



## Strategies for enhancing transdermal drug delivery-A review

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### ABSTRACT

Transdermal drug delivery systems (TDDS), also known as “patches,” are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. To cross the drug from transdermal patches to blood there are many barriers for transport. To increase the passage of drugs through skin permeation enhancers are widely used. The role of permeation enhancers are mentioned in this review, Apart from permeation enhancers there are some other strategies to increase the permeation of drugs through skin. In this review, we focused about various methods to enhance the permeation of drug from transdermal drug delivery through skin. © 2009 Trade Science Inc. - INDIA

### KEYWORDS

Transdermal;  
Permeation enhancers;  
Stratum corneum;  
Methods for enhancing the  
TDDS.

### 1. INTRODUCTION

The skin is the largest organ of the body, accounting for more than 10% of body mass, and the one that enables the body to interact most intimately with its environment. In essence, the skin consists of four layers: Stratum corneum (SC) (nonviable epidermis), Epidermis (viable epidermis), Dermis, and subcutaneous tissues.

The use of topical products was evident in ancient times, and there are reports of systemic benefits of topical anti-infective and hormonal agents in the 1940s. Modern transdermal patch technology was introduced in the late 1970s.

The main interests in dermal absorption assessment are in the application of compounds to the skin for local effects in dermatology (e.g., corticosteroids for dermatitis); For transport through the skin for systemic effects (e.g., Nicotine patches for smoking cessation) for sur-

face effects (e.g., sunscreens, cosmetics, and anti-inflammatory) to target deeper tissues (e.g., Nonsteroidal anti-inflammatory agents [NSAIDs] for muscle inflammation); and unwanted absorption (e.g., solvents in the workplace, agricultural chemicals, or allergens).

The skin became popular as a potential site for systemic drug delivery because it was thought to avoid the problems of stomach emptying, pH effects, and enzyme deactivation associated with gastrointestinal passage, to avoid hepatic first pass metabolism and to enable control of input.

### 2. Methods for enhancing drug delivery across skin

Overcoming the barrier status of skin is of prime concern for the success of a transdermal patch. A product development scientist often uses permeation enhancer(s) that increase the rate of transfer of drug(s) across the skin in addition to that there are some active and passive methods for Enhancing transdermal drug delivery. In this review, we focus regarding the different

## Regular Paper

TABLE 1: Mechanism of some classes of permeation enhancers

Class	Representative compounds	Mechanism of interaction with skin and enhancement of drug permeability
Water	Hydrating and occlusive topical preparations occlusive dressings	Hydrates the stratum corneum, evidence for increasing permeability of both hydrophilic and lipophilic compounds, increases fluidity or disorder of intercellular bilayers; occlusive dressing and vehicle prevent water loss from skin and provides full hydration.
	Alcohol	Co transports with the drug through the lipid channels, partial extraction of lipids
Organic solvents	Polyols (PG)	Replaces bound water in the intercellular space, enhances penetration of lipophilic drugs.
	Sulfoxides (DMSO)	Partition into the corneocyte, binds keratin; at higher concentration increases lipid fluidity and disrupts lipid packing
	Pyrrolidones	Interacts with both the keratin and lipid component of stratum corneum.
Fatty acids	Oleic acid	Increases fluidity of the intercellular lipids: shorter chain(c10-12) and branched or unsaturated chain fatty acids;the vehicle used might be synergistic.
Terpenes	Ascaridole ,1,8-cineole, L-menthol,D-Limonene	Disrupts intercellular lipid order, increases electrical conductivity, and indicates the opening of polar pathway in stratum corneum.
	Polysorbates(Tween)	Penetrates into skin, micellar solubilization of stratum corneum lipids.
Surfactants (nonionic,cationic, anionic)	Polyoxyethylene alkylphenols (Brij)	Penetrates into skin, extracts lipid from stratum corneum
	Sodium lauryl sulfate	Binds to intracellular keratin in comeocytes, removes some of the intercellular lipid, increases transepithelial water loss alter processing of epidermal lipids.
Azone	1-dodecylhexahydro- 2H-azepin-2-one and certain derivatives	Disrupts skin lipids in both the head groups and tail regions
	Phospholipids from soya or egg lecithin	Diffuses into stratum corneum, perturbs intercellular lipids, enhances drug partitioning into skin

methods to enhance the transdermal permeation.

### 2.1. Permeation enhancers

Human skin is a remarkably efficient barrier, designed to keep “our insides in and the outsides out”. This barrier property causes difficulties for transdermal/topical delivery of therapeutic agents. One long standing approach to increase the range of drugs that can be effectively delivered via this route has been to use penetration enhancers, chemicals that interact with skin constituents to promote drug flux. To date, a vast array of chemicals has been evaluated as penetration enhancers (or absorption promoters), yet their inclusion into topical or transdermal formulations is limited.

Although many chemicals have been evaluated as penetration enhancers in human or animal skins, to date none has proven to be ideal. Some of the more desirable properties for penetration enhancers acting within skin have been given as

- They should be non-toxic, non-irritating and non-allergenic.
- They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body-i.e. should not bind to receptor sites.

- The penetration enhancers should work unidirectional, i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body. When removed from the skin, barrier properties should return both rapidly and fully.
- The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
- They should be cosmetically acceptable with an appropriate skin “feel”
- The various permeation enhancers listed in TABLE 1 act by different mechanisms to increase the permeability of drugs across stratum corneum.

### 2.2. Passive methods for enhancing transdermal drug delivery

The conventional means of applying drugs to skin include the use of vehicles such as ointments, creams, gels and “passive” patch technology. More recently, such dosage forms have been developed and/or modified in order to enhance the driving force of drug diffusion (thermodynamic activity) and/or increase the permeability of the skin. Such approaches include the use of penetration enhancers<sup>[1]</sup>, supersaturated systems<sup>[2]</sup>, prodrugs or metabolic approach<sup>[3,4]</sup>, liposomes and other

vesicles<sup>[5,6]</sup>. However, the amount of drug that can be delivered using these methods is still limited since the barrier properties of the skin are not fundamentally changed.

### 2.3. Active methods for enhancing transdermal drug delivery

These methods involve the use of external energy to act as a driving force and/or act to reduce the barrier nature of the stratum corneum in order to enhance permeation of drug molecules into the skin. Recent progress in these technologies has occurred as a result of advances in precision engineering (bioengineering), computing, chemical engineering and material sciences, all of which have helped to achieve the creation of miniature, powerful devices that can generate the required clinical response. The use of active enhancement methods has gained importance because of the advent of biotechnology in the later half of the twentieth century, which has led to the generation of therapeutically active, large molecular weight (>500 Da) polar and hydrophilic molecules, mostly peptides and proteins. However, gastrointestinal enzymes often cause degradation of such molecules and hence there is a need to demonstrate efficient delivery of these molecules by alternative administration routes. Passive methods of skin delivery are incapable of enhancing permeation of such large solutes, which has led to studies involving the use of alternative active strategies such as those discussed here.

#### 2.3.1. Electroporation

The use of electro permeabilization, a method of enhancing diffusion across biological barriers was studied<sup>[3]</sup>. Electroporation involves the application of high-voltage pulses to induce skin perturbation. High voltages (=100 V) and short treatment durations (milliseconds) are most frequently employed. Other electrical parameters that affect delivery include pulse properties such as waveform, rate and number<sup>[8]</sup>. The increase in skin permeability is suggested to be caused by the generation of transient pores during electroporation<sup>[9]</sup>. The technology has been successfully used to enhance the skin permeability of 5 Transdermal Drug Delivery Systems, including biopharmaceuticals with a molecular weight greater than 7 kDa, the current limit for iontophoresis is described by Denet<sup>[10]</sup>. Other transdermal devices based on electroporation have been proposed by various groups<sup>[11-14]</sup> however, more clinical informa-

tion on the safety and efficacy of the technique is required to assess the future commercial prospects.

#### 3.3.2. Iontophoresis

This method involves enhancing the permeation of a topically applied therapeutic agent by the application of a low level electric current either directly to the skin or indirectly via the dosage form<sup>[15-19]</sup>. Increase in drug permeation as a result of this methodology can be attributed to either one or a combination of the following mechanisms: Electrorepulsion (for charged solutes), Electroosmosis (for uncharged solutes) and Electroperturbation (for both charged and uncharged).

Parameters that affect design of an iontophoretic skin delivery system include electrode type, current intensity, pH of the system, competitive ion effect and permeant type. The Phoresor<sup>TM</sup> device was the first iontophoretic system to be approved by the FDA in the late 1970s as a physical medicine therapeutic device. In order to enhance patient compliance, the use of patient friendly, portable and efficient iontophoretic systems have been under intense development over the years. Previous work has also reported that the combined use of iontophoresis and electroporation is much more effective than either technique used alone in the delivery of molecules across the skin<sup>[20-22]</sup>. The limitations of iontophoretic systems include the regulatory limits on the amount of current that can be used in humans (currently set at 0.5 mA cm<sup>-2</sup>) and the irreversible damage such currents could do to the barrier properties of the skin. In addition, iontophoresis has failed to significantly improve the transdermal delivery of macromolecules of >7,000 Da<sup>[23]</sup>.

#### 3.3.3. Ultrasound (Sonophoresis and phonophoresis)

Ultrasound involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre treatment. The proposed mechanism behind the increase in skin permeability is attributed to the formation of gaseous cavities within the intercellular lipids on exposure to ultrasound, resulting in disruption of the SC<sup>[24]</sup>. Ultrasound parameters such as treatment duration, intensity and frequency are all known to affect percutaneous absorption, with the latter being the most important<sup>[25]</sup>. Although frequencies between 20 kHz- 16 MHz have been reported to enhance skin permeation, frequencies at the lower end of this range (<100 kHz) are believed to have a more significant effect on transdermal drug delivery, with the delivery of

## Regular Paper

macromolecules of molecular weight up to 48 kDa being reported<sup>[26]</sup>. The SonoPrep® device (Sontra Medical Corporation) uses low-frequency ultrasound (55 kHz) for an average duration of 15 seconds(sec) to enhance skin permeability. The ability of the SonoPrep device to reduce the time of onset of action associated with the dermal delivery of local anaesthetic from EMLA cream was recently reported. In the study by Kost<sup>[27]</sup>, skin treatment by ultrasound for an average time of 9 sec resulted in the attainment of dermal anaesthesia within 5 min, compared with 60 min required for non treated skin. The use of other small, light weight novel ultrasound transducers to enhance the in vitro skin transport of insulin has also been reported by a range of workers<sup>[28-30]</sup>.

### 3.3.4. Laser radiation and photomechanical waves

Lasers have been used in clinical therapies for decades, and therefore their effects on biological membranes are well documented. Lasers are frequently used for the treatment of dermatological conditions such as acne and to confer “facial rejuvenation” where the laser radiation destroys the target cells over a short frame of time (~300ns). Such direct and controlled exposure of the skin to laser radiation results in ablation of the SC without significant damage to the underlying epidermis. Removal of SC via this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs. A design concept for a transdermal drug delivery patch based on the use of pressure wave has been proposed by Doukas and Kollias<sup>[31]</sup>.

### 3.3.5. Radio-frequency

Radio frequency involves the exposure of skin to high frequency altering current (~100 KHz), resulting in the formation of heat induced micro channels in the membrane in the same way as when laser radiation is employed. The rate of drug delivery is controlled by the number and depth of the micro channels formed by the device, which is dependent on the properties of the microelectrodes used in the device. The Viaderm device (Transpharma Ltd) is a hand held electronic device consisting of a micro projection array (100 micro-electrodes/cm<sup>2</sup>) and a drug patch. The microneedle array is attached to the electronic device and placed in contact with the skin to facilitate the formation of the micro channels. Treatment duration takes less than a second, with a feedback mechanism incorporated within the electronic control providing a signal when the micro

channels have been created, so as to ensure reproducibility of action. The drug patch is then placed on the treated area. Experiments in rats have shown that the device enhances the delivery of granisetron HCL, with blood plasma levels recorded after 12 hours(hr) raising 30 times the levels recorded for untreated skin after 24 hr. A similar enhancement in diclofenac skin permeation was also observed in the same study<sup>[32]</sup>. The device is reported not to cause any damage to skin, with the radio frequency induced micro channels remaining open for less than 24 hr. The skin delivery of drugs such as testosterone and human growth hormone by this device is also currently in progress.

### 3.3.6. 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<sup>[33]</sup> showed a magnetically induced enhancement in benzoic acid flux, which was observed to increase with the strength of the applied magnetic field. Other in vitro studies using a magnet attached to transdermal patches containing terbutaline sulphate (TS) demonstrated an enhancement in permeant flux which was comparable to that attained when 4% isopropyl myristate(IPM) was used as a chemical enhancer. In the same work the effect of magnetophoresis on the permeation of TS was investigated in vivo using guinea pigs. The preconvulsive time (PCT) of guinea pigs subjected to magnetophoretic. Brown. treatment was found to last for 36 hr, which was similar to that observed after application of a patch containing 4% IPM. This was in contrast to the response elicited by the control (patch without enhancer), when the increase in PCT was observed for only 12 hr. In human subjects, the levels of TS in the blood were higher but not significantly different from those observed with the patch containing 4% IPM. The fact that this technique can only be used with diamagnetic materials will serve as a limiting factor in its applicability and probably explains the relative lack of interest in the method.

### 3.3.7. Temperature (“Thermophoresis”)

The skin surface temperature is usually maintained at 32°C in humans by a range of homeostatic controls. The effect of elevated temperature (non-physiological) on percutaneous absorption was initially reported by

Blank<sup>[34]</sup>. Recently, there has been a surge in the interest of using thermoregulation as a means of improving the delivery profile of topical medicaments. Previous in vitro studies have demonstrated a 2-3 fold increase in flux for every 7-8°C rise in skin surface temperature. The increased permeation following heat treatment has been attributed to an increase in drug diffusivity in the vehicle and an increase in drug diffusivity in the skin due to increased lipid fluidity. Vasodilatation of the subcutaneous blood vessels as a homeostatic response to a rise in skin temperature also plays an important role in enhancing the transdermal delivery of topically applied compounds<sup>[35,36]</sup>. The in vivo delivery of nitroglycerin, testosterone, lidocaine, tetracaine and fentanyl from transdermal patches with attached heating devices was shown to increase as a result of the elevated temperature at the site of delivery. However, the effect of temperature on the delivery of penetrants >500 Da has not been reported. The controlled heat aided drug delivery (CHADD) patch (Zars Inc., Salt Lake City, UT) consists of a patch containing a series of holes at the top surface which regulate the flow of oxygen into the patch. The patch generates heat chemically in a powder filled pouch by an oxidative process regulated by the rate of flow of oxygen through the holes into the patch. The CHADD technology was used in the delivery of a local anaesthetic system (lidocaine and tetracaine) from a patch (S-Caine®) and found to enhance the depth and duration of the anaesthetic action in human volunteers, when the results obtained in active and placebo groups were compared.

Zars Inc., together with Johnson and Johnson, submitted an investigational new drug (IND) application to the FDA for Titragesia™ (a combination of CHADD disks and Duragesic Patches, the latter containing fentanyl for treatment of acute pain). Kuleza and Dvoretzky also have described a heat delivery patch or exothermic pad for promoting the delivery of substances into the skin, subcutaneous tissues, joints, muscles and blood stream, which may be of use in the application of drug and cosmetic treatments. All these studies described employed an upper limit skin surface temperature of 40-42°C, which can be tolerated for a long period (>1 hr). In heat-patch systems where patient exposure to heat is ≤ 24 hr. In addition, the issue of drug stability may also need to be addressed when elevated temperatures are used. Thermoperturbation refers to the use of extreme temperatures to reduce the skin barrier. Such perturbation has been reported in response to using high

temperatures for a short duration (30 ms), with little or no discomfort, using a novel patch system. These investigators developed a polydimethylsiloxane (PDMS) patch for non-invasive transdermal glucose sensing via thermal micro-ablation. Ablation was achieved by microheaters incorporated within the patch. The heat pulse is regulated by means of a resistive heater, which ensures that the ablation is limited within the superficial dead layers of the skin. Average temperatures of 130°C are required for ablation to occur within 33 ms, after which SC evaporation results. Other heat assisted transdermal delivery devices under development include the PassPort® patch (Althea therapeutics) which ablates the SC in a manner similar to the PDMS patch. The exposure of skin to low (freezing) temperatures has been reported to decrease its barrier function but has however not been exploited as a means of enhancing skin absorption. The final group of active enhancement methods entails the use of a physical or mechanical means to breach or by pass the SC barrier.

### 3.3.8. Microneedle based devices

One of the first patents ever filed for a drug delivery device for the percutaneous administration of drugs was based on this method<sup>[37]</sup>. The device as described in the patent consists of a drug reservoir and a plurality of projections extending from the reservoir. These microneedles of length 50-110 mm will penetrate the SC and epidermis to deliver the drug from the reservoir. The reservoir may contain drug, solution of drug, gel or solid particulates, and the various embodiments of the invention include the use of a membrane to separate the drug from the skin and control release of the drug from its reservoir. As a result of the current advancement in microfabrication technology in the past ten years, cost effective means of developing devices in this area are now becoming increasingly common<sup>[38-40]</sup>. A recent commercialization of microneedle technology is the Macroflux® micro projection array developed by ALZA Corporation. The macroflux patch can be used either in combination with a drug reservoir or by dry coating the drug on the microprojection array the latter being better for intracutaneous immunization. The length of the microneedles has been estimated to be around 50-200 mm and therefore they are not believed to reach the nerve endings in the dermo-epidermal junction. The microprojections/ microneedles (either solid or hollow) create channels in the skin, allowing the unhindered movement of any topically applied drug. Clin-

## Regular Paper

cal evaluations report minimal associated discomfort and skin irritation and erythema ratings associated with such systems are reportedly low. This technology serves as an important and exciting advance in transdermal technology because of the ability of the technique to deliver medicaments with extremes of physicochemical properties (including vaccines, small molecular weight drugs and large hydrophilic biopharmaceuticals). Describe the production of an intracutaneous micro needle array and provide an account of its use (microfabrication technology). Various embodiments of this invention can include a microneedle array as part of a closed loop system "smart patch" to control drug delivery based on feedback information from analysis of body fluids. Dual purpose hollow micro needle systems for transdermal delivery and extraction which can be coupled with electrotransport methods are also described by Trautman and Allen<sup>[41]</sup>. These mechanical microdevices which interface with electronics in order to achieve a programmed or controlled drug release are referred to as microelectromechanical systems (MEMS) devices.

### 3.3.9. Skin puncture and perforation

These devices are similar to the microneedle devices produced by microfabrication technology. They include the use of needle like structures or blades, which disrupt the skin barrier by creating holes and cuts as a result of a defined movement when in contact with the skin. Godshall and Anderson described a method and apparatus for disruption of the epidermis in a reproducible manner. The apparatus consists of a plurality of microprotrusions of a length insufficient for penetration beyond the epidermis. The microprotrusions cut into the outer layers of the skin by movement of the device in a direction parallel to the skin surface. After disruption of the skin, passive (solution, patch, gel, ointment, etc.) or active (iontophoresis, electroporation, etc.) delivery methods can be used. Descriptions of other devices based on a similar mode of action have been described by Godshall, Kamen, Jang<sup>[42]</sup>.

### 3.3.10. Needleless injection

Needleless injection is reported to involve a pain free method of administering drugs to the skin. This method therefore avoids the issues of safety, pain and fear associated with the use of hypodermic needles. Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin by using a suitable energy source.

Over the years there have been numerous examples of both liquid (Ped-O-Jet®, Iject®, Biojector2000®, Medi-jector® and Intraject®) and powder (PMED™ device, formerly known as powderject® injector) systems. The latter has been reported to deliver successfully testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin<sup>[43-45]</sup>. Problems facing needleless injection systems include the high developmental cost of both the device and dosage form and the inability, unlike some of the other techniques described previously, to programme or control drug delivery in order to compensate for inter subject differences in skin permeability.

### 3.3.11. Suction ablation

Formation of a suction blister involves the application of a vacuum or negative pressure to remove the epidermis whilst leaving the basal membrane intact. The cellpatch® (Epiport Pain Relief, Sweden) is a commercially available product based on this mechanism. It comprises a suction cup, epidermatome (to form a blister) and device (which contains morphine solution) to be attached to the skin. This method which avoids dermal invasivity, thereby avoiding pain and bleeding, is also referred to as skin erosion. Such devices have also been shown to induce hyperaemia in the underlying dermis in *in vivo* studies, which was detected by laser Doppler flowmetry and confirmed by microscopy, and is thought to further contribute to the enhancement of dextran and morphine seen with this method. The disadvantages associated with the suction method include the prolonged length of time required to achieve a blister (2.5 hr), although this can be reduced to 15-70 min by warming the skin to 38°C. In addition, although there is no risk of systemic infection when compared with the use of intravenous catheters, the potential for epidermal infections associated with the suction method cannot be ignored even though the effects might be less serious<sup>[46]</sup>.

### 3.3.12. Application of pressure

The application of modest pressure (i.e. 25 kPa) has been shown to provide a potentially non invasive and simple method of enhancing skin permeability of molecules such as caffeine<sup>[47]</sup>. These workers attributed the increase in transcutaneous flux to either an improved transappendageal route or an increased partition of the compound into the SC when pressure was applied. This method may also work because of the in-

creased solubility of caffeine in the stratum corneum caused by the increase in pressure.

### 3.3.13. Skin stretching

These devices hold the skin under tension in either a unidirectional or a multidirectional manner<sup>[48,49]</sup>. The authors claim that a tension of about 0.01-10 mPa results in the reversible formation of micropathways. The efficiency of the stretching process was demonstrated by monitoring the delivery of a decapeptide (1 kDa). Brown et al. across the skin of hairless guinea pigs by using a microprotrusion array. The results of the study showed that the bi directional stretching of skin after microprotrusion piercing allowed the pathways to stay open (i.e. delayed closure), thereby facilitating drug permeation to a greater extent ( $27.9 \pm 3.3 \text{ mg cm}^{-2} \text{ h}^{-1}$ ) than in the control group ( $9.8 \pm 0.8 \text{ mg cm}^{-2} \text{ h}^{-1}$ ), where the skin was not placed under tension after microneedle treatment. However, increased skin permeation in the absence of microneedle pre treatment was not found to occur. Other methods involving the use of skin stretching with subsequent use of delivery devices based on electrotransport, pressure, osmotic and passive mechanisms have also been suggested, but the value of skin stretching alone without the benefit of a secondary active delivery device remains to be seen.

### 3.3.14. Skin abrasion

These techniques, many of which are based on techniques employed by dermatologists in the treatment of acne and skin blemishes (e.g. microdermabrasion), involve the direct removal or disruption of the upper layers of the skin to enhance the permeation of topically applied compounds. The delivery potential of skin abrasion techniques is not restricted by the physicochemical properties of the drug, and previous work has illustrated that such methods enhance and control the delivery of a hydrophilic permeant, vitamin C vaccines and biopharmaceuticals<sup>[50-52]</sup>. One current method is performed using a stream of aluminum oxide crystals and motor driven fraises Sage and Bock also describe a method of pre treating the skin prior to transdermal drug delivery which consists of a plurality of microabraders of length 50-200 mm. The device is rubbed against the area of interest, to abrade the site, in order to enhance delivery or extraction. The microabraders/ microprotrusions terminate as blunt tips and therefore do not penetrate the SC. The device functions by removing a portion of the SC without substan-

tially piercing the remaining layer. Some of these methods are claimed to offer advantages such as minimal patient discomfort, increased patient compliance, ease of use and less risk of infection when compared with their more "invasive" predecessors such as ablation and the use of hypodermic needles/cannulas to deliver medicaments across the skin.

## 4. CONCLUSION

The increasing complexity of transdermal drug products, the growing number of medications available in such dosage forms, and reports of potential safety concerns contribute to the need for clinicians to understand the principles of transdermal drug delivery, safe usage techniques, and proper patient counseling points. The future for transdermal drug delivery hinges on how it is perceived by companies involved in drug discovery. In the past it has been used as an alternative to oral delivery to overcome problems associated with that route. If transdermal delivery continues to be viewed in this context then future advances are likely to be incremental, as the drugs will not have been selected with a view to their suitability for transdermal delivery. The emphasis of the suitable includes potent drugs where individualization of the dose is desirable. Another factor that might be important for the future direction of transdermal delivery is the current surge in interest in nanotechnology. Application of developments in nanotechnology could lead to systems where a single device could monitor drug levels by sampling through the skin and thus provide controlled delivery of the drug. The attractiveness of the transdermal route for application of this technology is obvious because of the accessibility of the device for adjustment, control and removal.

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