REVIEW ON PERMEATION ENHANCERS FOR TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT: Transdermal drug delivery is a potential route of systemic drug delivery and first pass effect**.** With advantage of ease of application, better patient's compliance but there is big hurdle while using it. Most of drug release cannot pass through stratum corrneum thatswhy permeation enhancer have used.
The present review includes the classification of permeation enhancers and their mechanism of action; also help in the selection of a suitable enhancer for improving the transdermal permeation of poorly absorbed drugs.

Keywords: Permeation enhancers, TDDS, Statrum corneum, Skin

I. INTRODUCTION

Transdermal drug delivery offers a very advantageous effective route for drug delivery compared to other routes of drug administration such as tablet capsule and having advantages such as bypassing the hepatic first pass metabolism, and longer duration of action[1,2] However, the barrier function of the skin outermost layer, the stratum corneum (SC) is one of the main limitations to it, and for this reason, skin penetration enhancers are gaining the greatest interest in pharmaceutical research era[3].

There are mainly three possible routes for percutaneous penetration of drug molecules, which include intracellular diffusion across the SC corneocytes, permeation through the SC intercellular lipid Spaces, and penetration through skin appendages[5]

To achieve therapeutically effective drug levels at the proper site through the transdermal drug delivery, the barrier properties of the SC must be modified to enable sufficient drug permeation. A lot of approaches have been used to alter the SC barrier properties, and the most commonly applied approach is the application of penetration enhancers (PEs), which have been used in TDDS since the 1960s[6]

II. SKIN AS A BARRIER TO DRUG PERMEATION

The outermost few microns of the skin, the Stratum Corneum,which is barrier part of the skin. This layer of the skin is the most impermeable, forming a laminate of compressed keratin-filled corneocytes attached in a lipophilic matrix [6]

2.1: Penetration enhancer

Permeation enhancers are as substances that are capable of promoting penetration of drugs into skin and transdermal therapeutic systems offers a more reliable mean of administering drug through the skin[7].

2.1.1. Ideal properties of permeation enhancer[8,9]

1. They must be pharmacologically inert, nonallergic, nonirritating, and nontoxic
2. It must have compatibility with excipients and drugs • It must not have any pharmacological activity in the body
3. Cosmetically it must be acceptable
4. It must be odorless, tasteless, and colorless
5. It should allow therapeutic agents into the body but should prevent the loss of endogenous material from the body, i.e. they should work unidirectional
6. It must have chemical and physical stability
7. It must have a reproducible and predictable duration of action
8. It must have a good solvent property[8,9]

III. Transdermal permeation pathways[10,11]

Transdermal permeation can take place by diffusion through:

A. Through the SC: By means of the transcellular route, drugs can pass through the corneocytes highly hydrated keratins are present in corneocyte, which provides an aqueous environment for which the hydrophilic drugs can pass. Hence, the transcellular pathway is a predominant pathway for hydrophilic drugs

B. Intercellular permeation: In intercellular pathway, the drug diffusing takes place by means of the continuous lipid matrix

C. Transappendaged permeation: Only 0.1% of the skin surface area is covered by the hair follicle and sweat glands which limit the area available for the applied drug formulation to come in contact with it. For many drugs, an aqueous pathway is considered desirable but as the sweat is traveling against the diffusion pathway of permeant, permeation may be limited. Lipid-rich sebum fills the sebaceous gland, which may present a barrier for hydrophilic drug.

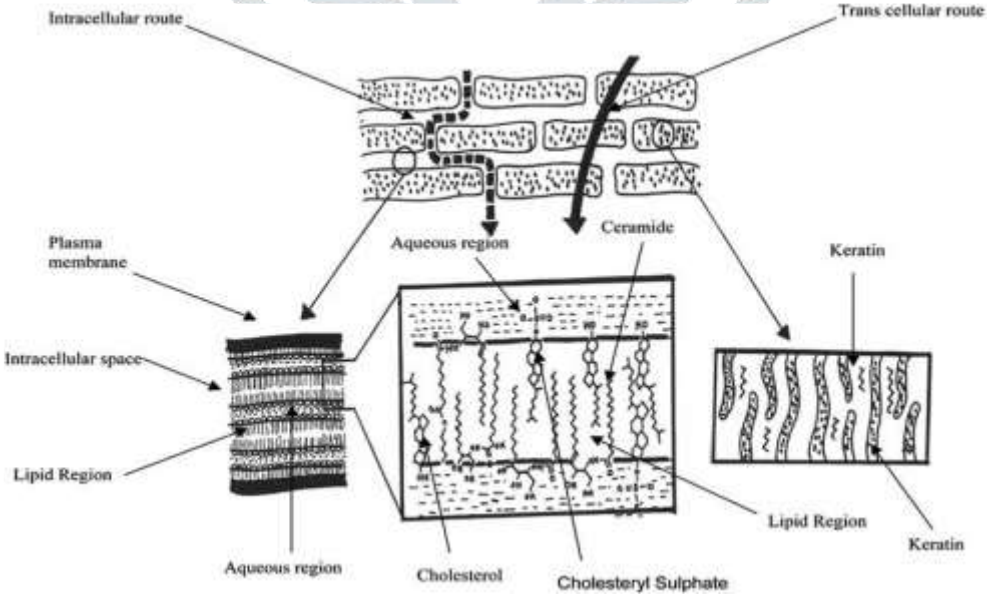

Fig 3.1.1: Simplified diagram of skin structure and macro routes of drug barrier at a penetration.[3]

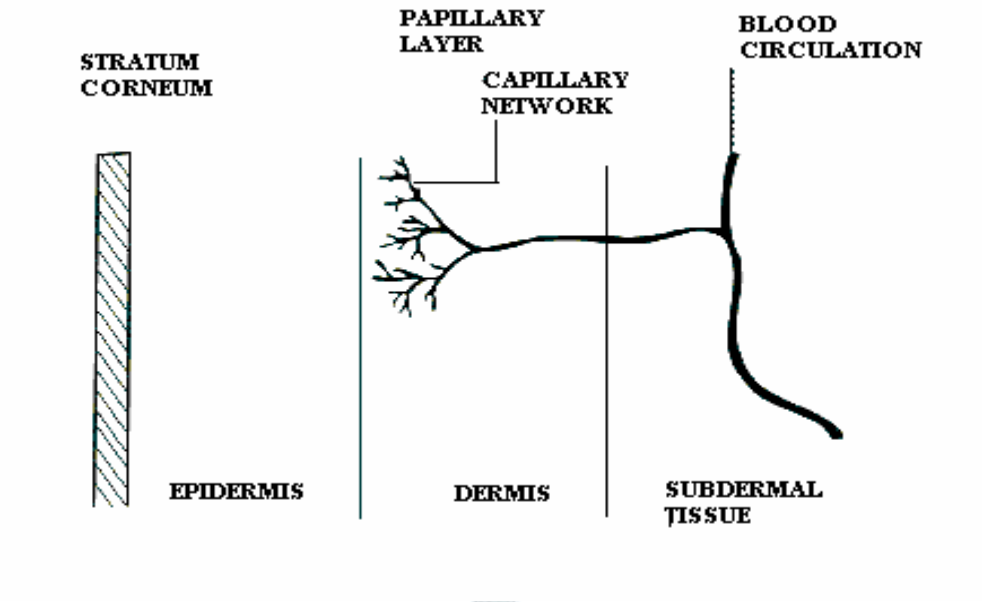

Fig 3.1.2: Simplified model of the human skin for mechanistic analysis of skin permeation.[5]

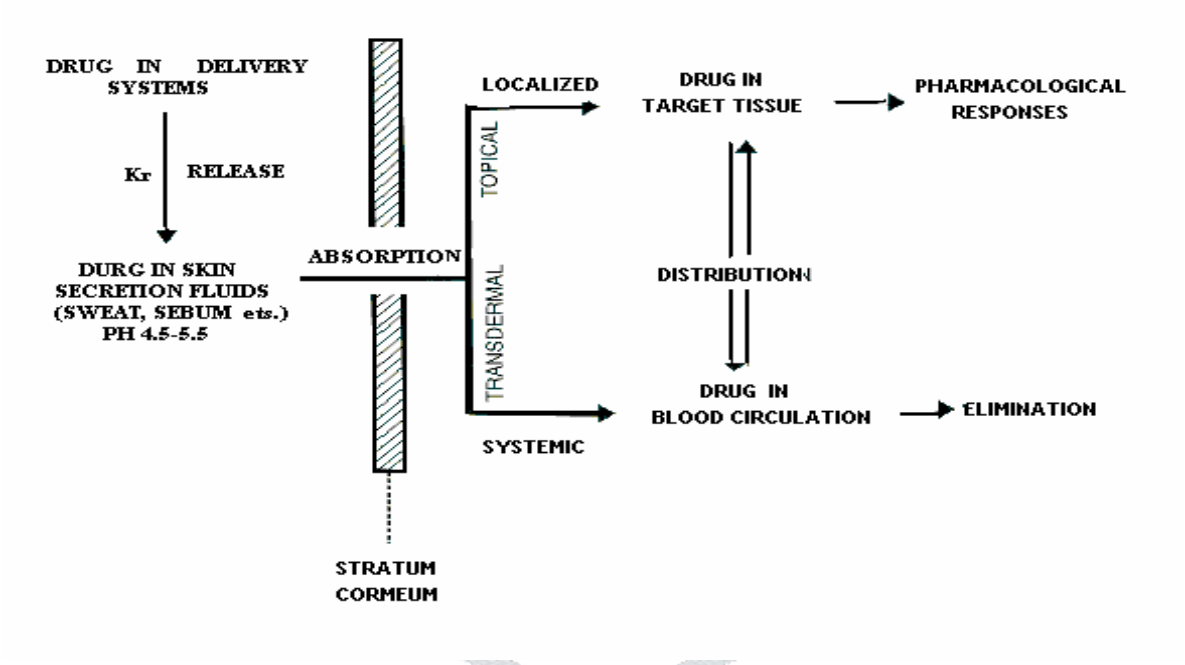

Fig 3.1.3: Percutaneous absorption of drugs for localized therapeutic action in the skin tissues or for systemic medications in the tissues: [4]

There are mainly three approaches for the penetration enhancement

3.1. Chemical approach

1. **Synthesis of lipophilic analogs:** Ethosomes can promote the penetration of lipophilic drugs into the skin, but the underlying mechanism is still unknown. The purpose of this study was to investigate the mechanism of transdermal permeation promotion of lipophilic drugs by ethosomes. The ethosomes could penetrate the skin via the percutaneous pathway of the hair follicle and stratum corneum, while during the process of penetration, the vesicles were broken and the phospholipids were retained in the upper epidermis, with the test compounds penetrating gradually. The superior percutaneous penetration

of ethosomes was linked to the synergistic effects of their ingredients. The percutaneous pathways of ethosomes included open hair follicles and stratum corneum pathways. In addition, the vesicles might break up during percutaneous penetration in the superficial layer of the skin, allowing the test compounds to keep permeating into the deeper layer alone, while the phospholipid was retained in the upper epidermis[11,12].

2. **Delipidization of stratum corneum**: Removal of stratum corneum by tape stripping and delipidization by a chloroform-methanol mixture, whose effects on the permeation were similar, increased the permeability coefficients of the derivatives, especially those of relatively hydrophilic derivatives[13]
3. **Co-administration of skin permeation enhancers.:** Chemical permeation enhancers (CPEs) are molecules that interact with the constituents of skin's outermost and rate limiting layer stratum corneum (SC), and increase its permeability. Designing and testing of new CPEs is a resource intensive task, thus limiting the rate of discovery of new CPEs[10]

This chemical approach can further classified according to their chemical class.

i. Sulfoxides : Dimethyl sulfoxide, Decylmethal sufoxide
ii. Alcohols : Ethanol
iii. Polyols : Propylene glycol
iv. Alkenes : long chain alkanes (C_7-C_{16})
v. Fatty acids: oleic acid
vi. Esters: Isopropyl myristate
vii. Amines and amides: Urea, Dimethyl acetamide, dimethyl formamide
viii. Pyrrilidones: N-Methylpyrrilidone, Azones
ix. Terpenes: Eugenol
x. Surface active agents: Cationic surfactants
xi. Cyclodextrines

3.2. Biochemical approach

1. Synthesis of bio-convertible pro-drugs: Prodrugs continue to attract significant interest in the transdermal drug delivery field. These moieties can confer favorable physicochemical properties on transdermal drug delivery candidates. Alkyl chain lengthening, pegylation are some of the strategies used for prodrug synthesis. It is usually important to optimize partition coefficient, water and oil solubilities of drugs[14]

2. Co-administration of skin metabolism inhibitors.

The intercellular domains of the stratum corneum, which contain a mixture of cholesterol, free fatty acids, and ceramides, mediate both the epidermal permeability barrier and the transdermal delivery of both lipophilic and hydrophilic molecules[15,4,5]

Eg : Dimethyl sulphoxides.

3.3. Physical approach

1. Iontophoresis: Iontophoresis is a process of transdermal drug delivery by use of a voltage gradient on the skin. Molecules are transported across the stratum corneum by electrophoresis and electroosmosis and the electric field can also increase the permeability of the skin.[4.5,10,16]

2. Sonophoresis : Ultrasonic energy: Sonophoresis is a drug delivery method where ultrasound is used to increase the absorption of topical compounds into the epidermis, dermis and skin appendages. The medication usually consists of hydrophilic molecules and macromolecules.The effects of ultrasound on the movement of drugs through intact living skin and into the soft tissues. Although the exact mechanism of sonophoresis is not known, drug absorption may involve a disruption of the stratum corneum lipids allowing the drug to pass through the skin [9, 16, 17]

3.Thermal Energy: Thermal ablation, also known as thermophoresis, involves the depletion or removal of the SC by the application of heat to enhance the drug permeation across the skin Thermal ablation is a physical technique in which the SC is selectively vaporized followed by its removal from the skin surface, without damaging deeper tissue.Therefore, the thermal exposure should be for short duration so that temperature gradient across the SC can be higher to maintain significant skin surface temperature compared with the underneath viable epidermis . It can be achieved in two ways: (i) moderate temperature (≤ 100 °C) and long time, and (ii) very high temperature (≥ 100 °C) and short period. It is worthy to mention that the duration of thermal exposure was ranged from 1 μs to 100 ms. However, the second option is in great use because the SC temperature will be significantly increased due to high temperature; at the same time; no damage is being caused to deeper tissue due to short period of exposure[17,18,19,20]

4. **Stripping of stratum corneum**: The dermatologists use various techniques to cause disruption on the topical skin surface for fast penetration of formulations used for the treatment of acne, scars, skin blemishes and hyper pigmentation. One such technique is microderm abrasion which comes under superficial skin resurfacing. During Microscissuining outer surface of the skin is eroded by using sharp microscopic metal granules. This leads to the formation of micro-channels in the skin. Studies have shown that this process can enhance angiogenesis permeation to 100 times[18,19]
5. **Hydration of stratum corneum**: **Enhancement** in skin **penetration** by **hydration** of the **stratum corneum**, or by use of chemical **enhancers** acting on the lipids and keratinized structures in the **stratum corneum**, partitioning and solubility effects is a promising tool in potential clinical applications.[15,21,22]

IV. CONCLUSION

Many drug are given via parenteral route it is very painful so we use transdermal technique which is non-invasive but problem is stratum corneum by using different permeation enhancers we enhance drug permeability into systemic circulation at high rate. Therefore different type of permeation enhancer research is very emerging area to study.

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