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## Review Article

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# Physical Approaches to Penetration Enhancement

## Abstract

Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. For transdermal delivery of drugs, stratum corneum is the main barrier layer for permeation of drug. So to circumvent the stratum corneum and to increase the flux through skin membrane, different approaches of penetration enhancement are used. Many reviews had described regarding iontophoresis, electroporation, sonophoresis, phonophoresis but other physical method of penetration enhancement like magnetophoresis, laser radiation and photomechanical waves, radio frequency, thermophoresis, microneedle based devices, skin puncture and perforation, needleless injection, suction ablation, application of pressure, skin stretching, skin abrasion are not exploited for reviews. These physical methods are used extensively to enhance permeation of drugs through skin. The review presents mainly the routes of penetration through skin and the physical approach of penetration enhancement to optimise the transdermal delivery system.

**Keywords:** Transdermal; Penetration enhancement; Physical method; Skin.

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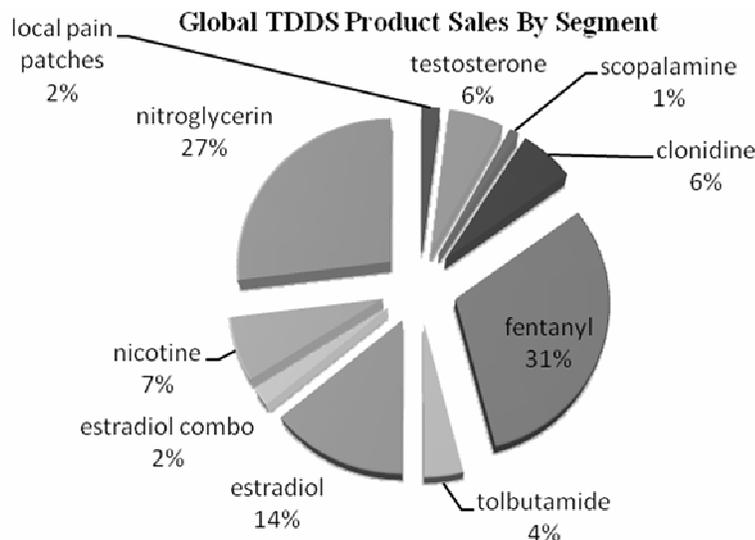
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## Introduction

Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl

for chronic pain, nicotine to aid smoking cessation, oestradiol (alone or in combination with levonorgestrel or norethisterone) for hormone replacement and testosterone for hypogonadism. Despite the small number of drugs currently delivered via this route, it is estimated that worldwide market revenues for transdermal products are US\$3 billion, shared between the USA, Europe and Japan at 56%,



**Figure 1:** Global transdermal drug delivery system (TDDS) product sales

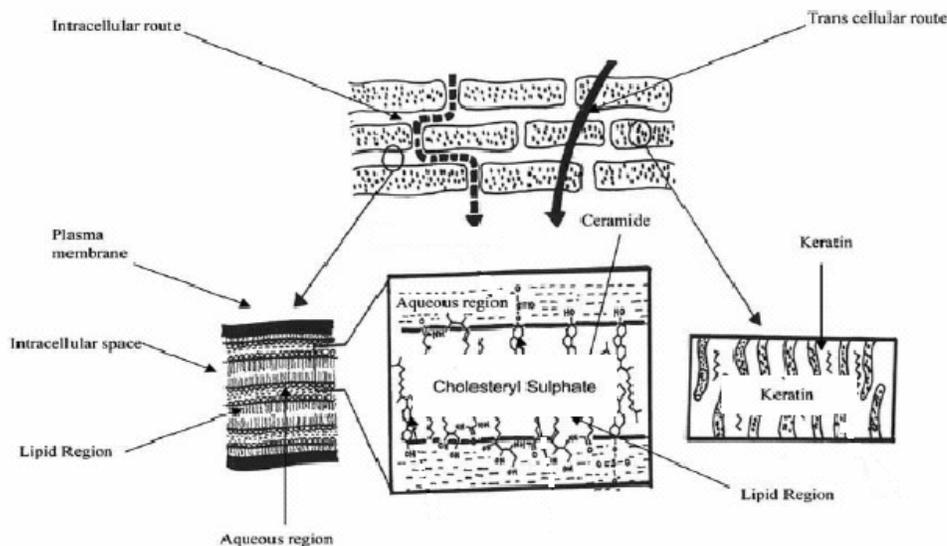
32% and 7%, respectively<sup>1</sup>. Around 40% of drug candidate under clinical evaluation are related to transdermal or dermal systems. In USA the most important clinical market out of 129 drug delivery candidate products under clinical evaluation, 51 % are transdermal or dermal systems. The worldwide transdermal patch market approaches £2 billion, yet is based on only ten drugs- scopolamine (hyoscine), nitroglycerine, tulobuterol, clonidine, estradiol (with and without norethisterone or levonorgestrel), testosterone, fentanyl and nicotine, with a lidocaine patch soon to be marketed<sup>2</sup>. New analysis published in 'U.S. Emerging Transdermal Drug Delivery Technologies Markets', reveals that this market generated revenues worth \$1.57 billion in 2002 and is likely to reach a staggering \$5.67 billion in 2009<sup>3</sup>. The global transdermal drug delivery system (TDDS) product sales given in segments is shown in Figure 1.

In order for transdermal drug delivery systems to be effective, the drug must obviously be able to penetrate the skin barrier and reach its target in required concentration. Significant effort has been devoted to developing strategies to overcome the impermeability of intact human skin. These strategies include passive and active penetration enhancement and technologies to

bypass the stratum corneum. This review describes the routes of penetration, how physical approach influence penetration and the physical methods that have been used to enhance penetration across human skin.

## Drug Delivery Routes Across Human Skin

The skin of an average body covers a surface area of approximately 2 square meters. Its thickness is approximately 2.97 mm; hair follicles are about 10-70 on every square centimeter and sweat glands 200-250 on every square centimeter. Skin is multilayered tissue consisting of epidermis, dermis and hypodermis. Outermost layer of epidermis is stratum corneum layer. These are compacted, flattened, dehydrated, and keratinized cells. Physiologically, they are inactive and are continuously shed with constant replacement of epidermis layer. They have the water content of only 20 % (other organs have up to 70%)<sup>4</sup>. Stratum corneum layer is the main barrier layer for permeation of drugs and hence permeation through this layer is the rate-limiting step. The diffusant has two potential entry routes to the blood vasculature, through the epidermis itself or diffusion through shunt pathway mainly hair follicles with their associated sebaceous glands



**Figure 2:** Structure of skin and mechanism of penetration into skin

and the sweat ducts. Therefore there are following two major routes of penetration<sup>5</sup> (i) Transcorneal penetration, which includes intracellular penetration and inter cellular penetration (Trans cellular) and (ii) Transappendegeal penetration. In intra cellular penetration drug molecule passes through the cells of the stratum corneum. It is generally seen in case of hydrophilic drugs. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water. Non-polar substances permeate through intercellular penetration. These molecules dissolve in and diffuse through the non- aqueous lipid matrix imbibed between the protein filaments<sup>6</sup>. In Transappendegeal Penetration (shunt pathway) the drug molecule may transverse through the hair follicles, the sebaceous pathway of the pilosebaceous apparatus or the aqueous pathway of the salty sweat glands. The transappendegeal pathway is considered to be of minor importance because of its relatively smaller area (less than 0.1% of total surface). However this route may be of some importance for large polar compounds<sup>7</sup>. The route through which permeation occurs is largely dependent on physico-chemical characteristics of penetrant most important being

the relative ability to partition into each skin phase<sup>8</sup>.

The transdermal permeation can be visualized as composite of a series in sequence as:

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.
2. Diffusion through stratum corneum and through viable epidermis.
3. Finally through the papillary dermis into the microcirculation.

The viable tissue layer and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid. Hence diffusion through the stratum corneum is the rate-limiting step. The stratum corneum acts like a passive diffusion medium. So for transdermal drug diffusion, a simple multilayer model can represent the various skin tissue layers (Figure 2).

## Need of Penetration Enhancement

Penetration enhancement is the most critical factor in transdermal systems, so as to improve flux. Flux (J) can be defined as the amount (M) of

material flowing through unit cross section (S) of a barrier in unit time (t). Flux can be given by:  $J=dM/S.dt$ <sup>9</sup>. Each phase of the membrane can be characterized in terms of diffusional resistance(R), which usually is the function of thickness (hs) of the phase, the permeant diffusion coefficient (Ds) within the phase, and the partition coefficient (Ks) between the membrane phase and external phase. It can be expressed as:

$$R=hs/Ds.Ks,$$

$$P= Ds.Ks/hs$$

where P is permeability coefficient. The permeability coefficient is related to membrane flux (J) as given  $J=APs(Cp-Cr)$ , where Cp-Cr is the difference in permeant concentration across the membrane and A is the area of application<sup>10</sup>.

## Approaches to Penetration Enhancement

Some ways for circumventing the stratum corneum barrier are as follows:

### A. Drug vehicle based:

1. Drug selection
2. Vesicles and particles
3. Prodrugs and ion pairs
4. Chemical potential of drug
5. Eutectic systems
6. Complexes

### B. Chemical penetration enhancers

1. Sulphoxides
2. Alcohols
3. Polyols
4. Alkanes
5. Fatty acids
6. Esters
7. Amines and amides
8. Terpenes
9. Surface active agents

### C. Physical method

1. Iontophoresis
2. Ultrasound (phonophoresis and sonophoresis)

3. Magnetophoresis
4. Electroporation
5. Laser radiation and photomechanical waves
6. Radio frequency
7. Thermophoresis
8. Microneedle based devices
9. Skin puncture and perforation
10. Needleless injection
11. Suction ablation
12. Application of pressure
13. Skin stretching
14. Skin abrasion

The current review deals with the physical approaches of penetration enhancement.

### 1. 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>11-15</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). The Phoresor™ device (Iomed Inc.) 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. Such improved systems include the Vyteris and E-TRANS iontophoretic devices. 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>16-18</sup>. Kalia Y.N. et al<sup>19</sup> carried out in vivo iontophoretic studies of zolmitriptan at multistep current profiles. Results suggested the feasibility of delivering therapeutic amounts of zolmitriptan at faster rate than those from existing dosage forms. In vivo iontophoresis of dexamethasone shows greatest penetration of drug in hip and shoulder joints where detectable drug level was measured in the cartilage<sup>20</sup>. Kari B.<sup>21</sup> carried out

iontophoresis of insulin, the result showed increasing the iontophoretic current from 0.2 to 0.4 mA produced 3 fold increase in serum insulin concentration. 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>22</sup>.

## 2. Ultrasound (phonophoresis and sonophoresis)

Ultrasound involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pre-treatment and is frequently referred to as sonophoresis or phonophoresis. 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>23</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>24</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 macromolecules of molecular weight up to 48 kDa being reported<sup>23,25,26</sup>. The SonoPrep® device (Sontra Medical Corporation) uses low-frequency ultrasound (55 kHz) for an average duration of 15 s to enhance skin permeability. This battery operated hand-held device consists of a control unit, ultrasonic horn with control panel, a disposable coupling medium cartridge and a return electrode. 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 et al.<sup>27</sup> skin treatment by ultrasound for an average time of 9 s resulted in the attainment of dermal anaesthesia within 5 min, compared with 60 min required for non-treated skin. The use of other small, lightweight novel ultrasound transducers to

enhance the in vitro skin transport of insulin has also been reported by a range of workers<sup>25,28-30</sup>. The first published report on sonophoresis dates back to 1950s. Fellingner and Schmidt<sup>31</sup> reported successful treatment of polyarthritis of the hand's digital joints using hydrocortisone ointment with sonophoresis. It was subsequently shown that hydrocortisone injection combined with ultrasound "massage" yielded better outcome compared to simple hydrocortisone injections for bursitis treatment<sup>32</sup>. In addition to joint diseases and bursitis, sonophoresis was tested for its ability to aid the penetration of a variety of drugs, mainly for localized conditions. Cameroy<sup>33</sup> reported success using carbocaine sonophoresis for closed Colle's fractures. In a series of publications Griffin et al. showed improved treatment of elbow epicondylitis, bicipital tendonitis, shoulder osteoarthritis, shoulder bursitis and knee osteoarthritis by combined application of hydrocortisone and ultrasound<sup>34-37</sup>. Improved dermal penetration using ultrasound was also reported for local anesthetics<sup>38-40</sup>.

## 3. 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>41</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% isopropylmyristate (IPM) was used as a chemical enhancer<sup>42</sup>. 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 treatment was found to last for 36 h, 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 h. 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.

#### 4. Electroporation

The use of electropermeabilization, as a method of enhancing diffusion across biological barriers, dates back as far as 100 years<sup>43</sup>. Electroporation involves the application of high-voltage pulses to induce skin perturbation. High voltages ( $\geq 100$  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>44</sup>. The increase in skin permeability is suggested to be caused by the generation of transient pores during electroporation<sup>45</sup>. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e. small molecules, proteins, peptides and oligonucleotides), including biopharmaceuticals with a molecular weight greater than 7 kDa, the current limit for iontophoresis<sup>46</sup>. Inovio Biomedical Corporation (San Diego, CA) has developed a prototype electroporation transdermal device, which has been tested with various compounds with a view to achieving gene delivery, improving drug delivery and aiding the application of cosmetics. Other transdermal devices based on electroporation have been proposed by various groups<sup>47-50</sup>; however, more clinical information on the safety and efficacy of the technique is required to assess the future commercial prospects. Although some sensation may be caused by direct excitation of nerves by the applied electric field, Electroporation is normally thought to be safe. Riviere et al. performed an in vivo evaluation of porcine skin, using histological scores and by scaling the degree of erythema, edema and recording the presence of petechia after electroporative applications<sup>51</sup>. The only skin alterations observed with electroporation were mild intraepidermal vacuolization and transient erythema.

In the Sharma et al. study<sup>52</sup>, 20 voltage pulses were used with lengths of 10, 20, 30, and 40 ms to enhance the in vitro delivery of terazosin hydrochloride through hairless rat skin. The results showed a fairly linear relationship ( $r^2=0.94$ ) between terazosin hydrochloride delivered and the pulse lengths. The Sharma et al. study also illustrated the importance of pulse number. With the same pulse length, an increase in the number of pulses resulted in a marked increase in the amount of terazosin delivered to the skin.

#### 5. 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 ( $\geq 300$  ns). 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 the SC via this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs<sup>53-55</sup>. The extent of barrier disruption by laser radiation is known to be controlled by parameters such as wavelength, pulse length, pulse energy, pulse number and pulse repetition rate<sup>53</sup>. A hand-held portable laser device has been developed by Norwood Abbey Ltd (Victoria, Australia). In a study involving human volunteers<sup>56</sup>, the Norwood Abbey laser device was found to reduce the onset of action of lidocaine to 3–5 min, whilst 60 min was required to attain a similar effect in the control group. The Norwood Abbey system has been approved by the US and Australian regulatory bodies for the administration of a topically applied anesthetic.

Pressure waves (PW), which can be generated by intense laser radiation, without incurring direct ablative effects on the skin have also been recently found to increase the permeability of the skin<sup>57-59</sup>. It is thought that PW form a continuous or hydrophilic pathway across the skin due to expansion of the lacunae domains in the SC. Important parameters affecting delivery such as

peak pressure, rise time and duration have been demonstrated<sup>60-61</sup>. The use of PW may also serve as a means of avoiding problems associated with direct laser radiation. Permeants that have been successfully delivered in vivo include insulin<sup>62</sup>, 40 kDa dextran and 20-nm latex particles.<sup>57</sup> A design concept for a transdermal drug delivery patch based on the use of PW has been proposed by Doukas and Kollias<sup>59</sup>.

## 6. Radio frequency

Radio-frequency involves the exposure of skin to high-frequency alternating current ( $\geq 100$  kHz), resulting in the formation of heat-induced microchannels 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 microchannels 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 microprojection array (100 microelectrodes/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 microchannels. Treatment duration takes less than a second, with a feedback mechanism incorporated within the electronic control providing a signal when the microchannels 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 h is 30 times the levels recorded for untreated skin after 24 h<sup>63</sup>. A similar enhancement in diclofenac skin permeation was also observed in the same study<sup>63</sup>. The device is reported not to cause any damage to skin, with the radio-frequency-induced microchannels remaining open for less than 24 h. The skin delivery of drugs such as testosterone and human growth hormone by this device is also currently in progress.

## 7. 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 et al.<sup>64</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<sup>65,66</sup> 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<sup>67</sup>. Vasodilation 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>68,69</sup>. The in vivo delivery of nitroglycerin<sup>68</sup>, testosterone, lidocaine, tetracaine<sup>70</sup> and fentanyl<sup>71</sup> 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<sup>72</sup>. 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<sup>73</sup>. Zars Inc., together with Johnson and Johnson, recently 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<sup>74</sup> 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 h). In heat-patch systems where patient exposure to heat is 24 h, such an upper limit may be necessary for regulatory compliance. In addition, the issue of drug stability may also need to be addressed when elevated temperatures are used. Thermo-perturbation 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<sup>75</sup>. These investigators developed a polydimethylsiloxane (PDMS) patch for non-intrusive 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<sup>76–78</sup> but has however not been exploited as a means of enhancing skin absorption.

### 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>79</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 µm 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>80–82</sup>. A recent commercialisation of microneedle technology is the Macroflux® microprojection array developed by ALZA Corporation. The macroflux patch can be used either in combination with a drug reservoir<sup>83</sup> or by dry coating the drug on the microprojection array<sup>84</sup>; the latter being better for intracutaneous immunization. The length of the microneedles has been estimated to be around 50–200 µm 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. Clinical evaluations report minimal associated discomfort and skin irritation and erythema ratings associated with such systems are reportedly low<sup>85</sup>. 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)<sup>86–88</sup>. Yuzhakov et al.<sup>82</sup> describe the production of an intracutaneous microneedle 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 microneedle systems for transdermal delivery and extraction which can be coupled with electrotransport methods are also described by Trautman et al.<sup>80</sup> and Allen et al.<sup>89</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.

### 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<sup>90</sup> described a method and apparatus for disruption of the epidermis in a reproducible manner. The apparatus consists of a plurality of microprotusions of a length insufficient for penetration beyond the epidermis. The microprotusions 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<sup>91</sup>, Kamen<sup>92</sup>, Jang<sup>93</sup> and Lin et al.<sup>94</sup>.

### 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<sup>®</sup>, Iject<sup>®</sup>, Biojector2000<sup>®</sup>, Medijector<sup>®</sup> and Intraject<sup>®</sup>) and powder (PMED<sup>™</sup> device, formerly known as powderject<sup>®</sup> injector) systems<sup>88</sup>. The latter has been reported to deliver successfully testosterone, lidocaine hydrochloride and macromolecules such as calcitonin and insulin<sup>95,96,97</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. In addition, the long-term effect of bombarding the skin with drug particles at high speed is not known, and thus, such systems may not be suitable for the regular administration of drugs. It may however be very useful in the administration of medicaments which do not require frequent dosing, e.g. vaccines.

### 11. Suction ablation

Formation of a suction blister involves the application of a vacuum<sup>98</sup> or negative pressure to remove the epidermis whilst leaving the basal membrane intact. The cellpatch<sup>®</sup> (Epiport Pain Relief, Sweden) is a commercially available product based on this mechanism<sup>99</sup>. 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<sup>100</sup>, 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 h), although this can be reduced to 15–70 min by warming the skin to 38°C<sup>100, 101</sup>. 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>102</sup>.

### 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>103</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 increased solubility of caffeine in the stratum corneum caused by the increase in pressure.

### 13. Skin stretching

These devices hold the skin under tension in either a unidirectional or a multidirectional manner<sup>104, 105</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) 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 ( $27.9 \pm 3.3$  mg cm<sup>-2</sup> h<sup>-1</sup>) than in the control group ( $9.8 \pm 0.8$  mg cm<sup>-2</sup> h<sup>-1</sup>), where the skin was not placed under tension after microneedle treatment. However, increased skin permeation in the absence of microneedle pretreatment 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.

#### 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<sup>55</sup> vaccines and biopharmaceuticals<sup>106-108</sup>. One current method is performed using a stream of aluminium oxide crystals and motor-driven fraises<sup>55, 109</sup> Sage and Bock<sup>110, 111</sup> 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 substantially 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.

## Conclusion

The search for the ideal skin penetration enhancer has been the focus of considerable research effort over a number of decades. Various penetration enhancement techniques is gaining wide popularity as it provides a non invasive and convenient means of systemic administration of drugs with poor bioavailability profile, short half life and with multiple dosing schedules.

Physical approaches penetration enhancement individually or in combination have been widely investigated in recent years. The strides made in the development of electronic, formulation and material technologies has made its clinical application possible. Much success has been reported in the literature concerning the delivery of small chemical compounds as well as oligonucleotides and peptides. Combinations of enhancement techniques provide easier and more accurate delivery of macromolecules and poorly water soluble compounds. The skin irritation associated with penetration enhancement techniques has been addressed by several studies and it is an issue preventing wide application of the technology. However, the combination of enhancement techniques may result in the need for less intense levels of current to reach therapeutically effective delivery amounts, and this will dramatically reduce the skin irritation problem.

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