Review Article

A Review on Chemical Permeation Enhancers used in the Formulation of Transdermal Drug Delivery System

ABSTRACT: Skin penetration enhancement technology is a rapidly evolving area that will greatly increase the quantity of transdermal drug delivery medications. Penetration enhancers are used to facilitate the movement of drugs through the skin barrier. Numerous methods exist for extending partition enhancement. The enhancers' contact with the polar head of the lipid groups is the potential means for increasing the penetration. Penetration enhancers improve the amount of free water molecules between the bilayer, leading to an improvement of the polar drug diffusion cross section. This article focuses on the different compounds assessed for improving penetration activity like sulphoxides, azones, pyrrolidones, alcohols and alkanols, glycols, surfactants and terpenes.

KEY WORDS: chemical penetration enhancers, drug permeation, Skin, Transdermal drug delivery, *Stratum corneum*

INTRODUCTION:

Targeted drug delivery system also called as smart technology which is employed to modify, localized, targeted, and have a specific respond to a particular tissue. The traditional system fails to achieve this goal that is localization of active ingredient to the diseased site or tissue. Skin targeting means when the aim is to deliver the drug to various skin layers through topical formulations. Penetration enhancers are the compounds used to boost the delivery of transdermal drugs that enter the skin to reversibly decrease the skin's resistance to barriers. Various chemical compounds, including sulphoxides, pyrollidines, fatty acids, azones, alcohols and glycols, surfactants, were evaluated for penetration enhancing activity. Penetration enhancers are found to be promising way to increase permeation of drugs [1] [2]. Chemical penetration enhancement mechanisms include disruption of Stratum corneum's highly ordered lipid structure, interaction with intracellular protein and enhanced drug partitioning along with co-enhancers.

Characteristics of an Ideal Penetration Enhancer:

1. It should not have any pharmacological action
2. It should be non-irritant, not to be toxic and allergenic to the living tissues
3. It should be quick in showing onset of action; well-defined suitable duration of action.

4. This should have reversible effect on SC's barrier property by the chemical penetration enhancer

5. It should be compatible with the delivery system chemically as well as physically

6. It should be properly introduced into the drug delivery system

7. It should have low cost, economic and pharmaceutical acceptable

Skin being the largest organ of human body formulates an indispensable barricade to the environmental conditions and an individual. Penetration of active ingredient via skin layers that is both on the surface as well as for local action below the upper layer gives rise to a topical drug delivery system [3].

Layers of skin:

1) **Epidermis:** The epidermis consists of cells of keratinocytes. Some cells are responsible for protein synthesis, i.e., keratin. Commonly known as protein bridges, desmosomes interact with keratinocytes. The four separate epidermis cell layers are produced by the various stages of keratin ripening. The uppermost skin epidermis differs in thickness from thin too thick on the eyelids i.e., 0.05 mm to palms of the hands and feet soles i.e. 1-1.3 mm respectively. Epidermis is further divided into 5 layers[4,5]:

(i) ***Stratum Basale:*** also known as basal or germinative cell layer; composed of keratinocytes which are dividing and not dividing. This layer is the epidermis' innermost layer that lies flanking into the dermis layer further connected through hemidesmosomes to the basement membrane. Contact sensitive locations such as the tips of fingers and the lip contain Merkel cells located in the basal layer. The stratum germinativum rests on a dermis- and epidermis-dividing basement membrane.

(ii) ***Stratum Spinosum:*** given a name spinous cell layer; these cells move upward after the reproduction and maturation of basal cells, forming stratum spinosum; Bridges between the cells called 'desmosomes;' which appear in a microscope as 'prickles,' aid in cell attachment. [6]. There are dendritic, immunologically active cells known as Langerhans cells which are derived from the bone marrow in the middle of this layer; In skin immunological reactions Langerhans cells have a major function; act as antigen-presenting cells (APCs).

(iii)*Stratum Granulosum*: also known as granular cell layer**.** Keratinocytes going upwards from stratum spinosum, are granular in shape [7].

(iv) *Stratum corneum:* also known as horny layer. This layer is the outermost with strong environmental contact. Keratinocytes are called keratinization or cornification which gives this layer its name [8]. There are 10-30 layers of lined dead cells or corneocytes in most parts of the skin with the exception in the palms and soles.

(v) *Stratum Lucidium:* It consists of a slight layer of apparent cells in situated in the middle. It signifies a changeover from the Stratum granulosum and Stratum corneum, and is typically not visualized in meager epidermis. Two layers of epidermis i.e., Stratum spinosum and Stratum granulosum are additionally assembled as the Malpighian layer [9].

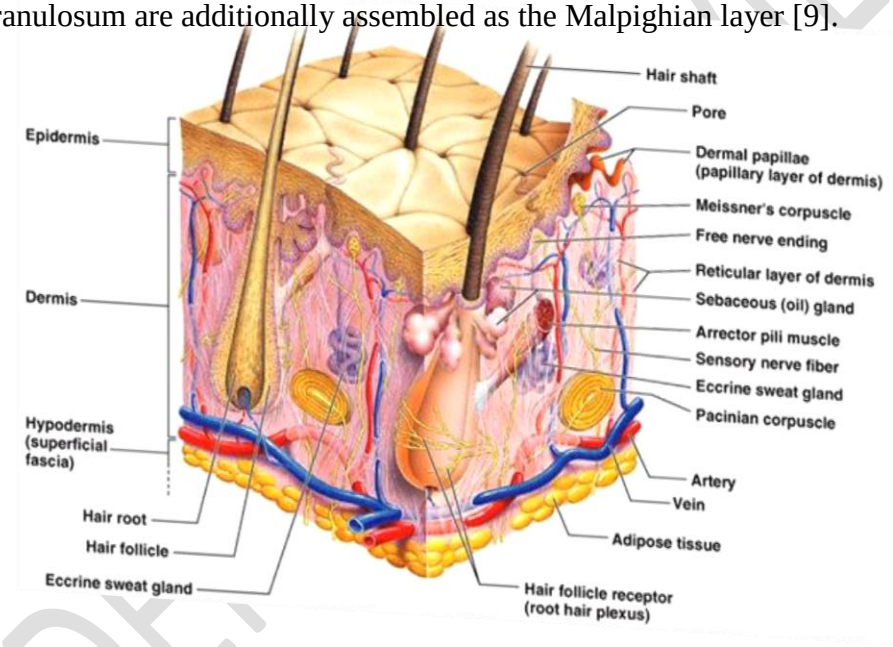

Figure 1: Diagram of Skin showing various parts

2) Dermis*:* Located below the epidermis layer comprising of tough and supportive matrix of cells. This layer displays thickness range, varying from 0.6 mm on the eyelids to 3 mm on the sole surface, hand palms and back. Thin papillary layer and thicker reticular layer are the two layers present in the dermis**.** The papillary layer of dermis is at the lower side, and is connected to the epidermis. It encloses thin and poorly woven collagen fibres [10]. These fibres constitute 70% of total dermis and provide strength and thickness. Within the deeper reticular layer thicker bundles of collagen run parallel to the skin surface, stretching from the base of the papillary layer

to the subcutis tissue. Elastin retains natural elasticity and durability while providing viscosity and hydration by proteoglycans. Sweat glands, root hairs, lymphatics and dermal vasculature are present within the fibrous tissue of the dermis.

3) Hypodermis: The hypodermis is the skin's innermost layer, and thickest one. This comprises loosely woven elastic fibers, blood vessels moving to the dermis, lymphatic vessels flowing from the dermis, nerve-free endings and Pacinian corpuscles, bursae in the area surrounding joints to allow the smooth passage of overlying tissue. It is the lowest layer of the skin made from loose connective tissue, separating the upper layers of the skin from the muscle tissue underlying them. It allows for quick movement of skin over the muscle. This also includes the lymph and blood vessels, nerves and fat cells.

Functions of Skin

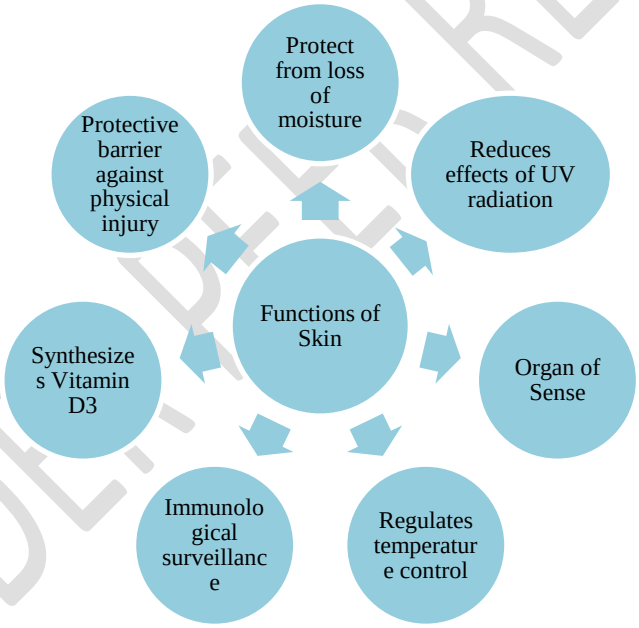

Figure 2: Representing functions of skin

Skin Permeation Pathways

Drug molecules penetrate through layers of skin directly across the *Stratum corneum* by various possible mechanisms such as via transappengeal route through the sweat glands, hair follicles and sebaceous glands [13-16], intercellular route and transcellular route as shown in **figure 3**. Shunt and appendageal route through the *Stratum corneum* are under debate since years due to lack of experimental models to show permeation through these pathways [17,18].

In-vitro studies evolves use of hydrated skin and behavior of lipid phase is variant as that of other biological membranes [19]. The *Stratum corneum* consists of 10 to15 layer of corneocytes [21-23].

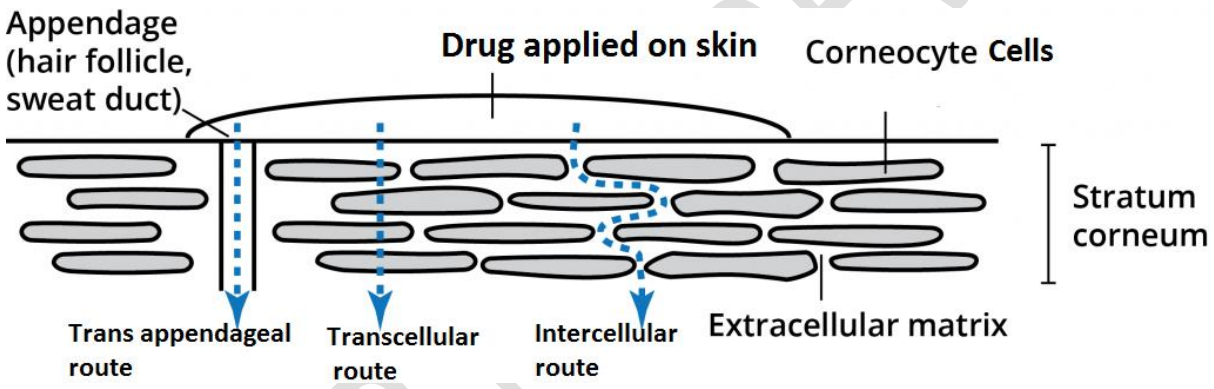

Figure 3: Drug Permeation Pathways via Skin

Types of various penetration enhancers

Sulphoxides and similar compounds

Dimethylsulphoxide (DMSO) is one of the earliest and most studied penetration enhancers. It is a solid aprotic solvent that exhibits hydrogen rather than water bonds with itself; it is colourless, odorless and hygroscopic and is also used in many fields of pharmaceutical sciences as a "popular solvent." In a vehicle, DMSO is used as a cosolvent for the commercial preparation of Idoxuridine for the treatment of severe herpetic skin infections, particularly those caused by

Herpes simplex [49]. Dimethyl acetamide (DMAC) and dimethyl formamide (DMF) are solvents which are similarly active with structures similar to those of DMSO. Both solvents also have a wide array of penetration enhancing activities, such as DMSO. Sulphoxides and similar compounds function as a result of the confirmation of intercellular keratin, from α helical to β sheet [15] as well as a protein effect. DMSO has also been shown to interact with the human Stratum corneum intercellular lipid domains. DMSO can be used for penetration enhancement up to 60 percent in concentration but this can induce erythema, scaling, hives, stinging and burning sensation [16,17]. The numerous other chemically related compounds were used to improve the capacity for penetration. One study reported the increased the flux of oxymorphone hydrochloride when Decyl methyl sulphoxide (DCMS) used in combination with alcohol [18].

Similarly various N, N-Dimethylmide compounds such as dimethylformamide and dimethylacetamide were investigated for enhancing permeation characteristics. However, DMF is causing permanent harm to the membrane [19-21]. The sulphoxides and associated compounds act by interacting with the proteins in the skin and changing the conformation from α to β sheets [22].

Azone

In particular, azone (1-dodecylazacycloheptan-2-one or laurocapram) was first molecule developed as a skin penetration enhancer. Azone is a colourless, odourless liquid with a melting point of −7 ° C. It is highly lipophilic in nature, soluble in mostly organic solvents and also compatible with them. It possesses low irritability, very low toxicity and no pharmacological activity. Azone would likely exert its permeation activity by interactions with the Stratum corneum's lipid zone. Azone in combination with other enhancer of the penetration such as propylene glycol augment the permeation of the polar compounds to a large extent [23].

Pyrrolidones

There were a variety of pyrrolidones and structurally similar compounds examined as potential penetration enhancers in human skin. In this group, N-methyl-2-pyrrolidone (NMP) and 2-pyrrolidone (2P) are the most widely studied enhancers [24]. Pyrrolidones were used as permeation promoters for various molecules, including hydrophilic and lipophilic permeants in terms of modes of action, dividing well into human Corneum stratum pyrrolidones. These can act

within the tissue by modifying the solvent structure of the membrane and pyrrolidones have been used to create 'reservoirs' within the skin membranes. The capacity for continuous release of a permeant from the Stratum corneum over extended periods of time is given by such an effect on a reservoir.

Nonetheless, clinical application of pyrrolidones is precluded due to adverse effects, as with most other penetration enhancers. NMP was used to improve captopril permeation in a transdermal patch of the matrix type [25]. Hydroxy ethyl pyrrolidine was used to achieve two fold increases in hydrocortisone permeation via rat skin [26].

Fatty Acids

A large range of long chain fatty acids have improved percutaneous drug absorption, the most common of which is oleic acid. The mechanism of action is studied using electron microscopic studies that show that the exposure to oleic acid induces a discrete lipid domain within the Stratum corneum bilayer lipids. The formation of these pools will result in permeability defects in bilayer lipids thus facilitating hydrophilic permeation through the membrane. Unsaturated fatty acids continue to increase the flux greatly compared with the saturated counterparts. Lauric acid is reported to increase the permeation of highly lipophilic drugs in combination with propylene glycol [27].

However Oleic acid being the major fatty acid used as a penetration enhancer found to be increase the flux of salicylic acid by 28 folds and 5 FU by 56 folds [28].

Alcohols, Fatty alcohols and Glycols

Ethanol is widely used in many transdermal formulations, and is the preferred solvent for patch use as well. If used at high concentration for prolonged periods, ethanol can eliminate some of the lipid fraction as a volatile solvent from the Stratum corneum; while not a 'enhancing' effect, such a process will certainly enhance the flux of drugs through the skins. The impregnation of ethanol into the Stratum corneum would alter the solubility properties of the tissue with a consequent increase in the membrane partitioning of drugs.

The operation of fatty alcohols (or alkanols) can also be penetration enhancing. These molecules are typically applied to the skin at concentrations between 1 percent and 10 percent in a co-

solvent. Propylene glycol (PG) is widely used as a medium for penetration enhancers, and when used with other penetration enhancers like oleic acid, synergistic activity is observed [29]. PG with ethanol, however, permeates well across the human Stratum corneum, and its mechanisms of action may be comparable to those proposed for ethanol. Permeation of the solvent through the tissue may alter the thermodynamic behaviour of the drug in the vehicle, resulting in a change in the diffusion drive force, a partition of the solvent into the tissue facilitating the absorption into the skin of the drug, and some minor disturbances may be caused by intercellular lipid packing within the bilayers of Stratum corneum [30].

Surface Active Agents

Surfactants are applied to the formulations to provide solubilization to active ingredients of lipophilic nature and thus have the ability to solubilize lipids within the Stratum corneum. Typically composed of a lipophilic alkyl or aryl fatty chain, surfactants are also identified along with a hydrophilic head group in terms of the presence of the hydrophilic moiety. Sodium lauryl sulphate (SLS) includes anionic surfactants, cetrimide and zephiran includes cationic surfactants, and non-ionic surfactants such as polyoxyethylene sorbitan esters and zwitterionic surfactants. Human skin can be affected by anionic and cationic surfactants [31, 32]. Non-ionic surfactants continue to be generally considered to be healthy. In chronic toxicity, surfactants are typically risky and most have been reported to increase the flux of permeating materials across biological membranes. By inducing fluidisation, non-ionic surfactants increase the absorption of stratum lipids. In one of the study reported, enhancing effects of non-ionic surfactants on penetration of piroxicam from the poloxamer gels were performed using Franz diffusion cells using rat skins as a donor. The efficiency of poloxamer gels as penetration enhancers was defined as an improvement factor. Among the evaluation of different non-ionic surfactants, polyoxyethylene-2-oleyl ether had the highest enhancing effects with an enhancement factor of 2.84 [32]. Nonionic surfactants, regarded as a safe class of enhancers, also provide a way to boost the skin's drug permeation.[33] Sebum can also be emulsified by non-ionic surfactants, thereby enhancing the thermodynamic drug coefficient and enabling it to penetrate into cells more effectively [33].

Urea

Urea is a hydrotropic agent used to treat conditions such as psoriasis, ichthyosis and other skin conditions that are hyperkeratotic. In combination with a vehicle or alone, Urea created substantial Stratum corneum hydration and, compared to the vehicle as such, improved barrier efficiency. Since urea itself only has minimal activity-enhancing penetration, attempts have been made to synthesise analogues that contain more powerful moiety enhancement. In the Stratum corneum keratinocytes, urea influences percutaneous absorption levels [34].

Essential oils and terpenes

In essential oils, terpenes are present and these compounds only contain carbon (C), hydrogen (H) and oxygen (O) atoms. The primary terpene found in the eucalyptus oil is 1,8-cineole and this molecule was one of a series of 17 monoterpenes and terpenoids tested as enhancers for the hydrophilic drug model. Eucalyptus, chenopodium and ylang ylang essential oils were found to be effective penetration enhancers in human skin as tested on in vivo crossing of drug 5-Fluorouracil. Terpenes such as menthol, cineole, etc. remain a common enhancer option for active delivery of moiety. It has been reported that with the use of 70 percent v/v isopropyl alcohol and 10 percent v /v eucalyptus oil, permeability of chlorhexidine greatly increased [35].

Limonene raises its permeation to five folds by contrasting limonene, geraniol, eucalyptus oil and pinene oxide to improve silver sulphadiazine permeation [36].

Phospholipids

Phospholipids as vesicles (liposomes) have been used in various studies to transport drugs through and across human skin. Nevertheless, several reporting's have utilized phospholipids as penetration enhancers in a non-vesicular shape drug delivery systems. There is no convincing fact to conclude that phospholipids interfere with the packaging of Stratum corneum, although it can be predictable by accounting or taking their physic-chemical properties into consideration. However, phospholipids may occlude the skin surface and thus may increase tissue hydration, which may increase drug permeation. This structure breakdown releases permeant into the vehicle where the drug may be poorly soluble and thus thermodynamic activity can be increased to facilitate drug delivery. The literature shows that phospholipids are ideal for enhancing permeation in the hydrophobic group comprising unsaturated fatty acids [37].

Table 1: Examples of penetration enhancers studied with the aim to enhance topical drug delivery

Permeant	**Permeation enhancers**	**Reference**
Piroxicam (Gel)	Urea, DMSO, Oleic acid, Oleyl alcohol, Linoleic Acid	[38]
Naloxone (topical formulations)	DMSO, Dimethyl acetamide, Dimethylformamide, Propylene glycol	[39]
Hydrocortisone (Hydrogels)	Terpenes (Nerodilol, Verbenone, Cineole)	[40]
Griseofulvin (Hydrogels)	Propylene glycol, N- methyl pyrrollidine	[41]
Diclofenac	Urea, Oleic acid, Limonene	[42]
Minoxidil (Vesicular system)	Transcutol, Labrasol, Cineole	[43]
Ascorbic Acid (Ethosomes)	Menthol, Oleic acid	[44]
Quercetin	Propylene glycol, Transcutol, PEG 400, Labrasol	[45,46]
Diclofenac sodium	Transcutol	[47]
Nystatin	PG, PEG 400, Ethanol, Oleic acid, Eucalyptus oil, DMF	[48]
Curcumin	Ethanol, tween 80, DMSO	[49,50]

CONCLUSION:

With the advancement of techniques, skin is becoming the one of the major route for administration of drug. Penetration enhancers are playing a crucial role for the absorption of drug through the skin. Use of chemical penetration enhancers are not only restricted to the *Stratum corneum* but also towards the deeper layers of skin. In this review, focus has been towards various chemical penetration enhancers and mode of action for improvement in drug penetration.

Ethical Approval:

As per international standard or university standard ethical approval has been collected and preserved by the authors.

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