A REVIEW: CHEMICAL PENETRATION ENHANCERS

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ABSTRACT
Skin penetration enhancers have been used to improve bioavailability and increase the range of drugs to be administered by topical and transdermal route. Enhancement in skin penetration via modification of the stratum corneum by hydration, or via use of chemical enhancers acting on the structure of the stratum corneum lipids and keratin, partitioning and solubility effects. The mechanism of action of penetration enhancers are used as an aid in potential clinical applications. Chemical penetration enhancers are present in a large number of transdermal, dermatological, and cosmetic products to aid dermal absorption of curatives and aesthetics.

Keywords: Stratum corneum, penetration enhancers, transdermal, chemical enhancers.

INTRODUCTION
Chemical penetration enhancers are present in a large number of transdermal, dermatological, and cosmetic products to aid dermal absorption of curatives and aesthetic. Chemical penetration enhancers used in transdermal products are usually pharmacologically inactive, capable of partitioning into the stratum corneum (SC), modifying its properties and thus enhancing drug permeation. Chemical enhancers are thought to enhance permeation through a number of mechanisms, mainly by the disruption of the ordered SC lipid structure and sometimes by the alteration of the SC keratinocytes (protein conformational change). Before moving further into chemical penetration enhancers, first one should understand the penetration enhancers, their types and its functions.

Penetration Enhancer

Penetration enhancers are used to promote the drug transport across the skin barrier. There are numerous mechanisms to increase penetration enhancement. The interaction of the enhancers with the polar head groups of the lipids is the possible way to increase the penetration. The lipid-lipid head group interactions and the packing order of
the lipids are changed which cause the facilitation of the diffusion of hydrophilic drugs. Penetration enhancer’s increases the content of free water molecules between the bilayer, which cause to an augmentation of the cross-section for polar drug diffusion\[1\].

There are three types of penetration enhancers (Table 1):

(1) Drug vehicle based
(2) Chemical penetration enhancer
(3) Physical penetration enhancer

**TABLE 1: CLASSIFICATION OF PERMEATION ENHANCERS**

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Drug vehicle based</th>
<th>Chemical penetration enhancer</th>
<th>Physical method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Drug selection</td>
<td>Azone</td>
<td>Iontophoresis</td>
</tr>
<tr>
<td>2.</td>
<td>Vesicles and particles</td>
<td>Pyrrolidones</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>3.</td>
<td>Prodrugs and ion pairs</td>
<td>Sulphoxides</td>
<td>Magnetophoresis</td>
</tr>
<tr>
<td>4.</td>
<td>Chemical potential of drug</td>
<td>Essential oil, Terpenes, and Terpenoids</td>
<td>Electroporation</td>
</tr>
<tr>
<td>5.</td>
<td>Eutectic systems</td>
<td>Oxazolidinones</td>
<td>Radiofrequency</td>
</tr>
<tr>
<td>6.</td>
<td>Complexes</td>
<td>Monoolein</td>
<td>Thermophoresis</td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td>Fatty acid</td>
<td>Skin stretching</td>
</tr>
<tr>
<td>8.</td>
<td></td>
<td>Alkyl-N, N-Disubstituted Aminoacetates</td>
<td>Skin abrasion</td>
</tr>
<tr>
<td>9.</td>
<td></td>
<td>Phospholipid</td>
<td>Needleless injection</td>
</tr>
<tr>
<td>10.</td>
<td></td>
<td>Urea</td>
<td>Application of pressure</td>
</tr>
</tbody>
</table>

(1) **Drug vehicle based**: Drug-vehicle based method of penetration enhancement does not change stratum corneum function like chemical and physical penetration enhancement method. This method is based on drug selection, vesicles and particles, prodrug, chemical potential of drug and eutectic system. The interaction of enhancers
with the stratum corneum and the development of structure activity relationships for enhancers will aid in the development of enhancers with optimal characteristics and minimal toxicity.[2]

(2) Chemical penetration enhancer: Chemical penetration enhancers are also called absorption promoters or accelerants. The properties of ideal chemical penetration enhancer are to be pharmacological inert, non toxic, nonirritating, non allergic, rapid onset of action, and suitable duration of action according to drug, inexpensive and cosmetically acceptable. Chemical penetration enhancers insert themselves directly between the hydrophobic lipid tails and change lipid packing which cause lipid fluidity and increase the drug permeation.[3]

(3) Physical penetration enhancer: There are numerous physical and electrical method is used for penetration enhancer. These include iontophoresis (by a small direct current – approximately 0.5 mA/cm2), phonophoresis (by low frequency ultrasound energy increases lipid fluidity), electroporation (by application of short micro- to milli-second electrical pulses of approximately 100-1000 V/cm to create transient aqueous pores in lipid bilayer) and photomechanical waves (laser-generated stress waves reported to cause a possible transient permeation of the stratum corneum).[4]

Function of Penetration Enhancer: On the basis of lipid protein partitioning concept, there are three main functions of penetration enhancers[5]:

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.

Effect of permeation enhancers on different formulations (Table No.2):
<table>
<thead>
<tr>
<th>Permeation Enhancer</th>
<th>Work</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azone</td>
<td>Effect of Azone on Shuangwu traumatic formula</td>
<td>The results show effective penetration enhancement was achieved by 3% (w/w) Azone</td>
<td>[24]</td>
</tr>
<tr>
<td>Pyrrolidones</td>
<td>Cardiovascular effects transdermally delivered bupranolol in rabbits</td>
<td>The results of this study penetration enhancers in the TDDS increased the in vivo delivery of buspropanol, thereby increased the beta-blocking activity of buspropanol by 50-60% higher than control.</td>
<td>[25]</td>
</tr>
<tr>
<td>Sulphoxides</td>
<td>Formulation and evaluation of transdermal patches of Ropinirole HCl.</td>
<td>Formulation containing DMSO was highest (194 g/cm²/h) as compared to ethanol (170 g/cm²/h) and SLS (178 g/cm²/h). Highest permeation coefficient was achieved using DMSO in formulation.</td>
<td>[26]</td>
</tr>
<tr>
<td>Essential oil</td>
<td>Essential oils were evaluated penetration enhancers towards 5-fluorouracil using excised human skin</td>
<td>Eucalyptus and chenopodium both are very effective, causing a near 30-fold increase in drug permeability coefficient. Ylang ylang was mildly effective (8-fold increase) and anise had little activity (3-fold increase)</td>
<td>[27]</td>
</tr>
<tr>
<td>Oxazolidinones</td>
<td>Feasibility of transdermal delivery of Fluoxetine</td>
<td>SR-38 is new and proprietary oxazolidinone class permeation. Enhancers has been reported to fluidization of the bilayer lipids in skin, thereby consequential enhanced permeation various compounds.</td>
<td>[28]</td>
</tr>
<tr>
<td>Monoolein</td>
<td>To examine the in vitro penetration of cisplatin (CIS) through porcine skin in the presence of different conc. of monoolein (MO)</td>
<td>MO did not act as an authentic penetration enhancer for CIS, but it improved the drug partition to the receptor solution improving CIS transdermal permeation.</td>
<td>[29]</td>
</tr>
<tr>
<td>Fatty Acid</td>
<td>The penetration and retention of cortisol into the skin layers</td>
<td>Linoleic acid + polyamine D 400 polymer achieve statistically higher cortisol penetration through the skin when compared to the commercial standard or the vehicle control.</td>
<td>[30]</td>
</tr>
<tr>
<td>Alkyl N,N Disubstituted Aminoacetate</td>
<td>Enhancement of skin permeation miconazole by dodecyl 2-(N,N-dimethylamino)</td>
<td>The solubility of MCZ in the gel was around 1% and the permeation rate was 1.3 g/cm²/h, which was about 2.5 times that from an aqueous</td>
<td>[31]</td>
</tr>
<tr>
<td>Chemical</td>
<td>Description</td>
<td>Effect</td>
<td>References</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------</td>
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<tr>
<td>Phospholipid</td>
<td>Saturated anionic phospholipids enhance transdermal transport by electroporation</td>
<td>In the presence of 1 mg/ml DMPS in the transport milieu, the flux of FITC-Dextran-4k was enhanced by 80-fold and reached 175 g/cm²/min. Thus, the use of lipid enhancer increases the upper size limit of transportable chemicals.</td>
<td>[32]</td>
</tr>
<tr>
<td>Urea</td>
<td>Influence of acute uraemia on percutaneous absorption nonsteroidal anti-inflammatory drugs</td>
<td>The 50 mmol/l conc. of urea (equal to uraemia) added to the gel ointment did not influence percutaneous absorption while 10% concentration of urea percutaneous absorption of indomethacin approximately 5 times decrease. Solubility of indomethacin increased in the presence of 10% urea in the gel more than two times.</td>
<td>[33]</td>
</tr>
</tbody>
</table>

The various types of chemicals have been used as a chemical penetration enhancer; some of the most commonly used chemical penetration enhancers are discussed below-

**AZONE**: For transdermal drug delivery, azone is one of the major classes of permeation enhancers. It enhances the penetration of large range of drugs like indomethacin, urea, methadone, 5fluorouracil, propanol hydrochloride. Azone increases penetration through stratum corneum by affecting the both lipophilic and hydrophilic route of penetration. Azone by increasing the fluidity of layer and partition in the aqueous region helps in increasing the penetration of hydrophilic drugs.

An experiment on transdermal permeation of beta-blockers revealed that azone possesses lipid-fluidizing ability and shows a strong facilitating effect on drug permeation. The peak permeability in human epidermis is an order of magnitude smaller than for mouse skin with the duration of Azone treatment required to achieve the full effect in human epidermis being twice that for mouse skin.

**PYRROLIDONES**: 2-pyrrolidone and N-methyl-2-pyrrolidone are the most widely used enhancers of this group. 2-pyrrolidone enhances permeation through the polar route of...
the skin by increasing the diffusivity, and reduces passage through the nonpolar route by decreasing diffusivity and partitioning \[^{10}\].

Pyrrolidones have been used as permeation enhancers for various molecules with hydrophilic (e.g. 5-fluorouracil and sulphaguanidine) and lipophilic (betamethasone-17-benzoate and progesterone) permeant. In recent studies, higher flux enhancements have been studied for the hydrophilic molecules. Recently N-methyl-2-pyrrolidone is working with limited success as a penetration enhancer for captopril when used into a matrix type transdermal patch \[^{11}\].

**SULPHOXIDES AND SIMILAR CHEMICALS:** Dimethyl sulphoxides (DMSO) is colourless, odourless, and hygroscopic and is often used in many areas of pharmaceutical sciences as a “universal solvent”. DMSO is also used topically to treat systemic inflammation \[^{12}\].

Although DMSO is an excellent accelerant, but it does create problems, such as, relatively higher concentrations of DMSO can cause erythema and wheal of the stratum corneum due to denaturing of some skin proteins \[^{13}\].

In starting, some remained within the tissue for hours and a small fraction was detected for days, decreasing steadily with time \[^{14}\].

**ESSENTIAL OILS, TERPENES AND TERPENOIDS:** Terpenes and terpenoids are appropriate skin penetration enhancers with low toxicity and irritancy. Essential oils, terpenes and terpenoids components of essential oils defined and classified by the ‘isoprene rule’. They are designated as generally recognized as safe (GRAS) by FDA. These chemicals have been mostly used in perfumery and other cosmetics. Mostly in numbers of monoterpenes enhance the permeation of various drugs in transdermal drug delivery. Carvone and eucarvone are classified as ketone monoterpen and terpenoid, respectively \[^{15}\].

The essential oils of eucalyptus, chenopodium and ylang-ylang have been used to be effective penetration enhancers for 5-fluorouracil transversing human skin \[^{16}\].

**OXAZOLIDINONES:** Oxazolidinones are a class of compounds containing 2-oxazolidone as part of the structure. Several oxazolidinones have been synthesized such as 4-benzylloxazolidin-2-one, 4-decyloxazolidin-2-one, 3-acetyl-4-decyloxazolidin-2-one, 3-methyl-4-decyloxazolidin-2-one, 3-methyl-4-benzylloxazolidin-2-one, and 5-
decylooxazolidin-2-one and used as chemical penetration enhancers. These are high molecular weight compounds, and have structural features similar to natural components (sphingosine and ceramide lipids) found in the upper skin layers. These are odourless and nonstaining in nature which makes them preferable choice for use in cosmetic and personal care products.

The mechanism of action of oxazolidinones may involve the interaction with stratum corneum lipids and can fluidize the bilayer lipids in the stratum corneum, thereby enhancing the skin penetration of various active ingredients\(^{[17]}\).

**MONOOLEIN**: Monoolein is a monoglyceride, biodegradable polar lipid, insoluble in water and has the property to self-associate. Monoolein is able to form a bicontinuous cubic liquid crystalline phase that can be used as a drug delivery system.

Traditionally, it is used as an emulsifier and food additive, but from last one decade it has been used as a skin penetration enhancer. Several studies have suggested that monoolein should be used for topical, rather than transdermal drug delivery.

Monoolein concentration influences its skin penetration enhancing ability. Monoolein concentrations from 5-70% (in propylene glycol formulations) on the topical delivery of cyclosporine A using excised porcine skin, found at a lower concentration of 5%, monoolein could improve only the topical delivery of cyclosporine A, while a 10% concentration enhanced both topical and transdermal delivery of the model drug. Further increase in its concentrations from 20% to 70% resulted in an increase in the topical delivery of cyclosporine A, but a decrease in the transdermal delivery of drug.

Monoolein may function by disruption of the lamellar structure of the bilayers in the stratum corneum, which leads to increased lipid fluidity in the stratum corneum. However, it may remove skin ceramides and solubilize lipophilic compounds in the skin. Although monoolein is non-toxic but it produces skin irritation in some cases\(^{[17]}\).

**FATTY ACID**: Oleic acid is a mono-unsaturated fatty acid and is reported to increase the permeation of lipophilic drugs through the skin and buccal mucosa by transdermal cellular pathway\(^{[18]}\). Most of these molecules when applied onto the skin surface permeate along the SC lipid domain and the organization of these regions is very important for the barrier function of the skin. The SC lipid composition and organization
differ from that of other biological membranes, with long chain ceramides, free fatty acids, and cholesterol and cholesteryl esters being the main lipid classes 19.

ALKYL-N, N-DISUBSTITUTED AMINOACETATES: Dodecyl-N, N-dimethylaminoacetate and dodecyl-2-methyl-2-(N, N-dimethylaminoacetate) (DDAIP) are introduced as skin permeation enhancer. These are insoluble in water, but soluble in organic solvents and in water and alcohol mixtures. The penetration enhancing activity is decreased by increasing the N, N-dialkyl carbon chain. The skin-irritating potential of the aminoacetates is very less, due to the biological decomposition of these enhancers by the skin enzymes to N, N-dimethyl glycine and the corresponding alcohols. Skin penetration is increased by the interaction with stratum corneum keratin and it increases the hydration efficiency resulting from these interactions 20.

PHOSPHOLIPIDS: Phospholipid penetrates the surface of stratum corneum lipid bilayer, and the enhancer effect of liposomes is based on the lipid mixing between liposomes and stratum corneum lipid bilayer. Different phospholipids, however, promote in different way drug permeation and affect differently the partitioning of drugs into the lipid bilayer, which explains the differences between phospholipids in promoting the dermal drug delivery.

Phospholipids, e.g. fluid-state EPC (L-a-phosphatidylcholine from egg yolk), may diffuse into the stratum corneum and enhance dermal and transdermal drug penetration, while many other phospholipids, e.g. gel-state DSPC (distearoylphosphatidyl choline), are not able to do this 21.

UREA: Urea is an odorless and colorless crystalline solid. Chemically, it is a slightly hygroscopic substance, good water solubility and weak alkaline properties. Urea is used in dermatology as a hydrating agent for the treatment of psoriasis, neurodermatitis and other hyperkeratotic skin conditions. Urea influences the stratum corneum keratinocytes with species-specific percutaneous absorption rates 22. The keratolytic properties of urea and its derivatives are used as penetration enhancer. The enhancing effect of urea derivatives is due to increase in the stratum corneum water content by these moisturizing agents. Its cause to increase the hydrophilic diffusion channels within the barrier 23.
CONCLUSION

Chemical penetration enhancer is used to enhance the delivery of therapeutically effective dose of the drug through the skin. In the pharmaceutical science literature, chemical enhancers have been used to enhance skin permeability. Chemical penetration enhancers are not only specific towards stratum corneum; they also penetrate into the deeper layers of the skin to viable epidermal cells and induce skin irritation responses. Numerous chemical compounds have been evaluated for penetration-enhancing activity, and different modes of action have been identified for skin penetration enhancement. Potential substances have been used for drug penetration-promoting effects with a low or no skin irritating potential. But still, a lot of work has to be done in the field of penetration enhancers.

REFERENCES


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