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Different Approaches Have been Performed to Enhance Transdermal Delivery of Drugs

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ABSTRACT

There is considerable interest in the skin as a site of drug application both for local and systemic effect. However, the skin, in particular the stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Rather than its barrier properties, strategies have been developed to deliver the drugs through the skin. Transdermal drug delivery systems allow delivery of a drug into the systemic circulation via permeation through skin layers at a controlled rate. In addition to the currently marketed formulations, new drugs are being formulated using the transdermal system because of the inherent advantage of administration by this route. This review describes enhancement techniques of permeation of drugs through skin, which can be enhanced by various methods including physical, electrical, chemical and formulation approaches. Studies have been carried out to find safe and appropriate permeation enhancers to promote the percutaneous absorption of a number of drugs. The mechanism of action of penetration enhancement techniques and their potential for clinical application are described in this review .

Key words: Transdermal, Permeation, Percutaneous, Penetration enhancement.

INTRODUCTION

The most common form of delivery of drugs is the oral route. While this has the notable advantage of easy administration, it also has significant drawbacks namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient (**Chen and Langer, 1998**). Several advances to this effect have been made in the last 2–3 decades and novel drug delivery systems have been brought (**Drachman, 1989**). A large contribution to these novel systems appeared as modifications of the active drug or use of formulation excipients to modulate drug pharmacokinetics, safety, efficacy and metabolism. One such approach is transdermal drug delivery which makes use of human skin as a port of entry for systemic delivery of drug molecules (**Thomas and Finin, 2004; Prausnitz, 1997**). However, the transdermal route is not used more widely because it is difficult to get sufficient amounts of drug across the skin. Skin acts as both physical and

biological barrier, it also performs a complimentary role; that of a transport regulator. Skin routinely regulates the flux of water molecules into and out of the body. It also permits the influx of a variety of small molecules that are fairly lipophilic log P ($N1.5$) and have molecular weight (MW) less than 500 Da (**Bos and Meinardi, 2000**). As a result, drug molecules currently administered via the transdermal route fall within a narrow range of molecular weight and lipophilicity. The biggest challenge in transdermal drug delivery today is to open the skin safely and reversibly to these high molecular weight hydrophilic drugs. Several technological advances have been made in the past couple of decades to overcome these challenges. So, skin penetration enhancement techniques have been developed to improve bioavailability and increase range of drugs which can deliver via transdermal route. This article reviews certain most widely investigated penetration enhancement techniques and their possible mechanisms.

PENETRATION ENHANCEMENT APPROACHES:

A) Formulation approaches

1. Prodrug

The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavorable partition coefficients. This is seldom described in the literature for transdermal drug delivery. It is an inactive pharmacological derivative of an active parent drug (**Albert, 1958**). It undergoes a spontaneous or enzymatic transformation that results in the free drug. Transdermal patches Naltrexone permeation can be increased through human skin by 2 fold by using a gemini prodrug, which is a prodrug comprised of two molecules of the same drug (**Hammell et al., 2004**). Also esters of gestodene, primarily to enhance the drug solubility in the matrix. By this means, the drug loading of the system could be increased without drug recrystallization (**Lipp et al., 1993**).

2. Ion pairs

Since charged molecules do not readily cross the stratum corneum, the technique of ion pairing has been investigated. The ion pair is believed to travel across the stratum corneum and afterwards dissociate into its charged species. In general, only mild penetration enhancement only about 2-fold can be achieved (**Valenta et al., 2000**).

3. Eutectic systems

Melting point of a drug influences solubility and hence skin penetration. According to the ideal solubility theory, the eutectic point is the lowest temperature at which a liquid phase exists in a 2-component system. Since the eutectic mixture of two components has a lower melting point than the

two single components, the penetration behavior of eutectic mixtures has been investigated. EMLA cream, a formulation consisting of a eutectic mixture of lignocaine and prilocaine applied under an occlusive film, provides effective local anesthesia for pain-free venipuncture and other procedures (**Heather, 2005**). A number of eutectic systems containing a penetration enhancer as the second component have been reported. In all cases, the melting point of the drug was depressed to around or below skin temperature thereby enhancing drug solubility. However, the interaction of the penetration enhancer with stratum corneum lipids also contributed to the increased drug flux.

4. Reduction of drug particle size

Micronization is a simple and renowned method to enhance drug dissolution. It is widely used to increase the release of poorly water soluble drugs from different drug delivery systems. Reduction in particle size leads to an increase in surface area and hence to a faster dissolution. Menorest® patch used this patch, which contains a micronized suspension of estradiol in an acrylate adhesive matrix (**Marty, 1996**). However, an increase in transdermal delivery is only possible if the dissolution of the drug in the therapeutic system is the rate limiting step of the drug delivery to the body.

5. Nanoparticles

Nanoparticles mediated drug delivery into the epidermis and dermis without barrier modification has encountered with little success. Where the barrier is compromised, however, such as diseased skin, there may be potential for enhanced particle penetration. The opportunities and obstacles for nanoparticle drug delivery are only just beginning to be explored in clinical trials. Advances in particle engineering, formulation science and an improved understanding of nanoparticle–skin interactions will undoubtedly lead to important clinically relevant improvements in topical drug delivery (**Jana et al., 2014**).

6. Liposomes

There are many examples of cosmetic products in which the active ingredients are encapsulated in vesicles. Although there are few commercial topical products containing encapsulated drugs, the possible penetration of liposomes across the stratum corneum is debated, but the general agreement is that they cannot pass the intact stratum corneum and act mostly locally (**Barry, 2001**). They need non-occluded conditions because they follow a local hydration gradient through the skin. It is also conceivable that contents of the aforementioned formulations (e.g., the phospholipids) interact with the lipids in the stratum corneum and thereby increase the drug penetration.

7. Niosomes

Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. In fact, if compared with conventional liposome's (phospholipids), niosomes (nonionic surfactant vesicles) offer higher chemical stability, lower costs, and great availability of surfactant classes. Niosomes seems an interesting drug delivery system in the treatment of dermatological disorders (**Agrawal et al., 2001; Maria et al., 2002**).

8. Ethosomes

Ethosomes are liposomes with high alcohol content capable of enhancing penetration to deep tissues and the systemic circulation (**Touitou et al., 2000**). It is proposed that the alcohol fluidizes the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate.

9. Transfersomes

These are vesicles composed of phospholipids as their main ingredient with 10-25% surfactant and 3-10% ethanol. Liposomes are too large to pass through pores of less than 50nm in size; transfersomes up to 500nm can squeeze to penetrate the stratum corneum barrier spontaneously. In some cases the transfersomes delivered with some physical enhancement method like iontophoresis for estradiol and microneedles for docetaxel (**Cevc et al., 1996**).

B) PHYSICAL Approaches

1. Removal of the stratum corneum

One attainable way to improve drug penetration across the skin is the (partial) removal of its predominant barrier, the stratum corneum. By this means, the molecules have to travel a shorter distance and they can reach the capillary system in the dermis faster. Several methods for stratum corneum removal have been described in the literature, including removal of the stratum corneum with motor-driven devices (**Friedland and Buchel, 2000**) or laser (**Dover et al., 2000**). Tape stripping, as the simplest method, is the removal of parts of the stratum corneum with corneocyte glue or adhesive tape. Microdermabrasion-treated skin showed an increase in the skin flux and the skin deposition of vitamin C by approximately the factor 20 compared to intact skin (**Lee et al., 2003**).

2. Needless injection

Needleless injection is a pain-free method to deliver drugs to the skin. It circumvents the pain, fear and safety concerns associated with the use of hypodermic needles. One example for a device able to transport particles in the skin is the PMED™ device. By forcing compressed helium with the drug formulation entrained in the gas through a special nozzle, the particles gain sufficient velocity for skin penetration (**Burkoth et al., 1999**). It is only used for solid particles that can be engineered to obtain tailored drug release. Drawbacks of this application are the high development costs and the inability to adjust the drug delivery to inter subject variability in skin permeation (**Brown et al. 2006**).

3. Microneedle systems

A more sophisticated approach to physically overcome the stratum corneum's barrier is the use of microneedle systems (**Prausnitz et al., 2002**). These devices are equipped with a multitude of microneedles that insert the drug underneath the stratum corneum. Either drug coated silicone needles or hollow metal needles (filled with drug solution) can be used for the purpose (**McAllister et al. 2003**). The needles penetrate the horny layer without destroying it and release the drug.

C) Electrical approaches

1. Sonophoresis

Sonophoresis is the enhancement of drug penetration across the skin by ultrasound. It can be subdivided into simultaneous sonophoresis and pretreatment sonophoresis. In the simultaneous approach, drugs are administered onto the skin and ultrasound is applied simultaneously. This method requires the patient to wear the ultrasound device during the treatment. The pretreatment approach uses ultrasound (e.g., the Sonoprep™ device) prior to the drug application. By this means, the skin is "permeabilized" and stays in a highly permeable state for several hours during which the drug is delivered through the skin. The latter method requires the determination of the degree of skin permeabilization prior to the drug application. For that purpose, correlations between the skin conductance and its permeability can be exploited (**Mitragotri and Kost, 2004**). It was also shown that sonophoresis enabled the transport of insulin, γ -interferon and erythropoietin across human skin in vitro (**Mitragotri et al., 1995**).

2. Iontophoresis

Iontophoresis is defined as the process in which the flux of ionic solutes into or through skin is enhanced by applying a voltage drop/electric field across the skin. The drug is applied under an electrode of the same charge as the

drug, and an indifferent counter electrode is positioned elsewhere on the body. The active electrode effectively repels the active substance and forces it into the skin (**Mazumder et al., 2007**). Increase in drug penetration by iontophoresis can be due to drug is forced across the skin by simple electronic repulsion of similar charges or the electric current enhances the permeation by inhibiting the skin ability to perform its protective barrier function. Also iontophoresis causes water, a very effective penetration enhancer, to enter the stratum corneum (SC) by electroosmosis. Iontophoresis is able to deliver small molecules (e.g., opioids, NSAID) but also peptides and proteins, e.g. luteinizing hormone releasing hormone, human parathyroid hormone and insulin could be successfully delivered in animal models (**Kalia et al., 2004**).

3. Electroporation

Electroporation is another electrical enhancement method which involves the application of short (microsecond or millisecond), high voltage (50-1000 volts) pulses to the skin. Electroporation creates new aqueous pathways in the lipid layers of the stratum corneum (**Chizmadzhev et al., 1995**). Larger macromolecules have also been delivered by electroporation, including insulin, vaccines, oligonucleotides, and microparticles. Moreover, during the application the sensation of pain has been reported, which may be a result of the main adverse effect: muscle contraction.

4. Magnetophoresis

Magnetophoresis is the term used to indicate application of a magnetic field and acts as an external driving force to enhance drug delivery across the skin. The increase in permeability can be contributed by the skin alteration. Magneto liposomes consist of magnetic nanoparticles wrapped by a phospholipid bilayer which can be successfully applied for drug delivery systems, magnetic resonance imaging markers for cancer diagnosis and thermal cancer therapy have been tested (**Hofman et al., 1995**).

5. Pressure Wave

Pressure waves generated by intense laser radiation, can increase the permeability of stratum corneum as well as the cell membrane. It is only applied for a very short time (100ns-1μs). It is thought that the pressure waves form a continuous or hydrophilic pathway across the skin due to expansion of lacunae (voids) domains in the stratum corneum. Also, the drug delivered into the epidermis can enter the vasculature and produce a systemic effect. Insulin delivered by pressure waves lead to reduction in the blood glucose level over many hours. The application of pressure waves does not cause any pain or discomfort and the barrier function of the stratum corneum

always recovers. Caffeine permeation has been reported for enhancing effect of such a mechanism (**Pliquett and Weaver, 1996**).

D) CHEMICAL METHODS (Use of penetration enhancers):

At present the most widely used approach to increase transdermal penetration is the use of chemical penetration enhancers (**Buyuktimkin et al., 1997**). These compounds diffuse into the skin where they interact with structures of the stratum corneum and alter its barrier function. According to Barry's Lipid-Protein-Partitioning theory (**Barry, 1991**) penetration enhancers basically employ one or more of the following mechanisms:

1. Disruption of the ordered intercellular lipids in the stratum corneum.
2. Interaction with the protein components inside the coenocytes.
3. Enhanced partitioning of the drug into the stratum corneum.

The ideal properties of a permeation enhancer (**Buyuktimkin et al., 1997; Williams and Barry, 2004**):

1. Pharmacologically inert.
2. Non-toxic, non-irritant, non-allergenic.
3. Rapid onset of action; predictable and suitable duration of action.
4. After removal of the enhancer the skin should immediately and fully recover its barrier function.
5. Impairment of the skin's barrier function only unidirectional to prevent the efflux of endogenous material.
6. Compatible with all components of the drug delivery system.
7. Odorless, tasteless and colorless (cosmetically acceptable).
8. Inexpensive.

1. Water

Water is the most natural penetration enhancer. Hydration appears to increase transdermal delivery of both hydrophilic and lipophilic permeants. The water content in the stratum corneum is under normal conditions approximately 15-20% (**Williams and Barry, 2004**). Water within the stratum corneum alters 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 (**Bond and Barry, 1988; Walkeley, 1972**). It was also suggested that the swollen corneocytes in the hydrated stratum corneum lead to a distortion in the stratum corneum's mortar-and-brick structure and consequently to new connections (**Elias et al. 2002**). These "pores" could be responsible for the faster permeation of molecules.

2. Sulfoxides and similar chemicals

Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. Which is often used as the "universal solvent", has excellent penetration enhancing effects on hydrophilic and lipophilic drugs (**Horita and Weber, 1993**). However, Problems with DMSO arise from the fact that high concentrations are needed for an optimum penetration enhancement, which can cause erythema and protein denaturing (**Kligman, 1965; Southwell and Barry, 1984**). Researcher's showed that healthy volunteers developed erythema, scaling, contact urticaria and stinging/burning sensations after being painted with DMSO twice daily for three weeks (**Kligman, 1965**). Since DMSO is problematic for use as a penetration enhancer, studies have investigated a similar chemically-related material as an accelerant. Dimethyl acetamide (DMAc) and dimethyl formamide (DMF) are similarly powerful aprotic solvents. Due to its potential toxicity and adverse reactions, it could not be a better choice.

3. Azone

Azone (1-dodecylazacycloheptan-2-one or laurocapram) was the first molecule specifically designed as a skin penetration enhancer. It improves the skin permeation of many hydrophilic and lipophilic drugs. Azone partitions into a bilayer lipid to disrupt their packing arrangement but integration into the lipid is unlikely to be homogeneous (**William and Barry, 2004**). Lipids isolated from human stratum corneum provide evidence that Azone exists as a distinct phase within the stratum corneum lipids (**Pilgram et al., 2001**). It is typically used in low concentrations (1-3%) and is far less effective when used in higher concentrations (**Williams and Barry, 2004**). Azone has a certain irritation potential (**Hirvonen et al., 1993**).

4. Pyrrolidones

Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-flourouracil) and lipophilic (progesterone and hydrocortisone) permeants. Pyrrolidone partitioning 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. However, erythema and contact dermatitis observed after use on human skin (**Jungbauer et al., 2001**).

5. Fatty acids

A variety of fatty acids can enhance skin permeation. 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 (**Goodman and Barry, 1989**). Saturated fatty acids with an alkyl chain length of approximately 12 and unsaturated fatty acids with an alkyl chain length of 18 attached to a polar head group show optimum enhancement (**Aungst et al., 1986; Williams and Barry, 2004**). They were also shown to increase the bilayer fluidity (**Prausnitz et al., 2004**). 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 transconfiguration. Cis-configuration fatty acids are more potent for disrupting the lipid packing order with in the bilayers (**Trommer and Neubert, 2006; Funke et al., 2002a**). 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 (**Scin and Lee, 2002**). Again, the drawback of their application is skin-irritating potential of fatty acids when used at higher concentrations.

6. 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 (**Friend et al., 1988**). Ethanol increases the flux of drugs across the stratum corneum (**Pershing et al. 1990**). A parabolic relationship between carbon chain lengths was observed. A decrease in the permeation was observed with three double bonds (**Andega et al., 2001**). D-Hexanol and D-octanol shows permeation enhancement by lipid extraction effect, whereas dDecanol did not change skin lipid content (**Dias et al., 2008**) Investigations of alcohols with different chain lengths found maximum enhancement for decanol (**Williams and Barry, 2004**).

7. Surfactants

A variety of surfactants have been used as skin penetration enhancer (**Karande et al., 2007**). Most surfactants show penetration enhancement and are known to have low chronic toxicity. They solubilize the lipids in the stratum corneum and thereby increase the drug flux across the barrier. In general, it seems that anionic surfactants have a more pronounced penetration enhancement effect than non-ionic (**Williams and Barry, 2004**).

8. Terpenes

Terpenes are a popular choice for penetration enhancers in transdermal drug delivery studies. These arenon-aromatic compounds only comprised of carbon, hydrogen and oxygen. They consist of repeating (C₅H₈) units (**Aqil et al., 2007**). A variety of terpenes showed permeation enhancing effects for lipophilic and hydrophilic drugs (**Buyuktimkin et al., 1997**). The essential oils of eucalyptus, chenopodium and ylangylang have been found to be

effective penetration. A mechanism has 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. They are a popular choice for formulators because the FDA classifies them as GRAS (generally regarded as safe), which facilitates their approval (Aqil et al., 2007).

Synergistic effects of chemical permeation enhancers

Penetration enhancer combinations can have synergistic effects (Funke et al., 2002a; Karande et al., 2004; Williams and Barry, 2004; Karande et al., 2006) due to various reasons, e.g., Synergistic effects have been demonstrated for many combinations, such as Azone and propylene glycol, Azone and Transcutol, oleic acid and propylene glycol, terpenes and propylene glycol, various combinations and alcohols, N-methylpyrrolidone and propylene glycol, urea analogues and propylene glycol (**Heather, 2005**). In these cases, permeation enhancer could facilitate the partition from the combined effects of the enhancer and solvent acting by different mechanisms. Probably the cosolvent, such as propylene glycol, acts to increase the concentration of mutually the permeant and the enhancer in the stratum corneum. In addition, the lipid fluidizing effect of the enhancer will increase the free volume within the lipid bilayers thus facilitating partitioning of both the permeant and solvent.

CONCLUSION

Ideal skin penetration enhancer has been the focus of considerable research effort over a number of decades. Nevertheless many potent enhancers have been discovered. 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 penetration enhancement techniques have been developed. These also improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. In recent years the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. Modern discovery techniques are applied for better understanding of the interaction of enhancers with the stratum corneum and the design of novel transdermal penetration enhancer with optimal characteristics and minimal toxicity.

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