Significance of Penetration Enhancers in Topical Drug Delivery System- A Review

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Abstract

Topical drug delivery is most acceptable and convenient route of administration of drug which are having short half and which are poorly soluble drugs. Along with it topical route also set to be challenging area for delivery of drug through stratum corneum. Traditionally permeation enhancers were designed to deliver drug molecules across skin into systemic circulation. Emergence of some other techniques for enhancement through modification of stratum corneum by hydration, or by using chemical or physical effects has remained area of interest. In this review, we represented an overview of the current strategies to overcome stratum corneum as a barrier for entry of drug molecule.

Keywords Hydration, poorly soluble drugs, penetration enhancers, stratum corneum.

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Introduction

The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system. First, the skin is an excellent permeability barrier refractive to nearly all but small lipophilic molecules, as is discussed briefly further in the text(Vineet Mathur*et et al*, 2010)**.** Drug delivery via the percutaneous route potentially has many advantages over intravenous and oral administration. The principal barrier to topical drug delivery is the stratum corneum which possesses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability (Mohammad Aqil*et et al***,** 2009)**.**Transdermal drug delivery is the administration of a therapeutic agent through intact skin for systemic effect. The method employed for modifying the barrier properties of the stratum corneum to enhance drug penetration and absorption through skin may be classified into the following categories;

chemical enhancement, physical enhancement, biochemical enhancement, supersaturation enhancement and bioconvertable prodrug **(**Pathan IB and Setty CM, 2009 and SainiS*et al,* 2014). Penetration enhancer use to increase the permeability of drug through skin.

Ideal properties of penetration enhancers

1. They should be non-toxic, non-irritating and non-allergenic.
2. It should be cosmetically acceptable**.**It should physically and chemically stable also it
3. Should be compatible with drug and excipient.

4. It should have no pharmacological activity within body.

5. It should be odorless tasteless colorless and inexpensive and have good solvent property. **(**Sushila Saini *et al* 2014).They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible**.**

6.When removed from the skin, barrier properties should return both rapidly and fully to normal. (Pathan IB and Setty CM, 2009)

Mechanism of action of penetration enhancers

Skin permeation enhancer may exert their effect through one of the combination of the following mechanism:

- By solubilizing the skin tissue component.
- Interaction with intracellular lipids leading to disruption with highly ordered lamellar structure.
- Interaction with intracellular proteins to promote permeation of the drugs through corneocyte layer.
- Improved partition of the drugs, co-enhancers, co-solvents into stratum corneum. (Patil UK and Saraogi R, 2014**).**

It is well known as that the stratum corneum lipids provide the primary barrier function of the skin. Therefore, it would be pertinent to understand their organization in order to fully elucidate the mode of action of permeation enhancer(Charles AB. *et al,* 2000).Different Penetration Enhancers have different mechanism of action. The miscibility and solution properties of enhancers can be responsible for enhanced transdermal delivery of water soluble drugs. Mechanisms for penetration enhancement of oil soluble drugs are due to partial leaching of epidermal lipids by this improvement of drug permeation through skin. (Saini S *et al*, 2014).

Objectives of using penetration enhancers in transdermal delivery

The ultimate goal of transdermal drug delivery is to ensure that compounds are delivered, preferably at a specific rate, to the systemic circulation. Penetration of drug to the dermal vasculature follows exposure of the skin to a dosage form from which the active must partition, followed by diffusion of the compound through the external strata to the dermis. Partitioning of the drug from the dosage form is highly dependent on the relative solubility of the drug in the component of the delivery system and in the stratum corneum. (Walker RB &Smith EW, 1996).

Mechanism of penetration enhancers On the basis of lipid protein partitioning concept, there are three main functions of penetration enhancers-

1. Lipid disruption: The enhancers change the structure of stratum corneum lipid organization and make it permeable to drugs. Many enhancers operate mainly in this way [e.g. Azone, terpenes, fatty acids, dimethyl sulfoxide (DMSO) and alcohols.

2. Protein modification: Ionic surfactants, decylmethylsulfoxide and DMSO interact with keratin in corneocytes and open up the dense protein structure and make it more permeable.

3. Partitioning promotion: Many solvents change the solution properties of the horny layer and thus increase the partitioning of a drug, coenhancer and cosolvent. Ethanol increases the penetration of nitroglycerin and estradiol through the stratum corneum.(Sudhir K *et al*, 2012)

Drug delivery routes across human skin

Drug molecules in contact with the skin surface canpenetrate by three potential pathways through the sweatducts, *via* the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum. The relative importance of the shunt or appendageal route versus transport across the stratum corneum has been debated by scientists over the years and is further complicated by the lack of a suitable experimental model to permit separation of the three pathways **(**Heather B, 2005).

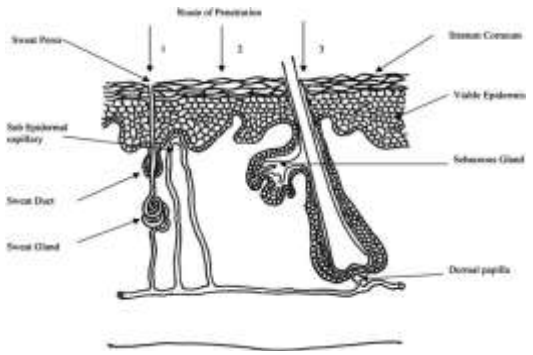

Fig. 1: Simplified Representation of Skin Showing Routes of Penetration;

(1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles)

The Intercellular pathway- Penetration between SC corneocytes is the pathway by which most compounds penetrate the skin.Most skin penetration enhancers were found to affect the intercellular lipid bilayers of which this route consists.

The Intrafollicular pathway -The amount of sebaceous glands on the total skin surface represents not more than 0.1%. Therefore there are scientists who believe that this route is not a significant penetration pathway for most molecules. When considering these openings as a possible route for penetration, it is important to understand the variations in follicle distribution among different body locations.

The polar pathway- This route is believed to be hydrophilic in nature. It is composed of aqueous regions surrounded by polar lipids that create the walls of microchannels. It is known to have a high penetration resistance to lipophilic compounds but low resistance to hydrophilic compounds (Nava D, 2005).

Physicochemical aspects of skin penetration (Raut SV*et al*, 2015).The drug diffusion through the skin is passive kinetic process that takes place down the concentration gradient from a region of high concentration to a region of lower concentration. Steady state equation can be described by Fick's first law of diffusion.

The equation describes rate of transfer (flux, J) of a diffusing substance through the unit area A of the membrane and diffusion coefficient, D to the concentration gradient across the membrane (dc/dx).

$$J = -AD\left(\frac{dC}{dx}\right) \quad (1)$$

The negative sign in eq. (1) is because the diffusion process occurs in the opposite direction to increased concentration.

Fick's second law of diffusion, Eq. (2) can be derived from eq. (1) to describe membrane transport under non steady state condition.

$$\frac{\partial C}{\partial t} = D\frac{\partial^2 C}{\partial X^2} \quad (2)$$

By maintaining the sink conditions in the receptor compartment and maximum fixed concentration in the donor compartment, the eq. (2) can be written as

$$J = AD\left(\frac{C_m}{h}\right) \quad (3)$$

Where, Cm is the concentration in the donormembrane interphase and h is effective diffusional pathlength. The Cm in the eq. (3) can be used to replace by vehicle membrane partition coefficient (K) as ratio between concentration of permeant in the membrane at the donor-membrane interface and the vehicle in which applied (Cv). Modified Fick's first law of diffusion describes the steady-state flux across the membrane eq. (4)

$$J_{ss} = \frac{ADKC_v}{h} \quad (4)$$

We can conclude that increased drug flux can be achieved by a change in D, K, and C. the compounds which are skin penetration enhancers should potentially change the solubility or partition behavior of the drug into stratum corneum or its diffusion properties or both. Sometimes change in thermodynamic activity of drug in the formulation manipulate the flux.

Stratum corneum as a barrier to drug permeation

Stratum corneum hydration is essential for proper function and appearance of the skin. The moisture content can be measured in vitro by means of gravimetric or electron microscopy, or by magnetic resonance techniques in vivo. The resolution of the latter technique is, however, currently not sufficiently high to enable isolated measurements on the stratum corneum. Compared with these techniques, assessment of stratum corneum hydration by means of electrical measurements (susceptance) represents an important reduction in instrumental cost and complexity.(Grimnes S and Martinsen, 2015)

Penetration Enhancer Types (Table 1).

1) Physical enhancers

Iontophoresis- In this technique small electrical current across the skin is applied to deliver ionized drug molecules and peptides at a faster rate than normal. Essential, the charged molecule is forced into the stratum corneum as it is repelled from the electrode of similar polarity. (Longsheng H *et al*, 2010).

Table 1: Techniques and Examples of Penetration Enhancers

Physical Enhancers	Iontophoresis, Sonophoresis, Magnetophoresis, Thermal Energy
Chemical Enhancer	Sulphoxides, Azones, Pyrolidone, Amines and Amides, Oxazolidinone, Fatty Acid an Ester, Surface Active Agents
Natural Enhancers	Cineole, Eugenol, D-Limonene, Menthol, Basil Oil, Clove Oil, Capsaicin
Miscellaneous Enhancers	Clofibric Acid, Phospholipids, Lipid Synthesis Inhibitors

Sonophoresis- Is the movement of drug molecules through the skin under the influence of ultrasound. His technique typically uses a low-frequency pressure wave of less than 100 kHz. The application of ultrasound to the skin can disrupt the stratum corneum lipid bilayer. As a result, drug molecules are allowed to permeate through the skin more easily. The combination of sonophoresis and iontophoresis significantly enhanced the transdermal delivery of certain drugs. (Longsheng H *et al*, 2010).

Magnetophoresis- Magnetic energy has been used in healing for thousands of years. Magnetophoresis is defined as the motion induced by a magnetic field on a particle of magnetic or magnetizable material. The term Magnetophoresis has also been used to describe the enhancement of drug permeation across a biological barrier by the application of a magnetic field. Enhancement of small molecules has been demonstrated using a range of magnetic technologies including static magnets and pulsed electromagnetic fields. The magnetic arrays used in static or moving mode offer advantages with respect to fabrication of devices. These can be incorporated into a transdermal patch or used as an applicator for a topical cream or gel. (Heather AE, 2017)

Thermal Energy- Heat influences permeability of blood vessels wall, which in turn increases total fluid circulation. Due to increase in total fluid, permeability of the drug molecules into the systemic circulation is enhanced. Heat also causessome changes in physiochemical properties of patches. Other than this, sweating and hydration of skin are also altered, which help to increase the penetration of drugs. Heat is expected to enhance the transdermal delivery of various drugs by increasing skin permeability, body fluid circulation, blood vessel wall permeability, rate-limiting membrane permeability, and drug solubility. Heat is known to increase the kinetic energy of the drug molecules and the proteins, lipids, and carbohydrates in the cell membrane. Heating prior to or during topical application of a drug will dilate penetration pathways in the skin, increase kinetic energy and the movement of particles in the treated area, and facilitate drug absorption. Heating the skin after the topical application of a drug will increase drug absorption into the vascular network, enhancing the systemic delivery but decreasing the local delivery as the drug molecules are carried away from the local delivery site. (Chauhan SB, 2017)

2) Chemical penetration enhancers

Sulphoxides- It is one of the old and widely used penetration enhancer. Due to certain drawbacks of DMSO. Due to this researchers came with the solution of findings of similar chemically related compound as penetration enhancers like Dimethyl acetamide and Dimethyl formamide. Sulphoxides are act as penetration enhancer by denaturing the protein and thereby to change intercellular keratin configuration. (Saini S *et al* 2014).

Azone- Azone belongs to the compounds which are specifically designed as transdermal penetration enhancers and prepared during the 70s of the twentieth century (Rajadhyaksha *et,* 1976). It contains a lipid alkyl chain and a large polar head group that are thought to be vital for its activity. Due to this it is highly lipophilic material. It Increases transport of variety of drugs which includes mainly, steroids antibiotics and antiviral drugs. It can be used at concentration 01-5% to the maximum of 1-3% (Saini S*et al* 2014).

Pyrrolidones- Pyrrolidones act as penetration enhancers due to their effects on the intercellular lipid bilayers in the stratum corneum. These enhancers penetrate into this region in such amounts that they alter the solubilizing ability of this site, thereby promoting drug partition into the skin. It generally act by producing reservoir effect which potentiate sustained release of a permeant from the stratum corneum over extended time periods.N-Methyl-2- Pyrrolidone widely used to enhance skin absorption.(R Jayachandra Babu *et al*, 2015)

Surface active agents- Surface active agents are generally added to formulation which helpsto solubilize lipophilic active ingredients. So, they can be solubilize the lipids within stratum corneum. Function by adsorption at interfaces and thus interact with biological membrane contributing to overall penetration enhancement of compounds.Three types of surface active agents are Cationic surfactant- Benzalkonium chloride, Cetyltrimethyl Ammonium bromide. Nonionic surfactant- dodecyl betaine. Anionic surfactant- Sodium lauryl sulphate. Function of Anionic and Cationic surfactant are they swell the stratum corneum and interact with intercellular keratin.

Oxazolidinones- Oxazolidinones are a new class of chemical agents which have the potential for use in many cosmetic and personal care product formulations; this is because of their ability to localize coadministered drugs in the skin layers, resulting in low systemic permeation. The structural features of these permeation enhancers are closely resembles to sphingosine and ceramide lipids, which are naturally found in the upper skin layers. It was proposed that these physical characteristics of the oxazolidinones may be beneficial in terms of a reduction in local toxicity because of the lack of effective absorption of the enhancers into the lower skin layers where irritation is likely to occur (Pathan IB and Setty CM, 2009).

Fatty acids and esters- Most fatty acids are straight-chain compounds with carbon chain lengths between 2 and 24. Medium chain (C6–C10) and long chain (C12– C24) fatty acids are used as skin penetration enhancers. These have been used as penetration enhancers mainly for lipophilic drugs and to a lesser extent for hydrophilic and peptides. A number of patents which describes the utility of fatty acids and their esters or alcohols as enhancers in transdermal formulations have been reported. Similarly, oleic

acid and lauric acid induced a 3.5 and tenfold higher permeation of ondansetronHCl as compared to oleyl alcohol and lauryl alcohol, respectively. In another study, oleic acid provided a several fold higher skin permeation of diclofenac sodium as compared to oleyl alcohol. All these studies indicate that fatty acids are more potent penetration enhancers than fatty alcohols. (Kanikkannn N, 2015).

Amines and amides- The effect of amino acids is assumed to be operative via their action upon keratocytes, the effect of esters of omega-amino acids Dimethyl acetamide a class of amides was the first to be identified as an enhancer, yet it is also a strong irritant. Of the amides of long aliphatic chain several methyl, butyl and isobutyl derivatives of N-dodecyl acetamide proved to be effective. (K. Bauerova *et al,* 2001).

3) Natural Enhancers (Essential oils, terpenes and Terpenoids)

Terpenes are a series of naturally occurring volatile oils which are composed of hydrocarbons and their oxygenated derivatives like alcohols, ethers, aldehydes, phenols, ketones, oxidase, carboxylic acids and esters. Terpenes are to be clinically acceptable penetration enhancers due to their high percutaneous enhancement ability, reversible effect on lipids of stratum corneum, less irritancy and less toxicity. According to skin permeation studies of using diffusion cells and excised animal skin, it was found that terpenes such as 1,8-cineole, menthol and limonene were effective in enhancing the skin penetration. (Patil UK *et al,* 2014)**.**

Conclusion

The efficacy of the penetration enhancer mainly depends on the way which is used to alter the lipid membrane or channels and create the pathways to reach to the systemic circulation. The partition coefficient is again very much important in determining the degree of penetration. The penetrants having high lipid solubility are able to provide more enhancements in bioavailability. It is also found in some literature that the concentration of penetration enhancers also plays a very vital role. As the concentration of the penetration enhancers increases, the drug molecule entry is facilitated and therefore the drug bioavailability increases. Research in this area has been proved the usefulness of penetration enhancers in the enhancement of drug permeation through skin. The penetration enhancement methods discussed in this review are most promising. Focus should be on skin irritation with a view to selecting penetration enhancers which possess optimum enhancement effects with minimal skin irritation which will ultimately leads to increase in patient compliance.

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