



CHEMICAL PENETRATION ENHANCERS: FOR TRANSDERMAL DRUG DELIVERY SYSTEMS

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ABSTRACT

The evolutionary development of the human skin as a protective potential barrier which keep noxious substances out of the body, also maintaining the body temperature and prevent excessive loss of water from the internal organs. Rather than its barrier properties, strategies have developed to deliver the drugs through the skin. One approach in improving transdermal drug delivery (across the skin) by reversibly decreasing the barrier resistance is the use of chemical penetration enhancers (CPEs). Numbers of compounds have been evaluated for penetration enhancing activity, including alcohols, azone, esters, glycols, fatty acids, pyrrolidones, sulphoxides, terpenes etc. The present review considers the various types of CPEs and their mechanisms of action. The emphasis is on in-vivo and in-vitro studies which focus on limitations associated with skin permeation collected data; penetration enhancers may disrupt the packing of intercellular lipid matrix, increasing drug partitioning into the tissue or intracellular keratin domains by acting as a solvent for the drug within the membrane. A further potential mechanism of action, for example as enhancers alters metabolic activity within the skin, or exerting an influence on the thermodynamic activity/solubility of the drug in its vehicle are also feasible, and also importance of penetration enhancers considered in this review.

Key words: Skin, Transdermal, Chemical penetration enhancers, Thermodynamic activity.

INTRODUCTION

Tablet, injection and to some extent topical preparations are comprise the frequently used drug delivery systems. Though drug delivery by oral route is so far most convenient and accepted route of drug delivery when repeated or routine administration is required [1]. There is considerable interest in delivery of drugs through skin to the systemic circulation and for local effect. However, the outer most layer of the human skin, stratum corneum; possess the formidable barrier to drug penetration thereby reducing bioavailability. Most of the drugs do not have ability to penetrate the stratum corneum so, skin penetration enhancement techniques have been developed to improve bioavailability and increase range of drugs which can be delivered via transdermal route. One approach that can effectively deliver the drug via this route is use of penetration enhancers. These are the chemicals which interact with the skin constituents and promote the drug flux. CPE's use in the transdermal formulations is

still limited as underlying mechanism of action is not evidently defined. This article reviews certain uses of more widely investigated penetration enhancers and their possible mechanisms.

There are many attributes which are exhibited by the penetration enhancers; however there is no any single chemical which can possess all the required properties. The present review discusses the important penetration enhancers used in transdermal drug delivery.

SKIN STRUCTURE

Skin is the largest human organ. The principal parts of the skin are the epidermis (superficial) and dermis (deep) [2,3]. The subcutaneous layer (hypodermis) is deep to the dermis and not part of the skin (Fig. 1). The types of cells in the epidermis are keratinocytes, melanocytes, Langerhans cells, and Merkel cells. It is avascular part. The dermis consists of papillary and reticular regions. It

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contains adipose tissue, hair follicles, nerves, sebaceous (oil) glands, and ducts of sudoriferous (sweat) glands. The epidermal layers from deep to superficial, are the stratum basale, stratum spinosum, stratum granulosum, stratum lucidum and stratum corneum (cells are surrounded by multilamellar lipid bilayers and constitute the outer 10-20µm of the epidermis). Stem cells in the stratum basale undergo continuous cell division, producing keratinocytes for the other layers.

THE SKIN BARRIER

The outermost layer of the skin is stratum corneum [4]. It attributes to the barrier function of the human skin. Properties of this barrier are based on specific content and composition. The bilayer lipids and surrounding corneocytes produces 'Brick-and-Mortar' model. Corneocytes are bricks and intercellular lipids act as mortar [5]. In 1994 'Domain mosaic model' was introduced which was more differentiated. Recently 'Membrane-folding model' [6] (Skin barrier formation) and 'Single gel phase model' [7] (Skin barrier structure and function) was proposed for stratum corneum characterization.

DRUG PERMEATION ROUTES

In the past decade much investigation took place on the route of drug penetration. The permeation of the drugs through the skin includes the diffusion through the epidermis and skin appendages. However, now recognized that major determinant route is through intercellular spaces [5,8-10]. There are two pathways: the intercellular lipid route between the corneocytes and transcellular route crossing through the corneocytes and intervening lipids (Fig. 2); intercellular spaces contains structured lipids and a drug molecule must cross variety of lipophilic and hydrophilic domains before reaching to the junction. The nature of this barrier is very heterogeneous perhaps it can be described by Fick's first law of diffusion [11].

PHYSICOCHEMICAL ASPECTS OF SKIN PENETRATION

The drug diffusion through the skin is passive kinetic process that takes place down the concentration gradient from a region of high concentration to a region of lower concentration. Steady state equation can be described by Fick's first law of diffusion. The equation describes rate of transfer (flux, J) of a diffusing substance through the unit area A of the membrane and diffusion coefficient, D to the concentration gradient across the membrane (dc/dx).

$$J = -AD \left(\frac{dc}{dx} \right) \quad (1)$$

The negative sign in eq. (1) is because the diffusion process occurs in the opposite direction to increased concentration. Fick's second law of diffusion, Eq. (2) can be derived from eq. (1) to describe membrane transport under non steady state condition.

$$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2} \quad (2)$$

By maintaining the sink conditions in the receptor compartment and maximum fixed concentration in the donor compartment, the eq. (2) can be written as

$$J = AD \left(\frac{C_m}{h} \right) \quad (3)$$

Where, C_m is the concentration in the donor-membrane interphase and h is effective diffusional pathlength. The C_m in the eq. (3) can be used to replace by vehicle membrane partition coefficient (K) as ratio between concentration of permeant in the membrane at the donor-membrane interface and the vehicle in which applied (C_v). Modified Fick's first law of diffusion describes the steady-state flux across the membrane eq. (4) [12].

$$J_{ss} = \frac{ADK C_v}{h} \quad (4)$$

We can conclude that increased drug flux can be achieved by a change in D, K, and C. the compounds which are skin penetration enhancers should potentially change the solubility or partition behaviour of the drug into stratum corneum or its diffusion properties or both [13]. Sometimes change in thermodynamic activity of drug in the formulation manipulate the flux.

CHEMICAL PENETRATION ENHANCERS

The literature contains reports describing various formulations which may contain materials which have penetration enhancing activity. There are variety of mechanisms for penetration enhancement by these substances rather they are generally classified based on their chemical structure. These classification are out of practical assistance since they can act on skin by variety of different mechanisms which may not always be straightforward to elucidate. Depending on their physicochemical properties, chemicals belonging to the same group may have different mechanism(s). These are classified as (Table. 1).

Alcohols

Short chain alcohols

Ethanol is the solvent of choice and commonly used in many formulations. Ethanol has been used to enhance flux of estradiol through human skin in vivo. Sometimes enhancement appears to be concentration dependent [14,15]. Although high concentration of the alcohol decreases permeation.

It shows permeation enhancement by various mechanisms. As a solvent can increase the solubility of the drug in the vehicle, permeation of the ethanol into stratum corneum can alter solubility properties of the tissue with improvement for drug partitioning into the membrane. It Modify thermodynamic activity of drug and concentration of drug increase beyond saturated solubility by ethanol evaporation which provide a supersaturated state with greater driving force for penetration. Rapid ethanol permeation across the skin has been reported, as solvent 'drag'. In addition ethanol as a volatile solvent may extract some of the lipid fraction which would clearly improve drug flux through skin.

Long chain alcohols

Much investigation on the effect of saturated and unsaturated fatty acid on permeation was done [16]. A parabolic relationship between carbon chain lengths was observed. A decrease in the permeation was observed with three double bonds. d-Hexanol and Doctanol shows permeation enhancement by lipid extraction effect, whereas d-Decanol did not change skin lipid content [17]. *In-vivo* studies suggests that lipid disorder brought by vehicles was proportional to the amount of vehicle present in the skin.

Amides

Azone® (1-dodecylazacycloheptan-2-one or laurocapram) was significantly designed as skin penetration enhancer [18]. Chemically it is hybrid of a cyclic amide with Pyrrolidone structure. Azone is colourless, odorless liquid with a melting point of -7°C and it possesses a smooth, oily but yet non-greasy feel. Azone is highly lipophilic material and soluble in and compatible with many organic solvents and having low irritancy.

Azone enhances the skin transport of various drugs. It promotes the flux of both hydrophilic and lipophilic drugs. Its efficacy is strongly concentration dependent and vehicle used. Azone is most effective at low concentrations, as employed between 1-5%. It shows permeation and penetration enhancement by interaction with lipid domains of stratum corneum by disrupting the bilayer lipids packing arrangement [19]. Lipids isolated from human stratum corneum provide evidence that Azone exits as a distinct phase within the stratum corneum lipids [20].

Esters

Alkyl and fatty esters are the frequently used candidates as skin penetration enhancers. Ester enhances the absorption 17-folds in rat skin. It was shown that monoglycerides affected the partition and free fatty acids affect the diffusion of drug [21]. It was found that contraceptive levonorgestrel can be best delivered by ethyl acetate [22]. 10% glycerylmonooleate in propyl glycol formulation enhance mutually topical and transdermal drug delivery [23]. Differential scanning calorimetric studies suggest that esters may be acting on stratum corneum lipids as similar to Azone and corresponding membrane-vehicle partition studies indicate the increase in partition coefficient with enhancer treatment compared to the control.

Glycols

Propylene glycol is most commonly used co-solvent among all polyvalent alcohols [24-26]. It shows penetration and permeation enhancement as well as opposite effect when used in the topical formulations [27]. Mechanism of action for the penetration enhancing effect of propylene glycol is hypothesized as by the solvation of keratin with in the stratum corneum by competition with water for hydrogen bonding sites and the intercalation in the polar head groups of the lipid bilayer [28].

Increased drug skin penetration was observed after the use of propylene glycol and fatty acid combination. Also the combination of propylene glycol and oleic acid led to greater absorption of tenoxicam, showing the synergistic effect [29].

Fatty acid

The fatty acids show a good penetration enhancing effect. The penetration enhancing effect is strongly influenced by the fatty acid and the vehicle used. The most popular of which is oleic acid. Unsaturated fatty acids were more effective enhancers than the corresponding saturated isomers [30]. More the unsaturation in the molecule, the more effective is the unsaturated fatty acids. Moreover, cis-configuration fatty acids are more effective penetration enhancers than trans-configuration. Cis-configuration fatty acids are more potent for disrupting the lipid packing order with in the bilayers [31,32].

Oleic acid has shown to be effective for many drugs, for example increasing the flux of salicylic acid 28-fold and 5-fluorouracil flux 56-fold through human skin membrane *in-vitro* [33]. It was revealed that oleic acid might increase the permeability via a mechanism involving perturbation of stratum corneum lipid bilayer and lacunae formation as penetration enhancing effect. As well as the spectroscopic investigation with oleic acid suggest that molecules at higher concentration form separate phases with in the bilayers [34]. This would lead to permeability defects within the bilayers and facilitate the permeation of hydrophilic compounds through the stratum corneum. Again, the drawback of their application is skin-irritating potential of fatty acids when used at higher concentrations.

Pyrrolidones

Pyrrolidones and related compounds have been investigated for their penetration enhancing effects. As, higher flux enhancement have been reported for hydrophilic molecules. N-methyl-2-pyrrolidone (NMP) and 2-pyrrolidone (2P) as well as 2-pyrrolidone-5-carboxylic acid are the most widely studied enhancers of this group [35-37].

Pyrrolidone partition well into stratum corneum and act by altering the solvent nature of the membrane. They generate 'reservoir' within skin membrane which offers sustain release potential of drug from stratum corneum for extended periods. Due to adverse reactions clinical use of Pyrrolidone is precluded [38]. Erythema and other skin-irritation reactions were observed after NMP use on human skin [39].

Sulphoxide

Dimethyl sulphoxide (DMSO) and decylmethyl sulphoxide (DCMS) are reported widely in the literature as skin permeation enhancer and co-solvent [40,41]. A range of mechanisms have been suggested for the skin permeation enhancement. Properties exhibited by DMSO as, displacement of bound water from keratin [42], extraction of skin lipids [43], change in keratin conformation and interaction with lipid alkyl chains in

stratum corneum [44]. The problem with DMSO, is the high amounts which appears to be needed for penetration enhancement and associated issues of irritation like Erythema, scaling, contact urticaria, burning and stinging [45]. Due to its potential toxicity and adverse reactions, it could not be a better choice.

Surfactant

A variety of surfactants have been used as skin penetration enhancer [46-48]. These include anionic, cationic and non-ionic surfactants. Surfactant activity depends on hydrophilic to lipophilic balance, charge and lipid tail length.

Anionic surfactants

Skin-irritation and damage to skin barrier is associated with sodium lauryl sulphate (SLS) [49]. The reported causes are interaction of SLS with lipids and keratin in the skin [50] and effects on epidermal differentiation [51].

Cationic surfactants

Many cationic surfactants have ability to act as penetration enhancer. Maximum enhancement effect were observed at alkyl chain lengths of 12 or 14 carbon atoms. Some cationic surfactants are reported as skin irritants e.g. Benzalconium chloride [52]. These compounds are not hopeful as candidates for penetration enhancement.

Non-ionic surfactants

These are less irritating than ionic surfactants. Tweens and brij are the most extensively investigated compounds in non-ionic surfactants [53]. Disc scanning colorimetric studies revealed that the surfactant interacted with skin to destructure lipids and thus increase permeability; however the ability of surfactant to influence skin permeation was dependent on the physicochemical properties of permeant.

Terpenes

Terpenes are a popular choice for penetration enhancers in transdermal drug delivery studies. These are non-aromatic ingredients of essential oils and consist of C, H and O only. The effect of particular terpene on skin depends on the physicochemical properties and its lipophilicity. It is revealed that smaller terpene with non-polar groups are better skin penetration enhancer [54-56].

A mechanism have been suggested as, they interact with intercellular lipids and influence the non-polar penetration route and also they may increase partition coefficient, drug solubility (i.e. increasing the thermodynamic activity of the drug) and lipid extraction[57]. Terpenes extracted from plants are good contenders because of their low irritation potential. They are designated as 'Generally Recognized as Safe' (GRAS) by the US FDA. The in vivo permeation of the hydrophilic drug antipyrine was increased 3-fold and lipophilic drug indomethacin was increased by 11-fold through Yucatan micro pigskin with terpene p-methane-3,6-diol, originating in the leaf of *Eucalyptus citriodora* [58].

Urea

Urea (NH_2CONH_2) is naturally obtained colourless and odourless solid substance used as hydrating agent in the treatment of scaling conditions such as psoriasis, ichthyosis and the hyperkeratotic skin conditions. Urea also has keratolytic properties, usually when used in combination with salicylic acid. Urea influences the stratum corneum keratinocytes with species-specific percutaneous absorption rates [59].

Miscellaneous

In addition to the other chemical penetration enhancers several other groups were studied for their enhanced drug transport across the skin.

Cyclodextrins

Cyclic non-reducing oligosaccharides such as cyclodextrins form inclusion complexes with variety of hydrophobic drugs there by increasing their partitioning and solubility in the aqueous solution and stratum corneum. Cyclodextrins are not able to permeate the skin under normal conditions. In combination with the lipophilic enhancers synergistic effect can be achieved. They doesn't enhance the flux of the test drug through stratum corneum, they influence the partition behaviour of the drug in the skin. It forms a complex with enhancer like quaternary ammonium salts and shift their critical miscellar concentration to higher values thereby decreasing the toxic effect of such enhancers [60].

Partially methylated- β -cyclodextrin (PM β CD) significantly reduced the skin barrier for Bupranolol, as shown by 1.7-fold increase in the flux by PM β CD pretreatment. Overall, cyclodextrins were found to be suitable for improving the solubility and penetration enhancement of Bupranolol [61].

Water

Water is the most natural penetration enhancer. Hydration appears to increase transdermal delivery of both hydrophilic and lipophilic permeants. Water with in the stratum corneum alter the solubility of a permeant and hence could modify partitioning from the vehicle in to the membrane. In addition, skin hydration may swell and open the structure of the stratum corneum leading to an increase in permeation [62,63].

Vitamin E

Vitamin E (α -tocopherol) has demonstrated effectiveness as a human skin penetration enhancer by increasing the permeability coefficient of radiolabeled hydrocortisone approximately 2-fold in excised cadaver skin. Skin permeability experiments were carried out in Franz (vertical) diffusion cells in infinite dose experiments. It is postulated that Vitamin E acts as a penetration enhancer by intercalating within the lipid bilayer region of the stratum corneum, thus altering the characteristics of the membrane affecting permeability, presumably by disordering gel phase lipids. Unlike other well-known enhancers, Vitamin E is generally thought to

be non-irritating, and additionally, possesses antioxidant and emollient properties [64].

Phospholipids

Many studies have been successfully employed phospholipids as penetration enhancers in the form of vesicles, microemulsions and miscellar systems. Phospholipids do not interact with the stratum corneum as individual molecule. They fuse with the lipid bilayers of the stratum corneum and thereby enhancing the partitioning of encapsulated drug as well as disruption of the ordered bilayer structure. This collapse liberates the poorly soluble drug into the vehicle and hence thermodynamic activity could be raised thus facilitating drug delivery [65,66].

SKIN IRRITATION AND TOXICITY DUE TO SKIN PENETRATION ENHANCERS

CPEs increase the skin permeability by reversibly damaging or altering the structure of stratum corneum. Many CPEs cause skin irritation or some adverse reactions. These chemicals alter the organized lipid structure, cell membrane and components. To study these interactions models developed using solubility parameters to predict drug/vehicle/skin interaction and potential

irritancy [67]. Many penetration enhancers has limited usefulness for clinical application because of their toxicity. Recently, investigation move towards potential enhancers classified as GRAS (Generally Recognized as Safe) by US FDA, such as essential oils, terpenes and polymeric enhancers [68,69].

FUTURE PROSPECTUS

The ideal skin penetration enhancer should be pharmacologically inert, non-toxic, non-irritating, and non-allergenic, also it should have a reversible action on skin. Additionally the enhancer should be compatible with the drug with permeation and/or skin residence time parameters. In regards of the drugs, permeation enhancer must be stable and aesthetically acceptable and also from a cost-of-goods and easy to source. Despite of investigation of number of CPEs some or all of these criteria's remains unfulfilled. A little investigation has been done on penetration rates and amount of penetration in the skin. Still much scope is there for investigation into the actual mechanism of many chemical penetration enhancers which are formerly in use. Although there is a scope in new CPEs, but the regulatory consent of such compounds are likely to be tedious.

Fig. 1 The human skin

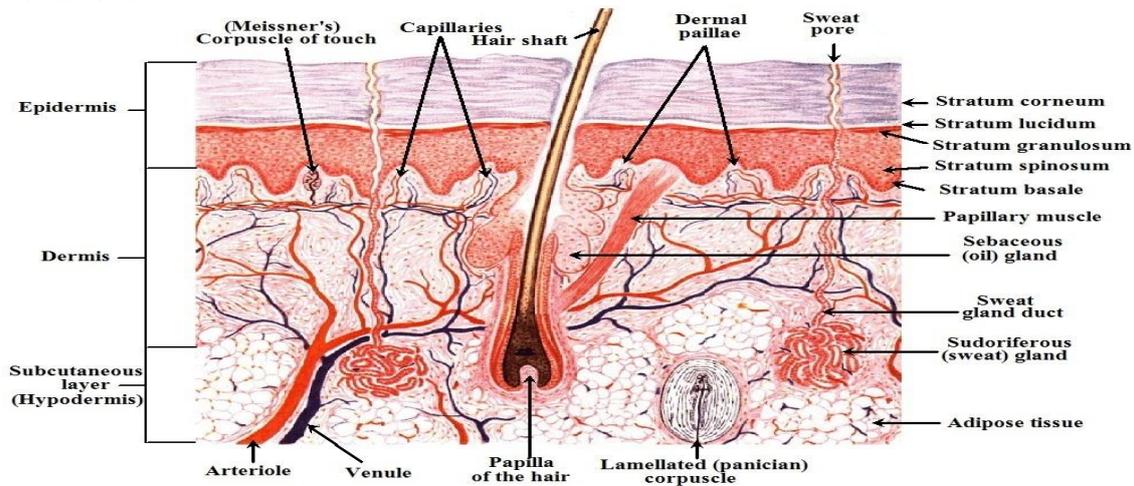


Fig. 2 Penetration routes through the stratum corneum: (i) Intercellular route (via the lipid matrix between the corneocytes). (ii) Transcellular route (across the corneocytes and the intercellular lipid matrix)

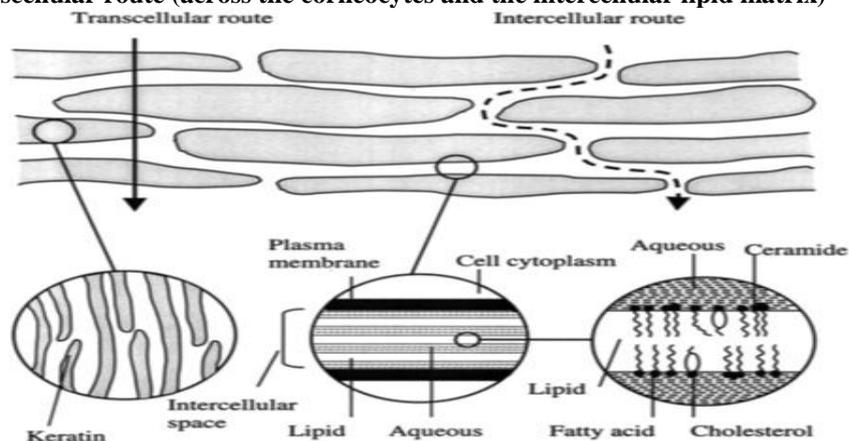


Table 1. Examples of penetration enhancers investigated in the literature.

Chemical Classification	Enhancer
Alcohols	Short chain alcohols Ethanol, Isopropyl alcohol Long chain alcohols Decanol, Hexanol, Octanol, Myristyl alcohol
Amides	Azone
Esters	Ethyl acetate, Oleyl acetate, Isopropyl myristate, propylene glycol monocaprylate, Octyl salicylate.
Fatty acids	Lauric acid, Linoleic acid, oleic acid, Palmitic acid, isostearic acid
Glycols	Propylene glycol, Dipropylene glycol, 1,2-butylene glycol
Pyrrolidone	N-methyl-2-pyrrolidones, 2-pyrrolidone.
sulfoxides	Dimethyl sulphoxide, Decylmethyl sulphoxide.
Surfactants	Anionic surfactants Sodium lauryl sulphate Cationic surfactants Alkylpyridinium halide, Alkyl dimethylbenzyl ammonium halides. Non-ionic surfactants Span 80, Tween 80.
Terpenes	Cineole, Eugenol, D-Limonene, Linalool, Menthol, Menthone.
Urea	Carbamide
Miscellaneous	Cyclodextrins, Water, Vitamin E, Phospholipids.

CONCLUSION

There are eternal efforts to improve transdermal drug delivery of drugs across the human skin. Attention in the search of ideal skin penetration enhancer has been the focus of considerable research efforts for many years. In most cases there enhancement effects are associated with toxicity, which limits their clinical application. A transdermal application is intended for systemic effects. To achieve therapeutically effective dose of the drug

through the skin, a chemical penetration enhancer is a major tool. To obtain substances which fully meets the requirements, one approach is to synthesize penetration enhancer with the desired properties by understanding the interaction of enhancer and developing structural activity relationship. Modern discovery techniques are applied for the design of novel transdermal penetration enhancer with optimal characteristics and minimal toxicity.

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