Dermal Clearance Model for Epidermal Bioavailability Calculations

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ABSTRACT: A computational model for estimating dermal clearance in humans of arbitrary, nonmetabolized solutes is presented. The blood capillary component employs slit theory with contributions from both small (10 nm) and large (50 nm) slits. The lymphatic component is derived from previously reported clearance measurements of dermal and subcutaneous injections of ^{131}I-albumin in humans. Model parameters were fitted to both blood capillary permeability data and lymphatic clearance data. Small molecules are cleared largely by the blood and large molecules by the lymph. The combined model shows a crossover behavior at approximately 29 kDa, in acceptable agreement with the reported value of 16 kDa. When combined with existing models for stratum corneum permeability and appropriate measures of tissue binding, the developed model has the potential to significantly improve tissue concentration estimates for large or highly protein-bound permeants following dermal exposure. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:2094–2108, 2012

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INTRODUCTION

Knowledge of the rate and extent of permeation of topical applications on skin is of great importance in dermatology, transdermal drug delivery, cosmetic science, and occupational safety. A quantitative description requires the understanding of not only the input rate of the permeant into the skin but also its output rate. A one-dimensional (1D) multilayer model allowing transient skin absorption calculations on a spreadsheet has been developed and described elsewhere.[1,2] A Java version of this program is available on the Web.[3] This three-layer model represents the stratum corneum, viable epidermis, and dermis as slabs with effective properties derived from underlying microscopic transport models. Capillary permeability was described by a simple relationship based on the Potts–Guy relationship to represent membrane permeability as in the Robinson model.[4] This relationship was adequate for small, moderately lipophilic permeants.[5] Here we present a clearance model more closely related to the capillary permeability literature and furthermore include lymphatic capillaries for the transport of large and highly protein-bound permeants. The primary purpose of the revised calculation is to make better predictions of skin concentrations of very hydrophilic and very lipophilic, low molecular weight skin permeants in the context of the spreadsheet skin absorption model.[1,2] Since small lipophilic compounds are often highly bound to proteins, it was important to include dermal clearance mechanisms for both small and large solutes into the model.

Capillary clearance has been widely studied for decades, yet the mechanisms involved in the transport of large solutes are still not fully understood. Several theories have been proposed, many tracing back to Renkin and coworkers.[6–9] The simplest of these is the pore/slit model.[10–12] More elaborate theories are available, such as the fiber matrix theory,[12–14] the two-pore theory,[15,16] the three-pore theory,[17,18] as well as complex 1D and three-dimensional theories.[19,20] These models differ in complexity with regard to the physiologic microstructure of the blood capillaries. The most established routes of transport of solutes across blood capillaries are between the endothelial cells and through the endothelial membrane.

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Controversy surrounds other routes such as vesicles and large pores.[21–23] Furthermore, although it is widely accepted that the glycocalyx layer is the primary sieving element for large solutes and proteins, some investigators do not believe that there is enough evidence to support this claim.[24] These models, and all the open questions associated with them, pertain only to the clearance via blood capillaries and do not address the competing mechanism of lymphatic clearance. Fewer studies have been dedicated to lymphatic clearance, and to our knowledge no quantitative models have been developed. Published studies focus on determining the lymph flow rate by either cannulation of lymph ducts[25–29] or by measuring the disappearance rate of large solutes from a specific site.[30–33] Dermal capillary clearance was modeled by Kretsos et al.[5] as a uniform first-order clearance through the blood capillaries into the systemic circulation. This simplified approach was adequate for the clearance of small permeants as well as moderately bound permeants. Here, we present a more general dermal clearance model based on a two-slit theory for blood capillary permeability, which, when combined with a slow lymphatic clearance, is sufficiently flexible to describe the clearance of all diffusing species including macromolecules and protein-bound solutes. It should be noted that heterogeneous pore theory, slit theory, and fiber matrix theory are equally efficient in describing the major features of capillary transport for small and large solutes and that there are no fundamental differences between these three concepts[24]; hence the selection of the two-slit theory for the present model is not essential, but rather is one of several nearly equivalent choices that could be made.

COMPUTATIONAL MODEL FRAMEWORK

Blood Capillary Clearance

Mass transport through capillary endothelia is often described by the Kedem–Katchalsky equations according to the principles of irreversible thermodynamics.[34,35] Here, these equations have been modified to include the effective exchange surface area S,[15,36] thus

$$J_s = P_{cap} S \cdot \Delta C + (1 - \sigma_f) J_v \bar{C} \tag{1}$$

$$J_v = L_p S (\Delta P - \sigma_d \Delta \pi) \tag{2}$$

where J_s is the solute flux per unit volume of tissue, J_v is the water flux per unit volume of tissue, P_{cap} is the total diffusive permeability to solutes, ΔC is the concentration difference across the membrane, σ_f is the solvent drag reflection coefficient (also known as the ultrafiltration coefficient) for the solute due to membrane restriction, $\bar{C}$ is the effective intramembrane solute concentration for convection, L_p is the hydraulic conductivity, ΔP is the difference between local capillary blood pressure and interstitial hydrostatic pressure, σ_d is the osmotic reflection coefficient, which describes the selectivity of the membrane to solutes contributing to osmotic pressure, and $\Delta\pi$ is the difference between colloid osmotic pressure in plasma and the interstitium. For ideal solutions containing a single solute, σ_f is equal to σ_d and is represented by σ, the reflection coefficient.[35,36] For more complex solutions, it is understood that the contributions of each solute must be summed to calculate the osmotic pressure; thus $\sigma_d \Delta\pi \rightarrow \sum_i \sigma_{d_i} \Delta\pi_i$. This formulation implicitly assumes that ΔC represents freely diffusing solute, equivalent to C_{free} in Ref. 5. This distinction will become important later.

The permeability of the capillary wall is described in terms of flow through a water-filled cylindrical pore or rectangular slit, essentially the cleft between two adjacent endothelial cells. The representation of the interendothelial cleft as a slit is morphologically more defensible than a cylinder; hence the slit theory was chosen as our working model.[15] The transport of macromolecules is a complex process that is riddled with controversy. We chose to use the framework of the two-pore theory presented by Rippe and Haraldsson,[15] wherein small pores dominate the transport of smaller solutes and larger pores allow the transport of macromolecules. It should be noted that the purpose of the present model is to describe the clearance of a solute from the interstitial space into the blood and lymph, which are regarded as sinks. Hence, we focus on unidirectional transport, although consequences for the more general case in which bidirectional transport occurs are discussed. Because it is limited to the steady state, the model in its present form will not be useful for studying swelling, inflammation, or other pathophysiological conditions.[15]

Following Rippe and Haraldsson,[15] we assume there are two populations of slits; one has half-width $W_s/2$ (small), the other $W_L/2$ (large). The following equations apply to each population of slits.

The hydraulic conductivity L_p for a slit of width W in a capillary wall can be calculated from Poiseuille's law[12,36]

$$L_p = \frac{L f W^3}{12 \mu \, \Delta x} \tag{3}$$

where L is the total slit length per unit area of vessel wall, f is the fraction of the length of the slit open to the full width W, μ is the water viscosity at 37°C, and Δx is the depth of the cleft from lumen to tissue.

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