

Review Article

Chemical Penetration Enhancers for Transdermal Drug Delivery Systems

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Abstract

Skin as an important site of drug application for both local and systemic effects. However in skin, the stratum corneum is the main barrier for drug penetration. Penetration enhancement technology is a challenging development that would increase the number of drugs available for transdermal administration. 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 word: Transdermal delivery; skin; chemical penetration enhancers.

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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. The worldwide transdermal patch market approaches £ 2 billion, based on only ten drugs including scopolamine, nitroglycerine, clonidine, estrogen, testosterone, fentanyl, and nicotine, with a lidocaine patch soon to be marketed¹. 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 effect³. In this article, we review some uses of the more widely investigated chemical penetration enhancers and discuss their possible mechanisms of action.

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 delivery³.

- 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 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 categories⁴:

1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement

4. Supersaturation enhancement
5. Bioconvertable prodrug

A brief review of skin structure

The skin can be considered to have four distinct layers of tissue³.

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 μm^2 stacked 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.

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 from 2000 to 3000 μm and consists of a matrix of loose connective tissue composed of fibrous

protein embedded in an amorphous 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 via⁵:

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 microroute 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^{13,14}. Some of the more desirable properties for penetration enhancers acting within the skin have been given as¹:

- 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.

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

Mechanism of chemical penetration enhancement

Penetration enhancers may act by one or more of three main mechanisms¹:

1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, co-enhancer 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 multilaminar 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 product². 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

$$dm/dt = D C_o K /h \text{-----} (1)$$

where C_o 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.

Chemical penetration enhancers

Chemical substances temporarily diminishing the barrier of the skin and known as accelerants or sorption promoters can enhance drug flux. Several types are known

Sulphoxides and similar chemicals

Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful aprotic solvent which hydrogen bonds with itself rather than with water. It is colourless, odourless and is hygroscopic 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 urticaria, stinging and burning sensation⁶.

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 aprotic 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 damage⁷. 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^{8,9}. DMSO may also extract lipids, making the horny layer more permeable by forming aqueous channels¹². 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 α helical to β sheet^{10,11}.

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%¹³. 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 lipid or separate domains within the bilayer¹⁴.

Pyrrolidones

Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-fluorouracil) 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 patch¹⁵. 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 periods¹⁶.

Fatty acids

Percutaneous drug absorption has been increased by a wide variety of long-chain fatty acids, the most popular of which is oleic acid. 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^{17,18}. Shin et al¹⁹ 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 triprolidone. Lauric acid in Propylene glycol

enhanced the delivery of highly lipophilic antiestrogen²⁰. Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5-fluorouracil flux 56-fold through human skin membrane *in vitro*²¹. The enhancer interacts with and modifies the lipid domains of the stratum corneum as would be expected for a long-chain fatty acid with cis- configuration¹³.

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-fluorouracil transversing human skin *in vivo*²². Cornwell et al²³ investigated the effect of 12 sesquiterpenes on the permeation of 5-fluorouracil in human skin. Pretreatment of epidermal membranes with sesquiterpene oil or using solid sesquiterpenes saturated in dimethyl isosorbide increased the absorption of 5-fluorouracil. L-menthol has been used to facilitate *in vitro* permeation of morphine hydrochloride through hairless rat skin²⁴ 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 treatment¹³.

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^{27,28}. The structural features of these permeation 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 layers²⁹. This compound has a higher molecular weight and lipophilicity than other solvent-type enhancers, physical characteristics that may be beneficial in terms of a reduction in local toxicity because of the lack of effective absorption of these enhancers into the lower skin layers where irritation is likely to be occur.

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 mechanism⁴.

Conclusion

Skin permeation enhancement technology is a rapidly developing field which would significantly increase the number of drugs suitable for transdermal drug delivery, with the result that skin will become one of major routes of drug administration in the next decade. 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.

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