

Prescription Versus Over-the-counter Moisturizers: Unraveling the Mystery



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Moisturizers are the single most important category of products in dermatology. Moisturizer formulations function as the vehicle in all lotion and cream prescription products. They can carry corticosteroids, retinoids, benzoyl peroxide, and topical antibiotics to the skin. Moisturizers also are the basis of all lotion and cream sunscreens. Further, moisturizers are an important active agent in all cosmeceuticals allowing substantiation of claims such as improved skin appearance, reduction in the appearance of fine lines, and alleviation of dryness.

More recently, moisturizers have adapted to the prescription realm in the role of barrier repair creams. Is there a difference between moisturization and barrier repair? It is an interesting question because moisturizers do not really moisturize the skin. While water may be the first ingredient in lotion moisturizer formulations, the water simply evaporates from the skin leaving behind oil-soluble ingredients suspended within the water phase with an emulsifier. This water does not moisturize the skin. Where then does the water come from that hydrates the skin in a moisturizer? The water comes from within the body and the moisturizer prevents the water from leaving the skin and evaporating into the lower humidity environment. Moisturizers actually function by creating an environment that is optimal for barrier repair, allowing the skin barrier to heal itself in the most efficient manner possible. Thus moisturization and barrier repair are really synonyms for the same process; however, prescription moisturizers are labeled as barrier repair products while over-the-counter (OTC) moisturizers are simply termed moisturizers.

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Repairing the Skin Barrier

Damage to the skin barrier results in increased water loss, thus signaling the body that intercellular lipid synthesis must be initiated. The skin barrier is formed by the protein-rich cells of the stratum corneum with intervening intercellular lipids. In the viable epidermis, the nucleated cells possess tight, gap, and adherens junctions with desmosomes and cytoskeletal elements that contribute to the barrier. Moisturizers attempt to mimic the intercellular lipids that are synthesized in the keratinocytes during epidermal differentiation and then are extruded into the extracellular domains. These lipids are composed of ceramides, free fatty acids, and cholesterol, which covalently bind to the cornified envelope proteins. Many moisturizers include these substances in an attempt to provide “natural” ingredients to aid in barrier repair. It is unlikely that externally applied ceramides, free fatty acids, or cholesterol get incorporated into the extracellular lipids, but they may aid in creating an environment for barrier repair, which is the rationale for most prescription moisturizers currently available.

Prescription Barrier Repair Moisturizers

Prescription barrier repair moisturizers possess many of the same ingredients found in the OTC market, yet these creams are different because the US Food and Drug Administration has approved them as a 510(k) device. The 510(k) device approval process was originally developed to insure the safety of equipment with an on/off switch. Lasers, light devices, cardiac pacemakers, and insulin pumps represent equipment requiring this type of approval. While creams are not traditionally thought of as “devices,” they received approval because they induce a physical change in the skin. This physical change was documented as an increase in skin hydration resulting from a decrease in water loss to the environment, known as transepidermal water loss (TEWL).

Barrier repair products place a water-impervious film over the skin surface, which decreases TEWL. Transepidermal water loss is elevated when the skin

barrier is damaged, representing the physiologic signal for barrier repair initiated by ceramide synthesis. There are a variety of different formulations that presently have 510(k) approval producing barrier repair by different mechanisms based on a variety of key ingredients. The key ingredients in the prescription moisturizers are all available in the OTC market; however, their value in barrier repair is discussed.

The Skin Barrier and Ceramide Replacement

As previously mentioned, ceramide synthesis is the first step in barrier repair. This recognition has led to a variety of OTC creams based on ceramide technology (CeraVe, Coria Laboratories; Curél, Kao Brands Company). Nine different ceramides have been identified and synthetically duplicated for inclusion in moisturizer formulations.¹ The ceramides are distinguished by their polar head group architecture as well as their hydrocarbon chain properties.² A ceramide-dominant, triple-lipid barrier repair formulation (EpiCeram, Promius Pharma) was designed to correct the lipid-biochemical abnormalities in atopic dermatitis. It contains *n*-capric acid, cholesterol, and conjugated linolenic acid. In addition, candelilla and petrolatum is included to decrease TEWL. It received US Food and Drug Administration approval in April 2006 for use as a nonsteroidal lipid barrier emulsion to manage the symptoms of dry skin associated with a variety of dermatologic diseases.³ It was compared to fluticasone cream in 121 patients with moderate to severe atopic dermatitis for 28 days. The researchers found that the ceramide device reduced SCORing atopic dermatitis (SCORAD) scores, decreased pruritus, and improved sleep habits; however, faster improvement was seen with the topical corticosteroid at day 14.⁴ The unique aspect of this cream is that the patented ratio of the triple-lipid combination mimics that of physiologic lipids.

Over-the-counter ceramide formulations contain similar ceramides to prescription formulations but do not utilize the patented ratio. To do so, they would have to purchase a license for use of the patent from the inventor. It is unknown how important the ratio is versus the presence of ceramides. While it is possible to demonstrate penetration of ceramides into the stratum corneum by analyzing tape stripping of the skin following application, it is hard to know exactly how these externally applied ceramides affect skin physiology. Because the skin heals itself eventually, with or without the external application of moisturizers, it is difficult to study the subtleties of moisturizer-expedited healing. Over-the-counter moisturizers cannot make the same claims as barrier repair device moisturizers,

but their ingredient disclosure and effect on the skin is similar.

Natural Hyaluronic Acid Humectancy and Barrier Repair

Maintaining proper water balance in the skin is key to keeping skin hydrated in a hostile environment. The skin must have some capacity to hold water or desiccation would occur immediately. The natural water holding material in the dermis is primarily hyaluronic acid, which is the same material used for injection as a cosmetic filler (Juvéderm, Allergan Inc; Restylane, Medicis Aesthetics Inc). These injectable hyaluronic acids are approved as devices and so are some prescription moisturizers based on hyaluronic acid. Topically, hyaluronic acid is known as a humectant, which is the technical name for substances that attract and hold water. Prescription hyaluronic acid moisturizers are available as high concentration foams combined with glycerin, dimethicone, and petrolatum (Hylatopic, Onset Therapeutics) and liquids in combination with glycerol and sorbitol (Bionect, JSJ Pharmaceuticals).

Does the inclusion of hyaluronic acid make a product a prescription? Not necessarily. Several high-end OTC cosmetic moisturizers contain hyaluronic acid. Is hyaluronic acid the only humectant in the marketplace? No. Glycerin, proteins, vitamins, propylene glycol, and polyethylene glycol are more commonly used, less expensive humectants. Humectant ingredients are included in all highly effective OTC moisturizers. The difference is that prescription moisturizers have submitted a 510(k) application based on the humectancy of hyaluronic acid while the OTC moisturizers have not.

Fatty Acids, Lipid Trilayers, and Barrier Repair

A different approach to skin moisturization is the use of free fatty acids. Free fatty acids are found in the intercellular lipids that reside between corneocytes to create a waterproof, moderately impermeable barrier. Scanning electron micrographs show the intercellular lipid bands as trilayer entities with a dimension of 3.3 nm. These bands usually occur in groups of 6 or 9 and are again essential for human life. It is estimated that the lipid layer has a total thickness of 13 nm and accounts for the inability of particles larger than 13 nm to penetrate the skin. Indeed, nanoparticles smaller than 13 nm can penetrate, causing the health concerns currently debated.

It is theorized that supplementing the skin with free fatty acids can lead to barrier repair. One such 510(k)-approved barrier cream contains palmitamide monoethanolamine (PEA) and olive oil, glycerin, and vegetable oil

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(Mimyx, Stiefel, a GSK company). Palmitamide monoethanolamine is a fatty acid that is said to be deficient in atopic skin, and it is theorized that replacing this fatty acid can hasten disease resolution.⁵ It is also thought that PEA, an analogue of cannabis, also may affect the itch pathways.

In an open-label study of 2456 patients, the intensity of erythema, pruritus, excoriation, scaling, lichenification, and dryness were substantially reduced with a combined score reduction of 58.6% when subjects applied the PEA-based barrier cream.⁶ However, there was no placebo in this uncontrolled prospective cohort study, which always presents challenges in data interpretation. Is it the olive oil and glycerin that are the active agents or the PEA? Olive oil has been touted to have many healing properties in the homeopathic literature. It is rich in essential fatty acids, perhaps accounting for its reputation as a heart-healthy cooking oil, which also have been shown to reduce signs of atopic dermatitis when topically applied to rodents. Certainly, animals fed essential fatty acid-deficient diets experience a condition similar to atopic dermatitis, but oral consumption is preferable to topical application. Olive oil also is on the list of facial comedones, being the culprit in pomade acne. While the final formulation has unique effects, it can be difficult to determine what ingredient really works, which is easy to do with prescription dermatologics where the main drug is identified followed by the other inactive constituents. This type of disclosure is not required of prescription device barrier creams.

Barrier Repair With Anti-inflammatory Agents

One of the earliest signs of barrier damage is the onset of inflammation, accounting for the redness and itching characteristic of dermatoses manifesting barrier issues. To alleviate symptoms, many barrier repair products incorporate anti-inflammatory agents derived from botanical sources. These anti-inflammatories are found in both OTC and prescription moisturizers. One currently marketed prescription barrier cream contains glycyrrhizic acid and *Vitis vinifera* extracts (Atopiclair, Graceway Pharmaceuticals, LLC). In addition, it contains allantoin, α -bisabolol, hyaluronic acid, and shea butter. Glycyrrhizic acid is a licorice extract that was reported to be safe by the Cosmetic Ingredient Review Expert Panel with the ability to block gap junction intracellular communication; however, it is cytotoxic at high concentrations.⁶ It is mainly used in moisturizer formulations as an anti-inflammatory.⁷ In an open-label multicenter study, the product was shown to reduce the median visual analog scale rating for itching in atopic dermatitis from

48.5 mm to 34.1 mm after 3 weeks of treatment with a further reduction to 24.6 mm after 6 weeks of treatment.⁸ In a second study of 142 pediatric patients aged 6 months to 12 years, the same formulation was compared to a vehicle cream and found to be statistically more effective in reducing the symptoms of mild to moderate atopic dermatitis.⁹

Licorice derivatives also are found in OTC moisturizers, especially those targeted for redness reduction in rosacea patients (Eucerin, Beiersdorf Inc). One formulation contains an extract of *Glycyrrhiza inflata*. There are many different species of licorice extracts, not all of which possess the same cutaneous effects. Some licorice extracts are used for skin-lightening purposes and not primarily as anti-inflammatories. Again, is the licorice extract the active anti-inflammatory ingredient in the barrier repair cream? Does it function like a naturally occurring topical corticosteroid to reduce the signs and symptoms of atopic dermatitis? Or, is it the hyaluronic acid humectant that is attracting water, which is trapped in the skin by the shea butter occlusive moisturizer? In reality, it may be hard to tell what is really working unless each of the “active agents” is tested separately in the same vehicle. Even then, it may be hard to separate the vehicle arm from the vehicle plus single ingredient arms. This is the challenge in designing clinical studies to validate the efficacy of barrier creams.

Vintage Ingredients for Barrier Repair

The oldest barrier repair product is petrolatum. Interestingly, it is an OTC ingredient found in many prescription barrier products. Petrolatum is a semisolid mixture of hydrocarbons obtained through the dewaxing of heavy mineral oils. Pure cosmetic-grade petrolatum is practically odorless and tasteless; however, other hydrocarbon contaminants in lower quality petrolatum may account for a distinct chemical smell noted with some products. Petrolatum first appeared in the United States Pharmacopeia in 1880 and has been a widely used ingredient in skin care products and topical pharmaceuticals ever since. It is interesting to note that petrolatum has never been duplicated synthetically. Some barrier repair creams contain petrolatum as their primary ingredient (Eletone, Ferndale Laboratories, Inc). Petrolatum remains the gold standard for barrier repair ingredients because it is the substance closest to the natural intercellular lipids and it can intercalate into the intercellular spaces.¹⁰

Another time-tested barrier repair ingredient used both in the OTC and prescription barrier cream realm is paraffin wax. Liquid paraffin combined with paraffin wax is the basis for a prescription barrier cream used

in the management of burns and radiation dermatitis (Biafine, Ortho Dermatologics). The wax provides an artificial barrier until healing can occur. In addition, it was demonstrated that the formulation was chemotactic for macrophages and increased the IL-1/IL-6 ratio in epidermal wounds in normal human volunteers.¹¹

Summary

The final question is what is the difference between prescription barrier repair products and moisturizers? I would say that the main difference is that the prescription barrier repair products have filed for a 510(k) device approval and the OTC moisturizers have not. Could the OTC moisturizers apply for 510(k) device approval and get accepted? Probably, but it is an added expense and not part of the marketing strategy of most consumer moisturizer companies. However, change is occurring rapidly in the 510(k) approval route. Not only is safety an issue, but efficacy also is becoming a criterion to support product claims. This change in 510(k) approval ideology is sure to be seen in dermatology with barrier cream products. There really is no mystery once the products are examined and compared in detail.

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