Transcellular Route of Diffusion through Stratum Corneum: Results from Finite Element Models

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ABSTRACT: Insight into the stratum corneum (SC) permeation pathway for hydrophilic compounds is gained by comparing experimental measurements of permeability and lag time (t_{lag}) with the predictions of a finite element (FE) model. A database of permeability and lag time measurements ($n = 27$) of hydrophilic compounds was compiled from the literature. Transcellular and lateral lipid diffusion pathways were modeled within a brick-and-mortar geometry representing fully hydrated human SC. Modeled t_{lag}'s for the lipid pathway are too brief to account for the experimental quantities, whereas the transcellular pathway with preferential corneocyte partitioning does account for them. Measured t_{lag}'s are highly correlated ($p < 0.0001$) with the compound's octanol-water partition coefficient, supporting the hypothesis of an aqueous-lipid partition mechanism in the permeation of hydrophilic compounds. The importance of the lag time for identifying the diffusion pathway is demonstrated. © 2006 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 95:2186–2194, 2006

Keywords: skin absorption; diffusion; transdermal; permeability; lag time; mathematical model; partition coefficient

INTRODUCTION

The pathway for diffusion of exogenously applied chemicals through skin will be determined by the physicochemical nature of the diffusing substance and its affinity to the various skin components, and also by the physicochemical nature and structural organization of the skin.[1] Despite decades of research, the preferred path (or paths) for diffusion within the stratum corneum (SC) has not been unequivocally identified.

It is now widely believed that lipophilic compounds will follow the intercellular lipoidal pathway,[2] but the pathway followed by hydrophilic compounds remains more speculative. A highly tortuous polar pathway has been postulated.[3–7] In support, permeation coefficients of these compounds do not correlate with their octanol-water partition coefficients[4] as they do for lipophilics. Furthermore, a possible transfollicular route is generally disregarded because of its small fractional area and because lag times are too long to be accounted for. This polar pathway could be intercellular, possibly through hydrophilic regions present in the lipid layers.[8]

Alternate hypotheses for hydrophilic chemical permeation are the lateral lipid pathway[9,10] and the transcellular pathway that has recently been championed by Kasting.[11,12] This study explores the feasibility of these two potential pathways. Our hypothesis is that experimentally observed lag times of hydrophilic chemicals are too long to be accounted for by the lateral lipid pathway, but that a transcellular route with preferential corneocyte partitioning can account for them. A database of

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measured permeabilities and lag times of hydrophilic compounds is compiled, and results of a finite element (FE) SC diffusion model are compared with these measurements.

METHODS

Finite Element Model

A two-dimensional FE model of diffusion within human SC was created using the software package ANSYS version 7.0 (Ansys, Inc., Canonsburg, PA). Details of the model formulation and solution have been described elsewhere.[13] Briefly, the distribution of concentration in space and time is solved numerically within a 2-D representation of human SC, consisting of two homogeneous phases: corneocytes and lipids. Boundary and initial conditions are applied to the model that mimic *in vitro* diffusion cell experiments. From these results, permeability coefficients and diffusional lag times can be calculated that depend on model geometry, corneocyte-lipid partitioning, and diffusivity within the corneocyte and lipid phases.

Stratum Corneum Geometry

The simplified geometry of a brick-and-mortar representation (Fig. 1) was selected because it has been demonstrated that this geometry adequately represents diffusion within a more complex and realistic heterogeneous SC structure.[13,14] Dimensions of the normal (unswollen) SC are based on typical human SC dimensions that were derived from various sources.[15–18] The normal SC geometry is modified to account for hydration-induced swelling.[19,20] The swollen corneocytes are 44 μm wide (d) and 3.5 μm in thickness (h). They are surrounded by 0.05 μm lipid layer, which makes a lipid layer between corneocytes (s) 0.1 μm thick while the top and bottom lipid layers are 0.05 μm thick. Ten corneocyte layers are included in the model ($n = 10$), which gives a total hydrated SC thickness of 36 μm. The short overlapping section (l_S) is 10.8 μm.

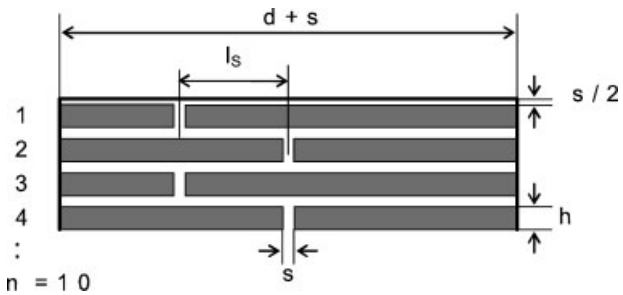

Figure 1. Geometric model of stratum corneum. Diffusion occurs through lipid layers and corneocytes and a partition coefficient is applied between these two phases. d, corneocyte width; h, corneocyte thickness; s, lipid thickness; l_s, length of short overlapping section; n, number of layers.

Corneocyte and Lipid Diffusivites

Corneocytes and lipids are considered to be homogeneous materials with isotropic diffusivities. The diffusion coefficients D_{cor} and D_{lip} are model inputs. Values were chosen to span a wide range of possible experimental values. For the transcellular path, D_{lip} and D_{cor} were varied from 10^{-11} to 10^{-7} cm^2/s; for the lipid pathway, D_{lip} was varied from 10^{-11} to 10^{-5} cm^2/s. For the purposes of the present study, no attempt was made to relate these values to actual diffusivities of specific compounds.

Application of Corneocyte-Lipid Partition Coefficient

At the boundaries between lipid bilayers and corneocytes, it is assumed that spontaneous chemical partitioning occurs. The partition coefficient $K_{cor\text{-}lip}$ is a model input that creates a discontinuity by constraining the following relationship between the concentrations at a boundary between a corneocyte and its surrounding lipid:

$$K_{cor-lip} = \frac{C_{cor}}{C_{lip}} \quad (1)$$

Since the FE method allows only one value for each variable in each spatial location or node, a method must be devised to apply this discontinuity at the boundary. This is achieved using a change of variables in one of the media to account for the partition coefficient. This method is described in detail and validated in Barbero and Frasch.[13]

Boundary and Initial Conditions, and Model Solution

Periodicity is applied at the lateral boundaries to impart infinite dimension in the transverse direction. Other boundary and initial conditions are applied that mimic infinite dose diffusion cell