

A Random Walk Model of Skin Permeation

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A new mathematical model for permeability of chemicals in aqueous vehicle through skin is presented. The rationale for this model is to represent diffusion by its fundamental molecular mechanism, i.e., random thermal motion. Diffusion is modeled as a two-dimensional random walk through the biphasic (lipid and corneocyte) stratum corneum (SC). This approach permits calculations of diffusion phenomena in a morphologically realistic SC structure. Two concepts are key in the application of the model to the prediction of steady-state skin permeability coefficients: "effective diffusivity" and "effective path length," meaning the diffusivity and thickness of a homogeneous membrane having identical permeation properties as the stratum corneum. Algebraic expressions for these two variables are developed as functions of the molecular weight and octanol-water partition coefficient of the diffusing substance. Combining these with expressions for membrane-vehicle partition coefficient and permeability of the aqueous epidermis enables the calculation of steady-state skin permeability coefficients. The resulting four-parameter algebraic model was regressed against the "Flynn data base" with excellent results ($R^2 = 0.84$; $SE = 0.0076$; $F = 154$; $N = 94$). The model provides insight into the contributions of stratum corneum diffusivity and effective path lengths to overall skin permeability and may prove useful in the prediction of non-steady-state diffusion phenomena.

1. INTRODUCTION

The potential significance of the dermal route of chemical exposure is now generally recognized. As the chemical industry has complied with increasingly stringent airborne concentration regulations, one response has been to substitute highly volatile compounds with those less volatile. This has created the potential for an increase in dermal absorption compared with respiratory uptake. The ability to accurately predict dermal absorption of workplace chemicals is thus a crucial component of quantitative risk assessment.

Chemicals penetrate the skin through passive diffusion, a mass transfer process that arises from

random molecular motions. Net mass transfer occurs when there is a concentration gradient of the chemical. The steady-state rate of permeant transfer across a homogeneous membrane is given by the following, based on Fick's first law of diffusion:

$$J_{ss} = \frac{K_{mv}D}{l} \Delta C \quad (1)$$

Here, J_{ss} is the steady-state flux or rate of mass transfer per unit area of membrane of thickness l , ΔC is the concentration difference between the two sides, and D is the diffusion coefficient, which represents chemical mobility within the membrane. The membrane-vehicle partition coefficient (K_{mv}) accounts for equilibrium differences in concentration between vehicle and the membrane. It is assumed in Equation (1) that the same vehicle is used on both sides of the membrane.

Although skin is not a homogeneous membrane, researchers in this field have adopted

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Equation (1) as a framework for the measurement of skin permeability. *In-vitro* diffusion experimental results are frequently summarized as a permeability coefficient k_p , defined as

$$k_p = \frac{K_{mv}D}{l} \quad (2)$$

Permeability is thus typically measured by dividing steady state flux by ΔC .

The skin's outermost layer, the stratum corneum (SC) is the primary barrier to chemical penetration. The SC consists of more or less parallel layers of dead, keratinized cells—the corneocytes—interposed with intercellular lipid lamella. The corneocytes are cellular remnants of the terminal differentiation of keratinocytes and consist primarily of filamentous keratins surrounded by a stable cornified envelope with a covalently bound lipid surface.⁽¹⁾ The intercellular regions are lipid lamellae formed from units consisting of two closely apposed lipid bilayers.⁽²⁾ The primary components of the lipid lamellae are ceramides, fatty acids, and cholesterol.

Neither diffusivity D nor path length l in Equations (1) and (2) are simple constants in the SC. If chemical mobility is different in intercellular lipid compared with proteinaceous corneocytes, then D will depend on which phase the chemical is dissolved in. This in turn depends on the partitioning of the chemical between the two phases. Furthermore, path length l cannot simply be considered the thickness of the skin membrane. A highly lipophilic chemical will partition primarily within the extracellular lipid phase of the stratum corneum; its path length will be long and tortuous compared with that of a chemical that partitions equally in the corneocyte environment.

The model described herein was particularly developed to investigate the contributions of stratum corneum structure and composition to skin permeability. Diffusion is represented by its fundamental molecular mechanism and is modeled as a “random walk” through a stratum corneum membrane that is realistic in both morphology and composition. This approach has a number of advantages. First, because it is based fundamentally on the physics of diffusion, the model can provide mechanistic insight into dermal penetration that is usually lacking in statistically based approaches such as regression or quantitative structure activity relations. Second, it explicitly accounts for the nonhomogeneous structural complexities of the skin

that govern permeability. Third, the model has been developed so that it can potentially account for non-steady-state diffusion phenomena such as lag times, finite doses, and repeated doses, which are important considerations in both occupational and environmental dermal exposures.

We assume in this article the simplest case in which corneocytes and lipids are distinct but homogeneous phases. Two concepts are key in application of the model: “effective diffusivity” (D^*) and “effective path length” (l^*), meaning the diffusivity and thickness of an equivalent *homogeneous* membrane having the permeation properties of the *heterogeneous* stratum corneum.¹ When defined as functions of a chemical's molecular weight (MW) and its octanol-water partition coefficient (K_{ow}), these concepts prove useful in describing diffusion processes of chemicals through the SC. Model predictions of skin permeability from the two independent variables of MW and $\log K_{ow}$ correlate well ($R^2 = 0.84, n = 94$) with measured data taken from the literature, using appropriate values for four adjustable parameters.

For a critical review of mathematical models of skin penetration, see Roberts *et al.*⁽³⁾ Wilshut *et al.*⁽⁴⁾ compared five regression models, and Vecchia and Bunge⁽⁵⁾ compared 22 correlations for estimating permeability coefficients.

2. METHODS

2.1. Model Stratum Corneum

Model calculations are based on the stratum corneum rendering depicted in Fig. 1. This rendering is modified from Schätzlein and Cevc⁽⁶⁾ and is based on a study of SC structural organization in the hairless mouse. It is assumed herein that both upper and lower surfaces of the SC are covered by a lipid film.

2.2. Diffusion Calculations

Diffusion through the stratum corneum is modeled as a random walk process that takes place within the model stratum corneum membrane depicted in Fig. 1. The membrane is mapped to a

¹The concept of an “effective diffusion coefficient” has a long history in the analysis of diffusion in heterogeneous media, apparently extending as far back as Maxwell in 1873. Reviewed by J. Crank, *The Mathematics of Diffusion*, 2nd ed., Oxford: Clarendon Press, 1975, pp. 266–285.

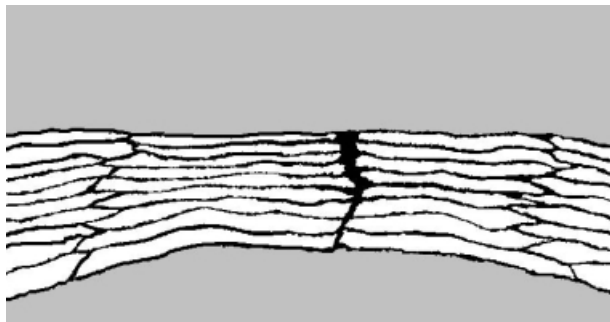


Fig. 1. Rendering of transverse section of stratum corneum used as structural basis of model. Corneocytes (white areas) are stacked in columns with significant intercalation between adjacent cells. Corneocytes are bound by continuous lipid layers (black areas). Adjacent clusters are separated by wide “gorges” (thick black area in center). Rendering adapted from Schätzlein and Cevc,⁽⁶⁾ based on measurements from mouse skin.

rectangular coordinate system so that any location is uniquely determined by a point (x, y) . A particle of diffusing substance is initially placed at random on the upper surface of membrane. The particle then undergoes a two-dimensional random walk within the transverse section of the modeled membrane.

At each computational time step n , a lateral $(\Delta x(n))$ and transverse $(\Delta y(n))$ displacement are calculated as follows. Two random numbers in the range $[-1, 1]$ are generated to determine the directions and relative magnitudes of the particle's displacement in the lateral and transverse directions. The magnitude of the particle's displacements depends on whether it is currently within the corneocyte or lipid phase, as governed by an independent variable D_{cor}/D_{lip} with D_{lip} held constant, and varies with the square root of the diffusion coefficient (Equation (3)). For example, if $D_{cor}/D_{lip} = 0.1$ and if the particle is within the corneocyte phase, then both $\Delta x(n)$ and $\Delta y(n)$ equal $\sqrt{0.1}$ times the displacements within the lipid phase. Maximum displacements are typically $\sim 1/2$ – $1/4$ the thickness of the lipid lamellar layers. Reduction of the maximum displacement by one-half did not alter results. For results presented herein, diffusion coefficients are independent of direction, i.e., the average (over many time steps within a given phase) Δx equals the average Δy .

The particle is thus allowed to jump to a new position by a displacement of $(\Delta x(n), \Delta y(n))$, as long as the new position is within the same phase (lipid or corneocyte) as the current position. Whenever a particle reaches a boundary between lipid and corneocyte, an attempt is made to jump between

the phases. The probability of a successful jump is determined by the chemical's corneocyte-lipid partition coefficient ($K_{cor-lip}$), which relates the steady-state chemical concentration in the corneocytes relative to the lipid phase, and is considered to be an independent variable of the model. As an example, if $K_{cor-lip} = 0.01$, a random integer between 0 and 100 is generated. If the particle is currently in the lipid phase, then it will remain there for any number between 1 and 100, or jump to the corneocyte only if the number is 0. Conversely, if the particle is currently in the corneocyte phase, it will remain there only if the number is 0, and will jump to the lipid for any number between 1 and 100. Thus, the model assumes instantaneous partitioning between the two phases. The idea of using D_{cor}/D_{lip} and $K_{cor-lip}$ as independent variables for diffusion simulations was suggested by Heisig *et al.*⁽⁷⁾

If a particle exits from one side (left or right) of the modeled membrane space, it instantaneously reappears at a corresponding location within the same phase at the opposite side of the membrane (periodic boundary condition). When the particle appears at the lower surface (bottom boundary) of the stratum corneum, it instantaneously disappears (0 concentration in receptor).

For any time step n , the location of a particle $(x(n), y(n))$ is determined from its previous location by $(x(n-1) + \Delta x(n), y(n-1) + \Delta y(n))$, and its squared displacement $r^2(n) = \Delta x^2(n) + \Delta y^2(n)$. A running sum of $r^2(n)$ is calculated and stored as a function of computational time step n . Over large n , the shape of the $r^2(n)$ vs. n curve closely approximates a straight line, the slope of which is proportional to diffusivity (Equation (3)).

2.3. Effective Diffusivity

We define an effective diffusivity D^* , a function of both D_{cor}/D_{lip} and $K_{cor-lip}$, as the diffusivity of a homogeneous membrane having the same permeability properties as the heterogeneous model stratum corneum under the given input conditions. In Fickian diffusion through a homogeneous membrane, the mean square displacement $\langle r^2 \rangle$ of particles undergoing two-dimensional random walks is related to diffusivity by:

$$\langle r^2 \rangle = 4Dt \quad (3)$$

where D is the diffusion coefficient and t is time. For an ensemble of particles in the heterogeneous

SC membrane, $\langle r^2 \rangle$ will average the effects of partitioning between phases and different molecular mobilities within the two phases.

Thus, for each particle, the slope of the $r(n)$ vs. n curve is calculated over the number of time steps required to traverse the membrane. Define $D'(D_{cor}/D_{lip}, K_{cor_lip})$ as the average of slopes for all simulated particles under the particular input conditions, normalized by the average of slopes for the input conditions corresponding to a homogeneous membrane ($D_{cor}/D_{lip} = 1$; $K_{cor_lip} = 1$). Effective diffusivity $D^*(D_{cor}/D_{lip}, K_{cor_lip})$ is then determined by multiplying $D'(D_{cor}/D_{lip}, K_{cor_lip})$ by a representative diffusion coefficient D_0^* (see Equation (11)).

2.4. Effective Path Length

Likewise, we define an effective diffusional path length $l^*(D_{cor}/D_{lip}, K_{cor_lip})$ as the thickness of a homogeneous membrane having the same diffusion properties as the heterogeneous model stratum corneum. For a homogeneous membrane initially with 0 concentration throughout, subsequently exposed to a finite amount of chemical M_0 in a thin layer at the upper surface while maintaining 0 concentration at the lower, the solution for accumulation of mass M below the membrane at time t is:

$$\frac{M(t)}{M_0} = 1 - 2 \sum_{n=0}^{\infty} \frac{(-1)^n e^{\left(\frac{-D^*(\gamma_n)^2}{l^{*2}}\right)}}{\gamma_n} \quad (4)$$

where

$$\gamma_n = (2n + 1) \frac{\pi}{2}$$

Model results for many particles yield discrete mass accumulation vs. computational time data points corresponding to these conditions. These data are regressed against Equation (4), keeping only the first four terms, which provides good representation except for very short times. The result gives a numerical value for D^*/l^{*2} , from which l^* is calculated using D^* derived as from above.

For each set of input conditions, anywhere from 50 to 500 particles were used to calculate D^* and l^* . The number used was considered adequate when a correlation $R^2 > 0.95$ resulted when fitting the data to Equation (4).

2.5. Model Application

A large quantity of data exists where the steady-state *in-vitro* permeability of chemicals from an

aqueous vehicle are reported using excised skin placed in diffusion cells. The permeability coefficient (k_p), which is a measure of the conductivity of the skin for a specific chemical, can be expressed in terms of chemical and membrane properties (Equation (2)). With water as the vehicle, Pugh *et al.*⁽⁸⁾ developed an expression for the membrane-vehicle partition coefficient (first term in Equation (2)), which they regressed from measurements of 45 chemicals ($R^2 = 0.84$):

$$\log K_{mv} = 0.59 \log K_{ow} - 0.024 \quad (5)$$

where K_{ow} is the octanol-water partition coefficient. All logarithms expressed herein are base 10.

The Flynn⁽⁹⁾ data set is a collection of human skin permeability coefficients from an aqueous vehicle, derived primarily from *in-vitro* measurements. The data include 97 measurements of 94 chemicals spanning a wide range of molecular weights (18–765) and $\log K_{ow}$ s (–2.25 to 5.49), made in a variety of laboratories under a variety of conditions. This database has been widely used in the development of skin permeability correlations (e.g., Reference 10). Three chemicals in the Flynn⁽⁹⁾ data set—ethyl benzene, styrene, and toluene—have reported permeabilities that have been called into question as being gross overestimations. These compounds were measured in an *in-vivo* setting, and it has been suggested that methodological error may be responsible for the overestimation.⁽⁵⁾ These chemicals were therefore eliminated from the Flynn database, which will henceforth be called the “modified Flynn database.”

To compare the random walk model predictions to experimental permeability coefficients, the model's independent variables $\log K_{cor_lip}$ and $\log(D_{cor}/D_{lip})$ must be expressed in terms of physical (measurable or derivable) properties. It is common to use the variables $\log K_{ow}$ and molecular weight (MW) as independent variables in predictions of skin permeability. The following are simple but realistic approximations.

First, it is reasonable to assume that $\log K_{cor_lip}$ is related to $\log K_{ow}$ in a manner analogous to Equation (5):

$$\log K_{cor_lip} = a \log K_{ow} + b \quad (6)$$

with the constraint that $a < 0$ to preserve the analogy of lipids to octanol and corneocytes to water.

For diffusion coefficients, a simple semitheoretical correlation follows from the “free volume”

theory originally developed to describe diffusion in synthetic polymers.⁽¹¹⁾ In its simplest form:

$$D = D_0 e^{cMW} \tag{7}$$

where D_0 is the diffusivity of an infinitesimally small molecule, and $c (< 0)$ expresses a retarding effect that includes the relationship between the molecular weight of the solute and its molecular volume, in relation to the free volume of the polymer. Equation (7) has been used by others in the development of skin diffusion models (e.g., References 10, 12, and 13) and has been adopted here to describe diffusivity in both lipids and corneocytes. Hence,

$$\begin{aligned} \log(D_{cor}/D_{lip}) &= \log(D_{0,cor}/D_{0,lip}) \\ &\quad + MW(c_{cor} - c_{lip}) \\ &= \log D_0 + cMW \end{aligned} \tag{8}$$

where $D_0 = D_{0,cor}/D_{0,lip}$ and $c = c_{cor} - c_{lip}$.

We considered using a more detailed “fiber-matrix” theory⁽¹⁴⁾ to account for diffusion within corneocytes. Combining that theory with the “free volume” theory for lipids resulted in an equation similar in form to Equation (8) but with more parameters, which led to only a small gain in overall model correlation with experimental data. Therefore, the simpler Equation (8) was adopted.

The random walk model is a model of diffusion through the stratum corneum only. Although the SC represents the rate-limiting barrier for most chemicals, an intact aqueous epidermal layer is present in most *in-vitro* experimental setups and is a significant hindrance to lipophilic compounds.⁽¹⁵⁾ Therefore, for the purpose of modeling skin permeability, we add an epidermal layer in series with the SC and assume as a first approximation that its permeability (k_{aq}) is a constant.

Thus, total skin permeability k_p is given by:

$$k_p = \frac{k_{sc} + k_{aq}}{k_{sc}k_{aq}} \tag{9}$$

with

$$k_{sc} = K_{mv}D^*/l^* \tag{10}$$

It should be noted that use of Equation (5) and Equation (10) implicitly assumes that the surface of the SC is covered with lipid, i.e., chemical flux occurs across the entire cross-sectional area of the membrane.

2.6. Calculations

The random walk model was programmed in Delphi 4 (Borland), an object Pascal-based development tool for Windows applications. Model runs typically take from minutes to days depending on input conditions. It should be noted, however, that although the random walk runs require substantial computational time, the results are regressed to a simple set of algebraic equations that are used to predict skin permeability. Regression analyses, including regression statistics, were performed using SigmaPlot 2000 (SPSS Inc.) and MathCad 2000 (MathSoft, Inc.). Both SigmaPlot and MathCad nonlinear regression use a Marquardt-Levenberg algorithm that yields parameter values that seek to minimize the sum of squared differences between observed (experimental) and predicted values of permeability coefficients.

3. RESULTS

3.1. Modeled Penetration from a Finite Donor

Fig. 2 shows random walk simulations for mass penetration through the stratum corneum, compared with the analytical solution (Equation (4)) for a homogeneous membrane. For these particular

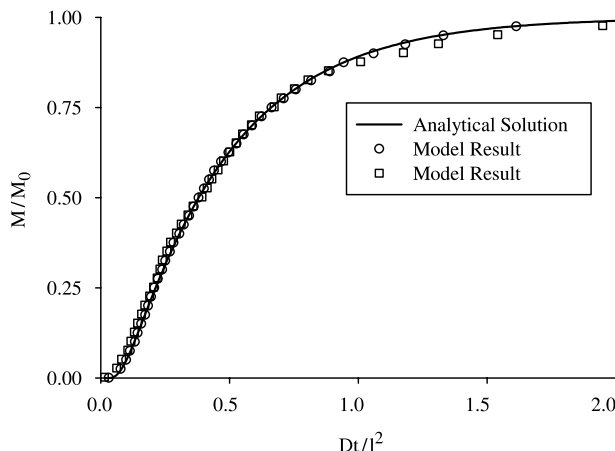


Fig. 2. Model results compared with analytical solution. Under certain simplifying conditions, the stratum corneum can be represented as a homogeneous membrane, and an analytical solution to the diffusion equation is possible. Here, modeled fractional solute penetration (M/M_0) through the SC (symbols) is compared with the appropriate solution to the diffusion equation (Equation (4)) (solid line). Model results represent values of diffusivity D differing by a factor of 100. t : time; l : membrane thickness.

model runs, $\log K_{cor_lip}$ was set at 0 (no preference for corneocyte or lipid phases) and two widely different values for D_{cor}/D_{lip} were used (1.0, 0.01). Results in both cases compare quite favorably ($R^2 > 0.99$) with the analytical solution.

3.2. Effective Diffusivity

Effective stratum corneum diffusivity (D^*) is displayed in Fig. 3 as a function of $\log K_{cor_lip}$ and $\log(D_{cor}/D_{lip})$. Here, D^* is normalized by D_0^* , which we define as the value of D^* at $\log K_{cor_lip} = 0$ and $\log(D_{cor}/D_{lip}) = 0$. We set D_0^* equal to 3.6×10^{-5} cm^2/hr , a typical value for diffusivity in polymers.⁽¹⁶⁾ Model results are individual symbols (circles). To facilitate model comparisons with experimental data, a closed-form expression was sought to describe the dependencies. Visual inspection of the model data in Fig. 3 suggested the following modification of the logistic function:

$$\log\left(\frac{D^*}{D_0^*}\right) = \frac{y}{1 + e^{-(x-x_0)/b}} \quad (11)$$

with

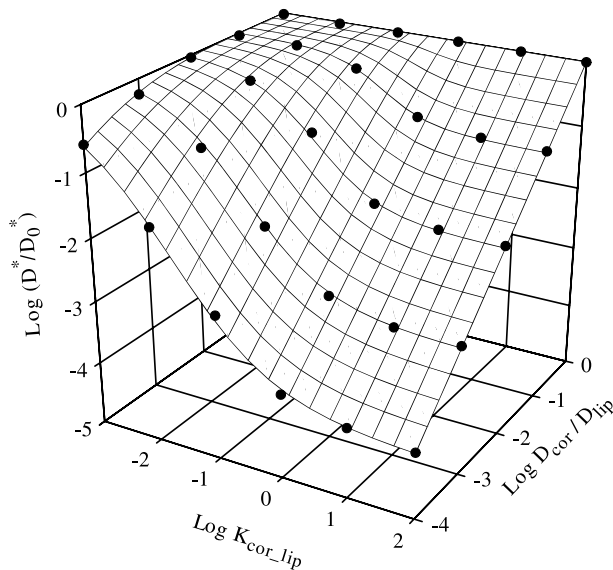


Fig. 3. Modeled effective diffusivity. Effective stratum corneum diffusivity (D^* ; see text for definition) as a function of corneocyte-lipid partition coefficient ($\log K_{cor_lip}$) and relative corneocyte-lipid diffusivity ($\log(D_{cor}/D_{lip})$). Symbols represent model results, while the mesh is the regression equation (Equation (11)) using parameter values found in Table I. D^* is normalized by $D_0^* = 3.6 \times 10^{-5}$ cm^2/hr .

$$\begin{aligned} D_0^* &= 3.6 \times 10^{-5} \text{ cm}^2/\text{hr} \\ x &= \log K_{cor_lip} \\ y &= \log(D_{cor}/D_{lip}) \leq 0 \\ x_0 &= a_0 + a_1 y \\ b &= b_0 + b_1 y \end{aligned}$$

Values of the four parameters a_0 , a_1 , b_0 , and b_1 were found by regression and are reported in Table I. The mesh in Fig. 3 is a plot of Equation (11) with these parameters; excellent ($R^2 > 0.99$) goodness of fit with the modeled points is observed. It should be noted that the values found for the four parameters do not depend on the value selected for the normalization factor, D_0^* .

3.3. Effective Path Length

Effective path length, normalized by SC thickness, is displayed in Fig. 4. Again, symbols represent individual model data points, as functions of $\log K_{cor_lip}$ and $\log(D_{cor}/D_{lip})$. Visual inspection suggested a strong dependence on $\log K_{cor_lip}$ and only a weak dependence on $\log(D_{cor}/D_{lip})$. Therefore, the following equation was adopted:

$$\frac{l^*}{l_0^*} = 1 + l_1 x + l_2 x^2 + l_3 x^3 \quad (12)$$

with

$$\begin{aligned} l_0^* &= 0.003 \text{ cm} \\ x &= \log K_{cor_lip} \end{aligned}$$

In Equation (12), l_0^* represents the thickness of the SC, which we set at 30 μm . Regression analysis yielded values for the three parameters, listed in Table I, resulting in $R^2 = 0.96$. The mesh in Fig. 4 is a

Table I. Parameter Values for Equation (11) and Equation (12)

Parameter	Value	Limits
D_0^*	$3.6 \cdot 10^{-5}$	$-3 \leq \log K_{cor_lip} \leq 5$
a_0	-0.1974	$-7 \leq \log(D_{cor}/D_{lip}) \leq 0$
a_1	0.3668	
b_0	0.2488	
b_1	-0.1340	
l_0^*	0.0030	
l_1	-0.9113	
l_2	0.9896	
l_3	0.3111	

Notes: $D_0^* = \text{cm}^2/\text{hr}$; $l_0^* = \text{cm}$; all others dimensionless. Limits: the limits of applicability of the independent variables of the equations. These correspond to $18 \leq MW \leq 765$; and $-2.25 \leq \log K_{ow} \leq 5.49$.

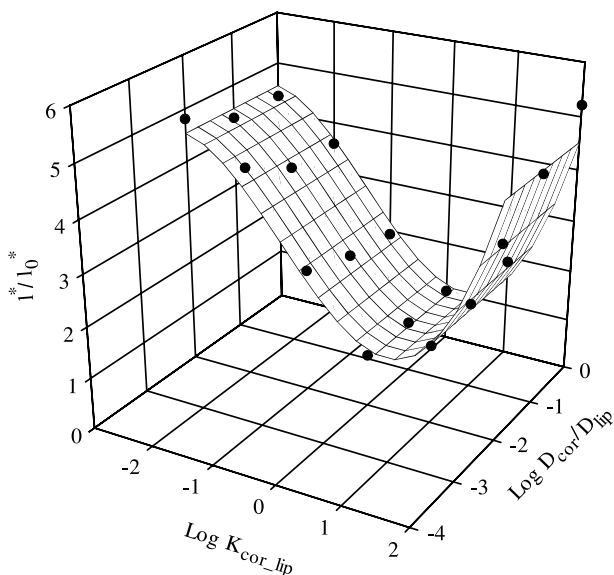


Fig. 4. Modeled effective path length. Effective stratum corneum path length (l^* ; see text for definition) as a function of corneocyte-lipid partition coefficient ($\log K_{cor_lip}$) and corneocyte-lipid relative diffusivity ($\log(D_{cor}/D_{lip})$). Symbols represent model results, while the mesh is the regression equation (Equation (12)) using parameter values found in Table I. l_0 is normalized by $l_0^* = 0.0030$ cm.

plot of this equation. Values found for the three parameters do not depend on the value chosen for l_0^* .

3.4. Steady-State Skin Permeability

Using the parameter values listed in Table I for D^* (Equation (11)) and l^* (Equation (12)), substituting Equation (6) and Equation (8) into Equation (11) and Equation (12), substituting Equation (5), Equation (11), and Equation (12) into Equation (10), and using Equation (10) in Equation (9) results

Table II. Parameter Values for Equation (6), Equation (8), k_{aq}

Parameter	Units	Value	SE	t
a	—	-0.8075	0.0482	-16.7
b	—	2.4194	0.2078	11.6
c	Da ⁻¹	-0.0087	0.0004	-22.0
k_{aq}	cm/h	0.1151	0.0123	9.4

SE: Standard error of estimate. t: t statistic ($P < 0.0001$ for all parameters, where P is the probability that the value does not differ from zero).

in an expression for skin permeability as a function of MW and $\log K_{ow}$. There are five variable parameters whose values can be found by nonlinear regression: a and b (Equation (6)); $\log D_0$ and c (Equation (8)); and k_{aq} . The parameter estimates are presented in Table II for regression against the modified Flynn database, and regression statistics for the model are presented in Table III. Regression analysis showed that $\log D_0$ (Equation (8)) is indistinguishable from 0 ($P = 1.0$); therefore, $\log D_0$ was set at 0. The physical meaning of this is that the diffusivities of an infinitesimally small molecule are the same in corneocytes and intercellular lipids.

Fig. 5a is a graph of the final regression equation for permeability k_p (Equation (9)), along with the modified Flynn data set. Fig. 5b displays \log measured k_p vs. \log modeled k_p , with the diameter of the symbols proportional to the MW of the compound.

For comparison, identical regression analyses were performed on five other mathematical skin permeation models: Potts and Guy,⁽¹⁰⁾ Potts and Guy as modified by Wilschut *et al.*,⁽⁴⁾ McKone and Howd,⁽¹⁷⁾ Cleek and Bunge,⁽¹⁸⁾ and Robinson as modified by Wilshut *et al.*⁽⁴⁾ The results of these analyses are presented in Table III. The equations of these models are listed for reference in the

Table III. Regression Statistics for Six Models

Model (Reference)	np	R^2	R^2_{adj}	SE	F Statistic
Frasch (herein)	4	0.84	0.83	0.0076	154
Modified Robinson (4)	4	0.80	0.79	0.0085	116
McKone and Howd (4, 17)	5	0.80	0.79	0.0085	87
Cleek and Bunge (18)	3	0.78	0.77	0.0088	158
Modified Potts and Guy (4)	3	0.73	0.72	0.6520	120
Potts and Guy (4, 9)	3	0.68	0.67	0.7039	96

Notes: The models were fitted to the modified Flynn database of 94 measurements. np: number of fitted parameters of model; R^2 : correlation coefficient; R^2_{adj} : R^2 adjusted to permit more realistic comparisons of models with different numbers of fitted parameters. SE: Standard error of the model estimate. F Statistic: Measure of the predictive value of the independent variables (higher F statistic indicates greater predictive value).

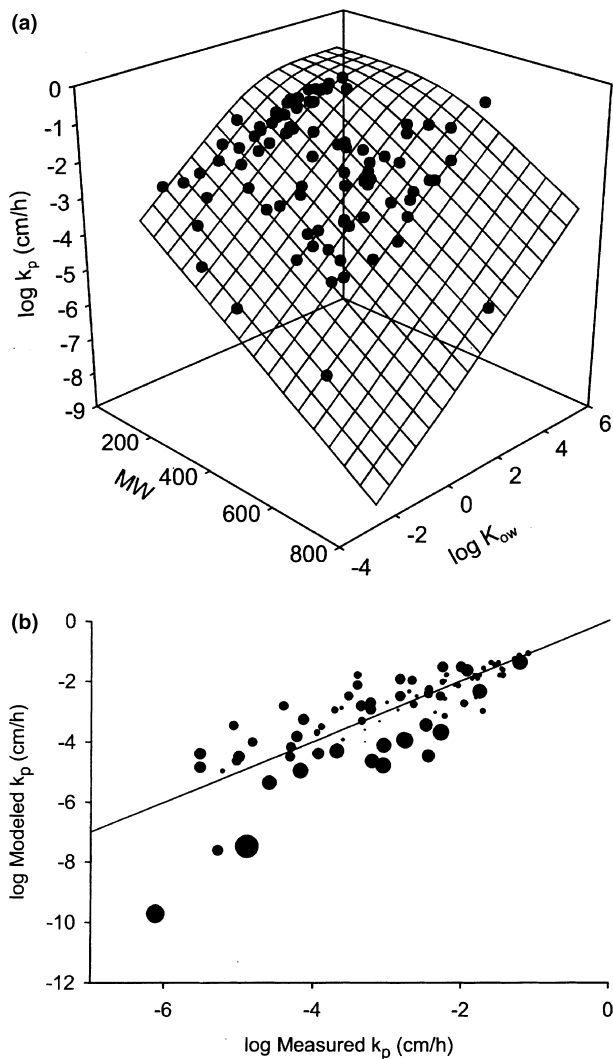


Fig. 5. Modeled and measured permeability. 5(a) Skin permeability (k_p , cm/hr) predicted by the model (mesh) and from the modified Flynn data set (symbols), as functions of molecular weight (MW) and octanol-water partition coefficient ($\log K_{ow}$). 5(b) Bubble plot of modeled and measured k_p . Diameters of symbols are proportional to the molecular weight of the chemical. Line of identity is also shown.

Appendix, and values for the coefficients are listed in Table AI.

4. DISCUSSION

4.1. Advantages of Random Walk Approach

The skin diffusion model presented herein employs a random walk process to simulate the diffusion of chemicals through the stratum corneum. Diffusion at its fundamental level arises from the random migration of molecules or small particles

owing to their thermal energy. As early as 1908, Einstein⁽¹⁹⁾ recognized that diffusion could be characterized by this "irregular motion" and derived the relationship in Equation (3). With the advent of modern computers, the random walk method has been employed in a number of studies of diffusion (e.g., References 20 and 21).

There are a number of advantages of this approach over others. First, as stated, the random walk method represents diffusion at the fundamental molecular level. Hence the model yields mechanistic insight into the diffusion of chemicals through the stratum corneum.

Another advantage is that the random walk approach permits diffusion modeling within a morphologically realistic stratum corneum. Because of the structural complexities of the SC, analytic solutions to the diffusion equation are impossible. The model described herein appears to be the only model that realistically accounts for the nonhomogeneous structural complexities of the skin, although Heisig *et al.*⁽⁷⁾ simulated the SC as a regular "brick-and-mortar" structure (like a brick wall) and examined effects of corneocyte staggering using a finite element numerical approach.

In principle, the random walk model could be applied to SC structures measured from any anatomical location from any species. Presumably, the general equations describing diffusional properties of the membrane (D^* (Equation 11) and l^* (Equation 12)) would be identical, but the parameter values would differ. In this way, the overall contribution of SC structure to measured skin permeability could be estimated. This would be useful, for example, in the extrapolation of skin permeability properties from animal to human, or to account for regional variability in human skin permeability. Investigations along these lines are continuing in our lab.

The model SC used here is two dimensional and diffusion through it is modeled as a two-dimensional random walk. It would be possible to perform similar analyses using a three-dimensional rendering of SC; any potential advantages of this, other than the satisfaction of increased realism, are unknown.

4.2. Effective Diffusivity and Path Length

Two concepts are key in the application of the random walk model to the prediction of skin permeability: effective diffusivity (D^*) and effective path length (l^*), defined as the diffusivity and

diffusional path length of a homogeneous membrane having the same permeability properties as the heterogeneous SC. The validity of these concepts depends on the ability of the heterogeneous model to mimic results obtained from a homogeneous membrane. That is, they require model results to simulate the analytical solution given by Equation (4), because regression of the model to Equation (4) yields the factor from which l^* is determined. Two examples are displayed in Fig. 2. For the entire input range examined, the minimum R^2 was 0.95. The largest deviations from Equation (4) occurred during the early time points with favorable lipid partitioning ($\log K_{cor_lip} \leq -2.0$). Presumably, this was due to the wide lipid “gorge” in the SC (Fig. 1), which creates a favorable rapid pathway for lipophilic substances.

There is currently debate regarding whether chemicals penetrate the skin primarily (or solely) via the highly tortuous intercellular (lipid) route, or if there exists in addition a transcellular route that includes both lipids and corneocytes.⁽²²⁾ The current model assumes *a priori* that a transcellular pathway is possible, but makes no assumptions regarding the relative importance of these two routes. This feature is one of the values of the modeling approach developed here—it can provide insight into possible mechanisms rather than have a particular mechanism imposed on it. It is noteworthy that the parameter values for coefficients of Equation (6) determined by regression analysis (a and b in Table II) indicate more favorable corneocyte partitioning over lipids. For $\log K_{ow}$ of 0, the model predicts over 200x chemical concentration in corneocytes compared with lipids. This prediction is contrary to currently held opinion that chemicals diffuse primarily via the lipid pathway (e.g., Reference 22) and warrants further investigation.

The shapes of the surfaces of $\log D^*$ (Fig. 3) and l^* (Fig. 4) are intuitively appealing. Consider first $\log D^*$. For $\log(D_{cor}/D_{lip}) = 0$, diffusivity within corneocytes is the same as that within the lipid phase. Therefore, regardless of chemical preference for either phase ($\log K_{cor_lip}$), molecular mobility will be the same in both phases. Consequently, effective diffusivity D^* will be the same and in fact will be identical to D in a homogeneous membrane. As molecular mobility within corneocytes lessens compared with that in lipids ($\log(D_{cor}/D_{lip}) < 0$), effective diffusivity D^* will be diminished. The extent

of the diminution depends upon lipid-corneocyte partitioning: for favorable corneocyte partitioning, ($\log K_{cor_lip} > 0$), D^* will depend mostly on corneocyte diffusivity. As lipid partitioning becomes more favorable, D^* is dictated mostly by lipid mobility. Equation (14) captures these features, including the asymptotic behavior, as long as $\log(D_{cor}/D_{lip}) \leq 0$.

The shape of the normalized effective path length curve (Fig. 4) is more complex. Consider the limit as $\log K_{cor_lip}$ approaches $-\infty$. The chemical is completely confined to the lipid layers and l^* will equal the average path length along these lipid layers. When $\log K_{cor_lip} = 0$, there is no favorable partitioning and the path length will equal the thickness of the SC. Finally, consider the limit where corneocyte partitioning is completely favored ($\log K_{cor_lip}$ approaches ∞): the chemical is completely confined within the corneocytes. In this case, there is a finite diffusivity, but no permeability (the chemical cannot escape the corneocyte). Hence l^* approaches infinity.

It should be noted that the equation chosen to describe l^* (Equation (12)) does not exhibit this asymptotic behavior. The parameter values derived from Equation (12) are valid only within the limited range of l^* examined. Furthermore, l^* exhibits more complex behavior that is not captured by Equation (12), which is an equation in only one variable ($\log K_{cor_lip}$): there is also some dependence of l^* on $\log(D_{cor}/D_{lip})$. Equation (12) was chosen empirically only because it appeared to be the simplest equation that captures the major features of l^* . Further refinements are certainly possible.

For the purpose of predicting steady-state skin permeability (Equation (10)), values were assigned to the variables D_0^* (Equation (11)) and l_0^* (Equation (12)), which can be considered to be baseline values for D^* and l^* . These were selected as physiologically realistic values, although l_0^* of 30 μm is large even for human SC, which is thicker than mouse SC. Regression of Equation (10) to the permeability data does not require both values to be set. The permeability constant is proportional to the ratio of D^* to l^* (Equation (10)); therefore, the ratio D_0^*/l_0^* can be allowed to be a variable parameter to be fitted. Alternatively, either D_0^* or l_0^* can be set and the other determined by regression. We found that this insignificantly increases R^2 (0.85 vs. 0.84); it was therefore decided to set realistic values for D_0^* and l_0^* as constants.

4.3. Steady-State Permeability

Despite the simplifications made here, regression analysis found parameter values such that 84% of experimental variability for the permeability constant can be explained by the model. The correlation coefficient with the modified Flynn data set, 0.84, is substantially better than that of the Potts and Guy equation (see Appendix) against the same data ($R^2 = 0.68$). The Potts and Guy equation is cited here for comparison because it appears to have become the standard against which more complex QSAR models are judged (e.g., References 23 and 24). Furthermore, the U.S. EPA recommends the use of this equation as the basis for assessment of dermal absorption.⁽²⁵⁾

Fig. 5b shows that the two largest deviations of model predictions compared with measured values occur with the compounds having the largest molecular weights, ouabain ($MW = 599$) and digitoxin ($MW = 765$). It is possible that the simple model described here fails to account for some additional molecular weight dependence of the diffusivity. Experimental evidence for this was given by Johnson *et al.*⁽²²⁾ The molecular weights of these compounds approach that of the lipids comprising SC lamella, and Equation (7) may no longer be valid. More data from compounds with large MW would be desirable.

Wilshut *et al.*⁽⁴⁾ published a comparison of five different mathematical regression models of permeability coefficients as a function of $\log K_{ow}$ and MW . The authors suggested a simple modification of the Potts and Guy⁽¹⁰⁾ equation (see Appendix), which increased R^2 calculated here to 0.73. The authors⁽⁴⁾ showed that the three "best" models, in terms of having the lowest residual variances (equivalent to highest R^2), were the "revised" Robinson model,⁽⁴⁾ the "revised" Potts and Guy model,⁽⁴⁾ and the McKone and Howd model⁽¹⁷⁾ (see Appendix for model equations). Cleek and Bunge⁽¹⁸⁾ presented a model where both steady- and non-steady-state dermal absorption are approximated with algebraic equations. Their steady-state equations have been modified here (Appendix) only to the extent that their published constant coefficients were allowed to be variable parameters whose values were determined by regression. When regressed against the modified Flynn data set, the correlation coefficients for all these models are less than that for the random walk model described herein (Table III). It should be noted that both the modified Robinson and the

McKone and Howd models contain parameters whose values (Table AI) may not be distinguishable from zero ($P > 0.5$).

We conclude that the random walk model is on par with the best current models in terms of its ability to predict permeability coefficients from $\log K_{ow}$ and MW . This may be somewhat surprising, considering that the stratum corneum structure on which the model is based (Fig. 1) was derived from mouse skin, while the permeability data were measured from human skin. This is clearly a weakness of the model, because human SC is thicker than hairless mouse SC and generally is less permeable.⁽²⁶⁾ Apparently, the model contains sufficient degrees of freedom that the parameter estimations are able to accommodate whatever significant differences exist between the two skin types.

4.4. Non-Steady-State Phenomena

A model that correctly predicts steady-state permeability will not, in general, also predict non-steady-state phenomena. This is because, while steady-state permeability depends on the ratio D/l , non-steady-state phenomena depend on the quantity D/l^2 , which cannot be determined without knowledge of both D and l . The model described herein yields separate values for effective diffusivity and effective path length, unlike other permeability models. Therefore, it is possible that this model can be used to predict non-steady-state phenomena. We are currently investigating this potential.

If these concepts (D^* and l^*) are valid, then the numerous analytical solutions to the diffusion equation for a variety of initial and boundary conditions^(3,27,28) become available for the prediction of skin diffusion dynamics. Roberts *et al.*⁽³⁾ in particular give a number of solutions for conditions that are relevant to the area of percutaneous absorption. While most of these solutions are in the form of infinite series and many require the solution of transcendental functions (e.g., Equation (4)), more computationally convenient forms using Laplace transform techniques with numerical inversion, have been described.^(3,29)

4.5. Conclusion

In conclusion, we have presented a mathematical model for skin permeation from an aqueous vehicle that is based on the fundamental molecular mechan-

ism of diffusion and accounts for the structural and chemical heterogeneity of the stratum corneum. We have demonstrated its ability to account for steady-state skin permeability measured from a diverse set of chemicals, and we suggest its potential for the prediction of non-steady-state diffusion phenomena. The model should prove useful in providing insight into the mechanisms underlying chemical permeability through skin and as a predictive model—*within the limits of applicability described herein*—where skin permeability measurements are lacking. Further refinements to the model are possible and are currently under consideration.

APPENDIX: EQUATIONS OF FIVE CORRELATION MODELS OF SKIN PERMEABILITY

Only the equations are presented here; for derivations, the reader should consult the citations. c_i s are regression parameters to be fitted. Values are presented in Table AI.

1. Potts and Guy:^(4,10)

$$\log k_p = c_1 + c_2 \log K_{ow} + c_3 MW$$

2. Modified Potts and Guy:⁽⁴⁾

$$\log k_p = c_1 + c_2 \log K_{ow} + c_3 \sqrt{MW}$$

3. Cleek and Bunge:⁽¹⁸⁾

$$k_p = \frac{k_{lip}}{1 + k_{lip} \sqrt{MW}/2.6}$$

with

$$\log k_{lip} = c_1 + c_2 \log K_{ow} + c_3 MW$$

4. McKone and Howd:^(4,17)

$$k_p = MW^{c_1} \left[c_2 + \frac{0.0025}{c_3 + c_4 K_{ow}^{c_5}} \right]^{-1}$$

5. Modified Robinson:⁽⁴⁾

$$k_p = \left[\frac{1}{k_{lip} + k_{pol}} + \frac{1}{k_{aq}} \right]^{-1}$$

with

$$\log k_{lip} = c_1 + c_2 \log K_{ow} + c_3 \sqrt{MW}$$

$$k_{pol} = c_4 / \sqrt{MW}$$

$$k_{aq} = 2.5 / \sqrt{MW}$$

Table AI. Parameter Values for Five Correlation Models

Model	Model Parameter				
	c_1	c_2	c_3	c_4	c_5
Potts and Guy	-2.811	0.635	-0.005	—	—
Modified Potts and Guy	-1.526	0.688	-0.181	—	—
Cleek and Bunge	-2.32	0.574	-0.005	—	—
McKone and Howd	-2.404	$-5 \times 10^{-6**}$	-0.089*	0.393*	0.500
Modified Robinson	-1.286	0.620	-0.159	$1 \times 10^{-10**}$	—

Notes: Units are such that $k_p = \text{cm/hr.}$; $P > 0.2$. **: $P > 0.5$. $P =$ probability that the parameter value does not differ from zero.

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