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New tools and approaches for predicting skin permeability

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This article reviews some new mathematical models and techniques used to predict and understand percutaneous penetration and transdermal delivery. These models are also useful for various enhancement strategies that can be used in dermal-penetration and formulation development studies. If appropriate, biophysical techniques can be combined with these new mathematical models and statistical analyses and it will be possible to understand the factors affecting penetration of molecules through skin. These factors, or parameters, can then be used to control the penetration rate when effective transdermal delivery or therapy is required or targeted.

Skin is the largest organ of the body with a surface area ~1.8–2.0 m^2 [1] and a weight of almost 9 kg [2]. It forms a unique and flexible interface between our internal milieu and the external environment and possesses sensory, thermoregulatory [3], metabolic [4] and immunological [5] functions. It is flexible enough to resist permanent distortion from movement and thin enough to allow stimulation. It also performs many ancillary functions, such as metabolism, and the production of sweat enables temperature control and excretion of waste products [3,6].

The skin is composed of three layers, subcutaneous tissue, dermis and epidermis (Figure 1) [2]. The discontinuous layer of sebum, a complex lipophilic fluid secreted by the sebaceous glands, is sometimes considered to be a fourth, outermost layer.

The stratum corneum is the outermost layer of the epidermis. In humans it consists of between 10 and 25 layers of dead, elongated, fully keratinised corneocytes that are embedded in a matrix of lipid bilayers [7,8]. This layer is only 6–10 μm thick [9] in most regions of the body but 0.4–0.6 mm thick in the palms of the hands and soles of the feet [10]. The stratum corneum consists of ~40% protein of which 80% is keratin. Keratin is a group of α-helical polypeptides ranging in size from 40,000–68,000 daltons [11]. The type and amount of lipid in the stratum corneum depends on body-site and, currently, it is generally accepted that skin permeability is affected by stratum corneum lipids [12].

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Penetration through skin

Although the skin has barrier function, some chemicals are able to penetrate it. The mechanism of penetration has been widely studied. The main resistance between stratum corneum and the epidermis cell layers for transdermal transport was first hypothesized by Rein in 1924 [13]. Schuplein and Blank [6] later established that transdermal penetration was limited by the stratum corneum itself, and that molecular impermeation was a passive process. Subsequently, Michaels *et al.* [14] showed that several drugs had significant permeability and determined their stratum corneum diffusion coefficients.

In the past 30 years, the hope of delivering therapeutic agents into the body through the skin has become a clinical reality. Starting with the first approval of scopolamine patches in 1979, transdermal delivery is now a viable way of delivering drugs. The rational design of new transdermal systems or formulations (and determination of risk assessments of transdermal exposures to chemicals) also requires an understanding of the process of penetration and the factors that determine it at the molecular level [15].

When a topical formulation is placed on the skin, the active drug has to penetrate from the stratum corneum into viable tissues (Figure 1). The main limiting factor for this process is the slow diffusion through the stratum corneum, which is known to be a dead layer [14,16–21]. The stratum corneum lipids are important for the barrier function [20,22]. There is increasing evidence that ceramides play a major role in structuring and maintaining the (lipid) barrier function of the skin. As such, they are considered to

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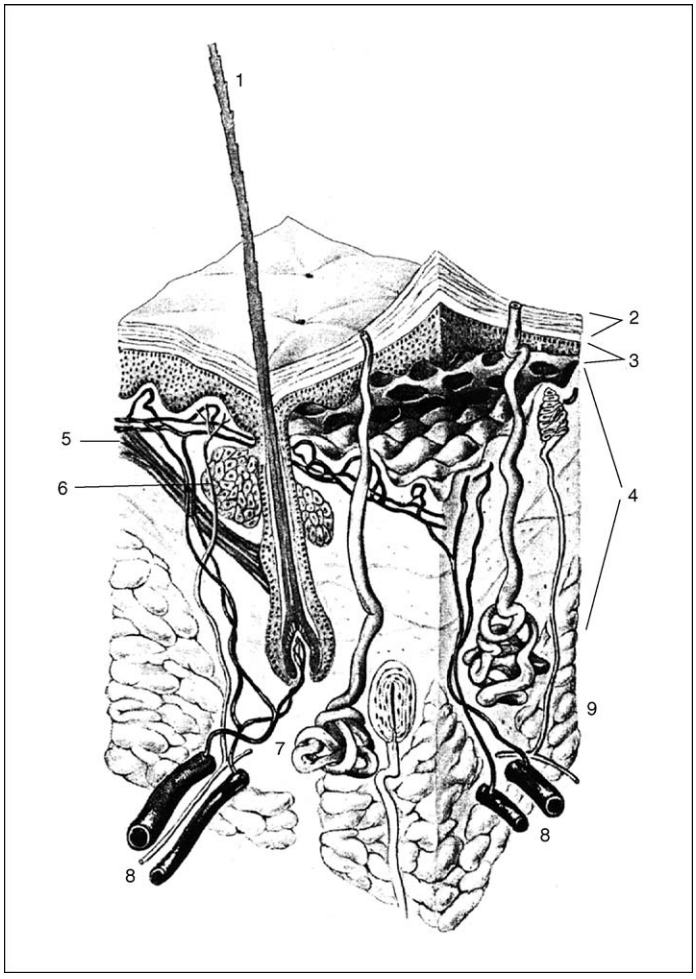

FIGURE 1

Schematic cross sectional view of skin structure. In this scheme the following structures are labelled: hair shaft (1); epidermis having an outermost layer, stratum corneum (2), and sequential inner layers, stratum granulosum, stratum spinosum and stratum basale (3); dermis (4); arrector pili muscle (5); sebaceous gland (6); sweat gland (7); blood vessels (8); and adipose tissue (9).

function as emolients, rendering the skin soft and conferring water-retention properties on the stratum corneum [23–26].

There are three main pathways that exist for passive transport of chemicals through the skin to the vascular network [6,27]: intercellular diffusion through the lipid lamellae; transcellular diffusion through the keratinocytes and lipid lamellae; and diffusion through appendages (hair follicles and sweat ducts).

Determination of penetration through skin

The most commonly used device for *in vitro* diffusion work and for determining penetration through skin is the Franz-type diffusion cell, or modifications of it. A donor compartment containing the permeant is separated from a receptor compartment by a membrane (excised human skin) [28–30].

Isolated and perfused whole rabbit ear or excised ear skin have also been used to determine the penetration of compounds through skin (*ex vivo* or *in vitro* experiments) [30–32]. Microdialysis experiments have also been performed to determine penetration of compounds through human skin under *in vivo* conditions [33].

Modelling of transport through the skin

Existing models

Several investigators have used the published human stratum corneum permeability coefficient (K_p, often expressed as log K_p) to predict skin permeability and they have examined the effect structural parameters of penetrants have on permeability [34–38]. This has led to the development of models. Using molecular descriptors that explain variations in physicochemical properties or biological activity of penetrants has resulted in the development of linear free-energy relationships (LFER) [39] and quantitative SAR (QSAR) [40]. QSARs are useful in predicting behaviour of novel compounds and provide insights into mechanisms of activity. Michaels *et al.* [14] have developed the concept of the stratum corneum being a two-phase region consisting of 'bricks and mortar', where the aqueous protein phase in the keratinocytes represents the bricks and the intercellular lipid phase represents the continuous mortar. The transport of the compound through the stratum corneum was assumed to be the sum of the diffusion through the lipid and protein. It was then concluded that diffusion through the lipid phase was ~500 times slower than diffusion through the protein phase [14]. Flynn [34] later stated that the density and compactness of the intracellular protein in the keratinocytes of the stratum corneum makes it almost thermodynamically and kinetically impossible for compounds to cross. It is now generally accepted that intercellular diffusion through the lipid lamellae is the predominant mode of transport. Flynn interpreted data from the literature in terms of a risk assessment and he concluded that penetration through the skin is related to the octanol–water partition coefficient (K_{oct}, often expressed as log K_{oct}). He proposed that a rough prediction of the skin permeability coefficient is sufficient to estimate the risk factor.

Earlier models and/or reports about the relationship between skin permeability and permeant properties [41–44] were inconclusive because they used small datasets; however, Flynn [34] published a collection of >90 log K_p and log K_{oct} values for compounds. This dataset formed the basis of a model for the prediction of log K_p from molecular weight (MW) and log K_{oct} [35]. These developed models provided variable results and have only limited statistical accuracy, possibly because of using data from different sources.

Other models developed for the prediction of permeability have used functional-group contributions [37] [model uses number of atoms (such as carbon, hydrogen, hydroxyl, etc.) and groups such as halide and amide, as well as aromaticity of the molecule, as predictors], molecular parameters [45] (model uses molecular volume (v), H-bond acceptor (α) and H-bond donor (β) ability and dipole properties (π) of the molecule as predictors) and Hildebrand solubility parameters [38] (model uses v, MW, cavity, melting point, bonding, log K_{oct}, activity coefficient and solubility of the molecule as predictors). Pugh *et al.* [46] criticized the use of the composite term, K_p, and reported the dependency of diffusion across the stratum corneum on MW and the scaled H-bonding values α and β. Wilschut *et al.* [47] have used log K_{oct} and $MW^{-0.5}$ as predictors and have questioned the reliability of some of Flynn's data.

A current trend in QSAR studies is the use of theoretical molecular descriptors that can be calculated directly from molecular structure. Using computational methods to determine them is fast