JAR Pharmaceuticals Ltd.
PHLODERM™ Skin Moisturizer

Phase 1: Preliminary Basic Science Report of Xerosis and Treatments

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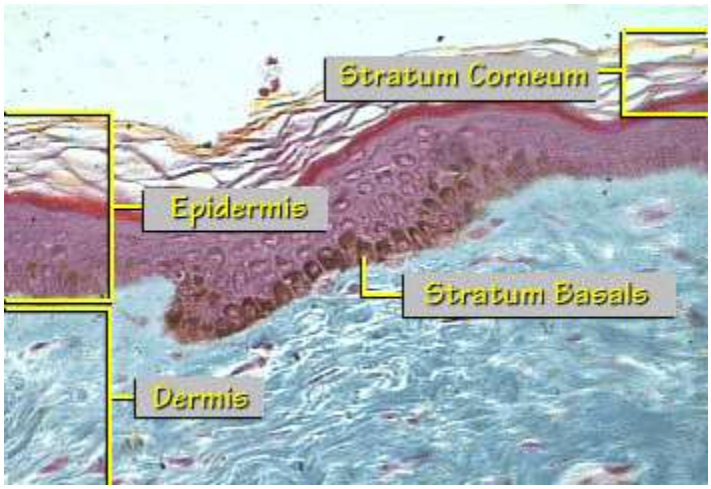
Your Skin

Your skin is your body's largest organ. It covers you from head to toe, it protects you, it keeps you warm and cools you down. It acts as a barrier to shelter you from external factors such as infection and environmental assaults such as sun, wind, heat, dryness and cold[1]. Your skin is divided into two primary layers: the outer epidermis and the inner dermis (Fig. 1). Every month new cells replace the epidermis in a process referred to as desquamation[2]. The main function of the epidermis is to produce the selectively permeable outer layer of your skin termed the stratum corneum. It is this layer that is responsible for protecting us against the external factors mentioned above. The stratum corneum is composed of corneocytes (dead cells) surrounded by a continuous lipid matrix. The barrier properties of the stratum corneum are highly dependent on its lipid content. For example, the absence of dietary lipids leads to unhealthy skin[3] that can be restored to normal skin by the topical application of essential fatty acids (EFA)[4].



Dry Skin or Xerosis

To maintain its integrity and have the softness and pliability of normal skin the water concentration of the stratum corneum should be between 20 and 35 percent[5]. Although there is no single biologic feature responsible for dry skin, anything that decreases the water content of the stratum corneum, such as the reduced humidity and cold weather associated with Northern climates, can accentuate it. Dry skin can range from 'winter itch' to grossly eczematized or dermatitic skin[6]. It most commonly appears at the extremities, including legs, feet, knees, elbows and hands, which are commonly subjected to microtraumas. Abnormally dry skin, termed xerosis, occurs as a result of transepidermal water loss (TEWL) from a disturbance in the barrier function of the stratum corneum[7]. As the integrity of the epidermis decreases, TEWL increases. Xerosis can cause cracks in your skin, which in turn opens the door for bacteria, viruses and fungi (pathogens) to enter our bodies. Since your skin is your first line of defense (known as innate immunity) against most pathogens, cracks in your skin often lead to infections. By applying moisturizers to your skin you can restore the epidermal integrity, thereby-mitigating TEWL and infections. Variations in the levels and types of lipids present in the stratum corneum

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can influence barrier function, water content and skin condition. Genetics, aging, diet (including drugs like diuretics), environmental factors (such as occupational exposure) and certain diseases (e.g., diabetes) all influence the lipids present in the stratum corneum.

Occupational Xerosis

Occupational xerosis occurs as a result of the natural moisturizing factors, including protective oils (i.e., lipids) being removed from your skin making the stratum corneum permeable[8]. This occurs with frequent handwashing seen in professions such as doctors, nurses, dentists and foodworkers; exposure to solvents (e.g., propylene glycol, glycerine, DMSO and certain alcohols) by chemical and oil workers and by extensive contact with water, soap, detergents and other degreasing agents. This loss of epidermal integrity makes skin more prone to cracking and subsequent infection. The prophylactic use of moisturizers, particularly emollients, can help protect and revitalize the lipid structure and prevent occupationally induced xerotic skin.

Diabetic Xerosis

Skin problems are a major concern among patients with diabetes, with as much as a third having skin disorders throughout their life. Not only is a diabetic patient's skin more susceptible to infection, it is also generally slower to heal. As a result, diabetics face the compounding problem of being more prone to infection and slower to heal if infection occurs. One of the principle causes of diabetic skin disorders is a nerve disorder termed neuropathy. Symptoms of peripheral neuropathy include numbness and sometimes pain in the hands, feet, or legs. Because of the loss of sensation, many skin traumas go unnoticed. This mechanical failure of the stratum corneum compromises the body's first line of immune defense (innate immunity) and can lead to infections[9]. These infections can become very serious, ultimately leading to amputations. Doctors estimate that nearly three quarters of all amputations caused by neuropathy and poor circulation could be prevented with careful skin care[10]. The use of moisturizers can retard moisture loss and help prevent dry, cracked skin helping to both preserve and re-establish skin integrity and plasticity[11].

Pharmacological Treatment of Xerosis

The early research of Dr. Irwin Blank pointed out that water was important for the moisturization and plasticity of the stratum corneum[12]. One common and effective way to combat dry skin is the frequent use of moisturizers, including emollients. Moisturizers work by leaving a protective layer on the skin allowing the stratum corneum to retain water for a longer period of time and prevent evaporation (i.e., reducing the TEWL) allowing for increased hydration. A quality moisturizer contains both humectant and occlusive ingredients to rehydrate the skin optimally. Humectants attract water from the viable skin layers to the stratum corneum and temporarily hold it there to provide moisture. Humectants can make the skin feel softer by smoothing-in holes in the stratum corneum through swelling. In contrast, occlusive moisturizing agents condition the skin by preventing evaporation (i.e., decreasing TEWL) from the skin surface.

1. Emollients

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Emollients are oily substances that help to maintain the soft, smooth, pliable feel and pleasing appearance of the skin. They function by filling in crevices between the desquamating corneocytes on the epidermal surface, and improve the skins lubrication by moisturization. The lipids in emollients help restore the normal barrier function of the skin and protect it from external influences. The length of time an application of emollient works depends on the season, the patient's occupation, and the types of preparations used.

2. Exfoliants

Exfoliants are substances that increase the desquamation rate of the corneocytes in the stratum corneum. In doing so, they stimulate the growth of new skin and restore the integrity of the epidermis[13]. The principal exfoliants commonly incorporated into skin care products are urea, and the hydroxy acids.

Urea
Urea, one of the natural moisturizing factors in the skin, functions as both a moisturizer and an exfoliant. It moisturizes your epidermis by disrupting hydrogen bonding, thereby exposing the water binding sites on the corneocytes. It also promotes desquamation (shedding) of the corneocytes, by dissolving the intercellular cementing substance holding them together[14].

Hydroxy Acids
The alpha and beta hydroxy acids are organic carboxylic acids having a hydroxyl group at the alpha or beta position respectively. Their function as exfoliant moisturizers on the skin can be significant. As mentioned above, exfoliation is fundamental to give the skin a rejuvenated appearance. Two of the first alpha hydroxy acids to reach the market were glycolic acid and lactic acid. Although these non-toxic organic acids were originally found in foods (sugar cane and sour milk respectively), they are currently produced synthetically. The only beta hydroxy acid is salicylic acid. The mechanism of action of the hydroxy acids is not yet completely understood, however it has been suggested that they increase exfoliation by interfering with ionic bonds, dissolving the intercellular cement between adjacent corneocytes, reducing intercellular adhesion[15,16].

3. Antioxidants
Ultraviolet light (e.g., sunshine) and environmental pollutants are known initiators of free radicals. Free radicals are highly reactive molecules that damage cellular membranes and DNA. Antioxidants function by scavenging and neutralizing free radicals. Vitamin A (retinoid), vitamin C and vitamin E are the most prominent vitamin-based antioxidants, each with specific benefits. They are added to skin creams in an effort to decrease the harmful effects of free radicals on cell viability. Despite the low concentration of vitamin E in the epidermis (about 1 nmol/g[17]) it remains the most important lipid soluble antioxidant occurring naturally in cell membranes[18]. Antioxidants prevent the oxidation of unsaturated fatty acids in the membranes of

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cells. Numerous clinical rejuvenating effects have been shown with the topical application of vitamin E, including visible improvement in the signs of aging skin[19].

Why Phloderm?

Phloderm™ combines the essential elements for rejuvenating dry skin, including emollients, exfoliants, antioxidants and natural cell-building phospholipids. It doesn't just 'sit on the surface', it penetrates. Most importantly, when applied it has no lasting greasy or waxy feel, leaving the skin smooth and supple[20]. In contrast, many popular commercial moisturizers perform only one of the above functions compared to Phloderm's™ total adjuvant action. This makes Phloderm™a revolutionary moisturizer for maintaining the viability and integrity of epidermis, particularly the stratum corneum barrier layer.

In addition to providing the essential elements for combating xerosis, Phloderm™ can be used as a penetrating vehicle for medicaments to counteract skin disorders accompanying dry skin such as rash, infections, eruptions due to insect toxins, dermatitis and eczema.

Figure 2 illustrates the transient structural changes that occur within the skin when certain elements of Phloderm™ are administered. It indicates how a medicament incorporated in Phloderm™ may be able to migrate to the underlying tissues and blood vessels.

The lipids present in the stratum corneum are also important for efficient barrier function[21]. By configuring molecules to assimilate with the lipid barrier, the components of Phloderm™ can perform both roles, transport through and repair of damaged epidermal barrier[22]. All of this makes Phloderm™ revolutionary as a moisturizer to help restore the skin's normal texture and barrier function.

Fig. 2. Low temperature scanning electron micrographs of intact (a), isolated and ethanol washed (b) and 250 mM lecithin microemulsion gel treated human stratum corneum over 5 days (c). [Reprinted from J. Control. Rel., 45, 131-140 (1997). F. Dreher et al., Interaction of a lecithin microemulsion gel with human stratum corneum and its effect on transdermal transport. With permission from Elsevier Science (Copyright)]

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