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Review Article

MECHANISMS, KINETICS AND MATHEMATICAL MODELLING OF TRANSDERMAL PERMEATION- AN UPDATED REVIEW

Mithun Bhowmick*, Tamizharasi Sengodan

Dept. of Pharmaceutics, Nandha College of Pharmacy and Research Institute, Erode, Tamil Nadu, India

***Corresponding Author: Email** bhowmick_theyoungscientist@ymail.com

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ABSTRACT

Percutaneous absorption involves passive diffusion of substances through the skin. The mechanism of permeation can involve passage through the epidermis itself or diffusion through shunts, particularly those offered by the relatively ubiquitously distributed hair follicles and eccrine glands. While exceptions to the rule are acknowledged, it is now generally believed that the trans-epidermal pathway is principally responsible for diffusion across the skin. Far more often than not, the main resistance encountered along this pathway arises in the stratum corneum. The phenomenon of percutaneous absorption can be visualized as consisting of a series of steps in sequence: sorption of a penetrant molecule onto the surface layer of stratum corneum, diffusion through it and the viable epidermis, and finally, at the papillary layer of the dermis, the molecule is taken up into the microcirculation for subsequent distribution. Knowledge of skin permeation kinetics and Mathematical modeling is vital to the successful development of transdermal systems.

Keywords: Percutaneous absorption mechanism, trans-epidermal pathway, follicular and glandular pathway, skin permeation kinetics, Mathematical modelling.

INTRODUCTION

Human skin is an effective, selective barrier to chemical permeation. Most small water-soluble non-electrolytes diffuse into the systemic circulation a thousand times more rapidly when the horny layer is absent. Among the various skin layers, Stratum corneum (SC) is the rate-limiting barrier to percutaneous drug transport due to its desquamating 'horny' properties comprising about 15–20 rows of flat partially desiccated dead keratinized epidermal cells. Due to the lipid - rich nature of the SC layer (40% lipids, 40% protein and only 20% water) and its low water content transport of hydrophilic or charged molecules across SC is low while transport of lipophilic drug molecules is higher due to their lipid miscibility with intercellular lipids around the cells in the SC layer.

Skin absorption pathways[3-10]

Skin absorption pathways can be divided into the transport:

(1) Epidermal route (across the intact SC)

(2) Trans-follicular (shunt pathway) Absorption (along the skin appendages)

The physicochemical properties of the drug as well as the nature of the formulation are the main factors influencing the choice of pathway.

1. Epidermal route[3-7]

For drugs, which mainly cross-intact horney layer, two potential micro routes of entry exists,

(a) The Trans-cellular (intra-cellular) route

(b) The Para-cellular (inter-cellular) route

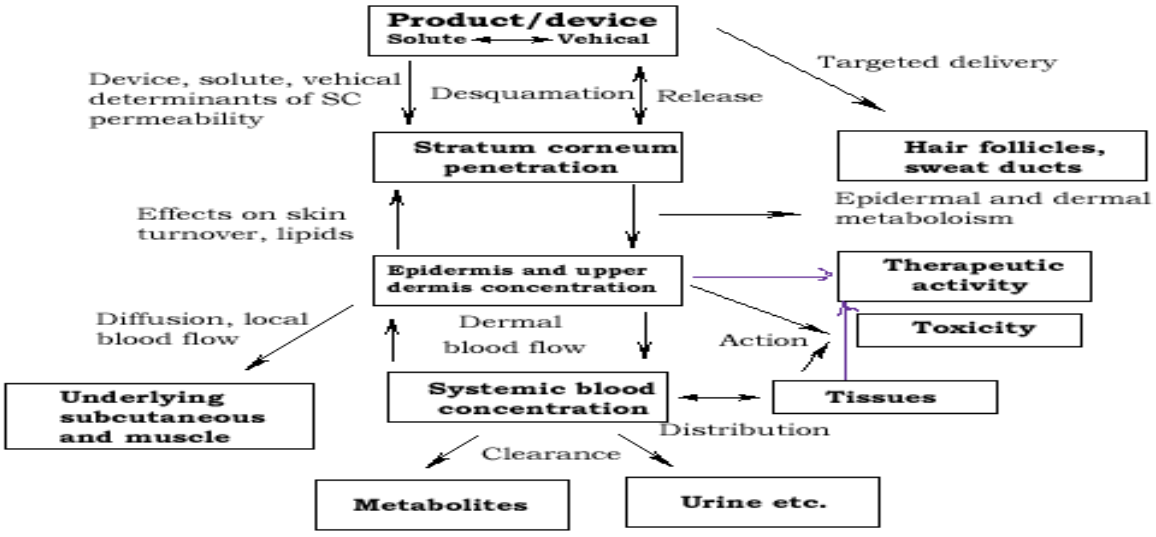


Fig.1: Schematic illustration of percutaneous permeation

(a) The Transcellular (Intracellular) route

Transcellular pathway means transport of molecules across epithelial cellular membrane. These include passive transport of small molecules, active transport of ionic and polar compounds, and endocytosis and transcytosis of macromolecules.

Under normal conditions the transcellular route is not considered as the preferred way of dermal invasion the reason being the very low permeability through the corneocytes and the obligation to partition several times from the more hydrophilic corneocytes into the lipid intercellular layers in the stratum corneum and vice versa. The transcellular pathway can gain an importance when a penetration enhancer is used, for example, urea which increases the permeability of the corneocytes by altering the keratin structure.

(b) The Paracellular (Intercellular) route

Paracellular pathway means transport of molecules around or between the cells. Tight junctions or similar situations exist between the cells. The principal pathway taken by a permeant is decided mainly by the partition coefficient (log k). Hydrophilic drugs partition preferentially into the intercellular domains, whereas lipophilic permeants (o/w log k >2) traverse the stratum corneum via the intracellular route.

The intercellular route is considered to be the predominantly used pathway in most cases especially when steady-state conditions in the stratum corneum are reached. Substance transport occurs in the bilayer-structured continuous intercellular lipid domain within the stratum corneum. Although this pathway is very tortuous and therefore much longer in distance than the overall thickness of the stratum corneum (~20 µm) and has been estimated as long as 500 µm. The intercellular route is considered to yield much faster absorption due to the high diffusion coefficient of most drugs within the lipid bilayer.

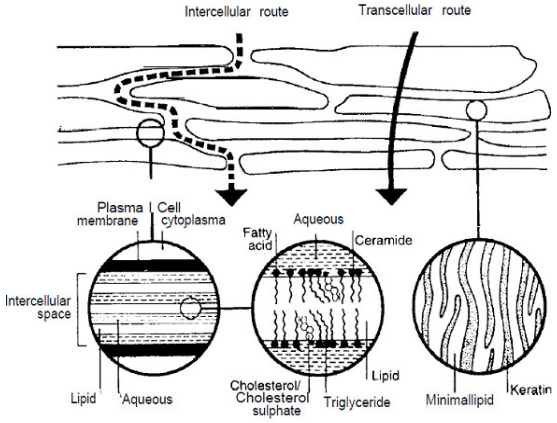


Fig.2: Possible micro routes for drug penetration across human skin

2. Trans-follicular (shunt pathway) Absorption (along the skin appendages)[8-10]

Skin appendageal route comprises transport via eccrine sweat glands, apocrine sweat glands and hair follicles with their associated sebaceous glands. These routes circumvent penetration through the stratum corneum and are therefore known as "shunt" routes.

Hair follicles: Hair follicles with their associated sebaceous glands are present all over the skin surface with the exception of lips, palms, and soles. Furthermore, hair follicles intersperse down to the subcutis offering permeation pathways deep into the skin. The density of hair follicles varies with species and body site. The sebaceous glands produce the sebum, which lubricates and protects the skin and is involved in the regulation of the pH on the skin surface.

Eccrine glands: Eccrine glands can be found on the entire body surface of humans except for the lips, external ear canal, clitoris, and labia minora. These glands play an important role in thermoregulation which is necessary for fluid and electrolyte homeostasis. They secrete a milky or oily odorless liquid which produces the characteristic body smell after metabolism through surface bacteria of the skin.

Apocrine glands: The apocrine glands are limited to specific body regions and are also coiled tubes. These glands are about ten times the size of the eccrine ducts extend as low as the subcutaneous tissues and are paired with hair follicles.

This Trans-follicular (shunt pathway) route is considered to be of minor importance because of its relatively small area, approximately 0.1 % of the total skin area. In contrast, in the initial stages of a skin absorption process and in the case of large hydrophilic compounds and ions invasion through the appendages may play a considerable role. Recent studies also report that the appendages route may be involved in the absorption of liposomes, nanoparticles, and cyclodextrin-inclusion complexes.

Kinetics of transdermal permeation[11-15]

For a systemically active drug to reach a target tissue, it has to possess some physicochemical properties which facilitate the sorption of the drug through the skin and enter the microcirculation. The release of a therapeutic agent from a

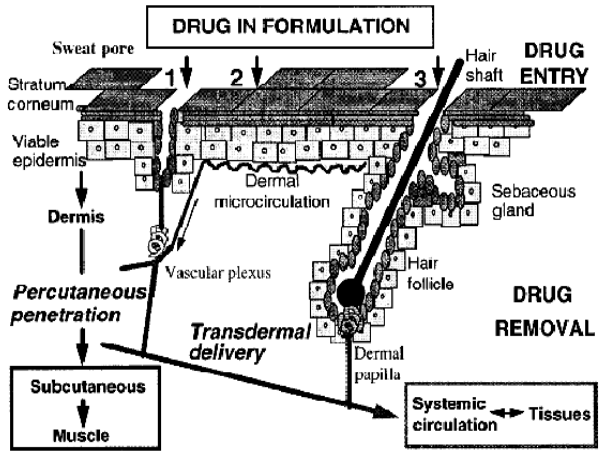


Fig.3: Absorption across the skin can occur through sweat ducts (1), intercellular regions of the stratum corneum (2) and through the hair follicles (3)

TDDS applied to the skin surface and its transport to the systemic circulation involves the following steps:

i. Dissolution within and release from the formulation,

ii. Partitioning into the outermost layer of the skin, SC,

iii. Diffusion through the SC,

iv. Partitioning from the SC into the aqueous viable epidermis,

v. Diffusion through the viable epidermis and into the upper dermis and

vi. Uptake into the local capillary network and eventually the systemic circulation

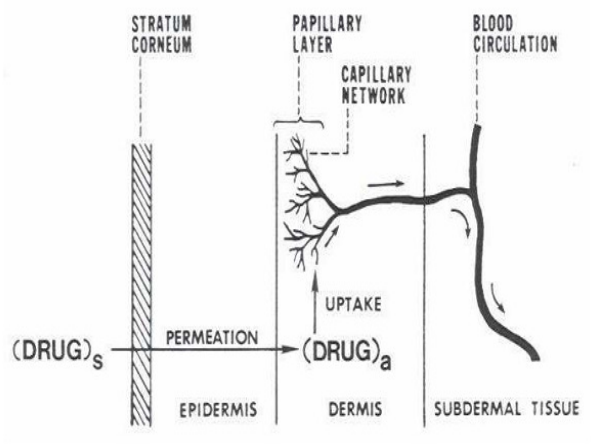


Fig.4: A multilayer skin model showing sequence of Transdermal permeation of drug for systemic delivery

Knowledge of skin permeation kinetics is vital to the successful development of transdermal systems. This permeation can be possible if the drug possesses certain physico-chemical properties. The rate of permeation across the skin (dQ/ dt) is given by:

$$\frac{dQ}{dt} = P_s (C_d - C_r) \qquad \text{Eq. 1}$$

Where, C_d = concentration of skin penetrant in the donar compartment (e.g., on the surface of *stratum corneum*)

C_r = concentration in the receptor compartment (e.g., body) respectively

P_s = the overall permeability constant of the skin tissue to the penetrant

$$P_s = \frac{K_s D_{ss}}{h_s} \qquad \text{Eq. 2}$$

Where, K_s is the partition coefficient for the interfacial partitioning of the penetrant molecule from a solution medium or a transdermal therapeutic system onto the stratum corneum, D_{ss} is the apparent diffusivity for the steady state diffusion of the penetrant molecule through a thickness of skin tissues and h_s is the overall thickness of skin tissues. As K_s, D_{ss} and h_s are constant under given conditions, the permeability coefficient (P_s) for a skin penetrant can be considered to be constant.

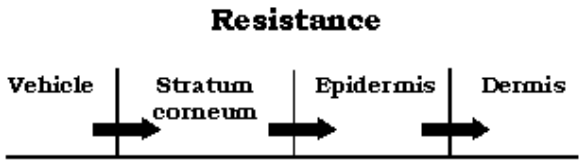
From Eq.1 it is clear that a constant rate of drug permeation can be obtained only when $C_d >> C_r$ i.e., the drug concentration at the surface of the stratum corneum (C_d) is constistently and substantially greater than the drug concentration in the body (C_r). then Eq. 1 becomes:

$$\frac{dQ}{dt} = P_s C_s \qquad \text{Eq. 3}$$

Permeability coffiecient = $K_s D_{ss} / h_s = 1/$ resistance

Resistance has many components

- Vehicle
- Stratum corneum (usually most significant)
- Epidermis
- Dermis



The resistance occurs one after another 'in series'

$R_{total} = R_{vehicle} + R_{stratum\ corneum} + R_{epidermis} + R_{dermis}$

$$\text{Total Permeability} = \frac{1}{R_{vehical}} + \frac{1}{R_{stratum\ corneum}} + \frac{1}{R_{epidermis}} + \frac{1}{R_{dermis}}$$

The membrane limited flux (J) under steady state condition is described by equation:

$$J = \frac{DK_{o/w}C}{h} \qquad \text{Eq. 4}$$

Where,

J = Amount of drug passing through membrane system per unit area per unit time.

D = Diffusion coefficient with in the membrane

h = Membrane thickness

K = Membrane / vehicle partition coefficient

C = Concentration gradient across the membrane[44]

Mathematical Models for Transdermal Permeation [2,8,11,15]

Along the course of skin permeation, a drug molecule will encounter a number of diffusional resistance which counteract its permeation through various skin tissue layers. The total diffusional resistance (R_s) that a drug molecule has to overcome during the course of permeation across the skin tissues and the subsequent uptake by the capillary network for transport to the general circulation, is described mathematically by:

$$R_s = R_{sc} + R_e + R_{pd} + R_t \qquad \text{Eq. 5}$$

$$= \frac{H_{sc}}{D_{sc}K_m} + \frac{H_e}{D_eK_e} + \frac{H_{pd}}{D_{pd}K_{pd}} + \frac{1}{FH_s} \qquad \text{Eq. 6}$$

Where, Subscripts

R- diffusion resistance

s- skin

H- thickness

sc- *stratum corneum*

D- diffusivity

e- epidermis

K- partition coefficient

pd- papillary layer

F- peripheral blood flow rate

Rt- transfer resistance

The transdermal permeability coefficient (P_{sc}) can be defined by the following mathematical expression:

$$P_{SC} = \frac{1}{R_{SC}} = \frac{K_{pa} D_{pg}}{H_{SC}} \left\{ \frac{1.16}{\left[\frac{0.16\ D_{pg}}{K_{pl} \cdot D_{lm}} + 1 \right]} + 0.0017\ K_{pl} \frac{D_{lm}}{D_{pg}} \right\}$$

Eq. 7

Where,

K_{pa} - distribution coefficient of the penetrant molecules between the protein gel and the applied penetrant solution at equilibrium.

D_{pg} – diffusion coefficient of the penetrant molecules in protein gel.

H_{sc} – thickness of *stratum corneum*

K_{pl} – distribution coefficient of the penetrant molecules between the lipid matrix and protein gel

D_{lm} – diffusion coefficient of the penetrant molecules in lipid matrix.

If the drug is applied on to the skin surface in a simple solution form, the concentration of the drug (C_b) absorbed into the body can be described by Eq. 8. If the pharmacokinetic pattern of the drug is known to follow a simple *one compartment model*

$$C_b = \frac{(Drug)_a}{V_d} \times \frac{K_a}{K_a - K_e} \left(Exp^{-Ket} - Exp^{-Kat} \right)$$

Eq. 8

Where,

$(Drug)_a$ – concentration of drug in the body

V_d – volume of drug distribution

K_a – rate constant for skin absorption

K_e - rate constant for drug elimination

If the drug is delivered to skin surface through a *zero-order* delivery system, then, at a steady state, a constant blood level will be achieved, which is a linear function of the rate of drug release (K_o) and is inversely proportional to the rate constant for drug elimination (K_e), and the volume of distribution (V_d).

Initial phase

Eq. 9

$$C_b = \frac{K_o}{K_e V_d} \left(1 - Exp^{-Ket} \right)$$

$$C_b = \frac{K_o}{K_e V_d} \left(1 - Exp^{-Ket} \right)$$

Steady phase

$$C_b = \frac{K_o}{K_e V_d} \left(1 - Exp^{-Ket} \right)$$

Eq. 10

Eq. 10 indicates that the blood levels of a drug can be controlled in a desired therapeutic range by programming the magnitude of K_o value of the delivery system, (Since both K_o & V_d terms are the intrinsic pharmacokinetic properties of the drug molecule).

On the other hand if the drug is administered via a Transdermal Drug Delivery System which releases the drug molecules at a *first-order* rate constant (K_1) the blood level of the drug will then be described by Eq. 11.

$$C_b = \frac{K_1 (Drug)_{dds}}{(K_1 - K_e) V_d} \left(Exp^{-Ket} - Exp^{-K_1 t} \right)$$

Eq. 11

In this case, C_b will be dependant on the drug dose level the drug delivery system, $(Drug)_{dds}$.

CONCLUSION

The assessment of percutaneous absorption of molecules is a very important step in the evaluation of any dermal or transdermal drug delivery system. A key goal in the design and optimization of dermal or transdermal dosage forms lies in understanding the factors that determine a good in vivo performance. Given the skin's structural and biochemical complexity, and the restrictions of in vivo and even in vitro experiments, mathematical analysis and modeling provide an attractive alternative, which, in spite of assumptions often grossly simplifying, may still offer some insights on the trend and influences of related factors. They have been proved to be valuable.

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