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Review article

Mechanisms of penetration and diffusion of drugs and cosmetic actives across the human Stratum corneum

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ABSTRACT

Based on the structure of the Stratum corneum (SC) the potential penetration/diffusion pathways of drugs and cosmetic actives through the SC are presented and discussed.

The well-known ***lipophilic pathway*** across the SC is presented and relevant examples are used to show that highly lipophilic molecules such as glucocorticoids, coenzyme Q10 etc. are accumulated in the SC and penetrate into the inner liquid like layer of the SC lipid bilayer by ***lateral diffusion***.

The diffusion into and across the SC of highly hydrophilic drugs and active substances such as urea, amino acids and peptides is still under discussion. Another diffusion pathway for the highly hydrophilic molecules via the corneocytes and the corneodesmosomes is presented and discussed, the ***corneocytary diffusion pathway***.

1. Introduction

The stratum corneum (SC) is the outermost layer of the mammalian epidermis. As such, it represents the body's main interface with its environment. It provides a strong penetration/diffusion barrier protecting the body from harmful influences like pathogens or exogenous molecules such as drugs and cosmetic actives. In the 1960 s, it was proven that this penetration barrier of the skin is located within the SC [1,2]. The SC consists of dead cells without a nucleus and a regular cell membrane, the corneocytes (COR). These cells are strongly interconnected via corneodesmosomes [2,3] and form a strong rigid skeleton. The COR are also strongly keratinized and surrounded by a coat of proteins and lipids, the cornified envelope (CE). This multi-layered envelope replaces the cellular membrane at this terminal stage of differentiation. It consists of an inner layer of cross-linked proteins bound to the keratin network, the cornified protein envelope (CPE) [4]. A monolayer of ω-hydroxy-ceramides (ω OH-CER), the cornified lipid envelope (CLE), is covalently bound to the surface of the cornified envelope [5–7]. A complex free multi-lamellar arranged lipid matrix (LM) fills the remaining free intercellular space. This matrix consists of ceramides (CER), free fatty acids (FFA) and cholesterol (CHOL) in an approximately equimolar ratio [8].

A lot of drugs and cosmetic actives ranging from lipophilic to hydrophilic, are delivered to the skin and most of them have to cross the SC. Molecules with a good balance between hydrophilicity and lipophilicity are able to easily penetrate the SC. They are also able to permeate into and across the SC bilayer. The following conditions are required for sufficient penetration across the SC: (1) adequate solubility in oil and water, (2) low molecular mass (<500 Daltons) and medium lipophilicity (log P: 1–3) [9].

Forslind proposed both one hydrophilic and one hydrophobic pathway through the skin barrier [10]. There is consensus in the literature that the following are potential pathways for drugs and cosmetic actives across the SC: (1) penetration via the SC lipid matrix, (2) intracellular diffusion via the COR and the corneodesmosomes (see Fig. 1).

On the other hand, the appendages account for only a fraction of the permeation and their contribution to epidermal penetration/diffusion is limited [11]. The follicular pathway is important for the delivery of nanoparticles with a specific diameter in connection with massage [12].

In order to study the mechanism of the passage of relevant molecules across the SC, the penetration/diffusion of both ***highly lipophilic drugs and actives*** such as glucocorticoids (GCs), coenzyme Q10 etc. and ***highly hydrophilic drugs and actives*** such as urea, amino acids, peptides etc. must be considered. Given the extremely different physicochemical properties of these molecules, it is likely that different penetration/diffusion pathways through the SC exist.

Therefore, this review addresses and discusses the potential penetration/diffusion pathways through the SC as well as the potential mechanisms of penetration and diffusion of highly lipophilic and highly hydrophilic molecules through a layer as complex as the SC.

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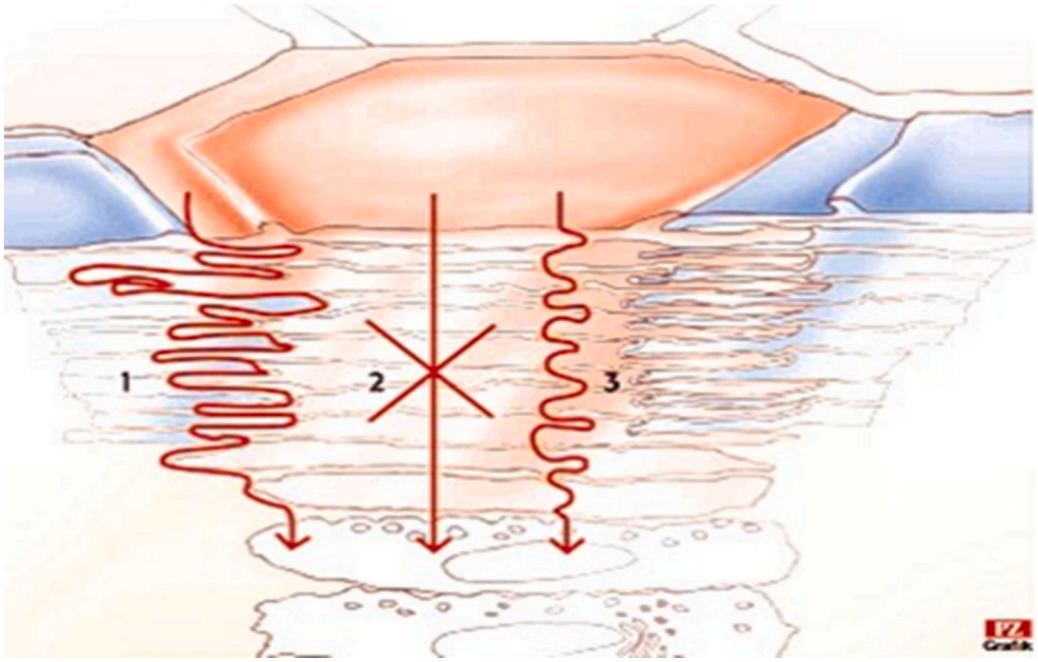

Fig. 1. Potential diffusion/penetration pathway across the Stratum corneum (SC1: intercellular pathway via the lipid preferred for lipophilic substances, 2: transcellular pathway – very unlikely, 3: new corneocytary pathway for hydrophilic substances.

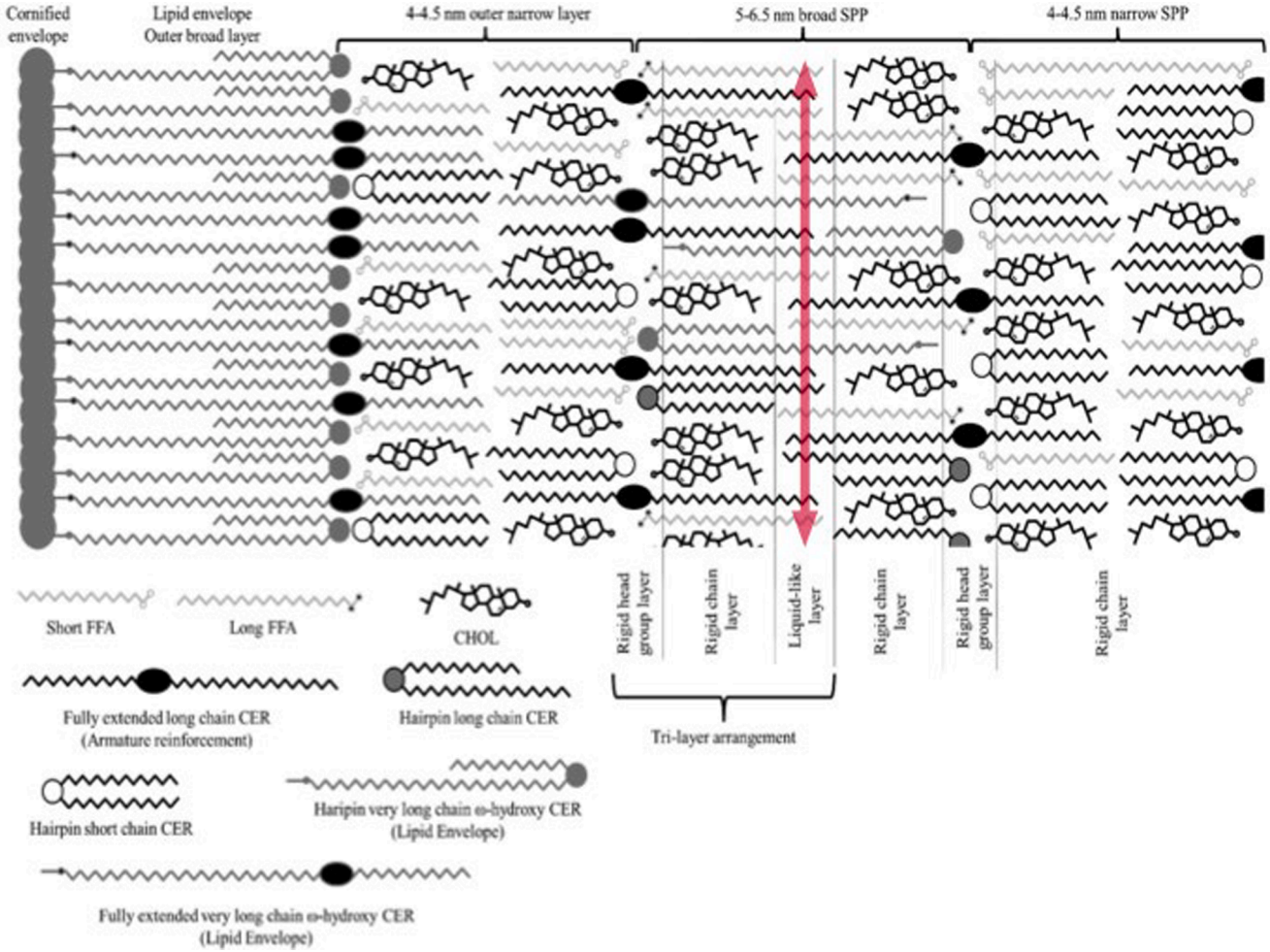

Fig. 2. The ***Unified Model*** of the Stratum corneum nanostructure according to Schmitt & Neubert, 2020, Red arrow: Lateral lipophilic diffusion pathway.

2. Penetration of highly lipophilic molecules across the Stratum corneum

Highly lipophilic molecules such as GCs, tacrolimus, coenzyme Q10, retinyl acetate etc. can easily penetrate the SC. They are able to form a depot in the SC by accumulating in the lipid bilayers of the SC [13]. GCs are even lipophilized for dermal administration, e.g. betamethasone valerate [14]. Other highly lipophilic actives such as coenzyme Q10 [15] and tacrolimus [16] can also pass through the SC, depending on the formulation used.

The penetration mechanism of lipophilic molecules in SC has been studied and discussed for many years.

Johnson et al. [17] measured the diffusion coefficients of nine lipophilic fluorescent probes in lipid extracts of SC. The authors suggested that these probes pass through the SC by lateral diffusion. Diffusion of solutes through the lipid bilayers by hopping between pockets of free volume was proposed by Mitragotri [18] for hydrophobic solutes.

In contrast, Wang, Kasting and Nitsche [19] suggested, on the strength of database and theoretical considerations, that permeation through SC is dominated by the transcellular pathway for most compounds regardless of their lipophilicity, which is a striking departure from recent models of skin permeability.

Based on a two-dimensional computational model of molecular diffusion through the SC Nitsche, Kasting and Nitsche [20] found that the diffusivity for the transport of solutes inside the SC lipid layer is typically $10^3 - 10^5$ times the diffusivity for the perpendicular direction. This statement emphasizes the relevance of the lateral diffusion within the SC lipid bilayers for highly lipophilic molecules.

Wang et al. [21] developed an extended diffusion model. They specified and confirmed the calculations of Wang, Kasting and Nitsche [19]. This model presents explicit predictions of both lateral and transdermal effective diffusivities of molecules. Wand et al. [21] showed that the lateral diffusion rate within the lipid layers is increased by the fourth power compared to the intrinsic permeability of the intercellular lipids in the transverse direction, both of them are characterized by the diffusion coefficients of different molecules.

Chen, Han and Lian [22] used model calculations to show that the preferred route for hydrophobic molecules through the SC is via the "relatively permeable intercellular lipids". Dos Santos et al. [23] found that the highly lipophilic retinyl acetate can easily penetrate the SC and is accumulated in the lipid bilayers of the SC.

Recently, a ***unified model*** of the nanostructure of the SC lipids was presented [24]. Based on neutron diffraction data, a three-layer arrangement of the SC bilayer of the small periodicity phase (SPP), which has a central liquid-like layer (see Fig. 2), is proposed. In this model, an overlapping central layer would always be present as a result of the varying length of the fatty acid chains. The assumed more liquid-like properties of this layer could have an important effect on the stability against shear stress and compression and could be important for the adaptability of the skin. Furthermore, this effect would be supported by the special properties of the CHOL, which has the highest mobility among the SC lipids and can even perform a flip-flop mechanism between two opposing bilayers. According to the entropy/enthalpy concept, the three layers, as proposed in the three-layer model, are of utmost importance for the barrier function. The two rigid outer layers repel molecules and prevent penetration in the transverse direction, and the middle layer could possibly have a trapping effect on penetrating highly lipophilic molecules as it has the best miscibility/solubility properties.

The *unified model* with a liquid-like middle layer is supported by Molecular Dynamic (MD) simulations presented by Das, Olmsted and Noro [25], Das, Noro and Olmsted [26], and Das and Olmsted [27]. These authors show results from atomistic molecular dynamics of selected SC lipid bilayers and multi-layers to probe the effect of these polydispersities and to isolate the effects of different kinds of polydispersity seen in selected SC lipids. Both the asymmetry and tail polydispersity were found to enhance partial tail interdigitation (a region occupied by chains from both the leaflets). The degree of interdigitation is closely associated with interleaflet friction.

Experimental data obtained using IR spectroscopy [28], solid state NMR [29], Raman spectroscopy and ^{2}H NMR show the co-existence of a "small pool of mobile lipids" in presence of the majority of rigid lipids [30]. It could be shown a special contribution of the long chain ceramides to the fraction of the mobile lipids [28,30].

Therefore, in summary, it is generally recognized in the literature that highly lipophilic molecules can easily penetrate into the lipid bilayers of the SC and that the mechanism of the penetration of these molecules through the SC is the ***lateral diffusion*** in the liquid-like layer of the SC lipid bilayers. New data show that the preferred pathway for lateral diffusion is the central liquid-like layer of the SC lipid bilayers (see Fig. 2).

3. Diffusion of highly hydrophilic molecules inside the stratum corneum

Experimental data on skin diffusion of highly hydrophilic molecules across the SC are still very limited and studying this process is a challenge.

First of all, there is clear evidence that CORs are accessible for at least a few diffusants. Water can easily and very effectively diffuse into the CORs [31–34]. MD simulations showed that water is not able to permeate vertically through SC model bilayers [25]. Therefore, it was assumed that water permeates via the CORs. Furthermore, theoretical simulations have shown that the CORs are able to swell without changing their volume [35] like tetrakaidekahedral-shaped cells [36].

Several larger hydrophilic molecules (usually dyes) were visualized inside the COR as shown by the different authors [37,38] using light and fluorescence microscopy.

In addition, it is reported in the literature that small hydrophilic molecules such as urea [39], small peptides [40,41] and amino acids [42] can pass through the SC using radioactive labelled peptides [40,41] and HPLC [42], respectively, and excised human skin [40,41] and pig ear skin [42]. However, it is unlikely that hydrophilic molecules can permeate across the SC lipid bilayers because the SC lipids have a very dense nanostructure and there is no water between the head groups of the SC lipid bilayer. There are only a few water molecules in the SC [33,43,44], which are only necessary for the formation of the tight network of hydrogen bonds in the head groups of the SC lipids.

There are several hypotheses in the literature about the diffusion of hydrophilic molecules into the SC. Potts and Francoeur [45] proposed the diffusion of hydrophilic molecules between the lipid headgroups in the lamellar lipids of the SC. Sznitowska, Janicki and Williams [46] suggested the polar pathway of penetration across the SC, which may be intercellular and is realized by aqueous regions surrounded by polar lipids forming a kind of microchannels. Mitragotri [17] also assumed that hydrophilic solutes permeate across the skin through imperfections in the lipid bilayers modelled as pores (see also [47]). However, the water content between the head groups of the SC lipids does not exist for this type of diffusion.

In contrast, Chen Han and Lian [21,48] proposed transcellular diffusion of hydrophilic molecules through highly resistive CORs. Yu and Kasting [49] also pointed out that transcellular transport is an important component of the polar SC pathway. Hussain et al. [50] showed that urea, taurine and amino acids can diffuse into isolated CORs. Moreover, hydrophilic diffusion enhancer molecules such as urea and taurine were found not to affect the nanostructure of SC lipids [51], showing that hydrophilic diffusion enhancers do not influence the nanostructure of the SC lipids. Therefore, it appears that they are not able to influence the lipophilic penetration pathway.

Hussain et al. [52] showed too that eight amino acids as well as taurine are in the position to diffuse easily into isolated CORs.

The uptake of hydrophilic amino acids into isolated CORs was only

Table 1
Effect of chemical permeation/diffusion enhancers on the corneocyte-water uptake coefficients ($K_{COR/W}$) of four selected skin relevant free amino acids (FAAs) according to Kahsay et al., 2024, [42].

FAAs	$K_{COR/W}$					
	Without enhancer	**PG**	**NMP**	**2-P**	**DMSO**	**Transcutol**
L-Arg	**1.04 ± 0.06**	1.09 ± 0.14	1.64 ± 0.07	1.32 ± 0.06	1.42 ± 0.05	**1.68 ± 0.16**
L-Ser	**1.08 ± 0.14**	0.98 ± 0.08	1.43 ± 0.06	1.21 ± 0.04	1.49 ± 0.17	**1.78 ± 0.17**
L-Gly	**0.98 ± 0.51**	1.01 ± 0.04	1.18 ± 0.10	1.16 ± 0.06	1.48 ± 0.06	**1.56 ± 0.15**
L-His	**1.03 ± 0.01**	1.39 ± 0.04	1.50 ± 0.05	1.56 ± 0.03	1.30 ± 0.04	**1.63 ± 0.14**

Where PG … propylene glycol, NMP … N-methyl pyrrolidone, 2-P … 2-pyrrolidone, DMSO … dimetylsulfoxid, Transcutol … diethylene glycol monoethyl ether.

increased by hydrophilic diffusion enhancers such as NMP (N-methyl pyrrolidone), 2-P (2-pyrrolidone) and Transcutol (diethylene glycol monoethyl ether), as shown in the Table 1 [42]. Transcutol appears to be most effective in enhancing the uptake of hydrophilic amino acids into the CORs.

Apparently, peptides with a higher molecular mass such as insulin can also pass through the SC if they are incorporated into colloidal formulations and in combination with the penetration enhancer DMSO [53]. The passage of the SC of the macromolecule heparin can be improved in the same way [54].

However, these results must be confirmed with other skin relevant macromolecules. In addition, it must be investigated whether and to what extend relevant hydrophilic macromolecules can diffuse into the CORs of the human SC. A further challenge is to provide evidence of the extent to which corneodesmosomes contribute to the diffusion of hydrophilic molecules into the SC via the proposed corneocytary pathway. However, new analytical tools such as MALDI-TOF imaging should be helpful to address this question and investigate whether and to what extent the corneodesmosomes contribute to this pathway. It should be kept in mind that each COR is connected to the next CORs via approximately 400 corneodesmosomes estimated based on electron-microscopic images (see [55]).

In summary, the passage of the CORs is apparently also essential for small hydrophilic molecules such as amino acids, urea and small peptides too to pass through the SC. Therefore, it is evident that small hydrophilic molecules can cross the SC via the **corneocytary diffusion pathway**.

4. Conclusions

The lipophilic penetration pathway is described in the literature for highly lipophilic molecules as follows: highly lipophilic molecules such as GCs, coenzyme Q10 etc. can easily penetrate and accumulate in the SC. They are able ***to diffuse laterally into the SC via the central liquid-like layer of the SC bilayer***.

However, the diffusion of highly hydrophilic drugs and cosmetic actives such as urea, amino acids and peptides into the SC is still under discussion.

In this review, an alternative diffusion pathway of highly hydrophilic drugs and actives via the CORs and the corneodesmosomes is discussed: the ***corneocytary diffusion pathway*** for highly hydrophilic molecules. The relevant papers are presented and discussed showing that (1) small hydrophilic molecules such as urea, amino acids and small peptides can diffuse into the SC, (2) small hydrophilic molecules such urea and amino acids can diffuse into the CORs, and (3) the diffusion of these small hydrophilic molecules into the CORs can be influenced with the help of hydrophilic diffusion enhancers.

The open and challenging questions for the future are: (1) Is it possible to identify relevant highly hydrophilic drugs and actives such as peptides within the corneodesmosomes using the new techniques such as MALDI imaging? (2) How can the diffusion of relevant hydrophilic molecules via the corneocytary diffusion pathway be influenced in order to transport molecules with higher molecular mass such as proteins, RNA and DNA via the corneocytary diffusion pathway into the SC? (3) How can hydrophilic molecules such as moisturizers be retained inside the CORs? (4) Is the cornified lipid envelope the limiting barrier for this corneocytary diffusion pathway?

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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