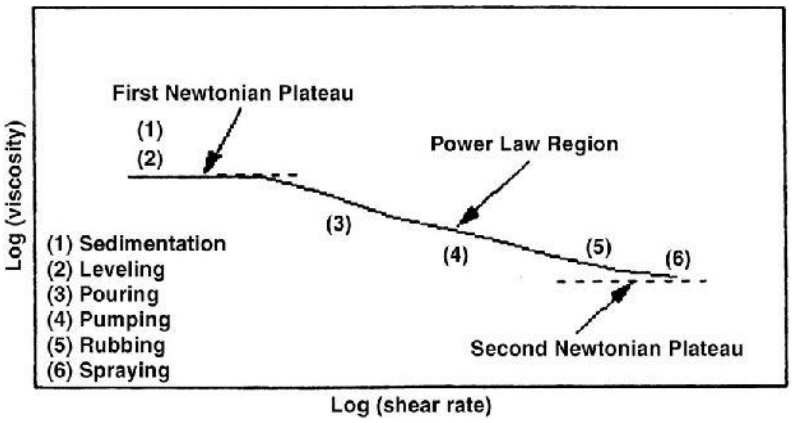

FIGURE 2 Schematic of full flow curve of non-Newtonian fluids.

examination of this figure, it is easy to see why non-Newtonian rheology is more common in personal care formulations than Newtonian (viscous) rheology.

At low shear rates, i.e., near at rest conditions, non-Newtonian fluids exhibit high viscosities that are relatively insensitive to shear rate and characterized by zero shear viscosity. The zero shear viscosity is known to be highly sensitive to the molecular weight and concentration of the rheological additives [2]. The rates of deformation associated with this region include sedimentation and levelling forces, and one can tailor the zero shear viscosity to combat these forces. At moderate shear rates the decrease in viscosity versus shear rate helps when pouring and pumping these fluids. At high shear rates it is found that a second Newtonian plateau in viscosity is reached usually characterised by the so-called infinite viscosity. The shear forces in this area are close in magnitude to forces developed during rubbing and spraying exercises. The low viscosities exhibited by the rheological additives in this region imply low resistance to rubbing and thus a smooth sensation of the substance during its application.

Elasticity

As discussed above, non-Newtonian fluids also exhibit elastic properties, i.e., when subjected to high shear rates, non-Newtonian fluids will exhibit elastic stresses. Figure 3 illustrates the elastic functions of the non-Newtonian fluids (c), (d), and (e) from Figure 1. Note that the elastic response tends to be seen at the higher shear rates.

It is generally observed that fluids that show more shear-thinning properties tend to show more elastic response [3]. This result is well demonstrated on comparison of the viscosity profiles of fluids (c), (d), and (e) in Figure 1 with their normal stress profiles in Figure 3. The rank order of shear-thinning performance for these fluids is fluid (e)>(d)>(c). An identical rank-order of elastic performance is seen for these same fluids in Figure 3.

The desirability of the elastic response will vary with the intended use of the personal care product. In the case of toothpaste, an elastic force is needed to increase extrudate spring back during the tube filling operation in toothpaste production or while dispensing it at home. However, excessive elasticity might not be desirable, as it may make the toothpaste too stringy. High elasticity is needed to stabilize foams, for example in shaving

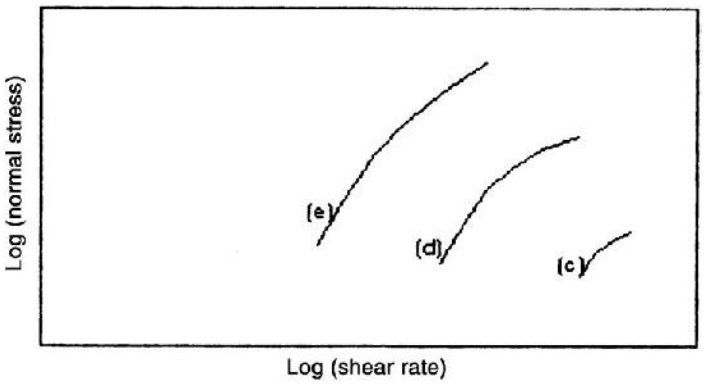

FIGURE 3 Schematic of elastic shear properties of non-Newtonian fluids.

creams, as it provides strength to film at the air/liquid interface in the matrix of bubbles. In the case of creams and lotions, a short texture with less elasticity may be desired.

Examples of substances that impart viscosity as well as elasticity to a fluid are cellulose ethers, xanthan gum, and crosslinked polyacrylic acids. Clays can impart viscosity without elasticity. In the following section, some of the many rheological additives available to personal care formulators will be highlighted. As will be seen, a variety of additives are available in the marketplace that allow formulators to create a range of viscosities and elasticities in the final product.

Interacting particulates such as smectic, hydrophilic and organoclays represent one class of materials used in personal care products that can impart non-Newtonian characteristics to formulations. At a very low concentration, they are known to impart significant viscosity enhancement to the base fluid without any significant elasticity. They typically exhibit a flow curve similar to fluid (C) in Figure 1. It is well-documented [4,5] that these materials cause gelling if used at higher concentrations.

In the case of polymers, their zero shear viscosity, shear-thinning, and elasticity characteristics are a function of their structural characteristics. The rigidity of the polymer, its weight average molecular weight, polydispersity, and degree of branching each play a part in determining these properties.

Water-soluble cellulose ether derivatives such as carboxymethylcellulose (CMC), hydroxyethylcellulose (HEC), hydroxypropyl cellulose, and methylcellulose impart pseudoplastic or shear-thinning rheology to formulations [6a,b]. This characteristic makes these polymers attractive candidates as thickening agents in personal care products.

For instance, this flow characteristic enables a product to pour as a rich, viscous solution from the container, yet be easily applied to a substrate like hair, as its viscosity reduces with shear. These polymers tend to impart high viscosities at low shear. They exhibit moderate shear-thinning behavior, but possess little elasticity at a moderate range of deformation rates, similar to the rheology profile of fluid (d) in Figure 1.

Some of the applications where these polymers are used include shampoos, conditioners, hair spray, and hair-styling gels, toothpastes, and denture adhesives.

This pseudoplastic rheology is particularly beneficial in surfactant-based haircare formulations like shampoos where cellulose ethers can be used to reduce or eliminate inorganic salt added for thickening [7]. Cellulosic thickeners can be used to achieve viscosities higher than possible with salt or even salt combined with alkanolamide. In many cases, even the alkanolamide can be replaced by the cellulose ether [8].

For example, incorporation of 1% hydroxyethylcellulose into a TEA-lauryl sulfate luxury shampoo increased the formulation viscosity from a Brookfield viscosity of 460 cps to a gel with a viscosity of 5300 cps [9].

Additional benefits can also be realised on incorporation of cellulose ethers into formulations. Unlike salt, cellulose ethers do not influence surfactant cloud points, and they can be used to viscosify surfactant systems that are difficult to thicken, such as imidazolidine-derived amphoterics, sulfosuccinates, and highly ethoxylated alkyl ether sulfates [10].

In other haircare applications, such as conditioning hair rinses, addition of a low level of hydroxyethylcellulose polymeric thickener can significantly increase finished product viscosity and improve shelf stability [11].

Cellulose ethers in general have this effect on product viscosity and shelf stability. Methylhydroxypropylcellulose effectively thickens sodium laureth sulfate; a surfactant commonly used in surfactant-based haircare formulations, yielding solutions with excel-

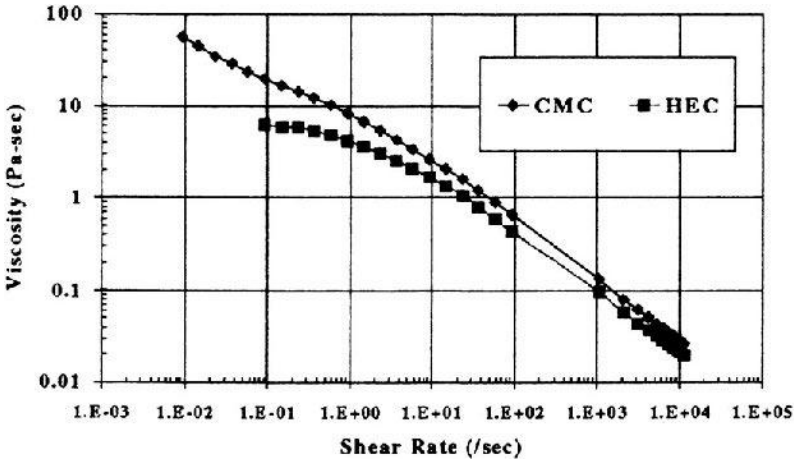

FIGURE 4 Flow properties of 1% cellulosic ether solutions at 25°C.

lent high temperature freeze/thaw stability. Cellulosics achieve this enhanced shelf stability by maintaining the viscosity of the formulation at room temperature, and during freeze/thaw cycling.

A typical rheological profile for two commercially available cellulose ether products, CMC and HEC, are shown in Figure 4. Note that the flow profiles for these materials resemble the profiles for fluids (d) and (e) in Figure 1.

SUSPENDING AGENTS

The storage stability of personal care formulations such as emulsions, suspensions and foams is of prime importance to formulators. Here again, rheological additives have been used widely to prevent sedimentation of solid particulates, prevent coalescence in emulsions, and halt collapse of foams. Rheological substances can impart suspending power to the base fluid. The polymer's yield stress or high viscosity at low shear rates are both used for this purpose. Fluids that possess a yield stress may experience flow only when the imposed stress on the fluid surpasses its yield stress. Below the yield stress the fluid displays solid like properties.

Among the polysaccharides, xanthan gum has been widely used as a suspending aid. Xanthan gum has a double helical structure and undergoes significant hydrogen bonding in solution. At rest or when subjected to very low deformations, a weak three dimensional network structure is the prevailing structure which gives rise to the yield stress [12]. When subjected to higher deformations, this structure can easily be broken down to give rheological behaviour similar to fluid (e) in Figure 1.

Other polysaccharides that exhibit yield stresses are kappa and iota carrageenans. These polysaccharides will also form weak gels and are used in personal care products for stabilization [6].

As discussed in the section on thickeners, cellulose ethers represent another class of polysaccharide-based rheological additives used as suspending aids.

Carboxymethylcellulose imparts a high viscosity at low shear to formulations, enabling it to effectively suspend solids. These characteristics are effectively described by

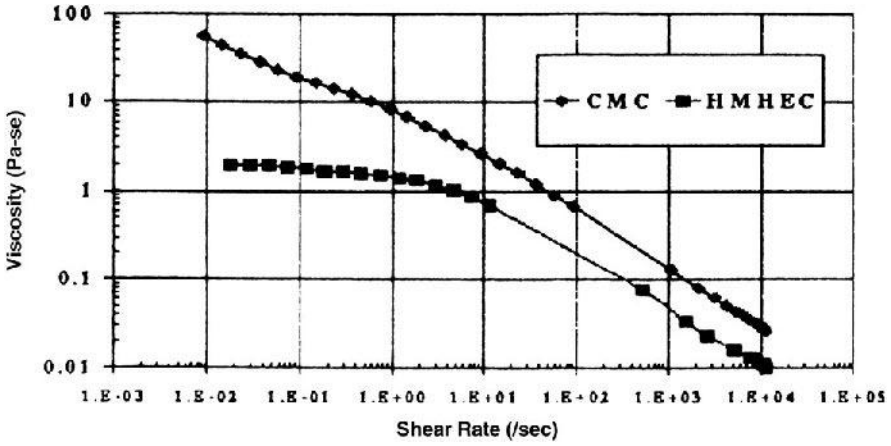

FIGURE 5 Flow properties of 1% cellulosic ether solutions at 25°C.

fluid (e) in Figure 1. CMC has a high capacity for water-binding, and it is generally used to effect rheology and prevent syneresis in high solids formulations [13].

Methylhydroxypropylcellulose has been shown to enhance shampoo lather by way of the water-binding, surface activity, and thermal gelation properties of this cellulose ether. This polymer can stabilize lather by a mechanism known as interfacial gelation [14].

Hydrophobically modified cellulose ethers, such as modified hydroxyethylcellulose, viscosify aqueous phases through both hydrogen-bond network formation and through the formation of three-dimensional networks due to hydrophobic interactions. This dual thickening mechanism makes modified hydroxyethylcellulose particularly effective at suspending solids [15]. The hydrophobic moieties may also associate with surfactant micelles, making modified hydroxyethylcellulose a particularly efficient thickener for surfactant-based systems [16].

Modified hydroxyethylcellulose finds use in many applications, including viscosity and structure development in shampoos, conditioners, and in hand and body lotions [17]. Typical rheological profiles for a modified hydroxethyl cellulose (HMHEC) and CMC are shown in Figure 5.

Salts of cross-linked polyacrylic acids also exhibit considerable yield stresses. However, unlike the other substances, their ensuing structures tend to be much more sensitive to electrolytes [18]. The properties of these materials will be further discussed in the next section.

Colloidal size materials, like fumed silica, are also used for stabilization [5]. Fumed silica can be processed to develop aggregate particles, and thus form weak three-dimensional structures. Stabilization can also be achieved directly by milling the materials to be used in the formulation to colloidal sizes to take advantage of colloidal forces for stabilization.

THIXOTROPIC AGENTS

So far it has been assumed that the non-Newtonian substances discussed are relatively insensitive to the time scale of flow. It is assumed that if the rate of deformation is ramped

up and then down, that there will be a superposition of both stress responses. This may not be the case, as will be demonstrated for toothpaste formulations, where the introduction of thixotropes proves quite useful.

As reviewed earlier in this section, viscosity describes the resistance of a liquid to flow and pseudoplasticity relates to the decrease in viscosity observed with increasing shear rates. Thixotropy, however, is a time-dependent phenomenon, defined as:

- The ability of the substance to exhibit lower viscosities as a function of shear rate and duration.
- And its ability to have its structure reformed over a period of time.

For toothpaste, a great effort has been directed towards optimisation of toothpaste physical attributes. These attributes are strongly dependent on rheological characteristics of the toothpaste system, such as viscosity, pseudoplasticity, thixotropy and low shear yield stress.

Various types of rheological additives find their utility in toothpaste formulations. To perform adequately, they must exhibit a strong three-dimensional structure in lean solvent systems while providing the optimum rheological characteristics described above. Toothpaste exhibiting combined properties such as thixotropic behaviour and high yield value are particularly useful.

The main function of thickening and binding agents in toothpaste systems is to impart adequate paste texture and rheology during preparation, storage and utilisation, good stability with no phase separation or syneresis, smooth and shiny aspect, and improved mouthfeel, foamability, and rinsability. These are directly linked with the rheological characteristics of viscosity, pseudoplasticity, thixotropy, and yield stress.

The thixotropy of a toothpaste system can be described by a rheogram representing a plot of shear stress against shear rate. The hysteresis area between the up curve and down curve is defined, as the energy required to break the network structure of the toothpaste. It gives an indication of the degree of thixotropy of the system as given in Figure 6.

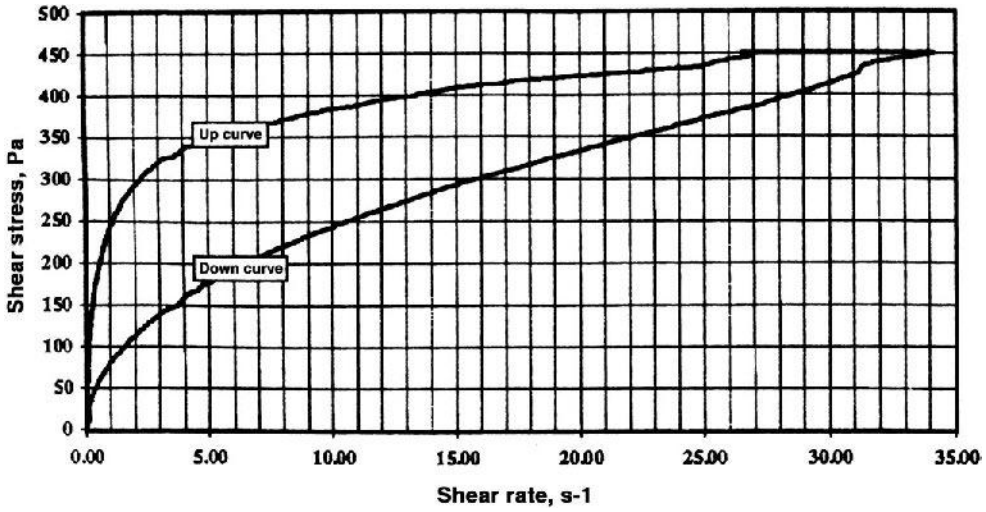

FIGURE 6 Flow behavior of a commercial gel toothpaste.

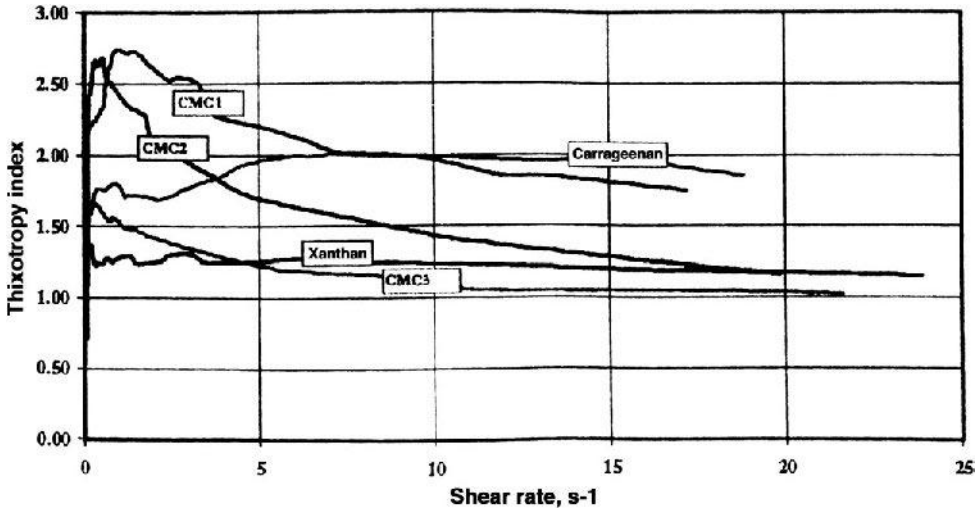

FIGURE 7 Thixotropy of medium water content cream toothpaste.

Five major rheological additive types are currently used in toothpaste systems. They are generally classified into four main categories: 1) natural, 2) modified natural, 3) synthetics, and 4) inorganic. These classes are represented respectively by 1) xanthan gum, carrageenan; 2) cellulose ethers; 3) crosslinked polyacrylic acids; 4) clays and amorphous silicone dioxide.

Figure 7 shows the thixotropic index (TI) of various gums in a cream toothpaste formulation. The thixotropic index is defined as the ratio of the up-curve viscosity to the down curve viscosity measured at the same shear rate. The higher the index, the more thixotropic is the dispersion. For reference a TI of 1.0 means that the dispersion is not thixotropic.

The figure clearly shows CMC 1 gives the most thixotropic structure to this formulation. For cellulose gums, the thixotropic index is shear rate dependent; the extent to which the structure rebuilds is dependent on the shear history to which the gums were subjected.

In comparison with the other gums, xanthan is not thixotropic. The thixotropic index of this formulation is not dependent on the shear rate. The structure is recovered almost instantaneously. Carrageenan has a higher thixotropic index than seen with xanthan gum, but it also recovers its initial structure very quickly.

Interacting fillers such as clay, fumed silica, and aluminum-magnesium hydroxide are also used as thixotropic modifiers in personal care products [19]. These materials tend to form complex networks or gels that show time-dependent rheological properties.

GELLING AGENTS

Hermans [20] suggested that the name gel should be given to systems that display the following features: 1) coherent, two-component systems formed by a solid substance finely dispersed or dissolved in a liquid phase; 2) exhibit solid-like behaviour under the action of mechanical forces; 3) both the dispersed component and the solvent should extend continuously throughout the whole system, each phase being interconnected.

Rheological characterization divides gels into two major classes, strong and weak gels. Strong gels possess the canonical features of true gels. They manifest typical behaviour of viscoelastic solids and rupture beyond a certain deformation value rather than flow. Weak gels resemble strong gels at low deformation rates but their three dimensional networks get progressively broken down at higher deformation rates and they flow as a dispersed system. Physical gels produced by these rheological substances are best described by their viscoelastic properties. Using dynamic oscillatory experiments, the elastic and viscous components of gels can be quantified by G′, the elastic modulus which is a measure of energy storage and G″, the loss modulus, a measure of energy dissipation at a given deformation. Physical gels will typically show G′ to be much higher than G″ when measured as a function of frequency. The slope of G′ values as a function of frequency best differentiates strong gels from weak gels. Strong gels exhibits a nearly flat G′ profile as opposed to weak gels that show a more positive slope [21].

There are several polysaccharides used in personal care formulations that can undergo gelation as a function of ionic strength, pH, and heat treatment. Gelatine, agar, pectins, alginates, and kappa carrageenans will undergo gelation to yield strong gels. Solid air fresheners are a good example of the type of strong gel character achievable with polymers such as carrageenans.

Salts of crosslinked polyacrylic acid, iota-carrageenan, and cellulose ethers, will also form gels and are used in personal care formulations that exploit weak gel properties. They are highly useful in skin creams, shaving gels, hair styling gels, and gel toothpaste formulations.

Literature and formulation ingredients in commercial creams and lotions suggest that a popular approach to providing both emulsification and stabilization is through a three-dimensional surfactant/cosurfactant network. Rheological characterization of commercial creams and lotions, performed using oscillation tests on a controlled stress rheometer, are shown in Figure 8. These results demonstrate the range of rheologies available on combination of different polymeric stabilizers with these surfactant structures [22].

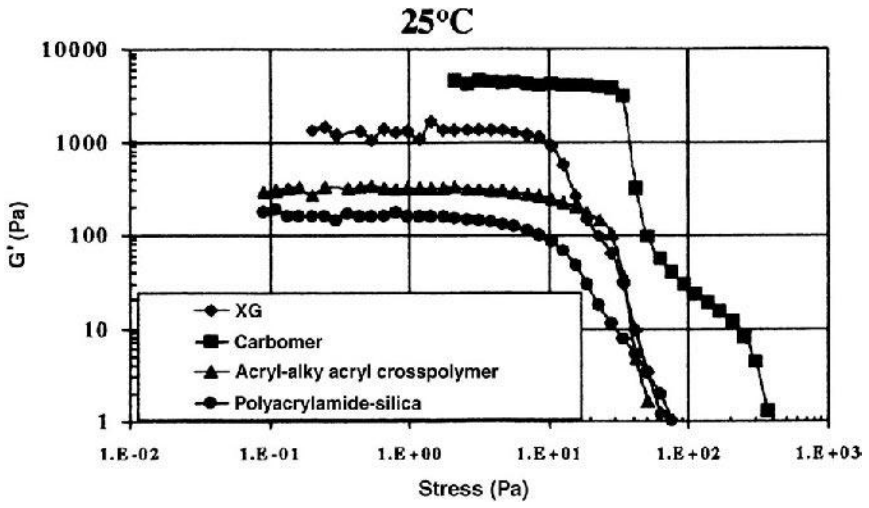

FIGURE 8 Viscoelastic properties of commercial creams and lotions at 25°C.

The surfactant-gel network system provides a yield stress, a high degree of elasticity, shear-thinning behavior, and time-dependent structure build-up (thixotropy). These rheological attributes are very important in the consumer's perception of skin feel during lotion application and rub-in.

The primary component of these liquid crystalline gel network systems is a cosurfactant. Cosurfactants are water-insoluble fatty amphiphiles that are too lipophilic to promote o/w emulsions. Cosurfactants combined with a small fraction of a water-soluble surfactant having a high hydrophilic-lipophilic balance (HLB), produce swollen lamellar-gel networks after thermal processing and cooling.

A physical gel forming rheological additive, such as a cellulose ether, cross-linked polyacrylate, clay, or xanthan gum is added to improve temperature stability and modify the rheology of these systems.

A plot of elastic modulus, G′ as a function of imposed stress for commercial creams containing xanthan gum (XG), crosslinked sodium polyacrylate (carbomer), Acrylate/C10-30 alkyl acrylate crosspolymer and polyacrylamide/silica is presented in Figure 8. The elastic modulus, G′, at low stresses is a measure of the gel rigidity of the sample. These results serve to distinguish the more solid-like creams, with G′ values $>$ 1000 Pa at low shear, from the more liquid-like lotions, with G′ values $<$ 1000 Pa at low shear.

Other materials that can form weak gels when given the appropriate mechanical treatment are silica gels and fumed silica. These materials are sometimes used in combination with other polymers to yield weak gels. They are used in toothpaste where it serves a dual role as an abrasive and a rheology modifier. The thickening silicas are the only inorganic products used extensively to structure toothpaste. They provide a good thickening effect and high thixotropic behaviour, but they lack the ability to bind water in the lean solvent slurry. As a result, they are unsuitable for syneresis control. Therefore, a water-soluble organic binder is necessary to modify the toothpaste rheology and to prevent water separation. Carboxymethylcellulose and carrageenans are often combined with silica for this purpose.

Due to the broad performance criteria that personal care products have to meet, most formulators find it necessary to use a mixture of rheological additives to achieve desired properties in final formulations. Mixtures of materials can bring significant synergy in desired properties. In conclusion, rheological additives significantly influence the mechanical, textural, stability, and ultimately the quality of personal care products.

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Silicones: A Key Ingredient in Cosmetic and Toiletry Formulations

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UNIQUE MATERIALS

Silicone is a generic name for many classes of organo-silicone polymer which consist of an inorganic siloxane (Si—O) backbone with pendant organic groups (usually methyl) (Fig. 1). It is this structure that gives silicones their unique combination of properties and, in particular, their surface properties.

Siloxane Backbone

The prime role of the siloxane backbone is to present the available methyl groups to their best advantage and it does this by virtue of its unique flexibility. In most hydrocarbons, the bond angles are very fixed and steric packing considerations often prevent the available methyls from adopting lowest surface energy orientations. In silicones, the Si—O bond length is significantly longer and the Si—O—Si bond angle flatter than comparable C—C and C—O bonds resulting in a very low barrier to rotation and making the polymer chains very flexible. This flexibility makes many orientations possible and provides ''free space'' to accommodate different sized substituents or to allow easy diffusion of gaseous molecules; a property useful in the formation of ''breathable'' films. Coupled with the low intermolecular forces between methyl groups, this flexibility also has a profound effect on the bulk as well as the surface properties of silicones. This is seen in the small variation of physical parameters with temperature and molecular weight, the low freezing and pour points of fluids, the low boiling points, the high compressibility and the retention of liquid nature to unusually high molecular weights. It also makes a number of structural and compositional variations possible, resulting in many families of silicones, including linear and cyclic structures, a wide range of molecular weights and varying degrees of branching or cross linking. Additionally, the siloxane bond is exceptionally strong providing the polymer with a high degree of thermal and oxidative stability and ensuring stability when formulated [1–3].

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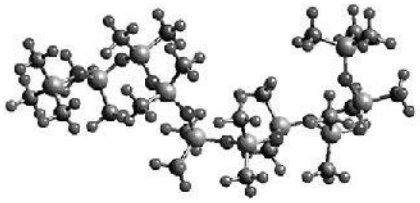
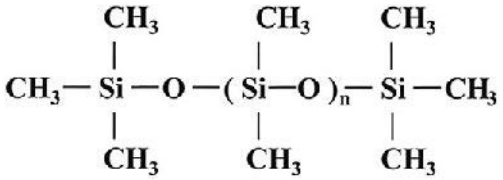




Dimethicone polydimethylsiloxane (PDMS)

FIGURE 1 Unique chemical structure of silicones.

Pendant Organic Groups

The key function of the organic (methyl) groups is to provide the intrinsic surface activity of the silicones. The order of increasing surface energy for single carbon based groups is —CF3 > —CF2— > —CH3 > —CH2—. Liquid surface tension measurements show that, as expected, the order of increasing surface activity is hydrocarbon, followed by silicone, and then by fluorocarbon. Interfacial tension measurements against water, however, show the order of increasing interfacial activity to be fluorocarbon, hydrocarbon, silicone. Silicones do not fit the simple pattern that a reduction in surface energy means an increase in hydrophobicity and interfacial tension because of their backbone flexibility, which allows them to adopt various orientations at different interfaces. The interfacial tension of silicone is also independent of chain length indicating high molecular chain freedom. In addition, critical surface tension of wetting values for silicones have been found to be higher than their liquid surface tension values, meaning that they are able to spread over their own absorbed film. This has an advantage in achieving complete, uniform surface coverage, facilitates the efficient spreading of other materials and results in smooth, lubricating films. In addition, due to the organic groups, the solubility parameters of silicones are significantly lower than those of water and many organic materials making them useful in forming barriers to wash-off or wear and increasing the substantivity of formulations. The introduction of functional groups such as phenyl, alkyl, polyether, amino etc. onto the backbone expands the properties and benefits of silicones further [1–3].

KEY INGREDIENTS IN THE COSMETICS AND TOILETRIES INDUSTRY

Silicones were first used in the cosmetics and toiletries industry in the 1950s, when low levels of medium-viscosity Dimethicone (polydimethylsiloxane) was used to prevent the whitening effect, characteristic of soap-based skin lotions. It was not until the 1970s, when formulators were concerned about the use of CFCs in aerosols, that silicones were considered more seriously as possible ingredients for cosmetic formulations and their unique properties began to be recognized. Since then, the use of silicones has expanded rapidly to virtually all segments and today, 43% of all new products being introduced into the U. S. market contain silicone, with many different types being used [4].

There are five main families of silicones which are used in the cosmetics and toiletries industry today:

1. Cyclomethicones (cyclosiloxanes) are volatile fluids with ring structures. The most commonly used materials are the tetramer, pentamer and hexamer or blends of these. They are good solvents and serve as good carriers for high molecular weight silicones that would otherwise be very difficult to handle. In

addition, they have very low heats of vaporisation compared to water or ethanol giving them a non-cooling feel when drying. Cyclomethicones are classified as non-VOC (volatile organic compounds) in the USA.

2. Dimethicones (polydimethylsiloxanes-PDMS) are linear structures ranging from volatile to non-volatile with increasing molecular weight. Volatile Dimethicones exist as fluids with viscosities of 0.65–2 mm^2/s. Non-volatile Dimethicones exist as fluids with viscosities of 5.0 mm^2/s up to gums. Dimethicone emulsions make handling of the higher molecular weight fluids easier.
3. Silicone blends consist of Dimethiconol or Dimethicone gums or Trimethylsiloxysilicates (highly crosslinked resins) dispersed in lower molecular weight Dimethicones or Cyclomethicones. They have been developed to improve ease of formulation and compatibility of high molecular gums or resins; used for their substantivity.
4. Dimethicone and Vinyldimethicone Crosspolymers or blends are silicone elastomers. They exist in powder form or as elastomeric silicone gels that are swollen with solvent (usually Cyclomethicone). The introduction of different functionalities into such products is also possible. They are used as rheology modifiers in skincare and antiperspirant products, providing a dry, powdery feel to formulations.
5. Functional Silicones:
   (a) Dimethicone Copolyols (silicone polyethers) are fluids or waxes where some of the methyl groups along the siloxane backbone have been replaced with polyoxyethylene or polyoxypropylene groups. The addition of polyoxyethylene substituents increases the hydrophilicity of silicones. Polyoxypropylene substituents are used to balance out this hydrophilicity by increasing the hydrophobic characteristics of the copolymer (16).
   (b) Phenyl Trimethicones are fluids where some of the methyl groups have been replaced by phenyl groups. The phenyl groups increase the refractive index and improve compatibility with organic materials.
   (c) Amodimethicones are fluids where some of the methyl groups have been replaced by secondary and primary amine groups. The polar amine groups have a profound effect on the deposition properties of the silicone, giving it an affinity for negatively charged surfaces, such as the proteinaceous surface of the hair. Emulsions of these fluids are commonly used.
   (d) Alkyl Dimethicones are fluids or waxes where some of the methyl groups have been replaced by alkyl groups. This results in a family of silicone-hydrocarbon hybrids with possibilities for variations in viscosities, softening temperatures and rheological characteristics. They have increased compatibility with organic materials.
   (e) Cyclomethicone (and) Dimethicone Copolyol or Laurylmethicone Copolyol are silicone emulsifiers. They show ampiphilic behaviour and have been designed to emulsify aqueous phases into silicones; usually Cyclomethicone or low-medium polarity organic oils.

SKINCARE, SUNCARE, AND DECORATIVE PRODUCTS

Skin Feel/Emolliency

The main reason that silicones are used in all types of skin care product is because of their sensory properties. Studies on the emollient properties of various materials have

shown that silicones deliver greater emolliency values than many commonly used cosmetic ingredients both, during and after application. They are described as smooth, velvety and non-greasy or oily and are able to impart this feel to cosmetic and toiletry formulations, improving the negative feel associated with other ingredients [5].

Cyclomethicones are used for transient effects giving slight lubricity, a light texture, fast spreading and good distribution of the product on application, whilst leaving no residual effects. They are often included in formulations to remove the greasy or oily feel of hydrocarbon-based emollients and are the basis for ''oil-free'' type claims [6]. They are used in light products for daily use such as facial cleansers, day creams or liquid foundations. Higher molecular weight silicones such as Dimethicone (and) Dimethiconol are used to give a more lubricious, longer lasting effect in richer, more nourishing skin treatment products such as night creams or after-sun products [7]. Silicone elastomers are used to give a dry, powdery feel to skincare formulations [8]. Silicones are also non-comedogenic/non-acnegenic unlike many occlusive, lipophilic fatty emollients which can promote comedone/acne formation on the skin [9].

Substantivity (Long-Lasting/Durability)

High molecular weight Dimethicones or Cyclomethicone (and) Dimethiconols form water-resistant films on the skin which can help prolong the effects of skin care, sun care or decorative products. This substantivity can be improved further by using Alkyl Dimethicones such as Cetyl Dimethicone or C30-45 Alkyl Methicone [7] (see Figure 2). The use of the substantivity of silicones to improve the substantivity of other ingredients in cosmetic and toiletry formulations has been demonstrated in sun care products. The addition of 2.5 wt% Cetyl Dimethicone to an oil-in-water sunscreen formulation shows excellent in vivo resistance to wash-off. The formulation has an in vivo SPF of 21.1 before immersion which reduces to 19.2 only, after immersion for 80 minutes [7] [10].

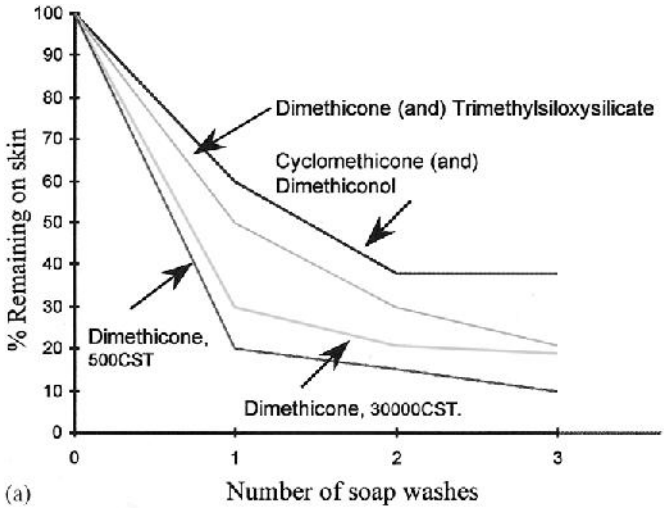
Cyclomethicones are the basis for long-lasting/non-transfer decorative products, especially lipsticks. They are used to disperse waxes and pigments, improve application and impart a pleasant skin feel, often replacing non-volatile hydrocarbon oils. When they evaporate, a uniform film of waxes and pigments remains which is resistant to transfer and wear [11].

Permeability/Controlled Moisturization/Protection Against Dehydration

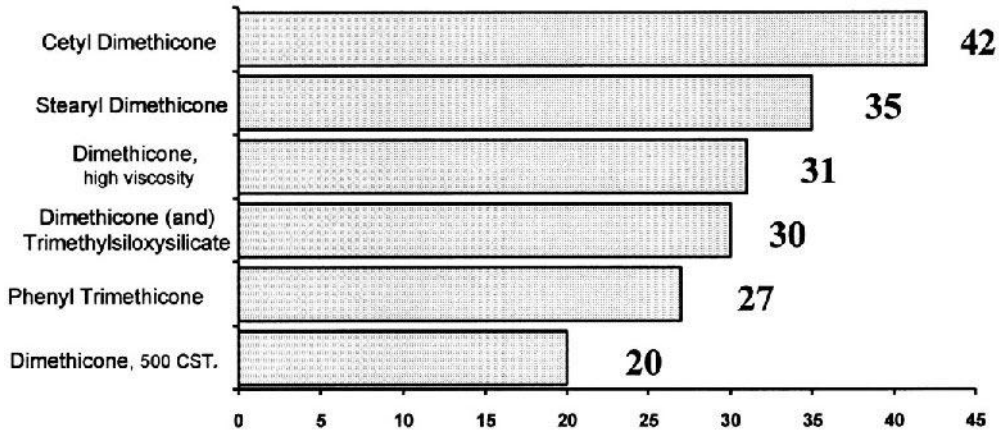
Due to the flexibility of the Si—O—Si backbone, the majority of silicones are permeable to water vapour, producing ''breathable'' films. This is an important parameter for cleansing products or colour cosmetics to avoid clogging pores. The presence of an alkyl group in the chain, however, reduces this permeability, resulting in silicones which can give controlled moisturization, e.g., Stearyl Dimethicone or moisturization (occlusivity) similar to petrolatum e.g. C30-45 Alkyl Methicone [7] [12].

Enhanced Efficacy

Apart from improving the feel and long-lasting benefits of skincare products, silicones can also enhance the efficacy of other ingredients in the formulation. Studies carried out on suncare products have shown that the Alkylmethicones can enhance the in vitro SPF of products containing either organic or inorganic sunscreens. For inorganic sunscreens,



(a)



(b)

FIGURE 2 Substantivity of different silicones, FTIR method.

a 100% increase in in vitro SPF was seen with an oil-in-water system containing 2 wt% Cetyl Dimethicone and a 75% increase in the in vitro SPF for a water-in-oil system containing C30-45 Alkyl Methicone [10] [12].

Protection

Dimethicone is listed in the FDA Monograph for Skin Protectant Drug Products for OTC Human Use in the United States [12]. Due to their hydrophobicity, silicones are used in protective hand creams to provide a water-resistant barrier against water-borne contami-

nants. Recent studies indicate that Cyclomethicone and Dimethicone may also prevent irritation caused by sunscreen agents [13].

Cleansing

The excellent spreading characteristics, dry non-greasy/oily feel, and good solvency of Cyclomethicones make them ideal for use in skin cleansers to help lift and remove dirt without stinging. They can be used alone or in combination with ingredients such as mineral oil. Silicone emulsifiers allow Cyclomethicone to be present in the continuous phase as well as allowing the incorporation of polar ingredients such as water, glycerine etc. This makes the formulation of rinsible foaming facial washes possible [14].

Water-soluble and water-dispersible Dimethicone Copolyols have shown benefits in foaming facial washes. They provide a creamy, more dense foam as well as improving the foam volume. In liquid body cleansing products such as foam baths, shower gels and liquid soaps, they can improve foaming and foam stabilization. They have also been recognized as additives that reduce eye and skin irritation from anionic surfactants [14,15].

Rheology Modification/Structural Integrity (Sticks)

As well as improving the aesthetics of formulations, silicones can also act as rheology modifiers. This is particularly applicable to water-in-oil or water-in silicone-type systems. One such silicone rheology modifier is the C30-45 Alkyl Methicone where 149% and 93% increases in emulsion viscosity have been observed for water-in-silicone and water-in-oil emulsions respectively with 2 wt% of the wax [7]. Rheology modification using 2–4 wt% Stearyl Dimethicone is believed to be part of the reason for the success of this product in enhancing the SPF of sun care products containing organic sunscreens [10]. These waxes are also used to maintain the structural integrity of stick or soft solid products, improving their feel and application. Silicone elastomers can also be used to modify the rheology of skin care and antiperspirant formulations. Such elastomers have the capacity to absorb large amounts of solvents such as Cyclomethicone or low-viscosity Dimethicone without exhibiting any syneresis. It is this property which allows them to successfully thicken formulations. The ability of elastomers to significantly modify the rheology of a formulation combined with their unique powdery feel has led to their use in antiperspirant products.

Formulating Flexibility

Silicones can be used in all types of skin care products ranging from simple oil-in-water gels or emulsions to water-in-silicone and water-in-oil emulsions, from crystal clear to white in colour. Silicone emulsifiers increase this flexibility further. They allow silicones to be present in the continuous phase as well as allowing the incorporation of polar ingredients such as water, glycerine etc. Matching the refractive index of the water phase with the oil phase in such emulsions makes the formulation of clear gels possible and adjusting the phase ratio determines the product form from lotions to gels. This technology is the basis for the clear antiperspirant gels seen on the market today. It is also possible to make non-aqueous emulsions using silicones to deliver hydrophilic ingredients or those that are sensitive to hydrolysis.

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HAIRCARE PRODUCTS

Hair Conditioning/Improved Combing

Various types of silicone are used to give different degrees of hair conditioning. Dimethicone Copolyols provide light conditioning due to their solubility in water and low level of substantivity. They can also help reduce eye irritation associated with shampoos and similar products that contain anionic surfactants. Higher molecular weight Dimethicones/Dimethiconols or Amodimethicones provide a higher level of conditioning due to their insolubility in water and greater substantivity. The latter have an affinity for negatively charged surfaces such as the proteinaceous surface of the hair, which contributes to their substantivity. Evaluation of the average detangling times of Dimethiconol (gum), Amodimethicone and Dimethicone (high viscosity fluid) emulsions at a 4% level in an illustrative two-in-one shampoo formulation indicates that they all show significant improvement over the untreated control tress with the Dimethiconol emulsion providing the best conditioning effect [16,17] (see Figure 3).

Synergistic effects have been observed between quaternary polymers commonly used in shampoos for conditioning and Dimethicone Copolyols. Better detangling results are observed for shampoos containing Dimethicone Copolyol and quaternary polymers than with the quaternary polymers or Dimethicone Copolyols alone [17]. Similar evaluation of silicones in conditioners, indicates that Dimethicone emulsions provides the best conditioning effect in rinse-off products and in permanent waving products, an emulsion of Trimethylsilylamodimethicone significantly reduces the wet and dry combing force.

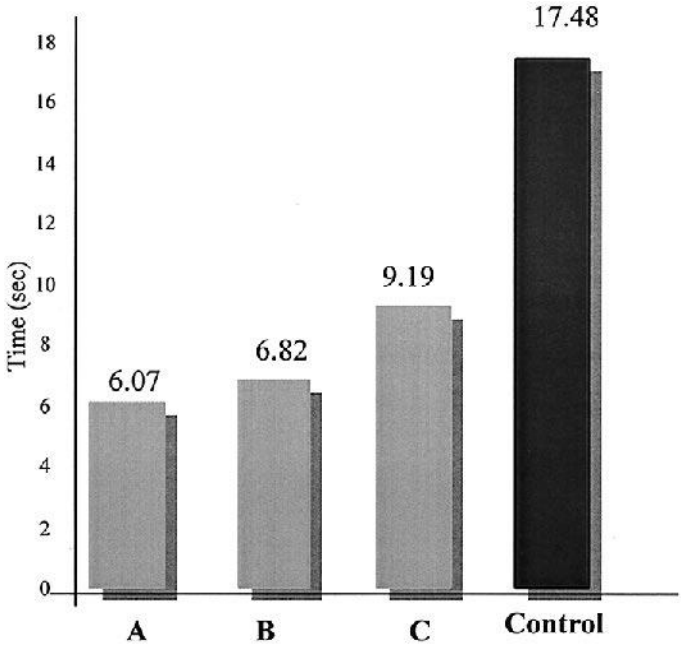

FIGURE 3 Hand detangling results on slightly bleached hair for diluted silicone emulsions. (A) Dimethiconol (and) TEA-Dodecylbenzenesulfonate, (B) Amodimethicone (and) Cetrimonium Chloride (and) Trideceth-12, and (C) Dimethicone (and) Laureth-23 (and) Laureth-4.

Combinations of silicones such as Cyclomethicone, silicone blends and Phenyl Trimethicone are the basis for anhydrous leave-in conditioners, sometimes referred to as ''cuticle coat'' products [16].

Sensory Enhancement

As in skincare, silicones impart a soft smooth feel to the hair. Sensory evaluations of cuticle coat formulations consisting entirely of blends of silicone showed that, in addition to ease of combing, they improve spreadability, silkiness and softness, gloss and perceived repair of split ends compared to the control [16,18].

Silicones as Drying Aids

Silicones such as Amodimethicone can help hair dry more quickly in comparison to drying aids such as Stearalkonium Chloride, preventing damage due to the use of hair dryers etc. [16].

Foam Boosting

Dimethicone Copolyols can be used to boost the foaming properties of shampoos as well as provide a light conditioning effect [16].

Reduced Flyaway

Tests comparing shampoo formulations containing quaternary polymers to those with quaternary polymers and Dimethicone Copolyols show an improvement in static control with the addition of the silicone. Sensory evaluation has also shown a reduction of flyaway with Dimethicone emulsions [16,18].

Improved Shine

Silicones, in particular Phenyl Trimethicone, are recognized for their ability to enhance hair shine and gloss along with adding softness, manageability, and smoothness to the abraded hair cuticle [16,19].

Natural-Look Fixatives

Because of their low surface tension, silicones spread easily to help fixative products distribute evenly on the surface of hair and improving their effectiveness. They are also used in conjunction with or as a replacement for organic plasticizers. Organic materials tend to be hydrophilic, which diminishes the holding power of a resin. In contrast, the hydrophobic nature of silicones helps repel water so there is less opportunity to reduce the resin's holding properties. The use of Dimethicone Copolyol as a resin plasticizer can also help give hair a more natural look [16].

Longer Lasting Permanent Wave and Coloring Products

Silicones, such as Amodimethicone, can be used to provide a more durable conditioning effect and a longer lasting permanent wave. Pretreatments containing silicone blends help prevent hair damage during the harsh perming process. In hair color products, blends of volatile and non-volatile silicone (Cyclomethicone and Amodimethicone) can be used to

seal in the hair cuticle and hold color. The volatile silicone evaporates, leaving behind a smooth, uniform film on the surface of the hair [16,20].

ANTIPERSPIRANT AND DEODORANT PRODUCTS

In addition to the benefits which silicones bring to skin care products such as improved feel, delivery of actives, low residue, formulating flexibility, etc., the following advantages are seen in antiperspirant and deodorant formulations [21].

Anti-whitening

Dimethicones, Phenyl Trimethicone or Alkyl Dimethicones have been shown to reduce/mask the whitening effect caused by antiperspirant salts by matching the refractive index [22].

Improved Spray Characteristics

Low levels of Cyclomethicone (and) Dimethiconol have been demonstrated to reduce the spray width, height, and particle size of antiperspirant pump spray and aerosol formulations, leading to a more directional spray with low mistiness and dustiness [21,23]. The silicone blend may also contribute to the substantivity of the antiperspirant active and lubricate the spray valve to prevent clogging.

Noncooling

The heat of vapourisation of volatile silicones such as Cyclomethicone is much lower than that of water or ethanol meaning that much less energy is required for them to evaporate. This leads to a noncooling effect in formulation [21].

The multifunctional benefits of silicones make them invaluable ingredients in today's cosmetic and toiletry formulations and with the introduction of more and more new silicones, this is a trend which is expected to continue well into the next millenium.

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Skin-Feel Agents

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INTRODUCTION

Skin-feel additives are substances conferring sensorial properties to a skincare product, triggering pleasant perception during application to the skin and after use. Effectiveness of sensory triggers is governed by their substantivity to the skin which occurs either by hydrophobic interaction, charge attraction, or a combination of these two factors. A large variety of cosmetic ingredients function as skin-feel/conditioning additives, comprising lipophilic materials, silicones, water-soluble polymeric substances (including proteins) and their cationic derivatives, and humectants, among others. The Cosmetic, Toiletry and Fragrance Association (CTFA) divides skin conditioning agents into various groups: emollients, occlusive materials, and miscellaneous substances including among others, cationic macromolecules and several surfactants.

This chapter will focus on skin-feel agents for rinse-off products, and more particularly for surfactant-based skin-cleansing products, such as facial cleansers, soap and syndet bars, shower gels and body washes, foam baths (or bubble baths), and bath oils. Shower gels, bars, and facial cleansers first contact the skin, even if only briefly, then are rinsed during the cleaning process; the substantivity of the conditioning agents is crucial to ensure sensory performances, otherwise they will be washed off and the end skin benefit will not be perceived by the user. For bath products intended to be heavily diluted for use, it is difficult to believe that skin-feel agents could function effectively, except perhaps in case of bath oils. Indeed, when bath oils are diluted in water they either float to the surface or lead to a coarse unstable o/w emulsion; when the body emerges from the bath, oils spontaneously stick to the skin because they are incompatible with water and are excluded from the ''bathing liquor.''

The advent of emollients in body-cleansing liquids occurred with the emergence in the early 1990s of the ''body washes'' referring to ''2 in 1'' foaming emulsions; before the development of this new product niche, cationic polymeric materials were the most-used skin-conditioning agents.

Sensorial performance profile of a body-cleansing product comes in a variety of signal attributes:

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- Feeling on the skin during use: spreading of a liquid (also related to product rheology), feel of a bar (slipperiness or roughness), foam feel related to foam quality (creaminess, density)
- Skin feel during rinsing, e.g., slipperiness, roughness of the skin, ''clean feel'' (squeaky feel) left by soaps
- Feel while drying the skin with a towel and feel on damp skin: softness, roughness, stickiness
- After feel and longevity of skin sensations: smoothness, softness, moisturization

All these product attributes are governed at first by e.g., the surfactant nature (amphoterics, nonionics, anionics), their total and relative concentrations, and the clinical mildness for the skin of the surfactant mixture, and can be further influenced or improved by judiciously chosen skin-conditioning agents.

Besides physical, clinical, and organoleptic characteristics of the body-cleansing product, several other imponderable parameters can act on the skin-feel performance and perception, such as usage habits, water hardness, skin condition of the user, and pilosity. Also, consumer expectations in terms of sensorial profile of a product depend on climatic (relative humidity, temperature) and sociodemographic parameters (e.g., sex, occupation, lifestyle, running-water availability), skin type and concerned body part (e.g., face, whole body), and product positioning (e.g., sport, moisturizing, nourishing, others).

Criteria of selection and constraints to be taken into account when choosing skin-feel agents are as follows:

- Solubility and compatibility with the surfactant system
- Sensitivity to electrolytes and pH
- Product physical form: bar, liquid
- Processability (bars) and ease of formulation
- Sensitivity to temperature
- Impact on finished product performance profile:
  on the foam: foam feel, volume and stability, creaminess, bubble structure
  on the product rinsability
  Induction of undesirable and unexpected secondary effects on skin feel when skin is damp (e.g., stickiness)
- Impact on finished product aesthetic:
  on fragrance perception and stability
  on product clarity when relevant
  on viscosity, rheological profile
  on color
- Origin: animal or vegetal, natural or synthetic
- Risk of skin sensitization
- Cost

EMOLLIENTS AND REFATTENERS

Introduction

The CTFA dictionary defines *emollients* as: ''cosmetic ingredients which help to maintain the soft, smooth and pliable appearance of the skin; emollients function by their ability to remain on the skin surface or in stratum corneum to act as lubricant, to reduce flaking,

and to improve the skin's appearance.'' Emollients are also described as *refatting additives* or *refatteners* in the case of bath products. The word *refattener* refers to substances improving the lipid content of the upper layers of the skin; they prevent defatting and drying out of the skin. Several emollients showing strong lipophilic character are identified as *occlusive* ingredients; they are fatty/oily materials that remain on the skin surface and reduce transepidermal water loss. The CTFA dictionary defines occlusives as: ''cosmetic ingredients which retard the evaporation of water from the skin surface; by blocking the evaporative loss of water, occlusive materials increase the water content of the skin.''

Overall, emollients and refatteners are oils and fats derived from natural origins or obtained by chemical synthesis; they are classified in nonpolar (paraffins and isoparaffins) and polar substances (esters and triglycerides); their chemical structure influences the interaction with the skin surface and affects their sensorial properties. As a class, they comprise lipids, oils and their derivatives, fatty acid esters, lanolin derivatives, and silicones and their organofunctional derivatives. Originally, emollients were developed for use in leave-on skin care products; formulation technology can aid the deposition of refatting additives on the skin from wash-off products and avoid that they rinse off with the surfactants; nevertheless, the large dilution factor in both products remains a significant hurdle for skin end benefit perception (except in bath oils).

Emollients and refatteners will provide after feel, but will also influence skin feel during usage, foam feel, and most of the time foam quantity and quality. The more hydrophobic the refattening additive, the more negative its impact on flash foam generation, foam quantity, and stability. In other respects, the more lipidic the material, the better its skin substantivity, and the easier the efficacy documentation; proof and substantiation of claims is of more and more importance in the frame of the Sixth Amendment of European legislation for cosmetics and toiletries.

Lipophilic Emollients and Occlusives

Occlusive materials comprise vegetable oils, triglycerides, mineral oil, natural or synthetic waxes, fatty acid esters, lanolin oil and its derivatives, and polydimethylsiloxanes, among others (Table 1). They form an occlusive layer on the skin, keeping water inside upper stratum corneum layers and consequently acting as moisturizers.

Mineral oil and vegetable oils as well as waxes generally produce heavy and greasy feeling on the skin. Hydrophobic fatty acid esters are an almost unlimited source of synthetic emollients and refatteners; they provide lighter and more pleasant skin feel than oils and waxes. Any fatty acid can be esterified by either ethylene glycol, or propylene glycol, or glycerin polymers, or isopropyl alcohol, or any longer chain alcohol. The feel they impart and their impact on foam is related to the fatty acid chain length; short chains (e.g., isopropyl myristate, octyl octanoate, and cocoate) deliver dryer feel and have lesser impact on foam than longer ones (e.g., stearates and isostearates), which are greasier and detrimental to foam quantity and stability [1].

Hydrophobic emollients are efficacious skin refatteners but not easily formulated in surfactant mixtures commonly used in liquid skin-cleansing product without proceeding to an emulsification step, which most of the time necessitates hot process. Highly hydrophobic refattening additives are not meant for foaming preparations but rather for bath oils. They have a detrimental impact on foam speed, quantity, and stability. Manufacturers circumvent this weakness of lathering capacity by providing a mechanical foaming device with the product: a puff or massage flower [2].

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TABLE 1 Emollients and Refatteners

Chemical structures or nature		INCI names
Fats/oils (triglycerides); hydrocarbons; waxes		petrolatum ceresin mineral oil wheat germ oil/wheat germ glycerides almond/peach oil coconut oil jojoba oil rape seed/olive/sesame oil sunflower/corn/safflower oil
Fatty acid esters: hydrophobic emollient esters	ethylene glycol esters polyethylene glycol esters propylene glycol esters polypropylene glycol esters isopropyl esters polyglyceryl esters alkyl esters	glycol stearate or palmitate or oleate PEG-5 octanoate propylene glycol myristate or laurate PPG-36 oleate isopropyl myristate or laurate or palmitate polyglyceryl-10-laurate or myristate octyl octanoate cetearyl octanoate octyl hydroxystearate
Fatty acid mono- and diglycerides		glyceryl oleate glyceryl laurate
Ethoxylated triglycerides		PEG-6 caprylic capric triglycerides PEG-4 caprylic/capric glycerides PEG-45 palm kernel glycerides PEG-20 almond glycerides PEG-60 corn glycerides PEG-18 palm glycerides hydroxylated milk glycerides
Ethoxylated mono- and diglycerides: hydrophilic emollient esters	ethoxylated glyceryl esters	PEG-7 glyceryl cocoate PEG-8 glyceryl laurate PEG-15 glyceryl laurate PEG-30 glyceryl cocoate PEG-78 glyceryl cocoate PEG-20 glyceryl oleate PEG-82 glyceryl tallowate PEG-200 glyceryl tallowate
Fatty alcohols		lauryl alcohol/oley alcohol octyldodecanol
Emollient ethers	ethoxylated/propoxylated fatty alcohols	PPG-5-laureth-5 PPG-5 ceteth 20 PPG-8 ceteth 20
	polypropylene glycol ethers	PPG-14 butyl ether PEG-4 lauryl ether PPG-15 stearyl ether PPG-50 cetyl ether PPG-3 myristyl ether

Abbreviations: INCI, international nomenclature for cosmetic ingredients; PEG, polyethylene glycol; PPG, polypropylene glycol.

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Soaps and syndet bars can easily accommodate waxes and oils without impairing their basic foaming and cleaning functions. Besides beeswax, petrolatum or ceresin, lanolin and jojoba oil, cocoa butter, and mineral oil, are other examples of skin conditioners commonly used in bars. Paraffin wax is often used in soaps and syndets not only for the smooth feel they impart to the finished bar, the mildness they bring to the formulation, but also for the role of plasticizer they play, adding firmness to the bar. Vegetal oils are included as skin-nourishing/refattening agents (e.g., almond, wheat germ, olive oils).

Fatty acid mono- and diglycerides [1,3] are prepared either by transesterification of triglycerides with glycerin or treatment of alkanoate with glycerin. Lipophilic character remains predominant in these esters; depending on chain length, they are soluble in surfactant solutions or they must be emulsified. Besides the improved skin feel they induce, they also reduce defatting of the skin possibly caused by surfactant-based cleansers. Monoglycerides of stearic, lauric, and palmitic acids (glyceryl monostearate, laurate, and palmitate) intervene in the composition of natural lipids of the skin. They adsorb and can be detected on skin after application through a skin-cleaning product [4].

Several mixtures of monoglycerides and mild foaming surfactants are commercially available; they claim improved foam qualities (bubble size, creaminess, and stability) and documentable skin-refattening properties [5,6]. On top of the skin feel improvement they bring, they will also reduce the degreasing effect of cleansers thanks to their lipophilic character and improve the compatibility of the surfactants with the skin [1]. An example of improvement in the skin barrier function and in skin tactile sensations has been shown for glyceryl oleate in a model shower-gel composition [5].

Hydrophilic Lipids

Hydrophilic lipids (Table 1) [1] are preferred for foaming skin-cleansing preparations. Ethoxylation and propoxylation make lipids more compatible with water and more easily soluble in aqueous surfactants solutions. One has to find the right balance between ethoxylation and skin substantivity; the more the lipids are ethoxylated, the more they are soluble, the less the impact on foam and skin substantivity, and the weaker their refattening properties.

Ethoxylated glycerides are obtained either by reaction of natural triglycerides with ethylene oxide (a complex end mixture is then obtained) or by ethoxylation of monoglycerides. They are often referred to as ''water-soluble vegetable oils''; their solubility in water will depend on the carbon chain length of starting glycerides and on the degree of ethoxylation.

Low ethoxylated triglycerides are still lipophilic enough to provide good refattening properties, leading to very pleasant skin feel, perceivable at quite high use levels. Ethoxylated mono- and diglycerides generally associate various properties beneficial to the skin. They are more or less refattening the skin, depending on chain length and ethoxylation ratio and act as anti-irritant or mildness additives; they confer slipperiness to the foam. Depending on chain length and ethoxylation degree they are either water dispersible or soluble. Among the low ethoxylates, PEG-7 glyceryl cocoate is one of the mostly used. This emollient depresses irritation of anionic surfactants and shows minimum impact on lathering profile. Higher ethoxylates of longer C chain length (PEG-200 glyceryl tallowate) are still substantive to the skin because of their high molecular weight, as well as provide a smooth feel, but because of their stronger hydrophilic character their refatting properties are less obvious to evidence [7].

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Ethoxylated/propoxylated fatty alcohols are useful light emollients: through an appropriate selection of optimum combination between parent alcohol chain length, propoxylation, and ethoxylation degree, these emollients can be formulated up to 2 to 3% in surfactant solutions with minimum impact on foam value.

Lanolin

Lanolin (Table 2) [8,9] is extracted from sheep wool grease; it is a complex mixture of esters of high molecular weight lanolin alcohols (aliphatic alcohols, sterols, and trimethyl sterols) and of lanolin acids; free lanolin alcohols, acids, and lanolin hydrocarbons are minors. Lanolin alcohols and lanolin oil are recommended as superfatting agents in soaps. Ethoxylation of the hydroxyl groups of lanolin or of its derivatives leads to hydrophilic, water-soluble lanolin compounds, offering a broad range of useful emollients to the formulator. Some moderately to highly ethoxylated derivatives, recommended for their good emolliency and moisturization properties, are processable in liquid skin cleansers with limited impact on foam profile; as an example, the 75 mol ethoxylated lanolin does not depress foam and is recommended as skin conditioner in soaps, liquid body-cleansing products, and bubble baths. Medium ethoxylates lanolin alcohols have limited impact on foam performances of body cleansing liquids; lower ethoxylates can be formulated in bars. Propoxylated lanolin alcohols are lipophilic emollients used in soap bars and in other cleansers based on synthetic surfactants.

Alkoxylated lanolin derivatives are obtained by reaction with mixtures of propylene and ethylene oxides in various ratios; they are more soluble than ethoxylated lanolin. They serve as refattening and foam stabilizing agents. Esterification of lanolin fatty acid with isopropyl alcohol provides a range of esters of various molecular weights. Medium molecular weight esters are used as superfatting agents in soaps.

TABLE 2 Emollients and Refatteners

		INCI names
Lecithin		propylene glycol (and) lecithin (and) sodium lauryl sulfate (and) disodium sulfosuccinate (and) cocamidopropyl hydroxysultaine (and) isopropyl alcohol
Lanolin and its derivatives		lanolin oil lanolin alcohol
	ethoxylated lanolin	PEG-75 lanolin
	ethoxylated lanolin alcohols	laneth-16 laneth-25
	propoxylated lanolin alcohols	PPG-30 lanolin alcohol ether
	alkoxylated lanolin	PPG-12 PEG-50 lanolin PPG-40 PEG-60 lanolin oil

Abbreviations: PEG, polyethylene glycol; PPG, polypropylene glycol.

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Lecithin

Lecithin (Table 2) is a natural mixture of polar and neutral lipids; the word *lecithin* is also used as the trivial name of a particular phospholipid: phosphatidylcholine. Main vegetable sources of lecithin used in personal-care products are soybean and maize, egg yolk is practically the only animal source of lecithin used in cosmetics and toiletries. The percentage of polar lipids and their fatty acid pattern are characteristic of the lecithin source.

Bare lecithin, a secondary product of Soya oil extraction, typically contains 60 to 70% polar lipids (mainly phospholipids, namely phosphatidylcholine, and glycolipids) and a remaining 25 to 35% Soy oil. This raw lecithin is further fractionated, purified, and chemically modified to allow easier processing and formulation in toiletry products. Emollient, refattening, and moisturizing properties of lecithin are guided by its content in phospholipids.

Lecithin softens, nourishes, and refattens the skin; it provides a nongreasy, long-lasting skin feel and improves foam feel and quality (creaminess, slipperiness, richness). Ready-to-use mixtures of phospholipids in surfactant solutions, free of residual Soya oil, are commercially available for an easy incorporation in liquids or bars; some of these compounds allow formulation of clear products.

Silicone Derivatives

For detailed information about silicones, lecturer will refer to Chapter 34. Only major materials used in body cleansing products will be briefly discussed here [10,11]. Predominant silicones used overall in personal-care products are polydimethyl siloxane, also named *dimethicones*. They are not soluble in water or in surfactant solutions; their incorporation into liquid cleansers requires an emulsification process. The length of dimethylsiloxane polymer chain dictates its molecular weight and hence its viscosity. Most commonly used materials have viscosities ranging from about 100 to several thousands centistokes. High– to medium–molecular weight dimethicones are occlusive, skin-protective emollients; lower molecular weights are dryer emollients, generally preferred for use in skin cleansers. Dimethicones have a detrimental effect on foam profile but are good film-forming agents, lubricants, imparting a nongreasy, nontacky silky feel as compared with ''heavier'' mineral or vegetable oils. They are used in soap bars, where they also aid mold release, and in 2-in-1 shower gels (body washes). Polymethylcyclosiloxanes or cyclomethicones are tetrameric or pentameric oligomers of the same backbone as polydimethylsiloxane, and show the same chemical and physical properties; they are low-viscosity fluids with relatively high volatility because of their low molecular weight and the weak intermolecular attractivity. Because they are not substantive, cyclomethicones are often identified as dry emollients; they deliver light, transient, and dry skin feel during product use.

Formulation of these nonpolar insoluble silicones requests hot emulsification process (nonionic emulsifiers) and proper emulsion stabilization.

Dimethicones are modifed or functionalized with other organic groups to modulate their solubility in water or in surfactant solutions (and consequently make them easier to formulate) and their skin substantivity properties. By adjusting the type and proportion of hydrophilic substituents, the resulting copolymer is soluble or dispersible in aqueous cosmetic products. The combination of the dimethicone structure with polyoxyalkylated substituents (ethylene or propylene oxide) yields dimethicone copolyols, which are copolymers more soluble in water with surface activity. They are foam boosters and stabilizers;

even if they are less film-forming than parent polydimethylsiloxanes, they significantly add to skin sensations during application (use) and provide excellent smooth and silky after feel [12]. They can be used to formulate clear, aqueous products. Blends of polydimethylsiloxanes with volatile and/or water-soluble derivatives are used to design a sensorial profile adapted to the finished product and its end use.

HUMECTANTS

The CTFA dictionary defines humectants as ''cosmetic ingredients intended to increase the water content of top layers of the skin'' (Table 3). Humectants are hygroscopic substances generally soluble in water. These ''moisture attractants'' maintain an aqueous film at the skin surface. The primary used humectant in personal-care products is glycerin; it tends to provide heavy and tacky feel which can be overcome by using it in combination with other humectants such as sorbitol.

Less expensive than glycerin, propylene glycol is the second most widely used humectant in cosmetic and toiletry products; it reduces viscosity of surfactant solutions and tends to depress the foam.

Low–molecular weight polyethylene glycol (PEGs from about 10 to 200 PEG units), amino acids and other constituents of skin natural moisturizing factors like sodium PCA and sodium lactate are also applicable for use in surfactant-based skin-cleansing products.

Humectants are not substantive to the skin and are easily rinsed-off after cleaning. Consequently, skin-feel improvement is not obvious to perceive and their efficacy in terms of skin moisturization is difficult to document. Glycerin, propylene glycol, 1,3-butylene glycol, or sorbitol are typically used in body washes, bubble baths, shower gels, or soaps to prevent the dessication of the product itself and the formation of a dry layer at the surface. They also ensure stability and clarity of liquid cleansers at cold temperatures.

Few substantive humectants can be mentioned. They are cationic in nature, which makes them absorbing to the negatively charged skin surface. In the quaternized polyal-

TABLE 3 Humectants

Chemical nature or structure	INCI names
	glycerin
	glycereth-26 and glycereth-7
	propylene glycol
	1,3 butylene glycol
	from PEG-8 to about PEG-200
	sorbitol
	sorbeth-6 to sorbeth-40
	xylitol
Ethoxylated methyl glucose	methyl gluceth-10/methyl gluceth-20
	amino acids
	lactic acid/sodium lactate
	sodium PCA
Substantive conditioning humectants	steardimonium panthenol
	lauryl methyl gluceth-10 hydroxypropyl dimonium chloride
	chitosan-PCA

Abbreviations: PEG, polyethylene glycol; PCA, pyrrolidone carboxylic acid.

koxylated methyl glucose derivative (lauryl methyl gluceth-10 hydroxypropyldimonium chloride), the hydrophilic moiety delivers humectant properties; the hydrophobic chain at the cationic end of the molecule ensures both substantivity and skin conditioning.

Chitosan-PCA is another example. Chitosan is a polycationic (at acidic pH) high–molecular weight polymer produced by deacetylation of chitin, the major constituent of invertebrate exoskeletons. Combining chitosan with pyrrolidone carboxylic acid (PCA) leads to a highly substantive, film-forming humectant material.

POLYMERS

Polymeric materials can interact both with protein of the skin surface and with skin lipids. Parameters influencing the interaction between skin surface and the polymers are as follows:

1. The positive charge density: the more cationic the character of the polymer, the better the polymer interaction with negatively charged skin surface.
2. The hydrophobicity of polymer: grafting of hydrophobic moieties on the polymer backbone favor van der Waals interactions with hydrophobic areas of the keratin.
3. The molecular weight of the polymer: the higher the polymer size, the more its substantivity to the skin (film-forming properties). However, very low–molecular weight polymers can easily penetrate the skin surface chinks and as such adsorb into the superficial stratum disjonctum.
4. The nature of surfactants neighboring the polymer in the finished product: the polymer can interact with surfactants either through their charges or through hydrophobic interactions; also, competition between polymer and surfactants for skin anchoring sites can occur. In both cases, deposition and adsorption of polymer onto the skin surface is weakened.

Natural Polymers and Their Chemically Modified Derivatives

Proteins

Proteins differ by (1) the source; (2) the molecular weight, (3) the amino acid (AA) composition, AA side groups, and electrical charge (more of cationic or of anionic AA); and (4) the chemically attached moieties (quats, fatty chains, silicone, etc.) on the peptide backbone (Table 4) [13–15].

Proteins can be from vegetable or animal origin. The most widely used animal protein is collagen from pork or beef; ''marine collagen'' (fish) is now an alternative source of collagen to traditional bovine-derived materials. Milk proteins, keratin, and elastin are also considered in cosmetics and toiletries. The shift away from animal-derived ingredients has resulted in an increased interest in plant-derived materials and increasing use of proteins from vegetable sources.

Vegetable/plant proteins are mostly associated with significant amounts of soluble and insoluble carbohydrates because of the extraction process; soluble carbohydrates confer dark color and strong odor to the raw material, and in some commercial grades carbohydrates have been removed. The combination of hydrolyzed vegetable proteins and oligosaccharides produces conditioning additives with synergistic moisturizing action and film-forming properties. Major vegetal starting materials are wheat gluten, almond meal, rice, oat, soya, and maize.

TABLE 4 Natural Polymers and Their Chemically Modified Derivatives

Chemical structure and origin		INCI names
Native proteins	solubilized in anionic surfactants	native wheat protein/lauryl ether sulfate complex
Protein hydrolyzates	animal source	hydrolyzed animal protein
		hydrolyzed collagen
		hydrolyzed milk protein
	plant derived	hydrolyzed vegetal protein
		hydrolyzed wheat protein/oligosaccharide complex
		hydrolyzed wheat protein and hydrolyzed wheat starch
		hydrolyzed oats
		hydrolyzed wheat gluten
Quaternized protein hydrolyzates	animal source	hydroxypropyl trimonium hydrolyzed collagen
	plant derived	hydroxypropyl trimonium hydrolyzed wheat protein
Fatty side chains grafted on protein backbone	native protein	wheat extract (and) stearic (and) sodium chloride
Quaternized fatty chains grafted	protein hydrolyzate	steardimonium hydrolyzed wheat protein or collagen
		lauryl or cocodimonium hydroxypropyl hydrolyzed collagen
		alkyl quaternary hydrolyzed soya protein
Copolymers	protein-PVP	hydrolyzed wheat protein/polyvinyl pyrrolidone copolymer
	protein-silicone	hydrolyzed wheat protein hydroxypropyl polysiloxane copolymer
	quaternized copolymer protein-silicone	hydroxypropyl trimonium hydrolyzed wheat protein polysiloxane copolymer

Abbreviation: PVP, polyvinyl pyrrolidone.

Proteins are functional over a wide range of pH. Nevertheless, because they are amphoteric materials, below their isoelectric point they carry a net positive charge which makes them substantive to the negatively charged skin surface. Film-forming properties of proteins and hydrolyzates are related to their molecular weight (the higher, the better). Overall, proteins convey a smoothing and moisturizing effect, and produce a soft and silky feel to the skin. They have a positive effect on foam profile: they increase foam stability, confer creaminess and density, as well as slipperiness to the foam. Proteins and hydrolyzates are also known for their ability to reduce the irritation caused by anionic surfactants and to combat skin dryness induced by detergents [16–19].

Some native proteins, such as elastin, keratin, or vegetable proteins, are insoluble. There exist soluble native collagen species; their use is restricted to some specialized

applications. In order to make native proteins suitable for a wide range of applications, they are converted into soluble hydrolyzates by chemical or enzymatic degradation. The sizes of resulting peptides depend on the hydrolysis process used: chemical processes give rise to broader molecular weight distributions and enzymatic digestion to narrower ones. Besides that, native proteins solubilized in various anionic surfactants (by formation of a protein-surfactant complex) are commercially available, allowing easy formulation of these film-forming, moisturizing, mildness additives. A wide range of protein hydrolyzates molecular weights is available, ranging from 500,000 down to 1000 d. Protein hydrolyzates of intermediate molecular weight (average 3000 to 5000 d) are the most widely used; they are less substantive than high–molecular weight proteins but provide smooth skin feel, slippery feel during use, and sensation of skin hydration.

Hydrolyzates are readily soluble and compatible with all classes of surfactants. Most of the commercially available proteins and derivatives have a characteristic odor and color. Furthermore, products formulated with proteins or hydrolyzates should be adequately preserved.

Chemically Modified Protein Derivatives

In order to increase interaction of proteinic material with skin surface, proteins or hydrolyzates are functionalized or chemically modified. Proteins possess reactive side chain amino and carboxyl groups, which are sites for further modification of their intrinsic properties (Table 4).

Hydrophobic interactions with the skin surface are favored and reinforced by grafting fatty carbon chains, and ionic interactions are maximized by grafting cationic moieties onto the protein backbone. Hydrolyzed protein copolymers combine substantivity and film-forming properties of parent proteins with characteristic sensorial properties of companion conditioning agents. These macromolecular protein complexes offer greater moisturizing and conditioning potential as compared with the individual components (20).

Native Proteins Coupled with Fatty Acids. These lead to macromolecular entity with dual hydrophilic/hydrophobic characteristics and physicochemical properties. Skin substantivity is guided both by the size of the starting protein and by the chain length (the hydrophobicity) of the fatty acid. The macromolecules are surface active and can be formulated in bars or liquids; they produce smooth, long-lasting skin feel. Long-chain fatty acid derivatives tend to decrease foam volume but confer creaminess, richness, and slipperiness to the lather.

Copolymers of Silicone and Proteins. These are obtained by covalent bonding of low–molecular weight polydimethylsiloxanes on amino groups of (vegetable) protein hydrolyzate. They combine beneficial properties of proteins (anti-irritant effect, substantivity, film-forming, soft afterfeel) with lubricity of silicone [21,22]. Quaternized protein-silicone copolymers are now commercially available.

PVP-Protein Copolymers. Proteinic component imparts substantivity and polyvinyl pyrrolidone (PVP) modifies the moisture retention and film-forming properties of the resulting copolymer. PVP maximizes film-forming and hydration properties of the protein. The PVP/protein ratio will modulate the profile of performance on the skin and the influence on lathering characteristics of surfactant-based skin cleanser.

Quarternized Protein Hydrolyzates. Cationic protein hydrolyzates are obtained by reacting the primary amine sites on the protein backbone with a tertiary amine, i.e., hydroxypropyl, propyl trimethyl ammonium, or alkyl trimethyl ammonium [23]. Covalent

attachment of quaternary groups strongly increases the cationic character of the protein hydrolyzate, making it further skin substantive and resistant to rinsing step. Covalent attachment of fatty quaternary groups (alkyl dimethyl ammonium) on peptides greatly improves both ionic and hydrophobic interactions with the skin. Alkyl chain can be lauryl myristyl, or stearyl. Alkyl trimonium hydrolyzed proteins are still water-soluble and compatible with all classes of surfactants. These hydrophobically modified cationic protein hydrolyzates are highly adsorbing to skin surface at all pH levels and offer skin substantivity at minimum concentration. They impart pronounced conditioning effect, and the lipophilic moieties provide emollient feel.

Overall, quaternized versions of a protein are many times more substantive than the parent protein hydrolyzate. Quaternization of a protein hydrolyzates raises their isoelectric point (IP) to pH 10 regardless of their initial IP values.

Cationic Guar Gum

Guar gum is a galactomannane polysaccharide derived from the endosperm of Cyamopsis tetragonolobus seeds (Table 5). Depolymerization of the gum by enzymatic or chemical processes allows modulation of its molecular weight, and consequently impacts its solubility, thickening properties, and the clarity of the finished product. Free hydroxyl groups on the polysaccharidic backbone can intervene in esterification and etherification reactions. Hydroxypropyl (HP) side groups improve guar compatibility with electrolytes. Cationic guar derivatives are obtained by reaction of HP guar with epoxypropyltrimethyl ammonium chloride; positive charge density of resulting guar hydroxypropyl trimonium chloride depends on substitution degree. Cationic guar derivatives are film forming, and impart soft, smooth, and silky feel to the skin. Moreover, they act as an anti-irritant for anionic surfactants and soaps, and have a positive effect on foam feel and quality [24,25].

TABLE 5 Natural Polymers and Their Chemically Modified Derivatives

Chemical structure	INCI names	Comments
Cationic cellulose derivatives	Polyquaternium 10	polymeric quaternary ammonium salt of HEC reacted with trimethyl ammonium substituted epoxide
	Polyquaternium 24	polymeric ammonium salt of HEC reacted with lauryl dimethyl ammonium substituted epoxide; average degree of substitution = 1
	PG-hydroxyethyl cellulose lauryl or coco or stearyl dimonium chloride	average degree of substitution > 1
Cationic guar derivatives	guar hydroxypropyl trimonium chloride	
	hydroxypropyl guar hydroxypropyl trimonium chloride	

Abbreviations: INCI, international nomenclature for cosmetic ingredients; HEC, hydroxyethylcellulose.

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Cationic Cellulose Derivatives

Polyquaternium 10 is a range of polymeric quaternary ammonium salts of hydroxyethyl cellulose (HEC) reacted with trimethyl ammonium substituted epoxide. Polyquaternium 10 solutions are non-Newtonian and are commercially available 1) in several viscosity grades depending on their molecular weights (they contribute to viscosity of formulations), and 2) with ''high'' to ''moderate'' cationic substitution. In vivo tests showed that these cationic cellulosic polymers protect the skin from aggression by anionic surfactants (Table 5) [26,27].

Polyquaternium 24 in a polymeric quaternary ammonium salt of HEC reacted with lauryldimethyl ammonium substituted epoxide. It is a hydrophobically modified polyquaternium 10. The degree of substitution with quaternary fatty chain is average 1 in Polyquaternium 24; a range of alkyl dimonium hydroxypropyl oxyethyl cellulose with higher proportion of substituted fatty quat groups (average degree of substitution is 1.2) is also commercially available.

The presence of fatty side chains on these quaternized cellulose ethers confers on them surface active properties and further participates in their very high skin-substantivity and their film-forming properties. They impart silky, smooth afterfeel. These alkyl quaternary cellulose polymers are soluble in water (longer C chains must be slightly warmed) and compatible with a wide range of surfactants; they have favorable influence on the lathering properties providing creaminess, density, slipperiness, and stability to the foam.

Synthetic Quaternized Polymers

An array of dimethyl diallylammonium chloride (DMDAAC)–based polymers and copolymers is commercially available. Their substantivity, film-forming properties, and resulting skin feel depend on both the molecular weight (ranging from about 400,000 up to 7 million) and the density of positive charges, which also dictates the compatibility of the polymer with anionic surfactants. These polymers generally make foam more dense and stable (Table 6) [28].

Inclusion of acrylamide into DMDAAC homopolymer (Polyquaternium 6 is not compatible with anionics) decreases the positive charge density leading to a skin-conditioning polymer more compatible with anionics (Polyquaternium 7) (29, 30). The same effect is obtained by copolymerizing DMDAAC with either acrylic acid (Polyquaternium 22) or with both acrylamide and acrylic acid (Polyquaternium 39). Polyquaternium 7 is probably one of the most often used synthetic cationic polymer in body-cleansing products; it is highly substantive to the skin, delivering soft, silky, moisturized afterfeel (28).

TABLE 6 Synthetic Quaternized Polymers

INCI names	Chemical structure
Polyquaternium 6	dimethyl diallyl ammonium chloride homopolymer
Polyquaternium 7	acrylamide/dimethyl diallyl ammonium chloride copolymer
Polyquaternium 11	poly(vinylpyrrolidone/dimethylaminoethyl methacrylate)
Polyquaternium 22	acrylic acid/dimethyl diallyl ammonium chloride copolymer
Polyquaternium 39	acrylamide/acrylic acid/dimethyl diallyl ammonium chloride terpolymer

Abbreviation: INCI, international nomenclature for cosmetic ingredients.

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Another widely used synthetic cationic polymer in liquids and in bar soaps is a quaternized copolymer of PVP and dimethylaminoethyl methacrylate (DMAEM) (polyquaternium 11). This PVP copolymer is available in molecular weights ranging from 100,000 to 1,000,000.

SURFACTANTS

Amphoteric surfactants are amino acid derivatives; their net charge varies with the pH in solution (Table 7). At pH below the isoelectric point they are positively charged in aqueous

TABLE 7 Surfactants

Chemical class/category	INCI names
Nonionics	
polyhydric alcohol esters	
sucrose esters	sucrose laurate or cocoate
methyl glucose esters	PEG-120 methyl glucose dioleate
	PEG-80 methyl glucose laurate
glucose ethers	alkyl polyglucosides
fatty acid alkanolamides	cocodiethanolamide
Amphoterics	
ampholytes	cocamidopropyl betaine
	olivamidopropyl betaine
	sesamidopropyl betaine
	oleamidopropyl betaine
	isostearamidopropyl betaine
	cocamidopropyl hydroxysultaine
	cocamidopropyldimethyl aminohydroxypropyl hydrolyzed collagen
propionates	alkylamino propionates
	alkyliminodipropionates
imidazoline derivatives	acylamphoacetate
Anionics	
phosphoric acid esters and salts	C9–C15 alkyl phosphate
	PPG-5 ceteth-10 phosphate
	Oleth-3 phosphate
acyl amino acids and salts	
acyl peptides	sodium cocoyl hydrolyzed protein
	sodium lauroyl oat amino acids
	TEA or sodium lauroyl animal collagen amino acids
acyl glutamates	sodium cocoyl glutamate
sarcosinates	sodium cocoyl or lauroyl sarcosinate
taurates	sodium methyl cocoyl taurate
sulfonic acids and salts	
sulfosuccinates	disodium laneth-5 sulfosuccinate
	disodium ricinoleamido MEA-sulfosuccinate
	disodium laureth sulfosuccinate
	disodium PEG-8 palm glycerides sulfosuccinate
isethionates	sodium cocoyl isethionate

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solution and can consequently adsorb more easily onto the skin. Alkyl chain length can also significantly act on the skin feel; some betaines based on C16/C18 cuts provide more greasy, refattened feel but also have detrimental effect on foam.

Polydimethylsiloxane grafted with a betaine moiety leads to an amphoteric surfactant combining substantivity, refattening properties as well as silicone typical skin feel profile.

Some nonionics are used for their emollient properties and excellent afterfeel; e.g., sucrose and methyl glucose esters as well as sucrose ethers. Fatty acid alkanolamides are often referred to as refatteners; these are not lipids but they confer a greasy slippery feel to the foam and impart a particular afterfeel on the skin that subjectively compares with refatting. Several mild anionic surfactants are known to provide improved skin feel (afterfeel) by themselves, e.g., sarcosinate, taurate, acylglutamate, and isethionate. Fatty acids–protein condensates salts also act as conditioning aids, imparting a pleasant, smooth feel to the skin. The inclusion of fatty acids in soap and syndet bars contributes to enhance skin feel during and after use, and produces creamier lather. Phosphoric acid fatty esters deliver soap-like skin feel: slipperiness during use, and very good rinseability leaving skin feeling ''clean'' and powdery.

Benefits brought by additional skin conditioning agents are sometimes hidden by a mild or very mild cleaning-surfactant system delivering by itself very good skin feel properties; the sensorial baseline is high to start with and the increment in performance brought by skin feel agent is leveled off, and sometimes not even perceivable. It is, however, important to notice that several mild anionic and most of the nonionic surfactants, if they provide a pleasant afterfeel, are characterized by a ''water feel'' (feel in solution) that is often unpleasant, with rough and drag feel sensations.

EXFOLIATING AGENTS

Skin scrub agents or body polishers are solid materials from natural origin (fine powder of seeds or shells of different vegetables), or are obtained by chemical synthesis (tiny beads of styrene or polyethylene) (Table 8). When the scrub agent–containing body-cleansing product is rubbed or massaged onto the skin, fine solid particles remove superficial skin horny layer by mechanical abrasion, leaving behind a fresh, smooth skin surface. They are the easiest additives for the consumer to perceive. Scrubbing particles can be suspended in liquid body cleanser thanks to structuring polymers like xanthan gum or carrageenan, which build a viscoelastic network in the surfactant matrix. The scrubbing agent must be carefully selected when formulating facial cleansers. The skin on the face

TABLE 8 Exfoliants/Scrubbing Agents

Apricot/walnut shells powder or flour
Corn cob
Jojoba beads
Polyethylene/styrene beads
Almond meal
Apricot/peach seed powder
Loofah
Maize scape powder

is more sensitive or delicate than that of the rest of the body. For facial application, the formulator should orientate his choices towards, e.g., soft clays or melting jojoba beads.

CONCLUSIONS

The overall skin-feel profile provided by a skin-cleansing product is conditioned by the huge variety of composition constituents. Many have been described in this chapter, but not exhaustively. Other factors can influence the sensations perceived by the consumer, like the presence of electrolytes or of thickening polymers in the product, as well as the water hardness in the user dwelling. It will be the responsibility of the formulator to consider all the potential synergisms or antagonisms in the finished product, in order to deliver the desired skin feel.

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36

Surfactants

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SOLUTION PROPERTIES OF SURFACTANTS

Surfactants for cosmetic use may be grouped into the following six categories: cleaning agents, emulsifying agents, foam boosters, hydrotropes, solubilizing agents, and suspending agents [1]. Most cosmetic products are formulated through the use of these surfactants as main ingredients. This section briefly surveys major surfactants for shampoos and rinses presently on the Japanese market. Basic solution properties of surfactants are then discussed.

Anionic Surfactants

Soaps for detergent have been in use since 3000 BC. Primary detergents in early shampoos before the 1950s were mainly potassium or ammonium salts of fatty acids. These soaps have good foaming performance in pure water, although only slightly so in hard water because of the formation of insoluble metal soaps [2]. Various synthetic surfactants have been developed during the past 50 years. They have come to replace soaps and are soluble even in hard water. The most common synthetic surfactants are alkyl sulfate (AS) and alkyl ether sulfate (AES). These initially appeared on the U.S. market more than 50 years ago, and liquid shampoos subsequently came to be used throughout the country in the 1960s. Ammonium or ethanolamine salts of AS and sodium or ammonium salts of AES were used on a particularly large scale for the preparation of many products. Through the use of ethylene oxide (EO) groups, AS increases solubility and reduces precipitate of Ca salt and foam volume. Increase in solution viscosity is essential for enhancing shampoo appeal to customers. Alkanol amides of fatty acids are effective for viscosity and foam enhancement.

Alpha–olefin sulfonate (AOS) is commonly used as an anionic surfactant in shampoos [3]. A surfactant is a mixture of hydroxyalkane and alkene sulfonates whose structures are shown in Figure 1. AOS exhibits excellent stability at low pH compared with AS or AES and is more soluble in hard water than AS. Increase in solution viscosity has been shown possible through the use of alkanol amides and anionic surfactants in combination.

Various surfactants as supporting ingredients are used in the absence of complete

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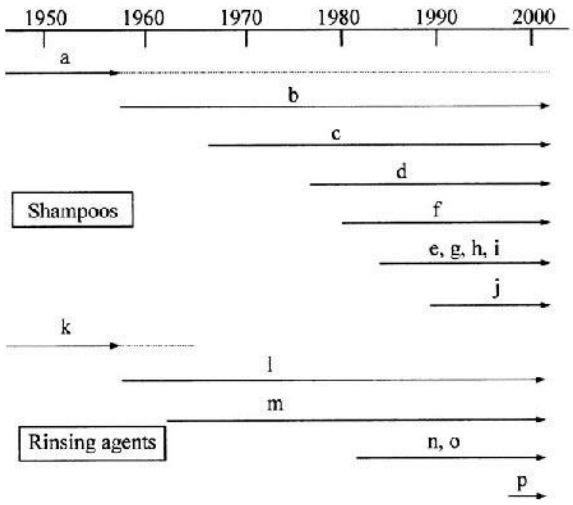

(a)

a: Carboxylic acid	R-COO-X
b: Alkyl sulfate	R-OSO$_3$-X
c: Alkyl ether sulfate	R-O(C$_2$H$_4$O)$_n$SO$_3$-X
d: α -Olefin Sulfonate	R-CH$_2$-CHCH$_2$SO$_3$-X
	R-CH$_2$CH(OH)CH$_2$CH$_2$SO$_3$-X
e: Sulfosuccinate	R-NHCOCH(CH$_2$COO-X)SO$_3$-X
f: N-Acyl glutamate	RCONHCH(C$_2$H$_4$COO-X)COO-X
g: N-Acyl- β -alaninate	RCON(H or CH$_3$)C$_2$H$_4$COO-X
h: N-Acyl methyl taurate	RCON(CH$_3$)C$_2$H$_4$SO$_3$-X
i: Alkylpolyglycoside	RO {Glucose}$_n$H
j: Acyl amidopropyl betain	RCONHC$_3$H$_6$N(CH$_3$)$_2$CH$_2$COO
k: Citric acid	HOOCCH$_2$C(OH)(COOH)CH$_2$COOH
l: di-Alkyl dimethylammonium salt	R(R')N(CH$_3$)$_2$-X
m: n-Alkyl trimethylammonium salt	RN(CH$_3$)$_3$-X
n: g-Alkyl trimethylammonium salt	R(R') CHCH$_2$N(CH$_3$)$_3$-X
o: N-Acyl Arginine ethyl ether	RCONHCH(COOC$_2$H$_5$)C$_3$H$_6$NHC(NH$_2$)=NH
p: N-Acyl Amidobutyl guanidium salt	RCONHC$_4$H$_8$NHC(NH$_2$)=NH

(b)

FIGURE 1 Surfactants for shampoos and rinsing agents on the Japanese market.

functional performances. Alkyl sulfosuccinates exhibit excellent foaming capacity, and their use is attended with low skin irritation provided AS is present [3]. In the 1980s, surfactants with low skin irritation came into popularity. Several amino acids have been developed for surfactant use, such as acyl glutamate [4]. These have excellent foaming, good biodegradability, and low skin irritation. Acyl amino acids such as lauroyl β-alaninate [5] and N-methyl β-alaninate [6] are presently in use. N-acyl methyltaurate [7] is also available and has been proven ideal for shampoo use with low skin irritation.

Nonionic and Amphoteric Surfactants

Nonionic surfactants are preferable to those that are anionic, but have found limited use owing to poor foaming capacity for shampoos. Alkanol amides and alkyl amine-oxides are used primarily as foam boosters and stabilizers [3]. Alkyl glucoside may be obtained through reaction of fatty alcohol with glucose; it is mild to the skin and has good foam stability [8].

Amphoteric surfactants are used in combination with anionic and nonionic surfactants to achieve greater shampoo mildness. A typical amphoteric surfactant is N-acyl amidopropyl betaine [3] featured by low skin irritation and foaming enhancement. Alkyl iminodiacetates may be obtained from fatty amines as mild surfactants [9]. The cocoylarginine ethyl ester (CAE) is prepared from arginine and shows high affinity to hair [10,11]. A new mild amphoteric surfactant, Amisafe, is derived from arginine [12] and functions as a cationic surfactant at weakly acidic pH and is readily adsorbed onto hair.

Cationic Surfactants

Because of the negative charge on the surface of hair, cationics strongly bind to hair and are difficult to remove by rinsing. When a shampoo containing soap has been used, acidic rinse containing citric acid may be applied to remove the alkali and metal soaps. Dialkyl ammonium salts are used in rinse formulations for shampoos containing AS and AES as main ingredients [13]. Quaternary ammonium salts containing mono- or dialkyl groups with 16 to 22 carbon atoms are presently in wide use. At the start of the 1980s, a milky lotion-type rinse came into prominent use. It was produced by adding oils to a gel comprising cationic surfactant, fatty alcohol, and water. Novel cationic surfactants are presently being produced. Quaternary ammonium salts made using long-chain Guarbet alcohol form lamellae liquid crystals even in cold water and are readily adsorbed onto hair [14]. Amido guanidine cationic surfactants (AG) with methylene groups as spacers between amide and guanidino groups [15] are available, and there is a hair conditioner containing AG with excellent moisturizing properties even at low humidity.

Micelle Formation and Surfactant Solubility

The high solubility of surfactants in water is very important in the preparation of cosmetic products. Surfactants show characteristic solubility because of the presence of hydrophobic groups, which squeeze out hydrocarbon chains of surfactants to bring about micelle formation [16]. A phase diagram of the two-component system is shown in Figure 2 [17]. At dilute surfactant concentration, micelle formation occurs above a critical temperature and at surfactant concentration above the critical micelle concentration (CMC). In region I, surfactant concentration is too low for micelle aggregation to occur, and consequently the surfactants dissolve into monomers. In region II, surfactant micelles are equilibrated with monomers. In region III, surfactant monomers are present along with precipitated hydrated solid surfactants. That is, the micelles comprise melting hydrated solid surfactants beyond the phase boundary curve between regions II and III. The point where the two phase boundary curves intersect is the Krafft point of a surfactant solution.

Liquid Crystals and Gels

Various intermediate phases may exist between solid and liquid states. At high surfactant concentration in Figure 2, several liquid crystalline phases can be seen to have formed. The liquid crystalline phases of surfactant-water systems are in the liquid state with a long-range repulsive order of one, two, or three [18,19]. With increase in surfactant concentration, the hexagonal (IV), cubic liquid crystalline (V), and lamellae phases (VI) are produced. The hexagonal phase consists of long rod micelles of surfactants hexagonally arranged. The lamellae phase comprises surfactant bilayers separated by water layers. The water layers vary in thickness from 10 Å to several 100 Å. The hexagonal and lamellae

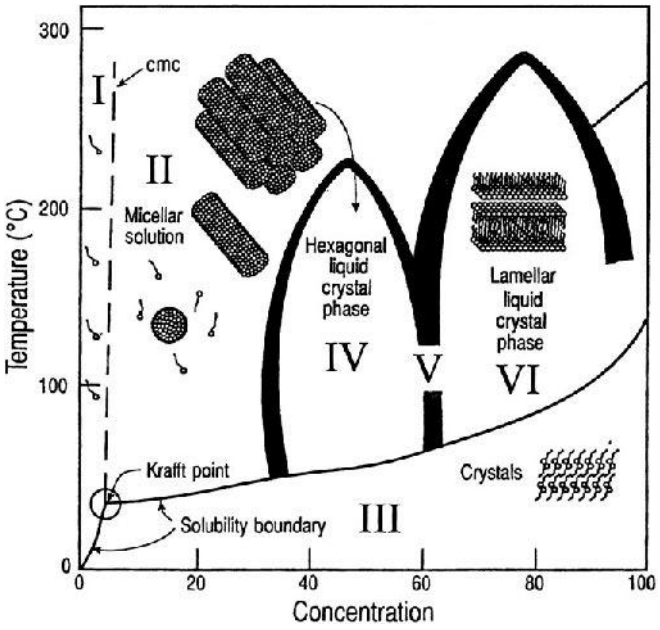

FIGURE 2 Schematic phase diagram of an ionic surfactant. (From Ref. 17.)

phases are optically anisotropic, whereas the cubic liquid crystalline phase is optically isotropic. The cubic phases may take on various structures such as packed spherical micelles in a cubic array, surfactant rods connected in a complex manner to form a continuous network, and bicontinuous networks with positive and negative curvature interfaces [19,20].

In liquid crystalline phases, hydrocarbon chains are in a liquid-like state. When these phases are cooled, a coagel phase consisting of hydrated crystals and a gel phase are formed as shown in Figure 3 [21,22]. The gel phase contains fairly ordered intermediate water, except for hydrated water, between surfactant bilayers. This phase is produced on warming the coagel phase when hydration interactions occur between counter ions. Phase diagrams for octadecyltrimethyl ammonium salts show the stability of the gel phase.

Phase Behavior of Nonionic Surfactants

Increase in nonionic surfactant aqueous solution temperature causes the development of two isotropic phases in solution, above what is called the cloud point. The hydrophilic/hydrophobic balance of a nonionic surfactant may differ considerably at this temperature, and consequently there is characteristic phase behavior in nonionics/hydrocarbon/water ternary systems, as is the case when using a plane of fixed 1 : 1 weight ratio of oil to water, as shown in Figure 4 [23]. At lower temperature, nonionic surfactants are highly soluble in water and form O/W microemulsions in a water-rich phase with excess oil. At higher temperature, they are highly soluble in oil and form W/O microemulsions in an oil-rich phase with excess water. At the phase inversion temperature, a three-phase system comprises a middle phase microemulsion, a nearly pure water phase, and an oil phase. Phase transition with temperature is indication of potential for cosmetic use.

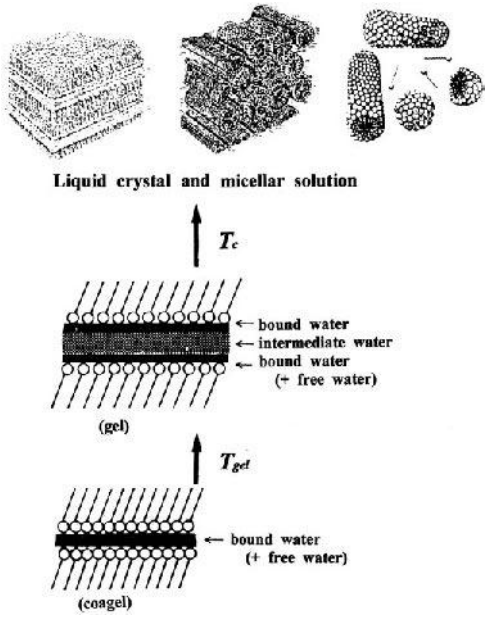

FIGURE 3 Changes in the aggregation of surfactants and water molecules in response to increase in temperature. (From Ref. 21.)

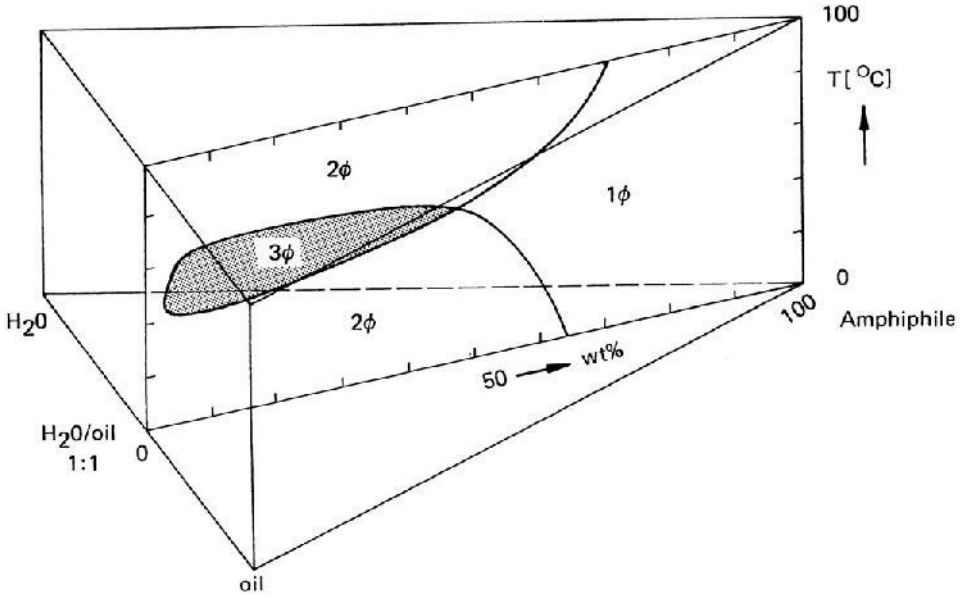

FIGURE 4 Vertical section of the phase prism of a ternary system for H_2O/Oil = 1/1. (From Ref. 23.)

FOAMING PROPERTIES OF SURFACTANTS

Foaming is an essential property of shampoos, skin cleansers, aerosols, shaving cream, mouthwash, and toothpaste, and its mechanism and stabilization have been studied [24–26]. This parameter is enhanced by the following [27]: (1) high viscosity in the liquid phase to retard hydrodynamic drainage; (2) high surface viscosity to retard liquid loss between interfaces; (3) surface effects to prevent thinning of liquid film, such as the Gibbs-Marangoni effect; (4) electrostatic and steric repulsion between adjacent interfaces to prevent drainage caused by disjoining pressure; and (5) gas diffusion from smaller to larger bubbles.

Methods for Foaming Assessment

Foam is a dispersion of gas bubbles in a liquid and the liquid film of each bubble is colloidal in size. Surfactant solutions often have the important feature of foaminess. This property may be defined as foam volume produced from a unit foam volume of solution and may be evaluated based on pressure or temperature and the particular method of formation [28,29]. Standard methods of formation are listed in Table 1. The method may be static or dynamic. Foaminess in this study was evaluated based on foam volume and lifetime. These factors are difficult to assess independently by conventional methods. Because of the complexity of the foam system, better methods are being sought.

Dynamic Surface Tension

Surface elasticity is a major factor determining thin liquid film stability [24]. Foam contains many bubbles separated by liquid films that are continuously enforced by dynamic change in the liquid, such as liquid drainage and bubble motion. In the case of surfactant-stabilized aqueous film, stretching causes local decrease in the surface concentration of the adsorbed surfactant. This decrease causes local surface tension increase (the Gibbs elasticity), which acts in opposition to the original stretching force. In time, the original surface concentration of the surfactant is restored. This time-dependent restoration force in thin liquid film is referred to as the Marangoni effect. Dynamic adsorption at the gas/liquid interface must thus be considered in the assessment of foam stability. Although there are various techniques for measuring equilibrium tension [30], the maximum bubble

TABLE 1 Standard Methods for Foaming Assessment

Principle	Classification	Method	Standard
Static methods	Poring	Ross & Miles Test	ASTM standard D 1173-53
		Modified Ross & Miles Test	ISO standard 696-1975(E)
	Shaking	Bottle Test	ASTM standard D 3601-88
	Beating	Perforated Disk Test	DIN standard 53902 part 1
	Stirring	Blemder Test	ASTM standard D 3519-88
Dynamic methods	Air injection	Diffuser Stone Test	ASTM standard D 892-92
			ASTM standard D 1881-86
		Gas Bubble Separation Test	ASTM standard D 3427-86
	Circulation	Recycling and Fall Test	AFNOR draft T73-421

Abbreviations: ASTM, American Society of Testing and Materials; ISO, International Standardization Organization; DIN, Deutsches Institut für Normung; AFNOR, Association Frances Normalization.

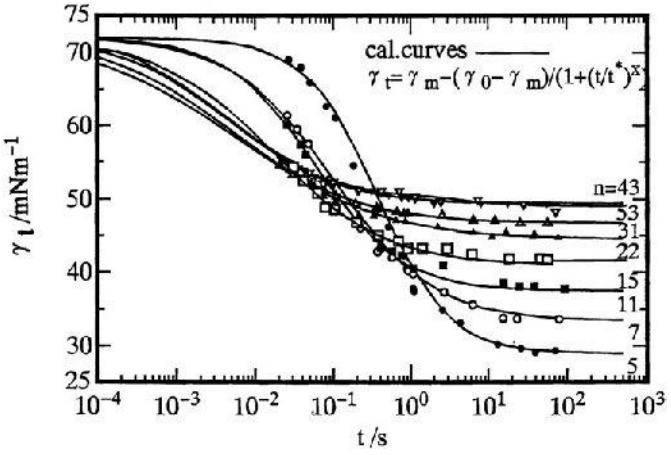

FIGURE 5 Effects of EO units on dynamic surface tension, γ_t, versus bubble surface lifetime, t, for 1 mM aqueous C12En solution at 25°C.

pressure method is used the most for this measurement to monitor dynamic surface tension on a short time scale.

A typical curve of dynamic surface tension shows induction, rapid fall, mesoequilibrium, and equilibrium [31,32]. All these parameters have significant effect on high-speed dynamics. Data for surface tension for aqueous solutions of polyoxyethylene dodecyl ethers (C12En), $C_{12}H_{25}O(C_2H_4O)_nH$, where n = 5 − 53, as a function of time, are presented in Figure 5. Maximum rate of decrease in surface tension $(d\gamma_t/dt)_{max}$, was determined based on the data [33]. Dynamic surface tension (γ_t) at constant surfactant concentration may be obtained as

$$\gamma_t = \gamma_m + (\gamma_0 - \gamma_m)/\{(1 + (t/t^*)^x\} \quad (1)$$

where γ_t is the surface tension of the solution at time, t; γ_m is the mesoequilibrium surface tension of the solution (where γ_t shows little change—$<$lmNm^{-1} per 30s—with time), γ_o is the equilibrium surface tension of the solvent, and t* and n are constants for a given surfactant. The parameter t* is the time for γ_t to reach a value midway between γ_o and γ_m, and decreases with increase in surfactant concentration. The curves obtained with Eq. (1) are widely fitted for the observed time scale, as shown in Figure 5. The $(d\gamma_t/dt)_{max}$ may be derived from Eq. (2) as

$$(d\gamma_t/dt)_{max} = -x(\gamma_0 - \gamma_m)/4t^* \quad (2)$$

Foamability and Foam Stability

Methods for foam formation and stability evaluation were established based on various sources of data, such as dynamic surface tension and liquid film movement, respectively, using a laminometer ($L_{lamellae}$). Ross-Miles foam behavior of aqueous C12En solution is shown in Figure 6. Initial foam height increased linearly with EO. Residual foam height decreased sharply with increase in EO. Dynamic surface properties of aqueous C12En solution are shown in Figure 7. The $(d\gamma_t/dt)_{max}$ increased linearly with EO, whereas $L_{lamellae}$ decreased sharply with EO. Dynamic foam behavior by these methods was found

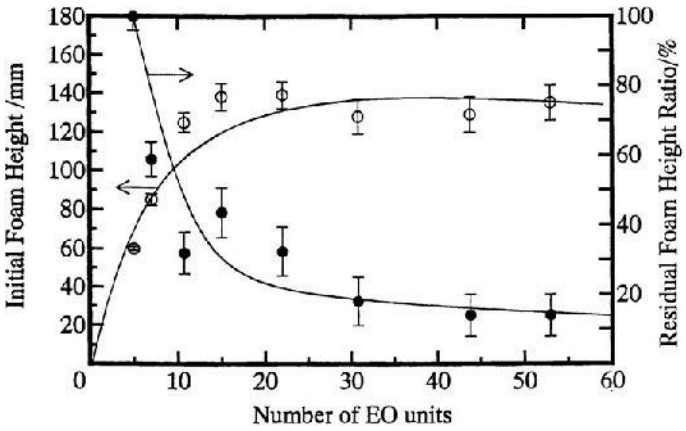

FIGURE 6 Effects of EO units on the Ross-Miles foam behavior for 1 mM aqueous C12En solution at 26°C.

consistent with conventional foam test results. Initial foam height in the Ross-Miles test was in good agreement with $(d\gamma_t/dt)_{max}$, and residual foam height in good agreement with $L_{lamellae}$. Foam formation would thus appear to depend primarily on the rate of adsorption of surfactants onto a gas/liquid interface and foam stability may also be a factor. For nonionic surfactants, initial foam height and stability are less compared with ionic surfactants in aqueous solution because of the large surface area per molecule of surfactant molecule. The effects of area per molecule (A) on foam stability and thinning of vertical films, monitored by FT-IR as a function of time, were examined [34,35]. Data for the Ross and Miles foam stability and aqueous core thickness of vertical foam film at rupture (D_{rup}) as a function of A are shown in Figure 8 [35]. Linear increase in D_{rup} with A was noted, whereas residual foam height sharply decreased with A. Nonionic surfactants that occupy less surface area would thus appear to promote the disruption of foam. Accord-

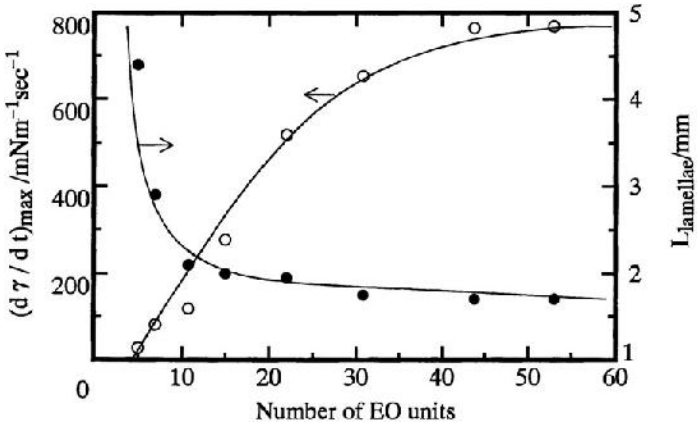

FIGURE 7 Effects of EO units on dynamic parameters for 1 mM aqueous C12En solution at 26°C.

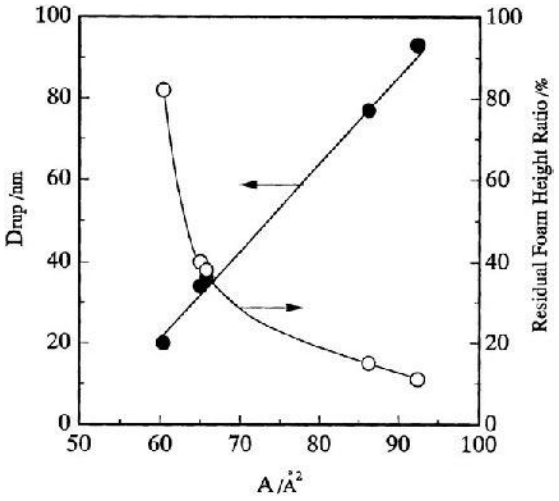

FIGURE 8 Effects of area per molecule (A) on Ross & Miles foam stability (5 min) and aqueous core thickness (D_{rup}) for 1 mM aqueous nonionics solution at ruptured 25°C.

ingly, hydrophobic interactions between surfactant molecules may significantly contribute to foam stabilization.

ADSORPTION OF SURFACTANTS

Adsorption at the solid/liquid interface is an important feature requiring consideration in mechanics, electronics, biological systems, agriculture, foods, and cosmetics. When the adsorption isotherm of a surfactant on a solid surface is measured, several quantitative aspects of surfactant adsorption can be clarified.

Adsorption of Surfactants on Inorganic Solid Surfaces

The surface properties of a solid surface primarily determine the adsorption capacity of a surfactant. There are nonpolar and hydrophobic surfaces, polar and uncharged surfaces, and charged surfaces [36]. Inorganic oxides using cosmetics (e.g., silica, alumina, titania) have charged surfaces. Thus, interactions between a charged surface and ionic surfactant should be understood for controlling the properties on the surface.

The adsorption of SDS onto alumina in aqueous solution has been studied extensively and the mechanisms of adsorption have been made clear [37,38]. The adsorption isotherm of SDS on alumina is presented in Figure 9 and comprises the following four regions [39]: region I with a slope of unity derived from electrostatic interactions between SDS and an oppositely charged solid surface; region II shows steep increase in adsorption attributable to surfactant aggregation at the surface through lateral interactions between hydrocarbon chains—the surface of alumina is not fully covered and there are still positive sites where adsorption may take place; in region III, decrease in the slope of the isotherm attributable to increased electrostatic hindrance of surfactant adsorption is evident—the transition from region II to III corresponds to the isoelectric point of the solid, in which the adsorbent and adsorbate have the same charge; and for region IV, there is maximum

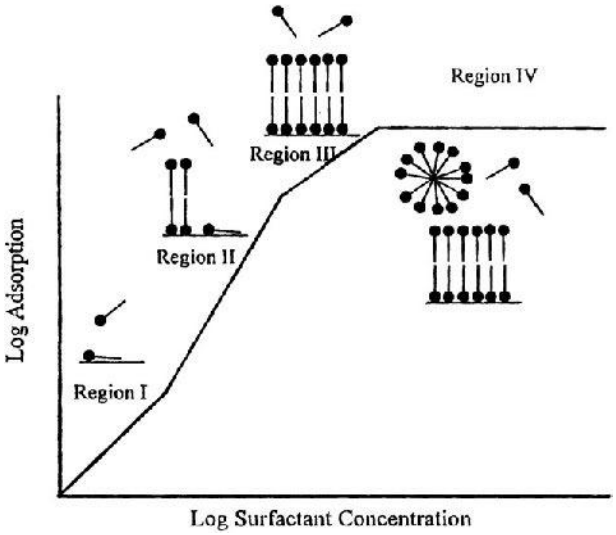

FIGURE 9 Schematic diagram of typical adsorption isotherm. (From Ref. 39.)

surface coverage at cmc and further increase in surfactant concentration has no effect on adsorption density.

Binding of Surfactant to Human Hair

The binding of a surfactant to human hair or wool has been well studied. The thermodynamic aspects of surfactant binding are thus considered in this section. The binding of ionic surfactants to globular proteins has been extensively investigated by thermodynamic analysis of binding interactions [40–44]. In consideration of the fine structure of human hair, surfactants should bind to the cuticle, cortex, and fibrils, all comprising proteins. Thus, continuous binding of a surfactant with human hair would appear the same as that of surfactants with globular proteins.

Binding isotherms of SDS for normal and damaged hair are shown in Figure 10 [45]. SDS bound to cold-waved hair increased remarkably compared with normal and bleached hair. Each isotherm has two regions. Region I shows Langmuir binding attributable to interactions of SDS with ionic sites on the surface of hair. For region II, there was noted sharp increase in adsorption as a result of surfactant aggregation at the surface brought about by lateral interactions between hydrocarbon chains. Damaged hair may possibly be an indication of disruption of disulfide crosslinks. This increase involving the consequent binding of SDS on polypeptides in the hair because of electrostatic repulsion among micelle-like clusters. Rigid disulfide bonds are maintained, and thus such binding was noted to a slight degree for the isotherms of normal hair. The binding isotherms of dodecyltrimethylammonium chloride (DTAC) for normal and damaged hair indicated no increase in binding.

In the Langmuir binding region, the equation of Klotz [Eq. (3)] has quantitative application, as

$$1/\gamma = (1/K \cdot n) \cdot (1/C) + 1/n \tag{3}$$

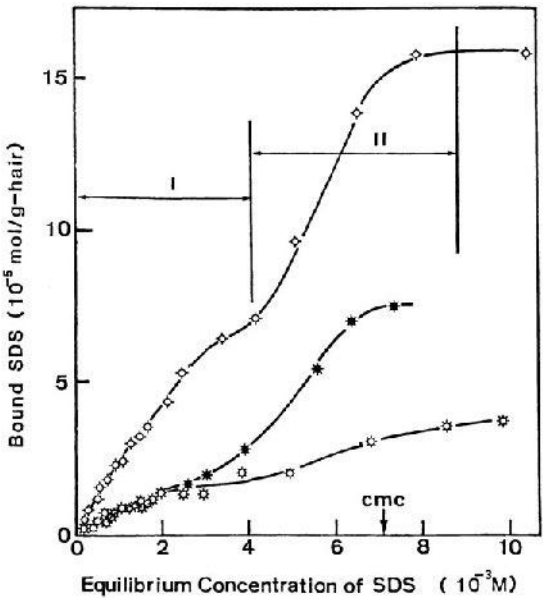

FIGURE 10 Binding of SDS to normal hair (✧), bleached hair (✱), and cold-waved hair (✧) at 25°C.

where γ is total bound surfactants; n, total number of binding sites; K, binding constant; and C, concentrations of surfactants at equilibrium. n and K may be obtained from plot of $1/\gamma$ versus 1/C. The free energy change, $-\Delta G$, is related to the binding constant as

$$-\Delta G = R \cdot T \cdot \ln K \tag{4}$$

Thermodynamic parameters for binding between surfactants and normal hair are listed in Table 2. n and $-\Delta G$ for anionic surfactants were the same in all cases regardless of alkyl chain length. $-\Delta G$, when SDS was bound to BSA, was twice that in the case of SDS binding to hair. In the case of BSA, electric and hydrophobic interactions contribute to the free energy change of binding. Electrostatic interactions between an anionic surfactant and hair would thus appear quite weak, and no alkyl chains at all would be in a hydrophobic area. n and $-\Delta G$ for cationic surfactants were also the same regardless of alkyl chain length. $-\Delta G$, in the case of DTAC binding to BSA and cationic surfactant binding to keratin powder, were the same as for binding to hair. The force of cationic surfactant

TABLE 2 Thermodynamic Parameters of Binding Between Ionic Surfactants and Normal Hair

Surfactants	n($\times 10^{-5}$ mol/g)	K($\times 10^{2}$ L/mol)	$-\Delta G$ (KJ/mol)
SDS (C12)	3.1	3.8	14.7
SDeS (C10)	4.0	2.2	13.4
SOS (C8)	3.5	2.9	14.2
DTAC (C12)	2.1	10.0	17.2
DeTAC (C10)	1.7	9.4	16.8

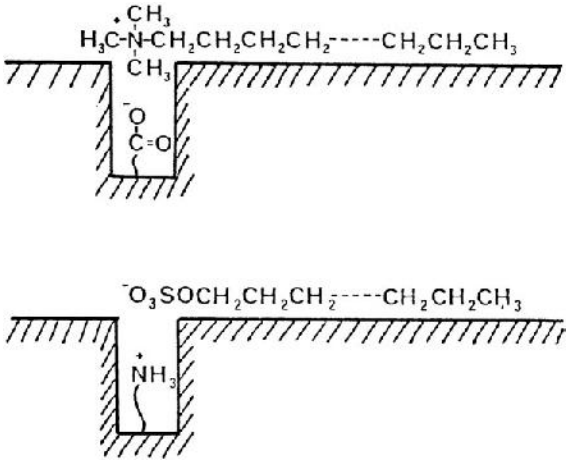

FIGURE 11 Schematic diagrams of the binding of surfactants to human hair.

binding to hair would thus appear to arise mainly from hydrophobic interactions and alkyl chains would not be present in a hydrophobic area on the surface of hair, as also in the case of anionic surfactants. Binding sites for ionic surfactants on hair are shown in Figure 11 [45]. Dissociated carboxyl and amino groups of polypeptides may possibly be present just inside the surface of the hydrophobic layer.

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Classification of Surfactants

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INTRODUCTION

The term ''surfactant'' applies to a group of molecules having both a hydrophilic part and a hydrophobic (or lipophilic) part. Surfactants modify the interfacial properties of the liquids in which they are incorporated; this property stems from their tendency to concentrate at the interfaces separating immiscible phases. Depending on the nature of the hydrophilic moiety ensuring the water-affinity of the molecule, major surfactants can be divided into anionic, cationic, amphoteric, and nonionic classes.

Regarding the hydrophobic moiety of the molecule, it is a hydrocarbon chain in most common surfactants; however, in some more specialized surfactants, this hydrophobic part can be a nonhydrocarbon chain such as a polydimethylsiloxane or a perfluorocarbon. The selection of a surfactant for the development of cosmetic products should be carefully performed, taking into account numerous factors. Among others, one should consider those directly related to functions to be fulfilled (detergency, emulsification, foam quality, rinsability, mildness for skin, skin feel, etc.), and also those related to cost, toxicity, and biodegradability. The aim of this chapter is to provide a classification of various commercially available surfactants. Various textbooks [1–4] or general articles [5,6] may usefully complete this survey.

IONIC SURFACTANTS

Anionic Surfactants

In aqueous solution, anionic surfactants form a negatively charged ion provided the composition pH is neutral to alkaline. The ionized moiety can be a carboxylate, sulfate, sulfonate or phosphate. Among most frequently used surfactants in skin care products, the alkyl sulfates and alkyl ethoxylated sulfates can be mentioned for their high foaming capacity. Anionics are generally used in association with other surfactants (nonionics or amphoterics), which bring improvements in the skin tolerance, in the foam quality, or in the product viscosity.

Other anionics are also used in personal products, as secondary surfactants, often for their milder profile and their low foaming properties (isethionates, sulfosuccinates, taurates, sarcosinates, phosphoric acid esters, acylglutamates, etc.).

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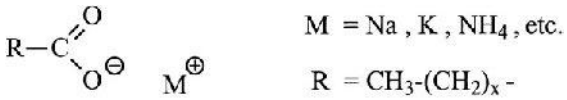
Carboxylates

Carboxylate Salts. Surfactants belonging to this class generally derive from oleochemistry; carboxylate salts (or soaps) can be directly produced by the alkaline hydrolysis (or saponification) of animal and vegetable glycerides or can result from the neutralization of fatty acids obtained by the acidification of carboxylates.

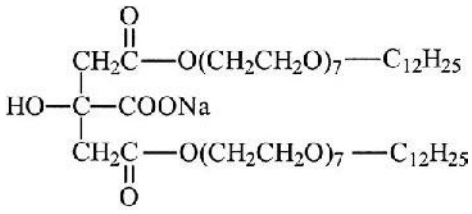
Saturated sodium soaps are extremely soluble in water up to C_8; they become less soluble up to C_{18} and insoluble above C_{20}. The fatty acids can be either saturated or unsaturated (starting from C_{16} chain lengths). Unsaturated fatty acids are prone to undergo oxidation and form oxides and peroxides, which cause rancidity and yellowing. Potassium soaps and salts of alkanolamines are more fluid and also more soluble than sodium salts. The extremely low solubility of alkaline earth and heavy metals fatty acid salts makes this class of surfactants less appropriate for use in hard water.



Alkyl carboxylate

The main application of fatty carboxylates is found in the soap bars widely used in the world for fabric handwash (generally based on tallow/coconut oil mixtures). Water-soluble soaps are mainly used in skin cleansers (soap bars or liquids), shaving products (sticks, foams, or creams) and deodorant sticks. Mixtures of fatty acids and their salts are used in ''acid soaps.'' Water-insoluble soaps form gels in nonaqueous systems and, because of their hydrophobicity, they can be appropriate surfactants for w/o emulsions.

Ester Carboxylates. This class of surfactants is a subcategory of the previously discussed surfactant group based on carboxylic acids; they are monoesters of di- and tricarboxylic acids. These esters are produced by condensation reactions involving different types of molecules; either an alcohol with a polycarboxylic acid (e.g., tartric or citric acid), or a hydroxyacid (e.g., lactic acid) with a carboxylic acid. The reacting alcohol may have been previously ethoxylated.



Sodium dilaureth-7 citrate

Because of their good foaming properties and substantivity on the hair, ester carboxylates are especially suitable in shampoos; in combination with alcohol ethoxy sulfate (AEOS), they provide reduced skin irritation. Short chain lactylates (i.e., issued from lactyllactic acid) are substantive on the skin and present humectant properties.

Ether Carboxylates. These surfactants are formed by the reaction of sodium chloracetate with ethoxylated alcohols. Because of the addition of ethoxylated groups, ether carboxylates are more soluble in water and less sensitive to water hardness compared

with conventional soaps. Also, keeping the best properties of nonionic surfactants, they do not exhibit any cloud point and show good wetting and foam stability. Ether carboxylates do not undergo hydrolysis in the presence of alkali or acids.

$$RO-(CH_2CH_2O)_n-CH_2-COONa$$

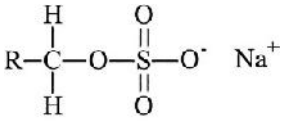
Alkyl polyglycol ether carboxylate, sodium salt

Ether carboxylates are used as general emulsifier and emulsion stabilizers. In the household, they are used in acidic toilet bowl cleaners. In personal care, they impart mildness, creamy foaming, skin-feel, and hair-conditioning benefits. Therefore, they are especially suitable in shampoos in combination with alcohol ether sulfates and possibly with cationics.

Sulfates

Alkyl Sulfates. Alkyl sulfates are organic esters of sulfuric acid; they vary by the length of the hydrocarbon chain and by the selected counterion. Alkyl sulfates are produced by sulfation of the corresponding fatty alcohols. The properties of alkyl sulfates depend mainly on the chain length and the degree of branching of the hydrocarbon chain, as well as, to a smaller extent, on the nature of the counterions. They are generally good foamers, more especially in hard water; best foam characteristics are obtained in the C_{12}–C_{14} chain length range.

Sodium lauryl sulfate (SLS) has a 12-carbon chain length and is one of the most common surfactants. It is not well tolerated by the skin. When the chain length increases (C_{14}–C_{18} range), surfactant penetrability through the stratum corneum decreases along with the irritation potential of the surfactant, but the foaming capacity is accordingly depressed. Chains with carbon number lower than 12 are better tolerated by the skin than SLS, but are smellier. Combination with other surfactants allows considerable improvement of the skin compatibility of lauryl sulfate while keeping a good foam. It is, however, less frequently used than its ethoxylated counterpart. Lauryl sulfate is available under the form of various salts: sodium lauryl sulfate (SLS), ammonium lauryl sulfate (ALS), magnesium lauryl sulfate [$Mg(LS)_2$], and triethanolamine lauryl sulfate (TEALS). Skin tolerance of lauryl sulfates is as follows: $Mg(LS)_2 > TEALS > SLS > ALS$.

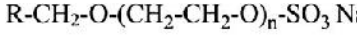


Sodium alkyl sulfate

Alkyl sulfates are used in cosmetics and personal-care areas (e.g., DEA lauryl sulfate in shampoos); they are associated with other surfactants and improve foaming characteristics of detergent systems. Pure SLS (sodium lauryl sulfate) is used in oral care and incorporated in dental creams, essentially as a foaming agent.

Alkyl Ether Sulfates. Alkyl ether sulfates (AES), which are also called alcohol ethoxy sulfates (AEOS), result from the sulfation of an ethoxylated alcohol. Compared with alkyl sulfates, the ether sulfates show higher water solubility, improved foam stability in hard water, and better skin tolerance. The viscosity of surfactant solutions of ether

sulfates is much more sensitive to the presence of electrolytes than alkyl sulfates; formulators often take advantage of this opportunity to bring liquid formulations to the desired viscosity by simply adjusting the salt level (e.g., NaCl). The higher the number of ethoxy groups (EO) in the molecule, the lower the surfactant ability to penetrate the stratum corneum and the less irritant for skin it will be. Similar ranking is true for eye irritation. Also, the foaming capacity decreases as ethoxylation degree increases.

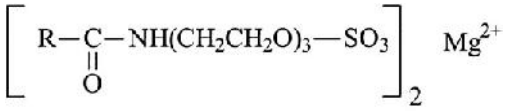


Sodium alkyl ether sulfate

Alkyl ether sulfates are used in domestic applications such as household cleaners, dishwashing liquids, and fabric care.

Alkyl ether sulfates are also extensively used in personal products such as liquid soaps, shower gels, foam baths, and, more especially, shampoos. Sodium lauryl ether sulfate (SLES) is today the most currently used primary tensioactive, especially under the forms of SLES-2 EO and SLES-3 EO, which combine good foaming and skin compatibility properties.

Amide Ether Sulfates. The amide ether sulfates are obtained by sulfation of the corresponding ethoxylated amide. The magnesium salts foam well and their skin compatibility is excellent.



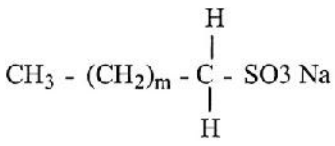
Magnesium PEG-3 cocamide sulfate

Because of their weak lipid removal effect, amide ether sulfates are used in very mild personal cleaners.

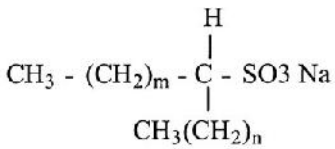
Sulfonates

On a chemical standpoint, there is an important difference between the previously discussed alkyl sulfates and the alkyl sulfonates: in the former, the sulfur atom is linked to the carbon chain via an oxygen atom, and in the latter, the sulfur atom is directly linked to the carbon atom.

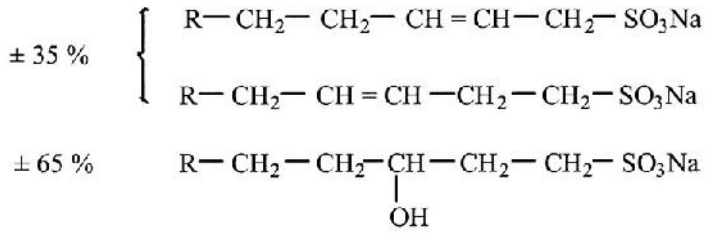
Alkyl Sulfonates. Three major types of alkyl sulfonates must be considered: the primary and secondary paraffin sulfonates (PS and SAS) and the α-olefin sulfonates (AOS). The paraffin sulfonates are very water-soluble surfactants, good foamers, and good o/w emulsifiers. Their solutions do not thicken easily upon salt addition. Therefore, they are particularly appropriate to formulate fluid liquids or highly concentrated products. The α-olefin sulfonates (AOS) have general properties fully comparable to LAS (see next section); they are good o/w emulsifiers, wetting, and foaming agents.



Primary sodium alkyl sulfonate



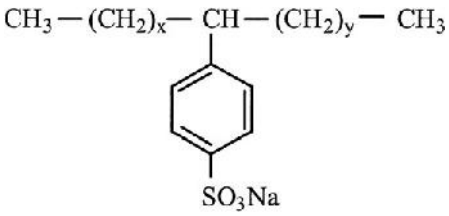
Secondary sodium alkyl sulfonate



Constituents of α-olefin sulfonate: sodium alkene sulfonates and sodium hydroxy alkane sulfonate

Alkane sulfonates (PS and SAS) are mainly used in Europe in detergent products. Alpha-olefin sulfonates have been mainly used in Asia as surfactants for heavy and light duty laundry detergents, synthetic soap bars, and household products. Because they are less irritating than alkyl-aryl sulfonates, they have also been used in the United States in several personal products (liquid soaps, bubble baths, and shampoos) as alternatives to alcohol ether sulfates. They are also marginally used in oral care formulations.

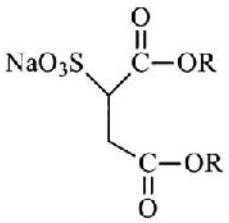
Alkyl Aryl Sulfonates. Today, the LAS (linear alkylbenzene sulfonate) is the most important surfactant on a volume basis, but its use in personal care is very limited because of a low skin compatibility. It is worth mentioning that some methyl or methyl-ethyl substituted aryl sulfonates, i.e., sodium xylene, toluene, or cumene sulfonates (SXS, STS, or SCS), although not showing typical surfactant properties, are used as hydrotropes (i.e., decreasing hydrophobic effects in aqueous systems).



Sodium linear alkylbenzene sulfonate

Sodium linear alkylbenzene sulfonate (LAS) is a very cost-effective surfactant that is extensively used in a broad variety of detergents for household, fabric care, and institutional and industrial products. Because of its too-high detersive action, LAS has a relatively low compatibility with skin and is only scarcely used in cosmetics except in some antiseborrheic preparations.

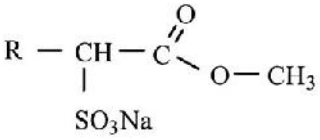
Sulfosuccinates. Sulfosuccinates are the sodium salts of alkyl esters of sulfosuccinic acid; they generally result from the condensation of maleic anhydride with a fatty alcohol, followed by a sulfonation with sodium bisulfite $NaHSO_3$. Some variants of sulfosuccinates are derived from other substituted fatty molecules such as fatty alcohol ethoxylates, fatty amines (yielding sulfosuccinamates), or fatty alkanolamides.



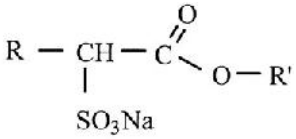
Sodium dialkyl sulfosuccinate

Monoesters disodium salts are the most common sulfosuccinates used in cosmetic applications. Monoesters of alkanolamines (sulfosuccinamates) are milder than monoesters of fatty alcohols (sulfosuccinates). Monoesters derived from ethoxylated alcohols or alkanolamides are extensively used in personal products and especially in shampoos; they are known for their mildness and skin-irritation reduction when used in association with other anionic surfactants.

Sulfo Fatty Acid Esters. These surfactants are sometimes known under their abbreviated names: FES for fatty ester sulfonate, MES for methyl ester sulfonate, or ASME for alpha sulfo methyl ester. Most of α-sulfo fatty acid esters derive from fatty acid methyl esters. In general, alkyl esters of α-sulfo fatty acid have excellent detergency (i.e., oil dispersing and emulsifying properties) when the molecule is dissymmetric (as in the case of the α-sulfo methyl esters). On the other hand, the α-sulfo esters, in which the sulfonate group is in the middle of the molecule (as in the case of long-chain alcohol esters), deliver good wetting but poor detergency.



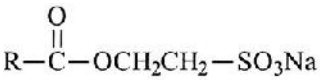
Methyl ester of α-sulfo fatty acid, sodium salt



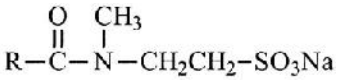
Alkyl ester of α-sulfo fatty acid, sodium salt

Alpha-sulfo methyl ester surfactants deriving from C_{16}–C_{18} fatty acid (e.g., ASMT, the tallowate) are appropriate for use in laundry detergents. ASME is also used in the formulation of syndet bars (laundry bars based on synthetic surfactants).

Fatty Acid Isethionates and Taurides. Fatty acid isethionates are usually prepared by reaction of a fatty acid chloride with sodium isethionate ($HO\text{-}CH_2\text{-}CH_2\text{-}SO_3\text{-}Na$), itself resulting from the addition of sodium bisulfite to ethylene oxide. These surfactants are insensitive to water hardness and show good wetting, foaming, and emulsifying properties. In addition, they are very mild and have excellent compatibility with the skin. Taurides (or taurates) are acylamino alkane sulfonates that have chemical structures close to isethionates. They can be used in association with other surfactants to increase the viscosity.



Fatty acid isethionate



Sodium methyl acyl tauride

Acyl isethionates have been used in shampoos and personal cleansers. They are also incorporated in syndet bars together with various soaps. The most currently used is the cocoyl isethionate.

Taurides (or taurates), which have the same expected properties as soaps (except the sensitivity to water hardness), had been extensively used in shampoos but have been replaced by AEOS. Today they are limitedly used in cosmetics mainly in foam baths and toilet bars. Taurides are also used in soap bars especially designed for laundering with seawater, in agriculture, and textile dying.

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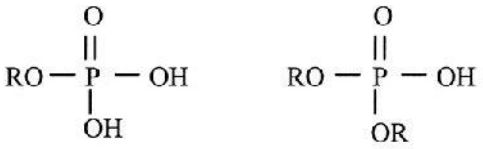
Phosphate Esters

This class of surfactants includes alkyl phosphates and alkyl ether phosphates.

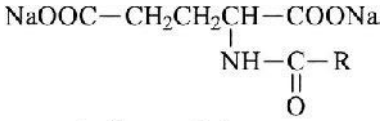


Alkyl phosphoric ester Dialkyl phosphoric ester

The use of phosphate esters as surfactants is especially useful in applications for which a particular tolerance to pH, heat, or electrolytes is required. They are also used in acidic cleaning products for household as well as industrial applications. Mild for the skin, alkyl phosphates sometimes enter the composition of facial and cleansing products.

Acylamino Acids and Salts

Acyl Glutamates. These surfactants are formed by acylation of a natural amino acid, the glutamic acid HOOC-CH_2-CH_2-CH(NH_2)-COOH (or α-aminoglutaric acid). These surfactants are mild for the skin and the eyes, deliver improved skin feel, but are poor foamers.

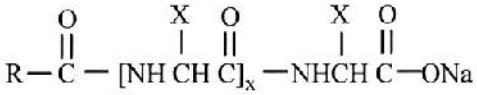


Sodium acyl glutamate

Acyl glutamates are mainly used in personal products such as shampoos.

Acyl Peptides. These surfactants are formed from hydrolyzed proteins (e.g., animal collagen). Depending upon the protein hydrolysis process (chemical or enzymatic), the average polypeptide molecular weight can vary from about 350 to 2000 and some free amino acids may be present in the hydrolysate. An acylation reaction occurs on the amine terminal functions and, possibly, on some side groups (e.g., the hydroxyls); it accordingly leaves free carboxyl groups which must be neutralized.

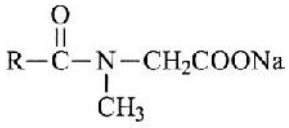
Products containing such surfactants are prone to be contaminated by various germs and have to be properly preserved.



Sodium acyl polypeptide (X= amino acids side groups)

Acyl peptides are mild surfactants designed for the personal-care area; they are especially used in shampoos because of their substantivity on the keratin of hair and, therefore, they effectively deliver the expected benefits of conditioning agents.

Acyl Sarcosides. Sarcosinates (or salts of acylamino acids) are the condensation products of fatty acids with N-methylglycine CH_3-NH-CH_2-COOH (or sarcosine).



Sodium acyl sarcosinate

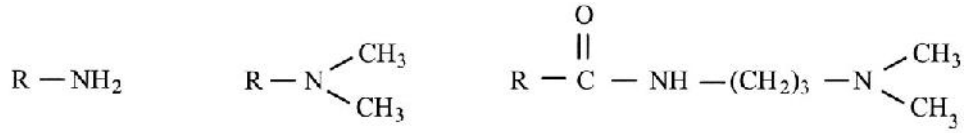
Sarcosinates are good surfactants for cosmetic usage because of their mildness to skin, substantivity on skin and hairs when incorporated in formulations around neutral pH, conditioning action, and foaming resistance in the presence of soaps or sebum. Incorporated in shampoos with alkyl sulfates, they boost the lather. Sarcosinates are also used as corrosion inhibitors.

Cationic Surfactants

From a very general standpoint, cationic surfactants differ from anionic and nonionic ones by the fact that they carry a positive charge. Their major interest in cosmetic industry resides in hair care; in this frame, they are use as hair conditioners and antistatic agents. Cationics are also found in the personal-care area as emulsifiers in some cosmetic preparations and as bactericidal agents.

Alkylamines

Primary, secondary, and tertiary alkylamines, and more especially their salts, are included in this surfactant class.

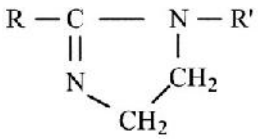


Alkylamine Dimethyl alkylamine Alkylamido dimethyl propylamine

Amines and their salts are mainly used in textile treatment and occasionally in rinse fabric softeners. Salts of amines are used in cosmetics together with other surfactants. Their usage is restricted to specialties; they exhibit conditioning and antistatic properties in haircare applications. Amido-amines are also used in cosmetic products.

Alkylimidazolines

Reaction of a fatty acid with a substituted ethylene diamine forms imidazoline. Heating the resulting, amido-ethylamine yields the imidazoline with a five-member substituted ring. The tertiary nitrogen atom can be quaternized.



R' = $CH_2CH_2NH_2$ => alkyl aminoethyl imidazoline

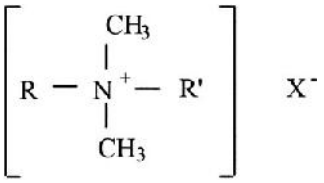
R' = CH_2CH_2OH => alkyl hydroxyethyl imidazoline

Imidazolines are cationic o/w emulsifiers. Considered to be irritating they are scarcely used in cosmetics as substantive hair conditioning agents.

Quaternary Ammonium Compounds

Quaternary ammonium compounds form a class of surfactants that contain a positively charged nitrogen atom linked to four alkyl or aryl substituents. The positive charge is permanent, regardless of pH.

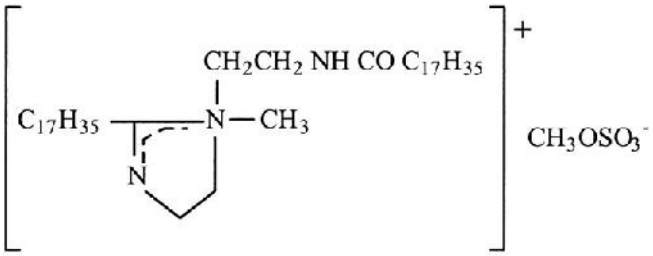
Tetra-Alkyl(-aryl) Ammonium Salts. Tetra-alkyl ammonium salts have the structure $[R_1R_2R_3R_4N^+]X^-$ where R_1, R_2, R_3, and R_4 are alkyl or aryl groups and X^- represents an anion. The water solubility of quaternaries mainly depends upon the nature of R substituents. Low solubility quaternaries can adsorb on various substrates and impart various useful conditioning effects (e.g., softening, antistat, corrosion inhibition). With the exception of N-alkyltrimethyl ammonium salts, quaternary surfactants usually show poor detergency, wetting, and emulsifying capacities. Quaternaries are generally not compatible with anionics because of the formation of a water-insoluble complex.



Quaternary compound

The major usage of quaternaries is related to their ability to adsorb on natural or synthetic substrates and fibers. They are widely used as softening agents in rinse fabric softeners. Their softening and antistatic properties are similarly exploited in hair conditioning shampoos or after-shampooing rinses. It is worth noting that, in cosmetic applications, quaternaries may cause ocular and local irritation. Among quaternaries, some are used as germicides and disinfectants (e.g., benzalkonium chloride).

Heterocyclic Ammonium Salts. Heterocyclic quaternaries are derived from heterocyclic aliphatic or aromatic compounds in which a nitrogen atom constitutive of the cycle is quaternized.



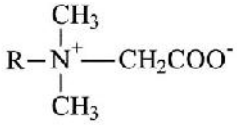
Imidazolinium quaternary compound

The quaternaries derived from imidazoline and morpholine are used as hair conditioners and antistatic agents. Those derived from aromatic heterocycles are used as germicides.

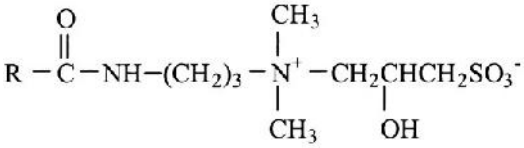
Alkyl Betaines. Alkyl betaines, which are N-trialkyl derivatives of amino acids ($[R_1R_2R_3]N^+CH_2COOH$), are classified as cationics because they exhibit a permanent positive charge. Because they also have a functional group able to carry a negative charge in neutral and alkaline pH conditions, they are often regarded—although this position is questionable—as ''amphoterics.'' The positive charge is always carried by a quaternized nitrogen while the anionic site can be a carboxylate (betaine), a sulfate (sulfobetaine or sultaine), or a phosphate (phosphobetaine or phostaine).

Betaines are good foaming, wetting, and emulsifying surfactants, especially in the presence of anionics. Alkylamido betaines deliver more stable foam and are better viscosifiers than alkyl dimethyl betaines. Betaines are compatible with other surfactants and they frequently form mixed micelles; these mixtures often deliver unique properties that are not found in the individual constitutive surfactants.

Betaines have low eye and skin irritation; moreover, the presence of betaines is known to decrease the irritation effect of anionics.



Alkyl dimethyl betaine

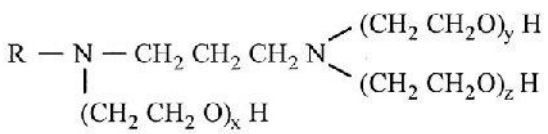


Alkylamidopropyl hydroxysultaine

Because of their ability to improve the skin tolerance against irritating anionic surfactants, and also because of their high price, betaines are usually used in association with other surfactants. Betaines are especially suitable in personal-care applications (e.g., shampoos, foam baths, liquid soaps, shower gels), fabric handwash products, and dishwashing products.

Ethoxylated Alkylamines

These surfactants can be considered as cationic or nonionic depending on the degree of ethoxylation and the pH at which they are used. Polyethoxylated amines are formed by ethoxylation of primary or secondary fatty amines.



$C_{12}H_{25}N\ [(CH_2CH_2O)_3H]_2$

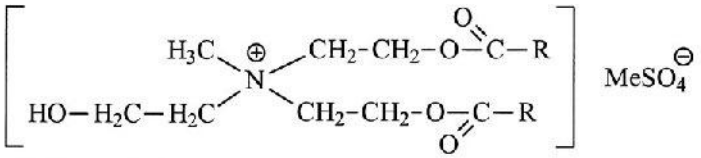
Laurylamine + 6 EO (or POE 6)

Alkyl propanediamine ethoxylate

The ethoxylated alkylamines have various application fields; they are generally exploited for their capacity of adsorbing on surfaces. In personal care, ethoxylated alkylamines are used as emulsifiers and hair-conditioning agents. Ethoxylated amidoamines find applications in rinse fabric softeners.

Esterified Quaternaries

Esterified quaternaries (or esterquats) are produced by the esterification of the hydroxyl group(s) of secondary or tertiary amino-alcohols with selected fatty acids.



Esterquat: N-Methyl-N,N-bis[$C_{16/18}$-acyloxy)ethyl]-N-(2-hydroxyethyl)ammonium-methosulfate salt

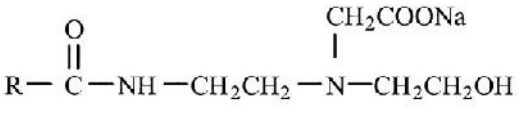
The esterquats are suitable substitutes for straight quaternaries. They present improved environmental profile and comparable softening properties compared with straight quaternaries.

Amphoteric Surfactants

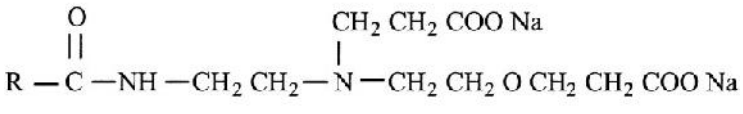
Amphoteric surfactants are characterized by the fact that these surfactants can carry both a positive charge on a cationic site and a negative charge on an anionic site. The use of amphoteric terminology is still more restrictive: the charge of the molecule must change with pH, showing a zwitterionic form at intermediate pH (i.e., around the isoelectric point). The surfactant properties are accordingly influenced by pH: around the isoelectric point the zwitterionic form takes place, exhibiting the lowest solubility; in alkaline conditions the anionic form is predominant, delivering foam and detergency; and in acidic conditions, the cationic form prevails, providing surfactant substantivity. Although betaines are commonly classified among amphoterics, this classification is improper because these surfactants never exhibit in single anionic form. Amphoteric surfactants are generally used as secondary tensioactives for their foam stabilizing effect, their thickening capacity, and their skin-irritation reduction capacity on alkyl sulfates and alkyl ethoxy sulfates.

Acyl Ethylenediamines and Derivatives

These surfactants are made by the reaction of an alkyl imidazoline with chloroacetic acid (yielding amphoglycinates) or with acrylic acid (yielding amphopropionates).



Acylamphoacetate

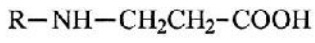


Acylamphodipropionate

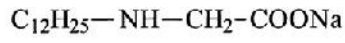
Amphoterics of this class are mainly used in personal products (e.g., coco amphocarboxy glycinate). Incorporated in baby shampoos, they reduce eye irritation. Other applications are fabric softeners, industrial cleaners, and car cleaners.

N-Alkyl Amino Acids or Imino Diacids

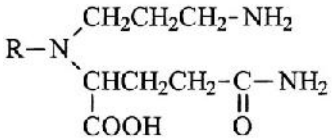
These molecules are chemical derivatives of amino acids that can be produced by the reaction of chloroacetic acid or acrylic acid with an alkylamine. Their compatibility with other surfactants is excellent. These surfactants are good emulsifiers and show optimal wetting and detergency under alkaline pH. They are good foamers at neutral and alkaline pH but lose their foaming properties under acidic conditions. They are substantive to surfaces and provide antistatic effects. They provide skin and eye irritancy reduction in combination with anionics.



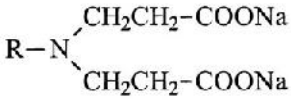
Alkyl aminopropionic acid



Sodium coco glycinate



Aminopropyl alkylglutamide



Sodium alkyliminodipropionate

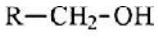
Amphoterics of this class are mainly used in personal products. Polycarboxylates deliver reduced eye irritation and provide hair-conditioning benefits. Their zwitterionic forms are substantive on the hairs.

NONIONIC SURFACTANTS

Nonionic surfactants do not dissociate into ions in aqueous medium. They generally deliver a weak to moderate foam. They are appreciated for their good skin and eye compatibility as well as for their anti-irritant potential when they are combined with anionics in appropriate concentration ratio. Therefore, numerous products for sensitive skin, babies, or the face incorporate nonionics as major surfactants.

Fatty Alcohols

Fatty alcohols are primarily used as a chemical precursor for the production of several other surfactants.



Fatty alcohol

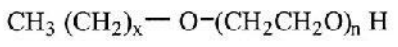
Because they are not water soluble, the use of fatty alcohols is very limited in liquid products. They are mainly used as opacifiers, thickening agents, and foam depressors (e.g., lauric alcohol).

Ethers

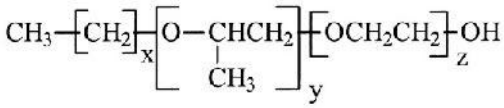
Alkoxylated Alcohols

This class of surfactants mainly covers ethoxylated or propoxylated alcohols. Ethoxylated alcohols (also called ''polyethyleneglycol ethers'' or ''PEG ethers'') are produced from the reaction of fatty alcohols with ethylene oxide (EO). Similarly, propoxylated alcohols (also called ''polypropyleneglycol ethers'' or ''PPG ethers'') are obtained with propylene oxide (PO). The HLB of ethoxylated alcohols can be adjusted by properly balancing the hydrophilic ethoxylated chain and the hydrophobic fatty chain. Ethoxylate nonionics are compatible with all surfactants. Some beneficial associations with ionic surfactants are often shown.

In the frame of personal-care applications, ethoxylated alcohols often result from the transformation of natural lipids. The nomenclature specific to cosmetic chemicals (i.e., INCI names[1]) is applied to these nonionics: they are denominated by using the root of the fatty acid name terminated by the suffix ''eth'' (contraction of ''ethoxylated''), directly followed by the ethoxylation degree (e.g., laureth-4, oleth-5, myristeth-7). As some raw materials yield on hydrolysis various fatty chain lengths, the names of the derived nonionics are either drawn from the natural source (e.g., laneth-16 for a lanolin-derived nonionic) or from the fusion of the constitutive fatty chains (e.g., ceteareth-20 for a combination of cetyl and stearyl).



Alkyl polyethyleneglycol ether or alcohol ethoxylate
(e.g., laureth 20 for x=11 and n=20)



EO/PO Alkyl Ether
(e.g., propyleneglycol capreth-4 for x=9, y=1, and z=4)

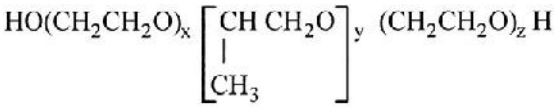
Applications of ethoxylated alcohols are numerous in industrial as well as in household products. When properly selected, alkoxylated alcohols are also useful for personal products as good emulsifiers and solubilizers. The cosmetic applications remain, however, limited because of their rather weak foaming capacity. Because they are prone to undergo degradation by oxidation, the following precautions can greatly improve the stability of

[1] The International Cosmetic Ingredient Dictionary provides a nomenclature of conventional names for cosmetic ingredients that are defined by the CTFA (The Cosmetic, Toiletry, and Fragrance Association).

ethoxylate nonionics: storage in the dark, minimal air contact, low temperature storage, avoiding storage of diluted products, and the addition of an antioxidant.

EO/PO Block Polymers

These polymeric surfactants have some similarity with the previously discussed alkoxylated alcohols. They consist in the combination of the assembly of PPG (hydrophobic part) and PEG chains (hydrophilic part). Such surfactants are known under the denomination ''poloxamers'' (INCI name) and are called EO/PO block copolymer nonionics. A major property of EO/PO nonionics is their low-foaming profile. As straight EO nonionics, EO/PO copolymers exhibit the cloud point phenomena. EO/PO nonionics are also mild surfactants.

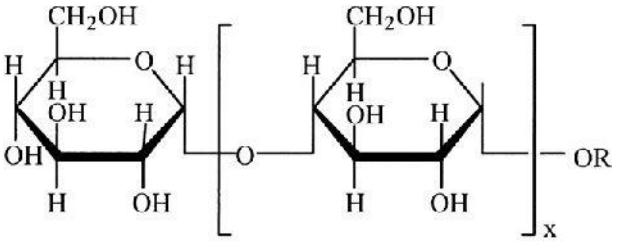


Ethoxylated PPG ether

These surfactants are especially useful for applications in which foaming must be significantly depressed, such as automatic dishwashing detergents, laundry detergents, and rinse aids. Because of their mildness, EO/PO block polymers also find applications in cosmetic products. They are generally used as emulsifying, solubilizing, or fluidizing agents.

Alkyl Polyglucosides

Alkyl polyglucosides are most often known by the simple abbreviation APG. APGs are produced by the alkylation of short-chain glucosides resulting from acidic alcoholysis of polysaccharides such as starch. Commercial products consist of mixtures of mono-, di-, and triglucosides. Accordingly the glucosidic chain varies between 1.2 and 3 depending on the production conditions. Surfactants of this class are good emulsifiers and provide good wetting and foaming profiles. Alkyl polyglucosides are compatible with all other surfactants. They show good chemical stability at neutral and alkaline pH, and are impaired under acidic conditions (pH <5).



Alkylpolyglucoside

APGs are used in detergents and personal-care cleansers (e.g., shampoos). They are claimed to be very mild for skin as well as to reduce the skin irritation potential of anionics. Additionally, they impart an excellent skin feel. Their thickening effect in the presence

of anionics and their foam stabilization capacity are also exploited in personal-care applications.

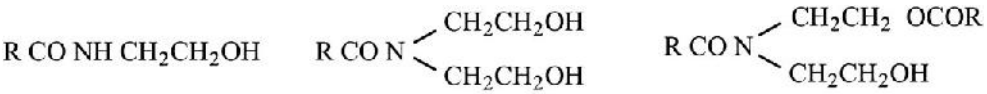
Ethoxylated Oils and Fats

This class of surfactants essentially covers ethoxylated derivatives of lanolin (i.e., aliphatic alcohols and sterols, fractionation products of wool fat) and of castor oil (i.e., fatty acids extracted from ricinus seeds). Ethoxylated products of lanolin and castor oil are good and excellent emulsifiers, respectively. These surfactants are mainly used in the cosmetic industry; their major interest is to offer the possibility of claims based on the natural origin of the constitutive surfactant systems.

Alkanolamides

Straight Alkanolamides

Alkanolamides are N-acyl derivatives of monoethanolamine and diethanolamine.



Monoalkanolamide Dialkanol amide Ester amide

Alkanolamides have been largely used in household detergent products; their consumption has now significantly declined because of the extensive use of alkyl ethoxylated detergent products. Because of their foam-boosting and viscosity-enhancing capacity in the presence of anionics, alkanolamides are also usefully incorporated in personal care, especially in shampoos.

Ethoxylated Alkanolamides

Reaction of an alkanolamide with ethylene oxide leads to an ethoxylated amide.

Polyethoxylated monoalkanolamide

It is more expensive than its corresponding ethoxylated alcohol and has therefore restricted usage. The benefits of thickening, foam stabilization, and dispersibility are exploited in personal-care cleansers.

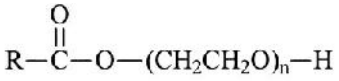
Esters

In this surfactant class, there are five major subcategories to be considered:

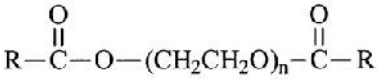
1. Ethoxylated fatty acids
2. Glycol esters, glycerol esters, and ethoxylated derivatives
3. Sorbitan esters and ethoxylated derivatives
4. Alkyl carbohydrates esters
5. Triesters of phosphoric acid

Ethoxylated Fatty Acids

This class of surfactants comprises mono- and diesters that result from the reaction of fatty acids with either ethylene oxide or polyethylene glycol.



PEG fatty acid ester



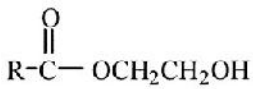
PEG fatty acid diester

Given their outstanding emulsifying properties, ethoxylated fatty acids are useful in domestic and industrial detergents, more especially in degreasing compositions. If properly balanced, combinations of esters with low and high ethoxylation provide excellent emulsifiers for creams and lotions. They are also used as mild cleaners or viscosifying agents (e.g., PEG-150-distearate). In cosmetics (shampoos), less water-soluble grade (i.e., ethylene glycol monostearate) is used as a pearlescent agent.

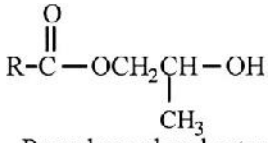
Glycol Esters, Glycerol Esters, and Ethoxylated Derivatives

A common point among the surfactants grouped in this class and the following two classes (sorbitan esters and alkyl carbohydrates esters) is that they all derive from the condensation reaction of a polyhydroxyl compound (e.g., glycol, glycerol, sorbitol, sucrose,) with a fatty acid. Some of them can be directly extracted from natural sources. The resulting esters can be additionally ethoxylated to increase their HLB value and, thereby, their solubility in water.

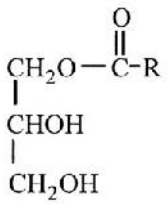
These surfactants show poorer wetting and foaming properties in comparison with alcohol-derived nonionics. Emulsifying properties are excellent. In general, esters and lower ethoxylates are appropriate for w/o dispersions whereas higher ethoxylates are more suitable emulsifiers for o/w dispersions.



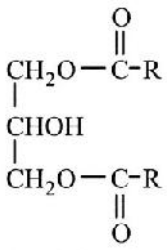
Ethylene glycol ester



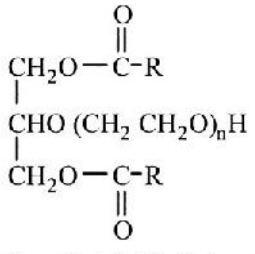
Propylene glycol ester



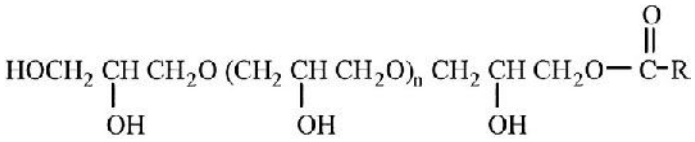
Monoglyceride



1,3-diglyceride



Polyethoxylated 1,3-diglyceride



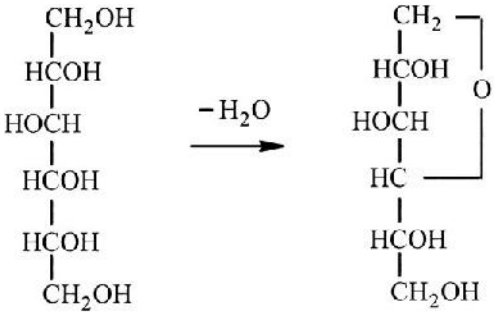
Polyglyceryl monoester

Because of their high compatibility, these surfactants are widely used in the cosmetic and food industry.

Glycol and glycerol esters are used in the pharmaceutical and cosmetic industries either as emulsifying agents or as oily compounds, refatting agents, emollients, and skin conditioners in various products such as creams, lotions, ointments, and gels. Stearate derivatives also deliver thickening and opacifying properties (e.g., the glyceryl stearate). Some are also used as pearlescent agents (i.e., glycol stearate and distearate). Ethoxylated derivatives are used as solubilizing agents, emulsifiers, and even as emollients. Some show effective thickening effect when combined with other surfactants (e.g., PEG-200 glyceryl stearate).

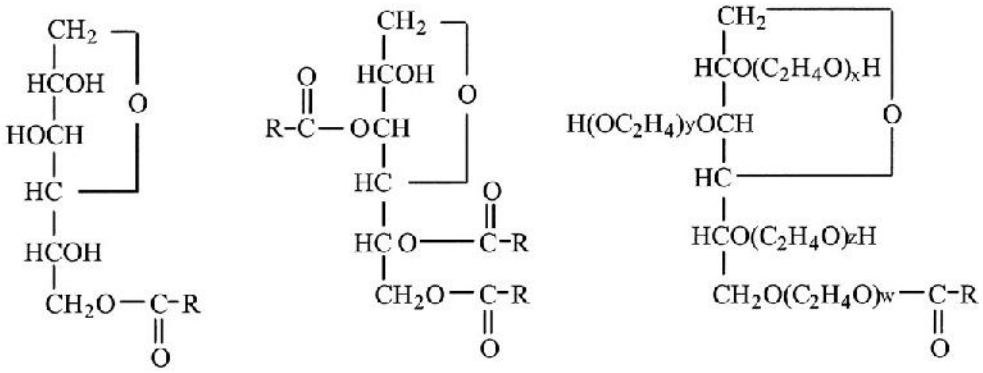
Sorbitan and Sorbitol Esters and Ethoxylated Derivatives

Sorbitan molecule is generated from the dehydration of the sorbitol molecule, which results in an internal ether bond.



Sorbitol 1, 4 Sorbitan

Sorbitol and sorbitan esters are obtained by acylation of hydroxyl groups, using most frequently natural fatty acids such as lauric, palmitic, stearic, or oleic. These surfactants can be optionally ethoxylated. Acylation (or ethoxylation) can occur on almost all hydroxyl groups present in the original polyol molecule.

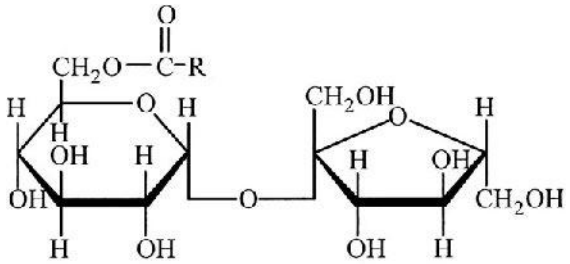


1, 4 Sorbitan monoester 1, 4 Sorbitan triester Polyethoxylated sorbitan

The field of application of sorbitan esters and their ethoxylated derivatives is identical to the one of glycol and glycerol esters (see previous section). The sorbitol esters with a higher degree of ethoxylation (e.g., sorbitol septaoleate 40 EO) are also used as spreading aids in emollient bath oils.

Alkyl Carbohydrates Esters

Surfactants of this class are better known as ''sugar esters'' or ''sucrose esters.'' The sucrose esters are obtained by transesterification of sucrose with fatty acid methyl esters or triglycerides. Surfactants of this class are good emulsifiers. Of great interest about such surfactants is their natural origin and good biodegradability. It is worth noting that some glucosides surfactants, e.g., the so-called saponins, are already present in nature and directly available from vegetal sources.

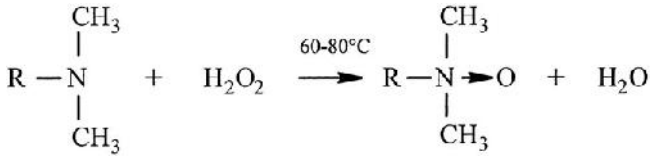


Saccharose fatty acid monoester

Sucrose esters are food-grade ingredients and have similar uses as the previously described glycol, glycerol, and sorbitan esters in the food and cosmetic industries. They are very mild surfactants and can be used as emulsifiers or as cleansing agents with emollient properties.

Amine Oxides

Amine oxides are produced by the oxidation of tertiary amines using a 35% hydrogen peroxide solution as the oxidizing agent. Amine oxides remain mainly nonionic in neutral and alkaline conditions (pH >7) but can become weakly cationic under acidic conditions. In current amine oxides, the initial reactives are alkyl dimethyl amines with chain lengths ranging from C_{12} to C_{18}. Amine oxides are compatible with all other surfactants. Amine oxides are also known to increase the skin compatibility of detergent products. A small amount of amine oxide increases the cloud point of nonionics.

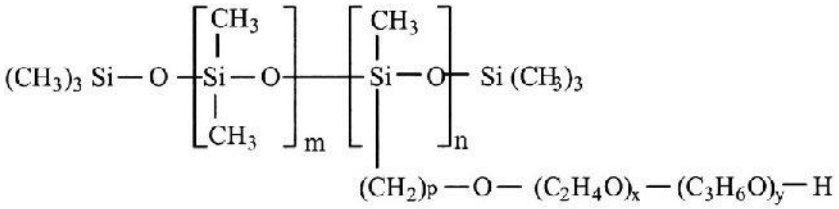


Incorporated in shampoos, amine oxides contribute to impart viscosity, reduce eye and skin irritancy, and enhance foam properties (more creamy). They are especially suitable in slightly acidic or neutral formulas.

NONHYDROCARBON SPECIALTY SURFACTANTS

Alkoxylated Polysiloxanes

Surfactants, which can be classified in the chemical group of organosilicones, are structurally derived from polydimethylsiloxanes in which some methyl are replaced by hydrophilic groups that can be of anionic, cationic, or nonionic nature. The nonionic derivatives are mostly represented by the polyether-polydimethylsiloxane-copolymers. The general structure of these surfactants is shown in structure 37. The hydrophilic chain(s) generally contain EO/PO block copolymers.



Polysiloxane-Polyether Copolymer (p generally equals 0 or 3)

These surfactants are specialty ingredients and are used in very different fields (e.g., painting, foam control, phytosanitary products). They are also used in cosmetics and haircare:

1. in cosmetic or personal-care products as emulsifiers in, e.g., protective creams, hydrating body milks, liquid soaps, and shave creams, and
2. in haircare products (e.g., shampoos, conditioners, gels, lotions, foams) to act as combing out auxiliaries, to reduce the irritancy of surfactant system, to provide improved skin feel, or to control the foam. The CTFA-adopted name of these surfactants is *Dimethicone Copolyol.*

Fluorosurfactants

Fluorosurfactants form a distinct group of surfactants besides the conventional surfactants based on hydrocarbon chains. Fluorosurfactants differ from hydrocarbon surfactants by the hydrophobic moiety of the molecule, which is made of perfluoroalkyls chains F—$(CF_2\text{-}CF_2)_n$-, in which n ranges from about 3 to about 8. Similarly to conventional surfactants, a rather broad variety of hydrophilic functions (e.g., ethoxylated chains, sulfonates, quaternaries, betaines) can be borne by fluorosurfactants. Depending on their nature, these surfactants show variable emulsifying and foaming characteristics. Although fluorosurfactants have some potential prospects in personal care (e.g., improved hair conditioning), we are not aware of any significant application in this field. We can, however, report their use in barrier creams that require good spreading and stable o/w emulsions.

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UV Filters

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INTRODUCTION

The presence of ultraviolet (UV) filters in skincare and cosmetic products represents a key benefit that cosmetics can provide consumers. The hazards of UV light exposure are well known. It is estimated that the incidence of nonmelanoma skin cancer in the United States exceeds one million cases per year [1]; UV-induced or photoaging accounts for 80% to 90% of visible skin aging [2]. UV radiation damages the skin by both direct effects on DNA and indirectly on the skin's immune system [3].

In animal models, sunscreens prevent the formation of squamous cell carcinomas of the skin [4]. The regular use of sunscreens has been shown to reduce the number of actinic or precancerous keratosis [5] and solar elastosis [6]. Sunscreens also prevent immunosuppression [7]. Double-blind photoaging studies show consistent improvement in the ''untreated'' control groups partly because of the use of sunscreens by all study subjects [8].

The cosmetic formulator has an expanding menu of active sunscreen ingredients for incorporation into a variety of cosmetic formulations. Selection is restricted by regulatory agencies in the country in which the final product is to be marketed. This chapter will concentrate on reviewing available UV filters.

DEFINITIONS

Ultraviolet radiation (UVR) reaching the Earth's surface can be divided into UVB (290–320 nm) and UVA (320–400 nm). UVA can be further subdivided into UVA I (340–400 nm), or far UVA, and UVA II (320–340 nm), or near UVA.

The sun protection factor (SPF) is defined as the dose of UVR required to produce one minimal erythema dose (MED) on protected skin after application of 2 mg/cm^2 of product divided by the UVR to produce one MED on unprotected skin. A water-resistant product maintains the SPF level after 40 minutes of water immersion. A very water-resistant or waterproof product is tested after 80 minutes of water immersion. If the SPF level is diminished by immersion, a separate SPF level may be listed. A broad-spectrum or full-spectrum sunscreen provides both UVB and UVA protection. Ideally this includes both UVA I and UVA II coverage.

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HISTORY

Two UV filters, benzyl salicylate and benzyl cinnamate, were first incorporated into a commercially available sunscreen emulsion in the United States in 1928 [9]. In the early 1930s, phenyl salicylate (Salol) was used in an Australian product [10]. Para-aminobenzoic acid (PABA) was patented in 1943, leading to the development of PABA derivative UV filters. During World War II, red veterinary petrolatum (RVP) was used by the U.S. military, encouraging the development of further UV filters in the postwar period.

In the 1970s, increased interest in commercial sunscreen products led to refinements and consumer acceptance of these products over the next two decades. Facilitated by growing awareness of the hazards of UVR, higher SPF products became the norm. Daily-use consumer products containing UV filters, including moisturizers, color cosmetics, and even haircare products, have become more prevalent in the past decade. Concerns related to the adequacy of sunscreen protection for the prevention of melanoma and photoaging in the last few years has led to greater interest in broad-spectrum sunscreen UV protection throughout the entire UVA range.

REGULATIONS

United States

Sunscreen products in the United States are regulated by the FDA as over-the-counter drugs. The Final Monograph for Sunscreen Drug Products for Over-the-Counter Human Use was recently issued (64 Fed. Reg. 1999: 64: 27,666–27,693), establishing the conditions for safety, efficacy, and labeling of these products. The number of allowable sunscreen ingredients has been reduced (Table 1), reflecting the lack of interest in some of the ingredients in previously issued tentative monographs. Avobenzone and zinc oxide have been added, expanding the available UVA I blockers. Minimum concentration re-

TABLE 1 FDA Sunscreen Final Monograph Ingredients

Drug name	Concentration (%)	Absorbance
Aminobenzoic acid	Up to 15	UVB
Avobenzone	2–3	UVA I
Cinoxate	Up to 3	UVB
Dioxybenzone	Up to 3	UVB, UVA II
Homosalate	Up to 15	UVB
Menthyl anthranilate	Up to 5	UVA II
Octocrylene	Up to 10	UVB
Octinoxate	Up to 7.5	UVB
Octisalate	Up to 5	UVB
Oxybenzone	Up to 6	UVB, UVA II
Padimate O	Up to 8	UVB
Phenylbenzimidazole sulfonic acid	Up to 4	UVB
Sulisobenzone	Up to 10	UVB, UVA II
Titanium dioxide	2 to 25	Physical
Trolamine salicylate	Up to 12	UVB
Zinc oxide	2 to 20	Physical

quirements have been dropped, providing that the concentration of each active ingredient is sufficient to contribute a minimum SPF of not less than 2 to a finished product. A sunscreen product must have a minimum SPF of not less than the number of active sunscreen ingredients used in combination multiplied by 2. Products with SPF values above 30 are allowed, but the SPF declaration for sunscreens with SPF values above 30 are limited to SPF 30 plus. The term ''sunblock'' is now prohibited. It was previously allowed for products that contained titanium dioxide. Consideration of labeling and testing procedures for UVA protection was deferred and will be addressed in the future.

Europe

In Europe, sunscreen products are considered to be cosmetics, their function being to protect the skin from sunburn. The Third Amendment of the European Economic Community (EEC) Directive provides a definition and lists the UV filters that cosmetic products may contain. This list is divided into two parts. Table 2 lists UV filters that are fully permitted updated through the 23rd commission directive of September 3, 1998. Table 3 currently lists the three UV filters that are provisionally permitted through June 30, 1999. The numbers referenced with ''S'' indicate COLIPA numbers (The European Toiletry and Perfumery Association). Unlike the U.S. FDA Monograph, the EEC Directive does not list physical UV filters despite their being used in products to enhance protection.

Australia

In 1992, sunscreens were declared to be drugs in Australia. The latest edition of Australian Standard 2604 was published in 1993 as a joint publication of Australia and New Zealand. Sunscreen products are classified as either primary or secondary, depending on whether the primary function of the designated product is to protect from UVR as opposed to a product with a primary cosmetic purpose. SPF designations greater than 15 are not permitted (SPF 15+ represents the maximum designation). In general, Australian Approved Names (AAN) for allowed active sunscreen ingredients are the same as FDA drug nomenclature with few differences.

Other Countries

Most non-EEC European countries follow the EEC Directive. Many other countries follow U.S. trends with their own provisions. In Japan, sunscreens are classified as cosmetics. Regulations for each individual country need to be consulted for selection of the various UV filters for incorporation into a sunscreen product to be marketed in a given jurisdiction.

MECHANISM OF ACTION

UV filters have been traditionally divided into chemical absorber and physical blockers based on their mechanism of action. Chemical sunscreens are generally aromatic compounds conjugated with a carbonyl group [11]. These chemicals absorb high-intensity UV rays with excitation to a higher energy state. The energy lost results in conversion of the remaining energy into longer lower-energy wavelengths with return to ground state. The evolution of modern sunscreen chemicals represents a prototype study in the use of struc-

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TABLE 2 UV Filters That Cosmetic Products May Contain (EEC Directive Annex VII—Part 2)

COLIPA number	Ref. number	Substance	Maximum authorized concentration
S 1	1	4-Aminobenzoic acid	5%
S 57	2	N,N,N-Trimethyl-4-(2-oxoborn-3-ylidenemethyl) anilinium methyl sulphate	6%
S 12	3	Homosalate (INN)	10%
S 38	4	Oxybenzone (INN)	10%
S 45	6	2-Phenylbenzimidazole-5-sulphonic acid and its potassium, sodium, and triethanolamine salts	8% (expressed as acid)
S 71	7	3,3′-(1,4-Phenylenedimethylene)bis[7,7-dimethyl-2-oxo-bicyclo-(2,2,1)hept-1-ylmethanesulphonic acid] and its salts	10% (expressed as acid)
S 66	8	1-(4-Tert-butylphenyl)-3-(4-methoxyphenyl) propane-1,3-dione	5%
S 59	9	Alpha-(2-oxoborn-3-ylidene)toluene-4-sulphonic acid and its salts	10% (expressed as acid)
S 32	10	2-Cyano-3,3-diphenyl acrylic acid, 2-ethylnexyl ester (octocrylene)	10% (expressed as acid)
S 72	11	Polymer of N-(2 and 4)-[(2-oxoborn-3-ylidene)methyl] benzyl acrylamide	6%
S 28	12	Octyl methoxycinnamate	10%
S 3	13	Ethoxylated ethyl-4-aminobenzoate (PEG-25 PABA)	10%
S 27	14	Isopentyl-4-methoxycinnamate (isoamyl p-methoxycinnamate)	10%
S 69	15	2,4,6-Trianilino-(p-carbo-2′-ethylhexyl-1′-oxy)-1,3,5-triazine (octyl triazone)	5%
S 73	16	Phenol,2-(2H-benzotriazol-2-yl)-4-methyl-6-(2-methyl-3-(1,3,3,3-tetramethyl-1-(trimethylsilyl)oxy)-disiloxanyl)propyl (drometrizone trisiloxane)	15%
S 78	17	Benzoic acid, 4,4′-((6-(((1,1-dimethylethyl aminocarbonyl)phenyl)amino)-1,3,5,triazine-2,4-diyl)diimino)bis-bis(2-ethylhexyl)ester	10%
S 60	18	3-(4′-Methylbenzylidene)-d-t camphor (4-methylbenzylidene camphor)	2%
S 61	19	3-Benzylidene camphor (3-benzylidene camphor)	2%
S 8	20	2-Ethylhexyl salicylate (octyl-salicylate)	5%

ture-activity relationships to design new active ingredients and has been well reviewed elsewhere [12].

Physical blockers reflect or scatter UVR. Recent research indicates that the newer microsized forms of physical blockers may also function in part by absorption [13]. Sometimes referred to as nonchemical sunscreens, they may be more appropriately designated as inorganic particulate sunscreen ingredients.

TABLE 3 UV Filters That Cosmetic Products May Provisionally Contain (Annex VII—Part 2)

COLIPA number	Ref. number	Substance	Maximum authorized concentration
S 8	5	2-Ethylhexyl-4-dimethyl-aminobenzoate	8%
S 40	17	2-Hydroxy-4-methoxybenzo-phenone-5-sulphonic acid and sodium salt (sulisobenzone and sulisobenzone sodium)	5% (expressed as acid)
S 16	29	4-Isoprypylbenzyl salicylate	4%

NOMENCLATURE

Sunscreen nomenclature can be quite confusing. They may be referred to by their chemical or trade name. In the United States, individual sunscreen ingredients are also assigned a drug name by the OTC Monograph. Annex VII of the European Union (EU) may use either a drug or chemical name. Australia has its own approved list of names (AAN). Table 4 lists the most commonly used names, including their primary listing in the International Cosmetic Ingredient Dictionary (INCI designation) [14].

INDIVIDUAL UV FILTERS

Sunscreen ingredients may be considered by dividing them into larger overall classes by chemical structure. They may also be classified by their absorption spectrum. Although the lists of UV filters approved by the various regulatory agencies may seem quite extensive, fewer are used with any degree of frequency. The discussion that follows will concentrate on those listed in Table 4.

UVB

PABA and Its Derivatives

Para-aminobenzoic acid, or PABA, was one of the first sunscreen chemicals to be widely available. Several problems limited its use. It is very water-soluble, was frequently used in alcohol vehicles, stained clothing, and was associated with a number of adverse reactions. Ester derivatives of PABA, mainly octyl dimethyl PABA or Padimate O, became more popular with greater compatibility in a variety of more substantive vehicles and a lower potential for staining or adverse reactions. Amyl dimethyl PABA or Padimate A is associated with facial stinging [15]. Glyceryl PABA (glyceryl aminobenzoate) is still permitted in the FDA monograph but is no longer available. Octyl dimethyl PABA is a most potent UV absorber in the mid-UVB range. Because of problems with PABA formulations, marketers have emphasized the ''PABA-free'' claim. Although still widely used [16], it is confused with PABA, limiting its use. The decline in the use of this PABA derivative, along with the demand for higher SPF products, has led to the incorporation of multiple active ingredients in a single product to achieve the desired SPF.

Cinnamates

The next most potent UVB absorbers, the cinnamates have largely replaced PABA derivatives. Octinoxate, or octyl methoxycinnamate, is the most frequently used sunscreen ingre-

TABLE 4 Sunscreen Nomenclature

CAS no.	Drug name (FDA)	INCI name	COLIPA no.	EU reference no.	Trade names	Solubility	Spectrum
150-13-0	Para-aminobenzoic acid	PABA	S 1	1	4-Aminobenzoic acid	Hydrophilic	UVB
70356-09-1	Avobenzone	Butyl methoxydibenzyl methane	S 66	8	Parsol 1789	Lipophilic	UVA I
104-28-9	Cinoxate	Cinoxate				lipophilic	UVB
118-56-9	Homosalate	Homosalate	S 12	3	Eusolex HMS	Lipophilic	UVB
134-09-8	Menthyl anthranilate	Menthyl anthranilate			Dermoblock MA, Neo Heliopan, Type MA	Lipophilic	UVA II
6197-30-4	Octocrylene	Octocrylene	S 32	10	Escalol 597, Eusolex OCR, Uvinul N-539-50	Lipophilic	UVB
5466-77-3	Octinoxate	Octyl methoxycinnamate	S 28	12	Neo Heliopan AV, Parsol MCX, Eusolex 2292	Lipophilic	UVB
88122-99-0	Octyl triazone	Octyl triazone	S 69	15	Uvinul T-150	Lipophilic	UVB
118-60-5	Octisalate	Octyl salicylate	S 20	8	Escalol 587, Eusolex BS, Uvinul O-18	Lipophilic	UVB
131-57-7	Oxybenzone	Benzophenone-3	S 38	4	Eusolex 4360, Neo Heliopan, Uvinul M40	Lipophilic	UVB, UVA II
21245-02-03	Padimate O	Octyl dimethyl PABA	S 78	17	Escalol 507, Eusolex 6007	Lipophilic	UVB
27503-81-7	Phenylbenzimidazole sulfonic acid	Phenylbenzimidazole sulfonic acid	S 45	6	Eusolex 232, Neo Heliopan Hydro	Hydrophilic	UVB
4065-45-6	Sulisobenzone	Benzophenone-4	S 78	17	Escalol 577, Uvinul MS 40	Lipophilic	UVB, UVA II

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dient [16]. Octyl or ethylhexyl methoxycinnamate is an order of magnitude less potent than Padimate O and requires additional UVB absorbers to achieve higher SPF levels in a final product. Cinoxate (Ethoxy-ethyl-p-methoxycinnamate) is less widely used. When a water-soluble cinnamate is indicated in a formulation, diethanolamine (DEA) methoxycinnamate may be used.

Salicylates

Salicylates are weaker UVB absorbers. They have a long history of use but were supplanted by the more efficient PABA and cinnamate derivatives. They are generally used to augment other UVB absorbers. With the trend to higher SPFs, more octyl salicylate (ethylhexyl salicylate) is being used followed by homomenthyl salicylate. Both materials have the ability to solubilize oxybenzone and avobenzone. Trolamine or triethanolamine (TEA) salicylate has good water solubility.

Camphor Derivatives

Not approved by the FDA for use in the United States, there are six camphor derivatives approved in Europe. 4-methyl-benbenzylidene camphor is the most widely used.

Octocrylene

2-Ethylhexyl-2-cyano-3,3 diphenylacrylate, or octocrylene, is chemically related to cinnamates. It can be used to boost SPF and improve water resistance in a given formulation. Octocrylene is photostabile and can improve the photostability of other sunscreens. It is very expensive and can present difficulties in formulation.

Phenylbenzimidazole Sulfonic Acid

Phenylbenzimadazole sulfonic acid is a water-soluble UVB absorber that can be used in the water phase of emulsion systems, in contrast to most oil-soluble sunscreen ingredients, allowing for a less greasy, more aesthetically pleasing formulation, such as a daily-use moisturizer containing sunscreen. Phenylbenzimidazole sulfonic acid boosts the SPF of organic and inorganic sunscreens. It can also be used in clear gels because of its water solubility.

UVA

Benzophenones

Although oxybenzone or benzophenone-3 absorbs most efficiently in the UVB range, absorption extends well into the UVA II range. It is used primarily as a UVA absorber, but boosts SPF values in combination with other UVB absorbers. Oxybenzone is supplied as a solid material, has poor solubility, and has a relatively low extinction coefficient. Sulisobenzone or benzophenone-4 is water-soluble, somewhat unstable, and used with less frequency.

Menthyl Anthranilate

Anthranilates are weak UVB filters and absorb mainly in the near UVA portion of the spectrum. They are less effective than benzophenones in this range and are less widely used.

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Butylmethoxydibenzoylmethane

Avobenzone, or Parsol 1789, has only recently been approved by the FDA for use in OTC sunscreens in the United States, having been used quite extensively in Europe for considerably longer. It provides strong absorption in the UVA I range with peak absorption at 360 nm. Because an agreed-upon standard for measuring UVA protection in the United States does not exist, a minimum-use concentration has been set at 2% with a maximum of 3%.

Avobenzone should not be confused with isopropyl dibenzoylmethane (Eusolex 8020), which had previously been available in Europe. The high incidence of adverse photosensitivity reported with the combination of isopropyldibenzoylmethane and methylbenzylidene camphor by coupled reactions in the late 1980s led to a decrease in its use in commercial [17]. In 1993 its production was discontinued and it is no longer listed in Annex VII. Reported sensitivity to butylmethoxydibenzoylmethane was on the basis of cross-reactivity to isopropyl dibenzoylmethane. Isolated allergy to butylmethoxydibenzoylmethane is rare [17].

Photostability refers to the ability of a molecule to remain intact with irradiation. Photostability is potentially a problem with all UV filters. This issue has been raised specifically with avobenzone [18], with photolysis shown in a specially designed in vitro system [19] that simultaneously irradiates and measures transmittance in situ. This effect may degrade other sunscreens in a formulation. The relevance of this testing to the in vivo situation remains unclear. Overall formulation may be critical in this regard.

Tetraphthalydine Dicamphor Sulfonic Acid

3,3′-(1,4-phenylenedimethylene)bis[7,7-dimethyl-2-oxo-bicyclo-(2,2,1)hept-1-yl]methanesulfonic acid (EU Ref. No. 7) or Mexoryl SX is a UVA blocker more recently available in Europe with comparable efficacy to avobenzone [20].

Physical Blockers

Some of the original sunblocks were opaque formulations reflecting or scattering UVR. Color cosmetics containing a variety of inorganic pigments function in this fashion. Titanium dioxide and zinc oxide are chemically inert and protect through the full spectrum of UVR. They offer significant advantages. Poor cosmetic acceptance limited the widespread use of these two ingredients until recently, when microsized forms have become available. By decreasing particle size of these materials to a microsize or ultrafine grade it is less visible on the skin surface.

Micropigmentary sunblocks function differently than opaque sunblocks of pigmented color cosmetics by absorbing and not simply reflecting or scattering UVR [13]. By varying and mixing particle sizes, differing levels of photoprotection are achieved throughout the UV spectrum. In addition to avobenzone, micropigmentary TiO_2 and ZnO offer the best available protection in the UVA II range.

Photoreactivity has been raised as an issue with these materials. Both TiO_2 and ZnO are semiconductors potentially absorbing light and generating reactive species [21]. These effects have been shown in vitro [22]. Coating these materials reduces their photochemical reactivity. The in vivo relevance of these effects has not been shown and both materials have a long history of safe use.

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Titanium Dioxide

TiO_2 was the first micropigment extensively used. Advantages include a broad spectrum of protection and inability to cause contact dermatitis. The use of rutile as opposed to anatase crystal forms of titanium dioxide lessens photoactivity. Newer materials are amphiphilic, designed to be dispersed in both water- and oil-emulsion phases. Particle size and uniformity of dispersion is key to achieving SPF. Primary particle size may be 10 to 15 nm with secondary particle assembly to 100 nm. Particle size needs to be less than 200 nm to achieve transparency.

Despite advances in the technology and understanding of these materials, whitening remains a problem secondary to pigment residue. Adding other pigments simulating fleshtones may partially camouflage this effect. The net effect may be that the user is inclined to make a less heavy application of product, effectively lowering SPF [23]. ''Hybrid'' formulations using a combination of chemical absorbers with inorganic particulates may represent a practical compromise.

Zinc Oxide

Zinc oxide was only recently approved as an active sunscreen agent for the FDA OTC Sunscreen Monograph. Reduced to a particle size of less than 200 nm, light scattering is minimized and the particles appear transparent in thin films [24]. ZnO has a refractive index of 1.9, as opposed to 2.6 for TiO_2, and therefore causes less whitening than TiO_2. ZnO may attenuate UVR more effectively in the UVA I range [25]. Microfine TiO_2 at an equal concentration offers somewhat more protection in the UVB range.

ADVERSE REACTIONS—TOXICITY

In a longitudinal prospective study of 603 subjects applying daily either an SPF 15+ broad-spectrum sunscreen containing octyl methoxycinnamate and avobenzone or a vehicle cream, 19% developed an adverse reaction [26]. Interestingly, the rates of reaction to both the active and vehicle creams were similar, emphasizing the importance of excipient ingredients in the vehicle. The majority of reactions were irritant in nature. Not surprisingly, a disproportionate 50% of the reacting subjects were atopic. Less than 10% of the reactions were allergic, with none of the subjects patch tested actually found to be allergic to an individual sunscreen ingredient.

Subjective irritation associated with burning or stinging without objective erythema from some organic UV filters [27] is the most frequent sensitivity complaint associated with sunscreen use. This is most frequently experienced in the eye area. Longer lasting objective irritant contact dermatitis may be difficult to distinguish from true allergic contact dermatitis. In a postmarket evaluation of sunscreen sensitivity complaints in 57 patients, 20 of the patients had short-lasting symptoms, 26 long-lasting, and 11 mixed or borderline symptoms [28]. Half of the patients were patch and photopatch tested, and only three showed positive reactions to sunscreen ingredients.

Contact and photocontact sensitivity to individual sunscreen ingredients has been extensively reviewed [17]. Considering their widespread use, the number of documented allergic reactions is not high [29]. PABA and PABA esters accounted for many of the early reported reactions, but with a decrease in their use reactions to benzophenones may be increasing [30]. Reactions to dibenzoylmethanes have previously been discussed. Fra-

grances, preservatives, and other excipients account for a large number of the allergic reactions seen [17].

Virtually all sunscreen ingredients reported to cause contact allergy may be photoallergens [31]. Although still relatively uncommon, sunscreen actives seem to have become the leading cause of photocontact allergic reactions [32,33]. Individuals with pre-existing eczematous conditions have a significant predisposition to sensitization associated with their impaired cutaneous barrier. The majority of individuals who develop photocontact dermatitis to sunscreens are patients with photodermatides [17].

CONCLUSION

A limited menu of UV filters for incorporation into sunscreen products is available to the formulating chemist, depending on regulatory requirements in an individual country or jurisdiction. With the demand for higher SPFs, the trend has been to use more individual and a wider variety of agents in newer products. Recent research in sunscreen efficacy has emphasized the need for products protecting against the full UV spectrum with a limited number of available agents. Regulatory agencies are very slow to approve new ingredients.

Sunscreen efficacy remains very dependent on vehicle formulation. Solvents and emollients can have a profound effect on the strength of UV absorbance by the active ingredients and at which wavelengths they absorb [34]. Film formers and emulsifiers determine the uniformity and thickness of the film formed on the skin surface, which in turn determines SPF level, durability, and water resistance [35]. Lastly, product aesthetics play a large role in product acceptance, particularly with sunscreens being incorporated into daily-use cosmetics. These constraints provide the sunscreen formulator with significant challenges in developing new and improved formulations.

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Vitamins

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INTRODUCTION

Vitamins consist of a mixed group of chemical substances that all occur in nature. Different from most other cosmetic ingredients, they are essential nutrients playing key roles in the metabolism of all human organs, including the largest human organ, the skin. The skin is often the first indicator of a dietary deficiency in one or more vitamins.

Laboratory and clinical studies have shown beneficial effects to the skin for some of the 13 vitamins when topically applied. This scientific evidence is the platform for the incorporation of this substance group in all kinds of cosmetic products.

The most widely used vitamins in cosmetics and toiletries are vitamin A, vitamin E, vitamin C, and panthenol (provitamin B_5). Vitamin E and vitamin C are antioxidants. They neutralize unstable oxygen molecules, the free radicals, thereby preventing the damage these highly reactive substances can cause to the skin. Vitamin A has shown to be effective in preventing, retarding, and restoring changes associated with the aging process, such as dry and scaly skin, photodamage, and the formation of wrinkles. Panthenol is incorporated into skin- hair- lip- and nailcare products mainly for its moisturizing property. In addition, panthenol has wound-healing and anti-inflammatory properties. Although not cosmetic properties, these are welcome side effects, in particular when cosmetics are applied to slightly damaged skin.

VITAMIN E

More than other tissues, the skin is exposed to various aggressive effects of the environment. Chemical and physical agents, such as ultraviolet (UV) light, ozone, heavy metals, and many others, cause permanent stress to the outermost cell layers of the skin. In particular, regular and excessive exposure to UV light induces damage and disease in the tissue. The skin becomes wrinkled, appears older, the immune system is weakened, and, more seriously, skin cancer can develop.

Up to 20% of the solar UVB impinging on the skin reaches the viable cells of the epidermis, and about 10% penetrates to the dermis [1]. An even higher portion of UVA and visible light can reach the dermis. The interaction of UV light with various skin components results in the formation of free radicals.

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The skin has enzymatic and nonenzymatic antioxidant systems. These work to prevent the formation of free radicals, which can harm the integrity of the cell structures and with it the normal function of the skin. One nonenzymatic antioxidant is vitamin E.

Chemically, vitamin E (tocopherol) (Fig. 1) is a chromanol derivative. It consists of two functional units, a chromane ring bearing a phenolic OH group and a branched side chain. The hydrocarbon chain is necessary for the proper orientation of tocopherol at its site of activity, whereas the chromanol part provides the antioxidant properties.

Vitamin E has a protector function. It is considered to be essential for the stabilization of biological membranes, particularly those containing large amounts of polyunsaturated fatty acids. Cell membrane lipids in the skin are under constant attack from free radicals formed both in the course of normal biological reactions as well as, in particular, by various external factors. Free radicals can take electrons from membrane lipids, which leads to the impairment of the membranes on one side. On the other side, new free radicals are then formed that continue the destructive work.

Vitamin E is considered the major free-radical chain-breaking antioxidant in membranes. It inactivates peroxyl radicals in the vicinity of the membranes and thus inhibits the propagation of lipid peroxidation. Vitamin E loses thereby its antioxidant power and itself becomes a low-energy radical. This tocopheryl radical is, however, unable to attack other molecules and thus initiate a new free-radical chain reaction. In a next step, the tocopheryl radical gets back its antioxidant properties: it is regenerated by a redox system to the active tocopherol.

Although lost antioxidants are continuously replaced and regenerated, oxidative stress, such as excessive exposure to UV light, can overwhelm the natural cutaneous antioxidant capacity and harm the insufficiently protected tissue. A great number of studies performed during the past 15 to 20 years deal with this problem, and some of them with the role of vitamin E in this process. Investigations include studies on the consequences of low levels of vitamin E in the skin, the influence of external factors on vitamin E concentration, and the possible use of topical vitamin E in the form of tocopherol or its ester vitamin E acetate to reduce or even prevent possible damage to the skin.

In an animal study by Igarashi, low levels of vitamin E increased lipid peroxide levels. Rats deficient in vitamin E showed significantly higher peroxide concentrations than normal animals. UV irradiation of the deficient animals led to a further significant increase [2]. Khettab applied vitamin E to the skin of hairless mice before UV irradiation and observed a reduction in epidermal lipid peroxidation compared with control [3].

Kondo examined the protective effect of vitamin E on UVB damage in human skin fibroblasts in vitro. He found a significant difference in surviving fibroblasts in the presence of 100 and 1000 μg α-tocopherol per mL culture fluid. The results suggest that vitamin E protects human skin fibroblasts against the cytotoxic effects of UVB [4].

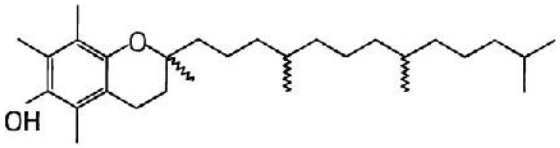

FIGURE 1 Structural formula of dl-α-tocopherol.

Interesting is the result of a study performed by Lopez-Torres et al., in which they investigated the effects of topical tocopherol on epidermal and dermal antioxidants and their ability to prevent UV-induced oxidative damage. Topically applied tocopherol to hairless mice in vivo increased dermal superoxide dismutase activity by 30% and protected epidermal glutathione peroxidase and superoxide dismutase from depletion after UV irradiation. Total and reduced glutathione levels in the epidermis were also increased, as were dermal vitamin C levels. The investigators conclude that topical administration of α-tocopherol protects cutaneous tissues against oxidative damage induced by UV irradiation [5].

Application of pure vitamin E acetate to the skin of hairless mice immediately after UVB irradiation reduced sunbum symptoms such as erythema, skin sensitivity, and skin swelling in a study carried out by Trevithick et al. [6]. Reduced erythema formation after UV irradiation was also reported by Roshchupkin [7] and Pathak [8].

In a human skin model, antioxidant depletion as a result of UV light exposure was shown by Podda [9]. Ubiquinol and ubiquinone in particular, as well as α-tocopherol to a lesser extent, were susceptible and decreased with higher UV light intensities to virtually non detectable levels. Partial impairment of the cutaneous antioxidant defense system, including vitamin E, by UV light was also observed by Fuchs [10].

Clement-Lacroix et al. tested the protector effect of vitamin E on immune suppression in human epidermal cells in vitro. Cultured cells preincubated with or without vitamin E were irradiated with UVA light. The investigators could show that incubation of cell cultures with vitamin E before irradiation partially protected the cells from the immunosuppressive effects of UVA radiation [11]. Finally, Weiser [12] and Miyamoto [13] have shown wound-healing properties of topical vitamin E acetate.

Vitamin E is used in cosmetics for everyday use to strengthen the natural antioxidant potency of the skin and thus to better cope with oxidative stress. Most of the scientific background for the topical use of vitamin E stems from observations in context with UV light. Vitamin E is often used, therefore, in suncare products for improvement of the protection achieved with the sun filters. Even high SPF factors still allow the penetration of some UV light onto and into the skin. Whereas the sun filters absorb or reflect most of the rays on the surface of the skin, vitamin E acts on the inside and reduces the risk of damage that could be caused by rays passing through the sun filter barrier. Vitamin E helps, therefore, in the prevention of symptoms caused by UV-induced skin damage such as wrinkling and irregular pigmentation.

In nature, Vitamin E appears as tocopherols, of which the alpha form has the highest biological potency. The unesterified form is present in wheat germ oil and other vegetable oils that are used in cosmetics as sources of Vitamin E. Most often used is dl-alpha tocopheryl acetate, because this ester is less prone to oxidation than free tocopherol. In the skin, vitamin E acetate is bioconverted into the biologically active antioxidant tocopherol [14,15].

VITAMIN A

Vitamin A (Fig. 2) and its derivatives belong to a large class of structurally related compounds, the retinoids. The term vitamin A is generically used for all derivatives of β-ionone that possess the biological activity of all-trans retinol or are closely related to it. The biological activities of the vitamin A derivatives are expressed in IU (international

units.) One IU corresponds to 0.3 μg retinol, 0.34 μg vitamin A acetate, and 0.55 μg vitamin A palmitate.

Vitamin A is best known for its involvement in maintaining normal vision. It exerts, however, a number of other functions in the human organism, of which its activity in the epidermis is of particular interest for cosmetics.

The architecture of the human epidermis is a complex stratified system, its renewal a complex process. Epidermal keratinocytes proliferate and differentiate in a multilayered pattern. These processes are balanced so that new basal cells are formed as the totally cornified cells are shed from the surface of the skin. Proliferation and keratinization of keratinocytes are the two key elements for the build-up of a healthy epidermis. In both processes, vitamin A plays the role of a regulator.

On cell proliferation, vitamin A has a stimulating effect, as has been shown in various studies [16–18]. As little as 10 μg vitamin A acetate suspended in 0.2 mL water applied to normal rat skin led to a clear increase in mitotic activity after only 4 hours. Much more pronounced and longer lasting was the effect with 100 μg vitamin A acetate. However, 24 hours after treatment, the mitotic index had returned to original levels with both concentrations [17]. As can be seen from this study, the effect of vitamin A is dose dependent and disappears after a certain time with decreasing concentration in the tissue. An increase in mitotic activity is the first step in an increase of the number of new keratinocytes formed [19], which results in a thickening of the epidermis [20–23].

In the process of aging, many aspects of the skin structure are altered because of a decreased metabolic activity of the human organism. A thinning of the epidermis is one of the characteristics of aging skin. The skin thereby loses part of its barrier function, and as a consequence of reduced water retention capacity it is often dry, scaly, or even cracks. Vitamin A can counteract this development by stimulating the cell-renewal process.

The effect on the keratinization process was investigated by Fuchs and Green [24]. Removal of vitamin A from the culture fluid of human keratinocyte cell cultures resulted in a reduced cell motility, an increased adhesiveness of the cells, and a prevention of pattern formation. They conclude that the nature of the keratins synthesized by the tissues is regulated by the concentration of vitamin A. Another symptom of skin aging is a decrease in collagen in the connective tissue. Skin collagen decreases linearly by about 1% per year throughout adult life [25]. Topical administration of vitamin A has shown significant dose-related changes in collagen content of the dermis. 0.1% vitamin A palmitate applied to skin of hairless mice for 14 days increased the collagen content by 88%, 0.5% vitamin A palmitate by 101% [20].

Vitamin A not only improves the barrier function of the skin but also its appearance and elasticity. Application of a lotion with vitamin A palmitate to the temples of a group of 40- to 60-year-old volunteers has shown an increase in elasticity by 14% after 2 weeks and by over 22% after 6 weeks [26].

There is evidence that UV light strongly affects vitamin A concentration in epidermis and dermis as was shown in animals and humans [27,28]. Particularly low were the levels when test animals were exposed to UVA near the absorption maximum of vitamin A. The regeneration of normal levels in the depleted tissue is very slow and took more than 1 week in rabbit ear skin [28].

Cluver and Politzer measured the vitamin A concentration in blood serum of humans after 1 hour of exposure to the sun. Depletion was observed immediately after exposure, which lasted at least a further 2½ hours [29]. It can be assumed that, under similar conditions, a depletion also takes place in the skin. The low blood levels could also be an

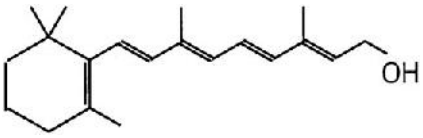

FIGURE 2 Structural formula of vitamin A alcohol.

explanation for the slow restoration of vitamin A in the skin. It cannot be excluded that low vitamin A levels in the skin after regular and excessive sun exposure are implicated in the typical changes seen in photodamaged skin, such as the thickened horny layer and the relatively thin rest of the epidermis. A common practice in treatment of photodamaged skin is the use of vitamin A acid. Although it is not proven, it can be hypothesized that retinoids could be involved in the process of photoaging. In most countries, however, vitamin A acid is classified as a drug and cannot be used in cosmetic products. Whether vitamin A esters have a similar effect to vitamin A acid, and whether they could be used not in the cure but in the prevention of photoaging, is presently under investigation. Some first results are available and show promising results.

Although vitamin A was one of the first vitamins discovered, the molecular mechanism of its activity is still largely unknown. Many attempts have been made to define in biochemical terms the manner in which it induces the differentiation of cells. Uncertainties still exist, but one pathway increasingly seems to explain most of the effects of various retinoids on different cell types. This pathway includes an oxidation of retinol (vitamin A alcohol) to retinal (vitamin A aldehyde), and subsequently a further bioconversion in a controlled mechanism to retinoic acid [30].

In cosmetics, vitamin A is used mainly in the ester forms: vitamin A palmitate and vitamin A acetate, as well as retinol. None of these forms are very stable when exposed to light or warmth. Special attention has to be paid, therefore, to the stabilization of vitamin A–containing cosmetic products and their handling during the manufacturing process. This is particularly true for retinol.

PANTHENOL

Panthenol (Fig. 3) is the biologically active alcohol analogue of pantothenic acid, a vitamin of the B-complex group, which is a normal constituent of skin and hair. Pantothenic acid, also called Vitamin B_5, carries out its function in the body as an element of co-enzyme A, a molecule composed of cysteamine, ATP, and pantothenic acid. This substance is present in all living cells and serves a vital role in the metabolism of a variety of enzyme-catalyzed reactions by which energy is released from carbohydrates, fats, and proteins. Skin manifestations of pantothenic acid deficiency are well known, and include cornification, depigmentation, and desquamation.

Pantothenic acid is an unstable substance. In topical preparations such as skincare, haircare, nailcare, and derma products, pantothenic acid is used in the alcohol form, called panthenol. Its use is based on its dual role as a vitamin precursor and as an ingredient with ideal cosmetic properties. When topically applied, panthenol is absorbed by the skin and can be bioconverted into pantothenic acid [31]. As such it exerts all functions of vitamin B_5.

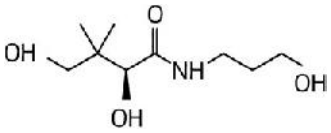

FIGURE 3 Structural formula of D-panthenol.

Because it has a distinct humectant character, panthenol acts as a skin moisturizer [32,33]. This hygroscopic substance not only provides water to the skin surface but it also penetrates deep into the epidermis and brings water to, and retains water in, the inside of the skin. Panthenol imparts a smooth, light feel to the skin without any greasiness or stickiness. Because it is well tolerated by the skin, it is an ideal and widely used ingredient in baby care products as well as in products for sensitive skin.

Topically applied panthenol stimulates epithelization as was shown by Weiser and Erlemann [12]. Superficial wounds treated with creams containing 5% panthenol reduced the healing time by 30% compared with placebo. Favorable effects were also reported in many kinds of skin disorders accompanied by inflammatory reactions such as burns [34], nipple fissures [35], eczemas [36,37], and many others. Another application field of panthenol is, therefore, derma products for wound healing and for soothing of inflammatory disorders where it is usually incorporated in concentrations of 5%. The concentrations in cosmetics vary mainly from 0.3 to 2%.

The use of panthenol in haircare products goes back to the early 1960s, when inflammatory reactions on the scalp were treated with panthenol-containing creams. Panthenol not only showed a soothing effect but also had beneficial effects on the hair.

Pantothenic acid is a natural constituent of human hair [38]. Stuettgen applied tritium-labeled panthenol intracutaneously by injection and could show a transport of radioactive material into the hair [39]. Stangl observed a significant increase of pantothenic acid concentration in the hair after topical application of panthenol over longer periods [38].

Panthenol acts as a humectant for hair. It builds up a thin moisture film on the surface of the hair and gives hair shine without making it greasy. Panthenol also penetrates into the hair cuticle and brings moisture to the cortex. This imparts good pliability and manageability properties to the hair, and improves its resistance to mechanical stress such as combing, brushing, and heat blowdrying.

Panthenol can also contribute to give hair more body. A thickening of the hair after 2 minutes exposure to a 2% water solution of panthenol was shown by means of scanning electron microscopy [39].

The main commercial forms are d-panthenol, dl-panthenol, and ethyl panthenol. All these forms are soluble in e.g., water, ethanol, and propylene glycol, but insoluble in fats and oils. Ethyl panthenol is an ether and available either as d-form or a racemic mixture of d- and l-form. Biological activity has only the d-form, because only d-pantothenic acid is incorporated into coenzyme A.

VITAMIN C

Vitamin C (Fig. 4) is certainly the best-known vitamin. Known also as ascorbic acid, it is a potent antioxidant, a scavenger of superoxide and peroxyl radicals, which are involved in lipid peroxidation in tissues such as the human skin.

Like vitamin E, vitamin C belongs to the natural nonenzymatic antioxidant defense system. Different from the lipophilic properties of tocopherol, ascorbic acid is water-soluble and acts in the more hydrophilic environment of the skin structure.

There is a wealth of literature available on functions of vitamin C in the human organism [41]. Of special interest for the cosmetic industry are those publications dealing with strengthening of the antioxidant system, stimulation of collagen formation, skin lightening, and treatment of hyperpigmentation. Vitamin C has also proven to have good wound-healing properties.

Darr et al. [42] investigated the antioxidant properties of vitamin C in porcine skin. Topical application of ascorbic acid not only resulted in a significant elevation of cutaneous levels of this vitamin but also protected the skin from UVB damage as measured by erythema and sunburn cell formation. In addition, they could show that UVB irradiation reduces the vitamin C levels in the skin. Similar reductions were reported by Podda [9] and to a lesser extent by Fuchs [10].

There are two possibilities of how vitamin C can participate in the inhibition of UV damage when applied to the skin: either it directly reacts with, or quenches, certain free radicals, or it helps to regenerate tocopheryl radicals formed in the course of lipid peroxidation prevention. Vitamin C is, therefore, an attractive molecule for use in skin cosmetics, particularly in combination with vitamin E.

Dermatologists have long observed that skin fibroblasts synthesize less collagen as they age and that too much sun increases the decline. Vitamin C could counteract this decline in two ways. Ascorbic acid is an essential cofactor in the hydroxylation of proline and lysine to form hydroxyproline and hydroxylysine, amino acids of importance to the function of collagen [43]. In addition, vitamin C stimulates the formation of collagen [43]. Thus vitamin C contributes to the formation of a strong matrix of the dermis and can be used in cosmetic products for the maintenance of healthy skin.

Ascorbic acid and its esters are also used as active ingredients in skin bleaching or skin lightening cosmetic products. This use is supported by publications such as that by Takashima et al. [44]. These investigators reported successful skin lightening in patients with chloasma which were treated with an ointment containing 3% magnesium ascorbyl phosphate.

There are mainly two possibilities how ascorbic acid can influence melanin to achieve a lightening of skin color: partial inhibition of formation of new melanin or modification of melanin already present, e.g., by promoting the conversion of formed melanin to the reduced form. Both mechanisms have been investigated and discussed for ascorbic acid [44,45]. Further studies are needed to clarify the exact mode of activity.

The most frequently used forms of vitamin C in cosmetics are ascorbic acid, ascorbyl palmitate, magnesium ascorbyl phosphate, and trisodium ascorbyl phosphate. The cosmetic industry shows great interest in the use of vitamin C, particularly as antioxidant for

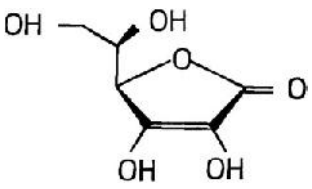

FIGURE 4 Structural formula of L-ascorbic acid.

the skin. Its use, however, has been limited to date due to the insufficient stability of ascorbic acid in aqueous solutions and the prices of some of the more stable derivatives.

OTHERS

Some other vitamins and vitamin precursors used in cosmetic products are biotin, niacinamide, vitamin D, vitamin B_6, beta-carotene, and, in a few products, vitamin K. For all these substances there exists a rationale for their use in cosmetics but there are either no studies or insufficient studies available that prove their efficacy when topically applied.

Systemic use of 2.5 mg biotin per day has shown good effect on brittle nails and has improved hair quality [46–49]. As it has good effect on these keratin structures, it can be assumed that this vitamin could also have interesting effects on the keratinization process in the epidermis.

Beta-carotene is known for its quenching activity on singlet oxygen. It would be an ideal partner for vitamin E and vitamin C to strengthen the antioxidant defense system of the skin. Oral supplementation with beta-carotene over several weeks has shown to reduce the risk of UV-induced skin damage [50].

Unfortunately for cosmetics, beta-carotene is a strong coloring agent and concentrations of more than 0.05% in a cosmetic product can lead to undesirable coloration of the clothes of its users. Low concentrations of beta-carotene are used in some cosmetics as natural coloring agent for creams.

Roccheggiani showed a depression of sebum production with the tripalmitate ester of vitamin B_6 [51]. Vitamin D could be an ideal partner for total sun blockers, as the UV-ray barrier of these products partly prevents the natural formation of vitamin D in the skin. Vitamin D is on the ''list of substances which must not form part of the composition of cosmetic products'' of the European Cosmetic Regulations. It can be used, however, in other countries.

CONCLUSION

Vitamins are a class of naturally occurring active ingredients with well-documented activities when topically applied. They are all essential substances for the well-being and health of the human organism, including the skin.

Thousands of studies have shown the safety and efficacy of systemically and topically used vitamins. In many cases, topical use is the only way to provide sufficient quantities of these highly active protector and care substances to be able to guarantee an optimal functioning of the skin. This is particularly true when the skin is stressed by factors such as UV light or environmental pollutants such as ozone, especially as these factors can often even destroy considerable quantities of the vitamins.

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Ellagic Acid: A New Skin-Whitening Active Ingredient

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Melanin is a key factor determining the color of skin. The enzyme tyrosinase plays the most important role in melanin synthesis (melanogenesis) [1,2]. Several tyrosinase inhibitors (chemicals, plant extracts, animal products) have been proposed, based on the view that melanogenesis can be controlled and skin-whitening products developed if tyrosinase activity can be suppressed. However, few have been put to practical use. In practice, it is difficult to develop these candidate materials from in vitro studies to approval for human use, even if inhibitory effects on mushroom-derived tyrosinase or pigment cells can be identified. In addition to showing adequate efficacy and safety, there are many problems to consider, such as stability of the products, production and marketing costs, and perception of the user.

Ellagic acid (EA) (Fig. 1) was approved in 1996 in Japan as the active ingredient of a quasidrug for the prevention of spots and freckles after developing sunburn from exposure to excess sunlight. EA, a naturally occurring polyphenol [3,4] containing four hydroxyl groups, is found in many plants such as strawberry, grape, green tea, eucalyptus, walnut, and tara. Generally, EA is produced by hydrolysis and purification from ellagitannin.

GENERAL PROPERTIES

Ellagic acid is a cream-colored powder slightly soluble in water and ethanol, in alkaline solution and pyridine, and practically insoluble in ether [4]. EA has high antioxidant activity [5], and is listed as a food additive in Japan. The hydroxyl groups of EA can chelate with metal ions [6,7].

IN VITRO STUDIES

Ellagic acid inhibits mushroom-derived tyrosinase competitively and in a dose-dependent manner; the inhibition constant (ki) is 81.6 μM [8]. The decrease in copper concentration and the reduction in tyrosinase activity by EA follow almost parallel patterns. Tyrosinase

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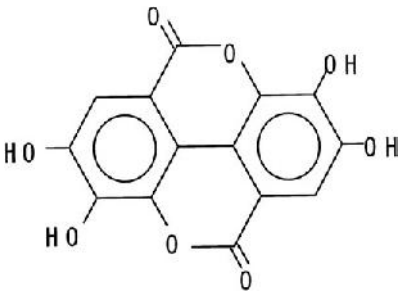


FIGURE 1 Ellagic acid.

activity, after inhibition by EA, partially recovers after addition of cuprous or cupric ion (Fig. 2).

Growth of B16 melanoma cells in culture medium was not suppressed by EA at concentrations of less than 4 μM. At 4 μM, the inhibition of tyrosinase activity was 38.3% and the decrease in melanin concentration 54.4%. Although the color of the cells (reflecting the melanin concentration) became whitened in the presence of EA, cell color reverted to the original shade when EA was removed from the culture medium (Fig. 3). The addition of other metals, in place of the copper compounds, did not lead to recovery of the enzymic activity.

These results show that the inhibitory effect of EA is reversible, effective only in its presence, and specific to copper compounds. It is proposed that EA chelates to copper ion(s) at the active center of tyrosinase, which is a metaloprotein containing copper. Further structural changes then make the tyrosinase inactive. Because the molecular structure of EA is planar, EA may be able to penetrate into the active center of tyrosinase easily. It is clear that EA inhibits tyrosinase because of its molecular structure as well as its ability to chelate with copper.

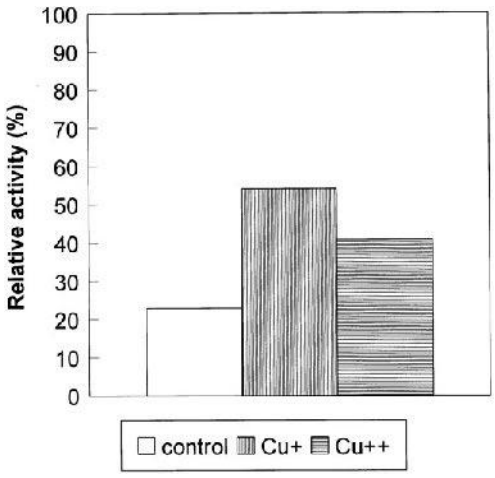


FIGURE 2 Effects of addition of copper ion on recovery of tyrosinase activity. Cu^{+} or Cu^{++} (5 mM) were added to tyrosinase during inhibition by EA.

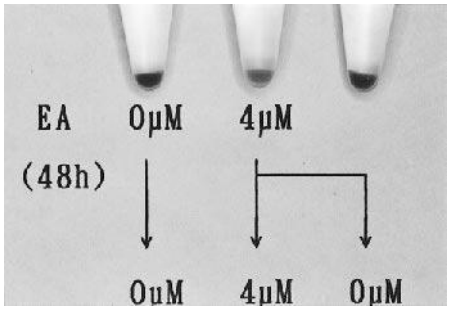
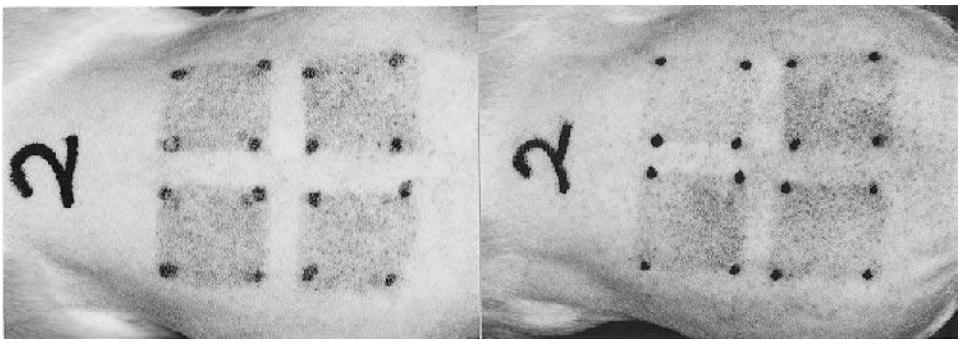


FIGURE 3 Effect of EA on melanoma cells. Cells were incubated with EA (4 μM) for 48 hours. Culture medium was changed to fresh medium in the presence or absence of EA (4 μM) and incubated for an additional 48 hours.

ANIMAL STUDIES

Brownish guinea pigs have melanocytes in their skin and the skin pigmentation is enhanced by ultraviolet (UV) light irradiation, similar to the human situation. The preventative effect of EA on skin pigmentation was investigated by applying EA topically, on the back, for 6 weeks and irradiating by UV for first 2 weeks [8]. The appearance of skin to which EA was applied became similar to normal skin. The melanin content of the skin to which EA had been applied was reduced, not only in the basal layers but also in the stratum spinosum, -granulosum, and -corneum, in comparison with the same structures in control sections to which EA had not been applied. Tyrosinase activity was similar. Furthermore, application of EA to the skin after UV-light irradiation had almost the same affect as applying EA concurrently with the initial irradiation.

According to the results of the studies using the brownish guinea pig, EA is a more efficient skin whitener and suppressor of pigmentation than arbutin or kojic acid, other active skin whiteners, at the same dose level (1%) (Fig. 4).



(a) (b)

FIGURE 4 Comparison of effects of some commercially available agents in preventing skin pigmentation induced by UV-light irradiation. Samples were applied for 4 weeks after UV-light irradiation (eight times): (a) before application; (b) after application for 4 weeks; (upper left) ellagic acid, (upper right) vehicle, (lower left) arbutin, (lower right) kojic acid.

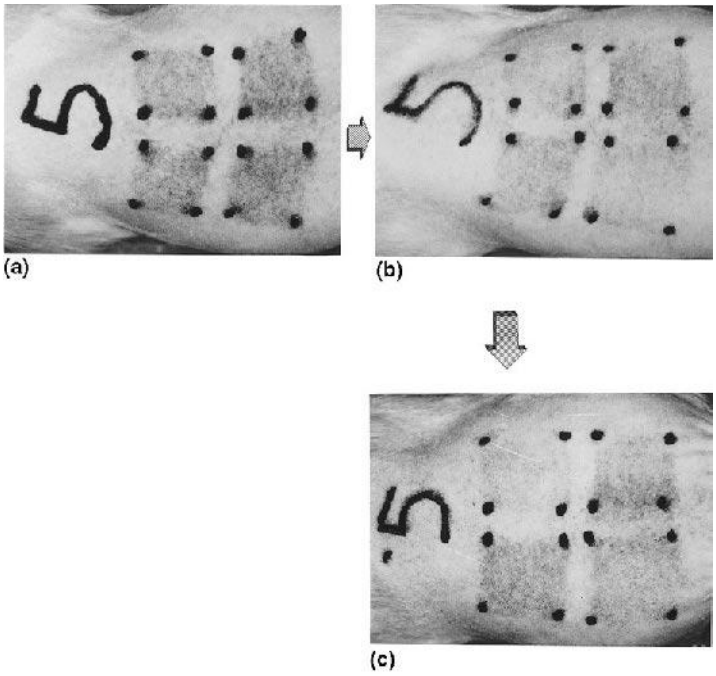


FIGURE 5 Effects of ellagic acid on UV-light induced pigmentation. Samples were applied for 4 weeks (a) after UV-light irradiation (eight times): (upper left) hydroquinone; (upper right) vehicle only; (lower left) control—no EA applied; (lower right) ellagic acid. After application was terminated (b), the same area was irradiated again (c).

Furthermore, the efficacy of EA was almost the same as that of hydroquinone (HQ), a well-known depigmentation agent (Fig. 5). When the same animals were subjected to UV irradiation again after completion of the application phase, normal skin pigmentation was observed in the EA-applied area as well as in the control areas, but only slight pigmentation was seen in the HQ-treated skin. The results of these investigations indicated that EA was not injurious to melanocytes but was a good inhibitor of tyrosinase activity. In comparison, HQ may be toxic to melanocytes.

EFFECT ON HUMAN SKIN

A skin cream containing EA was applied for 6 weeks to the brachium before each irradiation by UV light [9]. The sites were irradiated three times at 1 MED. Skin pigmentation was partially suppressed after only 1 week's application, and completely suppressed after 3 and 6 weeks' application (Fig. 6). Eighty-six percent of the efficacy of EA evaluated by a double-blind controlled test was rated ''moderately preferable'' or better (Fig. 7). Similar efficacy rates were calculated by the image analysis method. Side effects such as depigmentation were not observed throughout the application period.

Thus, EA can prevent the buildup of skin pigmentation after sunburn. It can also be expected to improve the appearance of pigmented skin such as melasma or freckles,

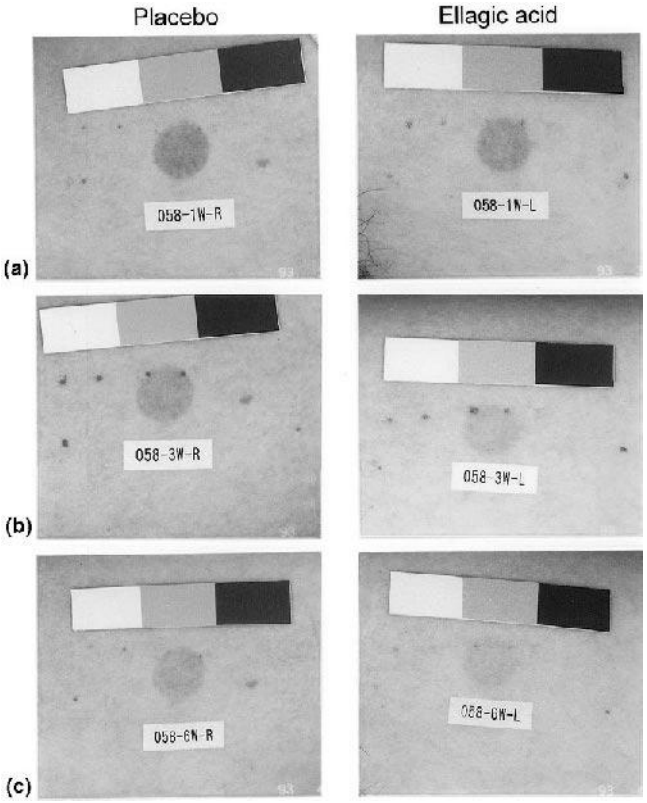


FIGURE 6 Effect of ellagic acid on UV-light induced skin pigmentation in human.

for such skin pigmentation is believed to follow similar mechanisms to that of sunburn, at least from the viewpoint of epidermic disorders, even if the mechanism of melasma and so on are not precisely clear. Many impressions that skin pigmentation appears to be lightened have been gathered from users of products containing EA. In practice, the characteristics of melasma, postinflammatory pigmentation, and other conditions appear to be improved by this application. EA is a promising skin-whitening active ingredient.

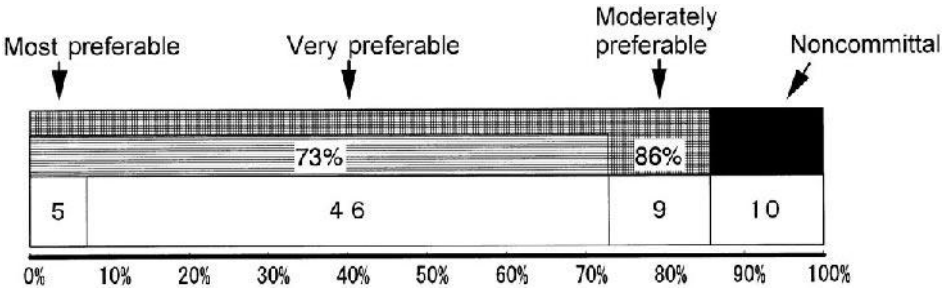


FIGURE 7 Efficacy for whitening effect on sunburn subjects.

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