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CHEMICAL PENETRATION ENHANCERS: AN APPROACH FOR BETTER TRANSDERMAL DRUG DELIVERY

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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. The skin, in particular the stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. The present review article includes the classification of permeation enhancers and their mechanism of action; thus, it will help in the selection of suitable penetration enhancers for improving the permeation of poorly absorbed drugs via transdermal route.

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Key Words
Stratum Corneum, Penetration, Penetration Enhancers, DMSO, Terpenes, Transdermal Delivery.

INTRODUCTION

The outermost layer of horny layer skin stratum cornium is about 10 micrometer thick but functions as major barrier towards inwards and outward flux of compounds[1]. It has therefore received considerable interest from research groups wishing to understand learn from and perhaps manipulate its barrier function including research activities in biology and medicine chemistry pharmacy and membrane technology stratum cornium is often modeled as brick-and-mortar[2]. Where the bricks are flattened keratin filled cells[3], the corneocytes, and the role of mortar is played by polar lipids arranged as stacked bilayers parallel to the skin surface. In 1994 Forslid proposed a domain mosaic model for the skin barrier where focus was on the lateral organization of the polar lipids in the bilayer[4,5] in the Domain Mosaic Model (DMM) the polar lipids are arranged laterally in a fashion similar to brick and mortar, but in this case the 'bricks' consists of polar lipids in a crystalline(gel) state as mosaic pieces surrounded by 'mortar' consisting of polar lipids in the fluid states. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation, oestradiol (alone or in combination with levonorgestrel or (norethisterone) for hormone replacement and testosterone for hypogonadism. Despite the small number of drugs currently delivered via this route, it is estimated that worldwide market revenues for transdermal products are US$3B, shared between the Europe at 32%, USA at 56% and Japan at 7%. In a recent market report it was suggested that the growth rate for transdermal delivery systems will increase 12% annually through to 2007. Transdermal products for cardiovascular disease, Parkinson's disease, Alzheimer's disease, depression, anxiety, attention deficit hyperactivity disorder (ADHD), skin cancer, female sexual dysfunction, post-menopausal bone loss, and urinary incontinence are at various stages of formulation and clinical development[6]. Consequently the daily dose of drug that can be delivered from a transdermal patch is 5-10 mg, effectively limiting this route of administration to potent drugs. Passive and active penetration enhancement and technologies are used to bypass the drugs through the stratum corneum[7]. Physical enhancement technologies such intophoresiel, elctroporation, phonophoresis, micro needles and jet injectors are used for penetration.

In the TDDS therapeutic agents are administred through intact skin for systemic effect. TDDS offers the following advantages over the oral route for controlled drug delivery[8,9].

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

CHARACTERISTICS OF CHEMICAL PENETRATION ENHANCERS

Some of the most desirable properties for penetration enhancers acting within the skin have been given as[10,11].

- 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 be cosmetically acceptable with an appropriate skin feel
- They should have no pharmacological activity within the body
- The penetration enhancers should work unidirectionally
- When removed from the skin, barrier properties should return rapidly and fully to normal.

ANATOMY OF SKIN

The skin has four layers-

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

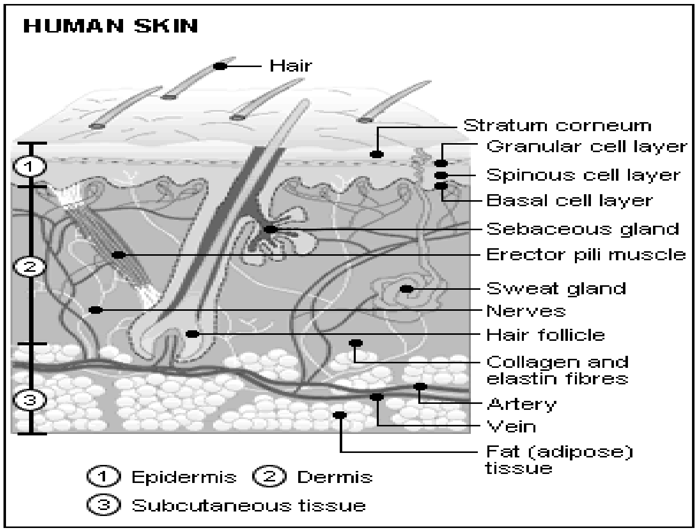


Figure: 1, Structure of Skin

Epidermis

a) **Non-viable epidermis (stratum corneum):**
The outer most layer of skin Stratum corneum consists of 25 to 30 rows of flat, dead cells completely filled with keratin[12]. These cells are continuously shield and replaced by cells from deeper strata the stratum corneum serves as an effective barrier against light and heat waves, bacteria, and many chemicals. Each cell is a flat, plate-like structure -34-44 µm long, 2536 µm wide, 0.5 to 0.25 µm thick -with a surface area of 750 to 1200 µm. Stratum corneum consist of lipid including phospholipids, glycosphingolipid, cholesterol sulfate, neutral lipid and protein.

b) **Viable epidermis:**
The Viable epidermis 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 is physiochemically similar to other living tissues[13]. Cells are held together by tonofibrils. The density of this region is not much different than water and it have about 90% water content.

Dermis

Dermis is the next part of the skin, it composed of connective tissue containing collagen and elastic fibers. The few cells in the dermis include fibroblasts, macrophages and adipocytes. The thickness range of dermis is from 2000 to 3000 µm. It is very thick in the palms and soles and very thin in the eyelids, penis and scrotum. It also tends to be thicker on the dorsal than the medical aspects of the body and thicker on the lateral than the medial aspects of the extremities. Blood vessels, nerves, glands and hair follicles are embedded in the dermis[14,15]. The outer portion of the dermis, about one-fifth of the thickness of the total layer, is named the papillary region. It consists of areolar connective tissue containing fine elastic fibers. Its surface aria is greatly increased by small, fingerlike projections called dermal papillae.

Subcutaneous connective tissue

It is actually not considered a true part of the structured connective tissue. The tissue is composed of loose textured, white, fibrous connective tissue containing lymph and blood vessels, secretary pores of the sweat gland and cutaneous nerves[16].

ROUTS FOR PENETRATION[17,18]:

1. Through the sweat ducts
2. Directly across the stratum cornium
3. Penetration via the hair follicle

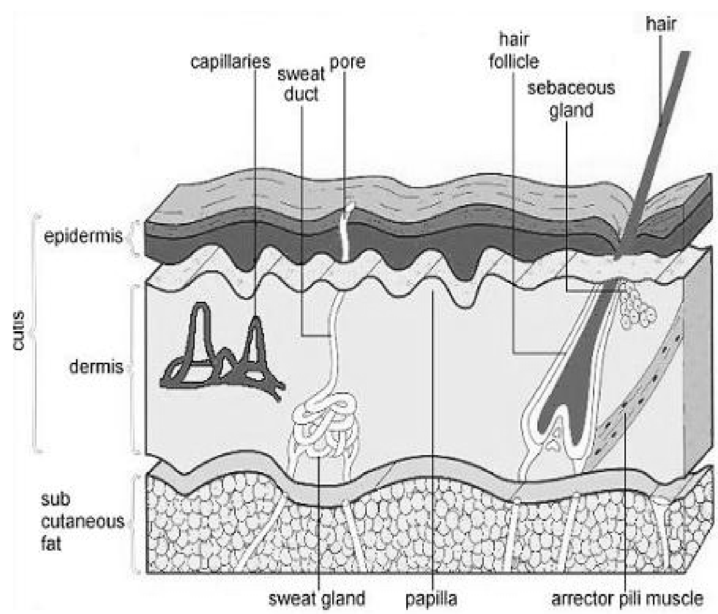


Figure: 2, Simplified presentation of skin showing routs of penetration, through the sweat ducts, directly across the stratum cornium, via the hair follicles

MECHANISM OF PENETRATION ENHANCEMENT

The Percutaneous penetration passage through the skin, involves:

- Dissolution of a drug in its vehicle,
- Diffusion of solubilized drug from the vehicle to the surface of the skin,
- Penetration of the drug through the layers of the skin.

The slowest step in the process usually involves passage through the stratum cornium, this is the rate that limits or controls the permeation[19]. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. In stratum corneum the fatty acid enhancers increased the fluidity of the lipid protein. Some enhancers act on both polar and non-polar pathway by altering the multilaminate pathway for penetration. Enhancers can increase diffusivity of drug through skin proteins[20]. 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 cornium, a simple equation given below for steady state flux. If we plot the cumulative mass of diffusant *m*, passing per unit area through the membrane, at long time graph approaches linearity and slope its yield the steady flux , dm/dt ;

$$dm/dt = D\ Co\ K\ /h$$

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.

According to the equation the ideal properties of a molecule that would penetrating stratum corneum very well. These are[21,22]:

1. Low mol. wt., preferably less than 600Da, when diffusion coefficient tends to be high.
2. Adequate soluble in both oil and water so that membrane concentration gradient may be high.
3. High but balanced partition coefficient of the solute between the membrane and the bathing solution
4. Low melting point, correlating with good solubility as predicted by ideal solubility theory

CHEMICAL PENETRATION ENHANCERS

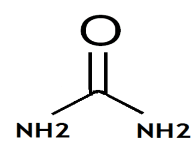
Chemicals penetration enhancers reduce the barrier capability of the stratum corneum in order to promote skin penetration. Many classes of chemicals penetration enhancers has been used including essential oils, terpenes, alcohols, azone analogues and dimethyl sulfoxide[23] (DMSO). Amin et al[24] studies the penetration enhancers like tulsi (basil) oil, eucalyptus oil, clove oil, black cumin oil, oleic acid and Tween 80 on the percutaneous absorption of model lipophilic drug carvedilol on rat abdominal skin. Resultant oil extract of lipids from stratum cornium and enhance the skin permeation.

Penetration enhancers activity expressed in terms of an enhancement ratio (ER):

$$\mathrm{ER} = \frac{\text{Drug permeability coefficient after enhancer treatment}}{\text{Drug permeability coefficient before enhancer treatment}}$$

Several types chemical substances which temporarily diminishing the barrier of the skin and enhance the drug flux

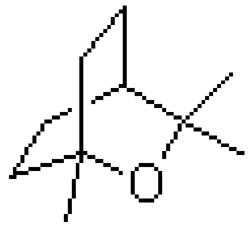
Urea



Urea

It promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier[25]. 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

Essential oil, Terpenes and Terpenoids

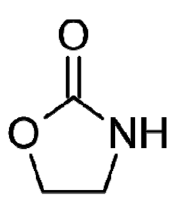


1,3,3-Trimethyl-2-oxabicyclo[2.2.2.]-octane

Terpenes are found in essential oils and compounds are comprising of only carbon, hydrogen and oxygen atoms, but no have aromatic ring. Numerous terpenes 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[26]. Cornwell et al 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 5flurouracil. L-menthol has been used to facilitate in vitro permeation of morphine hydrochloride through hairless rat skin[27] as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin[28-30].

The agent 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 using terpenes as penetration enhancers, the lag time for permeation was usually reduced, indicating some increase in drug diffusivity through the membrane following terpine treatment.

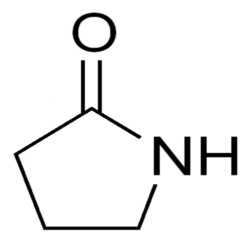
Oxazolidinoles



1,3-Oxazolidin-2-one

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[31,32]. 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 layers[33]. 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.

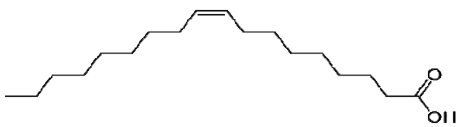
Pyrrolidones



2-Pyrrolidone

Pyrrolidones used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-flurouracil) and lipophilic (progesterone and hydrocortisone) permeants. N-methyl-2pyrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch. 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 permeate from the stratum corneum over extended time periods.

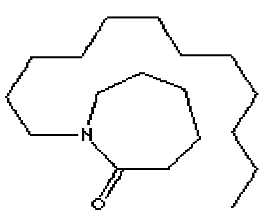
Fatty acids



(9Z)-Octadec-9-enoic acid

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[34,35] **.** Shin et al[24] studied various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid and capric acid) and nonionic surfactant (polyoxyethylene-2-oleyl ether, polyoxy ethylene-2-stearly ether) on the release of triprolidone. Lauric acid in Propylene glycol enhanced the delivery of highly lipophilic antiestrogen. 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 in vitro[36]. 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-configuration[37].

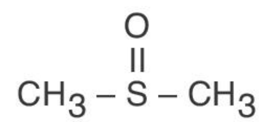
Laurocapran



1-Dodecylazacycloheptan-2-one; 1-Dodecylhexahydro-2H-azepin-2-one

Laurocapran (1-dodecylazacycloheptan-2-one or azone) was the first molecule specifically designed as a skin penetration enhancer. Azone is a colorless, odorless 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 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%[38] 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[39].

Dimethyl sulphoxides and similar chemicals



Dimethyl sulfoxide

Dimethyl sulphoxides (DMSO) is earliest and most widely studied penetration enhancers. It is a powerful aportic solvent. DMSO changes the water structure within the cell. It is use in many areas of pharmaceutical as a “universal solvent[40]. Dimethyl sulphoxides 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. However, at relative high concentrations, DMSO can cause erythema and wheal of the stratum corneum[42,43]. Denaturing of some skin proteins results in erythema, scaling, contact uticaria, stinging and burning sensation[44].

It 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· 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 [45,46]. DMSO may also extract lipids, making the horny layer more permeable by forming aqueous channels [47] . 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 ß sheet[48].A

CONCLUSION

The search for the ideal skin penetration enhancer has been the focus of considerable research effort over a number of decades. Although many potent enhancers have been discovered, in most cases their enhancement effects are associated with toxicity, therefore limiting their clinical application. 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. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity

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