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Effect of stratum corneum heterogeneity, anisotropy, asymmetry and follicular pathway on transdermal penetration

Ana M. Barbero*, H. Frederick Frasch

Health Effects Laboratory Division, National Institute for Occupational Safety and Health, 1095 Willowdale Road, Morgantown, WV 26505, USA

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ABSTRACT

The impact of the complex structure of the stratum corneum on transdermal penetration is not yet fully described by existing models. A quantitative and thorough study of skin permeation is essential for chemical exposure assessment and transdermal delivery of drugs. The objective of this study is to analyze the effects of heterogeneity, anisotropy, asymmetry, follicular diffusion, and location of the main barrier of diffusion on percutaneous permeation. In the current study, the solution of the transient diffusion through a two-dimensional-anisotropic brick-and-mortar geometry of the stratum corneum is obtained using the commercial finite element program COMSOL Multiphysics. First, analytical solutions of an equivalent multilayer geometry are used to determine whether the lipids or corneocytes constitute the main permeation barrier. Also these analytical solutions are applied for validations of the finite element solutions. Three illustrative compounds are analyzed in these sections: diethyl phthalate, caffeine and nicotine. Then, asymmetry with depth and follicular diffusion are studied using caffeine as an illustrative compound. The following findings are drawn from this study: the main permeation barrier is located in the lipid layers; the flux and lag time of diffusion through a brick-and-mortar geometry are almost identical to the values corresponding to a multilayer geometry; the flux and lag time are affected when the lipid transbilayer diffusivity or the partition coefficients vary with depth, but are not affected by depth-dependent corneocyte diffusivity; and the follicular contribution has significance for low transbilayer lipid diffusivity, especially when flux between the follicle and the surrounding stratum corneum is involved. This study demonstrates that the diffusion is primarily transcellular and the main barrier is located in the lipid layers.

1. Introduction

The main barrier for permeation through the skin resides in the stratum corneum (SC) [1]. The SC is heterogeneous [2], since it is composed of corneocytes surrounded by lipid layers and there is not a complete agreement on whether lipid layers or corneocytes are the main contributor to the permeability barrier [3]. It is now widely accepted that corneocytes are permeable and they should be included in the geometry of the permeation model [4–9]. The lipid layers are anisotropic—their permeability is direction-dependent—and this property greatly affects the diffusion characteristics in the skin [4].

The asymmetry of the SC with depth (termed vertical heterogeneity by some authors) has been demonstrated by detailed examination of its structure [9–12], by sorption and desorption tests [10], by in vivo non-invasive measurement data [13], by observations of the non-uniform SC swelling [6], and by in vitro study on intact and tape-stripped skin samples [14]. Asymmetry with depth could result from the increasing water content of the SC with depth, from 50% to 70% for fully hydrated SC and from 20% to 60% for partially hydrated SC [15], and this may imply an increase in the corneocyte diffusivity in the inner layers. Asymmetry, located in the lipid layers, is reflected by the decrease in the C—H stretch frequency associated with the lipid alkyl chains of outer layers of the SC [16]. A decrease in the lipid ordering may result in an increase in the lipid diffusivity in the outer layers. Watkinson et al. [17] tested the hypothesis of higher diffusivity in the surface of the skin with a model geometry of one and two isotropic slabs; they found that the concentration profiles when diffusivity is dependent on depth (diffusivity in the surface 3 times that of the inner layers) did not differ much from the profiles where diffusivity was kept constant with depth. Anissimov and Roberts [18] studied desorption with variable diffusion coefficients (linear, exponential, and two isotropic slab models) and variable partition coefficients (exponential, two slab, and exponential-constant models) and demonstrated that permeation is insensitive to diffusion and partition coefficient asymmetry. On the other hand, desorption flux could be explained by partition asymmetry. They concluded that partition coefficient asymmetry had more effect than

* Corresponding author.
E-mail address: abarbero@cdc.gov (A.M. Barbero).

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diffusivity asymmetry and should be included when modeling tape-stripping data. Mueller et al. [19] measured experimentally a biphasic concentration profile of clobetasol propionate (a logarithmic decrease on the top four to five tape strips and a constant low concentration in the inner layers) concluding that a variable partition coefficient was the main cause for this unexpected result. Furthermore, asymmetry could be caused by the degraded state of a protein—corneodesmosin—in the outer layers of the SC, possibly increasing corneocytes uptake toward the surface of the SC [20]. All these previous studies use geometry of one or two isotropic slabs to represent the SC.

Skin appendages, hair follicles and sweat ducts, constitute another pathway of permeation [10]. In spite of their small relative area, estimated as 0.1% [21] of the total surface area, their importance is revealed from observations of permeability of ions, highly polar molecules, and high molecular weight compounds, especially in initial transient times [21,22]. The follicular contribution could be of about 50% [23] to 60% [24], as measured by a sandwich system technique based on simplified mathematical assumptions [25,26]. Otberg et al. [27] observed larger absorption of caffeine, in an in-vivo study, when skin follicles were left open versus blocked (follicular contribution 35%). Trauer et al. [28] found a 58% follicular penetration of caffeine. By differential stripping technique, 10% to 24% of the total amount of finasteride in the stripping tapes was found in the hair follicles [29]. A simplified mathematical analysis of the follicular pathway, presented early on by Scheuplein [21], demonstrates that the smaller the permeability of a compound the more significant the role of appendages becomes [30]. A detailed mathematical model of local diffusion of unionized chemical species through a single hair shaft with follicular sheath surrounded by SC, viable epidermis, and dermis shows a high follicular penetration into dermal tissue, in concordance with experimental in vitro data [31,32]. Dancik et al. [32] presented concentration profiles of model permeants into the surrounding skin for different scenarios of permeability, partition and concentration. Mitragotri et al. [33] analyzed the diffusion through shunts assuming a smaller area fraction of the appendages, 1×10^{-4} or 0.01% of the total surface, claiming sebum reduces the area available for transport.

The input parameters for a percutaneous permeation model are geometric descriptors, affinity parameters, and transport parameters. The geometric descriptors are obtained from measurements and microscopic models of the SC [34]. The affinity parameters are the lipid and corneocyte partition coefficients. They can be obtained experimentally [35–37]; or from correlations as a function of the octanol-water partition coefficient regressed to experimental partition coefficients [38–42]. The dependency of the partition coefficient values on the method being employed, was pointed out as a caveat for obtaining an accurate model of permeation [3]. The transport parameters are lipid and corneocyte diffusivities. In general, they are computed from physico-chemical properties of solutes with correlations to experimental data [38]. A wide range of values of lipid and corneocyte diffusivities have been used in previous models. Whether the lipid or corneocyte is the main barrier of diffusion will greatly influence the permeability results and needs to be studied prior to the analysis of the SC asymmetry and follicular penetration. In the pioneering works by Yotsuyanagi and Higuchi [43], Michaels et al. [44] and Tojo [45], the lipids were considered the main barrier for diffusion. In contrast, in the models by Heisig [46] and Naegel-Hansen [35,47] the corneocytes were the main barrier for diffusion. Johnson et al. [48] developed the first SC model with anisotropic lipid but only lipids were included in the geometry. Frasch [49] and Barbero and Frasch [50] explored a full range of values. Wang et al. [4,51] introduced anisotropy in the lipid layers mathematically represented with a lateral diffusivity and a mass transfer coefficient for transbilayer hopping, with the lipid phase being the main diffusion barrier. Chen et al.'s model (2008) [52–55] included an isotropic lipid phase with the corneocyte being the main barrier to diffusion. In summary, of the most recent models, Wang et al. [4,51] and Johnson et al. [48] models locate the main barrier in the lipid phase, while Naegel-Hansen [35,47] and Chen et al. [52–55] models consider the corneocyte phase as the leading barrier.

This work addresses some unresolved issues [38] related to the impact of the SC structure on functionality. The objectives of this study are: the analysis of the effect of the location of the main barrier of diffusion, the presence of asymmetry with depth, and the inclusion of the follicular pathway on percutaneous permeation. First, analytical solutions of diffusion through a heterogeneous multilayer geometry or multi-laminate (ML) with each layer been isotropic are presented. Then, a 2 dimensional (2D) brick and mortar (B & M) geometry with anisotropic lipid layers is solved using a commercial finite element package COMSOL Multiphysics®. The SC asymmetry is represented with depth-dependent diffusivity and partition coefficient. Finally, this work analyzes the contribution of diffusion through appendages to total SC penetration.

2. Methods

2.1. Input parameters

A partition coefficient is defined as the ratio of concentrations of two phases at a boundary. Frequently, the partition coefficients are given with respect to water and the subscript w is often omitted. The lipid and corneocyte partition coefficients used in this study are defined as

$$K_{lip-w} = \frac{C_{lip}}{C_w} = K_{lip} \quad \text{and} \quad K_{cor-w} = \frac{C_{cor}}{C_w} = K_{cor}$$
$$K_{lip-cor} = \frac{C_{lip}}{C_{cor}} = \frac{K_{lip}}{K_{cor}} = \frac{1}{K_{cor-lip}} \tag{1}$$

where C_{lip} is the concentration in the lipid, C_w is the concentration in water, C_{cor} is the concentration in the corneocyte, and $K_{lip\text{-}cor}$ the partition coefficient between lipid and corneocyte. In this study these parameters are computed with functions of the octanol-water partition coefficient K_{ow} [35,38,40,42,56]. These relationships have a power law format as

$$K_{lip\ or\ cor} = a\,(K_{ow})^b \tag{2}$$

where the parameters a and b are obtained from correlations to experimental data sets, and they are given in Table 1. Hansen et al. [38] presented a review of correlations from several authors, as well as their own correlations. The datasets used to compute the correlation parameters a and b are heavily dominated by lipophilic data [38]. In Wang et al. [51], K_{cor} includes a modified fiber volume fraction, but for the comparison with the present study it should be calculated with the protein partition coefficient and the water sorption volume [57]. The partitions included in Table 1 correspond to their Model 2, fully hydrated SC. In Chen et al. [52–55], for $K_{ow} \geq 10$, K_{cor} is computed with Eq. (2) but for $K_{ow} < 10$, K_{cor} is computed as function of K_{lip}, as shown in Table 1.

In this work, the partition coefficients, K_{cor} and K_{lip}, are computed using the correlations from Hansen et al. [38] (from experimental data of 16 chemicals, r^2 of 0.85). The weight-based parameters were converted to volume-based parameters multiplying by the specific density,

Table 1
Parameters (volume-based) used to compute lipid and corneocyte partition coefficients from published works.

Authors	Partition coefficient	a	b	other
Hansen et al. [38]	K_{lip}	1.19	0.67	
	K_{cor}	7.33	0.32	
Wang et al. [51]	K_{lip}	0.43	0.81	
	K_{cor}	1.585	0.27	+ 0.807
Chen et al. [52–55]	K_{lip}	1	0.7	
	K_{cor} $K_{ow} \geq 10$	5.6	0.27	
	K_{cor} $K_{ow} < 10$			$(1 + K_{lip})/2$