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Percutaneous Absorption and Delivery Systems

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In recent years, two of the main problems confronting cosmetic chemists have been to obtain the absorption of cosmetic products through the skin layer, and to prove their clinical efficacy. In fact, the interference caused by all the products topically applied to the skin, mainly on the intercellular lipids of the stratum corneum (SC) but also on the cellular membrane of all the viable skin layers, determines both the minor or major efficacy of the cosmetic principles used and, of course, the eventual undesirable side effects that might arise.[1–3]

According to recent studies, SC is not an inert layer, as believed in the past, but a real "active wall" opposing the penetration of the environmental pollutants; furthermore, it regulates continuously the passage of water from the inside to the outside, maintaining the homeostasis of the skin and of the whole human body (Fig 1).[4,5] Before investigating the problems linked to the percutaneous absorption of topically applied substances, we deem it helpful to summarize our current understanding of the role that skin and stratum corneum perform as a protective barrier against environmental assaults.

The Epidermis

The epidermis is composed of four layers of cells at different stages of differentiation: the stratum basale separating the dermis and the epidermis. The proliferation of these cells makes the upper layers differentiate.[6] They are large, columnar cells forming intercellular attachments with adjacent cells through desmosomes and their attachment to the basal lamina seems to be regulated by hemidesmosomes, laminin, and integrins (Fig 2).[7–9] At this level they contain an extensive keratin network made up principally of keratins K 5 and K 14, whose structure contributes to prevent water loss as well as the absorption of foreign substances.[10] This function applies both to cosmetics and toxic agents, and while it is desirable in the latter, it is vitally necessary in the former. By a process we are only beginning to understand, cells migrate upward from this basal layer to the horny layer, acquiring the characteristics of a fully differentiated corneocyte, which is eventually sloughed at skin surface. Therefore, once cells leave the basal layer to enter the stratum spinosum (SP), they lose the capacity to divide, increase in size, and flatten, and their water content diminishes. The synthesis of the proliferation-specific keratins K5 and K14 is interrupted, and keratins K1 and K 10 aggregate to form filaments.[11] Cornified envelope precursors, such as involucrin,[12] also appear in the SP, as does the enzyme transglutaminase, which is responsible for the ϵ-(γ-glutamyl) lysine crosslinking of these substrates into the insoluble cornified envelope.[13] At this level, keratinocyte contains both a soluble and a membrane-bound form of transglutaminase. The membrane-bound form correlates with differentiation, and is thought to be responsible for the formation of the cornified envelope. Later, in the stratum granulosum (SG), these filaments are further packed together with filaggrin, a protein synthesized in this layer. This process results in the formation of macrofibrils. New granule-like structures are also formed, such as lamellar bodies and a stable protein envelope. The granules are two types[14]: the larger contains profilaggrin, the precursor of filaggrin,[15] and the smaller contains loricrin, a major component of the cornified envelope.[16] Therefore, the ultimate product of keratinocyte differentiation, the corneocyte, consists essentially of the cornified protein envelope filled with keratin bundles embedded in a lipid-enriched, intercellular matrix. Ceramides, cholesterol, and free fatty acids originating from the lamellar bodies and attached to its surface envelope seem to play an important role in the corneocyte cohesion, contributing also to the permeability barrier of the skin.[17]

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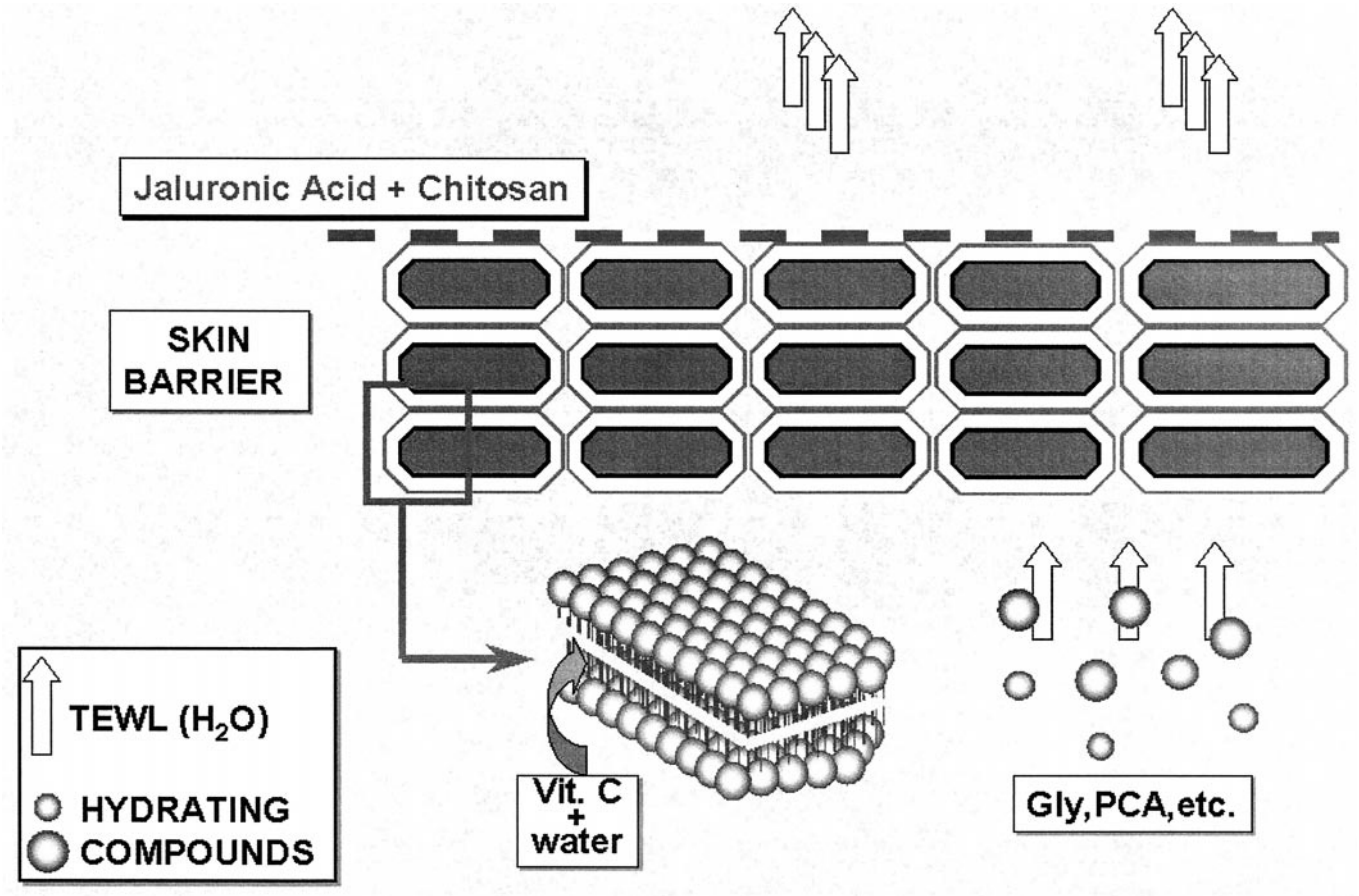

Fig. 1 A schematic diagram of SC, "active wall" necessary to regulate trans epidermal water loss (TEWL) from the inside to the outside of the skin. Glycine-pyrrolidon-carboxylic acid (PCA) and other natural compounds are continuously produced to link water and moisturize the skin. Hyaluronic acid and chitosanas are other chemicals used by the cosmetic industry to regulate the barrier activity.

Moreover, ceramidases, present in the SC, could modify the lipid lamellae by the degradation of ceramide to fatty acids and sphingosine.[18] When passing from the SG to the SC, the cells reach their final state as flat horny cells and the lipid lamellae are released into the intracellular space. Therefore, the structure of the skin changes from a close-packed aggregate of more or less cubital cells with conventional phospholipid membranes communicating each other freely, to a bricks-and-mortar structure in which the major lipids are between the cell forming the mortar. In this way, diffusion of aqueous material through the epidermis is blocked by these lipids, and the water contained therein cannot penetrate beyond the lipid-rich SG. This is an important physiological phenomenon because the hyaluronan-bound water in both the dermis and in the vital area of epidermis is critical for skin hydration, while water retention within the tissue is essential to maintain its flexibility and to provide the necessary hydration for the enzymes involved in various aspects of SC maturation to function.

Skin Lipids: Role and Function

As a matter of fact, in the initial state of cell differentiation, the lipid composition of the SC differs from that of the deep epidermis due to the disappearance of the phospholipid portion, while that of ceramides, fatty acids, and cholesterol increases.[19]

In this way, intercellular lipids are enzymatically modified to decrease their polarity and the natural moisturizing factors (NMFs) are produced at an early stage of the filaggrin degradation.[20] This transformation of the lipid provides the outer layers of the skin with a stable, waxy, and impermeable lipid barrier. Free saturated and unsaturated fatty acids play also an important role in the fusion process and formation of lipid lamellae. They build salts, have a pH-regulating effect, and can furthermore form solid or liquid crystalline areas within the membrane.[21,22] In fact, closely packed molecules have a degree of cristallinity, forming waxy solids or liquid crystals, whereas chains with bonds or side branches from the main chain cannot pack closely together and are liquids. Therefore, the functioning of

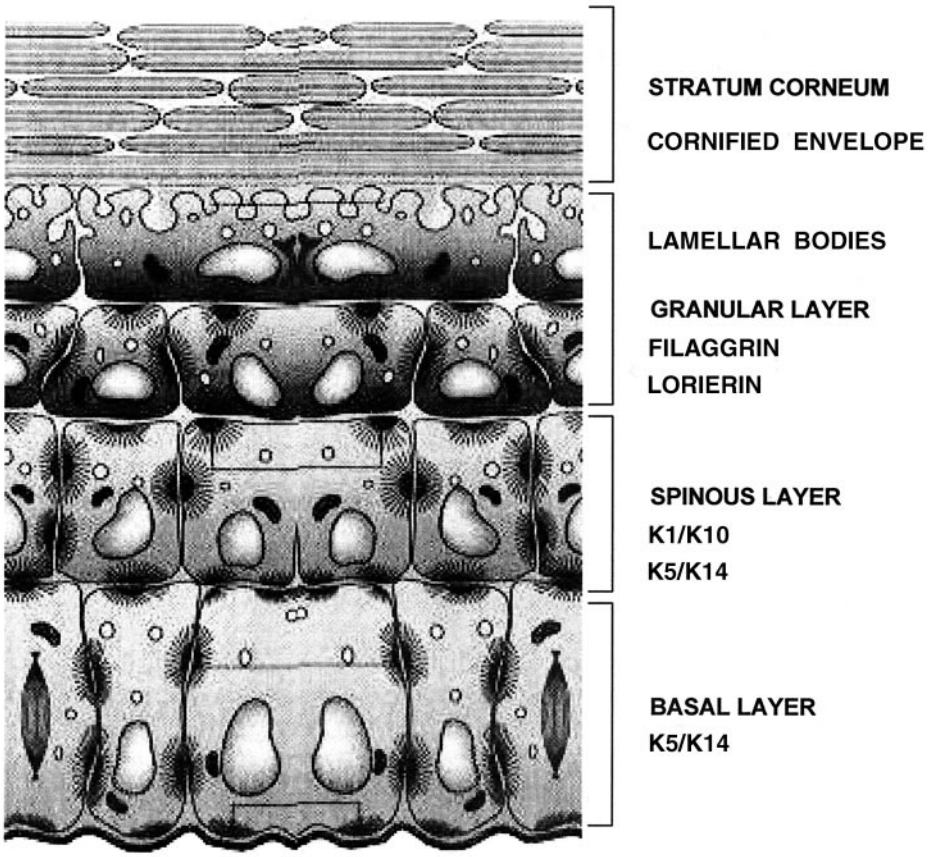

Fig. 2. Cartoon of the four layers of the cell epidermis at different stages of differentiation. Basal layer (BL) contains an extensive keratin network made up principally of keratins K5 and K14. When the cells leave BL, K1 and K10 expression is induced.

the skin barrier is regulated by, and dependent on, the types of lipids and if they are packaged in an orderly fashion.

The presence of amphiphilic lipids, such as phospholipids (half hydrophilic and half hydrophobic), is the logical consequence that allows the transportation processes to take place through the membrane and the water–lipid biochemical reactions of the interface related to them.[23] That is why the phospholipids represent 50% of the lipids of basal cell membranes and of spinosum cell membranes, and 25% of cells of the SG. Other important lipids are glycolipids, glycoproteins, and cholesterol, basic components necessary to the trans-membrane transportation processes.[24] In fact, it is known that cellular membranes can allow the passage of hydrosoluble substances through proteins and glycoproteins, while liposoluble compounds can enter the openings they produce through the double layers of phospholipids.

The membrane fluidity and its related passage openings depend on the types of lipids present and on the structure between them. The membrane will be more elastic (more permeable and fluid) when there are more unsaturated fatty acids, and more rigid (less permeable and more crystal-like) when saturated fatty acids and cholesterol prevail.[25] Cholesterol, in fact, which contains in its molecule 4 rigid rings of carbon tightly bound to each other, makes the membrane less flexible and less permeable.[26–28] For these reasons the SG, and especially the SC, have higher levels of glycosilceramides, ceramides, and cholesterol, which increase membrane rigidity.

In conclusion, phospholipids, such as phosphatidylcoline, and therefore a greater amount of unsaturated fatty acids, make the membrane more permeable and make all biochemical processes easier; while sphingolipids (ceramides) and cholesterol, which are rich in saturated fatty acids, make the membrane less permeable. Any variation, even the slightest, in the presence of these fatty acids can cause skin changes.[29] Therefore, the epidermal lipids have an influence on the coherence of the horny layer, and in this way, also influence the skin smoothness roughness.[30] Even NMF and the water content of the horny layer itself is partly determined by epidermal lipids, which influence the state of the so-called "dry or oily" skin.[31,32] It seems to be contradictory that water is required to build up the barrier against water, but the arrangement of hydrated hydro-

philic polar lipids is influenced by the water phase via liquid crystal formation. Moreover, it is now established that water controls the progressive process of desquamation, and that corneodesmosomal degradation is inhibited at low environmental humidity.[33] Hence, the intracellular spaces are not only filled with lipids but also, alternatively, with water layers.[31,34] On the other hand, as we have seen, ceramides, cholesterol, and free fatty acids act as a barrier and may alter skin permeability and physical properties by being present at different concentrations and interacting among ceramides, cholesterol, and free fatty acids differently.[35]

Investigating how these lipids are arranged is crucial to both evaluate the alterations induced by skin diseases and develop new systems of drug or cosmetic transcutaneous delivery.[36] So atopic dermatitis and acne are associated with low levels of ceramide-1 linoleate,[37–40] while psoriasis is associated with a decrease in ceramides 4, 5, and 6, and an increase in cholesterol.[41] In the xerotic skin, especially in winter, one finds an increase of fatty acids and a reduction of ceramides that are able to cause alterations in the structure of the lipid lamellae as well as in the bonds between corneocytes and desmosomes.[42] As a consequence, phenomena of hyperkeratosis begin that can be regulated, for example, with the cosmetic use of alpha-hydroxyacids (AHAs). These AHAs seem to be able, in fact, to restore the regular packing of the lipid lamellae, normalizing the cellular turnover.[43–46]

Another interesting therapeutic activity is carried out by phosphatidylcholine at the level of aceneic skin. The phosphatidylcholine, being rich in linoleic acid, can reduce the excess of lipids also at the level of the sebaceous gland, and lower the presence of squalene.[47–52] It permeates easily through the intercorneocytary lipids, penetrating also in the pilosebaceous duct, making the cell membrane more fluid and increasing the presence of linoleic acid at the level of the sebaceous gland. The increase in linoleic acid and the consequent reduction in squalene reduce the presence of sebum, greatly improving both acne and, in certain conditions, seborrheic dermatitis. For these reasons phosphatidylcholine seems to be an interesting compound for cosmetic use.[52]

Water and NMF

Water, too, has an important role as penetration agent, owing its solvent property and to the ability of imbibing the proteins.[53] Hence, in the deep layers of the epidermis, water, present in concentrations of about 60%, is fundamental as a vehicle of all the biochemical reactions. In the SC, water content of 10–15% is essential to keep the skin rigid, elastic, and young. In addition to the lipid lamellae, water, and corneocytes, a group of particular chemical substances is present: (a) aminoacids and salts coming from the secretion of sudoriparous and sebaceous glands; and (b) products coming from the degradation of keratins and lipids. All these substances have two fundamental roles: they cause the formation of the NMF and regulate the cutaneous pH.[54] The regulation of the cutaneous pH allows the skin to maintain itself always at a pH between 5.5 and 6.5 (tampon function). It seems that this acid pH regulates bacterial growth, avoiding the proliferation of so-called opportunistic fungi, yeasts, and bacteria that almost always cause infections. The NMF role is based on the fact that its constituents, among which pyrrolidon carboxylic acid (PCA) prevails, are all highly hydrosoluble and strongly hygroscopic. For these reasons, the NMF tends to keep the water at the level of the SC also when the relative environmental humidity stabilizes under 50%.

From a biological point of view the NMF, exclusively found in the corneocytes and frequently used in cosmetic dermatology, has an important role because it can maintain the skin moisturized and promote the regular epidermal cell turnover. Therefore, keratin acquires its elastic properties with the help of hydrated NMF, especially the neutral and basic free amino acid.[55] The importance of NMF is clear, and the correlation of its absence in disease conditions with concomitant horny layer abnormality is striking. There is insufficient NMF in severe dry skin, and in both psoriasis and itchyosis vulgaris it is virtually absent.

Percutaneous Absorption

As we have seen, the most important function of human skin is to act as a barrier by limiting water loss, electrolytes, and other body constituents while barring the percutaneous absorption of harmful or unwanted molecules from the external environment (Fig 3). SC contributes the rate-limiting step in the sequence of percutaneous absorption, although the viable tissue can hinder the penetration of very hydrophobic compounds. By the way, because transport mechanisms are diffusional, the role of stratum corneum as a barrier is intimately limited to its degree of hydration.[56] Hence, an increase in water permeability of the skin corresponds to an increase in permeability to topically applied compounds. As a matter of fact, the state of hydration of the SC is one of the most important factors in determining the rate of percutaneous absorption of a given solute; while the level of hydration is a function of the water concentration gradient between the dermis and the surface of the skin as well as the ability of the SC to "bind" water. That is why delivery of solutes through the skin is associated with a number of difficulties such as (1) the variability in percutaneous absorption due to site, disease, age, and species differences; (2) the skin "first-pass" metabolic effect; (3) the

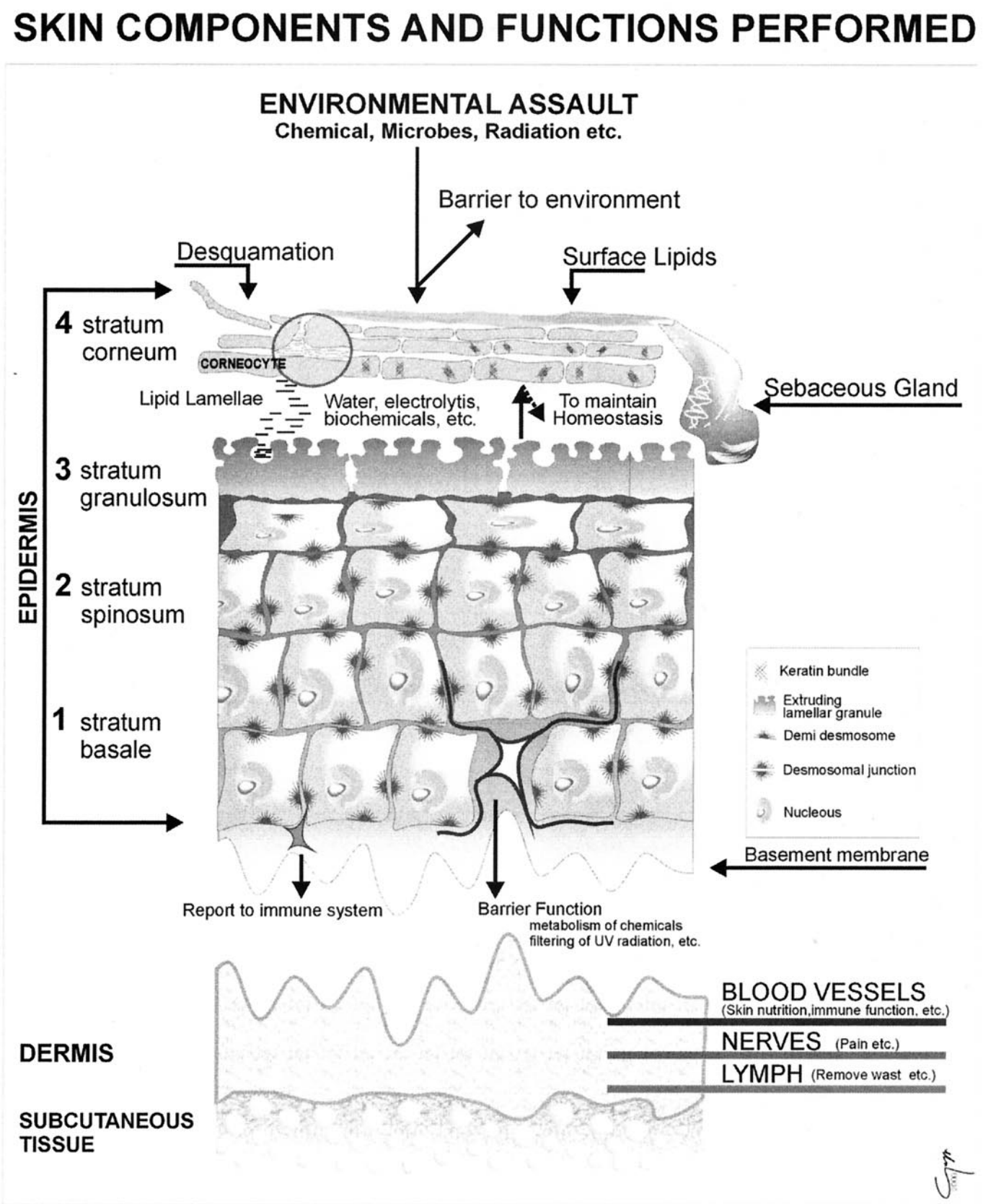

Fig. 3. Skin components and functions performed.

reservoir capacity of the skin; (4) irritation potential and other toxicity caused by topical raw material and active principles used; (5) heterogeneity and inducibility of the skin in both turnover and metabolism; (6) inadequate definition of bioequivalence criteria; and (7) an incomplete understanding of the technologies that may be used to facilitate or retard percutaneous absorption.[56] The available evidence indicates also that for most low-molecular-weight uncharged molecules, the primary penetration pathway is through the intercellular lipid, especially after long-term exposure, thought it does not exclude the possibility that these molecules can also enter the inner lumens of corneocytes.[57–59] There is additional evidence that other compounds can and do penetrate these cornified cells. It is well established, for example, that occlusion or immersion of skin in a bath leads to swelling of the corneocytes, consistent with the entry of water.[60] In fact, occlusion hydrates the keratin in corneocytes and increases the water content between adjacent intercellular lipid lamellae. In this way, an active compound diffusing through the intercellular lipid domains will distribute between the hydrophobic bilayer interiors and the aqueous regions separating the head groups of adjacent bilayers. SC hydration magnifies the latter environment and increases the "hydrophilic" character of SC somewhat. It follows that this leads, in turn, to a reduction in the stratum corneum-viable epidermis partition coefficient to the penetrant diffusant compound.[61] Therefore, the SC vehicle partition coefficient is crucially important in establishing a high initial concentration of diffusant in the first layers of the skin. The efficaciousness of cosmetic products, then, can be determined by the relationship established between the permeability coefficients of the SC and the structure features of the penetrants, such as the cosmetic carrier and the active principles used. Varying the physicochemical characteristics both of the carrier and of the active compounds used, the absorption degree through the cutaneous structure will vary. In fact, the permeability coefficient is influenced by hydrophobicity and size of penetrants, and naturally by the presence or absence of the electric charges and many other factors due to the characteristics of the application area. Of fundamental importance is the typology of the vehicle used. As a matter of fact, in terms of percutaneous absorption, the primary concern is related to release of the compound from the vehicle after application at the skin surface. Moreover, the evaporation of volatile components, such as water, at the skin surface from topical preparations significantly influences the diffusion of active principles into the SC. That is what happens using cosmetic emulsions oil and water (O/W), which modify themselves during and after their application on skin, losing some water because of evaporation. Thus the penetrant has to: (a) dissolve/partition into the surface lipids of the SC; (b) diffuse through the lamellar domains of the SC; (c) partition from the SC into the more hydrophilic viable epidermis; (d) diffuse through the epidermis and dermis; and (7) finally, only for the drugs and not for cosmetics, gain access to the systemic circulation through the cutaneous microvasculature.

Hence the importance of vehicle selection, which should suit the type of active principles and lipids used, the kind of effect expected from the usage of the cosmetic product formulated, and the typology and condition of the regional skin area to be treated.

We previously observed that moving upward to the cells of the SC from the SG, polar lipids disappear. In this migration they are replaced by apolar lipids such as ceramides, cholesterol, and free fatty acids organized into bilayer membranes. Such varied organization of intercellular lipids selectively regulates permeability of lipophilic molecules. On the other hand, corneocytes control and absorb water, and hydrophilic molecules act as depositaries of unwanted substances piercing the SC and work as filters against solar radiation. The facts confirm that vehicles can no longer be regarded as simple inert carriers of active compounds. For example a lipophilic vehicle will easily penetrate facial skin where the SC is lipid rich (10–20% by weight), while such a vehicle will have a difficult time penetrating the palm of the hand where lipids represent only 2% by weight (62) Enhancers, constituents that reversibly weaken the skin barrier, are used to modify and regulate the skin permeability, especially for drugs. In addition to the use of chemical molecules such as oleic acid or propylene glycol and other chemicals that are useful, for example, for transdermal delivery devices, such as patches,[63–70] there is also a great deal of interest in both iontophoresis and phonophoresis (ultrasound) as physical ehancers of absorption.[71,72] Iontophoresis enhances the skin penetration of small changed ions, and phonophoresis induces structural changes in the intercellular lipid domains, which reduces barrier properties. Both techniques are used in medical offices and in SPA full equipped by experts.

Cosmetic Delivery Systems

As we have seen, SC is a thin relatively impermeable membrane that provides the rate-limiting step in the process of percutaneous absorption. This membrane allows no molecule to pass readily, but nearly all materials penetrate to some extent. It is also clear that the major route of penetration across the SC is the intercellular lipids. As such, the rate at which permeation occurs is largely dependent on the physicochemical characteristics of the penetrant, the most important being the relative ability to partition into the intercellular lamellae.

Thus three major variables account for differences in

the rate at which different compounds permeate the skin: (1) the concentration of permeant applied, (2) the partition coefficient of the permeant between the SC and the vehicle, and (3) the diffusivity of the compound within the SC. The principal role of the cosmetic industry is to seek new effective products that combine proven biological activity and safety in usage, together with an efficient skin delivery system. The efficacy of any cosmetic product is determined by two factors: the intrinsic activity of the delivery of its ingredients, and their site of action. Thus, to be really efficient, an active ingredient needs to be delivered to the site of action at the right concentration for a sufficiently long period of time. This applies to all types of active materials, ranging from compound hair conditioners that need to be deposited onto the hair to do their work, to skin lighteners that need to penetrate the skin to inhibit the tyrosinase enzyme in melanogenesis.[73] Therefore, the role of a delivery system is to ensure that the right concentration of the right active principle is reaching the right site in the body for a sufficient period of time. Controlling the concentration and distribution of these actives within the SC or the viable cutaneous tissues is the key to optimizing their benefits.

Even if the site of action for most skin care cosmetics is the surface of the skin, a careful choice has to be made in the selection of the right type of carrier to be used for a determined active principle to obtain the expected result from a cosmetic product. Functional ingredients like UV filters, for example, should remain on the skin surface. If they penetrate, they would be beyond their site of action and so, from a functional point of view, skin penetration of these ingredients is not desired. For deodorants and antiseptics, the surface bacteria and fungi are the main target and effective surface bioavailability is important. The formulation must release the "active" so that the antimicrobial may penetrate the surface microcracks and fissures of the skin to attack the microorganisms that lurk there. Moreover, other active ingredients, such as antioxidants and skin lightening and anti-aging compounds, have to exert their activity in the viable epidermis or even the dermis.

The carrier of the system affects the delivery of active compounds in different ways, such as by interacting with the active agent, controlling the rate of release from the vehicle, altering SC resistance, or enhancing SC hydration.[74] Permeation enhancers, eventually incorporated in the system disturbing the packing of the SC lipid bilayers, may increase the skin delivery of the active used. Of course, the cosmetic degree of penetration through skin also depends on the type of carrier used and the characteristics of the active principles selected.

Many active surface compounds alter the permeability of the skin barrier after opening up the complex, dense structure of the SC. For example, some aliphatic acids, bases, and neutral compounds may change the impedance of excised human skin. The corresponding increases in water permeability arise from a combination of mechanisms, including the relation of binding forces between skin elements, the dissolution of components, and the hydration and subsequent swelling of the skin to form additional channels for permeation.[75]

Biological variability and variations in cutaneous permeability further complicate the situation in that the absorption rate varies widely for a specific substance passing through identical skin sites in different healthy volunteers.

New Trends in Cosmetic Delivery Technologies

The most desirable method to improve the performance of an active in a cosmetic formulation is an appropriate delivery system. Many innovative cosmetic technologies control the delivery of active ingredients, and they can be divided into three broad types: vesicular (liposomes and niosomes), molecular (cyclodextrines), and particulate (microcapsules and matrix particles).[76]

These technologies are in turn based on three distinct systems[77–79]: (1) closed, (2) open, and (3) polymeric reservoir. Moreover, there are subsystems within the closed-system category, the most notable being liposomes, cyclodextrins, microcapsules, and submicrocapsules/microspheres.[80] Closed systems consist primarily of total encapsulation whereby the active is enclosed or entrapped by a continuous wall or shell. Open systems do not have a continuous shell or membrane; these are particulate systems in which the external and internal phases are in contact through small channels present in the matrix. Both closed and open systems comprised solid substances that entrap either hydrophilic or hydrophobic ingredients. The third system is not a solid, but a polymeric reservoir, based on a partition mechanism (Table 1 and 2).

All of these new delivery systems achieve a balance between the physicochemical requisites for stability of active and inactive constituents, preservation against microbial spoilage, and presentation of the active molecules to the skin in a system that will allow appropriate release of the active to SC or viable skin layers. By making the active more available in the target tissue, efficacy can be maximized by controlling the concentration and distribution of these actives within the SC, and the benefits can be optimized.[81] In addition, the ideal cosmetic formulation has to ensure good spreadibility, elegance, and maximum patient acceptability.[82]

In simple terms, the general objective is to formulate also a cosmetic product that rubs into the skin to leave a residue that is undetectable to the eye and is neither tacky nor greasy. The tactile sensations of greasiness and tackiness arise from the properties of the vehicle constituents that form the film left on the skin.

Table 1. Closed Systems

	Liposomes	*Cyclodextrins*	*Microcapsules*	*Submicro Capsules*
Average Size	40–300 nm	Variable; 3-D structure	50–500 nm	0.1–1.0 nm
Wall Composition	Phospholipid, POE Alkyl Ethers, Fatty Acids, Ceramides, or Polyglycerol Ethers	Oligosaccharide matrix consisting of 6,7, or 8 glucopyranose units	Gelatin, Polyvinyl Alcohol, Ethyl Cellulose, Urethane	Gelatin, Alginate, Albumin, Carageenan
Mode of Action	Release occurs when the vesicle wall is disrupted while in contact with the SC	Release occurs when the complex is disrupted while in contact with the SC	Release occurs when the shell is disrupted by shear, abrasion or pressure, or by permeability	Release occurs when the matrix is disrupted by shear, abrasion or pressure, or by permeability
Other	May be unilamellar (single layer membrane) or multilamellar	Host complex can accomodate single molecule of active. Cd's are also hygroscopic	Composition of shell can function as membrane to control release.	Matrix can be coated or uncoated; release or nonrelease can be designed.

To this end, the selection of emollients[1] and surface active compounds is an important factor for the formulation of emulsions, such as for the spreading value of all the chemicals used.[2] Therefore, the chemical and physical characteristics of the formulation, as well as those of the individual ingredients, are nonsecondary aspects to be considered. Important criteria include spreading behavior, molecular weight, and the polarity of the selected ingredients. For specific cosmetic preparations, the chemical structure, hydrolytic stability, and the cloud point can also be important factors. To obtain a constant feeling of smoothness during application, a combination of low-medium and high-spreading emollients seems to be appropriate.[83]

Certain emulsifier systems also seem able to enhance skin performance characteristics of emollients[84], therefore, high performing formulations should have the right combination of these chemicals to achieve a maximum dermatological effect.

Closed Systems

Liposomes

Liposomes used in cosmetic products are microscopic spherical vesicles formed by the hydration of lipids (usually phospholipids). They comprise a bilayer membrane enclosing water within a phospholipid sphere. Their formation does not require the inclusion of surfactants or emulsifiers; they may be single- or multilamellar and vary according to lipid content, surface charge, and method of preparation. Liposomes are especially used in products intended to transport the both hydrophobic and hydrophilic actives into deeper skin layers. It is still not known if they penetrate through the skin.[85] Some studies indicate that their structure seems to be lost in the very first layers of the SC; however, recent studies have reported that there might be penetration into the deeper layers of the skin and liposomes may potentially act as transdermal transport system.[86,87] Because of their similarity with cellular membranes and their high biocompatibility, liposomes are also used without any added ingredients to improve skin condition or to ameliorate some pathologic changes. Some phospholipidic liposomes, based on soybean phosphatidylcholine, which is particularly rich in linoleic acid, seems to be active in acne formulation, as we have seen previously.

Different phospholipidic liposomes from soybean, named Plurilamellar Multivesicular Liposomes (PML), are also constructed.[88] They are liposomes entrapped by a colloidal hydrophilic matrix. With this microfluidizing technique it is possible to encapsulate large amounts of both hydrophilic and lipophilic active ingredients. Bilayer membrane vesicles, called niosomes, have also been constructed using single or two-tailed ether or ester derivatives of polyglycerol or polyoxyethylene.[89]

Cyclodextrins

Cyclodextrins, constituting 6,7, or 8 gluco-pyrannose units, are obtained by enzymatic degradation of starch. Forming a ring, these molecules have the primary hydroxyl groups on one side, and the secondary on the other side. The consequence of such a structure is that the external part of the ring molecule is hydrophilic,

[1] *Emollients have softening and soothing properties and may impart general smoothing by flattening the skin profile.*

[2] *Spreading is the expansion of a substance on a surface. The spreading value determines the surface area of the skin (mm^2) that is covered in a specific period of time (10 min).*

Table 2. Open Systems

	Microsponge	*Polymeric Liquid Reservoir*
Average Size	5–300 nm	Variable
Composition	Polymeric: usually cross-linked, substituted acrylate	Polyester or Polyurethane polymers: cross-linked or linear
Mode of Action	Release occurs via several different "triggers": applied physical pressure, skin temp., solvent for entrapped active, perspiration, and evaporation	Diffusion of active into the epidermis by partitioning mechanism: degree of skin penetration is dependent on geometry and molecular weight of polymer
Other	Porous and web-like systems: function through sorption-desorption mechanism.	Co-compatibility of the polymer with actives and excipients is related to the relative polarity of the polymer

while the internal cavity is rather hydrophobic.[90] Because cyclodextrins have low hydrosolubility, new production technologies have been developed for obtaining other more active derivatives, which have been used to improve the quality of cosmetic products. For their inclusion ability toward both hydrosoluble and liposoluble external compounds, cyclodextrins may be used to entrap components with drawbacks such as poor stability, poor water solubility, irritating effects, bad odor, etc.[91]

Cyclodextrins can reduce skin penetration and minimize side effects of some actives or may entrap single molecules, thereby increasing their bioavailability.

Microcapsules

The diameter of microcapsules may vary from 1 to 1,000 μm, and they may have a variety of structures, ranging from spherical and irregular shapes with one core to multicores, and even multilayer coating.[92]

The process of microencapsulation generally includes: (1) an emulsification stage, (2) the formation of an insoluble film around each particle, (3) the hardening (if necessary) of microcapsule walls to obtain the proper physical properties, and (4) the removal of the external liquid phase if it is necessary to obtain the microcapsules in a dry powder form. Naturally, the efficiency of the different microcapsules obtainable depends largely on their real bioavailability, which has to be demonstrated experimentally both in vitro and in vivo; however, they provide segregation of the active from other formulation components and good stability for oxidable actives. On the other hand, they also require sufficient shear force, pressure, or abrasion on application to facilitate release of actives.

Submicrocapsules

Belong to the category of the so-called nanocapsules,[93] submicrocapsules are a reservoir system comprising a continuous polymerized envelope surrounding a liquid or gelified core. The encapsulated actives are more often a dispersion or oily mixture. In this case, the interaction between two biopolymers with opposite electrostatic charge, such as gelatin and carboxymethylcellulose, may produce the phase separation responsible for the membrane formation. The entrapping polymers may be also composed of acrylic derivatives of polyalkylcyanocrylate or derivatives of copolymers such as styrene, lactic and glycolic acid, etc. By this methodology, for example, oily active compounds, such as vitamin E or A, may be entrapped into matricial alginic-agar microcapsules without emulsifiers.

The cosmetic benefits include emulsifier-free formulations, visual effect, a superb esthetic feel when applied to the skin, protection of the entrapped active ingredients, preventing side reactions with the rest of ingredients in the formula.

Nanotopes™

Nanotopes™ are a new carrier system for cosmetic actives constructed by ultrasmall spherical particles with a size of <30 nm and therefore smaller than the inter-corneocyte pores[94]. In contrast to phospholipid membrane systems, the monolayer membrane of the so-called Nanotopes™ comprises both phospholipids and a specific cosurfactant in a defined ratio. The cosurfactant acts as a membrane stabilizer and is inserted with its large hydrophilic conelike, head group, between the rather cylindrically shaped phospholipid molecule. The combination of cones and cylinders maintains homogeneous and dense membrane architecture that is less susceptible to surfactant interactions than conventional phospholipid membrane systems.

Open Systems

In these systems, the external and the internal phases are in contact through small channels that are present in the matrix. These systems employ materials that have the ability to crosslink polymers and to entrap active compounds by sorption mechanism.

Microsponge

Some polymeric systems obtained, named "microsponges," are effective in providing a time/concentration release of actives but are suitable for lipophilic actives only, and quite expensive. Moreover, the organic polymers used suffer a major drawback in that

they do not provide the necessary, photostability, for example, for sunscreen products; and small molecules are known to diffuse in and out of these polymers.[78]

Another interesting open system can be made of inorganic silica glasses through a so-called sol-gel process.[95] The matrix obtained is a porous glass in which the organic molecule is entrapped and the average pore size and the surface area distribution can be easily controlled. This sol-gel silica, transparent to the UV radiation in the range above 250 nm, is able to enhance the thermal and photochemical stability of the entrapped molecule. The final formulations have a pleasant feel and are transparent upon application on the skin.[96] Nylon microspheres are another methodology that is especially used in makeup formulations to provide a nice matte film on the skin, necessary to give a more natural and long-lasting effect to the final cosmetic product.[97] These microspheres represent a single way to deliver hydrophilic active ingredients in a dry lipophilic medium, and are also able to control excess oil secretion.

Polymeric Reservoir

Polymeric esters and urethanes utilize a partitioning mechanism that controls delivery of actives.[98] Polymer size and geometry control the degree of diffusion of the active into the SC. Therefore, the active ingredient partition into polyester is based on their relative solubility. This means that the actives have to be more soluble in the polyester than in the skin or the vehicle. For their specific characteristics these polyesters, compatible with a wide range of raw materials, are useful as topical delivery systems in formulations containing both lipophilic and hydrophilic actives. They seem to offer a good alternative to currently available topical delivery technologies that can be designed to deliver chosen actives to specific targets from select vehicles.

Conclusions

The present state of knowledge about the skin highlights a close interconnection among lipid metabolism, structure of the cutaneous barrier, and water content at the level of the SC. The final assembly of the lipid barrier is controlled by the conditions of the environment, and a functioning SC is essential for water homeostasis in mammals. On the other hand, the qualitative and quantitative lipid composition determines the function of the epidermal barrier and the activity of many lipid-dependent enzymes. Therefore, the raw materials and the active principles to be used for the cosmetic products have to be carefully evaluated in relation to the skin area to be treated and the effect to be obtained.[99] Hence, to achieve the desired efficacy, the fundamental consideration is the selection of the carrier that should be able to penetrate both through the horny layer and through the viable skin. Various carriers and different encapsulation methods are available, as we have seen previously. The speed at which the capsule dissolves and thus the speed at which the active is released can therefore be governed through selection of the carrier. These types of processes have to be adapted from related fields of application to the special cosmetic legislation and technology requirements for active encapsulation, which primarily restricts the selection of available shell and carrier material. These materials naturally have to be odor-neutral and safe for cosmetics. Consequently, a significant portion of today's research focuses on biomaterials selection.[100–102] On the process technology side, the methods that have primarily gained in significance recently have been those that are based upon fluid-bed processes, gelatin encapsulation, and extrusion. Such technologies as liposome encapsulation, molecular inclusion, and interfacial polymerization are presently still in the trial stages and will play a more important role in the future. Finally, the physicochemical characterization of carriers and formulations is an essential control for the achievement of a cosmetic product that is truly effective and free of side effects. Different methods have been described, of which polarized light and hot-stage microscopy, differential scanning calorimetry (DSC), and modulated DSC are used extensively. Dielectric spectroscopy may also be useful as a quality-control tool for the carriers in monitoring, for example, the effects on microstructure by moisture uptake on long-term storage.[103–106]

In conclusion, percutaneous absorption delivery systems represent a challenge for firms that aim to give more scientific validation to cosmetic products. To be really effective, each product should contain the right active principles in the right dose to be transported by the right carrier onto the selected skin area. These active principles have to be released by the carrier on the skin and remain there for the time needed to fulfill their function. In this way, it will be possible to manufacture cosmetic products that, according to international trends, can be named "cosmeceuticals."

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