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Chemical permeation enhancers for transdermal drug delivery: A brief review

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ABSTRACT

The transdermal route has been recognized as one of the highly potential routes of systemic drug delivery and provides the advantage of avoidance 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. The permeation of drug through skin can be enhanced by both chemical penetration enhancement and physical methods. In this review, we have discussed the chemical penetration enhancement technology for transdermal drug delivery as well as the probable mechanisms of action.

Key Words: Percutaneous absorption; Permeation enhancer; Skin; Stratum corneum; Transdermal.

INTRODUCTION

At present, the most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks; namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient [1].

To get rid of these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific) placement within the body thereby reducing both the size and number of doses. Trans-mucosal (mucosal), trans-alveolar (through the lung tissue), implantable (subcutaneous and deeper implants), injectable (intramuscular or subcutaneous) and transdermal (through intact skin), are such modes of delivery which have been explored extensively over the last 25 years, with varying degrees of commercial and therapeutic success [2].

One of the driving forces for the growth of TDDS is the increasing number of drugs that can be delivered to the systemic circulation, in clinically effective concentration via the skin portal. The delivery of drugs using skin as the port of entry is known as transdermal administration and the drug delivery systems are known as transdermal patches [1].“TDDS are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation.”The success of this approach is evidenced by the fact that there are currently more than 35 TDD products approved for the treatment of wide variety of conditions including hypertension, angina, motion sickness, female menopause, male hypogonadism, severe pain, local pain control, nicotine dependence, and recently, contraception and urinary incontinence [3].

Transdermal drug delivery is the administration of a therapeutic agent through intact skin for systemic effect. Transdermal drug delivery offers the following advantages over the oral route for controlled drug delivery [4].

- Avoidance of hepatic first pass metabolism.
- Ability to discontinue administration by removal of the system.
- The ability to control drug delivery for a longer time than the usual gastrointestinal transit of oral dosage form.
- The ability to modify the properties of the biological barrier to absorption.

The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect [4].

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 [5].

1. Chemical enhancement (includes use of chemicals that alters barrier function of the skin)
2. Physical enhancement (includes use of physical means like electric current or ultrasound energy to enhance transdermal drug absorption)
3.Bioconvertable prodrugs (use of bioconvertable prodrug forms which after bioconversion gives active drug)

A brief review of skin structure

The skin can be considered to have four distinct layers of tissue [4].

1. Non-viable epidermis (stratum corneum)
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue (hypodermis)

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.

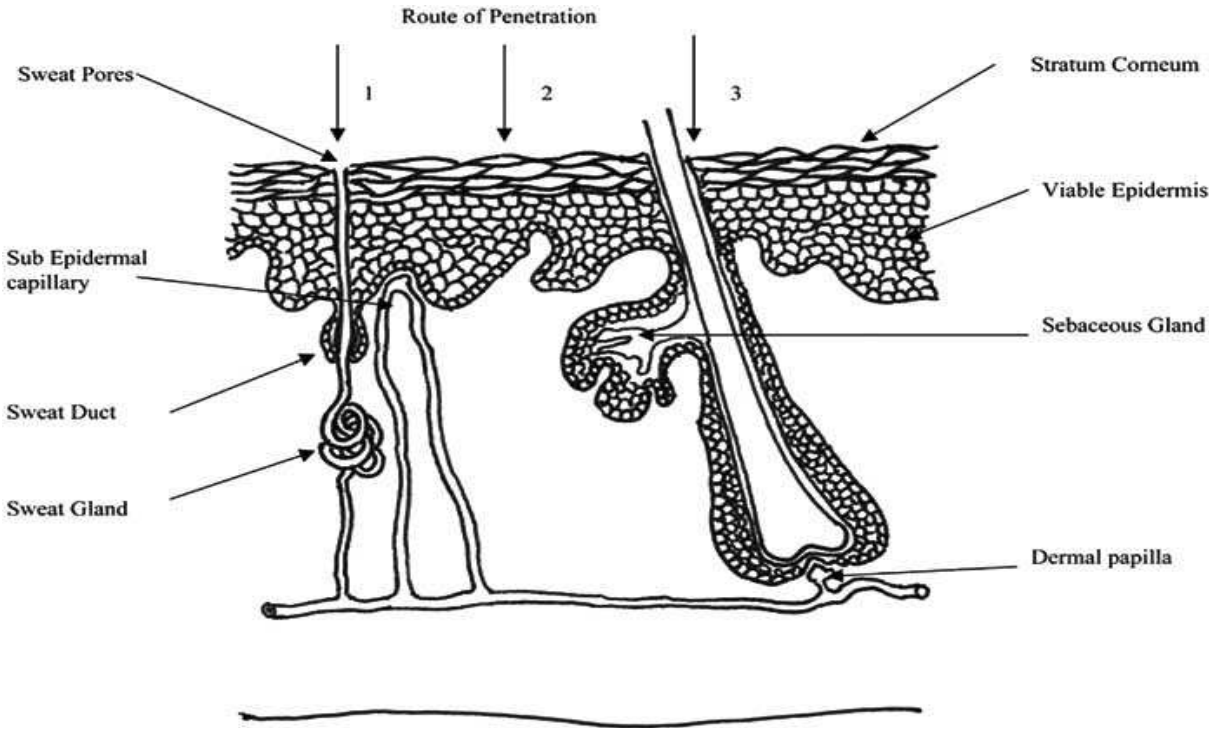

Fig. no. 1.Showing structure of Human skin

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%.

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 from2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance.

Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

Pathway of transdermal permeation

Permeation can occur by diffusion via [6]:

1. Transdermal permeation, through the stratum corneum.
2. Intercellular permeation, through the stratum corneum.
3. Transappendaged permeation, via the hair follicle, sebaceous and sweat glands.

Most molecules penetrate through skin via intercellular micro-route and therefore many enhancing techniques aim to disrupt or bypass its elegant molecular architecture.

Ideal characteristics of chemical penetration enhancers

Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells [7, 8]. Some of the more desirable properties for penetration enhancers acting within the skin have been given as [9]:

- 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 uni-directionally, 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.

Not surprisingly, no such material that possesses the above ideal properties has yet been discovered although some chemicals demonstrate several of the above attributes.

Permeation Enhancers:

Pyrrolidones:

N-methyl-2-pyrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch [10]. 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 [11].

Sulphoxides and similar chemicals:

Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful aportic solvent which hydrogen bonds with itself rather than with water. It is colourless, odourless and is hydroscopic and is often used in many areas of pharmaceutical sciences as a “universal solvent”. DMSO alone has been applied topically to treat systemic inflammation. DMSO works rapidly as a penetration enhancer - spillage of the material onto the skin can be tasted in the mouth within a second. Although DMSO is an excellent accelerant, it does create problems. The effect of the enhancer is concentration-dependent and generally cosolvents containing > 60% DMSO are needed for optimum enhancement efficacy. However, at these relative high concentrations, DMSO can cause erythema and wheal of the stratum corneum. Denaturing of some skin proteins results in erythema, scaling, contact uticaria, stinging and burning sensation [12].

Since DMSO is problematic for use as a penetration enhancer, researchers have investigated a similar chemically-related material as a accelerant. DMAC and DMF are similarly powerful aportic solvents. However, Southwell and Barry, showing a 12-fold increase in the flux of caffeine permeating across a DMF-treated human skin, concluded that the enhancer caused irreversible membrane damage [13]. DMF irreversibly damages human skin membranes but has

been found *in vivo* to promote the bioavailability of betamethasone-17-benzoate as measured by vasoconstrictor assay [14, 15]. DMSO may also extract lipids, making the horny layer more permeable by forming aqueous channels [16]. The mechanism of the sulphoxide penetration enhancers is widely used to denature protein and, on application to human skin, has been shown to change the intercellular keratin conformation, from helical to ß sheet [17, 18].

Oxazolidinones:
They have ability to localize co-administered drug in skin layers, resulting in low systemic permeation [19, 20]. 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 [21].

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 ºC 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% [7]. 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 [8].

Terpenes, terpenoids and essential oils:
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-flouorouracil transversing human skin *in vivo* [22].

Cornwell et al. [23] investigated the effect of 12 sesquiterpenes on the permeation of 5-flurouracil in human skin. Pretreatment of epidermal membranes with sesquiterpene oil or using solid sesquiterpenes saturated in dimethyl isosorbide increased the absorption of 5- flurouracil. L-menthol has been used to facilitate *in vitro* permeation of morphine hydrochloride through hairless rat skin [24] as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin [25, 26].

One mechanism by which this agent operates is to modify the solvent nature of the stratum corneum, thus improving drug partitioning into the tissue. Many terpenes permeate human skin well and large amounts of terpene have been found in the epidermis after application from a matrix type patch. Terpenes may also modify drug diffusivity through the membrane. During steady state permeation experiments using terpenes as penetration enhancers, the lag time for permeation was usually reduced, indicating some increase in drug diffusivity through the membrane following terpene treatment [7].

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 [5].

Alcohol, Glycol, and Glycerides:

Ethanol is the most commonly used alcohol as a transdermal penetration enhancer. It increases the permeation of ketoprofen from a gel-spray formulation [27] and triethanolamine salicylate from a hydrophilic emulsion base [28]. It also acts as a vehicle for menthol in increasing the penetration of methyl paraben [29].Ethanol in combination with TCP and with water were used as two cosolvent systems for zalcitabine, didanosine, zidovudine, tegafur, alclofenac, and ibuprofen. The permeation rate of zalcitabine, didanosine, and zidovudine increased as the volume fraction of ethanol in the two cosolvent systems was increased, and it reached a maximum at 50–60% v/v of ethanol [30]. Flux of tegafur, alclofenac, and ibuprofen was higher from the ethanol-water cosolvent system than from the ethanol-TCP system [31]. PG promoted the flux of heparin sodium [32] and verapamil hydrochloride [33]. A saturated solution of terpenes in a PG-water cosolvent system enhanced the flux of 5-FU, terpene activity being dependent on PG content and with the maximum flux obtained from formulations containing 80% PG. Also, PG increases drug partitioning and drug permeation [34]. PG, in combination with azone, increases the flux of methotrexate [35], cyclosporin A [36], and 5-FU [37]. Flux of estradiol was 10 times higher when PG was used in conjunction with 5% oleic acid [37]. Urea analogues were effective in enhancing the permeation of 5-FU only when PG was used as a vehicle [38]. Short-chain glycerides are also effective as permeation enhancers (e.g., TCP). For instance, glycerin tricaprylate (caprylic acid triglyceride) in combination with ethanol is used as a solvent system [30, 31]. TCP is an excellent hydrophobic vehicle and promoted the permeability of tegafur combined with ethanol [39]. Glyceryl monocaprylate enhanced the partitioning of papaverine across hairless ratskins [40]. Sefsol 318, a medium-chain glyceride, increased the permeation of papaverine hydrochloride by almost 820 times by increasing the fluidity of the lipoidal membrane of the stratum corneum [41].

Fatty Acids and Esters:

A large number of fatty acids and their esters have been used as permeation enhancers. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. Chi et al. [42] reported an increase of 6.5-fold to 17.5-fold in the permeation rate of flurbiprofen through rat skin by unsaturated fatty acids, while no significant increase was observed with saturated fatty acids. Moreover, they have a greater enhancing effect on lipophilic drugs. Addition of oleic acid to an Ethanol: water (50:50) cosolvent system markedly improved the skin permeation of zalcitabine, didanosine, and zidovudine, whereas addition of the same to ethanol: TCP (50:50) produced no enhancement across hairless rat skin. It was suggested that viscous TCP reduced the thermodynamic activity of oleic acid [30]. Oleic acid was found to be the most efficient enhancer for piroxicam, followed by linoleic acid [43]. Sodium oleate was found to be a better permeation enhancer than oleyl oleate when tested on indomethacin and urea [44]. The fatty acid extract of cod liver oil was found to be as good a permeation enhancer as oleic acid. The most effective transdermal penetration enhancer was palmitoleic acid, which resulted in a 640-fold increase in hydrocortisone flux through hairless mouse skin. Incorporation of pure cod liver oil in a PG vehicle did not improve the hydrocortisone permeability, suggesting that the unsaturated fatty acids have to be in the free form to be able to act as skin permeation enhancers. A 1- hr pretreatment of rabbit abdomen skin with 10% oleic acid in PG greatly enhanced the absorption of piroxicam from its gel [45].

Surface active agents:
Surface active agents function primarily by absorption at interfaces and thus interact with biological membranes contributing to the overall penetration enhancement of compounds. Cationic surfactants are more destructive to skin tissue causing a greater increases in flux than anionic surfactants [46]. Anionic surfactants may function by alteration of barrier function of the stratum corneum as a result of the removal of the water soluble agents that act as plasticizers [47]. Sodium lauryl sulphate has been implicated in reversible lipid modification with resultant disorganization of the stratum corneum and enhanced permeation [48]. In addition, non ionic surfactants are perforated to be able to emulsify sebum consequently altering partitioning potential of drugs in fever of enhanced permeation [49]. The permeation enhancement generated by these compounds may be dependent on the ability of the drug to partition between the free and bound and micelle form of enhancer.

Cyclodextrins:
Cyclodextrins are the biocompatible substances that can form inclusion complexes with lipophilic drugs with resultant increase in their solubility, particularly in aqueous solutions [50]. However cyclodextrins alone to be determined to be less effective as penetration enhancer than when combined with fatty acids and propylene glycol [51].

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