CHEMICAL PENETRATION ENHANCERS: AN APPROACH TO ENHANCE TRANSDERMAL DRUG DELIVERY
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ABSTRACT
The transdermal route has been identified as one of the highly potential routes of systemic drug delivery and provide the advantages of escaping of the first-pass effect, ease of use and withdrawal (in case of side effects), and better patient compliance. However, the major limitation of this route is the difficulty of permeation of drug through the skin. Stratum Corneum, the outer most layer of the skin, provides a protective barrier that prevents the loss of physiologically essential substances and provides greatest resistance to penetration and it is the rate limiting step of percutaneous absorption. Hence, to improve the transdermal drug delivery, penetration enhancers are used which penetrate into skin to reversibly decrease the barrier resistance. In this review, we have discussed the chemical penetration enhancers and their probable mechanisms of action.
INTRODUCTION:
Over the last 2-3 decades, the skin has become an important route for the delivery of drugs for topical, regional, or systemic action. The skin, however, has evolved as a physical and biochemical protective barrier, which prevents the loss of water from the body, and guards against entry into the body of external toxic chemicals and infectious agents, thereby maintaining homeostasis. This role of the skin as a barrier to the external environment renders the absorption and transdermal delivery of most drugs problematic. The stratum corneum, the outermost layer of the skin, provides greatest resistance to penetration and it is the rate limiting step of percutaneous absorption.\[1\]

A brief review of Skin Structure
The skin can be considered to have four distinct layers of tissue (Figure 1).\[2\]
1. Non-viable epidermis (Stratum Corneum)
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue (hypodermis)

1. Non-viable epidermis (Stratum Corneum)
Stratum corneum is the outer most layer of skin, which is the actual physical barrier to most substance that come in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. Each cell is a flat, plate-like structure - 34-44 μm long, 25-36 μm wide, 0.5 to 0.20 μm thick - with a surface area of 750 to 1200 μm² stocked up to each other in brick like fashion. Stratum corneum consist of lipid (5-15%) including phospholipids, glycosphingolipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

2. Viable epidermis
This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50-100 μm. The structure of the cells in the viable epidermis are physiochemically similar to other living tissues. Cells are held together by tonofibrils. The density of this region is not much different than water. The water content is about 90%.

3. Dermis
Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histologically in normal tissue. Dermis thickness range from 2000 to 3000 μm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance.
4. Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue, which is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves.

Routes of Drug Penetration

The diffusion of drugs across the normal intact skin involves two possible macro routes, the transappendageal and the transepidermal routes (Figure 2).[3]

The transappendageal pathway comprises transport via sweat glands and along the hair follicles with associated sebaceous glands. Their fractional area available for the drug transport is only about 0.1% of the total skin surface area.

The transepidermal pathway comprises the intercellular route, in which the drugs diffuse via the lipid domain between the corneocytes, and the transcellular route, in which the drugs diffuse across the corneocytes and the lipid matrix.

The intercellular route is believed to be the major pathway for the drug permeation.

![Figure 1: Structure of Skin](image_url)
Figure 2: Routes of Drug Penetration - Stratum Corneum. I = Intercellular, T = Transcellular, A = Appendageal

Percutaneous Absorption

The process of Percutaneous absorption can be described as follows (figure 3). When topically a drug system is applied, the drug diffuses out of its carrier or vehicle which is depend on where the molecules are placed down, it is divided into either the stratum corneum or the sebum filled ducts of the pilosebaceous glands. Inward movement of diffusion process continues from these locations to the viable epidermal and dermal points of entry. In this way the concentration gradient is established across the skin upto the outer reaches of skin’s microcirculation where the drug is swept away by the capillary flow and rapidly distributed in the whole body.[4]
Figure 3: Events governing Percutaneous Absorption

PENETRATION ENHANCERS
Penetration enhancers (also called accelerants or sorption promoters) are defined as substances that are capable of promoting penetration of drugs into skin, or their permeation through skin, by reversibly reducing the skin barrier resistance. An ideal penetration enhancer should have the following properties\[5\]

- They should be non-toxic, non-irritating and non-allergenic.
- They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body.
- The penetration enhancers should work unidirectionally, i.e., they should allow therapeutic agents into the body whilst preventing the loss of endogenous materials from the body.
• When removed from the skin, barrier properties should return both rapidly and fully to normal.
• They should be cosmetically acceptable with an appropriate skin feel.

**Function of Penetration Enhancers**

On the basis of lipid protein partitioning concept, there are three main functions of penetration enhancers [6]

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, decyl methyl sulfoxide 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, co enhancer and co solvent. Ethanol increases the penetration of nitro-glycerin and estradiol through the stratum corneum.

**Mechanism of chemical penetration enhancement**

Penetration enhancers may act by one or more of three main mechanisms:[5]

1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, coenhancer or solvent into the stratum corneum.

The enhancer act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increased the fluidity of the lipid protein portion of the stratum corneum. Some enhancers act on both polar and nonpolar pathway by altering the multilaminate pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development of the product. A useful way to consider factors affecting drug permeation rate through the stratum corneum is via the simple equation given below for steady state flux1. If we plot the cumulative mass of diffusant, \(m\), passing per unit area through the membrane , at long time the graph approaches linearity and its slope its yield the steady flux ,\(dm/dt\)

\[
\frac{dm}{dt} = \frac{D \ Co \ K}{h} \text{-------------------------- (1)}
\]

where, \(Co\) is the constant concentration of drug in donor solution, 
\(K\) is the partition coefficient of the solute between the membrane and the bathing solution, 
\(D\) is the diffusion coefficient and 
\(h\) is thickness of membrane.
From the above equation, we deduce the ideal properties of a molecule that would penetrating stratum corneum well. These are:

- Low molecular mass, preferably less than 600Da, when D tends to be high.
- Adequate solubility in oil and water so that membrane concentration gradient may be high.
- High but balanced (optimal) K (if too large, may inhibit clearance by viable tissue)
- Low melting point, correlating with good solubility as predicted by ideal solubility theory.

A BRIEF REVIEW OF VARIOUS CHEMICAL PENETRATION ENHANCERS

The various types of chemicals have been used as a chemical penetration enhancers, Some of the most commonly used penetration enhancers are discussed below:

Sulphoxides and similar compounds

Dimethyl sulfoxide (DMSO) is a molecule with a long history in pharmaceutics and is now well established as a penetration enhancer in topical pharmaceutical formulations. It is currently used for this purpose in diclofenac sodium topical solution and idoxuridine topical solution. This article reviews the mechanism of action of DMSO as a pharmaceutical penetration enhancer, the characteristics of the molecule that facilitate transdermal drug delivery, and studies of efficacy and safety. Dimethyl sulfoxide is a safe and effective mechanism for facilitating the transdermal delivery of both hydrophilic and lipophilic medications to provide localized drug delivery.[7] The permeation enhancers, DMSO at a concentration of 10% (w/w) has shown an improvement in the Transcutaneous Permeation of Alfuzosin HCl.[8] The insulin-loaded microemulsion containing 10% oleic acid, 38% aqueous phase, and 50% surfactant phase with 2% DMSO as permeation enhancer showed maximum permeation flux and can be transdermally administered in the treatment of insulin-dependent diabetes mellitus with improved patient compliance.[9] It was reported that penetration enhancer DMSO is used for transdermal drug delivery for ACV Increased percentage of DMSO 10% as compared to 5% in aqueous solution enhanced transdermal flux 2.36 fold greater.[10] The DMSO is useful for enhancing the skin permeability of acyclovir from transdermal therapeutic system containing carbopol 934 gel as acyclovir.[11]

Azone

Azone (1-dodecylazacycloheptan-2-one or laurocapran) was the first molecule specifically designed as a skin penetration enhancer. Azone is a colourless, odourless liquid with a melting point of -7 °C and it possesses a smooth, oily but yet non-greasy feel. Azone is a highly lipophilic material with a log p octanol / water of around 6.2 and it is soluble in and compatible with most organic solvents including alcohol and propylene glycol. Azone enhances the skin transport of a wide variety of drugs including steroids,
antibiotics and antiviral agents. Azone is most effective at low concentrations, being employed typically between 0.1-5% but more often between 1-3%.\textsuperscript{12} Azone partitions into a bilayer lipid to disrupt their packing arrangement but integration into the lipid is unlikely to be homogeneous. Azone molecules may exist dispersed within the barrier lipoid or separate domains within the bilayer.\textsuperscript{13}

**Pyrrolidones**

Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-flurouracil) and lipophilic (progesterone and hydrocortisone) permeants. N-methyl-2-pyrrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch.\textsuperscript{14} The pyrrolidones partition well into human stratum corneum within the tissue and they may act by altering the solvent nature of the membrane. Pyrrolidones have been used to generate reservoirs within the skin membrane. Such a reservoir effect offers a potential for sustained release of a permeant from the stratum corneum over extended time periods.\textsuperscript{15}

**Fatty acids and esters**

Percutaneous drug absorption has been increased by a wide variety of fatty acids and their esters, the most popular of which is oleic acid. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. It is of interest to note that many penetration enhancers such as azone contain saturated or unsaturated hydrocarbon chains and some structure-activity relationships have been drawn from the extensive studies of Aungst who employed a range of fatty acids, acids, alcohols, sulphoxides, surfactants and amides as enhancers for naloxone.\textsuperscript{16,17} Shin et al\textsuperscript{18} studied various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid and capric acid) and nonic surfactant (polyoxyethylene-2-oleyl ether, polyoxyethylene-2-stearly ether) on the release of triprolidine. Lauric acid in Propylene glycol enhanced the delivery of highly lipophilic antiestrogen.\textsuperscript{19} Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5-flurouracil flux 56-fold through human skin membrane \textit{in vitro}.\textsuperscript{20}

**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 due to their ability to localize co-administered drug in skin layers, resulting in low systemic permeation.\textsuperscript{21,22} The structural features of these penetration enhancers are closely related to sphingosine and ceramide lipids which are naturally found in the upper skin layers.
Oxazolidinones such as 4-decyloxazolidin-2-one has been reported to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers.\[^{23}\]

**Urea**

Urea promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier. Cyclic urea permeation enhancers are biodegradable and non-toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism.\[^{24}\]

**Alcohols, fatty alcohols and glycols**

Alcohols may influence transdermal penetration by a number of mechanisms. The alkyl chain length of the alkanols (fatty alcohols) is an important parameter in the promotion of permeation enhancement. Augmentation appears to increase as the number of carbon units increases, up to a limiting value.\[^{25}\] In addition, lower molecular weight alkanols are thought to act as solvents, enhancing the solubility of drugs in the matrix of the stratum corneum.\[^{25}\] Disruption of the stratum corneum integrity through extraction of biochemicals by the more hydrophobic alcohols almost certainly also contributes to enhanced mass transfer through this tissue.\[^{26}\]

Ethanol is the most commonly used alcohol as a transdermal penetration enhancer. Ethanol acts as a penetration enhancer by extracting large amounts of stratum corneum lipids. It also increases the number of free sulphhydryl groups of keratin in the stratum corneum proteins. Usually, pretreatment of skin with ethanol increases the permeation of hydrophilic compounds, while it decreases that of hydrophobic ones.\[^{27}\]

The molecular complexity of different glycol molecules is a determinant of their efficacy as permeation enhancers. Solubility of the drug in the delivery vehicle is markedly influenced by the number of ethylene oxide functional groups on the enhancer molecule; this solubility modification may either enhance or retard transdermal flux depending on the specific drug and delivery environment. The activity of propylene glycol (PG) is thought to result from solvation of α keratin within the stratum corneum; the occupation of proteinaceous hydrogen bonding sites reducing drug-tissue binding and thus promoting permeation.\[^{28}\] PG is widely used as a vehicle for penetration enhancers and shows synergistic action when used with, for example, oleic acid.

**Surfactants**

Many surfactants are capable of interacting with the stratum corneum to increase the absorption of drugs and other active compounds from products applied to the skin. Skin penetration measurements are valuable
in quantifying these effects and observing the influence of surfactant chemistry and concentration. A surfactant interacts with skin by depositing onto the stratum corneum, thereby disorganizing its structure. Then surfactant can solubilise or remove lipids or water-soluble constituents in or on the surface of the stratum corneum. Finally it can be transported into and through the stratum corneum. This last effect is related to the surfactant and stratum corneum protein interaction and epidermal keratin denaturation.\[29\] In general, anionic surfactants are more effective than cationic and nonionic surfactants in enhancing skin penetration of target molecules. Some anionic surfactants interact strongly with both keratin and lipids, whereas the cationic surfactants interact with the keratin fibrils of the cornified cells and result in a disrupted cell-lipid matrix. Nonionic surfactants enhance absorption by inducing fluidization of the stratum corneum lipids. Scheuplein and Ross reported that the capacity of the stratum corneum to retain significant quantities of membrane-bound water is reduced in the presence of sodium dodecanoate and sodium dodecyl sulfate.\[30\] This effect is readily reversible upon removal of the agents. These investigations proposed that anionic surfactants alter the permeability of the skin by acting on the helical filaments of the stratum corneum, thereby resulting in the uncoiling and extension of keratin filaments to produce keratin. Then they cause an expansion of the membrane, which increases permeability.\[30\] However, more recent findings suggest that impairment of the skin’s barrier properties is unlikely to result from changes in protein conformation alone. Based on differential scanning calorimetry results, sodium lauryl sulfate (SLS) disrupted both the lipid and the protein components. The amount of surfactant that penetrates the skin after the disruption of the skin barrier depends on the monomer activity and the critical micelle concentration (CMC). Above the CMC, the added surfactant exists as micelles in the solution and micelles are too large to penetrate the skin. The extent of barrier disruption and penetration enhancement of a surfactant is also strongly dependent on surfactant structure, especially alkyl chain length. In general, studies have shown that surfactants having 12 carbons in their alkyl chain cause more disruption to the skin barrier and allow drugs to penetrate more readily than those that have more or less than 12 carbons. The explanation for this optimum of 12 carbons is not known yet.\[29\]

**Essential oil, terpenes and terpenoids**

Terpenes are found in essential oils, and are compounds comprising of only carbon, hydrogen and oxygen atoms, but which are not aromatic. Numerous terpenes have long been used as medicines as well as flavoring and fragrance agents. The essential oils of eucalyptus, chenopodium and ylang-ylang have been found to be effective penetration enhancers for 5-flouroouracil transversing human skin in vivo.\[31\] Cornwell et al\[32\] investigated the effect of 12 sesquiterpenes on the permeation of 5-flourouracil in human
skin. Pretreatment of epidermal membranes with sesquiterpene oil or using solid sesquiterpenes saturated in dimethyl isosorbide increased the absorption of 5-flourouracil. L-menthol has been used to facilitate in vitro permeation of morphine hydrochloride through hairless rat skin as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin. [33]

**Table 1: Different classes of Penetration Enhancers and their mechanism of action** [34]

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrating</td>
<td>Water, Occlusive</td>
<td>Hydrates the Stratum Corneum</td>
</tr>
<tr>
<td>substances</td>
<td>preparations</td>
<td></td>
</tr>
<tr>
<td>Keratolytics</td>
<td>Urea</td>
<td>Increase fluidity and hydrates the Stratum Corneum</td>
</tr>
<tr>
<td>Organic</td>
<td>Alcohols, Polyethylene</td>
<td>Partially extracts lipids</td>
</tr>
<tr>
<td>solvents</td>
<td>glycol, Dimethyl</td>
<td>Replace bound water in the intercellular spaces</td>
</tr>
<tr>
<td></td>
<td>sulfoxide</td>
<td>Increase lipid fluidity</td>
</tr>
<tr>
<td>Fatty acids</td>
<td>Oleic acid</td>
<td>Increase fluidity of intercellular lipids</td>
</tr>
<tr>
<td>Terpenes</td>
<td>1,8-Cineole, Menthol</td>
<td>Open up polar pathways</td>
</tr>
<tr>
<td>Surfactants</td>
<td>Polysorbates, Sodium</td>
<td>Penetrates into skin, micellar solubilisation of</td>
</tr>
<tr>
<td></td>
<td>lauryl sulfate</td>
<td>Stratum Corneum</td>
</tr>
<tr>
<td>Azone</td>
<td>1-Dodecylazacycloheptan-2-one</td>
<td>Disrupts the skin lipids in both the head and tail region</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Skin permeation enhancement technique is a rapidly developing field which would sufficiently increase the number of drugs suited for transdermal drug delivery system that resulting the skin as a major route for administration. Research in this area has proved the usefulness of chemical penetration enhancers in the enhancement of drug permeation through skin. The chemical penetration enhancement methods discussed in this review are promising. Focus should be on skin irritation with a view to selecting penetration enhancers which possess optimum enhancement effects with minimal skin irritation.

**REFERENCES**