Advanced Drug Delivery Reviews 65 (2013) 208–220

Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Application of numerical methods for diffusion-based modeling of skin permeation ☆

H. Frederick Frasch *, Ana M. Barbero

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

ARTICLE INFO

Article history:
Accepted 3 January 2012
Available online 10 January 2012

Keywords:
Transdermal drug delivery
Stratum corneum
Unit cell problem
Finite difference method
Method of lines
Finite element method
Finite volume method
Random walk
Cellular automata
Smoothed particle hydrodynamics

ABSTRACT

The application of numerical methods for mechanistic, diffusion-based modeling of skin permeation is reviewed. Methods considered here are finite difference, method of lines, finite element, finite volume, random walk, cellular automata, and smoothed particle hydrodynamics. First the methods are briefly explained with rudimentary mathematical underpinnings. Current state of the art numerical models are described, and then a chronological overview of published models is provided. Key findings and insights of reviewed models are highlighted. Model results support a primarily transcellular pathway with anisotropic lipid transport. Future endeavors would benefit from a fundamental analysis of drug/vehicle/skin interactions.

Published by Elsevier B.V.

Contents

1. Introduction

Various aims motivate the considerable effort involved in the creation and solution of a proper mechanistic model of skin permeability.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Modeling the human skin barrier — Towards a better understanding of dermal absorption".

* Corresponding author. Tel.: +1 304 285 5755; fax: +1 304 285 6041.
E-mail address: HFrasch@cdc.gov (H.F. Frasch).

0169-409X/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.addr.2012.01.001

To enhance understanding of the physical/chemical processes underlying transdermal penetration; to predict permeability of given compounds; to investigate the range of variables that affect penetration; to assist in the design of experimental investigations—all are important objectives that may be met through the careful design and crafting of a realistic transport model along with the implementation of a sound solution scheme.

The skin's primary permeability barrier is its outermost layer, the stratum corneum, comprised of ~10-20 staggered layers of flattened remnants of basal keratinocytes. These corneocytes are embedded in a structured lipid lamellar matrix, organized as multiple bilayers with the hydrophilic head groups of lipid molecules aligned and their hydrophobic tails pointed inward toward the center of the bilayer. The corneocytes themselves are bounded by a compound envelope consisting of a cross linked cornified layer surrounded by covalently bound lipid, while their interior is a largely amorphous network of keratin fibers surrounding water of hydration. In approaching the complex heterogeneous structure that comprises the skin's barrier, the would-be modeler is confronted with numerous important decisions. How will the stratum corneum structure be represented? A broad range of structural complexity has been modeled, from 1 dimensional (1D) homogeneous slabs and laminates (multilayered slabs), 2D and 3D brick and mortar models and variants, to more complex 3D geometric representations. The rational application of a numerical method depends on the scale at which the skin is modeled. At all scales the tissue/material/structure through which permeant diffuses is characterized by a diffusion coefficient D_{eff} and a partition coefficient K_{eff} quantifying the solubility of a solute for the material (relative to water, say). Three model scales are considered here.

1. *Macroscopic models* represent skin as a multilamellar structure in which each tissue layer is characterized by effective properties K_{eff} and D_{eff} for a given permeant (Fig. 1A). Permeant concentration varies with one spatial coordinate (depth x), and interest usually lies in describing transient dermal absorption (time t enters). Thus, transient 1D diffusion problems arise, and at times a 2nd spatial dimension is included to model a finite patch or donor source applied to skin surface. These problems are usually most appropriately treated by the finite difference method or the method of lines.
2. *Microscopic models* seek to understand and predict how K_{eff} and D_{eff} depend on the geometry/spatial arrangement of the microscopic lipid and corneocyte phases, and upon corresponding physicochemical properties of each K_{lip}, D_{lip}, K_{cor}, D_{cor}. This averaging is accomplished by various types of homogenization theories (see e.g. [1,2]) which generally involve the formulation and solution of a steady state diffusion problem within a representative unit cell of the microstructure (Fig. 1B) in which the solute concentration is higher at one end of the unit cell than the other (which drives diffusion through the structure). K_{eff} and D_{eff} are obtained at the end in terms of integrals that sum up the permeant fluxes from all elements of the microstructure. The numerical need here is for methods that efficiently solve the diffusion equation in 2D or 3D domains incorporating two or more phases. Finite difference, finite element and finite volume methods have been used, and other methods could be applied as well.
   It should be emphasized that the transport properties K_{eff} and D_{eff} are formally obtained from a *steady state* unit cell problem. These effective properties may then be slotted into the macroscopic models to obtain transient diffusion solutions. Thus, the validity of the macrotransport model as a representation of the microscopic level of detail depends on the proper derivation and estimation of effective transport properties. These may be thought of as the partition coefficient and diffusivity of a homogeneous membrane that exhibits the same macro level transport properties (e.g., permeability k_p and lag time τ) as the complex heterogeneous structure. Accordingly we have:

$$k_p = K_{\text{eff}} \frac{D_{\text{eff}}}{h}$$
$$\tau = \frac{h^2}{6D_{\text{eff}}} \quad (1)$$

   where h is the thickness of the modeled domain (typically, the stratum corneum).
   In order to properly estimate these properties, one must first consider the micro level heterogeneous structure, then derive and solve a transport model that accounts for the complexities. Only then can the appropriate input parameters of an equivalent homogeneous membrane be derived.
3. Certain applications model the skin layer or layers at a microscopic level of detail, but make the domain so large that, instead of one unit cell, it encompasses the full macroscopic thickness of the skin layer (for example the stratum corneum), with a lateral domain

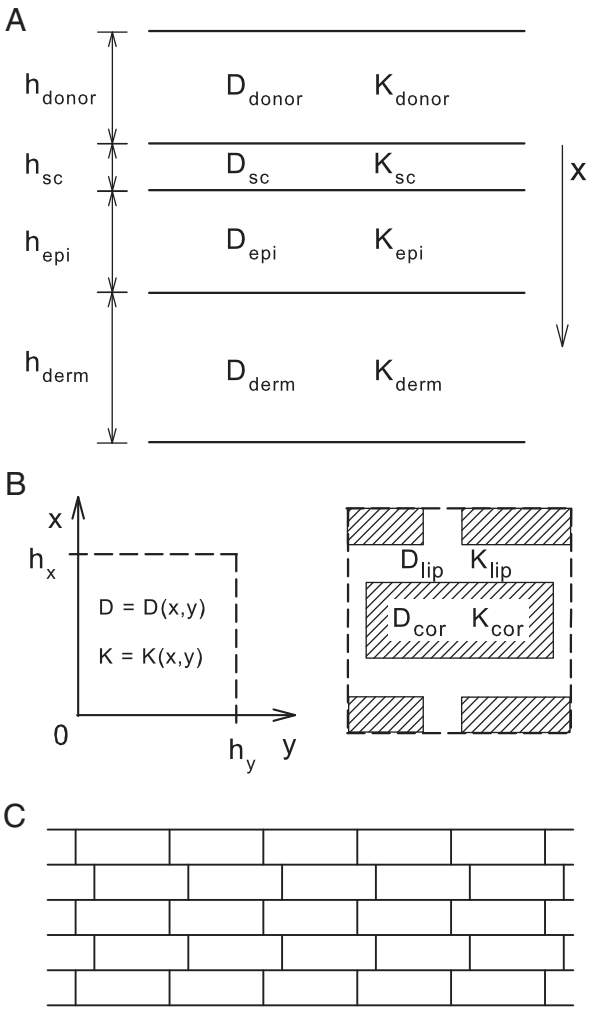

Fig. 1. Three scales of modeling applied to skin permeation. A. Macroscopic models represent skin as a multilamellar structure. Here, for example, donor, stratum corneum (sc), epidermis (epi), and dermis (derm) are characterized by phase-specific thicknesses h, diffusivities D and partition coefficients K. B. Microscopic models formulate effective transport properties based on the solution of a unit cell problem. Left: Continuum representation whereby D and K vary continuously with position. Right: Representative stratum corneum (brick and mortar) unit cell, dimensions greatly exaggerated, with phase-specific D, K. Shaded areas are corneocytes (cor); white represents intercellular lipid matrix (lip). C. Macroscale models may incorporate microscale details but cover large computational domains. Here, stratum corneum is represented as a 5 layer brick and mortar type structure. White areas are corneocytes; black lines represent lipid matrix.