Review Article
ISSN: 0974-6943

Kevin C. Garala et al. / Journal of Pharmacy Research 2009, 2(12),1804-1808

Available online through
http://jprsolutions.info

Chemical Penetration Enhancement: A Review

Kevin Garala*, Nidhi Faldu, Biswajit Basu, Ravi Bhalodia, Kuldeep Mehta, Bhavik Joshi

**Department of Pharmaceutics, Atmiya Institute of Pharmacy, Yogidham Gurukul, Kalawad Road, Rajkot-360005, Gujarat State, India.*

Received on: 23-08-2009; Accepted on:20-11-2009

ABSTRACT

Transdermal drug delivery system is now a promising drug delivery system. Modern transdermal drug delivery systems are products of basic pharmaceutical research that took place during the last third of the 20th century. The literature on transdermal delivery of drugs has been revised. The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood levels for longer period of time, decrease side effects, decrease gastrointestinal effect that occur due to local contact with gastric mucosa and improved compliance. The success of dermatological or transdermal drug delivery systems depends on the ability of the drug to penetrate into and/or permeate through skin in sufficient quantities to achieve desired therapeutic levels. In this article, the most recent chemical penetration enhancers on transdermal delivery systems is intended to summarize the progress in TDDS research and development (R&D).

Keywords: Transdermal Drug Delivery, Penetration Enhancement, Chemical Permeation Enhancers

INTRODUCTION

Drugs are rarely administered as pure chemical substances alone and are almost given as formulated preparation or medicines. These can vary from relatively simple solutions to complex drug delivery systems[1]. The commonly employed drug delivery systems include tablets, capsules, pills, injections and some extent topical and mucosal formulations. For most of the drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges[2]. Oral delivery is by far the easiest and most convenient way of delivering drugs especially when repeated or routine administration is required[3]. 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[4]. To overcome these difficulties there is a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal placement within the body thereby reducing both size and number of doses.

The goal of an ideal drug delivery system is to deliver a drug to a specific site, in specific time and release pattern. The traditional medical forms provide drug delivery with peaks, often above the required dose (Figure 1). The constant drug level in blood or sustained drug release to avoid multiple doses and bypassing of the hepatic "first-pass" metabolism are the main challenges for every delivery system[5]. This transdermal delivery system should not only control the therapy of drug but also do so in a patient compliant fashion. Effective delivery of the formulation in a physiologically compatible manner is thus the next hurdle in the drug development cycle. Careful selection of a delivery route or system is critical to success in the further stages of drug safety and metabolism. Human skin is an attractive portal for administration of active pharmaceutical ingredients. This route, referred to as the Transdermal Drug Delivery, which is an alternative route for systemic delivery of drugs through intact skin to reach the systemic circulation in adequate extent to elicit a desired therapeutic response[6]. The initiative of delivering drugs through the skin is ancient, as far back as the 16th century B.C., the Ebers Papyrus recommended that the husk of the castor oil plant be crushed in water and placed on an aching head[7].

In recent decades, transdermal drug delivery has been an active field of biomedical research with rapid development in both the extent and the depth of investigation. The success of transdermal delivery depends on the ability of the drug to permeate the intact skin in sufficient quantities to achieve its desired pharmacological action. The first transdermal patch (0.5 mg Scopolamine, TTS-S, Novartis, Basel, Switzerland) was approved by US Food and Drug Administration in 1979 to treat motion sickness[8,9]. Depending upon the drug, the time of duration of transdermal delivery is generally from 1 to 7 days[10]. The transdermal route is one of the major pathways for delivering potent therapeutic agents to the human body.

Advantages and Limitations

Transdermal drug delivery has many advantages over the conventional drug delivery and also some limitations which can be

***Corresponding author.**
Kevin C. Garala
Department of Pharmaceutics,
Atmiya Institute of Pharmacy,
Yogidham Gurukul, Kalawad Road,
Rajkot-360005, Gujarat State, India.
*Tel.: + 91-*9974664666
Telefax: +91-
E-mail: kevin_garala@rediffmail.com

discussed as follows.

Advantages[1, 6, 7, 11-13]

- Provides a noninvasive alternative to parenteral, subcutaneous and intramuscular injections.
- Avoids first-pass metabolism in the gastrointestinal tract and liver, which allows drugs having poor oral bioavailability and/or short biological half-lives to be administered at most, once a day, and which can result in improved patient compliance.
- Avoid the problems of gastric irritation, stomach emptying and pH effects.
- To enable control of input, as exemplified by the termination of drug delivery through removal of the device.
- Suitable for patients who are unconscious or suffering from vomiting.
- Decreases the dose to be administered.
- Not affected by food intake.
- Provides constant blood levels in the plasma for drugs with a narrow therapeutic window, therefore minimizing the risk of toxic side effects or lack of efficacy.
- Sustained release of drug for long durations to reduce the dosing frequency.
- Programmed delivery from conventional transdermal patches is not easy but the techniques that use active processes, such as an electric current, can deliver the therapeutic agent in a time-dependent manner.

Limitations[1, 6, 11, 14]

- The variability in transdermal absorption owing to site, disease, age and species differences.
- Only relatively potent drugs are suitable candidates for transdermal delivery as the natural limits of drug entry imposed by the skin's impermeability.
- Some patients develop contact dermatitis at the site of application from one or more of the system components, necessitating discontinuation.
- TDDS cannot achieve high drug levels in blood/plasma.
- The metabolic enzymes in the skin can may create a trouble, and some drugs are almost completely metabolized before they reach the cutaneous vasculature.
- Another problem that can arise, which is sometimes overlooked, is that some drugs can be broken down before penetration through the stratum corneum (SC) by the bacteria that live on the surface of skin.
- The use of transdermal delivery may be uneconomic.

For better understanding of transdermal drug delivery, the structure of skin should be briefly discussed along with penetration through skin and permeation pathways.

PERMEATION ENHANCEMENT

Transdermal permeation, or percutaneous absorption, can be defined as the passage of a substance, such as a drug, from the outside of the skin through its various layers into the bloodstream. The success of dermatological or transdermal drug delivery systems depends on the ability of the drug to penetrate into and/or permeate through skin in sufficient quantities to achieve therapeutic levels[15]. The penetration enhancers (also called sorption promoters or accelerants) which penetrate into skin to reversibly decrease the barrier resistance[16]. The impermeability of the skin has led to the development of a number of enhancement strategies.

Chemical Permeation Enhancers

Chemical enhancers also referred to as Chemical Penetration Enhancers or Chemical Permeation Enhancers (CPEs), are the moieties that can alter the stratum corneum barrier to promote the flux of therapeutic molecules across skin. The most enhancers interact with the intercellular lipid domain of the stratum corneum. The general mechanism by which skin permeation improve are the intercellular lipid matrix in which the accelerants may disrupt the packing motif, the intracellular keratin domains or through increasing drug partitioning into the tissue by acting as a solvent for the permeant within the membrane[16]. The chemical enhancement mechanism is to use solvents that permeate into the skin and act essentially as a carrier for the active. The other mechanism is one in which a component of the formulation permeates into the intercellular lipids where it intercalates and disrupts their structure[17]. This creates a region where diffusion is faster and permeation through the stratum corneum is improved.

I) Water

Earlier approach to improve transdermal and topical delivery of therapeutic agents is to use water. The water content of human stratum corneum is typically around 15-20% of the tissue dry weight, although clearly this varies depending on the external environment such as humidity. Soaking the skin in water, exposing the membrane to high humidities or, as is more usual under clinical conditions, occluding the tissue so preventing transepidermal water loss can allow the stratum corneum to reach water contents in equilibrium with that of the underlying epidermal skin cells. Hence, on occlusion, the water content of this outer membrane can reach to 400% of the tissue dry weight. Generally, increased tissue hydration appears to increase transdermal delivery of both hydrophilic and lipophilic permeants.

II) Sulfoxides

Dimethylsulfoxide (DMSO) is an aprotic solvent that has the ability to induce cell fusion and cell differentiation and enhance the drug permeability of lipid membranes[18]. Considering the small highly polar nature of this molecule it is feasible that DMSO interacts with the head groups of some bilayer lipids to distort to the packing geometry[19]. Further, DMSO promotes permeation by reducing skin resistance to drug molecules or by promotion of drug partitioning from the dosage form. DMSO can induce water pores in dipalmitoylphosphatidylcholine (DPPC) bilayers and propose this to be a possible pathway for the enhancement of penetration of active molecules through lipid membranes[18]. It has been postulated that DMSO denatures the intercellular structural proteins of the stratum corneum by disrupting the structure of the lipid chains. Furthermore, DMSO may alter the physical structure of the skin by elution of lipid, lipoprotein and nucleoprotein structures of the stratum corneum[20].

III) Pyrrolidones

A range of pyrrolidones and structurally related compounds have been investigated as potential penetration enhancers in human skin. Azone (1-dodecylazacycloheptan-2-one or laurocapram) was the first molecule specifically designed as a skin penetration enhancer. Azone enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents.

Azone is most effective at low concentrations, being employed typically between. Azone probably exerts its penetration enhancing effects through interactions with the lipid domains of the stratum corneum. Considering the chemical structure of the molecule (possessing a large polar head group and lipid alkyl chain) it would be expected that the enhancer partitions into the bilayer lipids to disrupt their packing arrangement; integration into the lipids is unlikely to be homogeneous considering the variety of compositional and packing domains within stratum corneum lipid bilayers[16]. Azone is known to show significant accelerant effects at low concentrations for both hydrophilic and hydrophobic drugs[20].

IV) 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.

Ethanol can exert its permeation enhancing activity through various mechanisms. Firstly, as a solvent, it can increase the solubility of the drug in the vehicle[16]. Further, permeation of ethanol into the stratum corneum can alter the solubility properties of the tissue with a consequent improvement for drug partitioning into the membrane[21]. Disruption of the stratum corneum integrity through extraction of biochemicals by the more hydrophobic alcohols contributes to enhanced mass transfer through this tissue[20]. As with water, ethanol permeates rapidly through human skin with a steady state flux of approximately 1 mg cm^2/h. Ethanol has been used to enhance the flux of levonorgestrel, estradiol, hydro-cortisone and 5-fluorouracil through rat skin[16] and of estradiol through human skin in vivo[22].

V) Fatty acids

Percutaneous drug absorption has been increased by a wide variety of long chain fatty acids, the most popular of which is oleic acid. More specifically, oleic acid has been found to decrease the phase transition temperatures of the skin lipids with a resultant increase in motional freedom or fluidity of these structures[20]. It is clear from numerous literature reports that the enhancer interacts with and modifies the lipid domains of the stratum corneum, as would be expected for a long chain fatty acid with a cis configuration oleic acid at higher concentration can also exist as a separate phase (or as 'pools') within the bilayer lipids[18]. The formation of such pools would provide permeability defects within the bilayer lipids thus facilitating permeation of hydrophilic permeants through the membrane. These enhancers can be used to promote delivery of both lipophilic and hydrophilic permeants.

VI) 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 stratum corneum and increasing the lipid fluidity by disruption of lipid packing. A similar mode of action is proposed for isopropyl myristate and, in addition, the aliphatic esters may influence partitioning between vehicle and skin by solubilization effects[20].

VII) Urea

Urea is a hydrating agent (a hydrotrope) promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier[20]. Urea alone or in combination with ammonium lactate produced significant stratum corneum hydration and improved barrier function when compared to the vehicle alone in human volunteers in vivo. Urea also has keratolytic properties, usually when used in combination with salicylic acid for keratolysis[16]. The modest penetration enhancing activity of urea probably results from a combination of increasing stratum corneum water content, the keratolytic activity and lipid disruption mechanisms.

VIII) Surface active agents

Surface active agents function primarily by adsorption at interfaces and thus interact with biological membranes contributing to the overall penetration enhancement of compounds[20]. Anionic surfactants include sodium lauryl sulphate (SLS), cationic surfactants include cetyltrimethyl ammonium bromide, the nonoxynol surfactants are non-ionic surfactants and zwitterionic surfactants include dodecyl betaine. Anionic and cationic surfactants have potential to damage human skin; SLS is a powerful irritant and increased the trans epidemeral water loss in human volunteers in vivo and both anionic and cationic surfactants swell the stratum corneum and interact with intercellular keratin[16].

IX) Essential oils and terpenes

Terpenes are found in essential oils, and are compounds comprising only carbon, hydrogen and oxygen atoms, yet which are not aromatic[16]. Both the mono and sesquiterpenes are known to increase percutaneous absorption of compounds by increasing diffusivity of the drug in stratum corneum 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 stratum corneum[20]. Cyclic monoterpenes generally showed stronger enhancement of curcumin than other terpenes, flavanoids and cholestanol[18]. Terpenes continue to be a popular choice of enhancer for delivering materials across skin membranes. For example, L-menthol has been used to facilitate in vitro permeation of morphine hydrochloride through hairless rat skin[16], imipramine hydrochloride across rat skin[23] and hydrocortisone through hairless mouse skin[24].

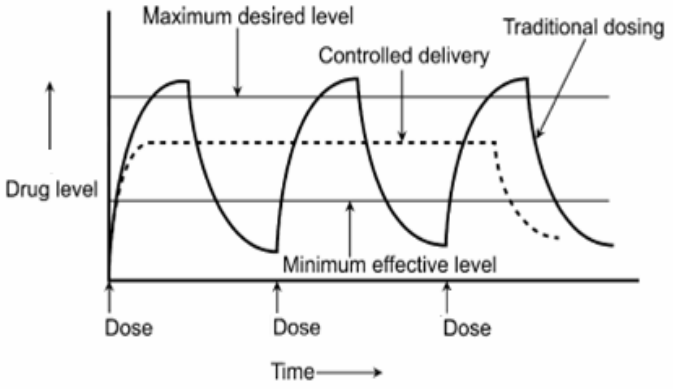

Figure 1: Drug concentration in blood during drug delivery

X) Solvents at high concentrations

In addition to the activities of penetration enhancers within the intercellular domain, high levels of potent solvents may have more drastic effects. They may damage desmosomes and protein like bridges, leading to fissuring of the intercellular lipid and splitting of the stratum corneum squames. Solvent may enter the corneocyte, drastically disrupting the keratin and even forming vacuoles[25].

XI) Cyclodextrins and Dendrimer

Cyclodextrins (CDs) are cyclic oligosaccharides possess a hydrophilic external surface and a hydrophobic cavity. They are thus highly soluble and effectively form inclusion complexes with hydrophobic organic compounds to enhance their solubilities[26-28]. However, cyclodex-trins alone were determined be to less effective as penetration enhancers than when combined with fatty acids, propylene glycol and polyvinyl pyrrolidone[20, 29]. Loftsson and Masson concluded that the effect on skin penetration may be related to cyclodextrin concentration, with reduced flux generally observed at relatively high cyclodextrin concentrations, whilst low cyclodextrin concentrations resulting in increased flux[30].

Dendrimer, also called arborols or cascade molecules[31] or artificial proteins[32], is derived from the Greek words dendron (tree) and meros (part)[33]. They are monodisperse, well-defined artificial macromolecules which have highly branched, three-dimensional features that resemble the architecture of a tree, having defined molecular weight and host-guest entrapment properties[34]. Furthermore, recent work has shown that PAMAM dendrimers enhanced the bioavailability of indomethacin in transdermal delivery applications[35]. Similarly, the drug tamsulosin was used as a model to study transdermal delivery utilizing PAMAM dendrimers. The dendrimers were found to be weak penetration enhancers[36]. However, no dendrimer driven effect was observed for the drugs ketoprofen and clonidine. As an explanation, dendrimer-triggered drug crystallization within the transdermal delivery matrix was discussed, allowing the formation of drug polymorphs that can or cannot facilitate transdermal delivery[37].

REFERENCES

1. Aulton M. E., Pharmaceutics: The Science of Dosage Form Design, 2nd Edition, Churchill Livingstone. 2002, 1-5.
2. Lesson 24: Concepts of Delivery System, www.rocw.raifoundation.org/ biotechnology/ MSc Bioinformatics/drugdelivery/lecture-notes/lecture-24.pdf.
3. Chen H. Langer R. Oral particulate delivery: status and future trends, Adv. Drug Deliv. Rev. 34, 1998, 339-350.
4. Chien Y. W. Transdermal controlled systemic medications. Marcel Dekker, Inc. USA. 1987, 1-21.
5. Stamatialis DF, Bernke JP, Miriam G, Saiful S, Srivatsa NM, Stephanie S, Matthias W, Medical applications of membranes: Drug delivery, artificial organs and tissue engineering. J Membr Sci. 308, 2008, 1–34.
6. Walters KA. Dermatological and Transdermal Formulations. Marcel Dekker, INC. New York.
7. Finnin BC, Morgan TM. Transdermal Penetration Enhancers: Applications, Limitations, and Potential, J. Pharm. Sci. 88, 1999, 955-958.
8. Wang F, Yang Y, Zhang X, Zhu X, Chung T, Shabbir M. Cellulose acetate membranes for transdermal delivery of scopolamine base. Materials Science and Engineering. C 20, 2002, 93–100.
9. Hampton T. Breaking barriers in transdermal drug delivery. JAMA. 293, 2005, 2083.
10. Robert L. Transdermal drug delivery: past progress, current status and future prospects. Adv Drug Deliv Rev. 56, 2004, 557-558.
11. Allen LV. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 8th Edition, Lippincott Williams & Wilkins, 2005, 298-315.
12. Karabiyikoglu M. New frontiers in transdermal drug delivery systems. Drug Delivery
Report Spring/Summer. 2007, 28-30.
13. Mojtaba S. Transdermal excipients effect on adhesion strength of a pressure sensitive adhesive. Iranian Polymer Journal. 12, 2003, 243-248.
14. Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. Vallabh Prakashan, 1st Edition, 2002, 411-447.
15. Walters K. A., Drug Delivery: Topical and Transdermal Routes. In: Swarbrick J., Encyclopedia of Pharmaceutical Technology, 3rd Edition, Volume 1, Informa Healthcare USA, Inc., New York, 1311-1325.
16. Williams A. C., Barry W., Penetration enhancers. Adv. Drug Deliv. Rev., 56, 2004, 603-618.
17. Hadgraft J., Passive enhancement strategies in topical and transdermal drug delivery. Int. J. Pharm., 184, 1999, 1–6.
18. Notman R, Massimo N, Brendan O, Jamshed A. Molecular Basis for Dimethylsulfoxide (DMSO) Action on Lipid Membranes. J Am Chem Soc. 128, 2006, 13982-13983.
19. Barry B. W., "Dermatological formulations: Percutaneous absorption", Drugs and Pharmaceutical Sciences. Marcel Dekker, Inc. New York. 1983, 1-39.
20. Roderick B, Swith E. The role of percutaneous penetration enhancers. Adv Drug Deliv Rev. 18, 1996, 295-301.
21. Megrab NA. Oestradiol permeation across human skin, silastic and snake skin membranes: the effects of ethanol/water co-solvent systems. Int J Pharm. 116, 1995, 101-112.
22. Pershing L., Lambert L., Knutson K., Mechanism of ethanol-enhanced estradiol permeation across human skin in vivo. Pharm Res. 7, 1990, 170-175.
23. Jain AK. Transdermal drug delivery of imipramine hydrochloride: I. Effect of terpenes. J. Control. Rel. 79, 2002, 93-101.
24. El-Kattan AF. The effect of terpene enhancer lipophilicity on the percutaneous permeation of hydrocortisone formulated in HPMC gel systems. Int J Pharm. 198, 2000, 179-189.
25. Menon G K. Ultrastructural effects of some solvents and vehicles on the stratum corneum and other skin components: evidence for an ''extended mosaic-partitioning model of the skin barrier'', In: M.S. Roberts, K.A. Walters (Eds.), Dermal Absorption and Toxicity Assessment, Marcel Dekker, New York, 1998.
26. Cai X. Environmental significance of the diclofop-methyl and cyclodextrin inclusion complexes. Journal of Environmental Science and Health Part B. 41, 2006, 1115-1129.
27. Pose B. Sulphamethizole-cyclodextrin hydroxy propyl methyl cellulose multicomponent complexes. Journal of Thermal Analysis and Calorimetry. 68, 2002, 657-.667.
28. Challa R. Cyclodextrin in drug delivery: An updated review. AAPS PharmSciTech. 6, 2005, E328-E357.
29. Siguroardottir AM. The effect of polyvinylpyrrolidone on cyclodextrin complexation of hydrocortisone and its diffusion through hairless mouse skin. Int J Pharm. 126, 1995, 73-78.
30. Loftsson T. Cyclodextrins in topical drug formulations: theory and practice. Int J Pharm. 225, 2001, 15-30.
31. Duncan R. Dendrimer biocompatibility and toxicity B. Adv. Drug Deliv. Rev. 57, 2005, 2215-2237.

32. Svenson S. Dendrimers in biomedical applications-reflections on the field. Adv Drug Deliv Rev. 57, 2005, 2106-2129.
33. Aulenta F. Dendrimers: a new class of nanoscopic containers and delivery devices. European Polymer Journal. 39, 2003, 1741-1771.
34. Yiyun C. Dendrimers as potential drug carriers. Part I. Solubilization of non-steroidal anti-inflammatory drugs in the presence of polyamidoamine dendrimers. European Journal of Medicinal Chemistry. 40, 2005, 1188-1192.
35. Chauhan AS, Sridevi S, Chalasani KB, Jain AK, Jain SK, Jain NK, Diwan PV. Dendrimer-mediated transdermal delivery: Enhanced bioavailability of indomethacin. J Control Rel. 90, 2003, 335-343.
36. Wang ZX, Itoh YS, Hosaka Y, Kobayashi I, Nakano Y, Maeda I, Umeda F, Yamakawa J, Kawase M, Yagi K. Novel transdermal drug delivery system with polyhydroxyalkanoate and starburst poly(amidoamine) dendrimer. J Biosci Bioeng. 95, 2003, 541-543.
37. Wang ZX, Itoh YS, Hosaka Y, Kobayashi I, Nakano Y, Maeda I, Umeda F, Yamakawa J, Nishimine M, Suenobu T, Fukuzumi S, Kawase M, Yagi K. Mechanism of enhancement effect of dendrimer on transdermal drug permeation through polyhydroxyalkanoate matrix. J Biosci Bioeng. 96, 2003, 537-540.

Source of support: Nil, Conflict of interest: None Declared