Review Article
ISSN: 0974-6943

Kevin C. Garala et al. / Journal of Pharmacy Research 2010, 3(8),1769-1774

Available online through
www.jpronline.info

Physical Penetration Enhancement Through TDDS: A Review

Kevin Garala*, Biswajit Basu, Abhay Dharamsi

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

Received on: 15-04-2010; Revised on: 12-05-2010; Accepted on:13-06-2010

ABSTRACT

The delivery of drugs into systemic circulation via skin has generated lot of interest in recent time. Transdermal drug delivery is now a promising route of drug delivery system. 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 transdermal drug delivery system depends on the ability of the drug to penetrate through the skin in sufficient quantities to achieve desired therapeutic levels. In this article, the most recent editorial briefing on transdermal drug delivery systems by physical enhancement is intended to summarize the progress made in TDDS research and development.

Key words: Transdermal Drug Delivery, Penetration Enhancement, Physical Penetration Enhancement,Microneedle, Iontophoresis

INTRODUCTION

Drugs are rarely administered as pure chemical substances alone and thus the most commonly employed drug delivery systems include tablets, capsules, pills, injections, topical and mucosal formulations. For most of the drugs, conventional methods of drug administration are effective, but some drugs are unstable and or toxic and have narrow therapeutic ranges[2]. Oral drug delivery is by far the most convenient mode 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 drawbacks 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).

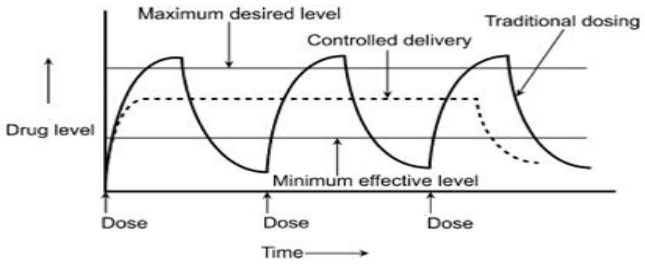

Figure 1: Drug concentration in blood during drug delivery

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 challenge in the drug development cycle. Careful selection of a delivery system is critical to succeed 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, 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 discussed as follows.

Advantages[1, 6, 7, 11, 12, 13]

- Provides a noninvasive alternative to parenteral, subcutaneous and intramuscular injections.
- Avoids first-pass metabolism in the gastrointestinal tract and liver, which allows drugs with 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 complications 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.

***Corresponding author.**
Kevin C. Garala
Department of Pharmaceutics,
Atmiya Institute of Pharmacy,
Yogidham Gurukul, Kalawad Road,
Rajkot-360005, Gujarat State, India.
Tel.: + +919974664666
E-mail:kevin_garala@rediffmail.com

- 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 ef fects or lack of efficacy.
- Sustained release of drug for long durations to reduce the dosing fre quency.
- 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 man ner.

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 deliv ery 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 discon tinuation.
- TDDS cannot achieve high drug levels in blood/plasma.
- The metabolic enzymes in the skin may create a trouble, and some drugs are almost completely metabolized before they reach the cuta neous vasculature.
- Another difficulty 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 surface of the skin.
- The use of transdermal delivery may be uneconomic.

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 transdermal drug delivery system depends on the ability of the drug to penetrate through the 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. These can be broadly divided into chemical approaches and physical penetration enhancement. In this article, the most recent editorial briefing on transdermal drug delivery systems by physical enhancement is intended to summarize the progress in TDDS research and development.

The stratum corneum (SC), most outer layer of skin, consists of a well-organised layer of dead corneocytes intercalated with lipids, which present a significant barrier to the diffusion of agents into the body. In order to overcome this barrier and enhance permeation, a number of chemical and physical enhancement techniques have been developed either alone or in combination. Though chemical enhancers increase delivery of agents by perturbing the SC barrier through interaction with proteins or by fluidization of the SC lipids, their extensive use is limited by their potential skin irritation[17]. However, due to low permeability coefficients of macromolecules, the enhancement effects required to ensure delivery of pharmacologically effective concentrations are likely to be beyond the capability of chemical enhancers tolerated by the skin.

Therefore, several technologies, based on physical disturbance or removal of SC layer, have been developed for the transdermal delivery of some troublesome drugs as the development of such techniques have overcome the limitations of chemical enhancement techniques[18, 19, 20]. Various techniques for physical penetration enhancement of permeants are summarized as follows.

Iontophoresis

The delivery of drugs into systemic circulation via skin has generated a lot of interest during last decade. Iontophoresis is one of the physical approaches in enhancement of transdermal permeation. The idea of applying electric current to enhance the penetration of electrically charged drugs into surface tissue was probably originated by Pivati in1747[21].

Iontophoresis is a non invasive method of boosting high concentration of a charged substance, generally medication or bioactive-agents, through a biological membrane by the application of a small electric current (usually 0.5 mA/cm^2)[22, 23]. Drug compounds can be classified chemically as ionic, zwitterionic or neutral. Ionic compounds can be further subdivided into cationic or anionic species. The proportion of the compound, which exists in the ionic state depends on whether the compound is a salt, an acid or a base, on its associated p*K*a or p*K*b values, and the pH of the solution/matrix in which it exists[24]. Coulomb's Law states that "like charges repel" which means that by placing a cationic solution under the anode, when a current is applied the positive ions will be drawn toward the cathode electrode. The human body conducts electrical signals very well, as demonstrated by neuronal action. Thus, when an electrode is applied to the skin, the current flows through the skin and the ionic substance is drawn into the body[25].

Iontophoresis is a symmetric process that transports ions across the skin in both directions. Anodal iontophoresis occurs when an anode electrode (+ Ve charge) is placed in a positively charged drug solution (cations) and cathode electrode (- Ve charge) is placed in a receptor solution in a near by location. Cathodal iontophoresis is the reverse of anodal iontophoresis and involves the movement of an anion (Figure 2).

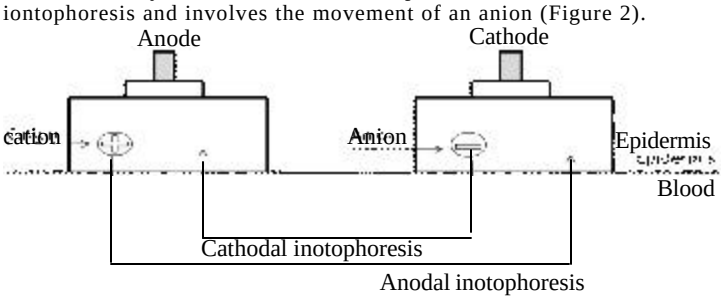

Figure 2: Anodal and Cathodal Iontophoresis

There are three possible pathways by which drug enters to the systemic circulation; transcellular (through cells), paracellular (around cells), or appendageal pathways (sweat glands, sebaceous glands, or hair follicles)[26]. Hair follicles have diameters on the order of tens of microns and could present shunt pathways for ion permeation across the highly resistive outermost layer (stratum corneum) of the epidermis[27]. At the pH 7.4, the skin is negatively charged[28] and because of this original negative charge in the superficial skin layers, it is relatively easy to introduce basic drugs[29]. Hence, a positively charged ion penetrates more easily across the skin than a comparably sized anion[30].

Three main mechanisms enhance molecular transport by iontophoresis:

i. Charged species are driven primarily by electrical repulsion (migration) from the drivingelectrode[31],
ii. The flow of electric current may increase the permeability of skin[18]
iii. The electroosmotic solvent flow, which enhances the flux of both charged and neutral molecules.

The electroosmotic flow occurs from anode to cathode, thus enhancing the flux of positively charged (cationic) drugs and making it possible to deliver neutral drugs[32]. The solvent flow states that iontophoresis causes water, a very effective penetration enhancer, to enter the stratum corneum by electroosmosis. Dissolved drugs can be carried across the skin along with the penetrating water during iontophoresis[20].

A large number of factors are involved in the movement of ions and molecules across the skin when an electric field is applied. Efficiency of transport depends mainly on polarity, valency and mobility of the charged species, as well as electrical current applied and formulation components[18, 33]. The relative importance of electrorepulsion and electroosmosis depends on the physicochemical and

electrical characteristics of the membrane and of the permeant.

In addition, the skin's negative charge can be reduced, neutralized, or even reversed by the iontophoresis of certain cationic, lipophilic species[34]. The skin behaves as a capacitor in an electric circuit, so that the effective current decreases with duration of continuous DC application. In order to avoid this polarization, pulsed DC iontophoresis have been effectively used[35].

Iontophoresis is a controlled release method in which the rate of drug delivery can be modulated after delivery has been initiated[36] by alteration of the applied current, thus tailoring therapy for specific conditions. The iontophoresis approach has been investigated for increasing skin permeability of ketamine[37], diclofenac[38], flurbiprofen[39], methotrexate[40, 41], nafarelin[42], timolol maleate[43], etc. Iontophoresis is often used in combination with various drug delivery methods to improve the transdermal transport which include chemical enhancers, electroporation, sonophoresis, microneedle, ion-exchange materials, laser etc[44, 45].

Electroporation

Transdermal drug delivery is enhanced by electroporation of the stratum corneum[46]. Skin electroporation (electropermeabilization)[47] creates transient aqueous pores in the lipid bilayers by application of short electrical pulses. These pores provide pathways for drug penetration that travel straight through the horny layer[48].

Two main pulse protocols have been employed to promote transport; intermittent application of short high-voltage pulses (about 1 ms and 100 V across the skin) and a few applications of long medium-voltage pulses (about 100 ms and > 30 V across the skin)[49]. During and after the physical disruption of the lipid bilayers of the stratum corneum, molecular transport occurs by electrophoresis[50], electroosmosis[51], and/or diffusion[52]. New aqueous pathways would be created within the stratum corneum due electroporation of its lipid bilayers[53]. Molecular transport through transiently permeabilized skin then occurs due to different mechanisms, mainly by electrophoresis and enhanced diffusion[50]. Thermal effects may be involved[54] and it is recognized that localized Joule heating associated with electroporation is likely to contribute to increased permeability of stratum corneum by lipid chain melting. Electroporation increase the permeation of transdermal delivery of large molecules[55]. The molecular weight of the permeants influencing the route of transport, the smaller the molecular weight, the more intracellular the penetration.

Ultrasound

Phonophoresis, or sonophoresis is a technique by which therapeutic ultrasound is used to introduce pharmacologic agents, usually anti-inflammatory or analgesic drugs, through intact skin into the subcutaneous tissues[56]. The ultrasonic energy (at low frequency) disturbs the lipid packing in stratum corneum by cavitation[18].

Application of low frequency ultrasound (20-100 kHz) enhances skin permeability more effectively than high frequency ultrasound (1-16 MHz). The mechanism of transdermal skin permeation involves disruption of the stratum corneum lipids, thus allowing the drug to pass through the skin. A corresponding reduction in skin resistance was observed due to cavitation, microstreaming and heat generation[57]. Reverse ultrasound technology may also be used for the extraction of interstitial fluid samples for analysis[58]. The low frequency (20 kHz) rather than therapeutic ultrasound (1 MHz) increases enhancement a thousand-fold[59]. Below a threshold value for cavitation (which depends on conditions), permeation is inversely proportional to frequency. Therapeutic ultrasound is normally generated by a transducer that converts electrical energy to ultrasound by utilising the piezoelectric principle. Ultrasound does not pass through tissues with 100% efficiency and much of the energy is attenuated by the dual processes of scatter and absorption. The amount of heat absorbed depends on the absorption characteristics of the tissue being irradiated and the amount of ultrasonic energy passing through it.

The intensities used by ultrasonic therapy devices, heat the tissues by a few degrees centigrade and this is thought to be a major factor of any biological effect. Absorption of the ultrasound depends upon the molecular weight of material and its physical properties[60]. The propagation of an ultrasonic wave within the skin has two main physical consequences: heating and cavitation, and these mechanisms may be linked as cavitation may cause heating[61]. The overall consequence is increased skin permeability due to increased fluidity of intercellular lipids by heating or mechanical stress and/or by enlarging intercellular space, or by creating permanent or transient holes through corneocytes and keratinocytes as a consequence of cavitation and/or by driving the drug and the vehicle through the permeabilize skin by convection. This increase in skin permeability to drugs may not persist after the end of sonication[62]. Other investigations have shown a possible deactivation of skin enzymes by ultrasound[63], effect of pulsed delivery, synergistic co-operation of ultrasound with iontophoresis[64], penetration enhancers[65] and electroporation[66], phonophoresis used to probe the relative contribution of the follicular route to the penetration of hydrophilic permeants[67]. Now, it is clear that the effect of ultrasonation depends on the nature of the drug, the formulation base, and the conditions of ultrasound application[68].

Photomechanical waves

Pressure waves (high amplitude pressure transients) generated by lasers is one of the newest platform of drug delivery. These pressure waves are compression waves and thus exclude biological effects induced by cavitation. Their amplitude is in the hundreds of atmospheres (bar) while the duration is in the range of nanoseconds to a not many microseconds, 100 ns – 1 As. In addition, the term photomechanical waves have often been used for laser generated pressure waves. Pressure waves have been used to permeabilize the SC and facilitate the transport of macromolecules into the viable skin[69]. They have also been shown to facilitate drug delivery into microbial biofilms[70]. PW can also permeabilize the nuclear envelope and facilitate the delivery of macromolecules into the cell nucleus[71].A single pressure wave is adequate to permeabilize the SC and allow macromolecules to diffuse into the epidermis and dermis[72]. Furthermore, drugs delivered into the epidermis can enter the vasculature and produce a desired systemic effect. For example, insulin delivered by pressure waves resulted in reducing the blood glucose level over many hours. A PW can facilitate the delivery of macromolecules, the size of proteins and DNA plasmids, in the epidermis and deep into the dermis. The PW does not transport the drug through the SC. The diffusion of the drug occurs under the concentration gradient through the channels produced by the PW. The mechanism of permeabilization is probably caused by the disruption of the hydrophilic domains of the SC. The application of pressure waves did not cause any pain or discomfort[73].

Magnetophoresis

Magnetophoresis utilizes the magnetic properties of materials by applying a magnetic field across a membrane. The magnetic field provides the driving force for substances with any of the following magnetic properties; ferromagnetism, paramagnetism, or diamagnetism[26]. The magnetophoresis approach has been investigated for terbutaline sulphate[74].

Radiofrequency-driven microchanneling

These radiofrequency currents created an array of microchannels across the stratum corneum deep into the epidermis[75]. The high frequency electrical current conducted through the aqueous medium of the stratum corneum generates heat that brings about an instant removal of cells beneath the electrode. Due to high velocity (1 ms per electrode), it is postulated that only heat conduction results in the creation of microchannels, and other mechanism such as electrochemical reaction do not take place. Skin electroporation, which is operated by low duty cycle, high intensity electric field pulsing, is also believed to create transient aqueous microchannels[50].

This forms RF-microchannels on the outer layer of the skin through ablation of cells. The microchannels are designed to penetrate only the outer layers of the skin, where there are no blood vessels or nerve endings, resulting in minimal skin trauma and neural sensation[75]. RFMicroChannels are formed rapidly (within a second), adding to the user's comfort. The dimensions and density of the RFMicroChannels created can be predicted and controlled carefully, depending on the requirements of the drug. This enables the required dosage of the drug to be controlled very precisely[76].

Microneedle

Microneedles (MNs) represent a unique technological approach to enhance drug permeation across the stratum corneum[77]. The development of microneedles those are long and robust enough to penetrate only the outer most layer of skin (stratum corneum), but short enough to avoid stimulating nerves has the potential to make transdermal delivery of drugs more effective[78]. The first microneedle arrays reported in the literature were etched into a silicon wafer and developed for intracellular delivery in vitro by Hashmi et al. Henry et al.[79] conducted the first study to determine if microneedles could be used to increase transdermal drug delivery.

Microneedles are classified between hollow and nonhollow solid microneedles[80]. Most of the work has focused on making microscopic holes in the skin by inserting solid microneedles made of silicon or metal. The ''poke with patch'' approach uses microneedles to make holes and then apply a transdermal patch to the skin surface. Transport can occur by diffusion or possibly iontophoresis if an electric field is applied. Another approach is ''coat and poke,'' where the needles are first coated with drug and then inserted into the skin. There is no drug reservoir on the skin surface; the entire drug to be delivered is on the needle itself. A variation on this second approach is ''dip and scrape,'' where microneedles are first dipped into a drug solution and then scraped across the skin surface to leave behind drug within microabrasions created by the needles[81].

Microneedles that encapsulate drug and subsequently dissolve or degrade in the skin have been fabricated from polymers, such as slow-degrading polylactic-co-glycolic acid and rapidly dissolving sugar[82]. For pure drug infusion, hollow microneedles provide means for actively driving a liquid drug into the tissue, which can lead to much faster rates of delivery that can be modulated over time. The microneedle array is applied to the skin surface so that the microneedles (usually about 150 µm in length)[83] crosses stratum corneum without going much deeper should be capable of delivering drugs into the permeable regions of skin without stimulating nerves found deeper in the tissue[84]. A broad range of compounds such as calcein (623 Da), insulin (6000Da), bovine serum albumin (66000Da) and polymeric nanoparticles are delivered at significant rates through skin permeabilized by microfabricated microneedles[20]. Extensive work was done on the delivery of insulin using microneedle to modulate the blood glucose level[85].

Macroflux®

Macroflux® technology is another novel transdermal drug delivery system that ALZA Corporation has developed to deliver biopharmaceutical drugs in a controlled reproducible manner that optimizes bioavailability and efficacy without significant discomfort for the patient[86]. The system incorporates a titanium microprojection array that creates superficial pathway through the skin barrier layer to allow transportation of therapeutic proteins and vaccines. When applied onto the skin manually or by an applicator, microprojections penetrate and create superficial pathways through the skin barrier layer to allow drug delivery. The array can be combined either with passive or iontophoretic delivery systems[87].

Needle-Free Injections

The earliest needle free injectors became available as early as 1866, when the French company H.Galante manufactured an "Apparatus for aqua puncture"[88]. Jet injections utilize a high-speed stream of fluid to puncture skin and deliver drugs intradermally, subcutaneously, and intramuscularly without the use of a needle. Jet injections were first developed in the 1940[89]. These devices have been found to have several advantages in human applications, including faster delivery of injected compounds to the circulatory system than traditional subcutaneous injections[90]. A jet injector device that is capable of delivering electronically controlled doses may offer improved consistency and reduced pain[91]. Jet injection is an important needle-free delivery method for administration of insulin, human growth hormone, and vaccines[92, 93]. Some of the needle free injectors under development are Intraject®, Implaject®, Jet Syringe®, Iject®, Mini-ject® and Crossjet®[20].

PowderJect system

The PowderJect system sprays solid particles (20-100 µm) through stratum corneum into lower skin layers, using a supersonic shock wave of helium gas. Powderject system involves the propulsion of solid drug particles into the skin by means of high-speed gas flow. This needle-free method is painless and causes no bleeding and damage to the skin[57]. The use of compressed gas to force solid drug particle through a convergent divergent nozzle using compressed helium. Drug particle velocities of up to 800 m/s were obtained at the nozzle exit. Adjusting the momentum density of the particles within the gas flow optimizes the depth of penetration of the drug particles. Particle velocity is controlled within the device by three parameters namely nozzle geometry, membrane burst strength and gas pressure. Powderject system consists of a gas canister that allows helium gas at high pressure to enter a chamber at the end of which drug cassette containing powdered drug between two polycarbonate membranes At the release, virtually instantaneous rupture of both membranes causes the gas to expand rapidly, forming a strong shock wave that travels down the nozzle at speed of 600–900 m/s. The leading products in development include lignocaine and levobupivacaine for local anaesthesia, proteins (follicle stimulating hormone and â-interferon) and hepatitis B, DNA and other vaccines.

Controlled Heat Aided Drug Delivery System

The use of heat to enhance percutaneous absorption has received increased attention in recent years[94]. Heat increases skin temperature that leads to increase in microcirculation and blood vessel permeability, thus facilitating drug transfer to the systemic circulation. Drug solubility, both in the patch formulation and within the skin increase with a rise in temperature. Zars, lnc (Salt Lake City, UT, USA) has developed a technology that takes advantage of heat's ability to increase transdermal permeation. This technology is known as Controlled Heat-aided Drug Delivery (CHADD) system. CHADD system is a small heating unit that can be placed on top of a traditional patch. An oxidation reaction within the unit provides heat at a limited intensity and duration. The disadvantage of this technology is that heat can slightly compromise the barrier function of the skin[95, 96].

Skin Abrasion

The skin abrasion technique involves the direct removal or disruption of the upper layers of the skin to facilitate the permeation of topically applied medicaments. Some of these devices are based on techniques employed by dermatologists for superficial skin resurfacing which are used in the treatment of acne, scars, hyper pigmentation and other skin blemishes[97, 98]. The abrasion methods reported in the literature include the use of adhesive strips, abrasive pads, and microdermabrasion. Microscission can rapidly and painlessly produce small, open microconduits (small holes) by means of a gas-entrained stream of inert, sharp particles on the skin[99]. Carlisle Scientific (Carlisle, MA) is currently in the process of developing a pen like handheld device called the microscissioner. In addition, Med Pharm Ltd. (Charlbury, United Kingdom) had recently developed a novel dermal abrasion device for the delivery of difficult to formulate therapeutics ranging from hydrophilic low molecular weight compounds to biopharmaceuticals. In vitro data have shown that the application of the device can increase the penetration of angiotensin into the skin 100 fold compared to untreated human skin20[91]. Increase in water permeability of rat skin that was subjected to both tape stripping and sandpaper abrasion, and indicated that the former technique caused more damage to the barrier than the latter one[100] but of Lactate dehydrogenase leaching shows that needle puncture to the stratum corneum is much safer than sandpaper abrasion[101].

Laser Radiation

This method involves direct and controlled exposure of a laser beam to the skin which results in the ablation of the stratum corneum without significantly damaging the underlying epidermis[102]. Removal of the stratum corneum using this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs[103]. A handheld portable laser device has been developed by Norwood Abbey Ltd. (Victoria, Australia) that has been approved by the U.S. and Australian regulatory bodies for the administration of a topically applied anaesthetic. However, the structural changes caused by this technique still need to be assessed for safety and reversibility, particularly at the higher intensities that may be needed to enhance the penetration of large molecular weight solutes where evidence of deeper level ablation effects exist[104]. The erbium: yttrium-aluminum-garnet (Er: YAG) laser promotes the transdermal delivery of narcotic analgesic and insulin[105].

REFERENCES

1. Aulton ME. 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. 1998; 34: 339-350.
4. Chien Y. W. Transdermal controlled systemic medications. Marcel Dekker, Inc. USA. 1987.
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. 2008; 308: 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. 1999; 88 (10): 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. 2002; C 20: 93–100.
9. Hampton T. Breaking barriers in transdermal drug delivery. JAMA. 2005; 293 (17): 2083-2085.
10. Robert L. Transdermal drug delivery: past progress, current status and future prospects. Adv Drug Deliv Rev. 2004; 56: 557-558.
11. Allen LV. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems. 8th Edition, Lippincott Williams & Wilkins, 2005.
12. Karabiyikoglu M. New frontiers in transdermal drug delivery systems. Drug Delivery Report Spring/Summer. 2007.
13. Mojtaba S. Transdermal excipients effect on adhesion strength of a pressure sensitive adhesive. Iranian Polymer Journal. 2003; 12 (3): 243-248.
14. Vyas SP, Khar RK. Controlled Drug Delivery: Concepts and Advances. Vallabh Prakashan, 1st Edition, 2002, 411-447.
15. Walters KA., 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. 2004; 56: 603-618.
17. Batheja P, Sobha R. Transdermal iontophoresis. Drug Delivery. 2007; 46-48.
18. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci. 2001; 14: 101–114.
19. Gordon RD, Peterson TA. Four myths about transdermal drug delivery. Drug Delivery Technology. 2003; 3 (4).
20. Kumar R, Philip A. Modified transdermal technologies: Breaking the barriers of drug permeation via the skin. Tro J Pharm Res. 2007; 6 (1): 633-644.
21. Gazelius B. Iontophoresis – Theory. http://www.perimed.se.
22. Roberts MS, Lai PM, Cross SE, Yoshida NH. Mechanism of transdermal drug delivery. Marcel Dekker Inc, New York, 1997, 291-49.
23. Gelfuso GM, Fabio VF, Tais G. The Effect of pH and ionic strength on topical delivery of a negatively charged porphyrin ($TPPS_4$). J Pharm Sci. 2008; 23: 1-9.
24. Fitzpatrick D, John C. Release characteristics of anionic drug compounds from liquid crystalline gels I: Passive release across non-rate-limiting membranes. Int J Pharm. 2005; 301: 226-236.
25. Hansen R. Iontophoresis. http://www.SportParma.com.
26. Coston AF, John K. Iontophoresis: modeling, methodology, and evaluation, Cardiovascular Engineering. An International Journal. 2001; 1 (3): 127-136.
27. Scott ER, Henry S. Iontophoretic transport through porous membranes using scanning electrochemical microscopy: Application to in vitro studies of ion fluxes through skin. Anal Chem. 1993; 65: 1537-1545.
28. Guy RH, Yogeshvar N, Begon M, Virginia M, Alicia L, Diego M. Iontophoresis: electrorepulsion and electroosmosis. J Control Rel. 2000; 64: 129-132.
29. Tyle P. Iontophoresis Devices for Drug Delivery. Pharm Res. 1986; 3 (6): 318-326.
30. Hirvonen J, Hueber F, Richard H. Current profile regulates iontophoretic delivery of amino acids across the skin. J Control Rel. 1996; 37: 239-249.
31. Peck KD, Hsu J, Li SK, Ghanem AH, Higuchi WI. Flux enhancement effects of ionic surfactants upon passive and electroosmotic transdermal transport. J Pharm Sci. 1998; 87: 1161-1169.
32. Abla N. Contributions of electromigration and electroosmosis to peptide, iontophoresis across intact and impared skin. J Control Rel. 2005; 108: 319-330.
33. Viscusi ER. Iontophoresis: The process behind noninvasive drug delivery. Regional Anesthesia and Pain Medicine. 2005; 30 (3): 292-294.
34. Delgado-Charro BM. Characterization of convective solvent flow during iontophoresis. Pharm Res. 1994; 11: 929-935.
35. Shibaji T. A mechanism of the high frequency AC iontophoresis. J Control Rel. 2001; 73: 37-47.
36. Schwendeman SP. Modulated drug release using iontophoresis through heterogeneous cation-exchange membranes: membrane preparation and influence of resin crosslinkage. Macromolecules. 1992; 25: 2531-2540.
37. Vranken JH, Dijkgraaf MG, Kruis, Dasselaar NT, Vegt MH. Iontophoretic administration of S(C)-ketamine in patients with intractable central pain: A placebo-controlled trial. Pain. 2005; 118: 224-231.
38. Fitzpatrick D, John C. Release characteristics of anionic drug compounds from liquid crystalline gels III: Chemical and iontophoretic enhancement of delivery across non-rate-limiting membranes. Int J Pharm. 2006; 325: 90-98.
39. Mathy F, Catherine L, Roger K, Veronique P. Study of the percutaneous penetration of flurbiprofen by cutaneous and subcutaneous microdialysis after iontophoretic delivery in rat. J Pharm Sci. 2005; 94: 144-152.
40. Alvarez-Figueroa MJ, Delgado-Charro MB, Blanco-Mendez J. Passive and iontophoretic transdermal penetration of Methotrexate. Int J Pharm. 2001; 212: 101-107.
41. Prasad R, Veena K, Sneb A, Rope K. Transdermal iontophoresis delivery of methotrexate: physicochemical considerations. Trends Biomater Artif Organa. 2005; 18(2): 187-190.
42. Delgado-Charro MB, Amalia M, Richard H. Iontophoresis of nafarelin: effects of current density and concentration on electrotransport in vitro. J Control Rel. 1995; 35: 35-40.
43. Stamatialis D F, Rolevink HHM, Koops GH. Controlled transport of timolol maleate through artificial membranes under passive and iontophoretic conditions. J Control Rel. 2002; 81: 335- 345.
44. Mitragotri S. Synergistic effect of enhancers for transdermal drug delivery. Pharm Res. 2000; 17 (11): 1354-1359.
45. Higaki K, Chomchan A, Toshikiro K. Strategies for overcoming the stratum corneum chemical and physical approaches. Am J Drug Deliv. 2003; 1 (3): 187-214.
46. Prausnitz MR. Transdermal transport efficiency during skin electroporation and iontophoresis. J Control Rel. 1996; 38: 205-217.
47. Pliquett U. A propagating heat wave model of skin electroporation. Journal of Theoretical Biology. 2008; 251: 195-201.
48. Teissie J. Electropermeabilization of cell membranes. Adv Drug Deliv Rev. 1999; 35: 3- 19.
49. Vanbever R. In vivo efficacy and safety of skin electroporation. Adv Drug Deliv Rev. 1999; 35: 77-88.
50. Vanbever R. Transdermal delivery of metoprolol by electroporation. Pharm Res. 1994; 11: 1657-1662.
51. Vanbever R. Transdermal delivery of fentanyl by electroporation. II. Mechanisms involved in drug transport. Pharm. Res. 1996; 13: 1359-1365.
52. Vanbever R. Transdermal permeation of neutral molecules by electroporation. J Control Rel. 1998; 54: 243-250.
53. Weaver JC. Theory of electroporation: a review. Bioelectrochem Bioenerg. 1996; 41: 135- 160.
54. Pliquett U. Mechanistic studies of molecular transport due to skin electroporation. Adv Drug Deliv Rev. 1999; 35: 41-60.
55. Lombry C. Transdermal delivery of macromolecules using skin electroporation. Pharm Res. 2000; 17 (1): 32-37.
56. Saliba S. Phonophoresis and the absorption of dexamethasone in the presence of an occlusive dressing. Journal of Athletic Training. 2007; 42 (3): 349-354.
57. Tang H, Wang C, Blankschtein D, Langer R. An investigation of the role of cavitation in low frequence ultrasound-mediated transdermal drug transport. Pharm Res. 2002; 19: 1160-1169.
58. Terahara T, Mitragotri S, Langer R. Porous resins as a cavitation enhancer for low-frequency sonophoresis. J Pharm Sci. 2002; 91: 753-759.
59. Mitragotri S, Farrell J, Tang H, Terahara T, Kost J, Langer R. Determination of threshold energy dose for ultrasound-induced transdermal drug transport. J Control Rel. 2000; 63: 41-52.
60. Meidan VM, Walmsley A, Irwin W. Phonophoresis - is it a reality? Int J Pharm. 1995; 118: 129-149.
61. Holt RG, Roy RA. Measurements of bubble-enhanced heating from focused MHz frequency ultrasound in a tissue-mimicking material. Ultrasound Med Biol. 2001; 27: 1399-1412.
62. Machet L,Boucaud A. Phonophoresis: efficiency, mechanisms and skin tolerance. Int J Pharm. 2002; 243: 1-15.
63. Hikima T, Hirai Y, Tojo K. The effect of ultrasound application on skin metabolism of prednisolone 21-acetate. Pharm Res. 1998; 15: 1680-1683.
64. Le L, Kost J, Mitragotri S. Combined effect of low frequency ultrasound and iontophoresis: application for transdermal heparin delivery. Pharm Res. 2002; 17: 1151-1154.
65. Johnson ME, Mitragotri S, Patel A, Blankschtein D, Langer R. Synergistic effects of chemical enhancers and therapeutic ultrasound on transdermal drug delivery. J Pharm Sci. 1996; 85: 670-679.
66. Kost J, Pliquett U, Mitragotri S, Yamamoto A, Langer R, Weaver J. Synergistic effect of electric field and ultrasound on transder mal transport. Pharm Res. 1996; 13: 633-638.
67. Meidan VM, Docker M, Walmsey A, Irwin W. Low intensity ultrasound as a probe to elucidate the relative follicular contribution to total transdermal absorption. Pharm Res. 1998; 15: 85-92.
68. Simonin J. On the mechanisms of in vitro and in vivo phonophoresis. J Control Rel. 1995; 33: 125-141.
69. Apostolos G. Transdermal drug delivery with a pressure wave. Adv Drug Deliv Rev. 2004; 56: 559-579.
70. Soukos NS. Photomechanical drug delivery into microbial biofilms. Pharm Res. 2000; 17:405-409.
71. Lin T. Nuclear transport by laser-induced pressure transients. Pharm. Res. 2003; 20: 879- 883.
72. Lee S. Permeabilization and recovery of the stratum corneum in vivo: The synergy of photomechanical waves and sodium lauryl sulfate. Lasers in Surgery and Medicine. 2001; 29: 145-150.
73. Lee S. Topical drug delivery in humans with a single photomechanical wave. Pharm. Res. 1999; 16: 1717-1721.
74. Murthy SN, Hiremath S. Physical and chemical permeation enhancers in transdermal delivery of terbutaline sulphate. AAPS PharmSciTech. 2001; 2 (1): 1-5.
75. Sintov AC, Igor K, Dorit D, Talli H, Sohn Z, Levin G. Radiofrequency-driven skin microchanneling as a new way for electrically assisted transdermal delivery of hydrophilic drugs. J Control Rel. 2003; 89: 311-320.
76. Trans Pharma Medical Ltd, A Unique and Comprehensive Approach to Transdermal Drug Delivery. Pharmatech. 2004; 1-4.
77. Wermeling DP, Stan L, David A, Harvinder S, Jyoti G, Mark R, Audra L. Microneedles permit transdermal delivery of a skin-impermeant medication to humans. PNAS. 2008; 105 (6): 2058-2063.
78. Stoeber B, Dorian L. Arrays of hollow out-of-plane microneedles for drug delivery. J Microelectromech Syst. 2005; 14 (3): 472-479.
79. Henry S, McAllister D, Allen M, Prausnitz M. Microfabricated microneedles: a novel method to increase transdermal drug delivery. J Pharm Sci. 1998; 87: 922-925.
80. Roxhed N, Christian G, Patrick G, Gerhard A. Penetration-enhanced ultrasharp microneedles and prediction on skin interaction for efficient transdermal drug delivery. J Microelectromech Syst. 2007; 16 (6): 1429-1440.
81. Prausnitz MR. Microneedles for transdermal drug delivery. Adv Drug Deliv Rev. 2004; 56: 581-587.
82. Lee JW, Park J, Prausnitz MR. Dissolving microneedles for transdermal drug delivery. Biomaterials. 2008, 29, 2113-2124.

83. Benson H, Namjoshi S. Proteins and peptides: strategies for delivery to and across the skin. J Pharm Sci. 200; 27: 1-20.
84. Kaushik S, Allen H, Donald D, Devin V, Smitra S, Mark G, Prausnitz M. Lack of pain associated with microfabricated microneedles. Anesth Analg. 2001; 92: 502-504.
85. Davis SP, Wijaya M, Mark G. Hollow metal microneedles for insulin delivery to diabetic rats. IEEE Transactions on Biomedical Engineering. 2005; 52 (5): 909-915.
86. Daddona P. Macroflux® transdermal technology development for the delivery of therapeutic peptides & proteins. Drug Deliv Tech. 2002; 2 (5): 54-57.
87. Lin W., Cormier M, Ahmad S, Angie G, Bonny J, Teng C, Gregory E, Peter E. Transdermal delivery of antisense oligonucleotides with micro-projection patch (Macroflux®) technology. Pharm. Res. 2001; 18 (12): 1789-1793.
88. Rathbone MJ, Hadgraft J, Roberts MS. (eds.) Modified release drug delivery technology. Marcel Dekker, Inc., New York, 2004, 126, 471-619.
89. Schramm BJ, Mitragotri S. Needle-free jet injections: dependence of jet penetration and dispersion in the skin on jet power. J Control Rel. 2004; 97: 527-535.
90. Houser TA, Joseph G, Brad J, Thomas J, Dachrit N, Eileen L and Frank K. Effectiveness of transdermal, needle-free injections for reducing pork carcass defects. Meat Science. 2004; 68: 329-332.
91. Stachowiak JC, Marcio G, Thomas H, Laleh J, Sapun H and Daniel A. Piezoelectric control of needle-free transdermal drug delivery. J Control Rel. 2007; 124: 88-97.
92. Kendall M. Engineering of needle-free physical methods to target epidermal cells for DNA vaccination. Vaccine. 2006; 24: 4651-4656.
93. Giudice EL and James D. Needle-free vaccine delivery. Adv Drug Deliv Rev. 2006; 58: 68-89.
94. Simon L. Analysis of heat-aided membrane-controlled drug release from a process control perspective. Int J Heat and Mass Transfer. 2007; 50: 2425-2433.
95. Murthy SN. Temperature influences the post electroporation permeability state of the skin. J Pharm Sci. 2004; 93: 908-915.
96. Zars Inc., Zars drug delivery technology. www. Zars.com/chadd.html.
97. Ferrara LA, Fleischman AJ, Benzel EC and Roy S. Silicon dermabrasion tools for skin resurfacing applications. Medical Engineering & Physics. 2003; 25: 483-490.
98. Rice P, Brown R, Lam D, Chilcott R and Bennett N. Dermabrasion - a novel concept in the surgical management of sulphur mustard injuries. Burns. 2000; 26: 34-40.
99. Herdon TO, Salvador G, Gowrishankar TR, Rox A, James C. Transdermal microconduits by microscission for drug delivery and sample acquisition. BMC Medicine. 2004; 2 (12): 1-11.
100. Nangia A, Patil S, Bret B, Anders B, Howard M. In vitro measurement of transepidermal water loss: a rapid alternative to tritiated water permeation for assessing skin barrier functions. Int J Pharm. 1998; 170: 33-40.
101. Wu X, Todo H, Sugibayashi K. Effects of pretreatment of needle puncture and sandpaper abrasion on the in vitro skin permeation of fluorescein isothiocyanate (FITC)-dextran. Int J Pharm. 2006; 316: 102-108.
102. Lee W, Shen S, Lai H, Hu C, Fang J. Transdermal drug delivery enhanced and controlled by erbium:YAG laser: a comparative study of lipophilic and hydrophilic drugs. J Control Rel. 2001; 75: 155-166.
103. Lee W, Shen S, Wang K, Hu C, Fang J. The effect of laser treatment on skin to enhance and control transdermal delivery of 5-flurouracil. J Pharm Sci. 2002; 91 (7): 1613-1626.
104. Wang KH, Fang JY, Hu CH, Lee WR. Erbium: YAG Laser pretreatment accelerates the response of Bowen's disease treated by topical 5-flurouracil. Dermatol Surg. 2004; 30(3): 441-445.
105. Lee WR., Shen C, Fang C, Ching L, Fang J. Skin pretreatment with an Er:YAG laser promotes the transdermal delivery of three narcotic analgesics. Lasers Med Sci. 2007; 22: 271-278.

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