INTRODUCTION

A moisturizer is an agent designed to make the stratum corneum softer and more pliable by increasing its hydration. A large number of preparations are available, most of which are marketed as cosmetic moisturizers ***(Bikowski, 2001; Loden, 2005).***

Moisturizers include mainly occlusives and humectants ***(Baumann, 2002).*** The classification of moisturizers, however, is not uniform. Some people include emollients in the classification ***(Draelos, 2000),*** while others believe emollients to be a separate entity ***(Fluhr et al., 2002).***

Occlusives are many different substances that can be utilized to occlude the stratum corneum and reduce transepidermal water loss (e.g. petrolatum)**.** Humectants are substances that absorb or help another substance retain moisture. An emollient is a substance that makes skin soft or supple**.** However, many emollients also function as humectants or occlusive moisturizers ***(Baumann, 2002)***.

Moisturizing creams marketed to consumers often contain trendy ingredients and are accompanied by exciting names and attractive claims. Moisturizers are also an important part of the dermatologist's armamentarium to treat dry skin conditions and maintain healthy skin. The products can be regarded as cosmetics, but may also be regulated as medical

products if they are marketed against dry skin diseases, such as atopic dermatitis and ichthyosis ***(Loden, 2005).***

Moisturizers can also serve as important adjective therapeutic modalities for patients with various dermatologic disorders including rosacea, retinoid-induced irritant dermatitis and psoriasis ***(Bikowski, 2001; Hagstromer et al., 2006).***

An ideal moisturizer should be effective in preventing water loss, make the skin smooth and supple, aid in restoring the lipid barrier and should also be suitable for sensitive skin i.e hypoallergenic, non-comedogenic, non sensitizing, absorbed rapidly and of long lasting effect ***(Baumann, 2002)***.

AIM OF THE ESSAY

The aim of this essay is to review the different types of moisturizers, their mechanism of action, properties and their relevant uses in dermatology.

SKIN BARRIER

Skin is a physical barrier to the environment as its primary function is to form a barrier between the external environment and the inside of the body. The exchange between the external and internal environment is a process that depends on the difference between the water concentration in the epidermis and that in the outside environment ***(Atherton, 2001).***

This cutaneous barrier resides in the stratum corneum (SC) layer of the epidermis which is composed of two components: protein enriched nonviable corneocytes with their natural moisturizing factor (NMF) and lipid laden intercellular domains ***(Harding and Scott, 2002)***. Not only does this barrier prevent the unwanted exogenous agents, such as microbes from entering the body, but also reduces the amount of water lost through the skin known as transepidermal water loss (TEWL). The SC also serves as a depot for storage of lipophilic drugs such as corticosteroids ***(Kligman, 2000a).*** Damage of this barrier causes dryness and dermatitis when skin is exposed to water, soaps, gloves, chemicals and harsh weather conditions. The repair of this damage is helped by moisturizers through the physical and chemical interaction of their ingredients with the natural skin barrier ***(Diepgen, 1996).***

Hydration of the skin

Water is essential for maintaining flexibility and elasticity of the skin ***(Imokawa, 2002).*** The function of moisturizers is to maintain the SC hydrated. Dehydrated skin loses elasticity and becomes rigid and brittle, which causes the skin to become rough and flaky ***(Verdier-Sevrains Bonte, 2007)***. The SC possesses approximately 30% water, 10% of which is bound to lipids and the remaining 20% which is resistant to solvent and water extraction, is closely dependent on presence of NMF. Healthy SC must be able to maintain an adequate level of water against the evaporative diffusion gradient created by a low relative humidity. The state of hydration of SC is governed by three factors: the water that reaches it from the underlying dermis, water lost from the surface by evaporation and the intrinsic ability of this layer to hold water ***(Harding et al., 2002).***

The primary water supply for the SC is the underlying tissue, provided its water-holding capacity is intact. Within the corneocytes, the presence of NMF depends on production of the protein filaggrin by the corneocytes and intracellular post processing of filaggrin, which is associated with orderly maturation ***(Clark, 2004).***

Transepidermal water loss is the most important factor in controlling loss of water in an intact intercellular lipid barrier. The presence of lipid layers impedes evaporation. Intracellular water content produces changes in the

corneocytes that give flexibility, allowing free movement without cracking or fissuring. Lack of hydration leads to a slow down in barrier recovery, reduced enzyme activity, and a shift in the pH of the SC ***(Harding et al., 2003; Rawlings et al., 2004).***

Epidermal development

In order to maintain water within the skin, epidermal keratinocytes undergo characteristic changes during their ascent through the epidermis that transform them from nucleated columnar basal cells to flat anucleated dead corneocytes. These changes include: loss of their nuclei and cytoplasmic organelles, and becoming filled with tonofilaments (keratin intermediate filaments (KIFs)) embedded in an amorphous proteinaceous matrix "Filaggrin" (Figure 1) ***(Downing and Stewart, 2000).***

In the basal cell layer, KIFs are composed mainly of keratins K5 and K14 ***(Roop et al., 1987).*** On entering the spinous cell layer, keratinocytes start on the one-way path of terminal differentiation. During this phase, K1 and K10 are upregulated. The keratin polypeptides readily polymerize in the cytoplasm forming KIFs which then aggregate into bundles ***(Collin et al., 1992).***

In the **granular cell layer** the keratohyaline granules (KHG) appear, KIFs continue to aggregate in large bundles, metabolic activity decreases and the keratinocytes begin to

lose their cytoplasmic organelles. The description of the cells in this layer results from the granular appearance produced by deposits of KHG which are seen by light microscopy and not from the appearance of lamellar granules (Odland bodies) which are much smaller and observed by the electron microscope. As the granular cells move towards the surface, KHG increase in size ***(Downing and Stewart, 2000).***

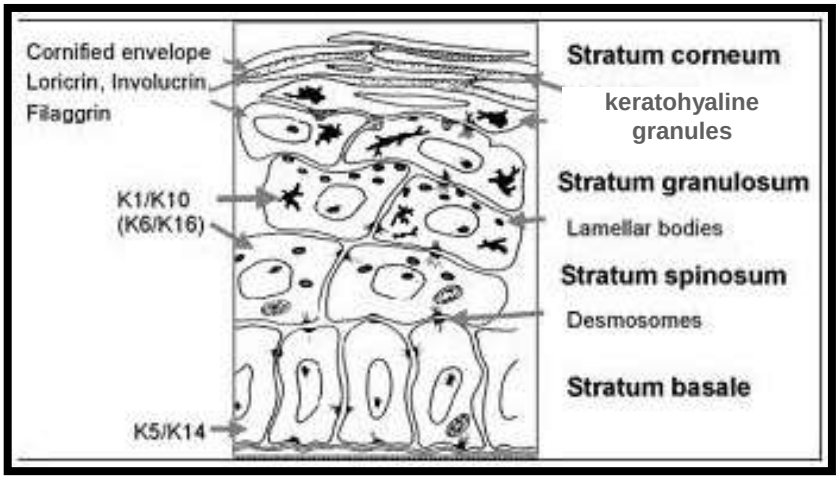


Fig. (1): Epidermal differentiation: During epidermal differentiation specific keratins and cornified envelope proteins as well as lipids are formed ***(Downing and Stewart., 2000).***

Profilaggrin is released from KHG and undergoes proteolysis and dephosphorylation by phosphatase enzyme (derived from lamellar granules) to form filaggrin. Filaggrin acts as a matrix protein and establishes precise, parallel rows of the already present KIF densely packing them into bundles with resultant formation of macrofibrils (Figure 2) ***(Presland et al., 1995).***

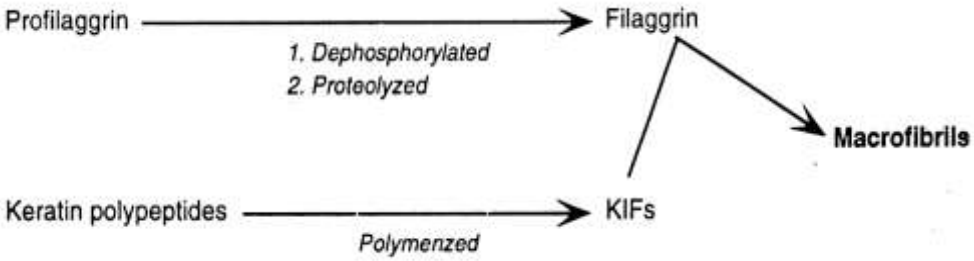


Fig. (2): The mechanism of profilaggrin in formation of macrofibrils ***(Presland et al., 1995).***

In **the cornified horny layer,** all keratinocytes are dead. In the lower SC, they are composed of a plasma membrane surounding an impermeable cornified envelope packed with keratin macrofibrils. In the upper SC, the plasma membrane becomes discontinuous and is replaced by the insoluble CE. The SC may be considered as a two-component system composed of corneocytes "bricks" and intercellular material "mortar" (Figure 3) ***(Tharp, 2004).***

1. **The corneocytes:** formed mainly of proteins: the impermeable CE packed with keratin macrofibrils and interfilamentous matrix protein "filaggrin".

2. **The intercellular material** (lipid lamellae) between the corneocytes which is the primary source of the epidermal water barrier. It is composed mainly of lipids, e.g. cholesterol sulfate derived from lamellar granules at the level of stratum granulosum (SG) ***(Kathi, 2003).***

In the outer SC, cholesterol sulfate is hydrolyzed by steroid sulfatase enzyme (also localized in the intercellular space) to cholesterol which activates the proteolytic degradation of desmosomes leading to separation of corneocyes and desquamation ***(Menon and Norlen, 2002).***

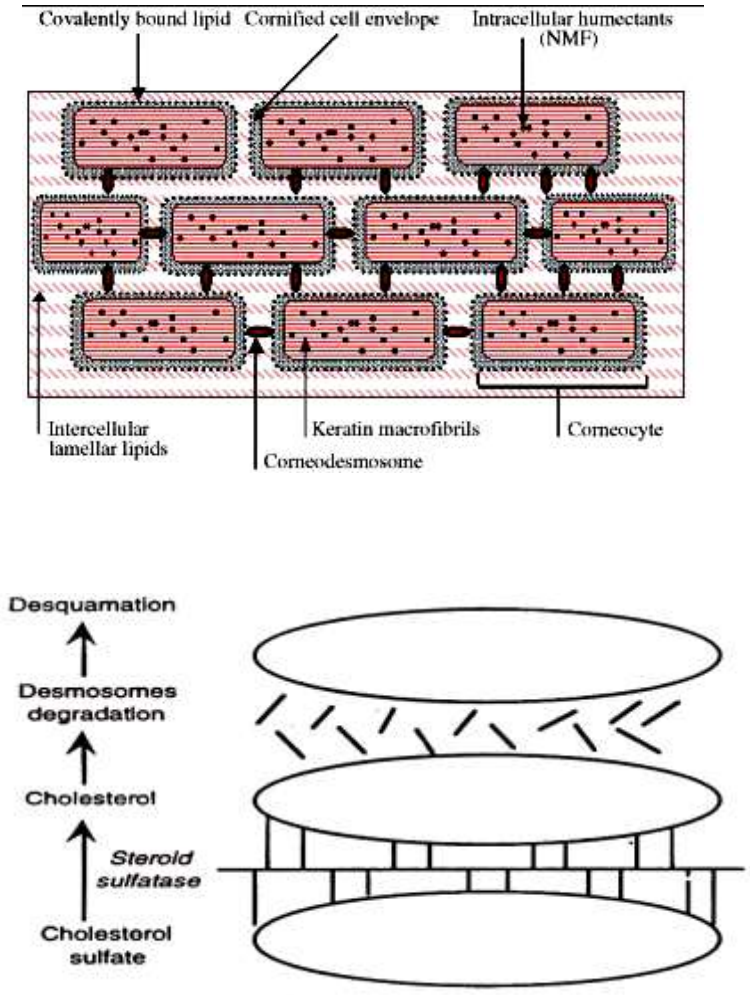


Fig (3): Brick and mortar arrangement of SC ***(Tharp, 2004).***

The SC is also viewed as a two compartment hydrophilic/ hydrophobic structure where the corneocytes with keratin protein hydrophilic (water-attracting) represent the bricks and the lipids represent the hydrophobic (water-repellent) mortar (Figure 4). This hydrophilic / hydrophobic partition plays a key role in determining drug permeation ***(Fendler, 2000).***

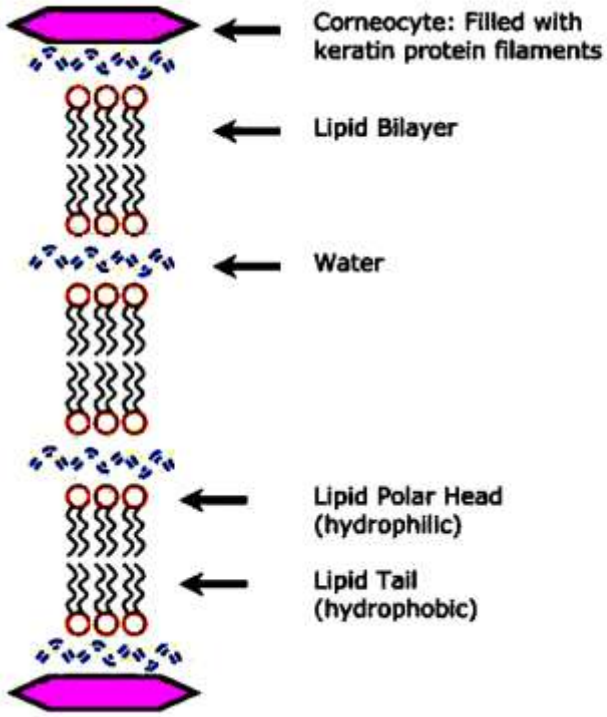


Fig. (4): Physical skin barrier: Corneocyte-lipid bilayers. The SC is divided into two compartments: hydrophilic and hydrophobic ***(Fendler, 2000).***

Corneocyte envelope (CE)

The CE forms a vital part of the permeability barrier of the epidermis. This explains a structure that consists of two parts: a thick layer adjacent to the cytoplasm which is composed of proteins and a thin layer on the exterior of the protein part which is composed of lipids. Cross-linked protein components of human epidermal CE include: involucrin, elafin, cystatin, small proline-rich proteins, loricrin, filaggrin and KIF ***(Downing and Lazo, 2000),*** as well as cystine-rich protein, S100 protein, annexins ***(Watkinson et al., 2002)*** and membrane associated proteins as envoplakin and periplakin. The primary lipids making up the CE around the cells are hydroxyceramides ***(Mc Grath et al., 2004).***

The biochemical composition of the corneocyte envelope is not homogenous. The outermost region of the cornified envelope is rich in involucrin. Deeper within the cornified envelope, involucrin is replaced by loricrin, but how this complex structure is formed is not understood. Once the cornified envelope is formed, it undergoes a maturation process as it migrates through the SC until it is eventually lost during desquamation ***(Watkinson et al., 2002).***

Epidermal lipids

The water content of the SC and skin surface lipids are important factors in the appearance and function of the skin. These lipids are responsible for the barrier function and are a

fundamental element in maintaining skin hydration ***(Baby et al., 2008).*** The overall composition of the lipids in the full thickness epidermis remains constant. Nevertheless, biosynthesis and translocation of the epidermal lipids within each cell continue and change with time ***(Downing and Stewart, 2000).*** Except for linoleic acid which is an essential fatty acid (must be derived from diet), all other lipids are synthesized de novo ***(Wertz and Michniak, 2000)***.

It was recognized that epidermal lipid composition changes dramatically due to differentiation. In the basal cells there is a small amount of cholesterol and high proportion of phospholipids, (phosphatidylcholine and sphingomyelin) ***(Harding et al., 2003).*** In the granular cells there is cholesterol, phospholipids, ceramides, glucosylceramides and free fatty acids. In the SC, the phospholipids are completely degraded, glucosylceramides are deglycosylated leaving ceramides in addition to cholesterol and free fatty acids. Therefore, there is a shift in the lipid components from polar hydrophilic lipids in the lower layers of the epidermis (basal layer to SG) to non polar hydrophobic lipids in the SC that give the skin the first line of defense in preventing water loss and thus up holding barrier function ***(Wertz and Michniak, 2000).***

The stratum spinosum (SS) shows the presence of lipid enriched specialized organelles (LBs) or lamellar granules. Morphologically, they are round or ovoid bodies and contain

parallel stacks of lipid-enriched disks enclosed by a trilaminar membrane (Figure 5) ***(Downing and Stewart, 2000).*** They are variable in size. Under normal physiological conditions, the main function of LBs is the supply of extracellular domains with specialized lipid components ***(Menon and Norlen, 2002).***

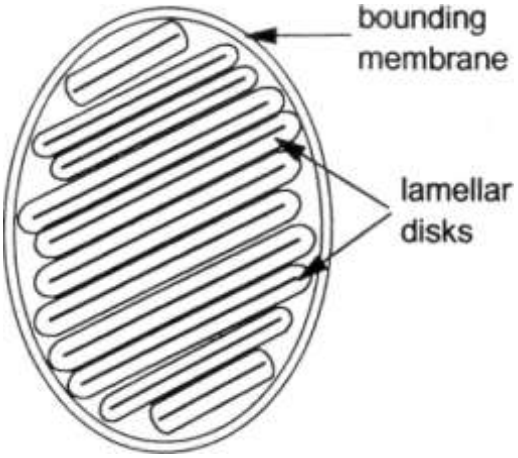
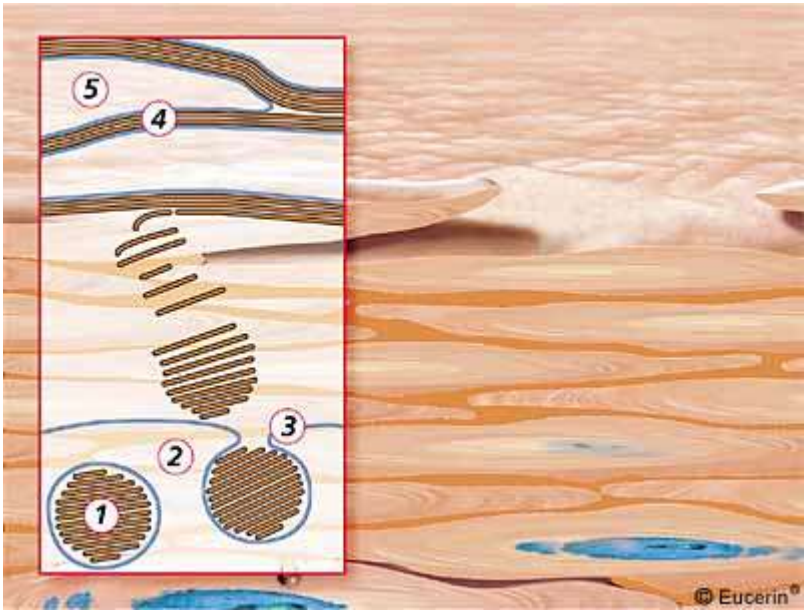


Fig. (5): Lamellar granule ***(Downing and Stewart, 2000).***

The lipid composition and moisture content of the epidermis change with increasing differentiation of the skin cells. Lipids are formed in the Golgi apparatus of the keratinocytes and stored in the Odland bodies. Through exocytosis, the contents of the Odland bodies are released into the extracellular space to form the epidermal lipids (Figure 6**)** ***(Downing and Stewart, 2000).***



Fig(6): The synthesis of epidermal lipids ***(Downing and Stewart, 2000).***

1. Odland bodies
2. SG cells
3. Exocytosis
4. Bilayer lipid membrane
5. SC cells**.**

Lamellar bodies contain lipids which are cholesterol, glucosylceramides and sphingomyelin in addition to catabolic enzymes including proteases, lipases, acid phosphatase and glucosidases. The LBs discharge their content of lipids and enzymes into the intercellular space where these lipids are acted upon by the enzymes especially lipases and glucosidases. Glucosylceramides are converted to ceramides 1-7 by B-glucocerebrosidase. Sphingomyelin is converted to ceramides 2, 5 by sphingomyelinase. Phospholipids are converted to free fatty acids by phospholipases. This alteration in lipid composition is called extracellular processing (ECP) ***(Elias et al., 2003).***

Lamellar bodies secretion is regulated by changes in calcium. Under basal conditions, lamellar body secretion is slow but sufficient to provide for barrier integrity. Following acute barrier disruption, calcium is lost from the outer layers of the epidermis leading to quick secretion of LBs. Following discharge of the lamellar disk contents from the lamellar granules, the stacks of disks slowly disperse in intercellular space, rearrange edge-to-edge and then fuse to form continuous intercellular lamellae. This is called translocation ***(Downing and Stewart, 2000)***. Lysosomal and other enzymes present in the extracellular compartment are responsible for the lipid remodeling required to generate the barrier lamellae as well as for the reactions that result in desquamation ***(Kathi, 2003).*** An analysis of the total lipid composition of the viable cells of the SC was obtained. These include ceramides, cholesterol, free fatty acids, cholesteryl esters and cholesterol sulfate ***(Menon and Norlen, 2002).***

Ceramides account for approximately 50 % of the total SC lipids. Ceramides are long chain sphingoid bases linked to fatty acids. There are seven ceramide classes. These are types 1, 2, 3, 4, 5, 6I, 6II. Ceramide 3 is divided into a and b ***(Demas, 2003).*** Acylceramides or ceramide 1 is known to be important for the barrier ***(Elias et al., 2003).*** It has been suggested that the lower amount of ceramides are related to the increased TEWL of dry atopic skin ***(Lindberg and Forslind, 2000).***