Mathematical Models of Skin Permeability: An Overview

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Abstract

Mathematical models of skin permeability play an important role in various fields including prediction of transdermal drug delivery and assessment of dermal exposure to industrial chemicals. Extensive research has been performed over the last several decades to yield predictions of skin permeability to various molecules. These efforts include the development of empirical approaches such as quantitative structure-permeability relationships and porous pathway theories as well as the establishment of rigorous structure-based models. In addition to establishing the necessary mathematical framework to describe these models, efforts have also been dedicated to determining the key parameters that are required to use these models. This article provides an overview of various modeling approaches with respect to their advantages, limitations and future prospects.

Key words: Transdermal, Stratum corneum, Permeability, Model, Theory. Mathematical, Exposure assessment

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1. INTRODUCTION

Mathematical models of skin permeability are highly relevant to the fields of transdermal drug delivery, assessment of dermal exposure to industrial and environmental hazards as well as in developing fundamental understanding of biotransport processes. The impact of such models on transdermal drug delivery has been particularly significant. Transdermal delivery provides an appealing alternative to other modes of drug administration. Transdermal patches, introduced first in the United States in 1979 for scopolamine delivery, are now available for a total of 19 drugs. Between 2003 and 2007, new transdermal delivery systems were introduced at a remarkable pace; one every 7.5 months (Prausnitz & Langer 2008). Expanding the scope of transdermal drug delivery to a wide range of drugs, however, has proved to be a significant challenge. Skin has evolved to provide a highly effective barrier for the permeation of xenobiotics and loss of water (Scheuplein & Blank 1971b). This has made it very challenging to deliver drugs across the skin. The outermost layer of skin, the stratum corneum (SC), is primarily composed of terminally differentiated keratinocytes (corneocytes) embedded in lipid layers (Elias 1983). The unique organization of the SC, in particular its lipid components, offers a substantial barrier to drug delivery and absorption of toxic substances (Potts et al 1991).

While major advances in our understanding of the fundamental mechanisms underlying skin permeation have been made in the past 70 years, topical and transdermal drug delivery has been practiced since ancient times. The Ebers papyrus, dating to 1550 B.C., offers numerous remedies and formulations for the management of skin conditions (Bryan 1930.). There are also reports of “flying ointment” in the historical literature where preparations containing

hallucinogenic substances were formulated in lipophilic bases (Rudgley 1993.). Such preparations were intended to be applied on a broomstick held between the legs, indicating an early knowledge of the importance of the formulation, site variation in permeability and the ability to achieve systemic effects using preparations applied to the skin.

The foundations of predictive modeling of transdermal and topical delivery were laid in the 1940's to 1970's. During this time it was recognized that partitioning and solubility were important factors that determine skin penetration. In the early 40's Rothman identified the importance of the physicochemical properties of the permeant such as solubility and the critical influence of the vehicle on permeation (Rothman 1943). In the mid 1950's Hadgraft and Somers observed that solutes with a balanced partition coefficient, that is, those that possess a log [octanol-water partition coefficient, *P*] between 1 and 3 are associated with optimum skin permeation (Hadgraft & Somers 1956). In the 1950's and 1960's efforts to understand how the skin permeation process could be predicted in a systematic manner were largely driven by the chemical defense industry (Treherne 1956; Tregear 1966.).

With the recognition that the transport processes in skin can be described by Fick's first law, Higuchi derived mathematical models that describe percutaneous absorption as a passive diffusion process in the vehicle and the membrane layers in series (Higuchi 1960). Using basic physicochemical principles, his seminal contributions also demonstrated the importance of the thermodynamic activity of the penetrating agent in permeation. Higuchi then built upon this model to lead to another seminal paper, published in 1961, entitled "Rate of release of medicaments from ointment bases containing drugs in suspension". This paper provided an

elegant set of equations to describe the rate of release of drugs from an ointment (Higuchi 1961). The resultant equations, which describe fundamental relationships between release rates, drug concentrations, diffusion coefficients and lag times, lay the foundation of the modern theories of skin permeation. The role of physical chemistry in the percutaneous absorption process was further emphasized by Blank and Scheuplein (Blank 1965; Blank et al 1967; Blank 1967; Scheuplein et al 1969; Scheuplein & Blank 1971a). Since then, a large number of efforts have been dedicated to describe various aspects of skin permeation. These models vary tremendously in scope, ranging from simple models that consider the SC (or sometimes the entire skin) as a single compartment to those that explicitly consider the structural complexity of the skin (e.g., the lipids, the corneocytes, or the keratin within the corneocytes).

This review summarizes the key developments in predictive modeling of skin permeation over the last 50 years and also looks to the future so that such approaches are effectively harnessed for the development of better topical and transdermal formulations and for improved assessment of skin exposure to toxic chemicals.

2. STEADY-STATE MODELS

The fundamental equation to describe skin transport under steady-state conditions when a skin membrane is exposed to a solute on one side can be given by Fick's first law. It simply relates the amount of solute, Q, crossing the skin membrane of area, A, over a time period, T, with the constant concentration gradient across the two interior surfaces of the skin, ΔC_s, the diffusion coefficient in the skin membrane, D, and the path length, h, as follows:

$$Q = DAT\Delta C_s/h \quad [1]$$

The fundamental assumptions of Eq. 1 are that the skin barrier, SC, behaves like a pseudo-homogenous membrane, and that its barrier properties do not vary with time or position. It is important to recognize that steady state can only be reached after the lag time for solute diffusion, which, for diffusion across a homogenous membrane is given by $h^2/6D$, has passed. The lag time can be estimated from the x-intercept of the linear portion of the plot depicting cumulative solute permeation as a function of time. Equation 1 is frequently expressed in terms of steady-state skin flux, J_{ss}, defined as:

$$J_{ss} = Q/(AT) = D\Delta C_s/h \quad [2]$$

Higuchi, in his forward looking article, expressed this flux more appropriately in terms of thermodynamic activity a_s rather than widely used concentration approximation (Higuchi 1960). Clearly, the maximum flux, J_{max}, will be seen when maximum solubility S_s of a solute in the SC is achieved, so that Eq. 2 can be written as:

$$J_{max} = DS_s/h \quad [3]$$

The thermodynamic activity for any given solute is generally defined by the fractional solubility of the solute in the skin (C_s/S_s). However, nonlinearity can arise as a result of solute-skin and solute-vehicle non-ideal interactions (Roberts MS 2002). In practice, such non-idealities are less likely at lower concentrations and it is more convenient to express concentrations in terms of the solute concentration in the vehicle (C_v) and a partition coefficient, K, of the solute between the skin and the vehicle as follows:

$$J_{ss} = KD\Delta C_v/h \quad [4]$$

Where $K = C_s/C_v$. In this section, we apply and further develop these principles to demonstrate the predictive value of mathematical models of skin permeability in defining the absorption of therapeutic and toxic compounds through the skin.

2.1 Quantitative structure-permeation relationship (QSPR) models

Since the ground-breaking work of Scheuplein and Blank (Blank et al 1967; Blank 1967; Scheuplein 1967; Scheuplein & Blank 1971b), who were the first to properly quantify the rate and extent of percutaneous absorption of diverse chemicals, mainly from aqueous solutions, considerable efforts have been devoted to the establishment of relationships between the molecular properties of solutes and skin permeation (Geinoz et al 2004). The objectives of such work have been broad, ranging, for example, from the identification and screening of potential drug candidates for transdermal delivery (Hadgraft 2003) to the assessment of potential risk following dermal exposure to hazardous chemicals, such as pesticides (Bouwman et al 2008).

The main focus of quantitative structure-permeation relationships (QSPRs) has been the assessment of a permeability coefficient (usually designated by k_p) which is defined as the steady-state flux of chemical across the skin (J_{ss}) normalized by the concentration gradient, ΔC_v:

$$k_p = \frac{J_{ss}}{\Delta C_v} \qquad [5]$$

Often the concentration of the chemical is essentially zero on one side of the skin and k_p is then the ratio of J_{ss} and C_v. By describing the skin as a single pseudo-homogenous membrane, it can be easily shown from Eq. 5 that k_p is defined as (Crank 1975):

$$k_p = \frac{K \cdot D}{h} \qquad [6]$$

By assuming that the SC is the rate limiting barrier, which is often the case, and by using *h* as the thickness of the SC, then *K* and *D* in Eq. 6 describe the partitioning and diffusion in the SC treated as a pseudo-homogeneous membrane.

Knowledge of k_p, coupled with the chemical's saturation solubility in the vehicle in which it contacts the skin ($C_{v,sat}$), permits an estimation of the maximum flux (J_{max}) of the molecule across the barrier:

$$J_{\max} = k_p \cdot C_{v,sat} \qquad [7]$$

When applying Eq. 7, it is important to note that k_p and $C_{v,sat}$ must be determined in the same vehicle; one cannot combine an aqueous k_p with a non aqueous $C_{v,sat}$. Clearly, J_{max} is an inherently more useful and practical parameter when evaluating the potential therapeutic benefit or toxicological risk of a topically or transdermally absorbed substance (Kroes 2007).

The vast majority of QSPR models provide algorithms to calculate k_p when the vehicle is assumed to be aqueous. This has happened for two principal reasons: First, over time, a substantial database of experimentally determined k_p values from aqueous vehicles has built up, allowing theoretical predictions to be directly compared with real measurements. Second, a physicochemical parameter that enables estimation of *K* is likely to be necessary for utilizing any algorithm developed for the calculation of k_p. The most obvious candidate in this regard is the octanol-water partition coefficient, *P*, values of which for many thousands of chemicals are available in the literature (or readily calculable using any number of approaches) (Leo et al 1971; Sangster 2010).

A combination of Eqs. 6 and 7 gives a more fundamental definition of J_{max} based on the permeant's solubility and diffusion coefficient in the SC:

$$J_{\max} = \frac{D}{h} \cdot C_{SC,sat} \qquad [8]$$

The limitation of Eq. 8 is that D/h and $C_{SC,sat}$ are not easily determined by experiment. Instead, Kasting *et al.* (Kasting 1992) provided two insightful steps to render the expression much more useful. First, it was proposed that $C_{SC,sat}$ might either be calculable from ideal solution theory, or estimated from the saturation concentration in model lipid solvents that mimic the SC, such as octanol or isopropyl myristate (C_{org}). Second, given that the lipids of the SC are highly ordered, the diffusional barrier was treated as a semisolid, like a polymeric membrane. Molecular transport was then considered to proceed via a 'free volume' mechanism, permitting the SC diffusivity to be modeled by Eq. 9 (Potts & Guy 1992):

$$D = D_0 \cdot \exp(-\beta \cdot V) \qquad [9]$$

where V is the molecular volume of the permeant, and D_0 and β are constants. With these modifications, Eqs. 8 and 9 could then be combined to produce a QSPR (Eq. 10) that is in good general agreement with experimental results (**Figure 1**)(Cooper 1987).

$$\log(J_{\max} / C_{org}) = \log(D_0 / h) - [\beta \cdot V / 2.303] \qquad [10]$$

Potts and Guy (Potts & Guy 1992) built upon this line of thinking and combined Eqs. 6 and 9 to give an expression for k_p as follows:

$$\log k_p = \log(D_0 / h) + \log K - [\beta \cdot V / 2.303] \qquad [11]$$

which they then wrote more generally as:

$$\log k_p = a + b \cdot \log P - c \cdot MW \qquad [12]$$

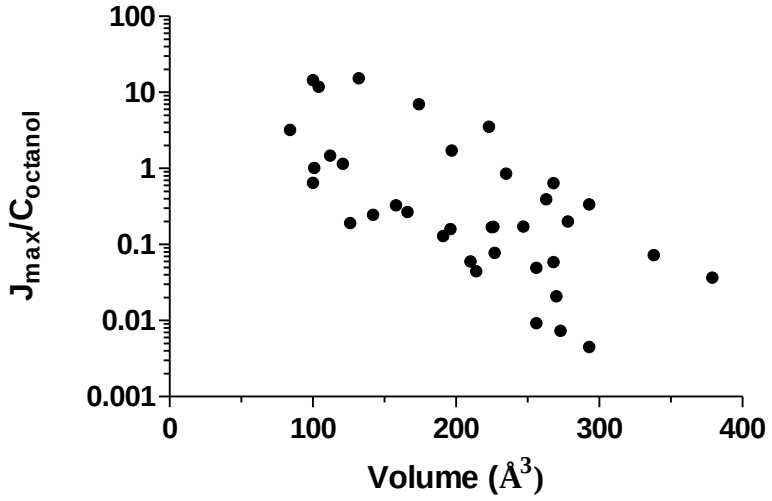

Figure 1: Experimentally determined maximum fluxes of chemicals normalized by their respective octanol solubilities plotted as a function of molecular volume (redrawn from (Cooper 1987)).

Key assumptions made while deriving Eq. 12 are that the SC-water partition coefficient could be replaced by a function of *P* and that molecular volume could be approximated by the chemical's *MW* (Potts & Guy 1992). Values of *P* are available for many thousands of chemicals in the literature or can be readily estimated using a number of approaches (Leo et al 1971). Potts and Guy then took advantage of a large compilation of published skin permeability coefficients from aqueous solution (Flynn 1990) to generate a QSPR that is now the most cited and applied QSPR model for predicting skin permeability:

$$\log k_p = -6.3 + 0.71 \log P - 0.0061 MW \qquad [13]$$

where the units of k_p are $cm \cdot s^{-1}$. The experimental values used to derive Eq. 13 encompassed chemicals with *MW*s ranging from 18 to over 750 and *log P* values from -3 to +6. The r^2 of the multiple regression was 0.67 suggesting that approximately two thirds of the variability in the

data was explained by the model. In writing Eq. 13, the rate-limiting transport barrier of the skin is implicitly assigned to the lipophilic SC and, as a result, it will generate unfeasible values of k_p for compounds that are extremely lipophilic. Acknowledging that the percutaneous absorption of such molecules is controlled by the underlying, more-aqueous-in-nature, viable epidermis (as had been deduced much earlier (Michaels et al 1975)), Cleek and Bunge (Cleek & Bunge 1993) derived an expression for estimating k_p that places an upper limit for highly lipophilic species:

$$k_p^{adj} = \frac{k_p}{1+\left(1400 \cdot k_p \cdot \sqrt{MW}\right)} \qquad [14]$$

where k_p is the permeability coefficient predicted by QSPRs for the SC from a water vehicle (with units of cm s^{-1}); for example, from Eq. 13. Comparison between experimental percutaneous absorption fluxes and those calculated using the Potts and Guy algorithm and the Cleek and Bunge adjustment is illustrated for 14 compounds in **Figure 2** (Guy 2010).

Several QSPRs have been proposed that build on the form of Eq. 13 (Abraham et al 1997; Abraham et al 1999). For example, the partition coefficient, *K*, can be more explicitly represented in terms of the compound's molecular volume, polarisability, hydrogen bond donor and acceptor activities and molar refractivity. Incorporating such additional sophistication can result in improved fits of the model to (typically) more limited datasets (Potts & Guy 1995). Additionally, QSPR equations with complicated molecular structure descriptors offer the potential for better mechanistic understanding. However, some of the literature k_p values used in these regressions may be anomalous (Degim 1998) or inconsistent with measurements from other laboratories (Vecchia & Bunge 2002b). Also, the ionization state of the compound in the

aqueous solution often is unclear, which will impact the permeability coefficient (k_p) calculated from the flux data. When these factors are combined with the inherent variability in experimental measurements of skin permeation (Southwell 1994), especially for those chemicals that penetrate poorly (typically molecules with low lipophilicity and/or high *MW*), the introduction of more complicated molecular structure descriptors often cannot be justified from a statistical point of view. Moreover, regression to more complex models may provide misleading mechanistic insight and over-interpretation of the data (Geinoz et al 2004).

Periodically, several of the published QSPRs have been comprehensively reviewed (Lian et al 2008). A detailed examination of 33 QSPRs was conducted in 2008 (Bouwman et al 2008) using a set of defined criteria for acceptability, which was met by four models (ten Berge ; McKone 1992; Moss & Cronin 2002; Magnusson et al 2004b); three of these were based upon the octanol-water partition and molecular weight. Notably, the substitution of *MW* for *V* in QSPR equations succeeds because *MW*/*V* is nearly constant (at approximately 0.9 g/mL) for most compounds (mostly hydrocarbons) in the databases used to develop the various QSPR equations (Vecchia & Bunge 2002b). However, using these QSPR equations for chemicals with significantly larger *MW*/*V* (e.g., halogenated chemicals) produces k_p estimates that are systematically low, but can be readily improved by adjusting the *MW* by the liquid density divided by 0.9 g/mL (Vecchia & Bunge 2002b). For example, using the adjusted *MW* of 63 for dibromomethane in (*MW* = 174, specific gravity = 2.497) in the QSPR equations provided better k_p estimates.

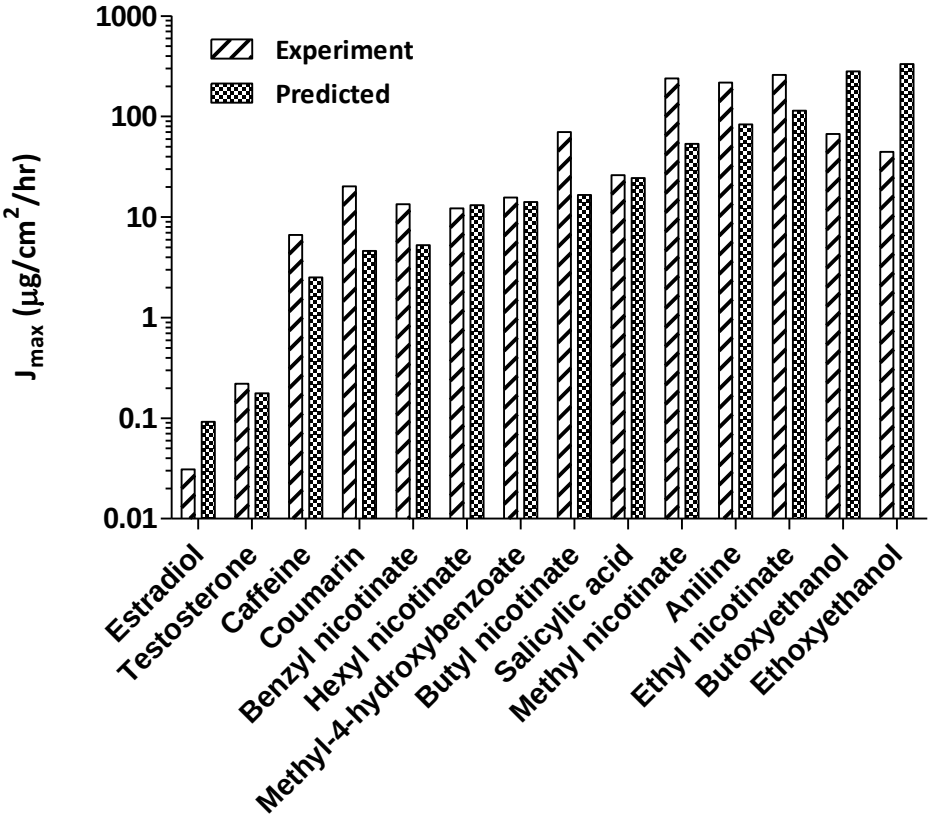

Figure 2: Comparison between experimental J_{max} values of various chemicals and those predicted using the Potts and Guy algorithm (Eq. 13) and corrected with the Cleek and Bunge equation (Eq. 14). The ratios of measured to theoretical values fall within the range 0.13 to 4.49; that is, well within an order of magnitude of the 'ideal' value of 1 (Guy 2010)**.**

While a majority of QSPR models try to predict k_p, it is the J_{max} that is a more practically relevant parameter. It can be estimated using experimental values of the aqueous saturation concentration along with k_p calculated from a QSPR model for an aqueous vehicle. Alternatively, a quantitative structure-activity model can be used to predict values for $C_{v,sat}$ that are used in Eq. 7. Using a third strategy, Magnusson *et al*. developed a QSPR model for J_{max}, rather than k_p. (Magnusson et al 2004a) Interestingly, in this approach log *P* becomes a less significant parameter compared to that in k_p-based QSPR models, and *MW* alone is sufficient to describe the bulk of the chemical-specific variation in the data. In later work, Zhang *et al*. showed that J_{max}

does show a parabolic, or even better, a bilinear relationship with lipophilicity for similar sized solutes (Zhang et al 2009). They showed that the relationship reflected the variation in stratum corneum solubility for the various solutes and that the diffusion constant was relatively constant across the series.

Research into the development of improved QSPRs continues. The strategies employed have sometimes been quite novel, and have brought new tools to bear on the problem. Such approaches include chemical structure-based approaches, for example, fragment descriptor and neural network-based modeling approaches using large pools of theoretical molecular descriptors (Katritzky et al 2006; Baert et al 2007; Luo et al 2007; Neely et al 2009), ensemble modeling using nearest-neighbor theories (Neumann et al 2006), topostructural, topochemical, shape and/or quantum mechanical indices (Basak et al 2007) and Gaussian process models (Lam et al 2010). Such approaches, though novel, have yet to find significant, "real-world" application.

While acknowledging that QSPRs are of enormous benefit, it must be realized that they have certain limitations. Perhaps most notably, they cannot be used when formulation components modulate the barrier properties of the skin. Extrapolation of the predictions from simple aqueous solutions to complex multi-component and/or multiphasic formulations is elusive and may be unachievable in some cases, although strategies that utilize experimental measurements of partial pressure (or other measures of thermodynamic activity) combined with maximum flux estimates show promise (Kurihara-Bergstrom et al 1986; Frasch 2010).

2.2. Structure-based models

Steady-state solute flux across the SC can be described by Eq. 2. This equation adequately describes diffusion across a homogeneous medium. Hence, as long as the corresponding parameters (diffusion coefficient, partition coefficient and diffusion length) are averaged over the entire SC and the microtransport processes within the SC are rapid compared to diffusion across the membrane (Brenner & Edwards 1993), Eq. 2 adequately describes permeation across the SC. In reality however, the structural heterogeneity of the SC and the likely presence of slow reversible binding phenomena make it immediately clear that such averaging, in spite of offering mathematical simplicity, does not always accurately represent the diffusion process in the SC. Accordingly, efforts have been put forth to account for the structural complexity of skin.

The SC consists of several layers of corneocytes (the bricks) with the space between them filled with lipids (the mortar), organized in the bilayer form. In one extreme scenario, it is assumed that the solute diffuses exclusively through the lipid region of the SC, which is the only continuous phase in the SC. This assumption is particularly applicable for highly lipophilic compounds, which partition almost completely into the lipid regions of the SC. Initial efforts to account for structural details of skin using mechanistic "brick-and-mortar" models were described by (Chandrasekaran et al 1978). Since lipids occupy only a small fraction of the SC area, the actual area available for diffusion is much smaller than the macroscopic skin area. Furthermore, permeants have to follow a tortuous path around the corneocytes to cross the SC (Figure 3). Taking this into consideration, the steady-state permeability of the SC can be expressed as follows:

$$k_p = \frac{\alpha D_{lip} K_{lip}}{h_{lip}} \qquad [15]$$

where, D_{lip} is the solute diffusion coefficients in the SC lipid bilayers, K_{lip} is the solute partition coefficient between the SC lipid bilayers and the vehicle and h_{lip} is the effective diffusion path length of the permeant in the SC lipids, which is longer than the actual thickness of the SC and α accounts for the fact that only a small fraction of the SC is occupied by lipids. The challenge is now shifted to determination of the parameters in Eq. 16. Numerous efforts have been dedicated towards this goal. A summary of these efforts is provided in section 4.

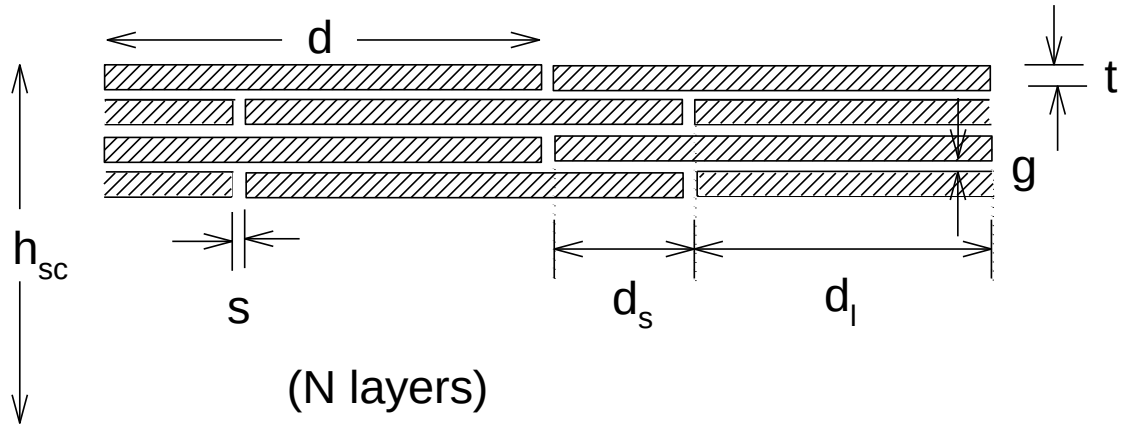

Figure 3. Schematic diagram for a brick-and-mortar model of the SC redrawn from (Johnson et al 1997a). Key model parameters are the corneocyte aspect ratio, $\alpha = d/t$; the lipid/corneocyte thickness ratio, $\beta = g/t$; and the offset ratio, $\omega = d_l/d_s$.

In reality, however, solutes may be able to enter the corneocytes and their diffusion through the corneocytes may contribute substantially to the overall permeation. Models have also been developed to allow solute diffusion through corneocytes (Nitsche et al 2006b; Wang et al 2006b; Wang et al 2007). These models, however, add considerable complexity to the calculation. They require additional parameters including diffusion and partition coefficients in the corneocytes, diffusion path length in corneocytes and mass transfer rate from lipids into corneocytes. Addition of this complexity to the model is justified when diffusion through conrnocytes contributes substantially to the overall permeability of the SC. In principle, the

possibility of solute penetration into corneocytes can be incorporated into the model by using a generalized equation to describe SC permeability as follows:

$$k_p = \frac{D_{SC} K_{SC}}{h_{SC}} \qquad [16]$$

where, D_{SC} is the average diffusion coefficient in the SC, K_{SC} is the average partition coefficient in the SC and h_{SC} is the average diffusion path length in the SC. This simplification again requires that the premises of effective medium theory are satisfied, notably that the microtransport and binding processes are much more rapid than macroscopic diffusion. Structural features of the SC can then be incorporated into the model by determining K_{SC} as the spatially-averaged value of partition coefficient in lipids and corneocytes (discussed in section 4). This, in combination with appropriate solution of the microtransport problem (also discussed in section 4) provides a numerical value of k_p from which an effective value of D_{SC} can be calculated. Wang *et al*. provided such an algorithm to determine the magnitude of the contribution offered by solute penetration into the corneocytes (Wang et al 2006b).

2.3. Porous Pathway model

In general, equations based on permeation through lipids adequately describe the permeation of lipophilic drugs across the SC; however, their applicability to hydrophilic drugs may be inappropriate. Accordingly, attempts have been made to develop models to describe the transport of hydrophilic molecules. Similar attempts made by virtue of the QSPRs were described in section 2.1. Here, we describe additional considerations.

Appendages (hair follicles and sweat ducts) are a likely pathway for permeation of hydrophilic solutes. Analysis of solute permeation through appendages has been reviewed in the literature (Meidan et al 2005) and is not discussed in detail here. However, appendages are unlikely to explain the entire transdermal transport of hydrophilic solutes. The average density of hair follicles in human skin is about 50-100 per cm^2 (Walters & Roberts 202; Scheuplein & Blank 1971b) and the area fraction occupied by the follicles is about ~10^{-3}. The majority of hair follicle area is occupied by the hair shaft. The sweat glands occupy an area fraction of about 10^{-4} (number density of 100-200 per cm^2). Assuming a solute diffusion coefficient through appendages of ~10^{-6} cm^2/s and an available area fraction of appendages of 10^{-4}, the contribution of appendages to skin permeability is of the order of 10^{-6} cm/hr (Simmonin 1995). However, many hydrophilic solutes permeate skin at a much faster rate (Mitragotri 2003a).

Ghanem and Peck introduced a model termed as porous pathway model to address this challenge (Peck et al 1994b). Several studies have subsequently built upon this model (Hatanaka et al 1990; Kim et al 1992; Morimoto et al 1992; Ruddy & Hadzija 1992; Dinh et al 1993; Yoshida & Roberts 1993; Peck et al 1994a; Lai & Roberts 1998, 1999). The general expression for permeability based on the porous pathway, k_p of a hydrophilic permeant is given by:

$$k_p = \frac{\varepsilon D_p^{pore}}{\tau \Delta x} \qquad [17]$$

where ε, τ, and Δx are the porosity, tortuosity, and thickness of the membrane, respectively, and D_p^{pore} is the diffusion coefficient of the permeant in the liquid-filled pores within the membrane. According to the hindered transport theory, D_p^{pore} is a function of both the permeant and the

membrane characteristics. D_p^{pore} was expressed as a product of the permeant diffusion coefficient at infinite dilution and permeant diffusion hindrance factor (Tang et al 2001a), which depends on the pore size. A number of reports of estimated pore size can be found in literature, all of which are based on hydrodynamic hindered transport theory (Deen 1987). Pore radii reported by various researchers typically range from 10-30 Å (Ruddy & Hadzija 1992; Yoshida & Roberts 1992; Dinh et al 1993; Yoshida & Roberts 1993; Peck et al 1994a; Li et al 1997; Higuchi et al 1999; Manabe et al 2000; Tang et al 2001b; Tezel et al 2002; Polat et al 2010; Polat et al 2011). Tezel et al. reported that the pore size has a distribution and more than 99% pores possessed a radius smaller than 100 Å (Tezel et al 2003). A few estimates of SC porosity and pore density have been reported in the literature, all of which are based on model calculations and range from 10^7-10^9 pores cm^{-2} (Pikal 1990; Kontturi & Murtomaki 1994; Mitragotri 2003b). The resultant simplified, approximate equation describing skin permeability to small hydrophilic solutes based on porous pathway theory can be given by the following:

$$k_P \approx 1.2\times10^{-2}\exp\left(-1.5r\right) \qquad [18]$$

where, r is solute radius in Angstroms and k_p is in cm/hr. Incorporation of porous pathway to describe transient permeation through skin has also been performed (Kushner et al 2007). In spite of success in describing the permeability of highly hydrophilic solutes, the use of the porous pathway theory to describe solute permeation has proved controversial largely due to lack of a connection between pores and skin structure. Specifically, relationships between estimated pore radii and pore densities and skin morphology have not been demonstrated.

3. TRANSIENT MODELS

The previous section emphasized steady state permeability across a membrane beyond the diffusion lag time (Eq. 2). In this section, we examine the time dependency of skin penetration and the various models used to describe them.

3.1. Basic models

The fundamental equation describing transient drug diffusion across the SC is given by Fick's second law as follows:

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial x^2} \qquad [19]$$

where C is the concentration of the permeating solute at time t at depth x within the skin. Key assumptions of Eq. 19 that are (a) the SC behaves like a pseudo-homogenous membrane, and (b) the diffusion coefficient and partition coefficient do not vary with time or position. To solve Eq. 19, the starting concentration C within the SC as well as the conditions for concentration or flux at the boundaries of the SC (i.e., at the outermost and inner most surfaces of the SC) must be specified. It is more convenient to modify Eq. 19 in terms of concentrations in the vehicle, as defined by a partition coefficient K of the solute between the skin and the vehicle. Accordingly, the partition coefficient K, which is absent in Eq. 19, will usually appear in one or both of the boundary conditions. Different solutions are obtained for different starting values of C and the boundary conditions. The parameters such as D and K required to solve Eq. 19 are generally the same as those discussed in section 2.2 and are discussed in section 4. Mathematical challenges associate with finding solutions are discussed in section 5.

3.2 Compartment models

Compartment models, also called pharmacokinetic (PK) models of skin, are often used to study the fate of chemicals entering and leaving the body. In combination with pharmacodynamic models relating concentration to the desired health effect, these PK models are potentially useful tools for risk assessments and predictions of transdermal drug delivery. These models treat the skin and also the body as one or several well-stirred compartments of uniform (average) concentration that act as reactors and/or reservoirs of chemical storage with transfer between the compartments depicted by first-order rate constant expressions. While permeation across the skin can be described using Eq. 19, it is often represented in a PK model as either a series of compartments to mimic the partitioning and diffusion processes in the stratum corneum or as one compartment and two compartments that separately distinguish the lipophilic SC and hydrophilic viable epidermis layers of the skin (Roberts & Anissimov 2005). A differential mass balance of chemical in the one-compartment skin layer produces the following equation:

$$V_{\text{skin}} \frac{\mathrm{d}\langle C_{\text{skin}} \rangle}{\mathrm{d}t} = k_1 \, C_{\text{v}} - k_{-1} \langle C_{\text{skin}} \rangle - k_2 \langle C_{\text{skin}} \rangle + k_{-2} \, C_{\text{b}} \qquad [20]$$

where $\langle C_{\text{skin}} \rangle$ is the position-averaged drug concentration in the skin layer, V_{skin} is the volume of the skin layer, and k_j (j = 1, -1, 2 and -2) are the rate constants describing drug transfer between the vehicle, skin and blood compartments. Variations of the concentration in the vehicle (C_v) and the concentration in the blood (C_b) are described by mass balances for these compartments including links to additional compartments representing the various tissues and metabolic process in the body. The two-compartment model of skin is given by:

$$V_{\text{sc}} \frac{\mathrm{d}\langle C_{\text{sc}} \rangle}{\mathrm{d}t} = k_1 \, C_{\text{v}} - k_{-1} \langle C_{\text{sc}} \rangle - k_2 \langle C_{\text{sc}} \rangle + k_{-2} \langle C_{\text{ve}} \rangle \qquad [21]$$

$$V_{ve}\frac{d\langle C_{ve}\rangle}{dt} = k_2\langle C_{sc}\rangle - k_{-2}\langle C_{ve}\rangle - k_3\langle C_{ve}\rangle + k_{-3}C_b \qquad [22]$$

where $\langle C_{sc}\rangle$ and $\langle C_{ve}\rangle$ are the position averaged concentrations in the SC and viable epidermis, respectively.

The advantage of using compartment models for skin is that the mathematical solution of even complex exposure situations (e.g., periodic exposures and evaporating solutions) combined with variable distribution and metabolism in and elimination from the body as well as variations in blood flow to the skin are represented by first-order differential equations that are easily solved by a number of standard software packages. These models are also simple enough to conduct probabilistic calculations allowing an assessment of the effects of variation in the system parameters.

In many papers with skin compartment models, the rate constants describing transfer to and from the skin compartment(s) have been determined by fitting to experimental data without relating the result to the parameters of skin (e.g., k_p, D, K, and h). Because variations of concentration with position are not described by compartment models, they cannot match all aspects of the behavior predicted by Fick's second law for a membrane with the same physical properties. It follows that different definitions of rate constants in terms of the skin parameters can be developed that match the behavior of the membrane model for different conditions (McCarley & Bunge 1998; Reddy et al 1998; McCarley & Bunge 2000). In a review of several one- and two-compartment models with rate constants expressed in terms of skin parameters, McCarley and Bunge have identified the underlying assumptions (including specified methods for estimating input parameters), and discussed how these affect the model's performance

(McCarley & Bunge 2001). Recently, the effect of the compartment model definitions on dermal absorption prediction was assessed by comparing model predictions with *in vivo* human experiments in which skin absorption of chloroform was determined from breath concentrations (Norman et al 2008).

3.3 Complex models

While most attention in the field of modeling of skin permeation has been focused on describing diffusion processes in the SC, it has been recognized that additional processes including binding and metabolism (Liu et al 1994) also play an important role in determining drug uptake. Binding is especially significant since many substances bind to keratin, which significantly influences their permeation across the SC.

Slow binding/partitioning kinetics in the SC

The effect of binding on transdermal transport in the context of the epidermal penetration has been discussed by Roberts *et al* (Roberts et al 2002), where the kinetics associated with the reservoir effect of the stratum corneum was considered. It was assumed in this work that binding is instantaneous, that is equilibration between bound and unbound states is fast compared to diffusion. The advantage of such an approach is that the modeling in this case is relatively simple with the diffusion coefficient (D) in the diffusion equation being replaced by an effective diffusion coefficient (D_{eff}), where $D_{eff}=f_u D$ and f_u is the fraction of solute unbound. As the fraction unbound is less than unity, binding leads to slower diffusion, and therefore longer lag

times. If binding/partitioning is not fast compared to diffusion, the single diffusion equation has to be replaced by coupled partial differential equations: (Anissimov & Roberts 2009a)

$$\frac{\partial C_u}{\partial t} = D\frac{\partial^2 C_u}{\partial x^2} - k_{on}C_u + k_{off}C_b \qquad [23]$$

$$\frac{\partial C_b}{\partial t} = k_{on}C_u - k_{off}C_b \qquad [24]$$

where C_b and C_u are concentrations of bound and unbound solutes, D is the diffusion coefficient of the unbound solute (bound solute is assumed immobile, or its diffusion is so slow that it can be neglected) and k_{on} and k_{off} are binding and unbinding rate constants. Taking Laplace transform of these equations and expression of $\hat{C}_b$ using $\hat{C}_u$ yields:

$$D\frac{d^2\hat{C}_u}{dx^2} = \left(s + \frac{sk_{on}}{s + k_{off}}\right)\hat{C}_u \qquad [25]$$

It can be noted that the only difference with the simple diffusion equation in the Laplace domain is that s is replaced by a function $g(s)$, where;

$$g(s) = s + \frac{sk_{on}}{s + k_{off}} \qquad [26]$$

Thus equations for the unbound concentration and flux through SC can be obtained by replacing s with $g(s)$ in the above equations. It has been demonstrated (Anissimov & Roberts 2009a) that modeling of penetration experiment is less affected by slow equilibration as compared with that of the desorption experiments. It is also reasonable to assume that experiments with finite donor doses will be significantly affected by slow equilibration, as later stages of the finite donor experiments resemble desorption processes. The slow equilibration in the SC has a pronounced effect in skin reservoir formation and needs further experimental investigation.

Using a physical model approach, Ando and co-workers developed equations to describe situations where simultaneous metabolism and transport of drugs occur in the skin (Ando et al 1977). Two situations were investigated. In the first situation, the drug was placed on the dermis side of a diffusion cell and did not penetrate the stratum corneum. In the second situation, the drug, placed on the epidermis side, penetrated the stratum corneum and then passed through the metabolizing epidermis. Expressions for determining the metabolic rate constant from experimental data along with concentration profiles and flux expressions were derived both for the drug and its metabolite. A model which required computer simulation and which incorporated non-uniform enzyme distributions, as well as composite membranes with many layers was later developed by the same group (Fox 1979).

These models did not consider metabolism in the stratum corneum but mathematical expressions derived by Hadgraft (Hadgraft 1980b) using an idealized physical model, took into account metabolism both in the upper and lower layers of the epidermis. Two routes of penetration were considered, firstly when the drug diffuses straight through the cells and secondly when the substrate passes through the intercellular channels. Hadgraft and Guy expanded the earlier physical model approach described by Hadgraft to incorporate Michaelis-Menten kinetics (Guy & Hadgraft 1982).

Liu and co-workers described a theoretical model to predict permeant transport across the skin for the situations in which there is significant co-transport of an enhancer solvent along with the principal permeant (Liu P 1992). The model successfully predicted the effects of

simultaneous transport of ethanol on metabolism and diffusion of β-estradiol in hairless mouse skin. Bando et al. developed a two-layer diffusion model which incorporates both polar and non-polar pathways and where metabolism in the viable layer was considered (Bando H 1996; Bando H 1997). Assuming first order metabolism kinetics, Laplace transformed equations were obtained to describe skin permeation of drug and metabolite.

Kretsos et al. developed a distributed diffusion-clearance model to take account of the spatial distribution of the vascular processes responsible for drug removal by the dermis (Kretsos et al 2004). This model quantifies molecular diffusion through the heterogeneous skin microstructure of the skin and characterizes vascular clearance as a volume-average clearance coefficient. More recently, a microscopic model describing the dermal capillary clearance process was described by Kretsos and Kasting (Kretsos & Kasting 2007). The model accounts for both convective-dominated transport in the capillaries as well as interstitial diffusion and the model was validated with published results for *in vivo* human skin permeation of hydrocortisone.

4. ESTIMATION OF PARAMETERS

A major issue in quantifying skin penetration and utilization of the models described in section 3 is the assessment of the key parameters defining skin permeability, namely partition coefficient, diffusion coefficient and diffusion path length. In this section, we discuss estimation of parameters that are necessary to predict skin permeability. As can be seen from the discussion so far, the required number of parameters may vary depending on the complexity of the model.

Here, we focus on three key parameters that are most commonly required to predict skin permeability, that is, partition coefficient, diffusion coefficient and path length.

4.1. *Partition Coefficient*

Diffusion through skin involves partitioning between multiple phases; e.g. between the SC lipids and the vehicle, the corneocytes and the vehicle, between the lipids and the corneocytes, and between the SC and deeper skin layers (e.g., the viable epidermis). In simple models describing partitioning into the SC from a vehicle, the multiphasic details of the SC are ignored, and the effective partition coefficient between the SC and the vehicle ($K_{sc/v}$) is estimated from structure-activity algorithms relating experimental measurements of $K_{sc/v}$ to one or more descriptors, *logP* being the most common (for example, see (Cleek & Bunge 1993; Roberts et al 1996) (Surber et al 1990a; Surber et al 1990b)) and the review by (Vecchia & Bunge 2002a):

$$K_{sc/v} = aP^b \qquad [27]$$

Typically, *a* has been reported to be close to 1, while *b* varies from about 0.4 to 0.9 depending on the data set used in the regression. As for the QSPR, the partition coefficient can be represented in terms of more complicated molecular structure descriptors with modest benefit (Vecchia & Bunge 2002a).

Expressions for estimating $K_{sc/v}$ have also been derived that consider the individual contributions of the lipid and corneocytes (Nitsche et al 2006b).

$$K_{sc/v} = \phi_{lip} K_{lip/v} + \phi_{cor} K_{cor/v} \qquad [28]$$

where $K_{lip/v}$ is the lipid-vehicle partition coefficient, $K_{cor/v}$ is the corneocyte-vehicle partition coefficient, and ϕ_{lip} and ϕ_{cor} are the volume fractions of lipid and corneocytes, respectively in the SC, which together sum to 1. In this approach, expressions are then required for $K_{lip/v}$ and $K_{cor/v}$.

Broadly speaking, two factors impact solute partitioning into lipid bilayers; a chemical factor which accounts for the fact that the environment in the lipid bilayers is more hydrophobic than the surrounding aqueous conditions and a physical factor, which accounts for the fact that lipid chains in the bilayer are highly organized, thus reducing the partition coefficient due to low free volumes (Egberts et al 1994; Tieleman et al 1997). The complexity of the physical contributions to partition coefficients has been reported for phospholipid bilayers based on molecular simulations and experimental measurements. For the phospholipids, organization of the lipid tails has been shown to vary substantially with the depth within the bilayer (Egberts et al 1994). Because the chains are more loosely packed near the center of the bilayer, solutes tend to partition preferentially near the bilayer center compared to near the head group (Marrink & Berendsen 1994; Mitragotri et al 1999). Extension of these findings to SC lipid bilayers has been challenging owing to their greater chemical and structural complexity; however recent studies have reported remarkable progress in this direction (Notman et al 2007b; Notman et al 2007a; Notman et al 2008; Das et al 2009). A statistical mechanical theory, called scaled particle theory has been utilized to simplify utilization of molecular details of structures in predicting skin permeability (Mitragotri 2002). This theory revealed that the contribution of physical factors, such as chain packing, is relatively small, especially when compared to the complexity that it adds to the calculations. Consistent with strategies for developing QSPR, it is reasonable to assume that the partition coefficient of a solute from water into SC lipids is comparable to that

into an isotropic solvent that reasonably mimics the chemical environment in the SC lipids. Several solvents including octanol, hexadecane, olive oil, butadiene, and dodecadiene, have been used as model solvents for SC lipids (Raykar et al 1988; Anderson & Raykar 1989; Xiang & Anderson 1994; Johnson et al 1997b; Yamamoto & Liljestrand 2004; Kwon et al 2006; Nitsche et al 2006a), although octanol is the most convenient for reasons discussed earlier (Johnson et al 1996).

After subdividing the corneocyte partition coefficient in Eq. [28] into contributions from water and protein binding (i.e., $\phi_{cor} = \phi_{pro} + \phi_{water}$, where ϕ_{pro} and ϕ_{water} are the volume fractions of proteins and water in the SC assumed to only exist within the corneocytes), Nitsche et al. (Nitsche et al 2006b) derived the following expressions for partitioning from a water vehicle by regressing the octanol-water partition coefficient to a large set of experimental $K_{sc/w}$ data according to the relationship described in Eq. [28] using the following expressions for the lipid-water and corneocyte-water partition coefficients:

$$K_{lip/w} = 0.35 P^{0.81} \qquad [29]$$

$$K_{cor/w} = \frac{5.4 P^{0.27} \omega_{pro} + \upsilon}{\left(\omega_{pro} \rho_{water} / \rho_{pro}\right) + \upsilon} \qquad [30]$$

In Eq. [30], ω_{pro} is the mass of protein per mass of dry SC (assumed to be 0.9), υ is the mass of water in the SC per mass of dry SC (which varies with hydration), and ρ_{water} and ρ_{pro} are the densities of water and protein, respectively. For nearly the same dataset used to derive Eqs. [29] and [30], Vecchia and Bunge (Vecchia & Bunge 2002a) determined a = 0.88 and b = 0.43 for an expression in the form of Eq. [27]. The expressions in Eqs. [29] and [30] can also be used in complex diffusion models of the SC, which require partition coefficients for the lipids and

corneocytes (Wang et al 2006a, 2007). Expressions have been derived to describe solute diffusion in dermis (Ibrahim & Kasting 2010), a topic that is not included in this discussion.

4.2. Diffusion coefficient

Diffusion coefficients in a composite, anisotropic medium like the SC must be carefully defined and judiciously applied. Passive transport across such a medium cannot always be defined in terms of a single diffusion coefficient, either because of the anisotropy or because the conditions for an effective medium description of the material are not satisfied (Brenner & Edwards 1993). The essential condition is that the time frame for equilibration of all microscopic processes must be much shorter than that for bulk transport across the system (Wang et al 2006a). Furthermore, the diffusion coefficient, like the partition coefficient, may change with concentration of the test material (Anissimov & Roberts 2004b), or in response to other chemical or physical perturbation of the system. A recently presented example in which a single diffusion coefficient does not describe transport in the SC is the absorption and desorption kinetics of water (Anissimov & Roberts 2009b). This result was interpreted in terms of slowly reversible binding of water to keratin. The slow kinetics of this process relative to transport times across the tissue preclude the use of effective medium parameters to describe the result. As another example, lateral and transverse diffusion coefficients within the SC are anticipated to have different values due to the anisotropy of the tissue (Wang et al 2006a). This discussion will focus on transverse diffusion across the SC, the problem of greatest interest for most applications.

The most common way to obtain the transverse diffusion coefficient of a permeant in the SC is from experimentally measured steady-state permeabilities in combination with an equilibrium partitioning experiment employing the same vehicle (Eq. 6). Diffusion coefficients so obtained will work when employed in an identical manner, i.e., to estimate steady-state flux across skin from the same vehicle. They are not guaranteed to work for other vehicles or even for transient calculations from the same vehicle, as was shown by Frasch and Barbero (Frasch & Barbaro 2003). This obviously limits their utility. Conversely, and for the same reasons, when diffusivities estimated from the lag time, t_L, of steady-state permeation studies as $h^2/6t_L$ are combined with experimental partition coefficient values, they may not yield accurate steady-state permeabilities. They have the advantage that the partition coefficient need not be known, but they have a disadvantage that experimental variability is high and may be complicated by swelling or shunt diffusion (Scheuplein 1967).

All other estimates of diffusion coefficients in the SC are model-based. They are only as good as the underlying model. Relative to values calculated from Eq. 6, they have the advantage of applying to a broader range of conditions including predictions for new permeants, if the model is valid. This has inspired a great deal of effort to develop such models, a few of which are discussed below. It is important to realize that the more complex models actually calculate flux under various conditions based on an underlying microscopic model. Below, we summarize some of the efforts put forth to describe diffusion coefficients in the SC.

Potts-Guy Model: The Potts-Guy Equation, in its commonly used form, is often referred to as a QSPR model; however the same equation has been rearranged to describe the diffusion

coefficient in the SC. The resultant equation is a model for a homogeneous lipid membrane for which the diffusivity is described using a free volume-like expression (Kumins & Kwei 1968).

$$D_{sc} / h_{sc} = \left(D^0 / h_{sc}\right) \exp(-\beta'' \cdot MW) \qquad [31]$$

where $D^0/h_{sc} = 10^{-6.3}$ cm/s, $\beta'' = -0.0061$ and *MW* is the molecular weight of the permeant. Equation 31 captures the most essential feature of SC diffusivity – it is a strongly decreasing function of the molecular volume (or approximately the molecular weight) of the permeant. The more complex microscopic models developed later in the field retain this essential feature.

Johnson-Blankschtein-Langer Model: Johnson and coworkers (Johnson et al 1997a) proposed that transdermal drug transport was dominated by lateral diffusion in the lipid layers (**Figure 3**). The lipids are anisotropic, but they are arranged such that permeants can travel across the SC without having to cross lipid headgroup regions (c.f. Model 1 in Ref. (Wang et al 2006a)). The corneocyte phase was considered to be impermeable. The lateral diffusion coefficient was estimated by fitting Eq. 6 to experimentally measured skin permeabilities. The diffusion coefficients thus measured compared well to the experimentally measured diffusion coefficients in isolated SC lipids using Fluorescence Recovery After Photobleaching (FRAP) experiments on fluorophores (Johnson et al 1996). These lateral diffusion coefficients exhibit a strong dependence of diffusivity on molecular weight for small permeants and a weaker one for large permeants as derived from Saffman-Delbruck theory for diffusion of proteins in cell membranes (Saffman & Delbruck 1975). The theory captured several aspects of SC diffusion, but required an inordinately long path length through the SC (3.6 cm) to reconcile observed diffusive lag times.

Wang-Kasting-Nitsche model: Wang et al. (Wang et al 2006a, 2007) proposed a composite model of the SC that retained a two-dimensional brick-and-mortar geometry similar to (Johnson et al 1997a), but allowed for a permeable corneocyte phase. Lipids were anisotropic, as in (Johnson et al 1997a), but two arrangements were considered (**Figure 4**).

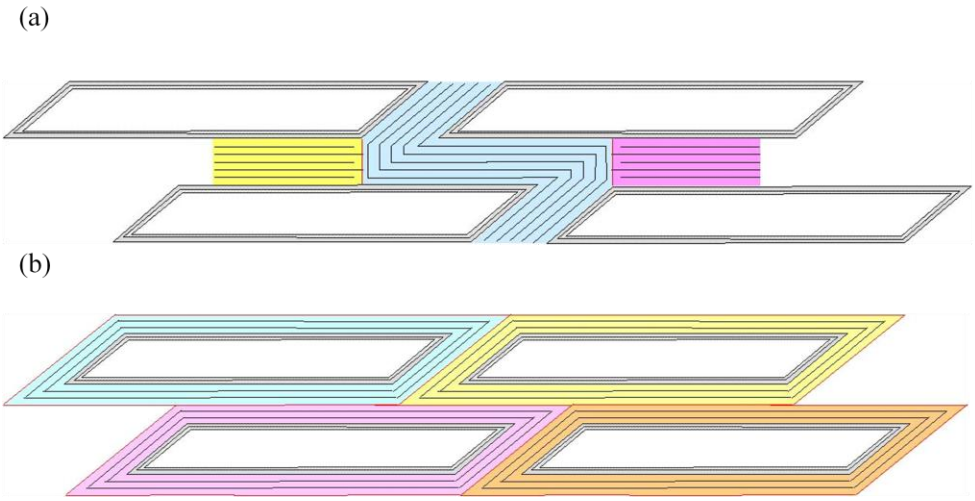

Figure 4. Alternative topologies of the intercellular lipid phase according to Wang et al. (Wang et al 2006a) (a) Model 1, admitting bilayers that continue indefinitely from unit cell to unit cell without interruption. (b) Model 2, in which each corneocyte is completely surrounded by intact lipid bilayers; here progress from one layer of corneocytes to the next requires a transbilayer transport step.

The lipid arrangement in Model 1 was similar to that described by Johnson *et al*. (Johnson et al 1997a), but Model 2 required permeants to cross many headgroup regions in order to traverse the tissue. A further elaboration was the addition of an SC hydration component to the model, so that both partially hydrated and fully hydrated SC could be represented. The model describes three microscopic transport coefficients in the SC: a lateral lipid diffusivity, D_{lat}, a transverse mass transfer coefficient, k_{trans}, for hopping across lamellar bilayers, and an isotropic corneocyte-phase diffusivity, D_{car}. A microscopic partition model is separately described (Nitsche et al 2006b). SC permeability was calculated from a finite difference representation of these models cast in terms of dimensionless parameters R and σ. R is essentially the ratio of transverse to

lateral diffusion rates in the lipids, whereas σ is the ratio of lipid to corneocyte permeabilities. The permeability surfaces calculated by this approach are shown in **Figure 5**. Among the conclusions generated from this approach were that the SC lipids were highly anisotropic, with transverse mass transfer generally much slower than lateral lipid diffusion (Wang et al 2007). Furthermore, most permeants of interest for pharmaceutical or dermal safety evaluation permeated the SC in a predominately transcellular manner (Wang et al 2007).

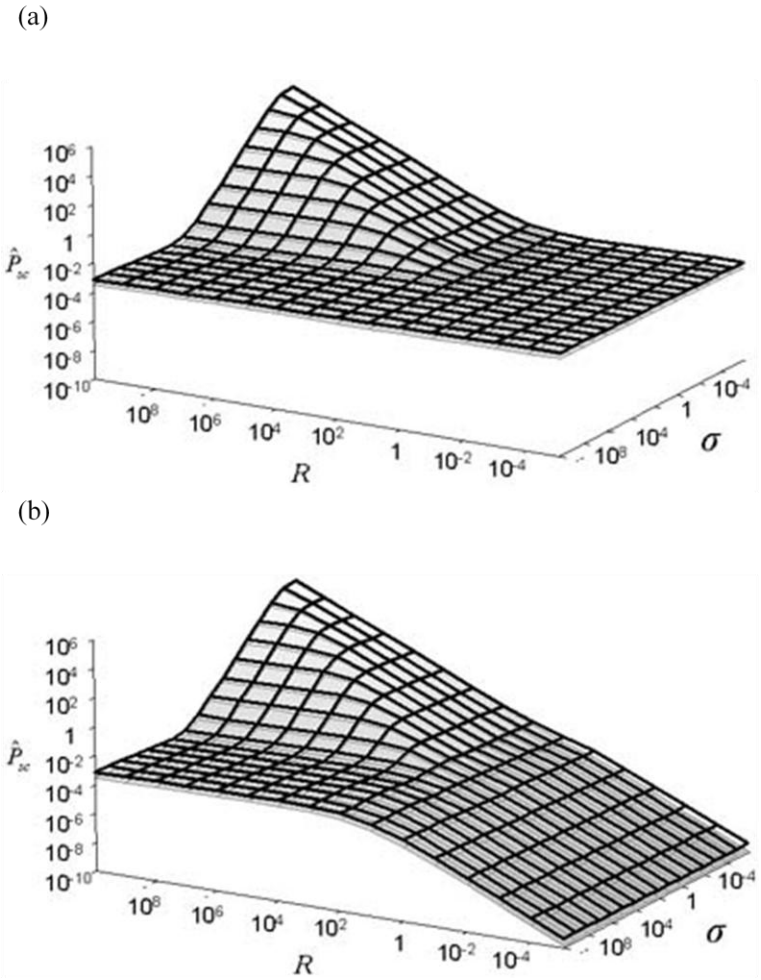

Figure 5. Dimensionless SC permeability surface for the model described by Wang et al. (Wang et al 2007) (a) Model 1 and (b) Model 2. In both parts, the (upper) surface defined by the mesh of thick lines represents swollen (fully hydrated) SC, and the (lower) gray surface with thin lines represents unswollen (partially hydrated) SC. The dimensionless parameters R and σ are described in the text.

Mitragotri Model: Mitragotri put forth an equation to describe solute diffusion in lipid bilayers using Scaled Particle Theory. This statistical mechanical theory allows for solute diffusion in all directions within the lipids (trans- and lateral) and provides an average value. This theory calculates diffusion coefficient based on the amount of work required to create a free volume to allow for solute diffusion. The average diffusion coefficient in the lipid bilayer was given by Eq. 32.

$$D_{lip} = 2x10^{-5} \exp\left(-0.46r^2\right) \qquad [32]$$

where, r is the solute radius in Angtroms and D_{lip} is in cm^2/s.

4.3. Diffusion path length/tortuosity

If the SC lipids comprise the primary route by which permeants enter and cross the tissue, then the geometry of the SC and the detailed arrangement of both corneocytes and lipids makes a great deal of difference in model calculations, as it affects the path length for diffusion. This subject has been discussed extensively since the first development of brick-and-mortar models (Michaels et al 1975); it is a key aspect of lipid pathway models such as (Johnson et al 1997a). If, on the other hand, diffusion is primarily transcellular, then the lipid tortuosity factor is of secondary importance. This is the position presented in (Wang et al 2007). Clearly, as the importance of corneocyte-phase transport is reduced, the impact of lipid tortuosity increases.

A detailed discussion of lipid phase tortuosity has been presented by Frasch and Barbero (Frasch & Barbaro 2003) in their finite element analysis of the SC lipid pathway. They studied transient diffusion through model SC structures including both ordered and disordered corneocyte phases. In this particular analysis, the corneocyte phase was considered to be

impermeable, a restriction later relaxed (Barbero & Frasch 2006). Frasch and Barbero found that diffusion in both the ordered and disordered SC models was well described by a homogeneous membrane model; however, both the effective diffusion coefficient, D^*, and the path length, h_{sc}^*, were different from the input variables. For the ordered structure shown in **Figure 3,** h_{sc}^* is given by:

$$h_{sc}^* = N(d + t + g). \qquad [33]$$

The value of D^* was not expressed so compactly; however, expressions for the flux and lag time relative to a homogeneous membrane having the same microscopic lipid diffusivity D_0 and thickness h_0 were given. The results were:

$$\frac{J_0}{J^*} = 1 + \frac{\alpha\phi}{\sigma} + \frac{\alpha^2\phi^2}{4(1-\phi)} \qquad [34]$$

and

$$\frac{t_{lag^*}}{t_{lag\,0}} = \frac{\sigma(1+\alpha\varphi)}{\alpha}\left(1 + \frac{\alpha\varphi}{\sigma} + \frac{\omega}{(1+\omega)^2}\frac{\alpha^2\varphi^2}{(1-\varphi)}\right) \qquad [35]$$

Here $\alpha = d/t$, $\sigma = s/t$, $\phi = t/(t+g)$ and $\omega = d_L/d_s$. Eq. 33 had been given previously by Johnson *et al*. (Johnson et al 1997a), and Eq. 35 has been corrected as discussed in (Frasch & Barbero 2004). Equations 33 and 35 have been fully validated for the case of isotropic lipids and impermeable corneocytes (Frasch & Barbaro 2003). However, both of these assumptions are challenged in recent SC models (Wang et al 2006a, 2007). More recently, Kushner et al. reported a structure-based model with two tortuosity factors to account for the effect of branched, parallel pathways on the transport of hydrophobic permeants through the lipid bilayers of the stratum corneum. Both steady-state and transient solutions to Fick's second law were provided (Kushner *et al* 2007).

5. MATHEMATICAL APPROACHES

The expression of transport of a solute across a skin barrier membrane involves a number of steps and phases in a space and time variant process. The formal description of this process as a single equation is not straightforward, other than as one or more approximations in definition of the transport conditions or in presentation of the solutions. Here, we begin with the conventional Laplace Transform approach used to solve diffusion equations, move to methods that allow variations in space and time in the transport process and various complexities to be better addressed. We conclude with a comment on how approximations may be used to summarize skin penetration data in the real world situation.

5.1. Laplace Transform solutions

Laplace transform is an integral transformation that is used to solve ordinary and partial differential equations. Its application to solving diffusion problems has been described in the well known book by Crank (Crank 1975) and by Carslaw and Jaeger for the analogous heat conduction problems (Carslaw & Jaeger 1959). In the notation common in the skin transport literature, Laplace transform of the C at *x* and *t* in the skin, $C(x,t)$, is defined as:

$$\hat{C}(x,s) = \mathcal{L}\{C(x,t)\} = \int_0^\infty C(x,t)e^{-st}dt \qquad [36]$$

where $\mathcal{L}$ designates the Laplace operator, *s* is the Laplace variable and the hat over the function (ˆ) denotes the Laplace transform. If the Laplace transform of a function is known it can be potentially inverted to time domain. Inverting back to time domain, however, is not trivial and

requires the knowledge of the theory of functions of a complex variable, although tables of Laplace transform (e.g.(Abramowitz & Stegun 1965)) often help the inversion process.

The most useful property of the Laplace transform in the context of solving differential equations is that it converts time derivatives into algebraic functions of position and *s*, thereby reducing the partial differential diffusion equation into an ordinary differential equation that is much easier to solve. The Laplace transform of the diffusion equation, Eq. 19, yields:

$$s\hat{C}(x,s) - C(x,0) = D\frac{d^2}{dx^2}\hat{C}(x,s) \qquad [37]$$

where $C(x,0)$ is the initial condition. If the skin starts out without any chemical, $C(x,0) = 0$, Eq. 37 has the general solution:

$$\hat{C}(x,s) = A(s)\sinh\left(\frac{x}{h}\sqrt{st_d}\right) + B(s)\cosh\left(\frac{x}{h}\sqrt{st_d}\right) \qquad [38]$$

where h is the thickness of the SC, $t_d = h^2/D$ is the characteristic time of diffusion, and $A(s)$ and $B(s)$ are functions of only *s*, which are be determined from the boundary conditions and h is the thickness of the SC. Equation [38] can also be further manipulated to calculate the transdermal flux and cumulative drug transport. The use of Laplace transforms for mathematical modeling of skin transport was pioneered by Hadgraft (Hadgraft 1979, 1980a) and Guy and Hadgraft who used the solution in the Laplace domain (Guy & Hadgraft 1980) to derive long and short time approximations of the total amount of drug that penetrated in the time domain.

The popularity of the Laplace transform in the skin literature has increased since the availability of scientific software (e.g. Scientist, MicroMath Scientific software) that can invert from the Laplace domain to the time domain and allowing regression to experimental data

without the extra work of first deriving a functional representation of the Laplace solution inverted into the time domain. With this type of software, having the Laplace solution is virtually as good as having solution written in terms of time. Anissimov and Roberts (Anissimov & Roberts 1999, 2001, 2004a, 2009a) have used the numerical inversion of Laplace transform solutions to the diffusion equation for simulations and data analysis of skin transport experiments. One of the useful properties of the Laplace transform is that it can be used directly (without inversion to the time domain) to determine some parameters. In transport through skin for the case of a constant donor concentration, such parameters are the steady-state flux and the lag time (Anissimov & Roberts 1999, 2001).

While Laplace transforms offer numerous advantages in solving diffusion equations, they also suffer from certain limitations. Most notably, to be solvable by the Laplace transform, the partial differential equations have to have coefficients that are independent of C. Also, the coefficients in the differential equation (e.g., the diffusion coefficient in Eq. 19) have to be independent of time (e.g. constants or functions of x only) for the Laplace transform to convert the partial differential equation into an ordinary differential equation of x only. This excludes important classes of problems in skin transport that involve the diffusion coefficient changing with concentration or time. For example, co-diffusion with a penetration enhancer or a diffusion coefficient that changes due to skin drying.

5.2. Finite Differences solutions

The finite difference approach to solving a differential equation or a system thereof involves replacing the differential equation with a set of difference equations that cover the requisite

space. There are many variations to this theme, the sophistication of which depends upon the problem to be solved. The most common difference approximations are centered differences, i.e., equations centered in space at the location where the approximation is made. As an example, the one-dimensional diffusion equation,

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial x}\left(D \frac{\partial C}{\partial x} \right) \qquad [39]$$

which is written to allow *D* to be a function of *x* or a function of *C*, which is a function of *x*, becomes, after differencing in space:

$$(\Delta x)^2 \frac{dC_i}{dt} = D_{i-1/2} C_{i-1} - (D_{i-1/2} + D_{i+1/2}) C_i + D_{i+1/2} C_{i+1}, \text{ i = 2, ..., N-1} \qquad [40]$$

Here the region in space governed by Eq. [40] has been subdivided into *N* equally spaced layers. In this scheme the concentrations C_i are defined at the center of each layer and the diffusivities $D_{Ii \pm ½}$ are defined at the edges of the layers. The layers i = 1 and i = *N* require special treatment because they incorporate the boundary conditions for the problem. This differencing scheme transforms the partial differential equation into a set of *N* ordinary differential equations (ODEs). The system of ODEs may then be solved by standard techniques (Press et al 1992), most of which involve integrating difference equations in time. A skin diffusion model employing Eq. 40 and a Crank-Nicolson time integration scheme is described in (Kasting et al 2008).

For systems involving widely varying distance scales, finite difference schemes with a variable spatial mesh have been developed. The mesh spacing broadens in the center of a layer and becomes very fine at interfaces where transport properties are discontinuous. Appropriate application of this methodology allows the development of extremely efficient integration routines with remarkable spatial resolution. A masterful application of this approach to the SC

brick-and-mortar diffusion problem, conceived in large part by Prof. J. M. Nitsche, is described by Wang et al. (Wang et al 2006a, 2007).

Finite difference methods are particularly advantageous for potentially nonlinear systems with either simple geometry or periodic geometry. Much of the efficiency is lost for disordered structures. Relative to finite element methods, finite difference methods can be much more efficient on periodic problems such as a regular brick-and-mortar SC structure. However, considerable skill is required to construct accurate approximations at boundaries and to implement an efficient variable mesh scheme. Relative to Laplace transform methods, the biggest advantages of finite differences are the ability to handle nonlinear problems and more complex boundary conditions. Both call for considerable skill by the operator.

5.3. Finite Element Method Solutions

The finite element method (FEM) is related to the finite difference method in that both offer approximate numerical solutions to linear or non-linear partial differential equations. The FEM is able to handle domains with complicated geometries and boundaries, including moving boundaries. The primary basis for the FEM is the discretization of a continuous domain of interest—here the skin—into a discrete set of connected subdomains. The resulting mesh of triangles or higher order polygons, referred to as elements, creates a finite dimensional linear problem whose solution can be implemented on a computer. In general, the density of the mesh varies across the domain, with greater density over those areas where greater precision in the solution is required. An example might be the regions in the stratum corneum near a boundary

between corneocyte and lipid domains. Owing to the complexity of the meshing and solution procedures, the FEM is frequently implemented using commercial software packages.

Rim et al. (Rim 2005) developed a finite element model consisting of two isotropic materials with different diffusion and partition coefficients, connected by an interfacial flux. The two materials are intended to represent a dermal patch or reservoir containing a drug of interest, and the skin. Addition of a permeation enhancer creates a coupled 2-component system with concentration-dependent diffusivities to account for interactions between drug and enhancer. *In vitro* experiments using a drug (fentanyl) and an enhancer (lauryl pyroglutamate) were used to examine the relative roles of enhanced diffusivity and partitioning. It was found that the latter more accurately accounts for the experimental observations, but the authors concede that other nonlinear processes may play a role.

Heisig et al used a related method, finite volumes, to solve both transient and steady-state transport of drugs through a biphasic brick and mortar model of stratum corneum (Fig. 3) with isotropic lipids and permeable, isotropic corneocytes (Heisig et al 1996). This work demonstrated the contributions of corneocyte alignment, relative phase diffusivity, and phase partitioning in the barrier properties of the SC. Subsequent extensions in both 2-d (Naegel et al 2008) and 3-d (Naegel et al 2009) skin models have been described, and the group has explored the role of drug binding to corneocyte elements on skin transport (Hansen et al 2009). The key finding is that steady-state binding data of lipophilic compounds can be described by a model that posits interaction with the cornified cell envelope.

Frasch and Barbero (Frasch & Barbero 2003) analyzed a finite element model of the stratum corneum lipid pathway to investigate effective path length and diffusional lag times in this path compared with a homogeneous membrane of the same thickness. Results of this analysis have been described above. This group also presented a transcellular pathway model, whereby permeants are granted access to the corneocytes via a corneocyte-lipid partition coefficient and separate diffusivity within corneocytes compared with lipids. The authors compared modeled membrane lag times with *in vitro* measurements (n=27) for hydrophilic compounds gathered from the literature. Results pointed to a transcellular pathway with preferential corneocyte partitioning as the likely diffusional path for hydrophiles. Lag times in the lipid path model were too brief to account for measured lag times, whereas the transcellular route could account for them (Barbero & Frasch 2006).

A secondary result from these investigations was the observation that the complex disordered geometric representation of the stratum corneum could be reduced to a simple, rectangular brick-and-mortar geometry with very similar results (Barbero & Frasch 2005). Furthermore, for many realistic combinations of corneocyte/lipid partitioning and diffusivity, the short vertical connections between bricks can be ignored and the problem can be reduced to a multilayer a-b laminate model, where "a" represents lipids and "b" corneocytes. This configuration is a good representation for the transcellular path with preferential corneocyte partitioning. Thus for many purposes, the complex geometrical arrangement of the stratum corneum can be reduced to a much simpler geometry for which simpler numerical algorithms, such as the finite difference method, can be applied. In fact, analytical solutions for steady-state flux and lag time have been published for the multilayer laminate model (Crank 1975).

Further refinement supports the idea of a "pseudohomogeneous membrane" model of stratum corneum. This means that, for purposes of estimating macro-level time dependent variables such as flux and penetrated mass, a homogeneous membrane approximation can be made which eliminates the necessity of explicitly accounting for the complex geometrical configuration of the stratum corneum. This conclusion is bolstered by more formal analysis using the method of homogenization (Rim et al 2008). The parameters of this reduced membrane—effective diffusivity, partition coefficient, and path length—can be estimated as described herein (Section 4). (Anissimov & Roberts 1999, 2001, 2004a; Frasch & Barbero 2008; Anissimov & Roberts 2009a).

5.4. Random Walk Method

Diffusion, at its fundamental level, arises from the random thermal motion of molecules suspended in a medium. This has led numerous investigators to use a "random walk" simulation as a model for diffusion. An unbiased random number generator coupled with local diffusion rules, are all that is required computationally. Many diffusion processes, such as molecular mobility, phase partitioning and binding, can be simulated by the generation of random integers. Frasch applied these processes to simulate diffusion within a complex geometric representation of the stratum corneum (Frasch 2002). He correlated diffusivity with the molecular weight of a compound, and related corneocyte-lipid partitioning to the octanol-water partition coefficient of the compound, so that model results could be regressed to measured permeability coefficients (k_p) from the Flynn data base (Flynn 1990). He found a correlation coefficient (r^2) of 0.84, compared with 0.67 produced by the Potts and Guy equation.

5.5 Estimation of Total Exposure

Up until this section, we have emphasized transport through an isolated skin membrane. In practice, however, the transport will need to be evaluated in the context of local or systemic action. The solute needs to reach at least the epidermis and potentially dermis to exhibit local or systemic toxicity. The generalized equation describing a steady state concentration C_{ss} is dependent on the steady state flux *Jss*, the *in vivo* bioavailability *F* (for instance accounting for loss due to local skin metabolism), the application area *A* and the clearance *CL* from either the skin (for a local effect) or from the body for a systemic effect (Dancik et al 2008):

$$C_{ss}=F.J_{ss}\,A/CL \qquad [41]$$

If the target is the epidermis, the epidermal concentrations $C_{ss,e}$ is related to the concentration in the vehicle C_v by the ratio of the permeability coefficient k_p to the dermal clearance CL_d (Roberts MS 2005):

$$C_{ss,e}=k_p\,C_v\,/(k_p+CL_d/K_e) \qquad [42]$$

Accordingly, if there is no clearance into the dermis due to poor blood flow and/or solubility, Eq. 42 shows that the epidermal concentration is given by K_eC_v, where K_e is the epidermis to vehicle partition coefficient. On the other hand, if the dermal clearance is very high, the epidermal concentration will be inversely dependent on that clearance, i.e. $C_{ss,e}\sim k_pK_eC_v/CL_d$. The time course for establishment of *in vivo* levels is also more complex than we have described in terms of transport across a skin membrane. Here, the time course for elimination from the dermal site or from the body as a whole further complicates the kinetic description. Further, there may be solute returning to the site from the blood that can complicate the profiles even further as we

have described (Singh P. 1993). For a fuller description of the principles of physiologically-based drug pharmacokinetics and pharmacodynamics in the skin, the reader is referred to (Dancik et al 2008).

One of the most challenging skin mathematical problems for a biologist is summarizing data for finite dose experiments. As a consequence, most biologists rely on using the steady state infinite dose solution described earlier in this review. Unfortunately, it has been shown that the penetration profiles for infinite and finite dose formulations can differ quite markedly (for example see (Cross et al 2001)). For a finite volume vehicle application the solute flux can be expressed in the Laplace domain [132]

$$\hat{J}(s) = \frac{dose}{A} \frac{1}{\cosh\sqrt{st_d} + V_{dN}\sqrt{st_d}\sinh\sqrt{st_d}} \quad [43]$$

where A is the area of application and $V_{dN} = \frac{V_{donor}}{AhK}$ and represents relative volume of the donor phase. Whilst experimental data for flux can be fitted by this equation using numerical Laplace inversion and regression software, it is not straightforward for many scientists. A simpler approach is to use the key features of the flux versus time profile after a finite dose to summarize the observed absorption, using model approximations to yield measures for partition and diffusion parameters after the finite dose application. For instance, the cumulative amount penetrated at any time t is simply the area under the curve of flux versus time to time t as determined by the trapezoidal rule or other simple method to estimate area. The peak flux (J_{peak}) is the peak in profile of flux versus time (usually a skewed to the left bell shape curve [132]) and time for that peak flux t_{peak} is most easily defined when the donor volume approaches zero, i.e.

$V_{dN} \to 0$, as occurs with a solvent deposited solid. The simplified expressions, first described by Scheuplein & Ross (Scheuplein & Ross 1974), are:

$$J_{peak} \approx 1.850 \; dose \; D/(h^2 A) \qquad [44]$$

$$t_{peak} \approx h^2/(6D) \qquad [45]$$

where *dose/A* is dose per unit area (and equals C_v multiplied by thickness of vehicle) [132]. It should be noted that Eqs. 44 and 45 are simple solutions for a homogeneous membrane slab and do not take into account SC heterogeneity [119] and slow binding within the SC [120] and thus might be considered as approximations for certain solutes.

6. SUMMARY AND OUTLOOK

Through the combined efforts of several investigators, mathematical modeling of skin has made outstanding progress in the last several decades and various models have been set forth. In particular, the QSPRs and other models described here are routinely used to assess, as a first pass, the likelihood that a drug can be delivered via the transdermal route. Such predictions provide an economic alternative to experimentation. Ultimately, these modeling approaches must be combined with a knowledge of the potency of the active at the target site so that therapeutically relevant candidates are progressed to final formulations (Cordero et al 2001). Real advances in our understanding of percutaneous penetration are best exemplified in those cases where models are underpinned by experiment. For example concentration profiles in skin

have recently been examined and solutions to Fick's second law of diffusion have been used in combination with skin stripping to separate the effects of the partition coefficient and the diffusion coefficient on permeation (Herkenne et al 2007). With the advent of Confocal Raman and other spectroscopic techniques it should now be possible to model and interpret experimental concentration profiles of both drug and excipient i*n vivo*.

Mathematical models also provide a means to assess the likelihood of systemic exposure upon dermal contact with toxic chemicals. However, the current level of sophistication and refinement in the mathematical modeling of chemical transport through skin has not found broad application in the areas of dermal exposure and risk assessments. There may be several reasons for this. First, many of the models are not easily accessible to the risk assessors and industrial hygienists who could use them. Second, many existing predictive models are limited to single chemicals in simple matrices such as water, whereas complex mixtures are the rule in most industrial and environmental settings. Third, there remains confusion on how to use the results from modeling. If a model estimates a permeability coefficient from a given vehicle, how can this information be used to predict the mass of chemical that penetrates the skin from a given exposure? Finally, there is a valid concern regarding the legitimacy and range of applicability of current models. An important challenge for the modeling community is to educate the risk assessment community on the appropriate uses and limitations of mathematical models.

In the United States, documented instances of the application of mathematical modeling to dermal risk assessment cite the use of permeability coefficients (k_p) and their model-based estimation. The US Environmental Protection Agency (EPA) provided guidelines for dermal risk

assessment in 1992 (EPA 1992) and advocated the use of the Potts and Guy (Potts & Guy 1992) equation for estimating k_p where experimental data are unavailable. Subsequent documents (EPA 2004) incorporate refinements based largely on contributions by Bunge and coworkers (Cleek & Bunge 1993; Reddy et al 2000) to estimate dermal absorbed doses from water and soil pathways. The Office of Pesticide Programs uses k_p for estimating an "absorbed dose rate" from swimming in areas treated with pesticides post-application (EPA 1997), and the Office of Solid Waste and Emergency Response uses k_p to calculate an "absorbed dose per event" for contact with chemicals in water at Superfund sites (EPA 2004). In a recent report, these are the only instances of the use of an estimate of dermal penetration among 24 reported equations used by the EPA for dermal exposure assessment purposes (EPA 2007). The US National Institute for Occupational Safety and Health (NIOSH) uses experimental or model-based estimates of k_p to calculate systemic uptake from skin exposure for comparison with uptake from inhalational exposure at the occupational exposure limit of the chemical. The comparison is used for the assignment of skin notations, which are hazard warnings used to alert workers and employers to the health risks associated with skin exposures to chemicals in the workplace (NIOSH 2009). Sahmel et al. (Sahmel 2009) present a number of model-based methods to estimate exposure and absorption of substances via the dermal route. The intended audience is industrial hygienists and risk assessors tasked with estimating dermal loading on skin, dermal absorption and penetration into the systemic circulation.

An important challenge and question from the perspective of the mathematical modeler is how much modeling can the data support. For example, if a classic diffusion cell experiment is performed, where steady state is established, often the data can only justify fitting a straight line

though the steady-state portion of the total amount of solute in the receptor measured as a function of time. On the other hand, if different types of experiments are performed and the data are analyzed simultaneously as in water penetration and desorption experiments (Anissimov & Roberts 2009a) or in the analysis of clobetasol propionate (Mueller et al 2003), one is forced to use more advanced modeling. Generally, in an experiment that does not directly measure the quantity under the investigation, more complex modeling is required, as in the work on *in vivo* skin penetration (Pirot et al 1997) (Norman et al 2008), where flux was deduced from data obtained from measuring concentration of the solute in tape strips and in the breath, respectively.

Another challenge is the large number of parameters that is required for more advanced modeling, which is often not readily available. If a simple diffusion model is used, three parameters are all that is needed (a partition coefficient, diffusion coefficient and path length). When spatial variability of all these parameters in the SC is also modeled, the number of parameters becomes staggering, with no realistic experiments to support this kind of modeling. Considering slow equilibration in the SC adds two extra parameters (binding and unbinding rates). A careful consideration is required, therefore, when adding complexity to modeling for the purposes of analyzing data. If donor concentration decreases by less than 20% during the experiment, it is most likely that the simplest infinite donor model can be applied, without adding an extra parameter for the volume of donor phase (which will be most likely be poorly determined from data fitting in this case) and solving the unsteady-state diffusion equation. Numerical finite element schemes for solving diffusion equation can easily handle 2D or even 3D problems given current computing speeds, but whether this voyage to extra dimensions helps in modeling skin penetration data has to be carefully considered by the modeler.

The ultimate challenge is probably to keep models simple enough, so that it is used by the experimental community, while still explaining some complex real world data. Such complexities might for example include the changing hydration (and thus diffusion coefficient) of the SC in realistic skin penetration scenarios. The co-application of penetration enhancers will also produce changing diffusion coefficients and partition coefficients, which at this stage can only be modeled by relatively complex models (in the sense of applying it to data) relying on finite element or finite difference schemes. Perhaps going back to compartment models, as previously suggested (Anissimov 2008), might address the issue of keeping it simple, while fitting the real data. (Vecchia & Bunge 2002a)

In the long-term, the utility of any mathematical model will be measured against some simple requirements: (i) that it offers mechanistic insight consistent with knowledge about skin barrier function and percutaneous absorption that has been deduced by validated, independent observations; (ii) that it predicts a parameter suitable for its intended use (e.g., a permeability coefficient, or a (trans)dermal flux); (iii) that it is comprehensible to skin scientists with "ordinary skill in the art", and that the descriptors required by the model are easily calculable or readily available in publicly-accessible sources; (iv) that it is broadly applicable across diverse chemical classes, not merely specific to one limited group of structurally-related compounds; and (v) that modification (which normally means additional complexity) to an existing model provides statistically significant results compared to existing methods.

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