

THERAPEUTIC MOISTURIZERS

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Moisturizers are complex formulations designed to maintain the water content of the skin between 10% and 30%. Water is essential to maintain skin plasticity and barrier integrity. Skin that is water deficient, such as the thickened skin commonly present over the heels, fissures readily with trauma and is rough to the touch. Water is necessary to allow skin distensibility, a mandatory requirement in an organ that is in constant motion. Skin hydration is important to maintain an intact skin barrier, tactilely perceived as smooth, soft skin.

This article begins by reviewing the barrier function of the skin to gain an understanding of the physiologic role moisturizers play in skin barrier repair. Then, substances that are used to provide skin moisturization and how they function in this role are discussed. Specialty additives to enhance skin functioning are reviewed. Lastly, a discourse on the currently available therapeutic moisturizers and their efficacy is presented, including the incorporation of hydroxy acids and vitamins. Moisturizers are probably the one skin care product that affects the condition of skin dramatically. Proper moisturizer selection can aid in the treatment of disease, whereas poorly selected, poorly formulated products can initiate the disease process.

EPIDERMAL LIPIDS

Moisturizers attempt to mimic the role of epidermal lipids in the skin barrier, although this goal has not been achieved completely by any currently available moisturizer formulation. There are three intercellular lipids implicated in epidermal barrier function: sphingolipids, free sterols, and free fatty acids.¹⁰ It is thought that the lamellar bodies, containing sphingolipids, free sterols, and phospholipids, play a key role in barrier function and are essential to trap water and prevent excessive water loss. The lipids are necessary for barrier function because solvent extraction of these chemicals leads to xerosis, directly proportional to the amount of lipid removed. The major lipid by weight found in the stratum corneum is ceramide, which becomes sphingolipid if glycosylated by the primary alcohol of sphingosine.²¹ Ceramides possess most of the long-chain fatty acids and linoleic acid in the skin.^{11, 39}

PHYSIOLOGY OF XEROSIS

Xerosis is a result of decreased water content of the stratum corneum, which leads to abnormal desquamation of corneocytes.⁴⁶ For the skin to appear and feel normal, the water content of this layer must be greater than 10%. Water is lost through evaporation to the

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environment under low-humidity conditions and must be replenished by water from the lower epidermal and dermal layers.⁴⁸ The stratum corneum must have the ability to maintain this moisture, or the skin feels rough, scaly, and dry. This is a simplistic view because there are minimal differences between the amount of water present in the stratum corneum of dry and normal skin. Xerotic skin is due to more than simply low water content.³⁶ Electron micrographic studies of dry skin show a stratum corneum that is thicker, fissured, and disorganized.

EPIDERMAL BARRIER REPAIR

Once the epidermal barrier has been damaged, signals must be transmitted to the intracellular machinery to initiate repair. Remoisturization of the skin occurs in four steps: (1) initiation of barrier repair, (2) alteration of surface cutaneous moisture partition coefficient, (3) onset of dermal-epidermal moisture diffusion, and (4) synthesis of intercellular lipids.^{24, 38} It is generally thought that a stratum corneum containing 20% to 35% water exhibits the softness and pliability of normal stratum corneum.

The physiologic signal initiating barrier repair through lipid synthesis is transepidermal water loss.¹⁸ Vapor-impermeable dressings do not produce the expected burst in lipid synthesis because transepidermal water loss drops to 0. Transepidermal water loss of 1% is sufficient for lipid synthesis. This fact explains the importance of vapor-permeable dressings in wound healing. Moisturizers, such as petrolatum, are able to facilitate barrier repair even though transepidermal water loss drops by 99%.¹⁴ Petrolatum permeates throughout the interstices of the stratum corneum, allowing barrier function to be reestablished.

MECHANISMS OF MOISTURIZATION

Once barrier damage has occurred, reconditioning can occur only if the loss of moisture is retarded. This is the goal of moisturizers, which function temporarily until skin integrity can be reestablished. There are two

main mechanisms used to rehydrate the stratum corneum: the use of occlusives and humectants.^{1, 3}

Occlusive Moisturizing Ingredients

Occlusives function to condition the skin by impairing evaporation of water to the atmosphere. They generally are oily substances through which water cannot pass. Occlusive substances can be broken down into several categories (Table 1).⁷ As mentioned previously, petrolatum is the most efficacious occlusive moisturizer. Lanolin rarely is used as a moisturizer because of its expense, characteristic odor, and possibility of allergic contact dermatitis. Of the oils, mineral oil is a frequently used ingredient but can reduce transepidermal water loss only by about 30%.

The newest category of occlusive moisturizers are silicones, such as dimethicone and cyclomethicone. These are popular ingredients because silicone is hypoallergenic, non-comedogenic, and without a strong odor. Silicone is used in many of the oil-free moisturizers on the market. *Oil-free* has come to mean that the product does not contain mineral or vegetable oils. Silicone is a clear

Table 1. OCCLUSIVE MOISTURIZING INGREDIENTS

Hydrocarbon oils and waxes
Petrolatum
Mineral oil
Paraffin
Squalene
Silicone
Dimethicone
Cyclomethicone
Vegetable and animal fats
Cocoa butter
Lanolin
Fatty acids
Lanolin acid
Stearic acid
Fatty alcohol
Lanolin alcohol
Cetyl alcohol
Polyhydric alcohols
Propylene glycol
Wax esters
Lanolin
Beeswax
Stearyl stearate
Vegetable waxes
Carnauba
Candelilla
Phospholipids
Lecithin
Sterols
Cholesterol

liquid with an oily feel but is not considered an oil in this application. It is a valuable ingredient to improve the esthetic characteristics of a moisturizer because it reduces the greasiness of petrolatum while enhancing efficacy.

Humectant Moisturizing Ingredients

Humectants function to attract water from the viable skin layers to the stratum corneum. Naturally occurring humectants found within the dermis include glycosaminoglycans, such as hyaluronic acid. Examples of synthetic humectants useful in moisturizer formulations are listed in Table 2.

Topically applied humectants draw water largely from the dermis to the epidermis and rarely from the environment. An ambient humidity exceeding 70% is necessary to allow humectants to hydrate the stratum corneum from the environment. Moisturizers that claim to *attract water to the skin* generally are not attracting external water to the skin surface. Remoisturization of the skin occurs from the inside out, rather than from the outside in. For this reason, the topical application of water in the form of mists or sprays is ineffective, unless an occlusive agent is immediately applied to trap the water on the skin surface.

Moisturizers that contain only humectants actually increase transepidermal water loss when applied to skin possessing a defective barrier. For example, application of topical glycerin enhances transepidermal water loss by 29%. A quality moisturizer formulation combines occlusive and humectant ingredients to rehydrate the skin optimally. Humec-

Table 3. EMOLLIENT INGREDIENTS

Alcohols
Octyl dodecanol
Hexyl decanol
Oleyl alcohol
Esters
Oleyl oleate
Octyl stearate
PEG-7 glyceryl cocoate
Coco caprylate/caprate
Myristyl myristate
Cetearyl isononanoate
Isopropyl myristate

tants also may allow the skin to feel smoother by filling holes in the stratum corneum through swelling. The ability of moisturizers to make the skin feel smoother is a property known as *emolliency*.

EMOLLIENCY

The terms *emollient*, *moisturizer*, and *lubricant* are sometimes used interchangeably by the dermatologist, when in actuality these words have a more precise meaning. *Emolliency* refers to the ability of a product to fill in the crevices between the desquamating corneocytes abundant in dry skin conditions. *Moisturizing* refers to the net decrease in transepidermal water loss after product application. *Lubrication* refers to the ability of the product to increase skin slip. All three qualities can be achieved through the use of substances known as *emollients* because substances with emollient properties also act to moisturize the skin and improve lubricity.

Emollient Substances

Emollients consist of oily substances with a variety of chemical characteristics from esters to alcohols (Table 3).⁴⁰ A common term found on some packaging is *alcohol-free*. There appears to be a misconception among patients and some dermatologists that all alcohols are drying. This is not true. Alcohols represent one of the most commonly used classes of emollients with excellent skin smoothing and moisturizing qualities. Perhaps the confusion is with rubbing alcohol, also known as *isopro-*

Table 2. HUMECTANT MOISTURIZING INGREDIENTS

Glycerin
Honey
Sodium lactate
Urea
Propylene glycol
Sorbitol
Pyrrolidone carboxylic acid
Gelatin
Hyaluronic acid
Some vitamins
Some proteins

pyl alcohol, which possesses astringent properties. It is not appropriate to advise patients to select moisturizers that do not contain the word *alcohol* on the ingredient list.

Table 4 lists emollients according to their greasiness. Certain emollients tend to impart a heavier feel to the skin, whereas others are more volatile. The tactile properties of the emollient selected determine the characteristics of the final formulation. Greasier emollients are harder to spread and more occlusive. Lighter emollients are easier to spread and less occlusive. Heavier emollients would be used in night creams and eye creams, in which occlusion is desirable. Day creams and lotions may be formulated with the medium-spreading emollients, whereas body lotions may employ the easy-spreading emollients. By selecting substances from the various groups listed in Table 4, the cosmetic chemist can tailor the feel and function of the moisturizer to its intended use.

Emolliency and Efficacy

The emollient selected for use in a given moisturizer depends, in part, on the other ingredients in the formulation and the intended function of the skin care product. Exfoliant moisturizers containing alpha hydroxy acids or salicylic acid require the selection of a branched alcohol emollient because monoester emollients hydrolyze in the presence of low pH. Careful ingredient selection is necessary to ensure that no substance interacts with others in the formulation.

Careful selection of emollients is important in sunscreen-containing moisturizers. It is

possible to change the absorption spectrum and the sun protection factor of a sunscreen-containing moisturizer simply by selecting a different emollient. For example, mineral oil, a commonly employed emollient in commercial sunscreen-containing moisturizer formulations, can shift the absorption spectrum of octylmethoxy cinnamate almost out of the UV-B range. Another commonly used group of emollients, alcohol alkoxylates, increase the absorption of octylmethoxy cinnamate in the UV-B and UV-A range. It is also important to consider the physical characteristics of the emollient when formulating a sunscreen-containing moisturizer. Substances that promote even spreading of the moisturizer on the skin keep the sunscreen active ingredient uniformly dispersed to provide the maximum UV light-absorbing potential. The sun protection factor of a sunscreen-containing moisturizer cannot always be predicted based on the incorporation of the active ingredient alone because the effect of the emollient is substantial. A more detailed discussion of sunscreens is provided in another article in this issue.

Esthetic Properties of Emollients

The esthetic properties of a moisturizer can be adjusted by combining emollients. For example, heavy emollients can be combined with lighter emollients to achieve an excellent occlusive moisturizer that is less greasy. The best formulations combine three to four different emollients with various spreading properties (Table 5). The easily spreading emollient gives the sensation of early smoothness, which dissipates quickly. The medium-spreading emollient, in combination with the easily spreading emollient, decreases the greasiness of the slow-spreading emollient, providing the long-lasting efficacy of the moisturizer formulation.

Some formulators believe that the ideal moisturizer should mimic closely sebum, which represents a mixture of emollients with different spreading abilities and tactile properties. Sebum is 28% free fatty acids, 32% triglycerides, 14% waxes, and 5% squalene, in addition to other lesser components. Many novel ingredients have been incorporated into

Table 4. AESTHETIC PROPERTIES OF EMOLLIENTS*

Oleyl oleate
Caprylic/capric triglyceride
Decyl oleate
Octyl dodecanol
Hexyl laurate
Octyl laurate
Isopropyl stearate
Isopropyl palmitate
Isopropyl myristate
Dibutyladipate

*Listed in order of decreasing greasiness.

Table 5. SPREADING CHARACTERISTICS OF EMOLLIENTS

Poor Spreadability/Greasy
Castor oil
Almond oil
Oleyloleate
Medium Spreadability/Creamy
Caprylic/capric triglyceride
Ocetyl dodecanol
Cetearyl isononanoate
Oleyl alcohol
Easy Spreadability/Nongreasy
Diethyl cyclohexane
Isopropyl stearate
Isopropyl myristate

moisturizers to mimic sebum and possibly to enhance skin functioning.

SPECIALTY INGREDIENTS IN MOISTURIZERS

Even though a better understanding of the stratum corneum barrier has been achieved, dermatologists and industry researchers continue to search for the substance, or combination of substances, that allows the skin to hold water. It is theorized that a natural moisturizing factor exists within the skin, consisting of amino acids, pyrrolidone carboxylic acid, lactate, urea, ammonia, uric acid, glucosamine, creatinine, citrate, sodium, potassium, calcium, magnesium, phosphate, chlorine, glucose, organic acids and peptides.⁴⁴ Some more sophisticated moisturizers attempt to mimic this combination of additives, but the perfect moisturizer has not been developed. This section focuses on the ingredients that are added to moisturizers to enhance their therapeutic potential.

Sodium PCA

Sodium PCA, the salt of 2-pyrrolidone-5-carboxylic acid, functions as a humectant.⁴⁷ It is typically used in concentrations of 2% or greater. Sodium PCA is an example of the attempt to duplicate the water-holding capacity of glycosaminoglycans in the dermis. It is hard to duplicate dermal constituents on the stratum corneum.

Urea

Urea, a component of the natural moisturizing factor discussed previously, is used by itself as a specialty moisturizer additive. It is valued for its ability to diffuse into the outer layers of the stratum corneum and disrupt hydrogen bonding, which exposes the water-binding sites on the corneocytes. Urea also promotes desquamation by dissolving the intercellular cementing substance between the corneocytes.³⁷ Urea enhances the water-holding capacity of the stratum corneum.

Alpha Hydroxy Acids

A new category of exfoliant moisturizer was created when alpha hydroxy acids (AHAs) entered the marketplace. This development established the concept of an *anti-aging* moisturizer. AHAs are a group of organic carboxylic acids distinguished by a hydroxy group in the alpha position. The linear, aliphatic nature of the AHA structure accounts for its water solubility and hydrophilic properties. The three subcategories of the AHAs consist of monocarboxylic acids (glycolic acid), dicarboxylic acids (malic acid), and tricarboxylic acids (citric acid).

The first hydroxy acids to reach the marketplace were glycolic acid and lactic acid. The newer, more sophisticated hydroxy acid formulations are now combining the hydroxy acids to create trihydroxy acids (THAs), or triple fruit acid formulations. For example, the monocarboxylic acid glycolic acid is combined with the dicarboxylic acid malic acid and the tricarboxylic acid citric acid. Although these combinations provide for enhanced marketing claims, no data are available to show the value of AHA cocktails. It is doubtful that the individual AHA entities can be distinguished in the final formulation.

Hydroxy acids have come under scrutiny from the US Food and Drug Administration (FDA) amid their popularity. The FDA evaluation was initiated when apoptotic cells were found in higher numbers in the dermis in skin exposed to UV radiation that had been pretreated with an AHA. The cause of this cell death has not been confirmed, but it has

been established that exfoliants do lower the minimal erythral dose (MED) of the skin. This situation can be explained by removal of the stratum corneum, which produces photoprotection through the scattering of light.

One method the FDA has considered to minimize irritation and sun sensitivity induced by AHAs is to limit the concentration and pH of products marketed directly to the consumer. All hydroxy acids perform better at low pH, but the optimal pH for formulation is determined by the pKa of the active ingredient. One method of controlling pH is by altering the concentration of the hydroxy acid. For example, 10% glycolic acid is 4 times more acidic than 1% glycolic acid, with the acidity being determined by electrostatic, inductive, and steric effects and by hydrogen bonding. Concentration alone does not predict the ability of the hydroxy acid to induce exfoliation, however.

The pH and free acid content of hydroxy acid preparations can be changed by buffering the product or through neutralization. Hydroxy acids can be neutralized with an inorganic alkali or organic base to raise the product pH. Glycolic acid preparations frequently are neutralized with sodium hydroxide, allowing for less cutaneous irritation. Completely neutralized glycolic acid, however, with a pH greater than 4.8, contains largely sodium glycolate, which has no anti-aging properties. Free acid is necessary for efficacy.

Hydroxy acid preparations also can be buffered to create a solution that resists pH change when an acid or alkali is added. This buffering is important because the pH of the product may change when it encounters eccrine and sebaceous secretions or the intercellular compartments of the skin. Buffering capacity does not correlate directly with irritancy, however, because highly buffered formulations may still cause cutaneous irritation.

The effects of hydroxy acids on the skin can be significant. Stratum corneum pH changes can remain for 2 hours after application, resulting in epidermal and dermal changes. The extent of these pH changes depends on concentration: Low concentration (1%) AHAs can alter the pH of the outer 3

layers of the stratum corneum, whereas higher concentration (10%) AHAs can affect the stratum corneum pH 10 to 20 layers deep. Application of a glycolic acid preparation to the skin yields a 2.4% concentration in the stratum corneum, an 11.6% concentration in the epidermis, and a 8.6% concentration in the dermis.⁴¹

The issue of hydroxy acid penetration through the skin is important. Data from the FDA study cited previously showed that AHAs ionize to polar molecules as they enter and diffuse through the stratum corneum. Penetration through the epidermis and into the dermis was found when an AHA radiolabeled moisturizer was placed on fresh abdominoplasty skin. Much greater absorption was seen at pH 3 over pH 7 as expected because the concentration of free acid is much higher at pH 3 and almost nil at pH 7. The penetration of the AHA produces a pH gradient from the surface to the dermoepidermal junction. The pH at the skin surface started out at 3 and rose to 5.3 by the time the AHA reached the stratum corneum. At the viable epidermal interface, the pH rose to 6.5 to 7.3. The skin tries to return to a neutral pH when acids are applied.

No regulations have been released, at the time of this writing, by the FDA regarding AHA concentration or pH. Many over-the-counter agents, such as acne treatments and sunscreens, are regulated by monographs issued by the FDA to ensure the safety of the public. Whether AHAs will be the subject of a future monograph to control their use is not known.

Beta Hydroxy Acid

Beta hydroxy acid (BHA) is approved as an exfoliant in the treatment of acne in over-the-counter products at a level of 2% or less. Cosmetic manufacturers commonly introduce salicylic acid into over-the-counter acne products because of its established safety profile. BHA has been rediscovered for its ability to improve the appearance of aged skin, through exfoliation of the skin surface and within pores.

Salicylic acid, the only BHA, is an organic

aromatic carboxylic acid with a hydroxy group in the beta position. This phenolic, hydrophobic, lipophilic compound is chemically unrelated to the AHAs. Salicylic acid is unique among the hydroxy acids because it can enter the milieu of the sebaceous unit, inducing exfoliation in the oily areas of the face. For this reason, it has been used for years by dermatologists as a comedolytic. It is also an excellent keratolytic. Salicylic acid is thought to function through solubilization of intercellular cement, reducing corneocyte adhesion.⁸

Many of the sensitive skin exfoliants incorporate salicylic acid at a concentration of 1.8% at a pH close to its pKa of 2.98. The salicylic acid can be added to exfoliant moisturizers, preferably containing a sunscreen, and exfoliant cleansers or toners. Exfoliation remains valuable in maturing skin because the natural mechanism for stratum corneum desquamation proceeds with decreased fervor as the body ages. It is likely that the concept of exfoliation will remain popular among consumers.

Combination Hydroxy Acids

Combination hydroxy acid formulations combine an AHA and the BHA salicylic acid. These products are not new chemical entities but are difficult to formulate optimally. This difficulty is due to the fact that only the free acid component of the hydroxy acid can provide antiaging benefit to the skin. The pKa for AHAs is 3.83, whereas the pKa for BHA is 2.98. Products must be formulated at a pH close to the pKa for optimal free acid concentration and optimal efficacy. One ingredient must be selected to be of primary importance and to dominate the formulation.

Combination hydroxy acid formulations do not offer the maximum benefits of AHA and BHA ingredients. Their popularity has waned because of this fact. Sometimes these products are referred to as *multiple hydroxy acid* products or *optimized hydroxy acid* products.

Polyhydroxy Acids

Polyhydroxy acids are chemically similar to AHAs but are larger-molecular-weight hy-

droxy acids that exfoliate only on the skin surface, intended to limit dermal penetration. The decreased dermal penetration theoretically means that there is less stinging, burning, and irritation, possibly allowing sensitive skin patients with rosacea or atopic dermatitis to find the products acceptable.

The issue of decreased dermal penetration was examined by Kraeling and Bronaugh²⁹ of the Office of Cosmetics and Colors, a division of the FDA. They found that a glycolic acid oil-in-water emulsion adjusted to pH 3 was extensively absorbed into and through human skin. Approximately 27% of the applied dose of glycolic acid was absorbed in 24 hours. This level was reduced to 21% for the longer-chain hydroxy acid 2-hydroxyoctanoic acid. This difference was not statistically significant. Their study did not evaluate gluconolactone, which is the most commonly used polyhydroxy acid in dermatologic products at the time of this writing. Much research continues on newer, less irritating polyhydroxy acid formulations.

Vitamin A

Many vitamins are being incorporated into topical preparations as specialty ingredients because they are inexpensive and safe. One of the first vitamins with documented skin benefit was vitamin A in the form of tretinoin. The entire family of natural and synthetic vitamin A-related derivatives is collectively known as *retinoids*. Retinoids are biologic modifiers that produce receptor-specific effects within the body, such as improvement in facial wrinkling, decreased tactile roughness, and lightening of solar lentigenes.^{17, 35}

In the plant kingdom, vitamin A (retinol) functions as a free radical scavenger, protecting plants from UV radiation damage. Plants especially high in vitamin A include spinach, carrots, sweet potatoes, squash, and cantaloupe. It has been recognized that vitamin A can decrease and reverse the signs of cutaneous aging.²⁸ The use of retinoids in the reversal and prevention of photoaging was discovered by Kligman, who noted that topical tretinoin improved wrinkling, lentigenes, roughness, and precancerous actinic kerato-

ses. The retinoids also have been shown to improve wound healing and striae distensae. Retinoids are the major prescription agent used for antiaging purposes.

The retinoids are difficult to formulate because of their inherent photoinstability. As antioxidants, they degrade immediately on light exposure to biologically inactive forms. For this reason, vitamin A oral supplements are packaged in amber bottles to prevent UV radiation exposure, and prescription retinoids are packaged in opaque metal or plastic tubes. Topical preparations in which the retinoid has oxidized turn yellow, an indication that some degradation has occurred.⁴³

Even though retinyl palmitate is the easiest retinoid to formulate topically in the over-the-counter market, it is not a biologically active form in the skin. Topical activity of retinyl palmitate is thought to occur after cutaneous enzymatic cleavage of the ester bond and subsequent conversion of retinol to retinoic acid. This cutaneous conversion of retinol to retinoic acid is responsible for the biologic activity of some of the new stabilized over-the-counter retinol preparations.⁹ Only small amounts of retinol can be converted by the skin, accounting for the increased efficacy seen with prescription preparations containing retinoic acid.

Vitamin A remains a popular additive to many skin care products. It is likely in most of these formulations that the vitamin A is added for marketing appeal or to function as a humectant moisturizer, if the concentration is significant. As discussed previously, some vitamins can function as humectants to attract moisture from the upper dermis to the epidermis. With the new developments in vitamin stability, more retinoids are sure to enter the prescription and over-the-counter market.

Vitamin C

The active form of vitamin C in the body is L-ascorbic acid, functioning as an antioxidant by scavenging and quenching free radicals and by regenerating vitamin E from its radical form.²⁵ Vitamin C also can act as an oxidant, however, only when in the presence of transition metal ions, such as iron. It is a

water-soluble vitamin found in vegetables and citrus fruits that has received tremendous popular press for its value in topical preparations.

It is well documented that vitamin C is necessary for wound healing because it is a cofactor for lysyl and prolyl hydroxylase, which stabilize the triple helical structure of collagen. Whether oral or topical supplementation of vitamin C enhances wound healing is controversial. Some investigators have shown enhanced cutaneous vitamin C levels after topical application of 10% L-ascorbic acid; this work was performed on a porcine model, however.⁶ Other human studies have shown a decrease in the minimal erythema dose and less erythema after UV-B exposure in subjects treated with topical 10% L-ascorbic acid.³⁴ Vitamin C also has been purported to produce lightening of skin dyspigmentation in the form of magnesium L-ascorbyl-2-phosphate.²⁷

More research is required before the benefits of topical vitamin C in humans can be confirmed. One of the problems in developing topical vitamin C preparations is the inactivation of the molecule on exposure to light, moisture, and oxygen. This occurs in topical formulations as well as in the skin, where the body reservoir of 1500 mg is rapidly depleted. At present, oral ingestion is the best way to maintain vitamin C concentrations in the skin until new developments occur in topical vitamin C stabilization.

Vitamin E

Vitamin E is another vitamin important to optimal functioning of the skin. Vitamin E includes the tocopherols and tocotrienols; however, the biologically active forms are alpha and gamma tocopherol. These forms function as lipid-soluble antioxidants, with alpha tocopherol possessing greater biologic activity than gamma tocopherol. Dietary sources of vitamin E include vegetables, oils, seeds, corn, soy, whole-wheat flour, margarine, nuts, and some meats and dairy products.³³

Vitamin E is found naturally in the membranes of cells and organelles. It prevents oxi-

dation of the polyunsaturated fatty acids of the phospholipids in the membranes by capturing singlet oxygen species.⁴ It also stabilizes the membranes against damage by phospholipase A, free fatty acids, and lysophospholipids.²⁶ The antioxidant capabilities of alpha tocopherol are due to its ability to function as a lipid radical scavenger able to terminate lipid radical chain reactions. In this reaction, a low-energy tocopheroxyl radical is formed; however, this radical cannot function further as an antioxidant. Regeneration can occur in the presence of vitamin C to allow the vitamin E to function again as a radical scavenger.²⁵ It may also protect membrane proteins containing selenium or sulfur. The vitamin E concentration in the epidermis is about 1.0 nmol/g.¹⁵ Even though its concentration in the body is relatively low, it is the most important lipid-soluble, membrane-bound antioxidant in the body.

A variety of claims have been made regarding the topical effects of vitamin E on the skin, including improved moisturization, increased softness, and better smoothness. Photoprotective effects have been evaluated for topical and oral preparations. Topically applied alpha tocopherol has been shown to inhibit UV-B-induced edema and erythema, conferring an sun protection factor of 3, after multiple applications.²³ This protection is thought to be due to its ability to absorb light marginally and function as a free radical-quenching, lipid-soluble antioxidant.³² Oral vitamin E was shown to confer no photoprotective effects, however.⁴⁵

It is important to separate the documented oral effects of a vitamin from the topical effects. There are two different vitamin delivery mechanisms to the skin. Vitamin E is an established antioxidant when consumed; however, there are limited data regarding its value as a topically applied antioxidant. In most topical preparations currently marketed, vitamin E, in the form of tocopheryl acetate, functions as a preservative to prevent oxidation of the product on the shelf. Tocopheryl acetate is remarkably stable but has no biologic activity. Tocopheryl acetate is an excellent skin conditioner and is included in many over-the-counter moisturizers for this purpose.

Panthenol

Humectant vitamins play an important role in skin moisturizers. One of the best vitamin humectants is panthenol. Panthenol is the biologically active alcohol form of pantothenic acid, also known as *vitamin B₅*, and is enzymatically converted to pantothenic acid in the skin. It is widely used topically as a skin-conditioning and hair-conditioning agent in moisturizers, shampoos, hairsprays, and hair styling aids. It can hold and attract water. This feature is important because water is the plasticizing agent found naturally in skin and hair. Many vitamin-enriched moisturizing creams and lotions contain panthenol in a concentration of 5%, which also has been shown to enhance wound healing. This is an example of a vitamin being used for its physical, rather than nutritional, properties in topical preparations.

Niacinamide

Vitamins also can function as exfoliants, which is the case with niacinamide. Niacinamide, also known as *nicotinamide*, is the pyridine-3-carboxylic acid amide form of niacin. It is a white crystalline solid that is soluble in water and stable to heat and oxygen. It is found in the body in all metabolically active tissues, including the skin.²⁰ Niacinamide does not produce the flushing experienced with niacin.⁴¹

Topical 4% niacinamide has been shown to be of dermatologic benefit in the treatment of papular and pustular acne in a 4% gel.¹² It also has been reported to aid in the treatment of bullous pemphigoid^{13, 22} and necrobiosis lipoidica.¹⁹ Other studies have shown the value of oral niacinamide in the prevention of insulin-dependent diabetes mellitus.³¹ The anti-aging cutaneous effects of niacinamide include the promotion of antitumor characteristics in keratinocytes³⁰ and the suppression of UV-B photocarcinogenesis.¹⁶

The beneficial cutaneous effects from the topical application of niacinamide, especially the improvement in photocarcinogenesis and its antitumor characteristics, have led to further research regarding the usefulness of nia-

cinamide as a moisturizer additive. It is easy to formulate because of its water solubility and stability in the presence of light and oxygen. Niacinamide also has been found to function as an exfoliant (M. G. Mercurio, personal communication). Many new, lesser known vitamins may become part of topical formulations in the future.

EFFICACY ASSESSMENT OF MOISTURIZERS WITH SPECIALTY INGREDIENTS

Many specialty ingredients are being included in moisturizer formulations. It is important for the dermatologist to assess the value of the additive accurately. Does it have any biologic benefit? Is it a possible source of cutaneous harm? Is the additive primarily of marketing value? What data are available in the scientific literature to document cutaneous benefits? This assessment is particularly important for vitamins, in which stability is an issue. Table 6 lists the requirements for biologic activity in vitamin-containing formulations. Products that do not meet these criteria are not biologically active vitamin preparations. Vitamins in many cases are added for other reasons besides biologic activity, however.

Table 7 summarizes some of the effects of oxygen, light, temperature, acid, and base exposure on vitamins. This table is helpful when assessing vitamin formulations. For example, it is impossible to create a biologically active vitamin A cream that contains free glycolic acid because vitamin A is biologically unstable in the presence of acids. These chemical incompatibilities are key to understanding the complexity of moisturizer formulation. Vitamin A may have been added to the

Table 6. CONSIDERATIONS FOR FORMULATING TOPICAL VITAMIN PREPARATIONS

Vitamin must be nontoxic and of cosmetic grade
Vitamin must be bioavailable in the vehicle selected with substantivity for the skin
Vitamin must remain in its biologically active form during manufacture, in its final packaging, and under consumer use conditions
Vitamin must reach the target tissue in its biologically active form

Table 7. VITAMIN STABILITY

Vitamin	Oxygen	Light	100°C	Acids	Bases
A	U	U	S	U	S
E	U	U	S	S	S
Niacinamide	S	S	S	S	S
Panthenol	S	S	U	U	U
C	U	U	U	S	U

U = unstable; S = stable.

glycolic acid lotion, but no biologically active vitamin A is present when the moisturizer is applied to the skin. Ingredient listings contain the substances that were placed into the mixing vat at the time of manufacture. They do not list the final form of the ingredients when placed on the skin by the consumer. These are some of the key points to consider when evaluating moisturizer specialty additives.

SUMMARY

Moisturizers have been adapted to perform many important roles on the skin surface. Simple moisturizers combine occlusives and humectants to enhance the water-holding capacity of the skin. The addition of carefully selected emollients can influence the esthetic properties of the moisturizer and the stability of the active ingredients. The addition of sunscreens to moisturizers has created a new product category with an added skin function. Further diversity in moisturizer formulation is created through the addition of specialty ingredients, designed to enhance the functioning of the skin. Moisturizers are an important part of the dermatologist's armamentarium.

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