International Journal of Pharmaceutics 418 (2011) 115–129

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

# Mathematical models of skin permeability: An overview

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ARTICLE INFO

*Article history:*
Received 1 December 2010
Received in revised form 14 February 2011
Accepted 16 February 2011
Available online 25 February 2011

*Keywords:*
Transdermal
Stratum corneum
Permeability
Model
Theory
Mathematical
Exposure assessment

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.

## 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 and 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 and Blank, 1971). 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 1940s to 1970s. During this time it was recognized that partitioning and solubility were important fac-

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doi:10.1016/j.ijpharm.2011.02.023

tors that determine skin penetration. In the early 1940s 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 1950s Hadgraft and Somers (1956) 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. In the 1950s and 1960s 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, and diffusion coefficients, 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; Scheuplein et al., 1969; Scheuplein and Blank, 1971). 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, $\Delta C_s$, the diffusion coefficient in the skin membrane, $D$, and the path length, $h$, as follows:

$$Q = \frac{DAT\Delta C_s}{h} \quad (1)$$

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. Eq. (1) is frequently expressed in terms of steady-state skin flux, $J_{ss}$, defined as:

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

Higuchi (1960), in his forward looking article, expressed this flux more appropriately in terms of thermodynamic activity $a_s$ rather than widely used concentration approximation. 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:

$$J_{max} = \frac{DS_s}{h} \quad (3)$$

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 et al., 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:

$$J_{ss} = \frac{KD\Delta C_v}{h} \quad (4)$$

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; Scheuplein, 1967; Scheuplein and Blank, 1971), 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 and Guy, 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, $\Delta C_v$:

$$k_p = \frac{J_{ss}}{\Delta C_v} \quad (5)$$

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):

$$k_p = \frac{K \cdot D}{h} \quad (6)$$

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:

$$J_{max} = k_p \cdot C_{v,sat} \quad (7)$$

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