

AN OVERVIEW ON THE SKIN PERMEATION

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ABSTRACT

Skin as an organ of protection covers the body and accomplishes multiple defensive functions. The intact skin represents a barrier to the ingress of xenobiotics and the egress of water, proteins, and plasma components from the organism. Due to its complex structure, the epidermal barrier with its major component, stratum corneum, is the rate-limiting unit for the penetration of exogenous substances through the skin. Over the past few decades a considerable work was done on delivery of drugs through the skin or to breach the skin barrier. This review gives about the information on the permeation of the molecules through the skin and models to predict the skin permeability.

KEYWORDS: Epidermal barrier, stratum corneum, permeation.

INTRODUCTION

Skin, being the largest and the outermost organ of the human body, accomplishes multiple defensive, regulatory functions^[1] and forms a unique interface between our internal and the external environment and posses sensory, thermoregulatory, metabolic and immunological functions. It is having a surface area~1.8-2.0 m^[2] and weight almost 9kg. It is flexible enough to resist permanent distortion from movement and thin enough to allow stimulation. It also performs some ancillary functions, such as metabolism, and the production of sweat and excretion of waste product. The skin is composed of three layers, subcutaneous tissue, dermis and epidermis. 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.

This layer is only 6–10 mm thick in most regions of the body but 0.4–0.6 mm thick in the palms of the hands and soles of the feet. 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. The type and amount of lipid in the stratum corneum depends on body-site and, currently^[2], it is generally accepted that skin permeability is affected by stratum corneum lipids

(ceramides (45–50%), cholesterol (25%) and free fatty acids (10–15%))^[3] and the most important as this serves as the barrier to both the ingress of xenobiotics and the egress of water (hence, maintain body temperature).^[4] The SC comprises of dead keratinocytes (protein rich cells) embedded in a lipid multilamellar matrix, and hence, the term “brick and mortar” structure is often employed to describe its architecture. The bricks represents the keratinocytes, while the mortar is composed of a diverse mixture of lipids including sphingolipids, fatty acids, free sterols, triglycerides and non-polar lipids. Molecules can permeate through the stratum corneum through either transcellular, intercellular or shunt routes (skin appendages).^[5-7]

Routes of Penetration

When a topical formulation is placed on the skin, the active drug has to penetrate from the stratum corneum into viable tissue.^[2] There are three potential pathways of diffusion from the surface of the skin into the subepidermal tissue through the hair follicles with their associated sebaceous glands, via the sweat ducts, or across the continuous stratum corneum between these appendages.^[8] The diffusional pathlength is therefore much longer than the simple thickness of the stratum corneum (~20 mm) and has been estimated as long as 500 mm. Importantly, the intercellular spaces contain structured lipids and a diffusing molecule has to cross a variety of lipophilic and hydrophilic domains before it reaches the junction between the stratum corneum and the viable epidermis. The nature of the barrier is thus

very heterogeneous and it is perhaps surprising that diffusion through it can be described by simple solutions to Fick's laws of diffusion.^[1,9,10]

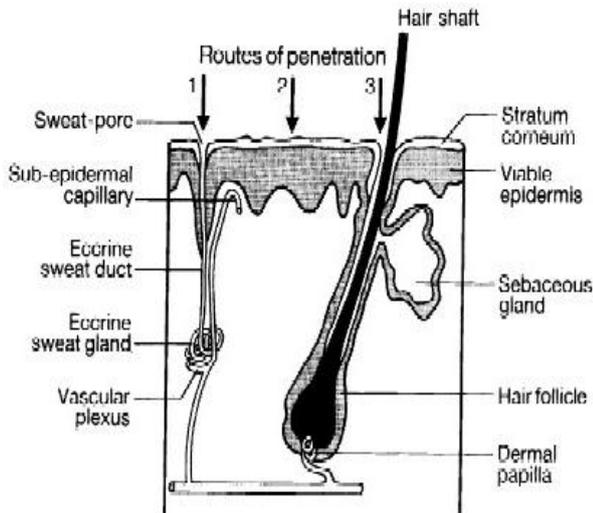


Diagram of skin structure and macroroutes of drug penetration: (1) via the sweat ducts; (2) across the continuous stratum corneum or (3) through the hair follicles with their associated sebaceous glands (Taken from 11).

a. Influence in accordance with fick's first law

Stratum corneum can be considered as a partition membrane, the penetration rate of drugs through the stratum corneum may be described by fick's first law. The drug flux, J , represents the penetrating drug mass per time and area unit. Penetration rate and flux are directly proportional to the drug permeability of the barrier P_B . If the partition coefficient $PC_{B/V}$ in Eq. (2) is replaced by Eq. (3), Eq. (4) is obtained.

$$\frac{-dc_v}{dt} = k_p \times c_v = D_B \times \frac{PC_{B/V} \times A/V_v \times c_v}{l} \quad \text{Eq 1}$$

$$J = P_B \times c_v = D_B \times \frac{PC_{B/V} \times c_v}{l} \quad \text{Eq 2}$$

$$PC_{B/V} = \frac{c_{sB}}{c_{sV}} \quad \text{Eq 3}$$

$$J = D_B \times \frac{c_{sB} \times c_v/c_{sV}}{l} \quad \text{Eq 4}$$

Where c_v is the drug concentration in the vehicle, $-dc_v/dt$ is the rate of the drug concentration decrease in the vehicle, k_p is the penetration rate constant, D_B is the effective drug diffusion coefficient in the stratum corneum, $PC_{B/V}$ is the partition coefficient of the drug between the barrier stratum corneum and the vehicle, l is the thickness of the stratum corneum, A is the area of application, V_v is the vehicle volume, P_B is the drug permeability of the barrier stratum corneum, c_{sB} is the drug solubility in the barrier stratum corneum and c_{sV} is the drug solubility in the vehicle.

According to Equation 4 flux can may be increased by increasing the drug diffusion coefficient in the barrier D_B and the drug solubility in the barrier c_{sB} or by increasing the drug concentration in the vehicle (supersaturated solutions^[12]) c_v or a decrease of the drug solubility in the vehicle c_{sV} ^[13] or by using physical enhancement strategies, such as iontophoresis or sonophoresis.^[14] Large molecules will tend to diffuse slowly, hence the MW term in Eq. (5), molecules with good solubility in both oils and water will permeate well. These tend to be compounds with low melting point would tend to indicate that a high partition coefficient will favour a high flux, however, large values of K tend to produce molecules that have poor solubility and in general molecules with a log K_{oct} , 1–3 have the optimum partition behaviour.

$$\log[kp/(cm \text{ h}^{-1})] = -2.7 + 0.71 \log K_{oct} - 0.0061 MW \quad \text{Eq 5}$$

Where K_{oct} is the octanol water partition coefficient and MW the molecular weight^[1].

Many permeants are weak acids or weak bases. Permeation will depend on the degree of ionisation and how ionisation influences the solubility in the applied phase and its partition into the skin. Ion-pair mechanisms have been proposed for permeation enhancement of ionic drug.^[15,16]

b. Importance of penetration routes

The non-polar substances only penetrate intercellularly and polar substances penetrate transcellularly through both the corneocytes and the lipid lamellae.^[17] Studies show that substances with a great polarity spectrum all penetrate via the intercellular route. The skin appendages only represent a volume fraction of 0.01–0.1% of the stratum corneum, resulting in a relatively small diffusion volume. Therefore, the penetration via the pore route should be less relevant. However, some studies show that penetration through pores and follicles has to be considered.^[13] Percentage follicular contribution was determined according to the equation:

$$\%FC = 1 - \left(\frac{2 \times J_{sand}}{J_{Ep}} \right) \times 100$$

Where $\%FC$ is the percentage follicular contribution to total percutaneous absorption, J_{sand} and J_{Ep} are the steady-state flux values for the sandwich and single epidermis.^[18]

Skin Permeability

There are four modes of solute diffusion through the stratum corneum. The first mode includes solute diffusion through lipid bilayers by hopping between free volume pockets, this mode is particularly important for transport of low molecular weight hydrophobic solutes ($M < 400\text{Da}$). The second mode includes solute motion due to lateral diffusion of lipid molecules. This mode

will be shown to be important for high molecular weight solutes ($M > 400\text{Da}$) that partition preferentially in lipid bilayers but possess low diffusion coefficients due to their large size. The third mode includes solute diffusion through pores (pore size distribution, skin porosity & skin tortuosity) and the fourth mode includes solute diffusion through shunt pathways. The skin permeability of solutes is mostly based on the physicochemical properties including molecular weight, $\log P$, solubility, melting point and hydrogen donor/acceptor capability. Transdermal transport of hydrophobic solutes is largely dependent upon skin's lipid bilayer. Mathematically, skin permeability of hydrophobic or hydrophilic solutes is described by following equation.

$$K_p = K_{p_{fv}} + K_{p_{lateral}} + K_{p_{pore}} + K_{p_{shunt}}$$

Where $K_{p_{fv}}$ shows permeability associated with free-volume type of diffusion through lipid bilayers, $K_{p_{lateral}}$ corresponds to permeability of hydrophobic solutes due to lateral diffusion of lipids, $K_{p_{pore}}$ corresponds to solute permeability through pores and $K_{p_{shunt}}$ corresponds to solute permeability through shunts (hair follicles and sweat ducts).^[19-21]

Predictive Models for Skin Permeability

Skin permeability is an important parameter in the assessment of potential toxicity of environmental agents or the feasibility of a drug for transdermal delivery. Although skin penetration can be determined experimentally, a simple model that can predict this descriptors, based on few inputs is valuable as compared to high risk assessment and drug delivery investigations. A number of algorithm and predictive models have been used to estimate the skin permeability coefficients these are: empirical and theoretical. Theoretical models are based on the contributions of the possible routes of percutaneous penetration and the interaction of elements of these routes with the penetrants. Empirical models rely on measured experimental permeability coefficients of series of chemicals and correlate them with the physicochemical properties. Earlier models includes the linear free energy relationship, Quantitative structure activity relationship and newer models includes the Artificial Neural Network Modeling, Probabilistic Analyses, Fuzzy Modeling, Biopartitioning Micellar Chromatography, Considering Lateral Free-Volume, Diffusion and Diffusion through Pores and Shunts, Principal component analysis and Probabilistic analysis.^[2,21,22]

Surrogates to Human Skin

Human skin is often difficult to obtain and many studies have been conducted using membranes similar to the human skin or used as a surrogate to human skin. Liquid membranes have been considered, but their structural simplicity cannot provide an adequate model of the heterogeneous nature of the intercellular channels. They can be made more realistic by the incorporation of lipids, which will form structured domains but even so there is little evidence to show that they can be used with

confidence as models for human skin. Polymeric systems have also been considered with the most simple being silicone membranes. Under limited conditions, correlations can be obtained between transfer rates through silicone and skin but these are when the chemical potential is the dominant effect controlling transport through the skin. More complex membranes such as Carbosil have also generated interesting correlations. Animal skin has been used extensively and the most reliable tissue appears to be from pig ear. Advances have been made using cultured skin but this tends to have more limited barrier function than the genuine tissue. This generally means that the 'gold star' studies are in vivo human followed by in vitro human.^[1]

Quantitative Methods for Determination of Drug in the Localized Skin

For selection of drug through the dermal or transdermal delivery system it is essential to understand the behavior of drug through skin. The parameters include the amount of active moiety accumulated in the different layers of the skin, as well as the flux through the skin in systemic circulation. The literature reports have documented various different methodologies for quantifying drug amounts within the skin. The techniques include skin extraction measurements, horizontal stripping & sectioning, removal of hair follicles, quantitative autoradiography and spectroscopic methods.^[24]

Non-Invasive In Vivo Methods for Assessment of the Skin Barrier Properties

In this scenario of precise quantification and standardization there is development of novel techniques with greater descriptive and accuracy properties. Different non-invasive methods for monitoring skin functions have been introduced, offering the advantages of precise and non-invasive methods-thus harmless investigation of the epidermal barrier properties in vivo (Table 1). Due to the complexity of its structure and functions, a single parameter is not sufficient to describe entirely the skin barrier. Thus a multi-parametric approach can be helpful in monitoring the epidermal barrier functions.^[25]

Table 1: An overview of the non-invasive methods and their applications.

Parameter	Method	Applications
TWEL	Open chamber	Epidermal barrier integrity under basal conditions and experimental disruption
	Closed chamber	Permeability barrier status
	Ventilated chamber	Disease monitoring (e.g., atopic dermatitis, OSAAD score) Effects of externally applied compounds on the skin barrier
SC hydration	Electrical methods (measurement of conductance, capacitance, or impedance)	Water content of the epidermis
	Microwave methods	Skin moisturization/hydration
	Spectroscopic methods	Water gradient in the SC (only shown in vivo by Raman spectroscopy) Efficacy of topically applied products (drugs, emollients) and claim support (hydrating effect)
Skin surface pH	Flat glass electrode measurement	Monitoring of skin surface acidity in a defined lifetime range, specific populations (ethnic groups, sensitive skin subjects), anatomical sites
	Tape-stripping techniques	Studying the role of pH for perturbed barrier restoration (link to the metabolic processes in SC)
	Fluorescent lifetime imaging	pH in dermatological and systemic disorders
	Use of pH-sensitive fluorescent dyes	Effects of topically applied substances (medications, cosmetics) on pH
Skin surface lipids	Photometric methods	Estimation of different parameters (sebum casual level, sebum excretion rate, sebum replacement time, instant sebum delivery, follicular excretion rate, and sustainable rate of sebum excretion)
	Solvent extraction	Assessment of skin greasiness/ skin type
	Cigarette paper pads	Anti-seborrheic efficacy of medications/cosmetics
	Bentonite clay	
	Lipid-sensitive tapes	
SC components	Tape harvesting methods (sequential tape stripping)	Investigations in epidermal barrier recovery after perturbation
	Cyanoacrylate strip	SC components (lipids, proteins, enzymes, cytokines, DNA, RNA)
	Solvent extraction	Oxidative stress assessment Topical drug availability/pharmacokinetics
Molecular	In vivo confocal	SC thickness (axial resolution of 2 μ m)
imaging of SC compounds	Raman microspectroscopy	SC water gradient
		Semi-quantitative assessment of SC lipids, lactate, urea, urocanic acid and other components

Enhancement Strategies

The constantly increasing interest in transdermal delivery derives directly from the advantages of the transdermal route compared with the oral route. However, the stratum corneum (the outermost layer of the skin) acts as a barrier to outside invaders entering the human body; it is hence responsible for the poor permeability of skin. This successful role becomes an obstacle to overcome when transdermal drug delivery is desired. To overcome the main limitation of transdermal delivery (low permeability), innovative technologies have been developed in an attempt to increase transdermal drug delivery as well as to facilitate the extraction of molecules for monitoring and diagnostic purposes.^[26] These technologies include iontophoresis^[27-30], electroporation^[30-33] and microneedle array.^[34,35]

Future Challenges

Transdermal delivery has gained a wide importance from the past few decades where it represents a viable way of

delivering a number of drugs with the potential to deliver many more using several enhancement approaches. Further research will be aimed to improve transdermal delivery and enabling commercialization of intelligent TTS including feedback loops, synthesis and development of more efficient penetration enhancers, better understanding skin irritation, immunology, and metabolism, and improving fluxes for a wide variety of molecules.

CONCLUSION

This review provides information about the movement of molecules or diffusion of molecules through the skin. The barrier function does provide a formidable barrier and the use of physical techniques such as iontophoresis, electroporation and ultrasound will undoubtedly have a future impact on delivery of drugs into and through the skin and other enhancement techniques includes chemical and biological approach to breach the skin barrier. It will only be possible with a fundamental

understanding of the properties of the skin. It will be necessary to understand how the physicochemical properties of the penetrant impact on the transport rate of the molecule. This review does not purport to be an exhaustive list of publications over the time span addressed, it represents papers that exemplify different points and ones which form the basis of our current knowledge base.

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