

A Review: Physical Penetration Enhancers For Transdermal Drug Delivery Systems

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Abstract: *Delivery of the drug via skin would provide a useful alternative to oral route and important site of drug application for local and systemic effects with minimum undesirable side effects. Skin penetration techniques have been developed to improve bioavailability and enhance the range of drugs for which transdermal delivery is a viable option. The permeation of drug through skin can be enhanced by chemical penetration enhancers. The present review article includes the classification of permeation enhancers and their mechanism of action; thus it will help in the selection of suitable penetration enhancer for improving the permeation of poorly absorbed drugs via transdermal route.*

Key word: *Transdermal delivery; skin; chemical penetration enhancers.*

I. Introduction

The main objective of transdermal drug delivery system is to deliver drugs into systemic circulation into the skin through skin at predetermined rate with minimal inter and intra patient variation. Currently transdermal delivery is one of the most promising methods for drug application. It reduces the load that the oral route commonly places on the digestive tract and liver. It enhances patient compliances and minimizes harmful side effects of a drug caused from temporary over dose and is convenience in transdermal delivered drugs that require only once weakly application. That will improves bioavailability, more uniform plasma levels, longer duration of action resulting in a reduction in dosing frequency, reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval compared to a decline in plasma levels with conventional oral dosage forms. Transdermal delivery not only provides controlled, constant administration of drugs, but also allows continuous input of drugs with short biological half lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Several important advantages of transdermal drug delivery are limitations of hepatic first pass metabolism, enhancement of therapeutic efficacy and maintenance of steady plasma level of drug. The developments of TDDS is a multidisciplinary activity that encompasses fundamental feasibility studies starting from the selection of drug molecule to the demonstration of sufficient drug flux in an *ex vivo* and *in vivo* model followed by fabrication of a drug delivery system that meets all the stringent needs that are specific to the drug molecule (physicochemical, stability factors), the patient (comfort and cosmetic appeal), the manufacturer (scale up and manufacturability) and most important economy.

Advantages of transdermal drug delivery

- Transdermal drug delivery enables the avoidance of gastrointestinal absorption with its associated pitfalls of enzymatic and pH associated deactivation.
- Avoidance of first pass metabolism.
- The lack of peaks in plasma concentration can reduce the risk of side effects, thus drugs that require relatively consistent plasma levels are very good candidate for transdermal drug delivery.
- As a substitute for oral route.
- The patch also permit constant dosing rather than the peaks and valley in medication level associated with orally administered medication.
- Rapid notifications of medication in the event of emergency as well as the capacity to terminate drug effects rapidly via patch removal.
- Avoidance of gastro intestinal incompatibility.
- Minimizing undesirable side effects.
- Provide utilization of drug with short biological half lives, narrow therapeutic window.

Disadvantages of transdermal drug delivery

- Transdermal drug delivery system cannot deliver ionic drugs.
- It cannot develop for drugs of large molecular size.
- It cannot deliver drugs in a pulsatile fashion.

Routes of drug penetration through skin

In the process of percutaneous permeation, a drug molecule may pass through the epidermis itself or may get diffuse through shunts, particularly those offered by the relatively widely distributed hair follicles and eccrine glands as shown in figure 1. In the initial transient diffusion stage, drug molecules may penetrate the skin along the hair follicles or sweat ducts and then absorbed through the follicular epithelium and the sebaceous glands. When a steady state has been reached the diffusion through the intact *Stratum corneum* becomes the primary pathway for transdermal permeation

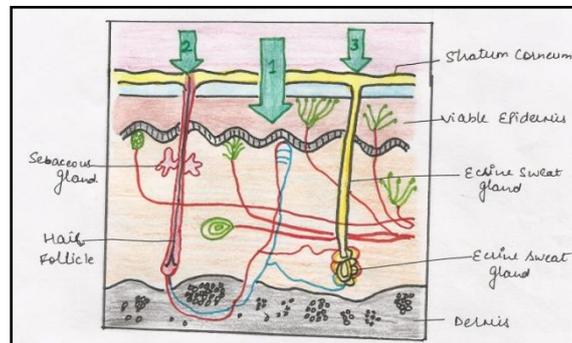


Fig. 1 Possible macro routes for drug penetration 1) Intact horny layer, 2) Hair follicles and 3) Eccrine sweat glands

For any molecules applied to the skin, two main routes of skin permeation can be defined:

- Transepidermal route
- Transfollicular route

Transepidermal route

In transepidermal transport, molecules cross the intact horny layer. Two potential micro-routes of entry exist, the transcellular (or intracellular) and the intercellular pathway as shown in fig. 2, 3

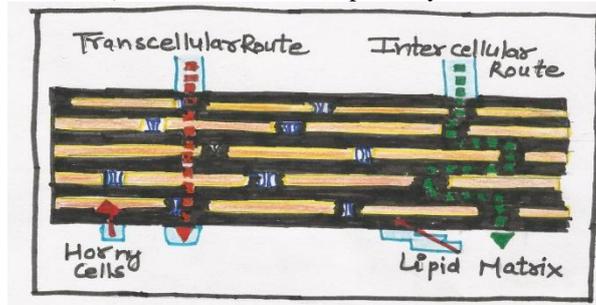


Fig. 2 Schematic representation of transepidermal route

Both polar and non-polar substances diffuse via transcellular and intercellular routes by different mechanisms. The polar molecules mainly diffuse through the polar pathway consisting of “bound water” within the hydrated *stratum corneum* whereas the non-polar molecules dissolve and diffuse through the non-aqueous lipid matrix of the *stratum corneum*. Thus the principal pathway taken by a penetrant is decided mainly by the partition coefficient (log K). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants (octanol/water log K > 2) traverse the *stratum corneum* via the intercellular route. Most molecules pass the *stratum corneum* by both routes.

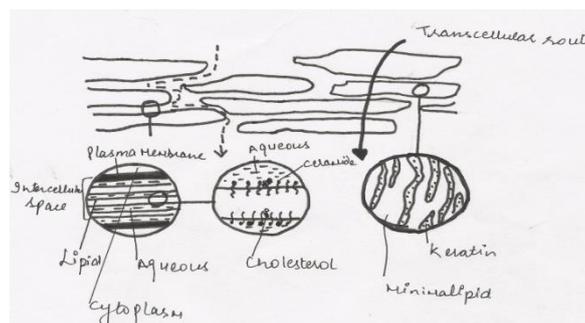


Fig. 3 Possible Micro routes for drug penetration across human skin intercellular or transcellular.

Transfollicular route (Shunt pathway)

This route comprises transport via the sweat glands and the hair follicles with their associated sebaceous glands. Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1% area of the total skin. This route seems to be most important for ions and large polar molecules which hardly permeate through the *stratum corneum*

Methods of enhancing transdermal delivery

It is very important to enhance the transdermal delivery so that drug can easily and quickly reach the systemic circulation and shows its effect. Following approaches are used to enhance the drug permeation through skin.

Physical approaches used for TDDS

As far as chemical enhancers are good but new techniques are also developed in which new physical methods are developed for the delivery of transdermal system or drug is enhanced form. These methods are enlisted as below:

Prodrug/ Drug

The prodrug approach has been used to enhance the transdermal delivery of drug with unfavorable partition coefficients the prodrug design involves addition of a promoiety to increase partition coefficient and also solubility and transport of the parent drug in the stratum corneum. Upon reaching the viable epidermis, esterases release the parent drug by hydrolysis thereby optimizing solubility in the aqueous epidermis.

Iontophoresis

Iontophoresis passes a few milliamperes of current to a few square centimeters of skin through the electrode placed in contact with the formulation, which facilitates drug delivery across the barrier. The parameters that effect design of a iontophoresis skin delivery system include electrode type, current intensity, pH of the system. Increase drug permeation as a result of this can be attributed to either one or a combination of the following mechanism: shown in fig.4 Electroporation (for charged solutes), Electro osmosis (for uncharged solutes) and Electro perturbation (for both charged and uncharged).

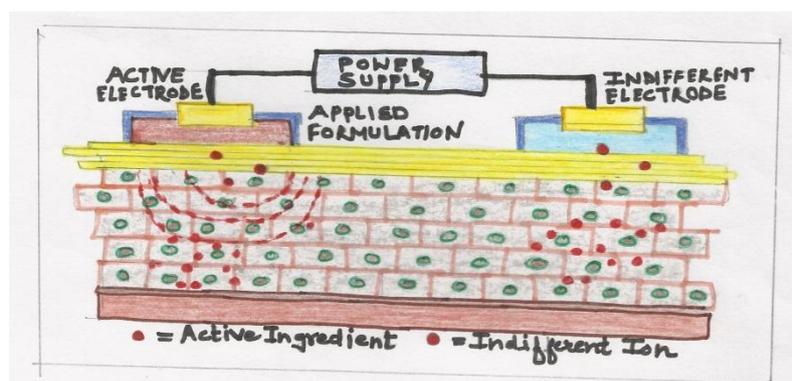


Fig.4 Basic principle of iontophoresis.

Eutectic system

A eutectic system is mixture of chemical compounds or elements that has a single chemical composition that solidifies at a lower temperature than any other composition. Transformation of solid drugs into a highly concentrated oily state at ambient temperatures exhibits improved skin permeability due to their thermodynamic activity in vehicle.

Electroporation

Electroporation is a method of application of short, high-voltage electrical pulses to the skin. That has been suggested to induce the formation of transient pores. High voltages (1000v) and short term duration (milliseconds) are most frequently employed. This technology is used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e, small molecules, proteins. Peptides, oligonucleotides) including biopharmaceuticals with molecular weight greater than 7 KDA. shown in fig. 5

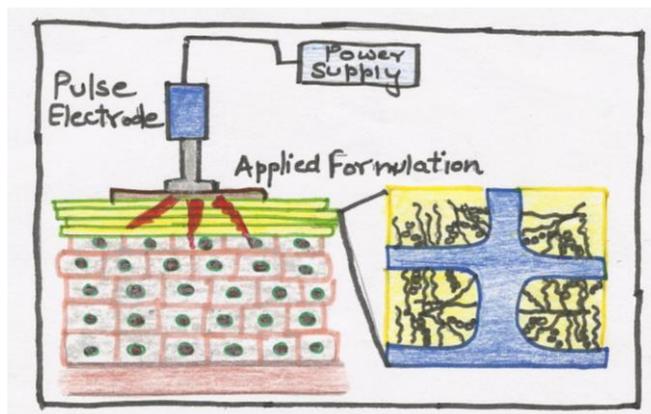


Fig. 5 Basic ppl of electroporation.

Use of ultrasound

Application of ultrasound, particularly low frequency ultrasound, has been shown to enhance transdermal transport of various drugs including macromolecules. It is also known as sonophoresis.

Magnetophoresis

It involves application of magnetic field that acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. It will enhance the permeability.

Microneedle based devices

Transdermal patches with microscopic projections called microneedles were used to facilitate transdermal drug transport. The microneedles of length 50-110 micrometer will penetrate stratum corneum and epidermis to deliver drug. shown in fig. 6

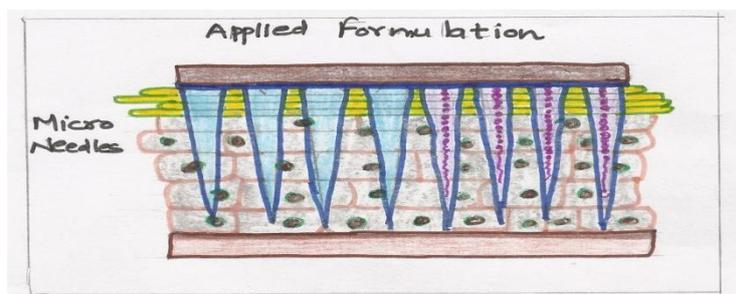


Fig. 6 Basic design of microneedle delivery device.

II. Conclusion

Skin permeation enhancement technology is a rapidly developing field which would significantly increase the number of drugs suitable for transdermal drug delivery, with the result that skin will become one of major route of drug administration in next era. Physical penetration enhancers are not only specific towards stratum corneum; also penetrate into the deeper layers of the skin to viable epidermis cells. A better understanding of the interaction of enhancers with stratum corneum and the development of structure activity relationship for enhancers will aid in the design of optimal characteristics and minimal toxicity.

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