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REVIEW ARTICLE

SYNERGISTIC ACTION OF PENETRATION ENHANCERS IN TRANSDERMAL DRUG DELIVERY

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ABSTRACT:

Transdermal drug delivery system is a desirable form of drug delivery because of the obvious advantages over other routes of delivery. One promising challenge in designing transdermal drug delivery system is to overcome the natural transport barrier of the skin i.e. the stratum corneum which is the rate limiting step in percutaneous absorption of drugs. Various penetration enhancers are now being used alone or in combinations to enhance the penetration of the drug through the skin. The main objective of the present study is to review the synergistic action of various penetration enhancers on the efficacy and safety of the drug. It has been found from the literature study that systems employing synergistic mixtures of penetration enhancers offer superior skin permeation enhancement as compared to those employing single penetration enhancer. Various chemical, physical and carrier approaches have also been reviewed to increase skin permeation of the drug.
Keywords: Transdermal, penetration enhancers, synergistic mixtures, permeation enhancement.

INTRODUCTION

Transdermal drug delivery system (TDDS) is defined as a dosage form, which when applied to the skin, deliver the drug through the skin at control rate to the systemic circulation[1]. Currently transdermal delivery is one of the most promising methods for drug application. Increasing number of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin[2]. Transdermal delivery not only provides controlled, constant administration of the drug but also allows continuous input of drugs with short half lives and eliminates pulsed entry into systemic circulation which often causes undesirable side effects. Transdermal delivery provides a leading edge over oral route and injectables by avoiding first pass metabolism and increasing patient compliance respectively[3]. Transdermal delivery involves the passage of the drug molecule from the skin surface into the stratum corneum under the influence of a concentration gradient and its subsequent diffusion through the stratum corneum into the blood circulation. The stratum corneum provides the greatest resistance to penetration and it is the rate limiting step in percutaneous absorption. Therefore transdermal delivery requires penetration enhancers to penetrate the drug through the skin. They facilitate the absorption of the drug through the skin by temporarily diminishing the impermeability of the skin[4]. Several researchers have studied the effect of combination of penetration enhancers like physical, chemical, and natural penetration enhancers to assess the plausibility of deriving synergistic benefits. Use of a combination of penetration enhancers is reported to mutually enhance the safety and efficacy of the drug by acting synergistically[5]. The main objective of the study is to review the synergistic effect of various physical, chemical and natural penetration enhancers on the penetration and efficacy of the drug through transdermal route.

Advantages of Transdermal Drug Delivery System

Transdermal Drug delivery system offers many advantages over the conventional dosage forms notably avoidance of hepatic first–pass metabolism, maintains constant blood level for longer period of time, offers less frequency of administration, decreases the dose to be administered, decreases unwanted side effects, the drug can be withdrawn in case of toxicity, minimizes inter and intra patient variability, increases patient compliance and offers large area of application in comparison with the buccal or nasal cavity[6].

Limitation with Transdermal Drug Delivery System

The outermost layer of the skin i.e. the stratum corneum provides the greatest resistance to penetration thereby limiting transdermal bioavailability of the drug and it is the rate limiting step in percutaneous absorption. Thus the transport of the drug across the skin membrane is a complex phenomenon. It is the cells of the stratum corneum which present the primary barrier to absorption of transdermally administered drugs. The drug molecule has to penetrate across the stratum corneum barrier in order to reach the deeper dermal region[7].

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Approaches to increase skin permeation

Chemical approach

- Use of penetration enhancers (chemical and natural penetration enhancers).

Carrier approach

- Vesicular carriers
- Microparticulate carriers[6]

Physical approach

- Iontophoresis
- Sonophoresis
- Electroporation
- Microfabricated microneedles

PENETRATION ENHANCERS: These are the substances that facilitate the absorption of penetrant through the skin by temporarily diminishing the impermeability of the skin. Penetration enhancers interact with structural components of stratum corneum i.e., proteins or lipids. They alter the protein and lipid packaging of the stratum corneum, thus chemically modifying the barrier functions of the skin leading to increased permeability of the drug through the skin. They are also known as **accelerants, absorption promoters** as they promote the penetration of topically applied drugs. Penetration enhancers can increase the drug diffusivity in the stratum corneum by dissolving the skin lipids or denaturing skin proteins. The type of enhancer employed has a significant influence on the design and development of the product.

Permeability can be enhanced by altering the structure of the skin or by increasing the solubility of the drug in the skin. Various penetration enhancers are now being used in combinations to assess the plausibility of deriving synergistic benefits and to investigate their effect on the permeation and efficacy of the drug[8].

Ideal characteristics of penetration enhancer: It should be pharmacologically inert, non-toxic, non-irritating, non-allergenic, compatible with the drug and excipients, they should not lead to the loss of electrolytes and body fluids, skin should immediately regain its barrier properties on its removal, it should readily formulate into dermatological preparations, transdermal devices and skin adhesives, it should be inexpensive and cosmetically acceptable. No single penetration enhancer can possess all the required properties. Several researchers are engaged in transdermal permeation studies using various penetration enhancers for several drug moieties[9].

Mechanism of penetration enhancer to enhance permeation of drug through skin: There are three main functions of penetration enhancers on the basis of lipid protein partitioning. First is the lipid disruption of the stratum corneum. The penetration enhancers modify the structure of the stratum corneum lipid organization and make it permeable to drugs so that drug can easily permeate through the skin. Second is the protein modification of the skin. They interact with keratin in corneocytes and open up the dense protein structure and make it more permeable for the drug. Third is the partitioning promotion, many solvents increase the partitioning of a drug, co-enhancer and co-solvent by changing the solution properties of the horny layer. Thus penetration enhancers act by altering the following path ways:

i. Polar pathway: This pathway can be altered by protein conformational change.
ii. Non-polar pathway: This pathway can be altered by altering the rigidity of the lipid structure.
iii. Polar/non polar pathway: It can be altered by altering the multilaminate pathway for penetrants[10].

Penetration enhancers can be chemical and natural depending on their origin.

CHEMICAL PENETRATION ENHANCERS: Various chemical penetration enhancers have been investigated for overcoming the stratum corneum barrier and enhancing the transdermal delivery of drugs. Chemical permeation enhancers are relatively inexpensive and easy to formulate, they offer flexibility in their design, are simple in application and allow the freedom of self administration to the patient[11].

Chemicals belonging to the same group can act on skin by different mechanisms depending on their individual physicochemical properties.

Water

Water is the most natural penetration enhancer. Hydration state of the stratum corneum is important in determining penetration enhancement of a given drug. Increased hydration of the stratum corneum enhances transdermal flux of a variety of drugs[12].

Hydrocarbons

Several hydrocarbons including 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. These permeation enhancers work by partitioning into the stratum corneum and disrupting the ordered lipid bilayer structure[13].

Alcohols

Alcohols are used as vehicles, solvents or penetration enhancers in improving transdermal delivery of drugs. These include alkanols, alkenols, glycols, polyglycols and glycerols. They 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[14-17].

Fatty Acids

The most commonly studied chemicals in this category are fatty acids. These chemicals 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. Examples include oleic acid and undecanoic acid. Oleic acid is an example in this category that is extensively studied as a permeation enhancer[18-20].

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Amines

Primary, secondary and tertiary, cyclic and acyclic amines have been used successfully in enhancing skin permeation of a variety of drugs. Amines may enhance skin permeation by partitioning into the lipid bilayers or improving drug partitioning into the skin[21].

Amides

Cyclic and acyclic amides form another large class of chemicals studied as permeation enhancers. Azone and its analogues along with pyrrolidones are the most extensively used amides[22].

Esters

Esters of fatty acids have been used in several studies and show skin permeation enhancement of a wide variety of drugs. Isopropyl myristate is the most widely studied ester along with several other esters of fatty acids. These chemicals generally work by partitioning themselves in the ordered lipid domains of the stratum corneum[23].

Surfactants

Surfactants are amphipathic molecules that consist of a non-polar hydrophobic portion usually a straight or branched hydrocarbon or fluorocarbon chain containing 8-18 carbon atoms, which is attached to a hydrophilic portion. The hydrophilic portion can be nonionic, ionic or zwitterions. Many of the properties of surfactants can be related to their ability to concentrate at phase interfaces, leading to a reduction in interfacial tension. In biological systems the effect of surfactants are complex; particularly their effect on cell and other membranes, and this can lead to alterations in permeability characteristics. Nowadays, a wide variety of surfactants are being used as skin permeation enhancers. Surfactants are usually used with a vehicle or solvent system and their activity depends upon the hydrophilic to lipophilic balance, charge and lipid tail length. Anionic and non-ionic surfactants are relatively more widely studied[2].

Terpenes, terpenoids and essential oils

Terpenes and terpenoids are usually the constituents of volatile oil. Terpenes have been utilized for a number of therapeutic purposes such as in antispasmodics, carminatives, perfumery and also as percutaneous absorption enhancers[24]. Terpenes are a popular choice for permeation enhancers in transdermal drug delivery system. This category includes a heterogeneous range of members and the effect of a specific terpene on skin depends upon its exact physicochemical properties, in particular its lipophilicity[25].

Sulfoxides

Dimethyl sulfoxide (DMSO) was the first chemical to be studied in depth as a permeation enhancer. Dimethyl sulfoxide is the most important compound of this category. DMSO is an aprotic solvent that has the ability to induce cell fusion and cell differentiation and enhance the permeability of lipid membranes. It is also an effective cryoprotectant[26].

Lipids

Phospholipids have been successfully used as permeation enhancers in the form of vesicles, microemulsions and micellar systems. Phospholipids do not have an appreciable effect when interacting with the stratum corneum as individual molecules. However, 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[14].

NATURAL PERMEATION ENHANCERS: Natural oils as permeation enhancers have received increasing attention due to their better safety profile[27]. Vegetable oils have been found to be effective permeation enhancers due to the presence of fatty acids. In some cases fatty acids have been reported to be more effective than terpenes and azone[28]. They offer many benefits as they are safe to use, easily metabolized in the body, and are easily available. Examples include corn (maize) oil, jojoba oil, olive oil and groundnut oil etc[29].

SYNERGISTIC EFFECT OF PENETRATION ENHANCERS

It has been reported in the literature that chemical penetration enhancers when used in combination or in different concentrations act synergistically to enhance the action of the drug by increasing the permeation of the drug through skin. A mixture of two or more solvents is one of the most widely studied formulation strategies to facilitate drug transport across the skin.

Rhee *et al.*, (2007) observed that the skin permeability of clebopride from a binary mixture of diethylene glycol monoethyl ether:isopropyl myristate (40:60) was 80-fold higher as compared to that from isopropyl myristate alone[30].

Krishnaiah *et al*., (2008) studied the effect of various water:ethanol solutions on skin permeation of ondansetron hydrochloride. They have found that a synergistic mixture of 60% v/v ethanol:water showed highest skin permeation in vitro[31].

Transdermal flux of highly lipophilic drugs such as antiestrogens can be enhanced by using a solvent combination of propylene glycol:lauric acid (90:10). The extraordinary permeation enhancement by this formulation is due to mutual permeation enhancement of these two enhancers and their synergistic lipid fluidizing activity in the stratum corneum[32].

Menthol:n-methyl pyrrolidone and isopropyl myristate:n-methylpyrrolidone mixed solvent systems have also been documented to show synergistic enhancement of transdermal delivery of formoterol fumarate[33].

Binary combinations of isopropyl myristate and short chain alkanols show transdermal flux enhancement of estradiol when compared to alkanols alone[34]. Identification of synergistic mixtures of chemicals requires screening of a large number of chemicals and formulations for synergistic interactions[35].

Gwak *et al.*, (2002) investigated the effect of vehicles and penetration enhancers on the in vitro permeation of tenoxicam from saturated solution through dorsal

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hairless mouse skin. Various types of vehicles including ester, alcohol, and ether types and their mixtures were used as vehicles and then a series of fatty acids and amines were employed as enhancers respectively. The results revealed that the combination of lipophilic vehicles like oleic acid, linoleic acid or oleyl alcohol and hydrophilic vehicles like propylene glycol can be used for enhancing the skin permeation of tenoxicam[36].

Tezel *et al.*, (2002) investigated the synergistic effect of ultrasound and surfactants on transdermal drug delivery. They found that surfactants possessing anionic and cationic head groups were more potent than those possessing nonionic head groups in increasing skin conductivity in the presence of ultrasound. Two mechanisms were shown to play a role on their synergistic effect. First, ultrasound enhances surfactant delivery into the skin and second, ultrasound disperses surfactant within the skin. They performed imaging experiments to assess the effect of ultrasound on delivery of a model permeant, sulforhodamine B into the skin[37].

Ganga *et al.*, (1996) investigated the effect of azone on the transdermal iontophoretic transport of metoprolol tartrate through human epidermis in vitro. Investigations were carried out to see whether there is any synergistic effect of azone in conjunction with iontophoresis. Azone caused increased transport of the drug through human epidermis and the transport was increased 130 fold during iontophoresis compared to passive flux. The results were supported by scanning electron microscopy studies of the epidermis[38].

Kikuchi *et al.*, (2005) studied the effect of EDTA and boric acid on the corneal penetration of CS-088, an ophthalmic agent. The corneal penetration of CS-088 was significantly enhanced in the presence of EDTA/ boric acid by apparently 1.6 fold. The permeability enhancing effect of EDTA and boric acid was apparently synergistic and concentration dependent on both EDTA and boric acid[39].

Fang *et al.*, (2008) studied the synergistic effect of menthol and ethanol on transdermal permeation and topical analgesia of tetracaine gel. To determine the efficacy of tetracaine gels for managing pain in human volunteers, a paralleled, double-blinded, placebo-controlled, randomized controlled trial design combined with verbal pain scores was performed. 70% ethanol in 5% methanol+ 70% ethanol/tertracaine gel not only improved the analgesic efficacy of the tetracaine gel through synergistically enhanced percutaneous permeation with methanol but also served as an antiseptic agent[40]. The in vitro skin delivery of furosemide was significantly improved by using a combination of oleyl alcohol and azone as permeation enhancers[41].

Mundada *et al.*, (2012) have disclosed in their research that by using a range of penetration enhancers flux rate of the drug can be enhanced. They have reported the formulation of topical gel of lornoxicam by using a range of chemical penetration enhancers such as Transcutol P, Labrasol and triton X-100. The results revealed that transcutol P in 2% concentration showed maximum flux rate for lornoxicam across skin among all penetration enhancers[42].

Synergistic effect of eutectic mixtures

Several eutectic systems of active drug along with a skin permeation enhancer have been studied in the literature. These systems are interesting since they provide two mechanisms by which skin permeation of an active drug across skin can be enhanced. In the first, they form a low melting mixture with the drug thereby improving its partitioning into the skin. In the second, they act on skin directly to disrupt its structure and further enhance drug permeation. This synergy in mechanism can be exploited by selecting the right permeation enhancer or enhancers to be combined with the drug. Eutectic systems of ibuprofen formed with terpenes and propranolol with fatty acids have been studied successfully for improved transdermal permeation of drugs[43].

Kang *et al., (*2000) showed that the lidocaine:menthol eutectic system enhanced permeation of lidocaine across shed snake skin[44].

Kaplun-Frischoff and Touitou showed enhanced permeation of testosterone across human cadaver skin when combined with menthol in a eutectic formulation[45].

Carrier approach and synergistic effect of vesicles

Vesicles are colloidal particles that are composed of concentric bilayers formed from self-assembly of amphiphilic molecules. Synergistic interactions between the components of the vesicles and between the vesicles and skin constituents are believed to be responsible for the superior skin permeation enhancement of vesicular systems[46].

Liposomes consist of lipids such as cholesterol and phospholipids and they work by encapsulating drugs in their core and increasing their deposition in the stratum corneum[47].

Mezei (1985) showed that triamcinolone acetonide concentrations in skin were observed to be 4-5 fold higher when delivered from liposomes as compared to other conventional formulations. One limitation of liposomes is that they are less effective in delivering drugs to deeper layers of skin[48].

Niosomes are composed of non-ionic amphiphiles (surfactants) and are similar in function to the liposomes. Several studies have documented the superiority of niosomes in enhancing permeation of drugs across the stratum corneum.

Paolino *et al.*, (2007) have disclosed that Niosomes formulated from a new non-ionic surfactant alpha, omega-hexadecyl-bis-(1-aza-18-crown-6) (Bola-surfactant), span 80 and cholesterol show significantly improved percutaneous permeation of ammonium glycyrrhizinate with respect to both the aqueous drug solution and a physical mixture between unloaded Bola-niosomes and the aqueous drug solution[49].

Ethosomes are relatively new types of vesicle systems, primarily composed of water, ethanol and phospholipids.

Rao *et al*., (2008) demonstrated that the transdermal flux of fenasteride from ethosomal formulations was 2 to 7 fold higher as compared to aqueous formulations[50].

Transfersomes are ultradeformable hydrophilic lipid vesicles that cross the skin under the influence of a transepidermal water activity gradient. Transfersomes consist of phospholipids and an edge activator that increases the deformability of the bilayers and is often a single chain surfactant such as sodium cholate, sodium deoxycholate, Span 60, Span 65, Span 80, Tween20, Tween 60, Tween 80 or dipotassium glycyrrhizinate[51-56].

Single chemical offer limited enhancement of skin permeability to drugs. Mixtures of chemicals can overcome this limitation owing to their synergistic interactions[35].

Physical techniques to increase transdermal drug delivery

Iontophoresis: It is a process which involves the transport of ionic or charged molecules into a tissue by the passage of direct or alternating electric current through an electrolyte solution containing the ionic molecules to be delivered using an appropriate electrode polarity. The process involves the transfer of ions into the body by an electromotive force. Ions with positive charge are driven into the skin at the anode and those with negative charge at the cathode. The current intensity should be increased slowly, maintained for the length of the treatment and decreased slowly at the end of the treatment. The current must be within comfortable tolerance of the patient with a current density less than 0.5 m.amp/cm^2 of the electrode surface. Placing a moist pad between the electrode plate and the skin is necessary for making a perfect contact. The drug should be applied through the electrode with correct polarity. The drawbacks associated with the iontophoresis technology include the possibility of electric shock, skin irritation, burns and cost of treatment[6].

Electroporation: The drawbacks associated with iontophoresis technology can be overcome to a certain extent by electroporation technology. This process involves the application of transient high voltage electrical pulse to cause rapid dissociation of the stratum corneum through which large and small peptides, oligonucleotides and other drugs can pass. The degree of enhancement achieved in-vitro is related to the applied voltage, number and duration of the pulses offering the possibility of a controllable phenomenon[6].

Sonophoresis: This process involves the usage of high frequency ultrasound waves. The application of low frequency ultrasound can increase the permeability of human skin to many drugs including high molecular weight proteins by several orders of magnitude, thus making transdermal administration of these molecules potentially feasible. Low frequency ultrasound is a non-invasive technology for transdermal drug delivery system[6].

Microfabricated Microneedles: It is a novel technology which employs micron-sized needles made from silicon. Microneedles penetrate the skin about 10-15 mm deep inside the skin but do not reach the nerves found in deeper tissue, so are painless. These microneedle arrays, after insertion into the skin create conduits for transport of drug across the skin. The drug after crossing the stratum corneum diffuses rapidly through deeper tissue and taken up by capillaries for systemic administration. A microprocessor is attached to a tiny pump for delivering tiny amounts of the drug. The microprocessor and the pump automatically inject the right dosage of the drug. They offer various advantages as they are mechanically strong, can be removed without difficulty as well as reinserted into skin multiple times[6].

SYNERGISTIC EFFECT OF CHEMICAL PENETRATION ENHANCERS AND PHYSICAL TECHNIQUES

Various chemical penetration enhancers and physical permeation enhancement techniques have been investigated for overcoming the stratum corneum barrier and enhancing the trandermal delivery of drugs. Use of a combination of enhancers is reported to mutually enhance the efficacy and also increase the safety of drugs[5].

Combination of ultrasound and sodium lauryl sulfate (SLS) was reported to result in synergistic enhancement in permeation of mannitol by Mitragotri (2000)[57].

Oh *et al*., (1998) have reported that the transdermal transport of zidovudine was enhanced synergistically when iontophoresis was used in combination with chemical enhancers like propylene glycol and oleic acid[58].

Ganga *et al*, (1996) showed that the combination of azone and iontophoresis enhanced transdermal permeation of metoprolol synergistically[38].

Srinisava *et al*., (2011) have reported that the transdermal transport of drug was enhanced when magnetophoresis was used in combination with chemical penetration enhancers like menthol, dimethyl sufoxide, sodium lauryl sulfate and urea. The enhancement factor due to combination of chemical penetration enhancers was additive and not synergistic[59].

Makhmal Zadeh *et al*., (2010) have reported the effect of chemical and physical penetration enhancers on trolamine salicylate permeation through rat skin. Transcutol and eucalyptus oil were found to be the most effective enhancers[60].

D.Prasanthi and P.K. Lakshmi (2013) have studied the synergistic effect of iontophoresis and chemical enhancers on transdermal permeation of tolterodine tartarate. They found that iontophoresis in combination with chemical enhancers like nerolidol, farnesol, tween 20 and N-lauroyl sarcosine is an effective method for treatment of overactive bladder[61].

Johnson *et al*., (2000) studied the synergistic effect of chemical enhancers and therapeutic ultrasound on transdermal drug delivery. It was concluded that bilayer disordering agents such as linoleic acid and ultrasound transform the startum corneum bilayers into a fluid lipid bilayer phase or create a separate bulk oil phase, thereby producing greater enhancements for larger solutes[62].

CONCLUSION

Use of a combination of penetration enhancers is reported to mutually enhance the efficacy and safety of the drug by acting synergistically. Synergistic systems employing combinations of penetration enhancers are more efficient in enhancing skin permeability compared to individual enhancers. It has also been reported from the literature that side effects associated with physical techniques can be reduced when they are used in combination with chemical enhancers.

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