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DRUG PENETRATION ENHANCEMENT IN TRANSDERMAL DRUG DELIVERY SYSTEMS BY CHEMICAL PENETRATION ENHANCERS

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ABSTRACT

The transdermal route has numerous advantages over the more traditional drug delivery routes. The skin is consider as a site of drug application for local and systemic effect. Transdermal drug delivery system provide a sustain release as well as reduce the intensity of action and thus reduce the side effects associated with its oral therapy. TDDS - an approach used to deliver drugs through the skin for therapeutic use as an alternative to oral, intravascular, subcutaneous and transmucosal routes. Transdermal delivers a drug through intact skin at a controlled rate into the systemic circulation. Delivery rate is controlled by the skin or membrane in the delivery system. The main obstacle to permeating drug molecules in systematic circulation is the outermost layer of the skin, stratum corneum. Skin penetration enhancement techniques have been developed to improve bioavailability. The penetration enhancer are agents that have no any therapeutic activity but can transport the sorption of the drug from drug delivery system on to the skin and/or their subsequent transdermal permeation through skin. Enhancement in skin penetration via modification in stratum corneum by hydration, or via use chemical enhancer by acting on the structure of the stratum corneum lipids and keratin, partition. Penetration enhancers are use to maintain the drug level in blood and to improve the efficiency of the drug. 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.

Key Words: Stratum corneum, Penetration enhancers, Transdermal drug delivery system, Chemical penetration.

INTRODUCTION

The application of medicaments to the skin is the oldest method for the skin treatment can be dated back many thousands of years. The ancient Greeks applied a mixture of water, olive oil and lead oxide as a balm to the skin. Lead oxide has astringent properties, and olive oil may act as an occlusive barrier, moisturising the skin [1]. The worldwide transdermal patch market approaches two billion pounds, based on some drugs including scopolamine, nitroglycerine, clonidine, estrogen, testosterone, fentanyl, and nicotine, with a lidocaine patch soon to be marketed [2]. TDDS, also known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin for systemic effect. Human skin provides a significant more surface area as well as various locations for drug absorption. Its uppermost layer – stratum corneum (SC) is the major barrier preventing compounds from inward and outward diffusion through skin. The SC is mainly composed of keratinized cells (corneocytes) embedded in a lamellar lipid-rich interstitium.

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 [3]. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects which is not easily eliminate by oral or other routes. Chemical permeation enhancers are relatively inexpensive and easy to formulate, they offer flexibility in their design, are simple in

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application and allow the freedom of self administration to the patient. Transdermal drug delivery offer the following advantages over the oral route for controlled drug delivery.

Advantages of transdermal drug delivery

Transdermal drug delivery systems offer several important advantages over more traditional approaches, including [4-6]

- ❖ Avoidance of hepatic first pass metabolism.
- ❖ Longer duration of action resulting in a reduction in dosing frequency.
- ❖ Improved bioavailability.
- ❖ 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.
- ❖ More uniform plasma levels.
- ❖ Reduced side effects and improved therapy due to maintenance of plasma levels up to the end of the dosing interval.
- ❖ The ability to modify the properties of the biological barrier to absorption.
- ❖ Reduced the intra and inter patient variability and this is particularly true for those situation in which drug release from the transdermal patch is slower than drug diffusion across the stratum corneum.
- ❖ Improved patient compliance and acceptability of the drug therapy.

Skin outer most layer is stratum corneum provide the protective layer that prevent the loss of physiogical essential substance and limit the diffusion of toxic chemical substance from the external environment to the body. But the stratum corneum is the main obstacle to permeating drug molecules in systematic circulation. Different method have been use to overcome the barrier property of the stratum corneum.

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 [7]

a. Chemical enhancement
b. Physical enhancement
c. Biochemical enhancement
d. Supersaturation enhancement
e. Bioconvertable prodrug

Pathway of transdermal permeation

Permeation can occur by diffusion via [8,9]

a. Transdermal permeation, through the stratum corneum.

Drugs entering the skin via the transcellular route pass through corneocytes, which containing highly hydrated keratin, provide an aqueous environment for which hydrophilic drugs can pass. The transcellular pathway to be the predominant pathway for highly hydrophilic drugs.

b. Intercellular permeation, through the stratum corneum.

The intercellular pathway involves drug diffusing through the continuous lipid matrix.

c. Transappendaged permeation, via the hair follicle, sebaceous and sweat glands.

The surface area occupied by hair follicles and sweat ducts is small (typically 0.1% of skins surface area), therefore limiting the area available for direct contact of the applied drug formulation. Sweat ducts are either empty or actively secreting an aqueous salt solution. Although an aqueous pathway across the skin is considered desirable for many drugs, permeation may be limited as sweat is travelling against the diffusion pathway of the permeant. Sebaceous glands are filled with a lipid rich sebum, which may present a barrier to hydrophilic drugs.

Most molecules penetrate through skin via intercellular microroute and therefore many enhancing techniques aim to disrupt or bypass its elegant molecular architecture. Here the penetration pathway is shown in figure 1.

Ideal characteristics of chemical penetration enhancers

Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells. Some of the more desirable properties for penetration enhancers have been given as [2, 10-14]

- ❖ They should be non-toxic, non-irritating and non-allergenic
- ❖ Rapid onset of action; predictable and suitable duration of action for the drug used
- ❖ They should have no pharmacological activity within the body. i.e. pharmacologically inert
- ❖ 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.
- ❖ Chemically and physically compatible with the delivery system
- ❖ It should be an excellent solvent for drugs
- ❖ The substance should formulate easily into semisolids, aerosols and skin adhesives
- ❖ Readily incorporated into the delivery system
- ❖ Inexpensive and cosmetically acceptable in terms of odour, colour, taste and texture.

Mechanism

Penetration enhancers may act by one or more of three main mechanisms [2]

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 penetration enhancer act by altering one or more of three pathways. 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 pathways like polar and nonpolar pathway by altering the multilaminate pathway for penetration. A simple equation is a useful way to consider factors affecting drug permeation rate through the stratum corneum for steady state flux [2]. 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 yield the steady flux, dm/dt

$dm/dt = D\ Co\ K\ /h$ ---------- (1)

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.

From the above equation, we conclude the ideal properties of a molecule that would penetrating stratum corneum well. These are:

- Low molecular mass, preferably less than 600 dalton (Da), 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 penetration enhancer also called as absorption promoter or accelerator. Chemical substances temporarily diminishing the barrier of the skin and can enhance drug flux. Chemical penetration enhancer inserts themselves directly between the hydrophobic lipid tail and change lipid packing which cause lipid fluidity and increase the drug penetration. [15]

Chemical permeation enhancers have been classified on the bases of their chemical structures rather than their mechanisms of action on skin. Such a classification is more beneficial since permeation enhancers can act on skin by a variety of different mechanisms. Chemicals belonging to the same group can act on skin by different mechanisms depending on their individual physico-chemical properties.

Sulphoxides and similar chemicals

Sulphoxides are compounds containing a sulfinyl group (S=O) attached to 2 carbon atoms. The most commonly used permeation enhancing sulphoxide is dimethylsulpoxide (DMSO). DMSO is often used in many areas of pharmaceutical sciences as a "universal solvent". It is a powerful aprotic solvent which hydrogen bonds with itself rather than with water. It is colourless, odourless and is hydroscopic in nature, miscible with both water and organic solvents, enabling it to be easily formulated into pharmaceutical preparations [14]. DMSO works rapidly as a penetration enhancer is concentration-dependent and generally cosolvents containing > 60% DMSO are needed for optimum enhancement efficacy. At the high concentrations, [16] DMSO can cause erythema, contact uticaria, stinging and burning sensation because of denaturing of some skin proteins and wheal of the stratum corneum.

Due to the problem with the DMSO researchers find new similarly powerful aprotic solvents DMAC and DMF. 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 [17, 18]. The mechanism of the sulphoxide penetration enhancers is widely used to denature protein. Raman spectroscopic studies relealed that DMSO changes the intercellular keratin conformation, from α helical to ß sheet [19, 20].

Azone

Azone is liquid in nature with a melting point of -7 ^{o}C, at room temperature, it is a clear liquid, with a molecular weight of 281 Da. It is colourless, odourless and it possesses a smooth, oily but yet non-greasy feel. Azone is a highly lipophilic with a log p octanol / water of around 6.2 and it is soluble and compatible with most organic solvents including alcohol and propylene glycol [21]. Its structure is containing a large polar head group and a C12 side chain. Azone has low irritancy, very low toxicity (oral LD50 in rat of 9 g/kg) and little pharmacological activity [22]. The important advantage of Azone is, it is most effective at low concentrations, these concentration level typically between 0.1- 5% but more often between 1- 3% [11]. Azone is an effective permeation enhancer for both hydrophilic and lipophilic permeants [23-25]. Example for this is, Azone was shown to enhance 5-fluorouracil penetration by 100-fold across hairless rat skin [26]. A combination of Azone and PG helps the penetration of hydrophilic drugs greatly [27]. Azone and PG combination increase penetration through the stratum corneum by affecting both the hydrophilic and lipophilic routes of penetration. Azone increases the fluidity of the lipid layer, while PG increases the water content of the proteinaceous region and helps azone partition into the aqueous region. Azone probably exerts its penetration enhancing effects through interactions with the lipid domains of the stratum corneum.

Pyrrolidones

Pyrrolidones used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-flurouracil) and lipophilic (progesterone and hydrocortisone) permeants. Pyrrolidones have greater effects on hydrophilic permeants than for lipophilic

materials, although this may be attributable to the greater enhancement potential for the poorer hydrophilic permeants. When formulated in a matrix-type transdermal patch of N-methyl-2- pyrolidone was employed with limited success as a penetration enhancer for captopril [28]. The pyrrolidones may act by altering the solvent nature of the membrane. Pyrrolidones have been used to generate reservoirs within the skin membrane, this reservoirs offers a potential for sustained release of a permeant from the stratum corneum over extended time periods [29].

Oxazolidinones

Oxazolidinones due to their ability to localize co-administered drug in skin layers, resulting in low systemic permeation [30, 31]. The structural features of oxazolidinones are closely related to sphingosine and ceramide lipids which are naturally found in the upper skin layers. Oxazolidinones such as 4-decyloxazolidin-2-ones has been reported to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers [32]. 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 irritation is likely to be occur at the lower skin layersbut this enhancer has the lack of effective absorption into the lower skin layers [8].

Hydrocarbons

Several hydrocarbons such as alkanes, alkenes, halogenated alkanes, squalane, squalene and mineral oil have been used as vehicles or penetration enhancers to increase permeation of a variety of drugs across the skin [33]. These permeation enhancers generally work by partitioning into the stratum corneum and disrupting the ordered lipid bilayer structure. In a series of experiments on skin permeation using alkanes of varying chain length (9–18 atoms), it was demonstrated that alkanes with 9–10 carbon atoms showed highest skin permeation enhancement of propranolol and diazepam while shorter alkanes (5–6 carbon atoms) showed highest permeation enhancement of caffeine [33,34].

Alcohol

Ethanol is one of the most commonly used permeation enhancers [35]. Ethanol is a relatively volatile solvent and will rapidly evaporate at skin temperature so easily remove from the skin. Ethanol loss from a formulation may lead to the drug becoming supersaturated, which influence drug flux across the membrane due to the changes will occur in concentration gradient. Alcohols can enhance skin permeation by a variety of mechanisms such as extraction of lipids and proteins, swelling of the stratum corneum or improving drug partitioning into the skin or solubility of the drug in the formulation [36, 37-41]. Chloroform and methanol mixture is said to be the most effective extractant, removing all lipids except the lipids covalently bonded to the corneocyte envelope. Ethanol is a milder solvent, extracting only some of the skin lipids [42]. Pretreatment of skin with ethanol increases the permeation of hydrophilic compounds, while it decreases for hydrophobic ones [43]. Megrab and collaborators [44] noted that the enhancement effect of ethanol was concentration dependent. After the investigation of authors they concluded that formulations containing high levels of alcohol were capable of dehydrating the skin, which may explain the concentration dependant action of ethanol.

Fatty acids

Percutaneous drug absorption has been increased by a wide variety of long-chain fatty acids. Examples of fatty acids employed as penetration enhancers include lauric acid, linoleic acid and oleic acid. Penetration enhancement has been depends on the number, position and type (cis/trans) of double bonds [14]. Generally, unsaturated fatty acids possessing the cis configuration are highly effective for enhancing the drug penetration [35]. Fatty acids enhance transport of drug molecules across the skin by a variety of mechanisms such as partitioning into the lipid bilayers and disrupting their ordered domains, improving drug partitioning into the stratum corneum and forming lipophilic complexes with drugs [45, 46]. Oleic acid is mono-unsaturated, the most popular fatty acid increase the penetration of lipophilic drugs through skin by trancedermal cellular pathway. 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 [47]. Lauric acid in Propylene glycol enhanced the delivery of highly lipophilic antiestrogen [48]. 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 [11].

Essential oil, terpenes and terpenoids

Terpenes are found in essential oils, and are compounds containing carbon, hydrogen and oxygen atoms, but which are non aromatic. The basic chemical structure of terpenes are consists of a number of isoprene (C_5H_8) unit, which is used to classify terpenes. Numerous terpenes are use as medicines as well as flavouring and fragrance agents. Terpenes are lipophilic substances with relatively high log Po/w values [35]. Examples of terpenes are carvone, cineole, menthone and eucarvone. Menthol is the most common terpene employed as a penetration enhancer. Effective penetration enhancers for 5-flouorouracil transversing human skin in vivo have been found from the essential oils of eucalyptus, chenopodium and ylang-ylang [49]. Physicochemical characteristics of the terpenes were found to strongly affect on drug penetration, agents containing oxygen having increased enhancing activity, and bicyclic terpenes having reduced

enhancing activity. Improving drug partitioning into the tissue by a one mechanism is, the agent operates is to modify the solvent nature of the stratum corneum.

Phospholipids

Phospholipids successfully used as permeation enhancers in the form of vesicles, microemulsions and micellar systems [50, 51]. In the form of self-assembled structures such as vesicles or micelles, they can fuse with the lipid bilayers of the stratum corneum thereby enhancing partitioning of encapsulated drug as well as disruption of the ordered bilayers structure [36, 38]. Phospholipids can occlude the skin surface and thus can increase tissue hydration, so that can increase drug permeation.

Surfactant

They are classified by presence of charged groups on the head moiety. A non-ionic surfactant carries no charge, anionic carries negatively and cationic carries positively charged head groups. In zwitterionic surfactant head contains two oppositely charged groups. Dioctyl sulphosuccinate, sodium lauryl sulphate, decodecylmethyl sulphoxide are anionic surfactants. Pluronic F127, Pluronic F68 are non-ionic surfactants [52]. Sodium lauryl sulphate (SLS) is an anionic surfactant, and acts on the horny layer in a concentration-dependant manner. At 1%, SLS was shown to markedly disrupt both lipid and protein components of the stratum corneum in an at least partially reversible manner [53]. Penetration of surfactant itself is known to cause irritation problems. Cationic surfactants are reportedly more irritating than anionics. The majority of surfactants used in penetration enhancement studies have been anionic or non-ionic.

Urea (amines)

For enhancing skin permeation of a variety of drugs primary, secondary and tertiary, cyclic and acyclic amines have been used successfully. They may enhance skin permeation by partitioning into the lipid bilayers or improving drug partitioning into the skin [54, 36, 40]. Urea has keratolytic properties, when it is use in combination with salicylic acid for keratolysis. Penetration enhancing activity of urea probably results from a combination of increasing stratum cornum water content and through the keratolytic activity. 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 [7].

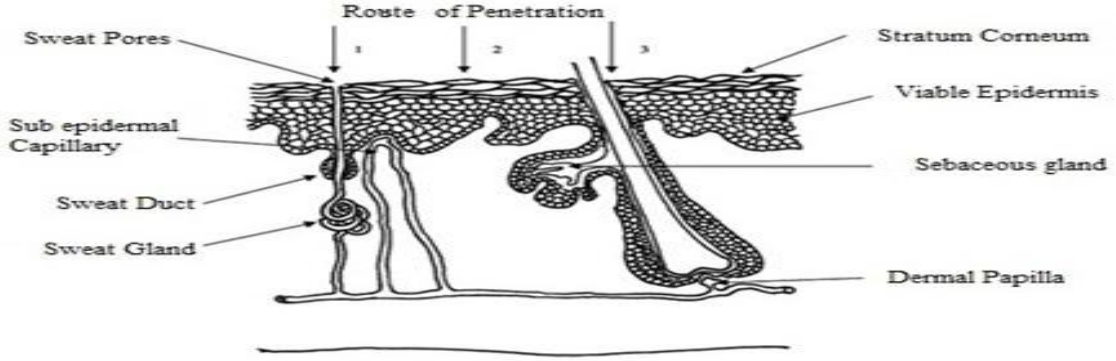
Cyclodextrin

Cyclodextrins are biocompatible substances that can form inclusion complexes with lipophilic drugs with a resultant increase in their partitioning and solubility, in the stratum corneum particularly in aqueous solutions [55]. Cyclodextrins alone were determined be to less effective as penetration enhancers than when combined with fatty acids and propylene glycol [56].

Water

Water is the most natural penetration enhancer [57].Hydration of the stratum corneum has been shown to increase the penetration of both hydrophilic and hydrophobic drugs [58, 59]. Hydration can be achieved by soaking the skin or using a formulation with high content of water. More commonly, occlusion is used to prevent natural water loss from the skin, so maintain the water level, thus stratum corneum water content moves towards equilibrium with the underlying layers. Typically, from thermal analysis and spectroscopic methodologies, some 25–35% of the water present in stratum corneum can be assessed as 'bound', i.e. is associated with some structural elements within the tissue [60]. The remaining water within the tissue is 'free' and is available to act as a solvent within the membrane for polar permeants.

Fig 1. Simplified representation of skin showing routes of penetration: 1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles.



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 compare to the other conventional dosage form in the next decade. The vast majority of topical and transdermal drug formulations are based on the passive diffusion of a low molecular weight, lipophilic drugs across the skin. But for very hydrophilic drugs or permeants with a molecular weight above 500 Daltons, skin penetration is generally poor. The membrane and membrane (stratum corneal, epidermis) in the body serve as a barrier and protect the body to the external environment, rendering the absorption of drugs. Penetration enhancers are applied to improve the efficacy of the drugs across the membrane .Different approaches are applied like chemical which offers the penetration by chemical changes or by use of chemicals such as Azone, sulphoxides, fatty acids, terpenoids. Formulations enhancer technique in which the carrier and complexing agents such as β cyclodexrin, these techniques are very useful in pharmaceutical industry as most of drugs have less permeable behaviour. 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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