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

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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.

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Contents

1. Introduction

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

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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

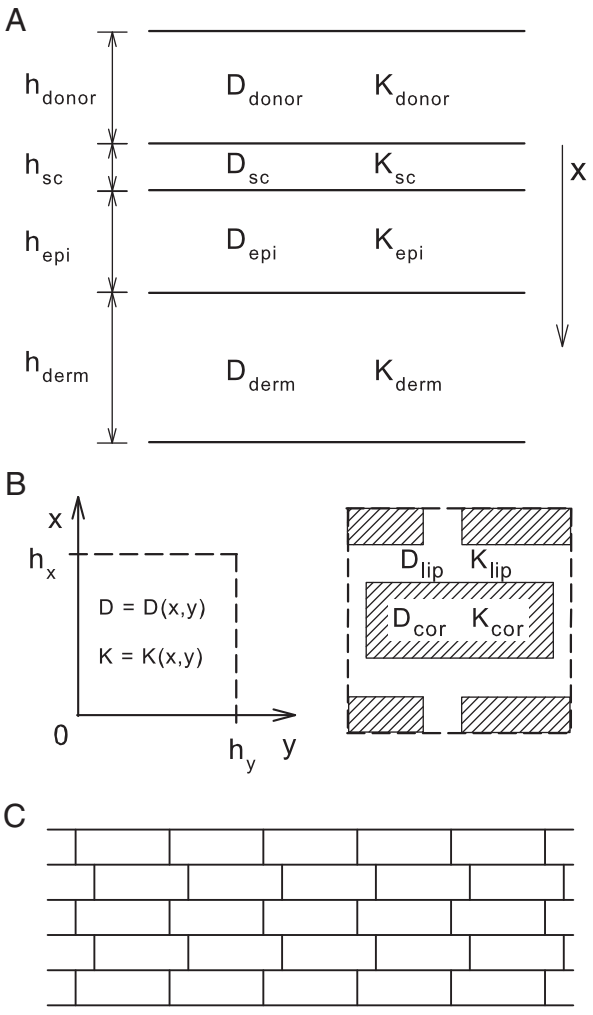

Fig. 1. Three scales of modeling applied to skin permeation. A. Macroscopic models represent skin as a multilamellar structure. Here, for example, donor, stratum corneum (sc), epidermis (epi), and dermis (derm) are characterized by phase-specific thicknesses h, diffusivities D and partition coefficients 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.

sufficient to minimize end effects (Fig. 1C). These large-scale problems involve 2 or 3 spatial coordinates, and also time. They can be approached by the methods applied to the unit cell problems, or by methods that have more of the character of direct numerical simulations, such as random walk, cellular automaton, or smoothed particle hydrodynamics. Effective transport properties may also be obtained through appropriate analysis of macroscopic models, although in a less rigorous mathematical approach than the unit cell problem.

Table 1 groups all of the models discussed in this review within one of these three applications and according to the employed numerical method.

Depending on the goals of the researcher, it may be appropriate to explicitly include more parameters characterizing more physics, such as rate/equilibrium constants for binding if the permeant gets held up by association with tissue components. Although the physicochemistry included in the models is not a numerical issue per se, it is very pertinent insofar as it shapes the nature and complexity of the mathematical model. Thus, additional questions arise as to the formulation of the model and the assignment of parameters therein. How will lipid layer diffusion be handled? Despite copious evidence to the contrary, the overwhelming majority of existing models (*vide infra*) have considered the lipids to be composed of homogeneous, isotropic material. Others [3] consider a tortuous porous network, arising from imperfections in the lipid bilayers, as a transport pathway. Only one group [4] has tackled the anisotropic diffusivity that arises from the lamellar organization of alternating polar and nonpolar regions. Are permeants confined to the lipid bilayers? Evidence of a chemically intransigent cornified cell envelope has inspired many to believe that corneocytes are impermeable, but the validity of this assumption has been discredited [5]. Can permeants bind to skin components? If so, what is the nature of the binding: reversible or permanent; linear or saturable? Are permeants metabolized during their transit through skin? How the investigator deals with these and many other questions has a profound influence on the complexity of the model formulation, the flexibility of the model in terms of its ability to realistically account for known physical and chemical processes, and of course on the validity and range of applicability of the model results.

A recent review [6] describes mathematical models of skin permeability and discusses some of the methods and models presented here. The present review, while restricted to the application of numerical methods to diffusion modeling and predicting skin absorption, is far more extensive in its coverage of this area. First, brief descriptions of the methods are provided. Some mathematics applied to simple examples are presented so that the reader may acquire a basic understanding of the mathematical foundations of the method. Next, we highlight the work of two groups of investigators who have achieved what may be recognized as the "state of the art" in numerical modeling of the skin permeation process. Following that is a more-or-less chronological summary of published models solved using numerical methods. Finally, some summary thoughts and ideas for future directions are provided. Any review is necessarily somewhat eclectic and it is impossible to address all research contributions. The papers discussed in this review represent coverage of an extensive, but not exhaustive, representative body of the numerically-based research in dermal absorption.

2. Brief descriptions of select numerical methods

The transport of chemical through skin is generally conceived of as a partition-diffusion process. The current review focuses on common numerical methods that have been used to solve the diffusion equation as it applies to the disposition of chemicals in contact with

Table 1
Models grouped according to application (scale and variables) and numerical method. Variables in bold are optional for the application.

	Macroscopic (multilayered slabs) (x, $\boldsymbol{y}$, t)	Microscopic (unit cell) (x, y, $\boldsymbol{z}$)	Macroscopic with microscopic details (x, y, $\boldsymbol{z}$, t)
Finite differences	Lindstrom and Ayres [33] Tojo [36,37] Wearley et al. [38] Kubota and Twizell [41] Kubota et al. [46] George et al. [47] Kurnik and Potts [48] Iordanskii et al. [52] Riley et al. [57] Kretsos et al. [27,28] Chaudhuri et al. [29,30]	Wang et al. [4,26] Nitsche and Frasch [31]	Charalambopoulou et al. [51] Marquez-Logo et al. [3]
Method of lines	Gienger et. al. [13] Gumel et al. [42] George [45] Manitz et al. [50]	□	Chen et al. [66,67] Lian et al. [68]
Finite Element	Rim et al. [58] Xing et al. [69]	Rim et al. [10,59,60]	Frasch and Barbero [55] Barbero and Frasch [56] Rim et al. [60] Kushner et al. [61]
Finite volume	□	Muha et al. [11]	Heisig et al. [21] Naegel et al. [22,24] Becker and Kuznetsov [62-64] Becker [65]
Random walk	Burnette [35] Kubota et al. [39,40]	□	Frasch [53]
Cellular automata	□	□	Zhong et al. [70]
Smoothed particle hydrodynamics	□	□	□

skin. The diffusion equation defines the distribution of the concentration C of chemical in time t and space:

$$\frac{\partial C}{\partial t} = \nabla\cdot(D\nabla C). \tag{2}$$

In this general formulation, diffusivity D may vary as a function of concentration and/or location. Additional terms may be added to account for chemical reactions such as binding to skin components or enzymatic changes; additional transport mechanisms such as convective flow, applied electrical field, thermal gradients, pressure gradients, etc. In any real application, Eq. (2) is considered together with a stipulation of *initial values* of the dependent variable C throughout the spatial region of interest, as well as *boundary conditions* that govern the evolution of C in time on the boundary of the region of interest.

As discussed in the Introduction, there are many situations in which a transport equation like Eq. (2) (together with associated auxiliary conditions) does not lend itself to an analytical solution. The investigator then has available a variety of methods that can be applied to obtain a numerical solution to the problem. Following are brief descriptions of some common numerical methods used to solve the transport equations applied to skin. The methods are organized according to their application to the three types of diffusion problems outlined in the Introduction. While some method may be particularly adaptable to the given problem, the chosen method, if properly implemented, will not affect the model output: all methods should yield the same result, within a small error that can, in principle, be made arbitrarily small with sufficient mesh or similar refinement of the numerical scheme. In practice, the selection of a numerical method is based largely on the training, familiarity, and preference of the investigator.

2.1. One-dimensional macroscopic problems

As an example of a macroscopic problem (Type 1), consider the oft-used simplifications of Eq. (2) where D is constant and C varies in only 1 direction, taken to be the x direction perpendicular to the skin surface:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2}. \tag{3}$$

Together with appropriate initial and boundary conditions, Eq. (3) has been used to model *in vitro* dermal uptake and absorption experiments. The idealized infinite dose experiment for a membrane of thickness h is specified by the following auxiliary conditions:

$$\begin{array}{ll} C(x,0) = 0, & 0<x<h, \\ C(0,t) = K_{mv}C_0, & t\geq 0, \\ C(h,t) = 0, & t\geq 0. \end{array} \tag{4}$$

Eq. (4) makes three statements: C is initially everywhere 0 (the skin starts out free of permeant); instantaneous partitioning of the chemical between vehicle and membrane (quantified by membrane-vehicle partition coefficient, K_{mv}) maintains a constant membrane concentration of permeant immediately adjacent to the donor solution at $K_{mv}C_0$; and C at the receptor surface ($x=h$) equals 0 for all time (sink condition in the receptor compartment).

2.1.1. Finite difference method

The motivation behind the finite difference method is the fact that a continuous *differential* equation can be approximated by a finite set of *difference* equations. Consider again the case of diffusion in 1 dimension with constant diffusivity (Eq. (3)). If both time and region of interest are divided into equally spaced points along both t and x axes such that

$$\begin{array}{ll} t_n = t_0 + n\Delta t, & n = 0,1,\ldots N, \\ x_j = x_0 + j\Delta x, & j = 0,1,\ldots J, \end{array} \tag{5}$$

then a reasonable approximation of Eq. (3) is

$$\frac{C\left(x_j,t_{n+1}\right)-C\left(x_j,t_n\right)}{\Delta t} = D\left[\frac{C\left(x_{j+1},t_n\right)-2C\left(x_j,t_n\right)+C\left(x_{j-1},t_n\right)}{(\Delta x)^2}\right]. \tag{6}$$

Finite difference schemes are concerned with deriving appropriate difference equations that maximize accuracy while minimizing instabilities. Note that in Eq. (6), the 2nd order spatial derivative (right hand side of Eq. (3)) is evaluated at time step t_n. Thus, each subsequent time step evaluation of Eq. (6) requires only information that has already been calculated. Now consider another reasonable approximation of Eq. (3), in which the 2nd derivative is evaluated at time step $(n+1)$ (i.e., t_n is replaced by t_{n+1} in the right hand side of Eq. (6)). In this case the solution requires simultaneous equations to be calculated over the entire spatial domain for each time step for $C(x_j,t_{n+1})$. Why, then, forgo the simplicity of Eq. (6)? It turns out that the latter scheme is unconditionally stable while the former is not [7]. In practical terms, the approximation errors damp out over time and equations do not "blow up" as the calculations progress in time. It further turns out that if one takes the *average* of the 2 approximations, both stability *and* accuracy are optimized [7]. The resulting scheme is called the Crank-Nicholson method:

$$\frac{C\left(x_j,t_{n+1}\right)-C\left(x_j,t_n\right)}{\Delta t} = \frac{D}{2}\left[\frac{\left[C\left(x_{j+1},t_n\right)-2C\left(x_j,t_n\right)+C\left(x_{j-1},t_n\right)\right]+\left[C\left(x_{j+1},t_{n+1}\right)-2C\left(x_j,t_{n+1}\right)+C\left(x_{j-1},t_{n+1}\right)\right]}{(\Delta x)^2}\right]. \tag{7}$$

Generalizations have been made to deal with 2D or 3D structures, and for variable D.

2.1.2. Method of lines

The method of lines (MOL) discretizes the spatial derivatives only and leaves the time derivative continuous. This leads to a system of ordinary differential equations, for which various efficient integration schemes exist. The 1D diffusion equation (Eq. (3)) can be represented as

$$\frac{dC}{dt} = D\left[\frac{C\left(x_{j+1},t\right)-2C\left(x_j,t\right)+C\left(x_{j-1},t\right)}{(\Delta x)^2}\right]. \tag{8}$$

If one were to solve Eq. (8) by the forward Euler method, the resulting equation is identical to Eq. (6). Thus the line of distinction between the MOL and other methods can be blurred. Spatial discretization in the MOL can be accomplished using finite differences, finite elements, or finite volumes, and schemes have been devised for higher dimensions and non-Cartesian coordinate systems [8].

2.2. Two- and three-dimensional microscopic problems

As an example of a microscopic problem (Type 2), the unit cell problem may be approached by consideration of the steady-state 2D version of Eq. (2),

$$\frac{\partial}{\partial x}\left(D\frac{\partial C}{\partial x}\right)+\frac{\partial}{\partial y}\left(D\frac{\partial C}{\partial y}\right) = 0, \tag{9}$$

posed in a rectangular unit cell ($0 \le x \le h_x$, $0 \le y \le h_y$) (Fig. 1B) subject to the conditions

$$\begin{aligned} &C(h_x, y) = C(0, y) + C_0 \quad \text{and} \quad \partial C/\partial x(h_x, y) = \partial C/\partial x(0, y) \quad \text{for} \quad 0 \le y \le h_y, \\ &C\left(x, h_y\right) = C(x, 0) \qquad \text{and} \quad \partial C/\partial y\left(x, h_y\right) = \partial C/\partial y(x, 0) \quad \text{for} \quad 0 \le x \le h_x. \end{aligned} \tag{10}$$

The fact that C is higher at the top than at the bottom of the unit cell effectively imposes a concentration gradient upon the unit cell (and all other unit cells, which are equivalent), which drives a solute flux. Appropriate evaluation of the resulting concentration field $C(x,y)$ yields the effective diffusivity [2]. Irrespective of the manner in which it is actually treated numerically, for purposes of presentation here, two- or multiphase character of the unit cell is represented formally here by a diffusivity that varies with position (for example being piecewise constant with values D_{lip} and D_{cor} in lipid and corneocyte phases of a unit cell of stratum corneum). A more generalized formulation would consider position-dependent partitioning as well as diffusivity (Fig. 1B). This problem is representative of the type of higher-dimensional unit cell problems arising in microscopic models aimed at understanding effective tissue properties.

2.2.1. Finite difference method

The 1D Crank Nicholson method described above can be generalized to deal with 2D or 3D structures, and for variable D, and thus can be adapted to the unit cell problem [4]. As one can imagine, the FDM is most readily applied to domains that can be divided into a regular grid, specifically interconnected rectangles (2D) or boxes (3D). Additionally, non-uniform mesh schemes and non-rectilinear coordinate systems have been developed for finite differences, broadening both their applicability and efficiency [9].

2.2.2. Finite element method

The finite element method (FEM) is another grid-based method for obtaining approximate numerical solutions to partial differential equations. The spatial domain is divided into an interconnected set of elementary shapes. These can be triangles (or tetrahedra for 3D geometries) or other higher order polygons, or even curvilinear elements. The points of intersection of the resulting mesh are called nodes. In general, the density of the nodes varies in different regions of the domain depending upon anticipated dynamics of the region. For example, the nodes will be dense in areas near the interface between lipid and corneocyte, as there may be dramatic changes in concentration and diffusivity within a very small area. The next step in solving a finite element model is to recast the governing differential equation into its "weak" or integral form. The differential equation is multiplied by a test function and then integrated. The test function can be thought of as a function that transfers the derivatives in the governing equation to the test function through the next step, which is integration by parts. This gives rise to an expression that contains the test function along with trial solutions that satisfy the appropriate boundary conditions. These test and trial functions are discretized, plugged into the weak form and solved via matrix operations.

As an example, consider the unit cell problem described above by Eqs. (9) and (10). The FEM is based on the fact that equations such as this can be formulated in their "weak" form in terms of an equivalent variational principle. In particular, $C(x,y)$, being that function that satisfies Eq. (9) in the unit cell, is equivalent to being that function that minimizes a certain integral over the unit cell. Solving Eq. (9) is equivalent to minimizing the integral

$$I = \int_0^{h_y} \int_0^{h_x} \left(D(x,y) \frac{\partial^2 C}{\partial x^2} + D(x,y) \frac{\partial^2 C}{\partial y^2} \right) dx dy. \tag{11}$$

Multiphase (e.g., lipid and corneocyte) contents of the unit cell are represented here formally by the notation $D(x,y)$, which allows the permeant to have different diffusivities in the two phases. Partitioning between phases can also be allowed for [10,11]. The solution is written as a superposition of basis (also known as interpolation) functions:

$$C = C_0 x/h_x + \sum_{i=1}^{N} k_i \psi_i(x,y), \tag{12}$$

where $\psi_i(x,y)$ are basis functions that have enough structure to represent any needed spatial variations in C. (Refer to [12] for a general discussion on the selection of basis functions). In the unit cell problem, these are periodic functions of position. In large-scale applications they are "local", i.e., non-zero only within a given finite element (and possibly its neighbors). Minimizing the integral I leads to a system of linear equations for the coefficients k_i. Once these are determined, the numerical approximation of $C(x,y)$ is complete. Analysis of $C(x,y)$ to produce effective diffusivity is exemplified by Rim et al.'s [10] Eq. (12).

We reemphasized here that although the effective transport properties K_{eff} and D_{eff} are obtained from a *steady state* unit cell problem, these may then be slotted into *transient* macroscopic models to obtain time-dependent macro transport properties.

The FEM offers several advantages over the FDM. Minimizing an integral is much less restrictive, in terms of element shapes, than the requirements to formulate general finite differences to approximate derivatives. Thus the FEM can easily be applied to triangular or higher order polygonal elements, whereas it would be technically complicated, if not impossible, to formulate finite difference schemes over these non rectilinear shapes. In this way the FEM easily handles complex geometries, disordered structures and heterogeneous media—as embodied, for example, by the stratum corneum. If the diffusion properties vary within the spatial region of interest, the FEM accommodates by varying the density of the mesh such that the accuracy of the solution is maintained over the entire domain. Complex boundary shapes are also handled by decreasing grid size to accurately represent the boundary.

The main disadvantage of FEM compared with FDM is that the implementation of FEM is more complicated. A fairly sophisticated level of training is necessary to generate and solve a custom finite element model. On the other hand, numerous general purpose software packages are available (for example, ANSYS and COMSOL Multiphysics have been used in skin permeation models described herein); these can be readily adapted to handle diffusion problems over user-defined domains. One potential difficulty with the FEM that requires attention is the imposition of a partition coefficient between dissimilar phases—for example lipid/corneocyte. This creates a discontinuity in concentration between the phases, but commercial FEM codes typically allow for only one value of concentration at any one node. The problem has been addressed and appropriate procedures have been worked out that apply to skin and other composite media [13-15].

2.2.3. Finite volume method

Yet another discretization technique is the finite volume method (FVM). The spatial domain is divided into a discrete mesh, the surfaces of which define small control volumes—"finite volumes"—within which the governing equations apply locally. Flux conservative equations are developed, and the divergence theorem is then applied to transform a volume integral containing the divergence of flux, into a surface integral, evaluated as fluxes over the surface of the volume.

Although the full capabilities of the method are realized in higher dimensional problems, it is explained most simply in the context of a 1D problem. Consider again the 1D diffusion equation with

constant D, Eq. (3). The flux, or rate of mass transfer per unit area, is defined as

$$F = -D\frac{\partial C}{\partial x}. \tag{13}$$

Therefore Eq. (3) can be recast as

$$\frac{\partial C}{\partial t} + \frac{\partial F}{\partial x} = 0. \tag{14}$$

Dividing the spatial domain x into finite segments with small boxes—finite volumes—enclosing each segment, centered at j, the average concentration at j is given by

$$\bar{C}_j(t) = \frac{1}{x_{j+\frac{1}{2}} - x_{j-\frac{1}{2}}} \int_{x_{j-1/2}}^{x_{j+1/2}} C(x,t)dx. \tag{15}$$

Integrating Eq. (14) in time leads to

$$C(x,t_2) = C(x,t_1) - \int_{t_1}^{t_2} \frac{\partial F(x,t)}{\partial x} dt. \tag{16}$$

Combining Eqs. (15) and (16) gives the average concentration at $t = t_2$:

$$\bar{C}_j(t_2) = \frac{1}{x_{j+\frac{1}{2}} - x_{j-\frac{1}{2}}} \int_{x_{j-1/2}}^{x_{j+1/2}} \left[C(x,t_1) - \int_{t_1}^{t_2} \frac{\partial F(x,t)}{\partial x} dt \right] dx. \tag{17}$$

The divergence theorem allows us, under certain conditions that we assume apply here, to substitute the volume integral of the divergence of flux, $\partial F/\partial x$, with values of F evaluated at the segment edges. This, along with Eq. (15), yields

$$\bar{C}_j(t_2) = \bar{C}_j(t_1) - \frac{1}{x_{j+\frac{1}{2}} - x_{j-\frac{1}{2}}} \left[\int_{t_1}^{t_2} F\left(x_{j+\frac{1}{2}}, t\right) dt - \int_{t_1}^{t_2} F\left(x_{j-\frac{1}{2}}, t\right) dt \right]. \tag{18}$$

Differentiating Eq. (18) with respect to time allows the original problem (Eq. (14)) to be reformulated in a manner that is conducive to numerical evaluation:

$$\frac{d\bar{C}_j}{dt} = \frac{1}{x_{j+\frac{1}{2}} - x_{j-\frac{1}{2}}} \left[F\left(x_{j-\frac{1}{2}}, t\right) - F\left(x_{j+\frac{1}{2}}, t\right) \right]. \tag{19}$$

The finite volume method is well suited to discontinuities such as are encountered in heterogeneous media. Unstructured meshes, similar to those in the FEM, are also allowed, but the level of precision permitted by higher order polynomials in FEM may not be readily achieved using the FVM [16].

2.3. Macroscopic models incorporating microscopic detail

These models consider microscopic level details, such as distinct lipid and corneocyte phase diffusivities and interphase partitioning, but include a large computational domain that encompasses the full macroscopic extent of the skin layer, e.g., the stratum corneum. Examples include brick and mortar type models (Fig. 1C) and others that consider disordered stratum corneum structure.

All of the preceding methods can and have been applied to this type of problem, or they may be solved by methods that have more of the character of direct numerical simulations, such as random walk, cellular automaton, or smoothed particle hydrodynamics. These methods capture the particle-based nature of diffusion while simultaneously allowing macro level effective properties to be derived. The full potential of either of the latter two methods has not been exploited, although both have qualities that make them amenable to modeling skin permeability.

2.3.1. Random walk method

It has long been recognized that diffusion arises from the random thermal motion of molecules. Einstein undertook investigations on the theory of Brownian motion (collected and reprinted in [17]) and related these random thermal movements to macro level diffusion theory. Consider a simple 1D random walk in which a collection of particles starts out clumped together. For each particle, flip a coin: if it comes up "heads", the particle moves to the left; if it comes up "tails", the particle moves to the right. Each particle moves independently of others and there are no interactions among them. Continued flipping of the coin for each particle reveals two key observations. First, on average, the particles go nowhere. They spread out, but the average of their displacement is zero. Second, Einstein demonstrated [18] that the mean square displacement of the particles is proportional to time:

$$\langle x^2 \rangle = 2Dt \tag{20}$$

Similar expressions apply to 2D and 3D random walks: only the multiplicative constant changes. In this way, the movement of particles undergoing a random walk can be related to the diffusivity or mobility D of the substance in the medium.

Random walk simulations can be undertaken in heterogeneous media with irregular boundaries. Local diffusion rules can be implemented to simulate phenomena such as partitioning (at a phase boundary, the particle flips between phases depending on the value of a partition coefficient that governs the steady-state concentration ratio between the media), anisotropic diffusivity (mobility parallel to the lipid bilayers differs from that in a transverse direction), binding (the particle becomes immobile when it hits a localized "binding site"), etc. Particles may get held up temporarily in a pathway of varying tortuosity and connectivity (e.g., a "porous" path). At a boundary, the particle may disappear (sink conditions) or be governed by any sort of flux, concentration or periodicity rules. An analysis of the collective behavior of many such individual particles undergoing random walks according to the same rules through the medium of interest allows the derivation of macro-level diffusion properties k_p and τ.

2.3.2. Cellular automata

Cellular automata (CA) are a class of discrete grid-based systems that have been employed to study a broad range of physical, chemical and biological systems. A cellular automaton consists of a regular grid of cells, each one obeying rules that govern its state depending on the states of other, neighboring cells. Rules are imposed so that the time evolution of CA states creates a realistic model of the phenomenon of interest. The appropriate CA rules to model diffusion were put forth by Chopard and Droz [19]. Consider a square lattice in which particles move horizontally and vertically. At time step Δt, particles travel a distance equal to the lattice spacing. Random motion is imparted by rotating all particles entering a particular site by the same angle. Possible angular rotations (°) for a 2D lattice are 0, 90, 180, or 270. Rotations are performed independently at each time step for each site, with probabilities that may vary for each possible direction. Appropriate boundary conditions can be imposed, and local diffusion rules can be implemented to account for heterogeneous structures. As with the random walk method, macro level diffusion properties are derived through observations of the collective behavior of the cells over time.

2.3.3. Smoothed particle hydrodynamics method

Smoothed particle hydrodynamics is a particle-based, mesh-free computational method (SPHM) that has been used for simulating such phenomena as fluid flows, impact fractures in solids, and large scale phenomena from meteor impacts to galaxy formation. Like the random walk method, the SPHM tracks particles that move throughout the space of interest—however, with one crucial distinction being that in smoothed particle hydrodynamics implementations, the

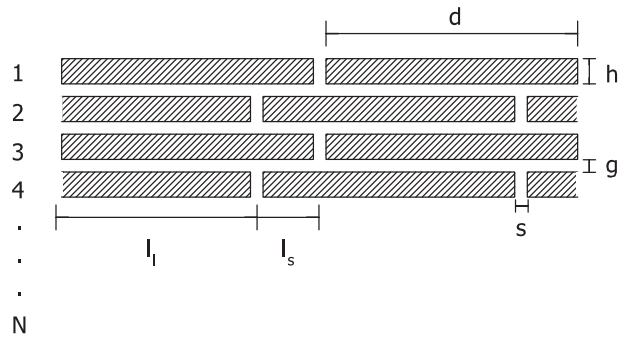

Fig. 2. Brick and mortar model. Originally proposed in 1975 by Michaels et al. [76], the *N*-layer model has been used by numerous investigators as a geometric representation of stratum corneum. Proportions are exaggerated for clarity. Corneocytes, represented as shaded areas ("bricks"), are of width d and thickness h. Lipids ("mortar") are of thickness s for the vertical slits and g for the horizontal layers. Typically, $s=g$. The longer section of overlapping corneocyte is designated l_l; the shorter section l_s. The geometry is characterized by dimensionless ratios $\alpha=d/h$, $\sigma=s/h$, $\phi=h/(h+g)$ and $\omega=l_l/l_s$ [77,78]. Brick and mortar models with disordered structure—variable ω—have also been explored, as have models with non-vertical slits and 3D extensions consisting of stacked, offset flattened cubes.

particles interact. Each particle is represented by information that includes its location in time, velocity, and concentration. A smoothing function calculates the contribution of each surrounding particle to a given particle in accordance with some weighting factor that diminishes along with distance from the particle. This has the effect of interpolating the properties of interest over the domain, and allows the SPH to approximate continuum (large scale) properties while maintaining the underlying particle-based behavior that forms the basis of the continuum. In a diffusion-based implementation of SPH, the particles move at discrete time increments in accordance with imposed rules. Appropriate implementation of boundary conditions has been a challenge as diffusion rules and weighting change near boundaries; this has recently been addressed by Ryan et al. [20]. To our knowledge, this method has not been employed to model skin permeation but is mentioned here for its potential to be used for this purpose.

3. State of the art numerical skin permeation models

There is more than one way to define the "state of the art" in numerical applications to skin permeation modeling. On the one hand, it may refer to the most complex 3D geometric model. This level of achievement has been accomplished through efforts of several individuals currently affiliated with Goethe University. Beginning in 1996 with Heisig et al.'s [21] finite volume model of non steady-state diffusion through a 2D biphasic brick and mortar model (Fig. 2), the German group has tackled increasingly complex structural representations of stratum corneum. Heisig et al. considered the stratum corneum to consist of 2 homogeneous phases, namely the elongated, flattened corneocytes surrounded by thin, continuous lipid layers. The significance of this "brick and mortar model" lay in its demonstration of the contributions of corneocyte alignment, lipid-corneocyte partitioning, and relative phase diffusivity on the barrier properties of the stratum corneum. In particular, they acknowledged the requirement of permeable corneocytes to explain long diffusion lag times.

Subsequent refinements explored a 3D extension of the brick and mortar model represented by stacked cuboid-type arrangement, as well as a 3D tetrakaidekahedral model [22]. In the later, the stratum corneum is modeled as stacked,14-sided polyhedra with each face either a hexagon or square (Fig. 3). These form a reasonable representation of corneocytes, and their space-filling nature (they can be interconnected with no gaps) allows intercellular lipids to be represented as a thin film, assumed to be isotropic, of constant thickness. The full model contains over 10^8 elements and is solved on a parallel processing supercomputer. Homogenization of the model allows the calculation of an effective diffusion coefficient [11], a matrix quantity which, when applied to a simple (3D) homogeneous membrane, gives results that are similar on a macro scale to those of the full computational model.

In collaboration with colleagues at Saarland University, the German group has parameterized their 2D brick and mortar model with coefficients derived from experimental data on 2 model compounds [23,24]. Good agreement is achieved when comparing experimental with modeled concentration/depth profiles, and the model provides insight into critical parameters that affect the observed quantities. An overview of the group's modeling efforts has recently been published [25].

An alternate view of the state of the art is that it refers to the model that provides the most comprehensive insight into the mechanisms underlying the dermal absorption process. This definition is represented by models developed through the collaborative efforts of Profs. Gerald B. Kasting of the University of Cincinnati and Johannes M. Nitsche of the University at Buffalo. They were the first—and heretofore only—to confront the fact that lipid bilayers are not homogeneous, a fact long known but until then unaccounted for by the modeling community. A schematic of their model is displayed in Fig. 4. The authors [4] envision anisotropic lipids to comprise 2 transport mechanisms (Fig. 4C). Molecules travel a path parallel to the bilayers via isotropic bulk diffusion. Additionally, they traverse lipid bilayer headgroups through a diffusive hopping mechanism, in which the underlying thermodynamics are conveniently summarized by a transbilayer mass transfer coefficient. Alternate lipid phase topologies are explored whereby continuous lateral pathways either are or are not present. The permeable corneocyte interior is regarded as a homogeneous, isotropic medium. Stratum corneum hydration state is modeled with corneocyte swelling, however dynamic changes are not incorporated.

The model was formulated using a finite difference scheme employing an oblique coordinate system with variable mesh size to form an efficient yet detailed solution space. Full parameterization of the model was undertaken by applying fundamental transport theory to existing experimental data from the literature [26]. The model quantifies the contributions from different elements of stratum corneum microstructure to permeability. Major insights from the model are that stratum corneum lipids are highly anisotropic; that this property has profound effects on skin permeability; and that a transcellular pathway is the predominate penetration route through the stratum corneum.

Homogenization of the full model permits the calculation of effective transport properties and these can be applied to geometrically simpler slab models so that additional processes can be studied in greater detail. A finite difference diffusion/clearance model has been described to examine drug distribution within various skin layers [27,28]. The diffusion and evaporation of finite dose volatile solvents applied to skin has also been described in detail [29,30], and theoretical investigations of the dynamics of diffusion with reversible binding have been undertaken [31] and applied to experimental data [32].

4. Chronological developments

Numerical skin permeation models are presented here in chronological order. Subsequent developments by the same author or group are described following the initial contribution, so the timeline below is not linear. Contributions mentioned in the previous section are not included in this timeline. Table 1 groups the models according to application scale and numerical method.

Lindstrom and Ayres [33] may have been the first to employ methods included in this review to predict drug transport through

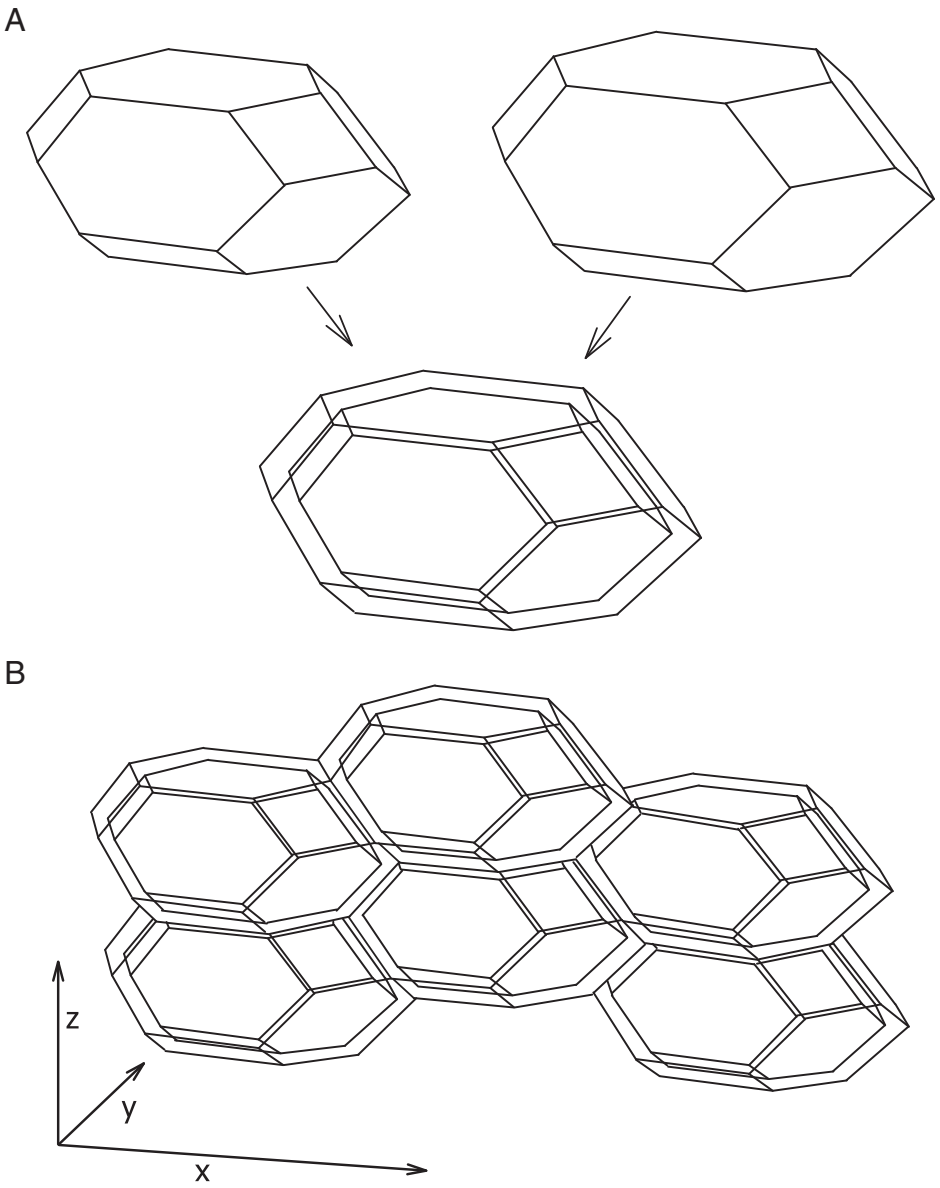

Fig. 3. Tetrakaidekahedron (TKD) model of stratum corneum structure, advanced by Naegel et al. [22]. TKD are not to scale. A: Corneocytes (smaller TKD, left) surrounded by lipids are envisioned as nested TKD. Isotropic lipids are confined to the space between smaller and larger TKD. B: These are stacked vertically and horizontally to create a 3D model of stratum coreum structure.

skin. A finite difference scheme was applied to the authors' nonlinear theoretical model [34] of drug dissolution and release from a suspension in a semi solid, such as an ointment, in contact with skin. Extensive numerical results were presented as functions of overall dissolution rate constant and initial volume fraction of ointment occupied by suspended drug. Drug release profiles depended on whether dissolution or diffusion was the rate limiting step.

Burnette [35] proposed a 1D random walk homogeneous membrane model of stratum corneum and showed that predicted fluxes agree with the analytical solution. Burnette imposed time-dependent changes in stratum corneum thickness and diffusivity and demonstrated how the time course of flux might be altered as a result of stratum corneum hydration.

Gienger et al. [13] modeled a 1D multi-layer transdermal drug delivery system as a polymer film drug depot, a microporous membrane, and adhesive layer, plus skin layer—all homogeneous—and solved the resulting equations using the method of lines with finite element spatial discretization. An empirical time-dependent diffusivity was employed within the polymer film to account for changes in diffusivity as the system hydrates. The model was parameterized with data from transdermal nitroglycerin experiments in addition to estimated values. The authors posit their model as a tool for preformulation studies of laminated patch delivery systems but the predictive value of the model was not explored.

Tojo [36] developed a 2 layer finite difference model consisting of stratum corneum and a viable layer. An additional term was added to the 1 dimensional diffusion equation (Eq. (3)) applied to stratum corneum to account for binding in accordance with a Langmuir isotherm. In the viable skin layer, no binding occurred but Michaelis–Menten metabolism kinetics was added. The skin model was coupled to a 2 compartment body model representing blood and tissue. Extensive simulations were performed to investigate the interplay among input variables. Subsequently, Tojo [37] modified his 2 layer skin model to investigate iontophoretic transdermal delivery. An applied electrical field plus a convective flow term caused by the electric potential were added. Both continuous and periodic electric field

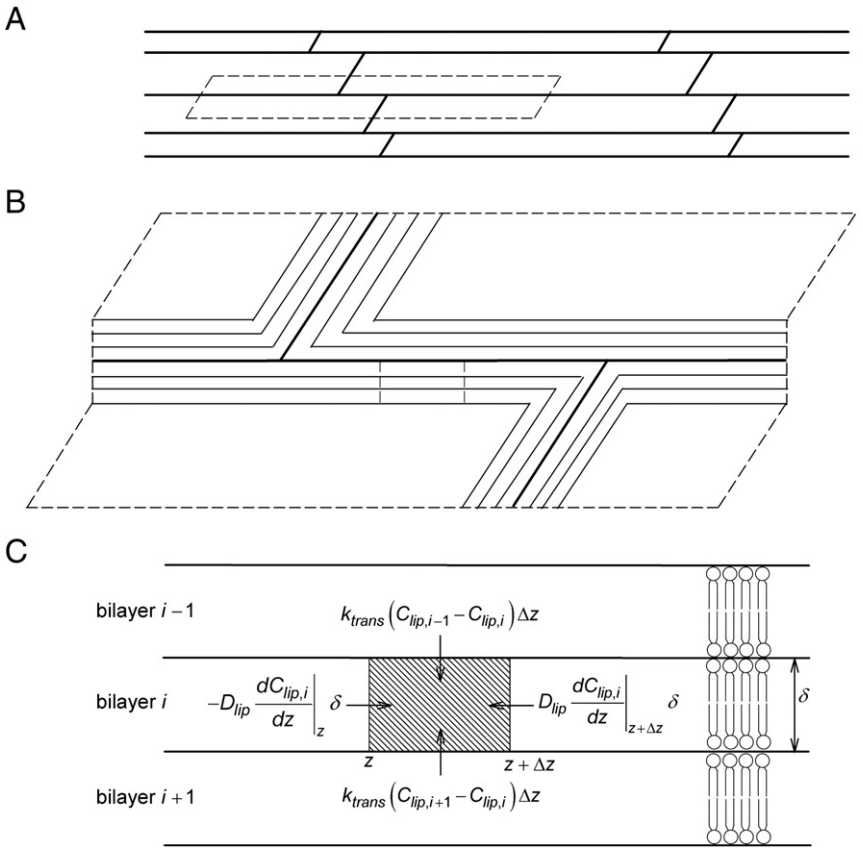

Fig. 4. Stratum corneum structure of Wang–Kasting–Nitsche model [4,26]. A: General organization of corneocytes and lipids. Corneocyte thickness varies with depth and hydration. Drawing not to scale. B: Unit cell. Highly exaggerated scale showing lipids represented as 6 parallel bilayers. C: Material balance for small section (shaded region) of lipid bilayer of length Δz and thickness δ. Lateral diffusion is characterized by D_{lip}, while transbilayer hopping is described by the mass transfer coefficient k_{trans}. Lipid molecule organization within bilayers is represented at right.

applications were considered and their effects on modeled drug permeation profiles were explored, and the author concluded that the model can be used to predict the iontophoretic enhancement ratio of transdermal polypeptide delivery. A subsequent manuscript [38] dropped the metabolism term and focused on the effects of binding on the transport of a series of amino acids. Model parameters were adjusted to match passive permeation experimental results, and then effects of modeled applied electrical field were compared with iontophoretic experimental results. It was demonstrated that binding dampens the iontophoretic enhancement, but the authors found more profound effects from tissue hydration, a phenomenon not included in their model.

Kubota et al. [39] employed a random walk method to investigate transdermal delivery from repeated administration of timolol from a patch. The 1D model domain consisted of a homogeneous membrane and did not require fine detail of random walk step sizes to account for heterogeneities, and thus the developed equations were identical to those of a finite difference scheme. The random walk model with additional skin layers was used to explore kinetics of a corticosteroid [40]. Kubota and Twizell [41] and Gumel et al. [42] presented numerical results using different solution strategies from a non-linear "dual-sorption" model and explored nonlinear permeation kinetics of timolol [43]. Chandrassekaran et al. [44] had originally developed the theoretical framework for the model that posits binding of permeants to skin components and temporary immobilization in accordance with a Langmuir isotherm. The numerical results demonstrated concentration-dependent changes in modeled lag time and relaxation time following drug removal. George [45] extended the non-linear dual-sorption model to include a 2nd spatial dimension and confirmed non-linear kinetic behavior owing to binding. Kubota et al. [46] explored a repeated dose model consisting of vehicle and skin. Skin concentration, flux and penetration from repeated dosing/removal of arbitrary durations were solved using a finite difference scheme and the method of lines. The authors assumed zero flux at the skin surface after removal of the vehicle, a condition that applies if the permeant is not volatile. George et al. [47] described a 2D model for percutaneous drug penetration through stratum corneum. Finite difference solutions for concentration profiles were given as a function of capillary clearance.

Kurnik and Potts [48] presented a 2 layer (patch + skin) finite difference model to explore crystal dissolution from a controlled release system coupled with diffusion into skin. They studied experimental release kinetics of estradiol as a function of initial particle size and showed that cumulative dermal penetration was not affected by this variable owing to orders-of-magnitude lower diffusivity in skin compared with patch.

Lee et al. [49] presented results using unspecified numerics from a coupled dual pathway model comprised of stratum corneum and viable epidermis. First order kinetics governed both the transfer of drug between transcellular and intercellular phases, and the metabolism of drug in both layers. Results for concentration profiles, flux and total penetration were presented over a range of input parameters.

Manitz et al. [50] used the method of lines to solve a 2D multilayer skin model consisting of vehicle, stratum corneum, epidermis and dermis. The goal was to model penetration of a drug plus penetration modifier. They employed a concentration-dependent drug diffusivity to account for the presence of a penetration modifier and employed a moving boundary to follow the penetration depth.

Charalambopoulou et al. [51] described a 2D brick and mortar model solved using a finite difference scheme with unstructured grids. The authors experimentally determined effective diffusion

constants using very small angle neutron scattering, and used this data to derive appropriate stratum corneum dimensions for corneocyte and lipid layer thicknesses so that modeled results matched the experimental values.

Iordanskii et al. [52] presented finite difference solutions to a 2 component model consisting of transdermal patch and artificial membrane. The idea was to explore parameters affecting the release kinetics of drug from the hydrogel polymer patch. They found that membrane diffusivity and patch-membrane partitioning were the rate controlling factors.

Frasch [53] presented a 2D random walk model through a disordered, anatomically realistic representation of the stratum corneum. The model included separate diffusivities within isotropic lipids and corneocytes, and partitioning between the 2 phases. Model results were formulated in a way that enabled regression with a large data base of measured permeability coefficients from aqueous vehicle [54], and a good level of correlation ($r^2 = 0.84$) was found. Subsequently, Frasch and Barbero [55] analyzed a finite element model of the lateral lipid pathway in stratum corneum to investigate effective path length and diffusion lag times. They formulated compact algebraic expressions for lag time and steady-state flux, relative to those quantities in a homogeneous membrane composed purely of lipid, based solely on stratum corneum geometric descriptors (described in Fig. 2). In this way they were able to demonstrate how lipid organization affects stratum corneum barrier properties. This theme was continued in a subsequent contribution that allowed for permeable corneocytes. Barbero and Frasch [56] compared modeled lag times with a data set of 27 *in vitro* measurements of hydrophilic compounds collected from the literature. Results supported a transcellular pathway with preferential corneocyte partitioning as the likely diffusional pathway for hydrophiles. Corneocyte holdup is the mechanism underlying the observed long lag times, which compare favorably with measured quantities.

Riley et al. [57] described a 1D finite difference model to simulate multiple intermittent doses, along the lines of Kubota et al.'s [46] model, but allowing for time- and location-dependent diffusivity. Riley et al. imposed a zero concentration boundary condition at the skin surface following removal of the dose; thus their simulations are restricted to highly volatile compounds.

Rim et al. [58] presented a nonlinear finite element model of diffusion and partitioning between 2 isotropic materials, representing a dermal patch and the skin. Coadministration of a penetration enhancer with a drug was modeled using enhancer concentration-dependent diffusivity and partition coefficient of the drug. Experimental data on fentanyl with an enhancer supported the proposed mechanism. Using the method of asymptotic expansions, Rim et al. obtained macroscopic (effective) diffusion coefficients for both 2D and 3D brick and mortar models with isotropic lipids and first impermeable [59], then later permeable [10] corneocytes. A multiscale transdermal modeling framework has also been presented [60]. Microscopic lateral lipid bilayer diffusion of the model compound fentanyl was simulated using molecular dynamics. Homogenization was applied to a 2D brick and mortar model with impermeable corneocytes and isotropic lipids to obtain effective diffusivity. The homogenized stratum corneum was then embedded in a macroscopic multilayer domain that also included patch, epidermis and dermis. Finite element simulations of drug transport through the multilamellar structure were undertaken.

Kushner et al. [61] extended Frasch and Barbero's [55] isotropic lipid pathway analysis and derived, from first principles, similar expressions for effective path length and diffusivity as functions of brick and mortar geometric descriptors. Their theoretical predictions compared favorably with results from their finite element model.

Becker and Kuznetsov [62-64] described a 3D finite volume model of skin electroporation to demonstrate electric pulse-induced lipid phase transitions, enhanced macromolecule transdermal delivery, and thermal tissue damage associated with Joule heating. Electroporation transiently permeabilizes the stratum corneum but also induces irreversible thermal damage above some threshold voltage. The composite nature of skin was shown to be crucial, with dermal and subcutaneous fat being particularly susceptible to thermal damage. Subsequently, Becker [65] described a thermodynamics-based model of electroporation. Structural changes within the skin were linked to applied electrical pulses through a lipid melt fraction, which describes the degree of lipid disorder as a function of stratum corneum specific heat. Lipid structural alterations were then related to increases in ionic and mass transport coefficients.

Chen et al. [66,67] and Lian et al. [68] described a 2D brick and mortar model with isotropic lipids and permeable corneocytes solved using the method of lines. The model was parameterized using physical chemical-based correlations, and model predictions compared favorably ($R^2 = 0.74$) with measured permeability coefficients from a diverse data base of 127 chemicals. The authors also demonstrated good correlation between predictions for 2 model compounds with tape strip data on SC penetration depth and time.

Xing et al. [69] presented a finite element model consisting of patch, stratum corneum and viable epidermis, each a homogeneous, isotropic surface. They introduced an "interphase contact algorithm" which is simply a discretized flux boundary condition to govern transport between 2 phases. The authors claim that interphase flux is proportional to the concentration difference between phases, but thermodynamic considerations would suggest that activity difference is the appropriate driving force. As formulated, the contact algorithm does not account for partitioning between the phases.

Zhong et al. [70] developed a cellular automaton brick and mortar model of transdermal drug delivery. A 2D grid of cells was constructed with each cell designated as belonging to the class corneocyte, lipid, or vehicle. Drug concentration in each cell is then governed by different probabilistic rules, and the evolution of the entire system proceeds at discrete time steps. The authors found that model results compare favorably with experimental tape strip data on estradiol amounts in stratum corneum and viable epidermis as functions of time, but give no indication on how model time is scaled, nor on how viable epidermis is modeled, nor on why only ~60% of the applied dose appears to be accounted for in the steady state model solution.

Marquez-Logo et al. [3] considered the stratum corneum to comprise a 3D porous medium and presented numerical results from a finite difference scheme. Transdermal transport of drug occurred via diffusion against an advective water flow caused by an imposed outward pressure gradient. Mass transport was hindered by the presence of impermeable corneocytes. Penetration profiles were altered by the presence of the outward pressure gradient, but net mass transfer of drug from surface inward occurred regardless of its magnitude.

5. Summary and future directions

Substantial mechanistic insight into the process of transdermal penetration has been gained through the developments described in this review. In particular, we now have a firm understanding of how the stratum corneum structure and organization affect both steady state and kinetic aspects of the skin's barrier property. While in the recent past it may have seemed adequate to posit a tortuous lipid pathway as the primary permeation path, it now seems apparent that this tortuosity by itself is inadequate to account for experimental observations of long lag times of certain permeants, particularly those of a hydrophilic nature. Transbilayer hopping and corneocyte holdup seem the most straightforward alternative [4]. Even though lateral lipid diffusivities are orders of magnitude higher than transverse diffusivity, molecules must nevertheless traverse the lipid bilayers in any reasonable representation of bilayer morphology. Affinity to and mobility through corneocytes then plays a crucial role in transporting material to the next set of lipid bilayers as the permeant traverses the depth of stratum corneum. Even though the diffusion barrier arises

mainly from the lipid phase, it is not the lateral pathway but rather transbilayer hopping that largely contributes, and the bulk of solute flux occurs via a transcellular pathway.

As skin transport models have become more complex, a concern is the consequence that more and more input parameters need to be estimated. An obvious way to go about this is simply to attempt to fit the model to a set of experimental data via regression analysis. In some cases where no direct measurements of parameters can be made, a carefully designed set of experiments may be used to estimate a limited parameter set. Examples of this approach include recent efforts to account for characteristics of permeation kinetics by binding of permeant to tissue components, with [32] or without [64] measured binding isotherms. As model complexity and the number of unknown parameters increases, however, the ability of experimental data to generate a unique and meaningful set of parameter values diminishes. Models that are simply exercises in parameter fitting do nothing to advance mechanistic insight and probably offer little predictive ability. The proper alternative under these circumstances is to apply fundamental transport theory to derive parameter estimates. This process typically also involves regression with existing data, but the analysis is driven by a firm theoretical foundation. This approach has formed the basis for reliably predictive models from Potts and Guy's seminal contribution [71] and is thoroughly realized in the comprehensive multiphase microscopic model of Wang-Kasting-Nitsche [26].

A theme that emerges from the preceding review is that in one sense, diffusion modeling has come full circle from simple homogeneous slab models, through detailed considerations of fine microstructure and distributed properties, back to slab models. The key has been the application of the mathematical homogenization procedure, by which effective transport properties may be derived through analysis of the unit cell problem [2]. When applied to multiphase skin permeation models [4,10,11,31,59] the process supports the use of a pseudo homogeneous membrane model of stratum corneum. This means that for purposes of estimating macro level outputs such as flux or total mass accumulation, a simple homogeneous slab model can replace the complex multiphase microscopic representation. The parameters of this reduced model—effective diffusivity, partition coefficient and thickness—can be estimated as summarized by Mitragotri et al. [6] (cf. Frasch [53], Wang et al. [26], Hansen et al. [23]). Analytical solutions for the homogeneous membrane model can be readily found through conventional methods. Additional distributed transport processes such as binding of drug to stratum corneum components can be handled in a similar manner [31].

It is apparent from the foregoing that future realistic models will have to include anisotropic lipid transport. Additional experimental data on transverse stratum corneum lipid transport would be helpful in order to elucidate this mechanism. Currently, values for the transbilayer mass transfer coefficient are deduced from stratum corneum permeability data [26]. A more fundamental understanding of this phenomenon would therefore be beneficial.

The postulate of the impermeable corneocyte has been debunked [5] and the idea that permeants traverse solely, or even primarily, a lateral lipid pathway seems to be eroding. The permeable corneocyte hypothesis is supported by several models described in this review [4,21,24,53,56] and it seems reasonable that future models should not *a priori* exclude a transcellular permeation path.

Recently, binding of permeants to stratum corneum components has been highlighted. Anissimov and Roberts [72] explained anomalous permeability/desorption kinetics of water by a slow, reversible binding process. Frasch et al. [32] demonstrated a substantial effect of binding of theophylline to stratum corneum on prolonging the permeation lag time, and Hansen et al. [73] have published an extended database of keratin binding. Nitsche and Frasch [31] developed the theoretical framework for reversible binding in heterogeneous membranes and derived appropriate effective binding rate constants for application to the homogeneous membrane approximation. Clearly, binding kinetics can have profound effects on transdermal drug delivery. While some details remain to be worked out, such as the nature of binding (covalent and irreversible, or reversible) and the form of the binding isotherm for particular compounds, it seems incumbent to include binding capacity in future model developments.

Future models would benefit from a fundamental physicochemical analysis of drug/vehicle/skin interactions. In the area of transdermal drug delivery, formulation components may alter the barrier properties of the skin. Co-administration of a penetration enhancer certainly modulates barrier properties, as do enhancement strategies such as electroporation, iontophoresis, and ultrasound. The foundation for the analysis of formulation thermodynamics was laid over 50 years ago in the groundbreaking work of T. Higuchi [74], but most of the models described herein have relied on simple empirical relationships to account for vehicle interactions. For example, effects of a penetration enhancer were modeled as enhancer concentration dependent changes in drug partitioning and diffusivity [58]. Such an empirical relationship permits exploration of effects of these changes on transdermal drug transport, but yields no insight into the mechanism of enhanced transport. One example of a fundamentally based approach is the thermodynamic electroporation model of Becker [65] in which the author related electroporation-induced structural changes within the skin to applied electrical pulses. Such an approach involves extensive theoretical analysis and requires coupled solutions of the electrical field, thermal energy, and transport coefficients, but the reward is a realistic framework upon which one can predict and optimize solute transport following electroporation. A comprehensive linear theory of transdermal transport including passive diffusion, iontophoresis, electroosmosis, current flow and forced convection was proposed by Edwards and Langer [75] and this could serve as a framework for modeling endeavors that aspire to incorporate these phenomena.

The value of any skin transport model lies in its ability to provide mechanistic insight into the skin's barrier function and to reliably predict skin permeation phenomena. At times these requirements may be met by the simplest 1D homogeneous slab models, but for situations that require more complex modeling, the tools are available to accomplish the task. It is hoped that this review may inspire others to further the bounds of numerical modeling of skin permeation.

Disclaimer

The findings and conclusions of this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health or the Centers for Disease Control and Prevention.

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