

THE PHARMA INNOVATION - JOURNAL

Recent Trends In Penetration Enhancer Used In Transdermal Drug Delivery System

Debjit Bhowmik^{1*}, Vazram Dasari², S.Duraivel³, K.P.Sampath Kumar³

1. Karpagam University, Coimbatore, TN, India
[E-mail: debjit_cr@yahoo.com]
2. Nimra Pharmacy College, Vijayawada, India
3. Department of pharmaceutical sciences, Coimbatore Medical College, Coimbatore, TN, India

The TDDS are defined as self-contained, discrete dosage forms which, when applied to the intact skin, deliver the drug(s), through the skin, at a controlled rate to the systemic circulation. Transdermal drug delivery is a viable administration route for potent, low-molecular weight therapeutic agents which cannot withstand the hostile environment of gastrointestinal tract and/or subject to considerable first-pass metabolism by the liver. Studies have been carried out to find safe and suitable permeation enhancers to promote the percutaneous absorption of a number of drugs. 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 the major routes of drug administration in the next decade. Research in this area has proved the usefulness of physical and chemical penetration enhancers in the enhancement of drug permeation through skin. The physical and chemical penetration enhancement methods discussed in this review are promising. Focus should be on skin irritation, with a view to selecting penetration enhancers which possess optimum enhancement effects with minimal skin irritation. The Transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to Transdermal or dermal system.

Keyword: Transdermal Drug Delivery System, Penetration Enhancer

1. Introduction

The delivery of drugs into systemic circulation via skin has generated much attention during the last decade. Transdermal therapeutic systems propound controlled release of active ingredients through the skin and into the systemic circulation in a predictive manner. Drugs administered through these systems escape first-pass metabolism and maintain a steady state scenario similar to a continuous intravenous infusion for up to several days. It is recognized that continuous intravenous (i.v) infusion is a superior mode of drug administration as

compared to the oral route not only to bypass hepatic “first-pass” metabolism but also to maintain a constant and prolonged drug level in the body. A closely monitored intravenous infusion can provide the dual advantage of direct entry of the drug into the systemic circulation and the control of circulating drug levels. However, such a mode of administration involves certain risks which necessitate hospitalization of the patient for close medical supervision of drug administration. It was realized and later demonstrated that the benefits of intravenous infusion could be

closely duplicated without its hassles by using the skin as the port of entry of drugs. This is known as Transdermal administration and the drug delivery systems are known as Transdermal therapeutic systems or Transdermal drug delivery systems (TDDS) or popularly as Transdermal patches. Successful transdermal drug delivery requires numerous considerations owing to the nature and function of the site of application. It should always be kept in mind that the basic functions of the skin are protection and containment. As per these rulings, it would seem exceptionally difficult to cross the skin for systemic absorption. However, with continuous exploration of the structure, function, and physicochemical properties of the skin, more and more new drug products are being developed for Transdermal delivery. The safe and effective drug delivery is the ultimate target for each and every new technology ever explored. The search for the ideal skin penetration enhancer has been the focus of considerable research effort over a number of decades. Although many potent enhancers have been discovered, in most cases their enhancement effects are associated with toxicity, therefore limiting their clinical application. 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. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity.

1.1 Merits of TDDS

Transdermal medication delivers a steady infusion of a drug over an extended period of time. Adverse effects or therapeutic failures frequently associated with intermittent dosing can be avoided. Transdermal delivery can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastro-intestinal irritation, low absorption, decomposition due to hepatic “first-pass” effect, formation of metabolites

that cause side effects, short half-life necessitating frequent dosing etc. The simplified medication regimen leads to improved patient compliance and reduced inter- and intra-patient variability. Self administration is possible with these systems. The drug input can be terminated at any point of time by removal of drug application from the skin surface. Substitutes oral administration when route is unsuitable as in case of vomiting, diarrhea and in unconscious patients. Achievement of efficacy with lower total daily dosage of drug by continuous drug input. Provides utilization of drugs with short biological half-life, narrow therapeutic window. Avoids risk and inconveniences of intravenous therapy. Reduces the chances of over- or under dosing through the prolonged, preprogrammed delivery of drug at the required therapeutic rate.

1.2 Demerits of TDDS

The drug must have some desirable physicochemical properties for penetration through stratum corneum (SC) and if the drug dosage required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult if not impossible. Daily doses of less than 5 mg/day are preferred. Skin irritation or contact dermatitis due to the drug, excipients and penetration enhancers used to increase percutaneous absorption of the drug is another limitation. Clinical need is another area that has to be examined carefully before a decision is made to develop a transdermal product. The barrier function of the skin changes from one site to another on the same person, from person to person and with age. Enzymes in epidermis may denature the drugs. Drugs that require high blood levels cannot be administered.

1.3 Pathway of Transdermal Permeation

The permeation of drugs through the skin includes the diffusion through the intact epidermis and through the skin appendages, i.e. hair follicles and sweat glands, which form shunt pathways through the intact epidermis. However, these skin appendages occupy only 0.1% of the total human skin surface and the

contribution of this pathway is usually considered to be small (with only a few exceptions having been noted). As stated above, drug permeation through the skin is usually limited by the SC. Two pathways through the intact barrier may be identified (Fig No. 2): the intercellular lipid route between the corneocytes and the transcellular route crossing through the corneocytes and the intervening lipids; that is, in both cases the permeant must diffuse at some point through the intercellular lipid matrix, which is now recognized as the major determinant of percutaneous transport rate.

Transdermal permeation of a drug involves the following steps:

1. Sorption by SC.
2. Penetration of drug through viable epidermis.
3. Uptake of the drug by the capillary network in the dermal papillary layer.

This permeation can be possible only if the drug possesses certain physiochemical properties. Skin is an important site of drug application for both local and systemic effects. However in skin, the SC is the main barrier for drug penetration. Penetration enhancement technology is a challenging development that would increase the number of drugs available for transdermal administration. Significant advancement has been made, in the last two decades, in achieving a better control in the delivery through the skin. Research has been directed to find ways of delivering different types of drug molecule with the A strategy to enhance the skin permeation in the present study is the use of permeation enhancers. One of the easiest approaches to enhance the permeation rate is the use of penetration enhancers. These are the substances added to pharmaceutical formulation in order to increase the membrane permeation or absorption rate of a co-administered drug.

1.4 Ideal Characteristics of Chemical Penetration Enhancers

Ideally, penetration enhancers reversibly reduce the barrier resistance of the SC without damaging the viable cells. Some of the more desirable properties for penetration enhancers acting within the skin have been given as:

1. They should be non-toxic, non-irritating and non-allergenic.
2. They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.
3. They should have no pharmacological activity within the body—i.e. should not bind to receptor sites.
4. The penetration enhancers should work unidirectionally, i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
5. When removed from the skin, barrier properties should return both rapidly and fully.
6. The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
7. They should be cosmetically acceptable with an appropriate skin 'feel'.

1.4.1 Chemical Enhancers

Mechanism of chemical penetration enhancement
Penetration enhancers may act by one or more of three main mechanisms:

1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, coenhancer or solvent into the stratum corneum.

1.4.2 Classification of Chemical penetration enhancers

1. Sulphoxides- DMSO, DMF.
2. Azones- 1-dodecylazacycloheptan-2-one
3. Pyrrolidones- N-methyl-2-pyrrolidone

4. Essential oil, terpenes and terpenoids-sesquiterpene oil, L-menthol
5. Oxazolidinones- 4-decyloxazolidin-2-one
6. Fatty acids- lauric acid, myristic acid and capric acid
7. Glycol- diethylene glycol and tetraethylene glycol
8. Nonic surfactant- polyoxyethylene-2-oleyl ether, polyoxy ethylene-2-stearly ether.

1.4.3 Types of Permeation Enhancers:

Different classes of permeation enhancers are as Follows:

a) Sulfoxides

Dimethylsulfoxide (DMSO) is an effective penetration enhancer that promotes permeation by reducing skin resistance to drug molecules or by promotion of drug partitioning from the dosage form. It has been postulated that DMSO denatures the intercellular structural proteins of the SC, or promotes lipid fluidity by disruption of the ordered structure of the lipid chains. Along with these, DMSO may alter the physical structure of the skin by elution of lipid, lipoprotein and nucleoprotein structures of the SC.

b) Alcohols

Alcohols may influence transdermal penetration by a number of mechanisms. The alkyl chain length of the alkanols is an important parameter in the promotion of permeation enhancement. Lower molecular weight alkanols are thought to act as solvents, enhancing the solubility of drugs in the matrix of the SC.

c) Polyols

The activity of propylene glycol is thought to result from solvation of α keratin within the SC; the occupation of proteinaceous hydrogen bonding sites reducing drug-tissue binding and thus promoting permeation.

d) Alkanes

Long chain alkanes (C7-C16) have been shown to enhance skin permeability by non-destructive alteration of the SC barrier.

e) Fatty acids

Selective perturbation of the intercellular lipid bilayers in the SC appears to be the major mode of enhancing activity of the fatty acids.

f) Esters

Esters such as ethyl acetate are relatively polar, hydrogen bonding compounds that may enhance permeation in a similar manner to the sulphoxides and formamides by penetrating into the SC and increasing the lipid fluidity by disruption of lipid packing.

1.5 Amines and amides

a) Urea

Urea promotes transdermal permeation by facilitating hydration of the SC and by the formation of hydrophilic diffusion channels within the barrier. Cyclical urea permeation enhancers are biodegradable, non-toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group.

b) Dimethylacetamide and Dimethylformamide

These compounds are less potent penetration enhancing chemical alternatives to DMSO. At low concentrations their activity as enhancers is a result of partitioning into the keratin regions. At higher concentrations they increase lipid fluidity by disruption of lipid packing as a result of solvation shell formation around the polar head groups of the lipids.

c) Pyrrolidones

Pyrrolidone and its derivatives are reported to interact with both keratin and with lipids in the skin. Azone is known to show significant accelerant effects at low concentrations for both hydrophilic and hydrophobic drugs and is one of the few enhancers that have been developed commercially. Differential scanning calorimetric studies have shown that azone affects lipid structures of the SC. In addition, azone is reported to decrease transition temperatures within lipid bilayers to induce formation of a liquid phase with a resultant increase in lipid fluidity.

d) Terpenes

Terpenes are found in essential oils, and are compounds comprising of only carbon, hydrogen and oxygen atoms, but which are not aromatic. Numerous terpenes have long been used as medicines as well as flavoring and fragrance agents.⁷ Terpenes are generally considered as less toxic and have less irritant effects compared to surfactants and other skin penetration enhancers, and some terpenes have been characterized as Generally Recognized As Safe (GRAS) by the US FDA. They have high percutaneous enhancement ability, reversible effect on the lipids of SC, minimal percutaneous irritancy at low concentrations (1-5%). Moreover, a variety of terpenes have been shown to increase percutaneous absorption of both hydrophilic and lipophilic drugs.¹¹ Both the mono- and sesquiterpenes are known to increase percutaneous absorption of compounds by increasing diffusivity of the drug in SC and/or by disruption of the intercellular lipid barrier. A further mechanism of activity that has been postulated is that the terpenoids increase electrical conductivity of tissues thereby opening polar pathways within the SC. Surface active agents function primarily by adsorption at interfaces and thus interact with biological membranes contributing to the overall penetration enhancement of compounds. Cationic surfactants are more destructive to skin tissues causing a greater increase in flux than anionic surfactants. The latter, in turn, produce greater increases in flux than non-ionic surfactants. Anionic surfactants may function by alteration of the barrier function of the SC as a result of removal of water soluble agents that act as plasticizers. Sodium lauryl sulphate has been implicated in reversible lipid modification with resultant disorganization of the SC and enhanced permeation. In addition, non-ionic surfactants are purported to be able to emulsify sebum, consequently altering partitioning potential of drugs in favor of enhanced permeation. The permeation enhancement generated by these compounds may be dependent on the ability of

drug to partition between the free and bound or micellar form of the enhancer.

e) Cyclodextrins

Cyclodextrins are bio-compatible substances that can form inclusion complexes with lipophilic drugs with a resultant increase in their solubility, particularly in aqueous solutions. However, cyclodextrins alone were determined to be less effective as penetration enhancers than when combined with fatty acids and propylene glycol.

1.6 Basic Components Of Transdermal Drug Delivery Systems

The components of Transdermal devices include:

1. Backing layer.
2. Drug containing reservoir.
 - a. Polymer matrix.
 - b. Drug.
 - c. Permeation enhancers.
 - d. Plasticizers.
3. The release control layer.
4. The adhesive.
5. The peel strip.

Backing layer must be impermeable to drugs and enhancers if used and as a result it is usually impermeable to water vapor that is occlusive. The most commonly used backing materials are alupoly, polyester, polyethylene co-extruded films or metalized polyester laminated with polyethylene. The film can be either clear flesh colored or metalized. Backing membranes are flexible and provide a good bond to the drug reservoir, prevent drug from leaving the dosage form through the top and accept printing. It protects the product during use on the skin.

1.6.1 Drug Containing Reservoir

a) Polymer Matrix

The Polymer controls the release of the drug from the device. The development of transdermal systems requires judicious selection of a polymeric material or a series of polymers whose diffusive characteristic will be such that a

desirable permeation rate of a specific drug or other bio-active agent can be obtained.

The polymer should meet the following requirements:

- i. Molecular weight, glass transition temperature and chemical functionality of polymer must allow proper diffusion and release of the specific drug.
- ii. The polymer should not chemically react with the drug.
- iii. The polymer and its degradation products must be non-toxic.
- iv. The polymer should not decompose on storage or use of the device.
- v. The polymer should be inexpensive.
- vi. The polymer must be easy to manufacture and it should yield itself into the desired product and should allow incorporation of large quantities of active component without deterioration of its mechanical properties.

1.7 Polymer Used in TDDS

Polymers that can be used in the Transdermal formulations are:

a) Natural Polymers

Cellulose derivatives, Zein, Gelatin, Shellac, Waxes, Proteins, Gums and their derivatives, Natural rubber, Starch etc.

b) Synthetic Elastomers

Polybutadiene, Hydrin rubber, Polysiloxane, Silicone rubber, Nitrile, Acrylonitrile, Butyl rubber, Styrenebutadiene rubber, Neoprene etc.

c) Synthetic Polymers

Polyvinyl alcohol, Polyvinyl chloride, Polyethylene, Polypropylene, Polyacrylate, Polyamide, Polyurea, Polyvinylpyrrolidone, Polymethylmethacrylate, etc.

d) Drug

For successfully developing a TDDS, the drug should be chosen with great care. The following are some of the desirable properties of a drug for transdermal delivery.

e) Physicochemical properties

1. The drug should have a molecular weight less than approximately 1000 daltons.
2. The drug should have affinity for both lipophilic and hydrophilic phases.
3. The drug should have a low melting point.

f) Biological properties

1. The drug should be potent with a daily dose of the order of a few mg/day.
2. The half life ($t_{1/2}$) of the drug should be short.
3. The drug must not induce a cutaneous irritant or allergic response.
4. Drugs which degrade in the g.i.t or/are inactivated by hepatic first-pass effect are suitable candidates for Transdermal delivery.
5. Tolerance to the drug must not develop under the near zero-order release profile of Transdermal delivery.
6. Drugs which have to administered for a long period of time or which cause adverse effects to non-target tissues can also be formulated for transdermal delivery.

g) Plasticizers

These are used to prevent the films from becoming brittle.

An ideal plasticizer should possess the following properties

1. Should not show any pharmacological action of its own.
2. Should be chemically and physically stable.
3. Should be compatible with the drug and the formulated components.
4. Should be colourless, odorless and tasteless.
5. Should be non-toxic, non-allergenic & non-irritant.

h) Release control layers

1. The rate controlling membrane can be either a micro-porous or a non-porous

polymeric membrane with defined drug permeability.¹²The membrane can be constituted with any of the polymers discussed earlier.

i) Adhesives

2. The fastening of all transdermal devices to the skin has so far been done by using a pressure sensitive adhesive which can be positioned on the face of the device or in the back of the device and extending peripherally.

Both adhesive systems should fulfill the following criteria:

- (i) Should adhere to the skin aggressively, should be easily removed.
- (ii) Should not leave an unwashable residue on the skin.
- (iii) Should not irritate or sensitize the skin.

The face adhesive system should also fulfill the following criteria.

- (i) Physical and chemical compatibility with the drug, excipients and enhancers of the device of which it is a part.
- (ii) Permeation of drug should not be affected.
- (iii) The delivery of simple or blended permeation enhancers should not be affected.

Peel Strip

1. The peel strip prevents loss of drug that has migrated into adhesive layer during storage and also protects the finished device against contamination. Polyester foils and metallized laminates are the choices.

Packet

2. Packet guards the patches against drug loss and contamination on storage. The patches are individually packed in heat sealed foil pouches.

1.8 Approaches Used in the Development of TDDS

Several techniques have been successfully developed to provide a mechanism of rate control over the release and transdermal permeation of drugs.

a) Magnetophoresis

This method involves the application of a magnetic field which acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability. In vitro studies by Murthy showed a magnetically induced enhancement in benzoic acid flux, which was observed to increase with the strength of the applied magnetic field.

b) Microneedle

Basic design of microneedle delivery system devices. Needles with or without hollow centre channels are placed onto the skin surface so that they penetrate the SC and epidermis without reaching the nerve endings present in the upper epidermis.

c) Electroporation

Skin electroporation (electropermeabilization) creates transient aqueous pores in the lipid by application of high voltage of electrical pulses of approximately 100–1000 V/Cm for short time(milliseconds). These pores provide pathways for drug penetration that travel straight through the horny layer. This technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size including biopharmaceuticals with molecular weights greater than 7kDA.

d)Iontophoresis

Iontophoresis can be defined as the process in which the flux or rate of absorption of ionic solutes in to or through skin is enhanced by applying a voltage drop / electric field across the skin. The amount of compound delivered is directly proportional to the quantity of charge

passed; it depends on the applied current, the duration of current application and the area of skin surface in contact with the active electrode compartment.

e) Phonophoresis

Phonophoresis is the use of ultrasound to enhance the delivery of topically applied drugs. Phonophoresis has been used in an effort to enhance the absorption of topically applied analgesics and anti-inflammatory agents through the therapeutic application of ultrasound. Phonophoresis has been shown to be ineffective for some treatments, where it did not increase the efficacy of absorption of drugs, or did not improve the outcome more than the use of ultrasound alone.

3. Conclusion

The permeation of drugs through skin can be enhanced by various methods including physical methods such as iontophoresis, phonophoresis, electroporation and by chemical penetration enhancers etc. The Transdermal route has been recognized as one of the highly potential routes of systemic drug delivery. However, the major limitation of this route is the difficulty of permeation of drug through the skin. Studies have been carried out to find safe and suitable permeation enhancers to promote the percutaneous absorption of a number of drugs. The present review highlights various categories of penetration enhancers; the involved mechanism leading to a judicious selection of suitable penetration enhancers for improving the Transdermal permeation of poorly absorbed drugs.

4. References

1. Dalvi UG, Zatz J. Effects of nonionic surfactants on penetration of dissolved benzocaine through hairless mouse skin. *J Soc Cosmet Chem.* 1999;32:87-94.
2. Kushla GP, Zatz JL. Correlation of water and lidocaine flux enhancement by cationic surfactants *in vitro*. *J Pharm Sci.* 1991;80:1079-83.

3. Lopez A, Llinares F, Cortell C, Herraes M. Comparative enhancer effects of Span® 20 with Tween®20 and Azone® on the *in vitro* percutaneous penetration of compounds with different lipophilicities. *Int J Pharm.* 2000;202:133-40.
4. Froebe CL, Simion FA, Rhein LD, Cagan RH, Kligman A. Stratum corneum lipid removal by surfactants: Relation to *in vivo* irritation. *Dermatologica.* 1990;181:277-83.
5. Aulton ME. *Pharmaceutics -The science of dosage form design.* 2nd ed. Philadelphia (US): Churchill Livingstone; 2002.
6. Swarbrick J. *Encyclopedia of pharmaceutical technology. Surfactants in pharmaceutical products and systems.* 3rd ed. Vol. 6. Informa Healthcare, CRC press hardcover; 2006.
7. Reiger MM, Rhein LD. *Surfactant in Cosmetics.* Vol. 68. New York: Marcel Dekker; 1997.
8. Lee CK, Uchida T, Kitagawa k, Yagi K, Kim NS, Goto S. Skin permeability of various drugs with different lipophilicity. *J Pharm Sci.* 1994;83:562-65.
9. Scheuplein RJ, Ross L. Effects of surfactants and solvents on the permeability of epidermis. *J Soc Cosmet Chem.* 1970;21:853-73.
10. Walker RB, Smith EW. The role of percutaneous penetration enhancer. *Adv Drug Del Rev.* 1996;18:295-01.
11. Nokhodchi A, Shokri J, Dashbolaghi A, Hassan-zadeh D, Ghafourian T, Barzegar-jalali M. The enhancement effect of surfactants on the penetration of lorazepam through rat skin. *Int J Pharm.* 2003;250:359-69.