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Penetration of Surfactants into Skin

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Synopsis

Surfactants possess the ability to reduce surface tension at low concentrations, resulting in emulsification, foaming, wetting, and solubilizing. As a versatile industrial material, surfactants can be widely used as additives in the industrial field as different as textile, metal processing, mineral processing, new materials, industrial cleaning, construction, and pharmaceuticals. The most extensive application of surfactants perhaps is in the household and cosmetic industries, such as laundry detergents, dishwashing detergents, facial and body cleansers, and preparation of emulsions and creams. However, the extensive use of detergents, cleaners, and cleansers on skin may cause itching, redness, and dryness termed as surfactant-induced irritation, which is at least, partially due to surfactant penetration into skin. To understand how surfactants penetrate into skin, this review summarizes the penetration models proposed by researchers in the past two decades, including the surfactant monomer penetration model, the surfactant micelle and submicelle penetration model, and the recently proposed surfactant charge density and penetration correlation model that demonstrates the correlation between the surfactant charge density and skin penetration.

INTRODUCTION

Surfactants are usually constituted of hydrophilic polar groups and hydrophobic nonpolar hydrocarbon chains (or rings). Because of the special amphiphilic structure, they can reduce surface tension and facilitate foaming, emulsifying, dispersing, wetting, and osmosis, all of which contribute to their extensive applications in the chemical industry.

The specific applications are presented in Table I.

SURFACTANTS

Surfactants, an abbreviation for surface active agent, are amphiphilic or amphipathic molecules which could orient themselves at the boundary of two immiscible phases. The hydrophilic or water-loving portion of the surfactants would be soluble in the aqueous solution. Conversely, the hydrophobic or water-hating portion of them would be absorbed in the nonaqueous solution (as the oleaginous phase or air) (1,2).

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Table I
Specific Applications of Surfactants in Different Fields

Field	Specific applications
Washing industry	Soap, kitchen detergent, shampoo, laundry detergent, and decolorizer
Pharmaceutical industry	Wetting agent, adhesive, lubricant, coating material, slow/controlled release formulation, dispersing agent, solubilizer, emulsifying agent, and germicide
Food	Food emulsifying agent, food defoaming agent, thickening agent, and preservative
Cosmetics industry	Emulsifiable paste, wetting agent, and foaming agent
Petrochemical industry	Lubricating oil, anticorrosive agent, and sealant,
Textile industry	Fluorescent whitening agent, antistatic agent, softening agent, emulsifying agent, and detergent,
Agriculture	Pesticide dispersing agent and wetting agent

On adsorption of the surfactants to the two immiscible phases, the repellent force between the phases is reduced, and, also, the free energy at the phase boundary is reduced. As more and more surfactants gather at the interface, the free energy per unit area of the interface or the surface tension gradually decreases (1). To stay steadily at the boundary of two immiscible phases, a surfactant is supposed to possess a characteristic structure, enabling itself to integrate two immiscible phases into one single phase. Generally, a surfactant monomer is mainly composed of (i) a hydrophilic part that contacts the aqueous phase in the solution and (ii) a hydrophobic part that rejects the aqueous phase (3). The hydrophilic part is usually a polar group. On the other hand, the hydrophobic part is often a nonpolar group, such as a long-chain hydrocarbon. Take water and oil, two immiscible phases, for instance; the surfactants in the water and oil mixture will gather along at the water–oil interface, and the hydrophilic section of the surfactant is dissolved in the water layer, whereas the hydrophobic side is immersed in the oil layer.

Only surfactant monomers are capable of reducing surface tension (1). When the concentration of the surfactant increases and is saturated at the two-phase boundary, the aggregation of the surfactant monomers referred to as the micelle is usually formed. Take air and liquid phases as example; in the aqueous solution, when there is no space for the extra surfactant monomers at the air–liquid interface, the extra monomers will enter into the aqueous solution and their hydrophobic parts will gather together to reject the aqueous environment, forming micelles with the hydrophobic groups facing inward and the hydrophilic groups orienting outward (1). The concentration of surfactants above which micelles are formed is defined as the critical micelle concentration (CMC) (1,4). The diagram of the surfactant monomer and micelle, and the relationship of the surfactant monomers and micelles are described in Figures 1–3.

The functions of surfactants include (i) emulsification—surfactants work as emulsifiers to reduce the water–oil interfacial tension, forming stable emulsion (5); (ii) wetting action; (iii) solubilization; (iv) detergency—rollup is one of the mechanisms describing how surfactants remove sebum and dirt (6); and (v) foaming. Based on the various physicochemical properties of surfactants, they have extensive civil and industrial applications, such as laundry detergents, emulsifiers, food additives, cosmetics, and drug delivery (5,7). This review article mainly focuses on the surfactants used in the skin-cleaning products.

The classification of surfactants can be based on the structure of the hydrophilic parts, consisting of anionic surfactants, cationic surfactants, nonionic surfactants, and amphoteric

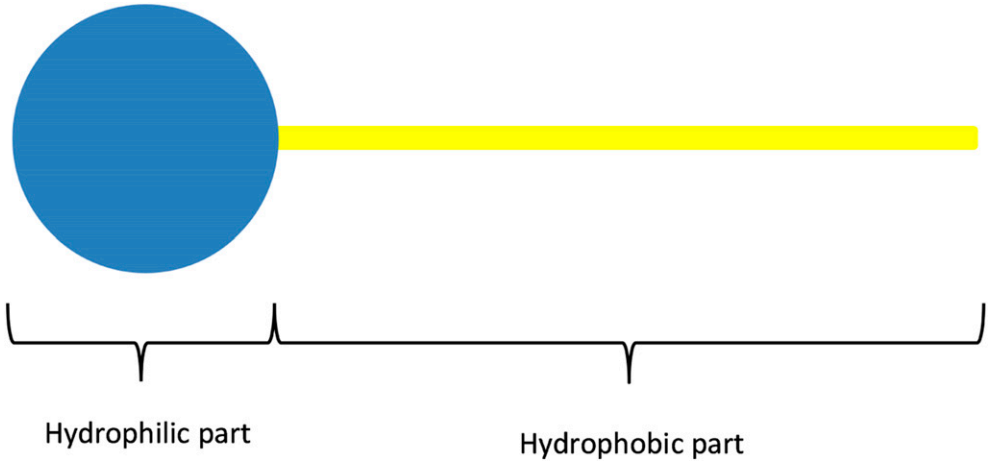

Figure 1. Diagram of surfactant monomer.

surfactants (2,8). Anionic surfactants account for the vast majority of surfactants used in cleaning products, including (i) soap surfactants: soap surfactants can be prepared by hydrolysis of triglycerides (TS) into a mixture of various long-chain carboxylates, and this process is called saponification. Soap has strong cleaning and foaming abilities, but it is not gentle to skin. Other drawbacks of soap surfactants include high pH (usually greater than 10) use condition and incompatibility with hard water. Soap precipitates at low pH or forms precipitations with magnesium and calcium ions in hard water (8); (ii) synthetic sulfate, sulfonate, and isethionate surfactants, such as sodium dodecyl sulfate (SDS), sodium lauryl sulfate (SLS), sodium laureth sulfate, sodium C14-16 olefin sulfonate, and sodium lauroyl isethionate. They are slightly milder to the skin than soap surfactants, especially for isethionate surfactants. Unlike soap, they can be used in hard water and in a wide pH range of 3–11; and (iii) amino acid–derived surfactants, especially acyl glutamate and acyl glycinate, which are popular ingredients in mild skin-cleansing products.

Nonionic surfactants are the second largest surfactant class. They are not ionized in the solution, and thus are not sensitive to the ions in hard water, are not easily affected by pH, and have good compatibility with other types of surfactants, such as anionic surfactants, to formulate skincare products or cleaning detergents (8). Fatty alcohol ethoxylates or CmEn is one of the most important types of nonionic surfactants. They possess stable chemical structures and strong cleaning abilities. One of the most important or interesting features of fatty alcohol ethoxylates is that they exhibit reverse solubility versus temperature behavior in water, i.e., they have cloud point—the temperature at which the solution becomes cloudy. The cloud point generally increases when the hydrophilic part or the number of oxyethylene units becomes larger and is strongly dependent on cosolutes including electrolytes and polyols (1).

Cationic surfactants, the third largest group of surfactants, are actually not as much used as anionic and nonionic surfactants in skin care. They are often added to skin products as preservatives, softener, and conditioner (6). The hydrophilic parts of the cationic surfactants are usually amine and quaternary ammonium based. The amines only function as a surfactant in the protonated state, and thus they are not compatible with high pH, whereas

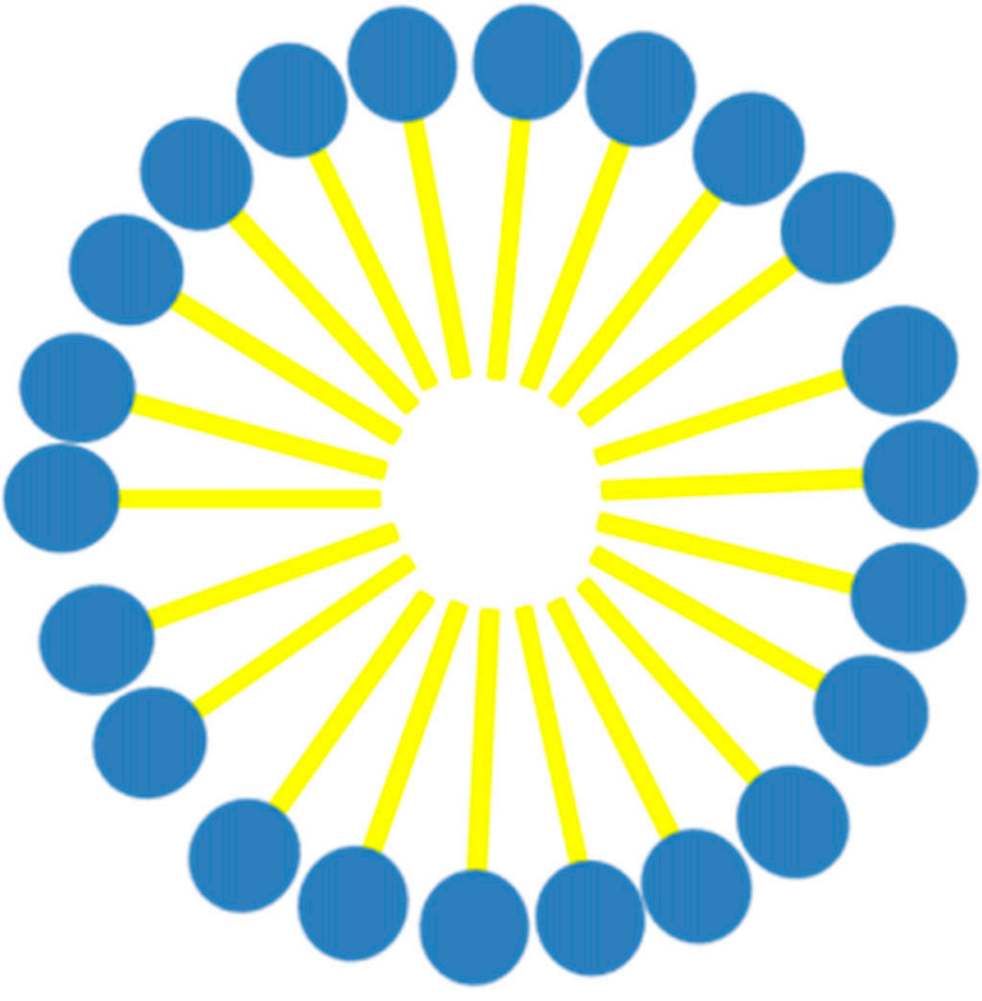

Figure 2. Diagram of surfactant micelle.

quaternary ammonium compounds are not pH sensitive. Cationic surfactants show higher toxicity than most other classes of surfactants, and therefore they are often used as preservatives (9,10).

Amphoteric surfactants are the smallest surfactant class probably because of the high price. Their hydrophilic part contains two charged groups. As a result, amphoteric surfactants are stable in both acidic and basic conditions, but pH change will affect their physicochemical properties. When pH is at the isoelectric point, the amphoteric surfactants possess similar properties as the nonionic surfactants. When pH is above or below the isoelectric point, the amphoteric surfactants show properties resembling those of anionic or cationic surfactants, respectively. In addition, amphoteric surfactants are mild to skin and eyes, enabling them to have a wide range of applications (11). Some typical examples of the four surfactant categories are presented in Table II.

Thanks to the particular physicochemical properties, anionic surfactants and nonionic surfactants are used as the main surfactants in skin-cleansing formulations. As mentioned

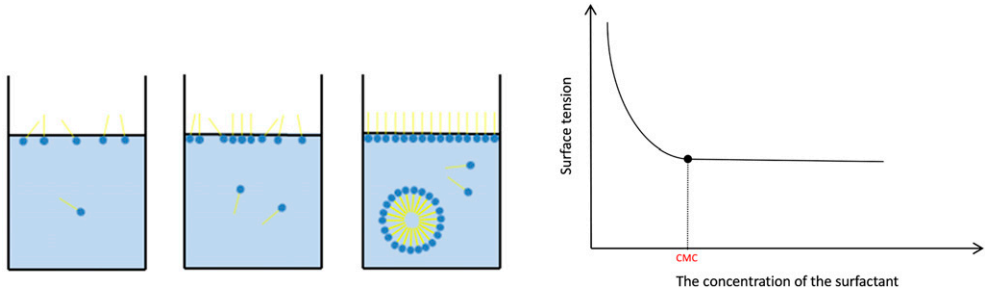

Figure 3. Relationship of the surfactant monomers and micelles.

earlier, the toxicity of the cationic surfactants enables them to be mainly served as disinfectants. In addition, the amphoteric surfactants are usually used in combination with other surfactants (e.g., a standard shampoo formulation contains one anionic and one amphoteric surfactant (6)). Nevertheless, anionic surfactants and nonionic surfactants are the most common agents used in general skin-care products. The anionic surfactants mainly serve as detergents, emulsifiers, and foaming agents, whereas nonionic surfactants can be used alone or are usually mixed with anionic surfactants to form mixed micelles or some structured phases, which, to some degree, reduce the irritation of some anionic surfactants to the skin barrier. This review article emphasizes on the anionic and the nonionic surfactants mainly used in the facial care products.

Skin cleaning is the first step in modern skincare routines and is essential to the skin hygiene. Surfactants have been used in this field for a long period (2). They undoubtedly have the ability to clean the skin. On the other hand, the surfactants in the facial care products, occasionally, may cause some undesirable effects to skin, including dryness, pruritus, redness, and even inflammation. When it comes to the cause of these irritation symptoms, besides some genetic reasons in particular populations—the groups with the sensitive skin—and the environmental factors (12), they are probably connected with the penetration of surfactants into the skin, resulting in adverse impacts to the skin substances such as proteins and lipids (4), which eventually lead to skin irritation. To avoid this, consumers prefer to choose mild facial cleansing products. Nevertheless, there is still a lack of

Table II
Four Categories of Surfactants and Typical Examples

Category	Examples	
Anionic surfactants	Soap surfactants ($RCOO^-$)n M	Sodium stearoyl lactylate
	Sulfate surfactants RO-SO3-M	SDS
	Sulfonate surfactants R-SO3-M	Sodium dodecyl benzene sulfonate
	Amino acid–derived surfactants	Acylated amino acids (N-acyl l-glutamates and N-acyl glycinates)
Nonionic surfactants	Fatty alcohol ethoxylate surfactants	Poloxamer
	Polyhydric alcohols surfactants	Span class
Cationic surfactants	Benzalkonium bromide	
	Dialkyldimethylammonium surfactants	
Amphoteric surfactants	Lecithin	
	Betaine	

fundamental understanding in the mechanism of surfactant penetration into skin. Since the beginning of the 21st century, a number of original researches have investigated various surfactants' penetration and proposed the relevant penetration models to explain how these surfactants pass through skin. This review article summarizes the current understandings and progress of the surfactant penetration into skin, mainly focusing on anionic and nonionic surfactants because they are frequently used in skin-care products.

SKIN STRUCTURE

Study of the human skin structure is essential to have a better understanding of how surfactants penetrate and interact with skin. The skin is the largest organ of the human body. It works as a barrier to isolate and protect the internal organs and tissues from the external environment (13,14). The skin comprises three basic layers: subcutaneous tissue, dermis, and epidermis. The basic structure of the human skin is presented in Figure 4.

The subcutaneous tissue is the innermost layer of the skin structure. The average thickness of this layer is about 4–9 mm, but the actual thickness depends on the individual. The subcutaneous tissue contains some fat tissues which provide elasticity and work as a shock absorber for nerve endings and blood vessels including arteries and veins. The dermis, a connective tissue layer between the epidermis and the subcutaneous tissue, is full of collagen and elastin fibers, which provides a tough cell matrix for the human skin (15). In this layer, there are some arrector pili muscles, artery and vein vessels, and nerves extended from the subcutaneous tissue (16). In addition, some sweat glands, sebaceous glands, and hair follicles pass through the skin surface, originating from the subcutaneous layer and the dermis layer (17). The density of the hair follicles is approximately 10–70 on every centimeter square of the skin area. The outmost layer of skin termed the epidermis, which

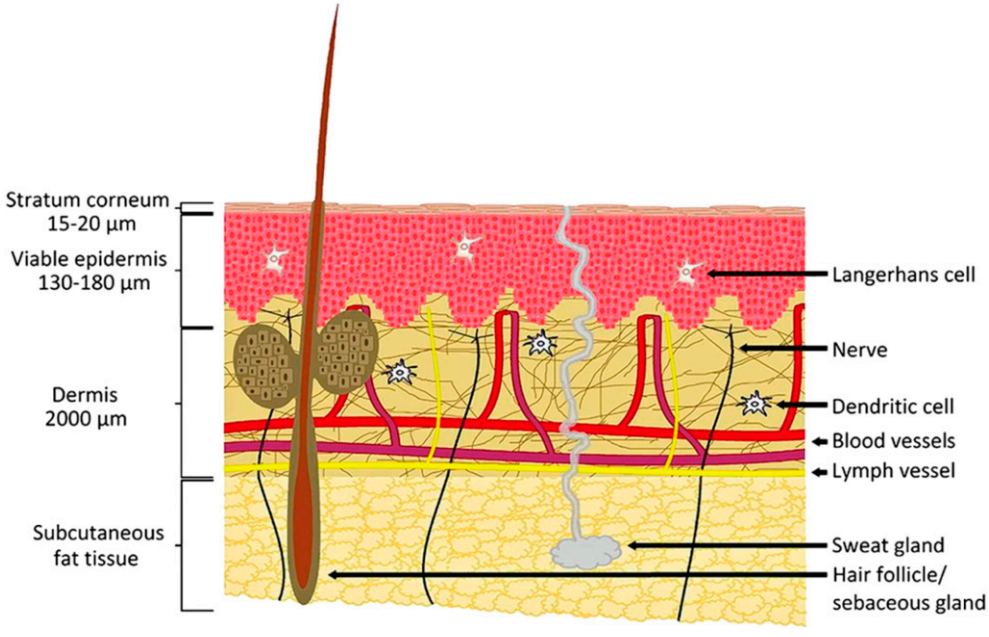

Figure 4. Human skin diagram (Reprinted from (16) with permission. Copyright 2012 Elsevier).

is around 0.05- to 1-mm thick, directly contacts with the outside environment (13). The epidermis consists of keratinocytes and other components such as Langerhans cells, melanocytes, and Merkel cells (18). The keratinocytes, as one of the most important components in the epidermis, form a protective barrier to keep the skin hydrated internally (19). The epidermis can be further divided into the viable epidermis, i.e., the inner layer, including the basal cell layer, spinous cell layer, and granular layer, and the nonviable epidermis, i.e., the outer layer, also called the stratum corneum (SC). The distinction among the various epidermis layers depends on the mature stages of the keratinocytes. From the basal cell layer (the innermost epidermis layer) to the SC (the outermost epidermis layer), the mature stages deepen, so do the density and flattening of the cells.

One of the popular models to describe the SC structure is termed as the "brick and mortar." The "brick" represents the corneocytes (20) which are the most mature stage of the keratinocytes—the dead keratin-filled cells (21). The corneocytes are surrounded by the cell envelopes (protein shells). The cell envelopes serve as the protective layer for the corneocytes. Situated at the external of the cell envelopes is a layer of bonded lipids, which forms the cornified lipid envelope with the protein shells (22). The external bonded lipids build compatibility between the corneocytes and the intercellular lipids (23). The natural moisturizing factor (NMF) is an important substance in the corneocytes which can only be found in the SC. NMFs are water-soluble compounds and are mainly composed of about 40% free amino acids, 12% of sodium salt of pyroglutamic acid, 12% of lactic acid salts, 7% of urea, and 18.5% of inorganic salts (4,24). NMFs occupy 5–30% of the total dry weight of the SC, and their quantity has an influence on the degree of skin dryness (25,26). The "mortar" consists of two parts: one is the intercellular lipids, which is mainly made up of approximately 50% of ceramides (CERs), 15% of free fatty acids, 25% of cholesterol (CHOL), and 10% of CHOL esters (4). The intercellular lipids play an important role in maintaining the skin structure (4,20). Lipid matrix exists in both the crystalline state and the liquid crystalline state (27,28). Liquid crystalline is the state after the substance melted or dissolved in solvents. It is the middle phase between the liquid and crystal, which loses the rigidity of solid substances and has the fluidity of liquid (29). Because of the fluid nature, the lipids in the liquid crystalline state are relatively permeable. Furthermore, the solid lipid crystalline states mainly consist of two phases: the orthorhombic (OR) and the hexagonal (HEX) phases. Their main function is to ensure the integrity of the skin barrier structure (30). The OR phase is considered as the most solid structure among the three structures (OR/HEX/liquid crystalline state), whereas the liquid crystalline state is the most fluid (22).

The other part of the "mortar" is the corneodesmosomes, which are proteins connecting the corneocytes together, providing strength for the skin structure (31). Consequently, the coexistence of the lipid matrix and the corneodesmosome proteins serves as an important factor that enables the SC to act as the tight barrier against the penetration of the external stimulus and other harmful substances (32). Windsor and Burch first discovered that the skin barrier is located in the SC and its stability is directly linked with the states of the lipids and the proteins in the SC (23).

THE IMPACT OF SURFACTANTS TO SKIN

With the constant upgrade of skin-cleansing formulations, the function of the cleansers is not just limited to dirt removal. The mild cleansing and the skin feel after moisturizing

recently become the important criteria for consumers to choose products. Nevertheless, some surfactants in the cleansing products may still exert certain adverse impacts to the skin. It is not uncommon that some surfactants can be detrimental to the skin barrier, thereby causing a series of skin problems, such as dryness, tightness, itch, irritation, and even inflammation. As mentioned earlier, the integrity of the skin barrier is associated with the lipid matrix and proteins in the SC. There are usually two transepidermal pathways for surfactants penetrating into the skin. One is the intracellular route, which allows the molecules to diffuse through the corneocytes. This route is mainly for transporting the hydrophilic or polar solutes. The other pathway is to transport the lipophilic or nonpolar solutes via intercellular lipids. The transepidermal pathways suggest surfactants in skincare products could interact with the proteins and the lipids in the SC, which may change the status of the skin barrier (33,34). The two pathways described earlier are presented in Figure 5.

THE IMPACT OF SURFACTANTS TO INTERCELLULAR LIPIDS

The impact of surfacants to the lipid matrix could be specified in three possible mechanisms: (i) the detergency ability of the surfactants removing dirt and excess oil as well as the lipids from the skin surface, (ii) the mixing between the skin lipids and surfactants leads to the disorganization of the skin lipid matrix, and (iii) the lipids in the SC are extracted and solubilized into the surfactant solutions (35). To illustrate how surfactants affect the

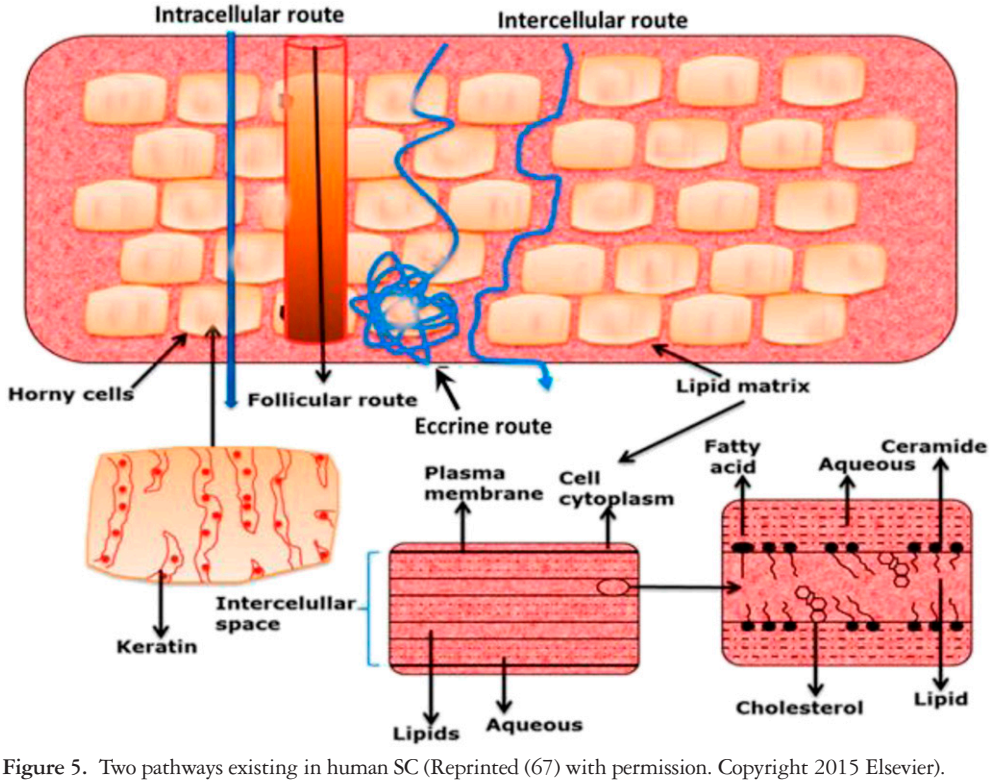

Figure 5. Two pathways existing in human SC (Reprinted (67) with permission. Copyright 2015 Elsevier).

skin lipid matrix, Lémery et al. (35) studied this at three different levels: (i) the investigation of the skin polarity change which is the key to the skin wetting by surfactants. The increase in the skin polarity implies that the surfactants tend to remain on the skin surface; (ii) using infrared spectroscopy in the attenuated total reflectance mode to characterize the disorganization extent of the lipid matrix induced by different surfactants. The shift of the stretching peak from 2,849.8 to 2,850.5 cm^{-1} indicates the phase change from the OR to the HEX, and the shift from 2,850.7 to 2,854.2 cm^{-1} suggests the HEX phase changes to the liquid crystalline state (36). As the fluidity of the lipid structure increases, the disorganization of the lipid matrix increases as well; and (iii) quantitative analysis of the change in the SC lipids by using High Performance Liquid Chromatography (HPLC). The HPLC characterization revealed the amount of total extracted skin lipids as well as the relative changes in the various lipids, i.e., squalene, TS, CERs, and CHOL (35,37–39). They are the four model compounds representing the main skin sebum and lipid components. Motta S et al. found out that when there was damage in the skin barrier, the CER contents presented a decreasing trend (40). CHOL is the most important sterol in the SC. When its synthesis is impeded or its content decreases, the skin barrier dysfunction occurs (41). Squalene in sebum can effectively block the chain reaction of free radicals and inhibit sebum peroxidation, thereby protecting the skin from external stimulation. TS play a vital role in skin injury repair. Consequently, the contents of the squalene and TS are also important to judge skin conditions (42,43). Any variation in the structure, content, and proportion of these four lipid components can impact the skin barrier functions. In the study conducted by Lémery et al. (35), they chose 10 common commercial surfactants (as shown in Figure 6) from different categories: two anionic surfactants (sodium stearoyl lactylate and SLS), two cationic surfactants (cetyltrimethylammonium chloride and distearyldimonium chloride), and six nonionic surfactants (PEG-100 stearate, laureth-23, PEG-12 dimethicone, hydrogenated lecithin, PEG-25 hydrogenated castor oil, and polyoxyethylene sorbitan laurate). The corresponding results are summarized in Table III (35).

Lemery et al. (35) demonstrated that SLS, and cetyl trimethylammonium chloride (CTAC) were considered to be the most irritating surfactants. They remained on the skin surface, disorganized the SC lipid matrix, and extracted most of the skin lipids. On the other hand, the PEG-12 dimethicone and the polyoxyethylene sorbitan laurate had no obvious effects on the skin barrier compared with the rest surfactants (35). They did not induce a shift in the skin polarity or a change in the lipid crystalline structures. In addition, these two nonionic surfactants did not dissolve or remove any significant amount of the skin lipids. These two mild surfactants both possess large PEG head groups, suggesting that they are hindered from the skin barrier (44).

THE IMPACT OF SURFACTANTS TO PROTEINS

Proteins belong to biomacromolecules. Different amino acids are polymerized and folded into a three-dimensional structure (45,46). Proteins are copolymers possessing both hydrophilic and hydrophobic parts, in which the hydrophilic groups can be both ionic or nonionic (47). In general, the interactions between surfactants and proteins include two stages: nonoperative binding and co-operative binding (1). The nonoperative binding is also named site-specific binding. The surfactant monomers in this stage attach to the specific sites of proteins. This binding occurs especially in the presence of ionic surfactants,

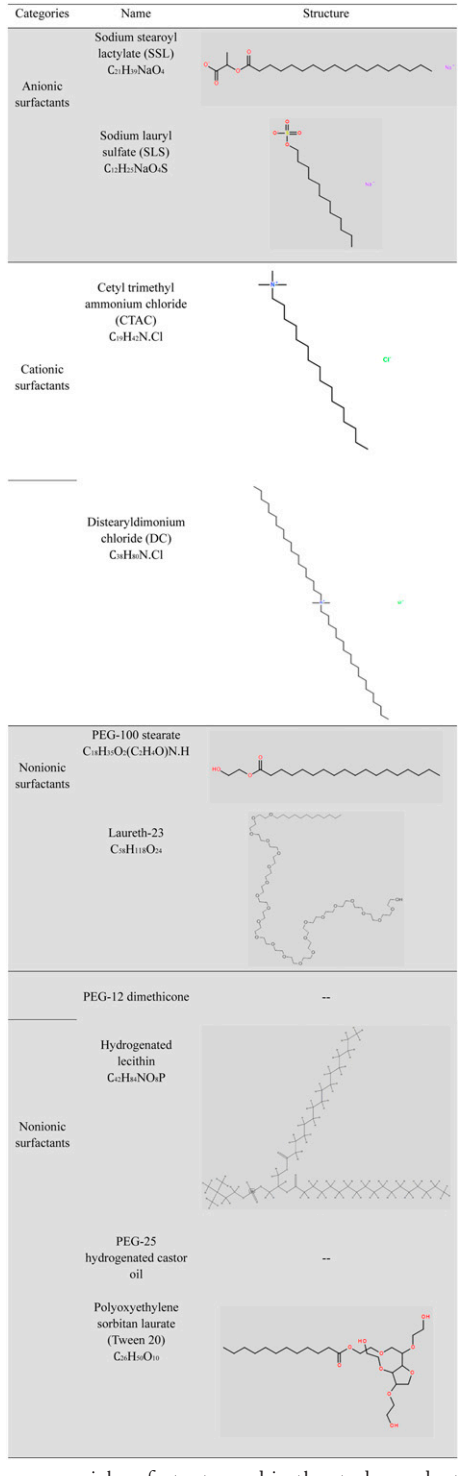

Figure 6. Ten common commercial surfactants used in the study conducted by Lémery et al. (35).

Table III
The Effect of 10 Surfactants on the Skin barrier. The "+" Marks an Evident Effect of Surfactants

	Polarity of skin	Lipid matrix disorganization of skin	Lipid extraction of skin
SLS	+	+	Total+
SSL	+		TS+ CHOL+
DC	+	+	TS+ CERs+ CHOL+
CTAC	+		Total+
Laureth-23	+	+	CHOL+
Polyoxyethylene sorbitan laurate			CERs+ CHOL+
PEG-100 stearate	+		Squalene+ CHOL+
PEG-12 dimethicone			CHOL+
PEG-25 hydrogenated castor oil	+	+	CERs+ CHOL+
Hydrogenated lecithin	+	+	CERs+ CHOL+

but this interaction is not free energetically favorable in the case of nonionic surfactants. In the second co-operative binding stage, the surfactants aggregate to form micellar structures interacting with proteins, destroying their secondary structures. In this case, unfolding of the spiral structures of proteins would occur, and the biological activities would also be lost (4). If the proteins in skin are denaturized by surfactants, they would be solubilized in the surfactant solution, and the skin would also swell (4).

The behaviors of mixed surfactants dissolving proteins were studied by Moore et al. (48). In detail, they investigated how surfactants—SDS/$C_{12}E_n$ ($n = 4$, 6, and 8) mixtures—dissolved the zein protein. Zein is a mixture of proteins with an average molecular weight from 25,000 to 45,000, and thus it is insoluble in water. However, surfactants can promote the zein aqueous solubility, and this solubility is correlated with the physicochemical properties of surfactants. The solubilization of zein by surfactants is analogous to the interactions of surfactants with skin proteins (49). In addition, the skin swelling due to surfactants interacting with skin proteins can further promote the penetration of surfactants and other ingredients in the cleansing products, inducing skin irritation (4,33,48). As a result, the zein protein is a good material to evaluate skin mildness of surfactants.

Demonstrated by Moore et al. (48), SDS indeed promoted the dissolution of the zein protein. Three possible reasons for the favorite interaction between the zein protein and SDS were proposed: (i) the protein backbone protects the hydrophobic patches which expose at the outside of surfactant micelles from the external aqueous environment, (ii) the hydrophobic side chains of the zein protein have the ability to enter the internal hydrophobic core of micelles, and (iii) the interaction between the positively charged protein and the negatively charged SDS contributes to the dissolution of the zein protein. Moreover, nonionic surfactants or certain amphoteric surfactants seldom cause serious zein dissolution compared with anionic and cationic surfactants (48). The polar heads of nonionic surfactants or certain amphoteric surfactants reduce the micelle charge density,

which induces the electrostatic interaction between the zein protein and SDS. In addition, the sizes of polar heads of nonionic surfactants or certain amphoteric surfactants could increase the steric hindrance, thereby reducing the access of the hydrophobic side chains of proteins into internal micelles and the exposure of hydrophobic parts of surfactant micelles to the external environment (48).

THE PENETRATION OF SURFACTANTS INTO SKIN

As discussed earlier, one reason to cause the surfactant-induced skin irritation is the contact between surfactants and the lipids/proteins in the skin barrier. If the surfactant penetration into the skin can be inhibited, its contact with skin lipids/proteins can be reduced, so is the surfactant-induced skin irritation. To achieve this, the understanding in the mechanism of the surfactant penetration into the skin is essential. In the past two decades, many scientists have researched this topic. To summarize, there has been mainly three hypotheses respecting the mechanism of surfactant penetration into the skin.

THE SURFACTANT MONOMER PENETRATION MODEL

A widely accepted view of the surfactant penetration is termed as the *monomer penetration model*. This model explains that surfactant monomers can access the pathways through the skin barrier because they possess relatively small sizes. When the surfactant monomers penetrate into the skin barrier, they interact with skin proteins and lipids, inducing skin irritation. On the other hand, when the concentration of surfactant monomers reaches the CMC, micelles are formed, which have relatively larger sizes and lower surface activity (50). Consequently, they lack the ability to penetrate into the skin barrier. The monomer penetration model had been investigated by many researchers, including Ghosh and Blankschtein (51). Sodium cocoyl isethionate (SCI) was studied because it was considered as a mild surfactant. Past studies demonstrated that SCI did not induce serious irritation compared with other anionic surfactants (52). Ghosh and Blankschtein (51) recorded the shift of skin electrical current versus SCI concentration, which did not change further beyond the CMC of SCI. This clearly indicated that the SCI micelles lack the ability to penetrate into the skin.

THE SURFACTANT MICELLE AND THE SUBMICELLE PENETRATION MODEL

The surfactant monomer penetration model suggests that the penetration of the surfactant into the skin is dose independent—the amount of surfactants presented in the skin would not increase further when the surfactant concentration exceeds the CMC. However, skin penetration of SDS showed contradicting results. Moore et al. (50) studied the relationship between the SDS concentration and the amount of SDS penetrating into the skin. The results demonstrated that when the concentration of SDS was beyond the CMC, the amount of SDS in the skin barrier still increased without any limitation. As a result, the penetration behavior of SDS could not be simply explained by the monomer penetration model (53). Through the experiments directed by Ghosh and Blankschtein (51), they found out that the SDS micelles had the ability to penetrate into the skin. Moreover, SDS skin penetration beyond the CMC was predominated by the SDS micelles. This is proposed as the surfactant micelle penetration model.

Clearly, contradicted behaviors were observed from the penetration experiments of SCI and SDS. Consequently, researchers did a series of studies and proposed hypotheses to perfect the surfactant penetration model. The CMC of SCI is indeed lower than that of SDS, inducing a smaller amount of monomers existing in the solution and the formation of micelles at a lower concentration (51). According to the monomer penetration model, a surfactant with a lower CMC is unlikely to cause high skin penetration and induce serious irritation (54), which partially explains why SCI is milder than SDS (55). But how about the penetration behaviors of SCI micelles? To answer this question, Ghosh and Blankschtein (51) measured the radius of SCI micelles and the average aqueous pore radius resulting from skin exposure to SCI by using dynamic light-scattering. The results as well as their comparison to SDS and control are presented in Table IV.

Apparently, SCI micelles are larger than SDS micelles, which were also larger than the average aqueous pore radius. This indicated that SCI micelles face steric hindrance to penetrate into the skin barrier. On the other hand, SDS micelles are small enough to be able to enter the skin aqueous pores. Therefore, micelle size is an important factor to determine the surfactant penetration behaviors. Moreover, SDS is capable of increasing both the aqueous pore size and the number density; thus, it could alter the skin structure, inducing skin irritation (51). Ghosh and Blankschtein (51) demonstrated that SCI only slightly induced skin perturbation, thanks to its large micelle size and its ability to reduce aqueous pore radius/density. As a result, SCI is a good candidate to be applied to mild cleansing.

Hill et al. (56) and James-Smith et al. (57,58) proposed the submicelle penetration model. This hypothesis was based on micelle kinetics—micelles are rapidly breaking and reforming continuously (57–59). This dynamic state is described in Figure 7. The dynamic state includes two types of relevant time scales: fast relaxation time and slow relaxation time. Fast relaxation time is used to measure the time needed for the surfactants to enter or come out of the micelles. Slow relaxation time describes the time used for the micelles to completely form or completely integrate. In this equilibrium, some monomers could form aggregations smaller than micelles termed submicelles or premicelles. James-Smith et al. (58) observed SDS submicelles were presented at the concentration of 3–4 times CMC. Later, LeBard et al. (59) used the molecular dynamic simulations to investigate the dynamic change of a nonionic polyethylene glycol (PEG) surfactant, C7E6 solution, at low concentrations. Premicelles were identified at concentrations below the CMC, and their concentration increased with increasing total concentration below the CMC, reaching a plateau above the CMC, where these premicelles exist in equilibrium with free monomers and full-size micelles (59). Because of the smaller sizes, the submicelles may have the ability to penetrate into the skin barrier (56–58). To verify this hypothesis, Hill et al. (57) adjusted the SDS micelle stability by mixing with dodecyl trimethylammonium bromide (C_{12}TAB) at various ratios and observed that addition of C_{12}TAB lowered the ability of SDS to perturb skin barrier properties

Table IV
Micelle Radius and the Average Aqueous Pore Radius after Skin Exposure to SCI/SDS/Phosphate-buffered saline (PBS) Control Solutions

Types of solution	Micelle radius, r (A)	Average aqueous pore radius, $r_{\text{pore (A)}}$	Aqueous pore number density, $(\varepsilon/\tau)_{\text{normal}}$
SCI solution	33.5 ± 1	29 ± 5	2 ± 1
SDS solution	19.5 ± 1	33 ± 5	7 ± 1
PBS control solution	Not applicable	20 ± 3	1

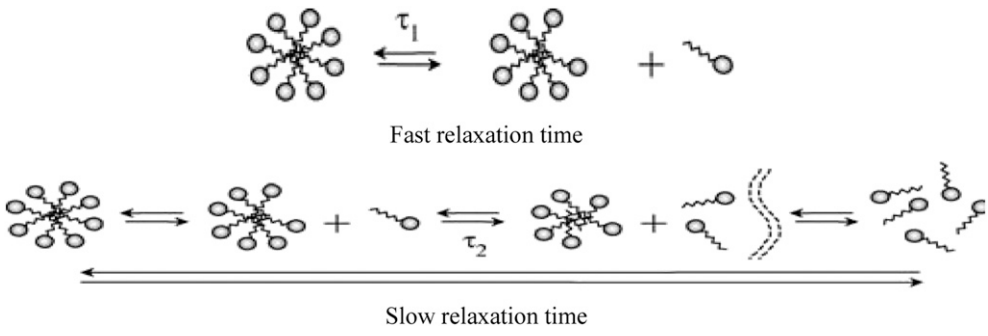

Figure 7. The dynamic state of surfactants at a certain concentration of surfactants (Reprinted from (58) with permission. Copyright 2007 Elsevier).

by decreasing the concentration of SDS monomers and submicelles. This indicates submicelles indeed possess the ability to penetrate into the skin.

A NEW PROPOSED MODEL: SURFACTANT CHARGE DENSITY AND PENETRATION CORRELATION

To find out which model is the most sophisticated to explain the surfactant penetration, Morris et al. (60) well studied the physicochemical parameters of surfactants that could influence their skin penetration: (i) the CMC, representing the amount of surfactant monomers in the solution; (ii) the micelle radius, showing the steric hindrance of micelles; and (iii) the zeta potential, correlating with the micelle charge density.

Morris et al. (60) used the radiolabeled SDS (^{14}C-SDS) to investigate 16 different surfactant systems *in vitro* on the human cadaver skin. The 16 surfactant systems and their physicochemical parameters are listed in Table V. The study indicated that only (i) the CMC and (iii) the zeta potential showed a clear correlation with the radiolabeled SDS penetration. Interestingly, the SDS micelle radius did not show a clear correlation, which was inconsistent with the previous findings. Morris et al. (60) hypothesized this was attributed to the short residence time of surfactants contacting the skin in the experiment. When the skin barrier is exposed to surfactants for a longer period, the micelle size would have an impact on the surfactant penetration. When anionic surfactant solution comes into contact with the skin, monomer penetrates the skin and binds to proteins, increasing the electrical charge on the protein network and causing the skin structure to swell. This allows for progressive surfactant binding in deeper layers of the skin, resulting in enhanced skin swelling (57,61). Therefore, surfactant micelles and submicelles may additionally be able to penetrate and swell the skin structure. The more charged the surfactant system and the longer the surfactant exposure time, the more the binding to the skin proteins, speeding up the penetration process (33,34,57). Zeta potential is known to correlate with the charge density of colloids in solution, and that is the reason why it was revealed to correlate with the surfactant penetration in the study.

METHODS TO REDUCE SURFACTANT PENETRATION INTO SKIN

All the hypotheses with respect to surfactant penetration discussed earlier suggest that the surfactant penetration is related to the steric interaction between the surfactant monomers/submicelles/micelles and the average aqueous pore radius/number density. Consequently, increasing surfactant monomer/micelle size and/or reducing average aqueous

Table V
CMCs, Micelle Diameter, and Zeta Potential of 16 Surfactant Systems Tested by ^{14}C-SDS

Surfactant system	CMC, mM	Micelle diameter, nm	Zeta potential, mV
SLS	3.15 ± 0.03	2.73 ± 0.19	−54.1 ± 3.8
SLS in NaCl (0.01 M)	2.64 ± 0.31	3.43 ± 0.16	—
SLS in NaCl (0.05 M)	1.43 ± 0.12	4.86 ± 0.26	—
SLS in NaCl (0.10 M)	1.06 ± 0.07	5.51 ± 0.15	—
SLS in NaCl (0.25 M)	0.671 ± 0.0015	0.628 ± 0.06	—
SLS with 2% PEO	2.30 ± 0.18	3.04 ± 0.12	−24.2 ± 0.7
SLS with Dimethyl dodecyl amine oxide	4.86 ± 0.22	126 ± 20	−77.5 ± 3.6
SLS with Lauramidopropyl betaine	0.526 ± 0.032	4.10 ± 0.30	−52.9 ± 6.5
SLS with Lauric acid	9.26 ± 0.08	2.26 ± 0.10	−72.7 ± 4.1
Sodium dodecyl benzene sulphonate	2.00 ± 0.08	3,94 ± 0.07	−47.9 ± 5.1
SLE_1 S	1.32 ± 0.04	2.26 ± 0.15	−46.1 ± 4.5
SLE_3S	0.452 ± 0.037	2.19 ± 0.06	−27.6 ± 2.3
SLI with LAPB	0.289 ± 0.023	4.07 ± 0.41	−63.0 ± 6.3
$C_{12}E_6$	0.0695 ± 0.0014	25.3 ± 1.1	−7.2 ± 0.9
SLS with $C_{12}E_5$	0.0993 ± 0.0022	1.85 ± 0.06	−39.4 ± 4.7
SLS with $C_{12}E_6$	0.0992 ± 0.0034	1.91 ± 0.17	−32.5 ± 1.4

pore radius/number density could play an important role in skin barrier protection. Binding surfactants with other bulky molecules such as nonionic surfactants and polymers is one of the common methods to increase surfactant micelle size (62). For example, mixing C12E6 with SDS reduces SDS CMC and induces its micelle growth (63), thereby limiting SDS monomer and micelle skin penetration and reducing SDS-induced skin irritation.

In the experiments directed by Moore et al. (50), Polyethylene oxide (PEO) was mixed with SDS in solution. Hydrophilic polymers like PEO are known to form micelle-like complexes with anionic surfactants such as SDS, with the polymer forming a corona around the anionic surfactant micelles. An obvious increase in the average SDS micelle radius from 20 to 25 A was observed with the addition of PEO. This binding effectively reduced SDS skin penetration attributed to the steric hindrance and/or the slow diffusion of SDS.

Adding humectant to the surfactant solution is known to improve the skin mildness by providing hydration (64,65). Ghosh and Blankschtein (66) demonstrated that it is also an effective way to reduce surfactant penetration. In their study (66), electrical currents served as an index to reflect the amount of SDS presented in the skin barrier. The results indicated that the amount of SDS in the skin continuously increased when the pure SDS concentration exceeded the CMC. However, it was not the case for the mixture of SDS in 10% glycerol solution.

Ghosh and Blankschtein (66) stated three hypothesizes to account for the reduced SDS penetration by adding 10% glycerol: (i) the glycerol addition reduced the SDS CMC; (ii) the addition of the 10% glycerol increased the SDS micelle size, hindering them from penetrating into the skin; (iii) 10% glycerol reduced the radius and/or the density of the aqueous pores in the skin barrier. Both (i) and (ii) hypotheses were proved to be invalid. The data in Table VI demonstrated that the 10% glycerol addition effectively reduced the average pore radius and the pore number density in the skin.

Table VI
Skin Aqueous Pore Radius and Normalized Pore Number Density Resulted by Various Solutions

Solution	Average pore radius, r_{pore} (A)	Normalized pore number density, $(\varepsilon/\tau)_{normal}$
SDS	33 ± 5	7 ± 1
SDS with 10% glycerol	20 ± 5	3 ± 1
PBS control	20 ± 3	1
10% glycerol	11 ± 4	0.5 ± 0.1

See references 68., 69., 70., 71., 72., 73.

CONCLUSION AND PERSPECTIVES

The focus of this article is to summarize the state-of-the-art understanding of surfactants' penetration into the skin, which have been studied by many researchers for decades. Nevertheless, an explicit surfactant penetration model still could not be given so far. It is likely that different penetration hypotheses play a role simultaneously, and a combination of all the mechanisms enables surfactant penetration into the skin. With respect to mild cleansing, the addition of nonionic/amphoteric surfactants, hydrophilic polymers, or humectants such as glycerol can minimize the skin penetration of anionic surfactants, reducing the occurrence of skin irritation. On the other hand, a complete prevention of surfactant penetration into the skin is difficult and challenging, implying that surfactants can be used as penetration enhancers for transepidermal-active delivery.

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