194b Fundamental Investigation of Transdermal Transport Models for Hydrophobic and Hydrophilic Drugs

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Modeling the transdermal transport of hydrophobic and hydrophilic drugs is a critical aspect of drug delivery research. Due to the physico-chemical interactions of hydrophobic and hydrophilic drugs with the stratum corneum, the outermost skin layer, different transdermal transport models need to be developed for hydrophobic and hydrophilic drugs. The stratum corneum is composed of corneocytes surrounded by lipid lamellar bilayers, which are arranged in a brick-and-mortar structure. Since a significant portion of the stratum corneum is lipid-rich, the stratum corneum behaves like a hydrophobic membrane. As a result, hydrophobic drug transport occurs primarily within the intercellular lipid lamellar bilayers that are present in this barrier, while a different transdermal transport model - the porous-pathway model - has been introduced to describe the transport of hydrophilic permeants across the stratum corneum. In this model, it is assumed that aqueous pore channels traverse the hydrophobic stratum corneum.

For hydrophobic drugs, we have modified Fick's diffusion model, from first-principles, to incorporate the physical structure and geometric parameters characterizing the stratum corneum to improve our ability to evaluate the vehicle-to-bilayer partition coefficient, K_b, and the lipid bilayer drug diffusion coefficient, D_b, from permeation experiments. This structure-based geometric diffusion model was compared to simulated diffusion experiments conducted using the finite-element software program, FEMLAB. Our new model was able to evaluate K_b and D_b to within an error of 2-3% for the average structure of the human stratum corneum membrane. Experiments are being conducted to demonstrate our ability to evaluate K_b and D_b directly from a single permeation experiment in the context of the new model. This new modeling approach offers an improvement over current methods of determining K_b and D_b, which require measuring the drug octanol-water partition coefficient and the drug transdermal permeability in separate experiments.

Recent modifications to the porous-pathway model for hydrophilic permeants have proposed the existence of a size distribution in the radii of the aqueous pore channels. We have reexamined the impact of the pore radius distribution on the modeling of the skin porosity and the hindrance factor for the diffusion of hydrophilic drugs through pore channels. In addition, we have reexamined whether physical methods used to enhance the skin transdermal permeability of hydrophilic drugs (for example, ultrasound) lead to the creation of more pore channels having a similar pore radius distribution, or whether the formation of new pore channels resulting from the use of physical enhancing methods alters the pore radius distribution.