Drug Delivery, 13:175–187, 2006

ISSN: 1071-7544 print / 1521-0464 online
DOI: 10.1080/10717540500455975

Taylor & Francis
Taylor & Francis Group

Dermal and Transdermal Drug Delivery Systems: Current and Future Prospects

Marc B. Brown
King's College London, Pharmaceutical Sciences Research Division, and MedPharm Ltd., London, United Kingdom

Gary P. Martin, Stuart A. Jones, and Franklin K. Akomeah
King's College London, Pharmaceutical Sciences Research Division, London, United Kingdom

The protective function of human skin imposes physicochemical limitations to the type of permeant that can traverse the barrier. For a drug to be delivered passively via the skin it needs to have adequate lipophilicity and also a molecular weight <500 Da. These requirements have limited the number of commercially available products based on transdermal or dermal delivery. Various strategies have emerged over recent years to optimize delivery and these can be categorized into passive and active methods. The passive approach entails the optimization of formulation or drug carrying vehicle to increase skin permeability. Passive methods, however do not greatly improve the permeation of drugs with molecular weights >500 Da. In contrast active methods that normally involve physical or mechanical methods of enhancing delivery have been shown to be generally superior. Improved delivery has been shown for drugs of differing lipophilicity and molecular weight including proteins, peptides, and oligonucletides using electrical methods (iontophoresis, electroporation), mechanical (abrasion, ablation, perforation), and other energy-related techniques such as ultrasound and needless injection. However, for these novel delivery methods to succeed and compete with those already on the market, the prime issues that require consideration include device design and safety, efficacy, ease of handling, and cost-effectiveness. This article provides a detailed review of the next generation of active delivery technologies.

Keywords Dermal, Drug Delivery, Permeability, Skin, Transdermal

Human skin, the integument of humans, has a multifunctional role. One of the most important functions is its ability to act as a protective barrier against the ingress of foreign material (chemicals, microbes) and the loss of excessive endogenous material such as water. The barrier function of the skin is thus reflected in its multilayered structure (Figure 1). Each layer is known to represent different levels of cellular or epidermal differentiation. The top or uppermost layer of the skin, known as the stratum corneum (SC), represents the end product of the differentiation process. The SC, therefore, is comprised of dead cells (corneocytes) interdispersed within a lipid rich matrix. It is the "brick and mortar" architecture and lipophilic nature of the SC, which primarily accounts for the barrier properties of the skin (Elias 1983). The SC also is known to exhibit selective permeability and allows only relatively lipophilic compounds to diffuse into the lower layers. As a result of the dead nature of the SC solute transport across this layer is primarily by passive diffusion (Scheuplein and Blank 1971) in accordance with Fick's Law (Flynn, Yalkowsky, and Roseman 1974), and no active transport processes have been identified.

Transdermal delivery is a term that should be restricted to the situation in which a solute diffuses through the various layers of the skin and into the systemic circulation for a therapeutic effect to be exerted, e.g., treatment of withdrawal symptoms using nicotine. Dermal (topical) delivery should only be used to define a targeting to the pathological sites within the skin, which involves ensuring minimal systemic absorption. Drug localization of this type is important in the treatment of dermatological conditions such as skin cancer, psoriasis, eczema, and microbial infections, where the seat of the disease is located in the skin. Examples of possible drug target sites in the skin are shown in Figure 1; however, for a number of dermal conditions, the actual site and local mechanisms of drug action still remain unclear.

ADVANTAGES AND DISADVANTAGES OF DERMAL/TRANSDERMAL DELIVERY

Like many alternative routes of delivery, the skin has both benefits and limitations when compared with more conventional methods such as oral drug delivery. These are detailed in Table 1.

Overcoming the Barrier

Over the past 25 years numerous studies have been performed to overcome some of the problems associated with skin delivery. The growth of technologies based on these studies, until recently, has been relatively slow. However, the techniques that

Received 18 May 2005; accepted 20 July 2005.
Address correspondence to M. B. Brown, MedPharm Ltd., Franklin Wilkins Bldg., 150 Stamford St., London SE1 9NH, UK. E-mail: marc.brown@kcl.ac.uk

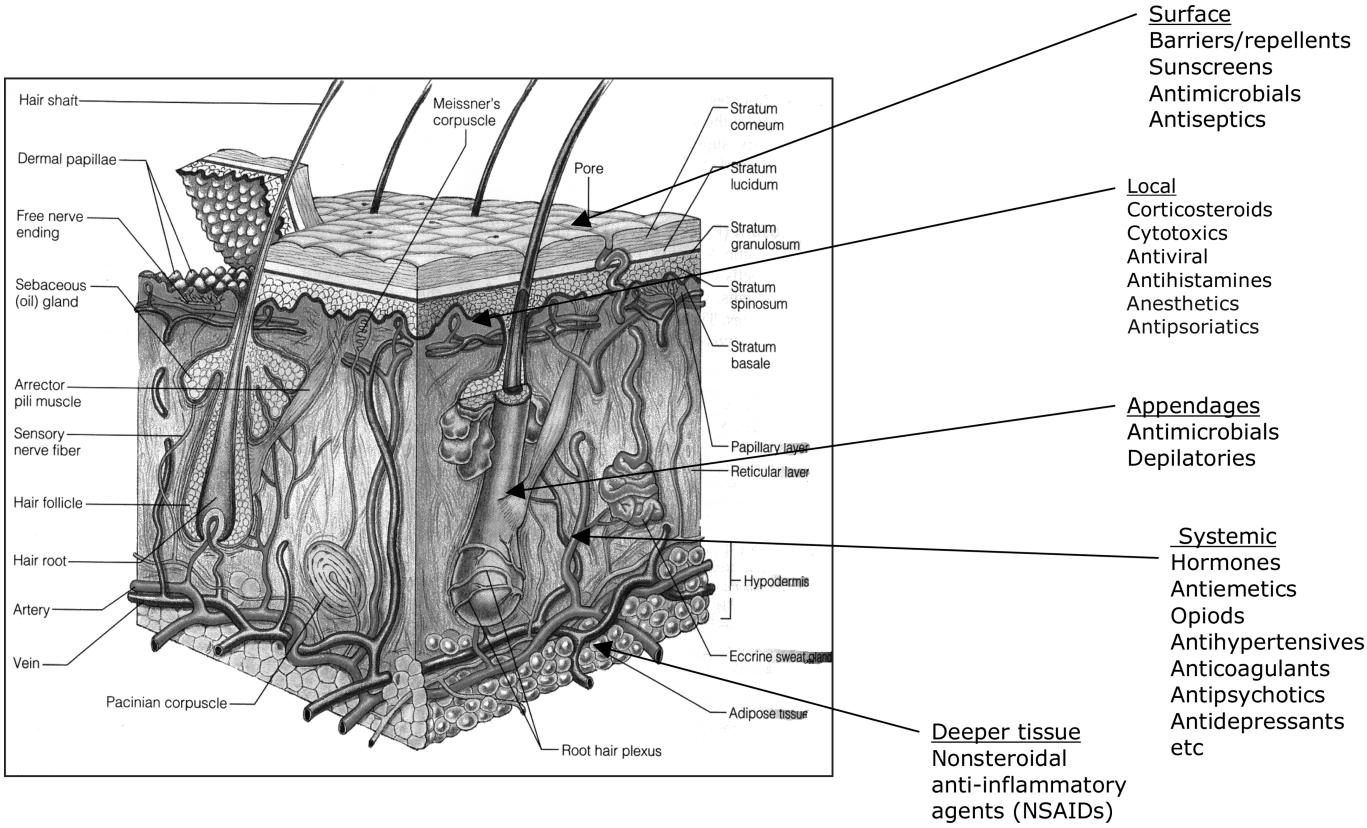

FIG. 1. Anatomy and physiology of the skin shows the potential targets or site of action for cosmetics and drugs (reprinted by permission of Pearson Education, Inc. from Marieb 1997).

have emerged over the years can be divided into passive or active methods.

Passive Methods

The conventional means of applying drugs to skin include vehicles such as ointments, creams, gels, and "passive" patch technology. More recently, such dosage forms have been developed and/or modified 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 (Williams and Barry 2004), supersaturated systems (Pellet et al. 2003), prodrugs or metabolic approach (Tsai et al. 1996; Elias et al 2003), liposomes, and other vesicles (Mezei 1993; Schreier and Bouwstra 1994; Cevc 1996, 2003; Godin and Touitou 2003). However, the amount of drug that can be delivered using these methods is still limited because the barrier properties of the skin are not fundamentally changed. For example, patch-type transdermal products on the market are employed to deliver only a small number of drugs (see Table 2), which tend to have the properties outlined in Table 1 Although such systems do not overcome the physicochemical restrictions already discussed, they offer an improvement in dose control, patient acceptance, and compliance compared with the semisolid formulations.

Problems encountered with the patches currently on the market include irritancy and poor adhesion. In addition, for cosmetic and patient comfort reasons there is a limit to the size of the patch, i.e., $\leq$40 cm sq ideally, which limits the amount of drug that can be delivered. This problem reportedly has been overcome with the use of Dot Matrix™ technology (Noven Pharmaceuticals) to achieve high concentrations of drug (or more than one drug) within adhesive patches of a realistic area for application, e.g., Vivelle–Dot® (Novartis AG). For a more detailed review on patches, the reader is referred to the following authors: Cleary (1991), Cleary (1993), Hadgraft (1996), Ghosh Pfister, and Yum (1997), and Venkatraman and Gale (1998).

Active Methods

The advent of biotechnology in the latter half of the 20th century has led to the generation of therapeutically-active, large molecular weight (>500 Da) polar and hydrophilic molecules, mostly peptides and proteins. This class of materials tends to be extensively degraded by enzymes in the gastrointestinal tract if given by oral delivery; hence, there is a need for alternative routes of administration and suitable drug delivery systems. Passive methods of skin delivery are incapable of enhancing permeation of such large solutes, which has led to studies involving alternative strategies referred to as active methods. These methods of

TABLE 1
Benefits and limitations associated with cutaneous delivery

Benefits	Limitations
• The avoidance of first pass metabolism and other variables associated with the GI tract such as pH, gastric emptying time (Cleary 1993; Henzel and Loomba 2003; Kormic et al. 2003). • Sustained and controlled delivery over a prolonged period of time (Varvel et al. 1989; Yang et al. 2004). • Reduction in side effects associated with systemic toxicity i.e., minimization of peaks and troughs in blood-drug concentration (Cramer and Saks 1994; Kormic et al. 2003). • Improved patient acceptance and compliance (Payne et al. 1998; Jarupanich et al. 2003; Archer et al. 2004). • Direct access to target or diseased site, e.g., treatment of skin disorders such as psoriasis, eczema, and fungal infections (Colin Long 2002). • Ease of dose termination in the event of any adverse reactions either systemic or local. • Convenient and painless administration (Cleary 1993; Henzel and Loomba 2003). • Ease of use may reduce overall health care treatment costs (Whittington and Faulds 1995; Frei et al. 2003). • Provides an alternative in circumstances where oral dosing is not possible (in unconscious or nauseated patients) (Kormic et al. 2003).	• A molecular weight less than 500 Da is essential to ensure ease of diffusion across the SC (Bos and Meinardi 2000), since solute diffusivity is inversely related to its size. • Sufficient aqueous and lipid solubility, a Log P (octanol/water) between 1–3 is required for the permeant to successfully traverse the SC and its underlying aqueous layers for systemic delivery to occur (Yano et al. 1986; Lee et al. 1994). • Intra-and intervariability associated with the permeability of intact and diseased human skin. This implies that there will be fast, slow and normal skin absorption profiles resulting in varying biological responses (Southwell, and Wood Ford 1994, 1984; Larsen et al. 2003). The barrier nature of intact SC ensures, that this route is only applicable for very potent drugs that require only minute concentrations (e.g. 10–30 ng/ml for nicotine) in the blood for a therapeutic effect (Cleary 1993). • Pre systemic metabolism; the presence of enzymes in the skin such as peptidases and esterases might metabolize the drug into a form that is therapeutically inactive, thereby reducing the efficacy of the drug (Steinsträsser and Merkle 1995). • Skin irritation and sensitization; referred to as the "Achilles heel" of dermal and transdermal delivery. The skin as an immunological barrier may be provoked by exposure to certain stimuli, this may include drugs, excipients, or components of delivery devices resulting in erythema, oedema, etc. (Hogan and Maibach 1990; Carmichael 1994; Toole et al. 2002; Murphy and Carmichael 2000).

permeation enhancement involve the use of external energy to act as a driving force and/or act to reduce the barrier nature of SC. Such approaches promise to lead to advances in the efficiency of transdermal delivery.

Recent progress in these technologies has occurred as a result of advances in precision engineering (bioengineering), computing, chemical engineering, and material sciences, which have all helped the creation of miniature powerful devices that can generate the required clinical response. The various classes of active systems under development are shown in Table 3.

ENHANCING SKIN PERMEABILITY

Electrically Assisted Delivery

The use of electropermeabilization, as a method of enhancing diffusion across biological barriers, dates back as far as 100 years (Helmstädter 2001). Electrical methods of enhancing skin methods include iontophoresis and electroporation

Iontophoresis

This method involves the application of a low level electric current either directly to the skin or indirectly via the dosage form to enhance permeation of the topically applied therapeutic agent (Wang et al. 1993; Turner, Kalia and Guy et al. 1997; Banga 1998; Guy et al. 2000). 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), electro osmosis (for uncharged solutes), and electropertubation (for both charged and uncharged). Figure 2 shows a simple iontophoretic set up illustrating the diffusion of charged or uncharged solute during ionotophoresis.

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 (Banga, Bose and Ghosh 1999). Extensive literature exists on the many types of drugs investigated using iontophoretic delivery and the reader is referred to in the following extensive reviews: Tyle (1986), Banga (1998, 1999), Kalia et al. (2004). The launch of commercialized systems of this technology has either occurred or is currently under investigation by various companies (Table 4).

The Phoresor™ device (Iomed Inc.) was the first iontophoretic system to be approved by the Food and Drug Administration (FDA) in the late 1970s as a physical medicine

TABLE 2
Examples of some commercially available transdermal "passive" patches (modified from Panchangula 1997)

Drug/manufacturer	Trade name	System type	Therapeutic use
Scopolamine			
ALZA/Ciba	Transderm® Scop	Reservoir	Alleviate motion sickness
Nitroglycerin			
Novartis	Transderm®-Nitro	Reservoir	Treatment/prevention of angina
Schering Plough	Nitro-Dur®	Matrix	
Schwarz	Deponite	Sandwich	
Clonidine			
Boehringer Ingelheim	Catapres-TTS	Reservoir	Treatment of hypertension
Estradiol			
ALZA	Estraderm®	Reservoir	Relief of postmenopausal symptoms
Novartis	Vivelle-Dot	Matrix	
Testosterone			
ALZA	Testoderm-TTS®	Matrix	Male hypogonadism
Nicotine			
ALZA	Nicoderm®	Reservoir	Smoking cessation
Lidocaine			
Endo	Lidoderm®	Matrix	Postherpetic neuralgia
Fentanyl			
Janssens- Cilag	Duragesic®	Reservoir	Pain management
ALZA	TTS—Fentanyl		
Oxybutynin			
Watson	Oxytrol	Matrix	Overactive bladder

therapeutic device. Iontophoretic systems are regulatory-approved mainly for administering drugs into the body for medical purposes and specialized uses such as diagnosis of medical conditions (e.g., cystic fibrosis) and glucose monitoring. 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.

The Vyteris lidocaine delivery system for local dermal anesthesia is a system that reportedly eliminates the pain and other inconveniences associated with conventional methods of administering anesthetics such as the slow onset of action. The Vyteris

TABLE 3
Classification of active methods of enhancing skin permeation

Active method	Type
Electrical methods	Iontophoresis
	Electroporation
Mechanical methods	Microneedle/puncture/perforation
	Abrasion
	Needless injection
	Suction
	Stretching
Miscellaneous	
	Ultrasound
	Magnetophoresis
	Radio frequency
	Laser and photomechanical waves
	Temperature

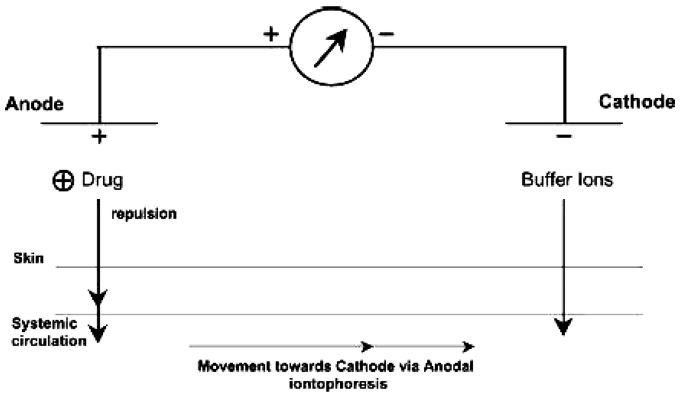

FIG. 2. Basic iontophoretic set-up illustrates direction of solute movement with respect to electrode type. (Reprinted by permission of Elsevier Ltd from Wang et al. 2005).

TABLE 4
Examples of iontophoretic and other electrotherapeutic systems approved for medical use or under development

Company	System/Device name	Status
Iomed Inc. (Salt Lake City, UT, USA)	Phoresor®	FDA approved for local dermal anesthesia
Vyteris Inc. (Fair Lawn, NJ, USA)	Lidosite®	FDA approved for localized pain treatment
ALZA Corporation	E-TRANS®	NDA submitted
Cygnus Inc. (Redwood, CA, USA)	Glucowatch®	FDA approved for glucose monitoring in diabetics
Birch Point Medical Inc. (St Paul, MN, USA)	Iontopatch®	FDA approved for physical medicine and rehabilitation
Novosis AG (Miesbach, Germany)	EES (electrode scanning system)	Under development
BioPhoretic Systems (Framingham, MA, USA)	Acyclovir Direct®	Phase 3 clinical trials
Aciont Inc (Salt lake City, UT, USA)	Accuresis™	Under development
General Medical Company (Los Angeles, CA, USA)	Lectro Patch®	Under development
BioElectronics Corporation (Frederick, MD, USA)	ActiPatch™	FDA approved for wound healing, pain, and swelling

delivery system comprises a patch (two preloaded reservoirs) and a dose controller. The main reservoir is composed of a flexible adhesive pad that is prefilled with the local anesthetic, lidocaine (and a vasoconstrictor, epinephrine, to maintain therapeutic concentrations of the active agent at the target site), while the other reservoir contains saline to complete the circuit. The electronic dose controller is small, reusable, battery-powered, easily wearable, and is designed to deliver multiple applications. A preprogrammed microcomputer forms an integral part of the system, which controls the electrical charge. The patch and controller are connected through an interface. This delivery system may be used for other therapeutic agents; however, the New Drug Application (NDA) submitted to the FDA is solely for delivery of lidocaine. Delivery of other therapeutic agents with this system is currently under investigation (Vyteris, no date).

E-TRANS® technology developed by the ALZA Corporation also works on the principle of electrotransport to deliver drugs. It is a transdermal patch applied via a self-adhesive backing to the patient's upper outer arm or upper chest. This operates in a similar manner to the Vyteris system. The NDA application is based on the ability of this system to enhance the delivery of fentanyl into the systemic circulation via the skin (Gupta et al. 1998, 1999). Fentanyl is an opioid analgesic used in the treatment of acute pain and the E-TRANS fentanyl system reportedly allows patient-controlled delivery of this pain medication and represents an improvement in pain management compared with intravenous injections and oral dosing methods (Alza 2005).

The reported limitations of iontophoretic systems include the amount of electric current that can be used in humans (regulatory limits currently are set at 0.5 mA cm^{-2}) 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 >7000 Da (Kanikkannan 2002).

Electroporation

Electroporation involves the application of high voltage pulses to induce skin perturbation. It has been proposed that transient pores are generated during electroporation, which may account for the increase in skin permeability (Weaver, Vaughan, and Chizmadzhev 1999). 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 (Banga et al. 1999). 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 that 7kDA, the current limit for iontophoresis (Denet, Vanbever, and Préat 2004).

The enhanced delivery of naked DNA to the skin also has been achieved *in vivo* using hairless mice; a 100- fold stimulation of gene expression was observed compared with that obtained by intradermal injection (Zhang et al. 2002). The ability of electroporation to improve the therapeutic efficacy of an already existing transdermal drug, fentanyl also has been demonstrated (Vanbever et al. 1998; Southam, Bernstein, and Noorduin 2001). The latter study is based on the E-TRANS® patch system that employs electrotransport mechanisms to enhance delivery. Previous work also has 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 (Bommannan et al. 1994; Chang et al. 2000; Badkar and Banga 2002).

Genetronics Inc. (San Diego, CA, USA) has developed a prototype electroporation transdermal device, that has been tested with various compounds with a view to achieving gene delivery, improving drug delivery, and aiding the application of cosmetics (Genetronics 2005). Other transdermal devices based on electroporation have been proposed by various groups (Pliquett, Vaughan, and Weaver 1999; Zhang, Hofmann, and Rabussay 2001; Sugibayashi, Kubo, and Mori 2002); however, more clinical information on the safety and efficacy of the technique is required to assess the future commercial prospects.

Mechanical Methods

These methods entail the use of a physical or mechanical means to breach or bypass the SC barrier.

Microneedle-Based Devices

One of the first patents ever filed for a drug delivery device for percutaneous administration of drugs was based on this method (Gerstel and Place 1976). The device as described in the patent consists of a drug reservoir and a plurality of projections (microneedles of length 50–100 μm) extending from the reservoir (Figure 3), that will penetrate the stratum corneum and epidermis to deliver the drug. 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. The reservoir may contain drug, solution of drug, and gel or solid particulates. The inventor claims the ability to overcome the barrier properties of the SC via the use of projections and also deliver the active agent at a controlled rate either for local or systemic effect.

As a result of the current advancement in microfabrication technology in the past 10 years, cost-effective means of developing devices in this area are now becoming increasingly common (Trautman et al. 2000, 2001; Yuzakhov et al. 2001). A recent commercialization of microneedle technology is the Macroflux® microprojection array developed by ALZA Corporation.

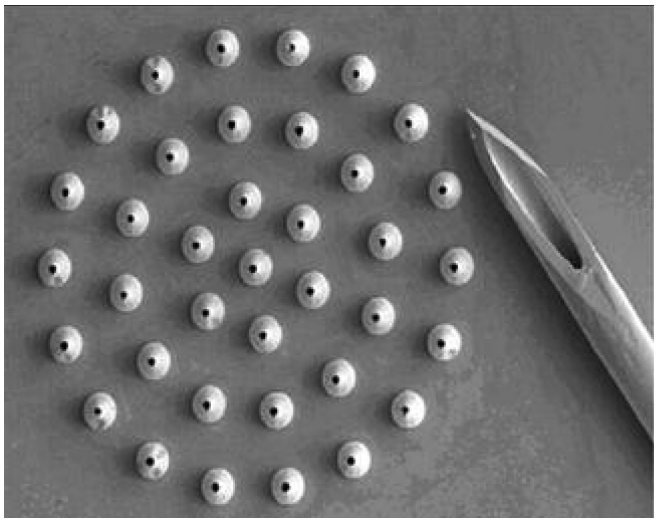

FIG. 3. A microneedle array system (needles ~150 μm in length and fabricated from silicon) (reproduced with permission of Georgia Institute of Technology research news publication).

The Macroflux® patch can either be used in combination with a drug reservoir (Lin et al. 2001a) or by dry coating the drug on the microprojection array (Matriano et al. 2002); the latter being better for intracutaneous immunization. The lengths of the microneedles are estimated at 50–200 μm and are not believed to reach the nerve endings in the dermoepidermal 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 (Kaushik et al. 2001). This technology serves as an important and exciting advance in transdermal technology due to the ability of the technique to deliver medicaments with extremes of physicochemical properties (including vaccines, small molecular weight drugs, and large hydrophilic biopharmaceuticals) (Prausnitz 2004; Martanto et al. 2004). For example, in mice, a microneedle based system enabled topical gene transfer resulting in reporter gene activity of up to 2880-fold greater than topical controls (Mikszta et al. 2002). The Macroflux® device also has been coupled with electrotransport systems (E-TRANS®), that can provide controlled drug delivery (Alza 2005) and has been found to be very efficient in *in vivo* delivery of an antisense oligodeoxynucleotide (Lin et al. 2001a).

Yuzhakov et al. (2001) describes the production of an intracutaneous microneedle array and provides an account of its use (microfabrication technology). The device is made up of a reservoir from which microneedles protrude. Various embodiments of this invention include (i) a patch that can perform intracutaneous drug delivery, (ii) an iontophoretically or microneedle enhanced transdermal drug delivery system to achieve a high rate of drug delivery and sampling of body fluids, and (iii) 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 that can be coupled with electrotransport methods also are described by Trautman *et al.* (2000), Down et al. (2001), Allen et al. (2002). These mechanical microdevices that interface with electronics to achieve a programmed or controlled drug release are referred to as microelectromechanical systems (MEMS) devices.

Skin Abrasion

Abrasion techniques involve 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 used by dermatologists for superficial skin resurfacing (e.g., microdermabrasion) in the treatment of acne, scars, hyperpigmentaion, and other skin blemishes. The delivery potential of skin abrasion techniques are 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 (Lee et al. 2003) vaccines, and biopharmaceuticals (Mikszta et al. 2001, 2003).

Mikszta et al. (2001) described an applicator comprising an abrasive pad coated with the substance to be delivered or held in a reservoir attached to the patch. A patent filed by Sage and Bock (2001) described a method of pretreating the skin prior to transdermal drug delivery or sampling via a device that consists of a plurality of blunt plastic microneedles that do not penetrate the SC. The device functions by removing a portion of the SC without substantially piecing the remaining layer. Miniaturization of such devices has yet to be seen, and the issues of safety and patient discomfort still remain.

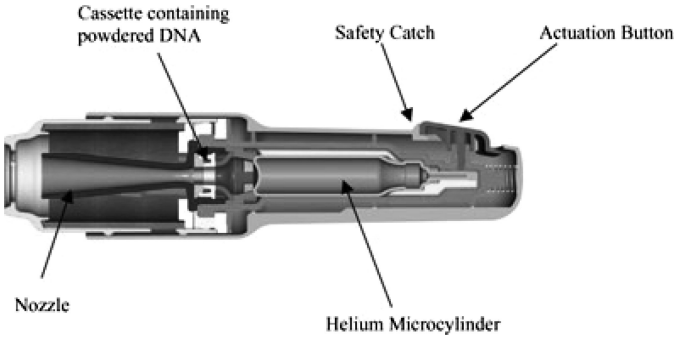

FIG. 4. DNA-Particle Mediated Epidermal Delivery (PMED) device (reprinted by permission of PowderMed Ltd.).

Skin Puncture and Perforation

These devices include the use of needle-like structures or blades, that disrupt the skin barrier by creating holes and cuts as a result of a defined movement when in contact with the skin and are similar to the microneedle devices produced by microfabrication technology. Godshall and Anderson (1999) 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) or active (iontophoresis, electroporation), delivery methods can then be used.

A skin perforating device comprising alternately disposed needle disks and spacers has been claimed to enhance transdermal permeation (Jang 1997). Rotational movement of such a unit reportedly creates minute uniform cuts in the skin. A skin perforation technique also has been reported to successfully facilitate the delivery of DNA via the skin (Ciernik and Krayenbuhl 1996). Descriptions of other devices based on a similar mode of action have been described by Godshall (1996), Kamen (1998), Jang (1998) and Lin, Theewies, and Cormier (2001b).

A drug delivery device based on the use of blunt needles has been developed by Imprint Pharmaceuticals. The device referred to as the Imprinter™, is mounted in a handheld device, and precharged with an actuator that allows acceleration from 0 to 60 mph in 1/20,000 of a second (Crocker, Maynard, and Little 2001). The inventors claim that such rapid application means that the pain (discomfort) and bruising associated with injection are absent. The device reportedly is able to deliver low to high viscosity formulations and also solid particulates to different depths of the skin, nail, sole, and scalp.

Needless Injection

Needleless injection is reported to involve a pain-free method of administering drugs to the skin. Over the years there have been numerous examples of both liquid (Ped-O-Jet®, Iject®, Biojector2000®, Medi-jector®, Dermajet®, Preci-jet®, Injex™, and Intraject®) and powder (PMED™ device formerly known as powderject® injector, see Figure 4) systems. The latter device has been reported to deliver successfully testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin (Muddle et al. 1997; Longbridge et al. 1998; Burkoth et al. 1999). This method of administering drugs circumvents issues of the safety, fear, and pain associated with hypodermic needles. Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin using a suitable energy source.

The PMED™ device consists of a helium gas cylinder, drug powder sealed in a cassette made of plastic membrane, a specially designed convergent-divergent supersonic nozzle, and a silencer to reduce the noise associated with rupturing of the membrane when particles are fired. The mechanism of action involves forcing compressed gas (helium) through the nozzle, with the resultant drug particles entrained within the jet flow reportedly travelling at sufficient velocity for skin penetration. Its use is restricted to solid particulates, which although may be an advantage in maintaining chemical stability of the drug, means that drug particulates have to be engineered to certain specifications for optimized delivery. As a result, the effect of particle size, shape, density, and morphology, helium cylinder pressure, nozzle geometry, and configuration on the dermal delivery properties of the device all have to be specified (Longbridge et al. 1998; Burkoth et al. 1999).

Problems facing needless injection systems include the high developmental cost of both the device and dosage form and the inability, unlike some of the other techniques described, to program or control drug delivery to compensate for intersubject differences in skin permeability. In addition, the long-term effect of bombarding the skin with drug particles at high speed is not known. Thus, such systems may not be suitable for the regular administration of drugs. It may, however, be very useful in the administration of medicaments that do not require frequent dosing, e.g., vaccines. This is the logic behind the single use disposable PMED device unlike the former multiple use powderject device. With regard to the PMED device, the therapeutic agent (vaccine) is normally precipitated onto microscopic gold particles (mean particle diameter 1–3 μ) that act as suitable carriers

due to inertness and appropriate density needed to deliver the vaccine to the antigen-presenting cells located in the epidermis.

The future of such a device remains unclear, as indicated by some of the recent failures and takeovers of companies working in this area. Norwood Abbey Ltd (Australia) claims to have developed portable needle-free injector systems, that are cheaper to manufacture and also overcome some of the limitations described above. The Norwood needle-free injector system operates by an extremely fast and powerful contractile fiber-activated pump that fires the drug at a velocity that enables skin penetration (Norwood Abbey 2005).

Suction Ablation

Formation of a suction blister involves the application of a vacuum or negative pressure to remove the epidermis, while leaving the basal membrane intact (Svedmann 1995). This method of removing the skin barrier also is referred to as skin erosion. Since dermal invasion is avoided, such discomfort as pain and bleeding reportedly are not associated with this technique. The cellpatch® (Epiport Pain Relief, Sweden) is a commercially available product based on this mechanism (Svedmann 1995). It comprises a suction cup, epidermatome (to form a blister) and device (contains morphine solution) to be attached to the skin. In an *in vivo* study by Svedman et al. (1996), the delivery of dextran of various molecular weights (3–70 kDa) and morphine was achieved with this method. The plasma levels of morphine observed were reported to be comparable to that achieved via intravenous infusion. In another study (Svedmann, Lunin, and Svedman 1991), the same authors demonstrated *in vivo* that the antidiuretic peptide, vasopressin, when delivered using the device, achieved comparable plasma bioavailability (∼100%) to that of direct intravenous infusion. The removal of the epidermis by suction was found to cause hyperemia in the underlying dermis, which was detected via laser Doppler flowmetry and confirmed via microscopy. The authors stated that the observed hyperaemia may have further contributed to the enhanced permeation observed. The potential of this method as a diagnostic tool has also been previously reported (Svedman and Suedman 1998; Fugiwara and Matsumoto 1998; Saito, Kajiwara, and Saito 1999).

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 (Svedmann et al. 1996, 1998). In addition, while there is no risk of systemic infection compared with intravenous catheters, the potential for epidermal infections associated with the suction method cannot be ignored, even though the effects might be less serious (Down and Harvey 2003).

Application of Pressure

The application of modest pressures (i.e., 25 kPa) has been shown to provide a potentially noninvasive and simple method of enhancing skin permeability. The enhancing effect of such a mechanism on caffeine permeation has been reported by Treffel et al. (1993). These researchers 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. The authors further stated that while the latter does not necessarily enhance flux, the solubility of caffeine in the SC might be increased under pressure, since certain physicochemical properties of solutes such as solubility depend on pressure.

Skin Stretching

Cormier et al. (2001) described an expandable skin stretching device that holds the skin under tension in either a unidirectional or multidirectional manner. The authors claim that a tension of ∼0.01 to 10 mP results in the reversible formation of micropathways that facilitates the diffusion of drugs across the SC until the applied force is removed and the skin is allowed to return to its original configuration. The efficiency of the stretching process was demonstrated by monitoring the delivery of a decapeptide (1 kDa) across the skin of hairless guinea pigs using a microprotrusion array. The results of the study showed that the bidirectional stretching of skin after microprotrusion piercing allowed the pathways to stay open (i.e. delayed closure). This facilitated drug permeation to a greater extent ($27.9 \pm 3.3\ \mu g/cm^2$ h) than in the control group ($9.8 \pm 0.8\ \mu g/cm^2$ h), where the skin was not placed under tension after microneedle treatment. The use of expandable devices to enhance microneedle piercing also has been reported by Neukermans et al. (2001). These authors recommended the use of the stretching method with delivery devices based on electrotransport, pressure, osmotic, and passive mechanisms. However, increased skin permeation in the absence of microneedle pretreatment was found not to occur. Thus, the use of such a stretching technique alone to enhance drug permeability across the skin requires further investigation.

MISCELLANEOUS METHODS

Ultrasound (Sonophoresis and Phonophoresis)

Ultrasound involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or via pretreatment, and is frequently referred to as sonophoresis or phonophoresis. Ultrasound parameters such as treatment duration, intensity and frequency are all known to affect percutaneous absorption, with frequency being the most important (Mitragotri 2004). 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 (Mitragotri, Blankschtein, and Langer 1995, 1996). 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 (Mitragotri et al. 1996). The reversibility of the

technique, demonstrated in living human skin, promotes insulin delivery and water transport through skin (Mitragotri et al. 1995, 1996; Singer et al. 1998).

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 handheld 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 anesthetic from EMLA cream recently was reported (Katz et al. 2004). In the study by Katz et al. (2004), skin treatment by ultrasound for an average time of 9 s resulted in the attainment of dermal anesthesia within 5 min, which was comparable to the 60 min required in for nontreated skin. Further clinical studies on the device involving insulin are reported to be ongoing, following successful *in vivo* delivery of insulin using animal models (Tachibana 1992; Mitragotri et al. 1995; Boucaud et al. 2002). The use of other small, lightweight novel ultrasound transducers to enhance *in vitro* skin transport of insulin also has been reported by Smith et al. (2003).

Laser Radiation and Photomechanical Waves

Laser treatment frequently is used for dermatological conditions such as acne and to confer "facial rejuvenation" where the laser radiation destroys the target cells over a short frame of time (~300 ns). Direct and controlled exposure of a laser to the skin results in the ablation of the SC without significantly damaging the underlying epidermis. Removal of the SC via this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs (Jacques et al. 1988; Lee et al. 2001a, 2003). Parameters such wavelength, pulse length, pulse energy, pulse number, and pulse repetition rate are known to affect the extent or degree of barrier disruption (Jacques et al. 1988). Laser treatment in transdermal therapy reportedly offers advantages such as controlled removal of tissue, short treatment time, a painless method of delivery, and mild adverse effects.

Lasers have been used in clinical therapies for decades; therefore, their effects on biological membranes are well documented. As such a handheld portable laser device has been developed by Norwood Abbey Ltd. (Victoria, Australia). In a study involving human volunteers (Baron et al. 2003), the Norwood Abbey laser device reduced the onset of action of lidocaine to 3–5 min, while 60 min were required to attain a similar effect in the control group. The Norwood Abbey system has been approved by the United States and Australian regulatory bodies for the administration of a topically applied anesthetic.

Pressure waves (PWs), generated by intense laser radiation without incurring direct ablative effects on the skin, also have been found to increase the permeability of the skin (Lee et al. 1998,1999; Doukas and Kollias 2004). The use of PWs also may serve to avoid problems associated with direct laser radiation. It is thought that PWs form a continuous or hydrophilic pathway across the skin due to expansion of the lacunae domains in the SC. A synergistic effect between PW and the application of sodium lauryl sulphate solution also has been reported (Lee et al. 2001b). Important parameters affecting delivery such as peak pressure, rise time, and duration has been demonstrated (Mulholland et al. 1999; Lee et al. 2001b). Permeants that have been successfully delivered *in vivo* include insulin (Lee et al. 2001c), 40 kDa dextran, and 20 nm latex particles (Lee et al. 1998). A design concept for a transdermal drug delivery patch based on PWs has been proposed by Doukas and Kollias (2004).

Radiofrequency

Radiofrequency thermal ablation has been used extremely for electrosurgery and ablation of malignant tissues. This involves exposure of skin to high frequency alternating current (~100 kHz) and results in the formation of heat-induced microchannels in the membrane similar to when laser radiation is employed. The practicality of using this as a skin delivery method has been investigated by Transpharma Ltd. that have produced a Viaderm™ device. It consists of a hand held electronic device, microprojection array (contains ~100 microelectrodes/cm^2), and a drug patch. The microelectrode array is attached to the electronic device and then placed onto the skin to allow exposure to the radiofrequency. This facilitates the formation of the microchannels, after which the drug patch is placed on the treated area. Treatment lasts less than a second, and has a feedback mechanism incorporated within the electronic control that provides a signal when the microchannels have been created to ensure reproducibility of action. The drug delivery rate is controlled by the number and depth of microchannels formed, which depends on the properties of the microelectrodes in contact with the skin during treatment.

Experiments in rats have shown the device to enhance the delivery of granisetron HCL, with blood plasma levels recorded after 12 hr rising to 30 times higher levels than that recorded for untreated skin after 24 hr (Sintov et al. 2003). A similar enhancement in diclofenac skin permeation also was observed in the same study (Sintov et al. 2003). The device is reported not to cause any damage to skin with the radiofrequency-induced microchannels remaining open for less than 24 h. The skin delivery of drugs such as testosterone and human growth hormone by this device also is in progress (TransPharma Medical 2005).

Magnetophoresis

In this method a magnetic field is applied and acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field also might induce structural alterations that could contribute to an increase in permeability. *In vitro* studies by Murthy (1999) 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 that was comparable to that attained when 4% isopropyl myristate (IPM) was used as a chemical enhancer (Murthy and Hiremath 2001). In the same article, 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 was higher but not significantly different from that observed with the patch containing 4% IPM. The elimination of TS, after application of either patch-containing drug also was reported to be significantly prolonged when compared with oral administration (Murthy and Hiremath 2001). The fact that this technique can only be used with diamagnetic materials serves as a limiting factor in its applicability and probably explains the relative lack of interest in the method.

Temperature ("Thermophoresis")

The effect of elevated temperature (nonphysiological) on percutaneous absorption was initially reported by Blank, Scheuplein, and Macfarlane (1967). Recently, there has been a surge in interest in using thermoregulation to improve the delivery profile of topical medicaments. Skin surface temperature is normally maintained at 32°C by the homeostatic functions of the human body. Previous *in vitro* studies (Clarys et al. 1998; Akomeah et al. 2004) have demonstrated a 2–3-fold increase in flux for every 7–8°C rise in skin surface temperature. The heat-enhanced effect was attributed to both an increase in drug diffusion in the dosage form (vehicle) and skin, with the latter attributed to an increase in skin lipid fluidity (Ogiso et al. 1998). Under *in vivo* conditions, the increase in blood supply to the surface of the skin as a result of increased temperature also plays an important role in enhancing the transdermal delivery of a topically applied compound (Klemsdal, Gjesdal, and Bredesen 1992; Hull 2002). The *in vivo* delivery of nitroglycerin (Klemsdal et al. 1992), testosterone, lidocaine, tetracaine (Shomaker, Zhang, and Ashburn 2001) and fentanyl (Ashburn et al. 2003) 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 over 500 Da has not been reported.

In addition, Stanley, Hull, and Rigby (2001), described a controlled heat-aided drug delivery (CHADD) patch, that generates a controlled periodic increase in skin surface temperature, to improve dermal administration of lidocaine. The CHADD patch can be attached to a transdermal patch to facilitate delivery of the medicament. Heat is generated chemically in the powder-filled pouch by an oxidative process, that is controlled by the availability of oxygen to the chemical components in the patch. The patch contains a series of small holes at the top surface, which regulates the flow of oxygen into the patch, resulting in the generation of a controlled heat mechanism that can last for up to 24 h, depending on the size of the holes. The CHADD technology (Zars Inc., Salt Lake City, UT, USA) was used in the delivery of a local anesthetic system (lidocaine and tetracaine) from a patch (S-Caine®) and found to enhance the depth and duration of the anesthetic action in human volunteers when the results in active and placebo groups were compared (Shomaker et al. 2000). 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 contains fentanyl for treatment of acute pain) (Zars 2005).

Kuleza and Dvoretzky (2001) 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 drug and cosmetic treatments. All the studies described above 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 h, such an upper limit may be necessary for regulatory compliance. In addition, drug stability may need to be addressed when elevated temperatures are used.

Thermopertubation refers to the use of extreme temperatures to reduce the skin barrier. Such perturbation has been reported in response to using high temperatures over a short duration (30 ms), with little or no discomfort, using a novel patch system (Paranjabe et al. 2003). These investigators developed a polydimethylsiloxane (PDMS) patch for nonintrusive transdermal glucose sensing via thermal microablation. Ablation was achieved by microheaters incorporated within the patch. The heat pulse is regulated by a resistive heater, that ensures 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) that ablates the SC via a similar manner as the previously described PDMS patch. The exposure of skin to low (freezing) temperatures has been reported to decrease its barrier function (Kasting and Bowman 1990; Yazdanian 1994; Babu et al. 2003) but has not been exploited as a means of enhancing skin absorption.

THE FUTURE

The market for transdermal devices has been estimated at U.S. $2 billion (Barry 2001) and this figure represents 10% of the overall U.S. $28 billion drug delivery market. Such figures are surprising when we consider that the first transdermal patch was granted a licence by the FDA in 1979, and only an additional 9 drugs have been approved since that time. This short list of "deliverables" highlights the physicochemical restrictions imposed on skin delivery.

Transdermal drug delivery has experienced a healthy annual growth rate of 25%, which outpaces oral drug delivery (2%) and the inhalation market (20%) (Grosh 2000). This figure certainly

will rise in the future as novel devices emerge and the list of marketed transdermal drugs increases. The emergence of such devices will increase the use of the skin as a route of administration for the treatment of a variety of conditions.

However, subjective and objective analysis of these devices is required to make sure scientific, regulatory, and consumer needs are met. The devices in development are more costly and complicated compared with conventional transdermal patch therapies. As such they may contain electrical and mechanical components that could increase the potential safety risks to patients due to poor operator technique or device malfunction. In addition, effects of the device on the skin must be reversible, since any permanent damage to the stratum corneum results in the loss of its barrier properties and hence its function as a protective organ.

Regulatory bodies also will require data to substantiate the safety of the device on the skin for either short- or long-term use. Thus, for any of these novel drug delivery technologies to succeed and compete with those already on the market, their safety, efficacy, portability, user-friendliness, cost-effectiveness, and potential market have to be addressed.

REFERENCES

Akomeah, F., Nazir, T., Martin, G. P., and Brown, M. B. 2004. Effect of heat on the percutaneous absorption and skin retention of 3 model penetrants. *Eur. J. Pharm. Sci*. 21:337–345.

Allen, M. G., Prausnitz, M. R., McAllister, D. V., and Cross, F. P. M. 2002. Microneedle devices and methods of manufacture and use thereof. Patent (Serial Number *U.S. 6, 334,856*).

Alza Website. 2005. Retrieved on 3 January 2005 from the World Wide Web: http://www. alza. com/

Archer, D. F., Cullins, V., Creasy, D. W., and Fisher, A. C. 2004. The impact of improved compliance with a weekly contraceptive transdermal system (Ortho Evra) on contraceptive efficacy. *Contraception* 69:189–195.

Ashburn, M. A., Ogden, L. L., Zhan, J., Love, G., and Bastsa, S. V. 2003. Pharmacokinetics of transdermal fentanyl delivered with and without controlled heat. *J. Pain* 4:291–297.

Babu, R. J., Kanikkannan, N., and Kikwai, L., et al. 2003. The influence of various methods of cold storage on the permeation of melatonin and nimesulide. *J. Control. Rel* 86:49–57.

Badkar, A. V., and Banga, A. K 2002. Electrically enhanced transdermal delivery of a macromolecule. *J. Pharm. Pharmacol*. 54:907–912.

Banga, A. K. 1998. *Electrically Assisted Transdermal and Topical Drug Delivery*. London: Taylor and Francis, pp. 13–28.

Banga, A. K., Bose, S., and Ghosh, T. K. 1999. Iontophoresis and electroporation: comparisons and contrasts. *Int. J. Pharm*. 179:1–19.

Baron, E. D., Harris, L., Redpath W. S., et al. 2003. Laser assisted penetration of topical anaesthesia. *Arch. Dermatol*. 139:1288–1290.

Barry, B. W. 2001. Novel mechanisms and devices to enable successful transdermal drug delivery. *Eur. J. Pharm. Sci*. 14:101–114.

Blank, I. H., Scheuplein, R. J., and Macfarlane, D. J. 1967. Mechanism of percutaneous absorption III. The effect of temperature on the transport of non-electrolytes across the skin. *J. Invest. Dermatol*. 49:582–589.

Bommannan, D. B., Tamada, J., Leung, L. and Potts, R. O. 1994. Effects of electroporation on transdermal iontophoretic delivery of luteinizing-hormone-releasing hormone (LHRH) in vitro. *Pharm. Res*. 11:1809–1814.

Bos, J. D., and Meinardi, M. M. 2000. The 500 Dalton rule for skin penetration of chemical compounds and drugs. *Exp Dermatol*. 9:165–169.

Boucaud, A., Garrigue, M. A., and Machet, L., et al. 2002. Effect of sonication parameters on transdermal delivery of insulin to hairless rats. *J. Control. Rel*. 81:113–119.

Burkoth, T. L., Bellhouse, B. J., and Hewson, G., et al. 1999 Transdermal and transmucosal powdered delivery. *Crit. Rev Ther. Drug Carrier. Syst*. 16:331–384.

Carmichael, A. J. 1994. Skin sensitivity and transdermal drug delivery. A review of the problem. *Drug Saf*. 10:151–159.

Cevc, G. 1996. Transferosomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration and transdermal drug delivery. *Crit. Rev. Ther. Drug Carrier Syst*. 13:257–388.

Cevc, G. 2003. Transferosomes: innovative transdermal drug carriers. In *Modified Release Drug Delivery Technology*, eds., Rathbone, M. J., Hadgraft, J. and Roberts, M. S., 533–560. New York: Marcel Dekker.

Chang, S. L., Hofmann, G. A., and Zhang, L., et al. 2000. The effect of electroporation on iontophoretic transdermal delivery of calcium regulating hormones. *J. Control. Rel*. 66:127–133.

Ciernik, I. F., and Krayenbuhl, B. H. 1996. Puncture mediated gene transfer into skin. *Hum. Gene. Ther*. 7:893–899.

clarys, P., Alewaeters, K., Jadoul, A., et al. 1998. In vitro percutaneous penetration through hairless rat skin: influence of temperature, vehicle and penetration enhancers. *Eur. J. Pharm. Biopharm*. 46:279–283.

Cleary G. W. 1991. Transdermal drug delivery. *Cosmet Toil*. 106:197.

Cleary, G. W. 1993. Transdermal delivery systems; a medical rationale. In *Topical Drug Bioavailability Bioequivalence and Penetration*, eds. Shah, V. P., and Maibach, H. I., 17–68. New York: Plenum Press.

Colin Long, C. 2002. Common skin disorders and their topical treatment, In *Dermatological and Transdermal Formulations* Walters KA., ed, New York: Marcel Dekker, pp 41–60.

Cormier, M., Trautman, J., and Kim, H. L., et al. 2001. Skin treatment apparatus for sustained transdermal drug delivery. Patent (serial number *WO 01/41864 A1*).

Cramer, M. P., and Saks, S. R. 1994. Translating safety, efficacy and compliance into economic value for controlled release dosage forms. *Pharmacoeconomics* 5:482–504.

Crocker, P., Maynard, K., and Little, M. 2001. Pain free blunt needle injection technology. *Innov. Pharmaceut. technol*. 9:111–115.

Denet, A. R., Vanbever, R., and Préat, V. 2004. Skin electroporation for topical and transdermal delivery. *Adv. Drug. Del. Rev*. 56:659–674.

Doukas, A. G., and Kollias, N. 2004. Transdermal delivery with a pressure wave. *Adv. Drug. Del. Rev*. 56:559–579.

Down, J., Harvey, N. G., and Martin, F. E., et al. 2001. Skin permeability enhancing device to withdraw or administer a substance and method of manufacture. Patent (serial number *WO 0193946*).

Down, J., and Harvey, N. G. 2003. Minimally invasive systems for transdermal drug delivery. In *Transdermal Drug Delivery*, eds. Guy R. H. and Hadgraft, J., 327–360. New York Marcel Dekker.

Elias, P. M. 1983. Epidermal lipids, barrier function and desquamation. *J. Invest. Dermatol*. 80:44–49.

Elias, P. M., Feingold, K. R., and Tsai, J., et al. 2003. Metabolic approach to transdermal drug delivery. In *Transdermal Drug Delivery*, eds. Guy, R. H, and Hadgraft, J., 285–304. New York: Marcel Dekker.

Flynn, G., Yalkowsky, S. H., and Roseman, T. J. 1974. Mass transport phenomena and models. *J. Pharm. Sci*. 63:479–510.

Frei, A., Andersen, S., Hole, P., and Jensen, N. H. 2003. A one year health economic model comparing transdermal fentanyl with sustained-release morphine in the treatment of chronic non-cancer pain. *J. Pain Palliat. Care. Pharmacother*. 17:5–26.

Fugiwara, H., and Matsumoto, T. 1998. Sampling device of suction effusion fluid. Patent (serial number *U.S. 5,782,871*).

Genetronics Wesite. 2005. Retrieved on 31 January 2005 from the World Wide Web: http://www. genetronics. com/

Gerstel, M. S., and Place, V. A. 1976. Drug delivery device. Patent (serial number *U.S. 3,964, 482*).

Ghosh T. K., Pfister W. R., and Yum S. I. 1997. In *Transdermal and topical Drug Delivery Systems*. Illinois: Interpharm Press.

Godin B., and Touitou, E. 2003. Ethosomes: new prospects in transdermal delivery. *Crit. Rev. Ther. Drug Carrier*. 20:63–102.

Godshall, N. 1996. Micromechanical patch for enhancing delivery of compounds through the skin. Patent (serial number *WO 9637256*).

Godshall, N., and Anderson, R. 1999. Method and apparatus for disruption of the epidermis. Patent (serial number *U.S. 5,879, 326*).

Grosh, S. 2000. Transdermal drug delivery-opening doors for the future. *Euro. Pharm. Contractor (November).* 4:30–32.

Gupta, S. K., Southam, M., Sathyan, G., and Klausner, M. 1998. Effect of current density on pharmacokinetics following continuous or intermittent input from a fentanyl electrotransport system, *J. Pharm. Sci*. 87:976–981.

Gupta, S. K., Sathyan, G., and Phipps, B. 1999. Reproducible fentanyl doses delivered intermittently at different time intervals from an electrotransport system. *J. Pharm. Sci*. 88:835–841.

Guy, R. H., Kalia, Y. N., and Delgado-Charro, M. B. 2000. Iontophoresis: electrorepulsion and electroosmosis. *J. Control. Rel*. 64:129–132.

Hadgraft, J. 1996. Pharmaceutical aspects of transdermal nitroglycerin. *Int. J. Pharm*. 135:1–11.

Helmstädter, A. 2001. The history of electrically assisted transdermal drug delivery (iontophoresis). *Pharmazie* 56:583–587.

Henzel, M. R., and Loomba, P. K. 2003. Transdermal delivery of sex steroids for hormone replacement therapy and contraception. A review of principles and practice. *J. Reprod. Med*. 48:525–540.

Hogan, D. J., and Maibach, H. I. 1990. Adverse dermatologic reactions to transdermal drug delivery systems. *J. Am. Acad. Dermatol*. 22:811–8144.

Hull, W. 2002. Heat-enhanced transdermal drug delivery: A survey paper. *J. Appl. Res. Clin. Exp. Ther. 2*. Retrieved on 20 February 2006 from the World Wide Web: www.jrnlappliedresearch.com/articles/Vol2Iss1/Hull.htm.

Jacques, S. L., McAuliffe, D. J., Blank, I. H., and Parrish, J. A. 1988. Controlled removal of human stratum corneum by pulsed laser to enhance percutaneous transport. Patent (serial number *U.S. 4, 775, 361*).

Jang, K. 1997. Skin perforating device for transdermal medication. Patent (serial number *U.S. 5,611,806*).

Jang, K. 1998. Skin perforating apparatus for transdermal medication. Patent (serial number *U.S. 5,843,114*).

Jarupanich, T., Lamlertkittikul, S., and Chandeying, V. 2003. Efficacy, safety and acceptability of a seven-day, transdermal estradiol patch for estrogen replacement therapy. *J. Med. Assoc. Thai*. 86:836–845.

Kalia, Y. N., Naik, A., Garrison, J., and Guy, R. H. 2004. Iontophoretic drug delivery. *Adv. Drug Del. Rev*. 56:619–658.

Kamen, D. 1998. System for delivery of drugs by transport, Patent (serial number *WO 98/11937*).

Kanikkannan, N. 2002. Iontophoresis based transdermal delivery systems. *Biodrugs* 16:339–347.

Kasting, G. B., and Bowman, L. A. 1990. Electrical analysis of fresh excised human skin: a comparison with frozen skin. *Pharm. Res*. 7:1141–1146.

Katz, N., Shapiro, D., Herrmann, T., Kellogg, S., Warner, N., Kost, J., and Custer, L. 2004. Ultrasound pretreatment of skin enhances the onset speed of EMLA cream. *Anesth & Analg.* 98:371–376.

Kaushik, S., Hord. A. H., Denson, D. D., McAllister, D. V., Smitra, S., Allen, M. G., and Prausnitz, M. R. 2001. Lack of pain associated with microfabricated microneedles. *Anesth Analg.* 92:502–504.

Klemsdal, T. O., Gjesdal, K., and Bredesen, J. E. 1992. Heating and cooling of the nitroglycerin patch application area modify the plasma level of nitroglycerin. *Eur. J Clin. Pharmacol*. 43:625–628.

Kormic, C. A., Santiago-Palma, J., Moryll, N., et al. 2003. Benefit-risk assessment of transdermal fentanyl for the treatment of chronic pain. *Drug Saf*. 26:951–973.

Kuleza, J., and Dvoretzky, I. 2001 Multipurpose drug and heat therapy system. Patent (serial number *WO 01/58408*).

Larsen, R. H., Nielsen, F., Søresen, J. A., and Nielsen, J. B. 2003. Dermal penetration of fentanyl: Inter- and intraindividual variations. *Pharmcol. Toxicol*. 93:244–248.

Lee, S., McAuliffe, D. J., and Flotte, T. J., et al. 1998. Photomechanical transcutaneous delivery of macromolecules. *J. Invest. Dermatol*. 111:925–929.

Lee, S., Kollias, N., McAuliffe, D. J., et al. 1999. Topical drug delivery in humans with a single photomechanical wave. *Pharm. Res*. 16:514–518.

Lee, W. R., Shen, S. C., Lai, H. H., et al. 2001a. Transdermal drug delivery enhanced and controlled by erbium: YAG laser: A comparative study of lipophilic and hydrophilic drugs. *J. Control. Rel*. 75:155–166.

Lee, S., McAuliffe, D. J., Flotte, T. J., et al. 2001b. Permeabilization and recovery of the stratum corneum in vivo: the synergy of photomechanical waves and sodium lauryl sulphate. *Lasers. Surg. Med*. 29:145–150.

Lee, S., McAuliffe, D. J., Mulholland, S. E., and Doukas, A. G. 2001c. Photomechanbical transdermal delivery: the effect of laser confinement. *Lasers Surg. Med*. 28:344–347.

Lee, S., McAuliffe, D. J., Mulholland, S. E., and Doukas, A. G. 2001d. Photomechanical transdermal delivery of insulin in vivo. *Lasers. Surg. Med*. 28:282–285.

Lee, W. R., Shen, S. C., Wang, K. H., et al. 2003. Lasers and microdermabrasion enhance and control topical delivery of vitamin C. *J. Invest. Dermatol*. 121:1118–1125.

Lin, W. Q., Cormier, M., Samiee, A., et al. 2001a. Transdermal delivery of antisense oligonucleotides with microprojection patch (Macroflux®) technology. *Pharm. Res*. 18:1789–1793.

Lin, W. Q., Theeuwes, F., and Cormier, M. 2001b. Device for enhancing transdermal flux of sampled agents. Patent (serial number *WO 01/43643*).

Longbridge, D. J., Sweeney, P. A., Burkoth, T. L., and Bellhouse, B. J. 1998. Effects of particle size and cylinder pressure on dermal powderject® delivery of testosterone to conscious rabbits. *Proc. Int. Symp. Control Rel Bioact. Mat.* 25:964.

Marieb, E. N. 1997. *Human Anatomy and Physiology*. 4th ed. San Francisco: Benjamin Cummings, pp. 146.

Martanto, W., Davis, S. P., and Holiday, N. R. 2004. Transdermal delivery of insulin using microneedles in vivo. *Pharm Res*. 21:947–952.

Matriano, J. A., Cormier, M., and Johnson, J., et al. 2002 Macroflux technology: a new and efficient approach for intracutaneous immunization. *Pharm. Res*. 19:63–70.

Mezei, M., 1993. Liposomes and the skin. In *Liposomes in drug delivery*, eds. Gregoriadis, G., Florence, A. T., and Patel, H. New York: Harwood Academic, pp. 125–137.

Mikszta, J. A., Britingham, J. M., and Alarcon, J. 2001. Applicator having abraded surface coated with substance to be applied. Patent (serial number *WO 01/89622 A1*).

Mikszta, J. A., Alarcon, J., Britingham, J. M., et al. 2002. Improved genetic immunization via micromechanical disruption of skin barrier function and targeted epidermal delivery. *Nat. Med*. 8:415–419.

Mikszta, J. A., Britingham, J. M., and Alarcon, J., et al. 2003. Topical delivery of vaccines. Patent (serial number *U.S. 6, 595, 947 B1*).

Mitragotri, S., Blankschtein, D. and Langer, R. 1995. Ultrasound mediated transdermal protein delivery. *Science*. 269:850–853.

Mitragotri, S., Blankschtein, D., and Langer, R. 1996. Transdermal delivery using low frequency sonophoresis. *Pharm. Res*. 13:411–420.

Mitragotri, S. 2004. Low frequency sonophoresis. *Adv. Drug. Del. Rev*. 56 :589–601.

Muddle, A. G., Longridge, D. J., and Sweeney, P. A., et al. 1997. Transdermal delivery of testosterone to conscious rabbits using powderject (R): A supersonic powder delivery system. *Proc. Int Symp. Control. Rel. Bioact. Mat*. 24:713.

Mulholland, S. E., Lee, S., McAuliffe, D. J. and Doukas A. G. 1999. Cell loading with laser generated stress waves: the role of stress gradient. *Pharm Res*. 16:514–518.

Murphy, M., and Carmichael, A. J. 2000. Transdermal drug delivery systems and skin sensitivity reactions, incidence and management. *Am. J. Clin. Dermatol.* 1:361–368.

Murthy, S. N. 1999 Magnetophoresis: an approach to enhance transdermal drug diffusion. *Pharmazie* 54:377–379.

Murthy, S. N., and Hiremath, R. R. 2001. Physical and chemical permeation enhancers in transdermal delivery of terbutaline sulphate. *AAPS PharmSciTech.* 2:1–5.

Neukermans, A. P., Poutiatine, A. I., and Sendelbeck, S., et al. 2001. Device and method for enhancing microprotrusion skin piercing. Patent (serial number *WO 0141863*).

Norwood Abbey Website. 2005. Retrieved on 31 January 2005 from the World Wide Web: http://www. norwoodabbey. com/indexresdev. htm

Ogiso, T., Hirota, T., Masahiro, I., et al. 1998. Effect of temperature on percutaneous absorption of terodiline and relationship between penetration and fluidity of stratum corneum lipids. *Int. J. Pharm*. 176:63–72.

Pachangula, R. 1997. Transdermal delivery of drugs. *Ind. J. Pharm*. 29:140–156.

Paranjape, M., Garra, J., and Brida, S., et al. 2003 A PDMS dermal patch for non-intrusive transdermal glucose sensing. *Sens Actuators A* 104:195–204.

Payne, R., Mathias, S. D., and Pasta, D. J., et al. 1998. Quality of life and cancer pain: satisfaction and side effects with transdermal fentanyl versus oral morphine. *J. Clin. Oncol*. 16:1588–93.

Pellet, M., Raghavan, S. L., Hadgraft, J. and Davis, A. F. 2003. The application of supersaturated systems to percutaneous drug delivery. In: *Transdermal Drug Delivery*, eds. Guy, R. H., and Hadgraft, J., 305–326. New York: Marcel Dekker.

Pliquett, U., Vaughan, T.. and Weaver, J. 1999. Apparatus and method for electroporation of tissue. Patent (serial number *U.S. 5,983,131*).

Prausnitz M. R. 2004. Microneedles for transdermal drug delivery. *Adv. Drug Del. Rev*. 56:581–587.

Sage, B. H., and Bock, C. R. 2001. Method and device for abrading the skin. Patent (serial number *EP 1086719*).

Saito, S., Kajiwara, Y. and Saito, A. 1999. Method and apparatus of sampling effusion fluid. Patent (serial number *U.S. 5,882,317*).

Schreier, H., and Bouwstra, J. 1994. Liposomes and niosomes as topical drug carriers: dermal and transdermal drug delivery. *J. Control. Rel*. 30:1–15.

Scheuplein, R. J., and Blank, I. H. 1971. Permeability of the skin. *Physiol Rev*. 51:702–747.

Shomaker, T. S., Zhang, J., Love. G., et al. 2000. Evaluating skin anaesthesia after administration of a local anaesthetic system consisting of an S-Caine^{TM} patch and a controlled heat-aided drug delivery (CHADD^{TM}) patch in volunteers. *Clin. J. Pain*. 16:200–204.

Shomaker, T. S., Zhang, J., and Ashburn, M. A. 2001. A pilot study assessing the impact of heat on transdermal delivery of testosterone. *J. Clin. Pharmacol*. 41:677–682.

Singer, A. J., Homan, C. S., Church, A. L., and McClain, S. A. 1998. Low frequency sonophoresis: pathologic and thermal effects in dogs. *Acad. Emerg. Med*. 5:35–40.

Sintov, A., Krymbeck, I., and Daniel, D., et al. 2003. Radiofrequency microchanneling as a new way for electrically assisted transdermal delivery of hydrophilic drugs. *J. Control. Rel*. 89:311–320.

Smith, N. B., Lee, S., Maione, E., et al. 2003. Ultrasound mediated transdermal transport of insulin in vitro through human skin using novel transducer designs. *Ultrasound. Med. Biol*. 29:311–317.

Southam, M., Bernstein, K. J., and Noorduin, H. 2001. Device for transdermal electrotransport of fentanyl and sufentanil. Patent (serial sumber *U.S. 6,216,033*).

Southwell, S., Barry, B. W., and Woodford, R. 1984. Variations in permeability of human skin within and between specimens. *Int. J. Pharm*. 18:299–309.

Stanley, T., Hull, W., and Rigby, L. 2001. Transdermal drug patch with attached pocket for controlled heating device. Patent (serial number *U.S. 6,261, 595*).

Steinsträsser, I., and Merkle, H. P. 1995. Dermal metabolism of topically applied drugs: pathways and models reconsidered. *Pharm. Acta Helv*. 70:3–24.

Sugibayash, K., Kubo, H., and Mori, K. 2002. Device and electrode for electroporation. Patent (serial number *WO 01/28624*).

Svedman, P., Lunin, S. and Svedman, C. 1991. Administration of antidiuretic peptide (DDVAP) by way of suction de-epithelialised skin. *Lancet*. 337:1506–1509.

Svedman, P. 1995. Transdermal perfusion of fluids. Patent (serial number *U.S. 5,441,490*).

Svedman, P., Lundin, S., and Höglund, P., et al. 1996. Passive drug diffusion via standardized skin mini-erosion; methodological aspects and clinical findings with new device *Pharm. Res*. 13:1354–1359.

Svedman, P., and Svedman, C. 1998. Skin mini-erosion sampling technique; feasibility study with regard to serial glucose measurement. *Pharm. Res*. 15:883–888.

Tachibana, K. 1992. Transdermal delivery of insulin to alloxan-diabetic rabbits by ultrasound exposure. *Pharm Res*. 9:952–954.

Toole, J., Silagy, S., and Maric, A., et al. 2002 Evaluation of irritation and sensitisation of two 50 microg/day oestrogen patches. *Maturitas* 43:257–263.

TransPharma Medical Website 2005. Retrieved on 31 January 2005 from the World Wide Web: http://www. transpharmamedical. com/technology_rf. html

Trautman, J., Cormier, M. J., Kim, H. L., and Zuck, M. G. 2000. Device for enhancing transdermal agent flux. Patent (serial number *U.S. 6,083,196*).

Trautman, J., Wong, P. S., Daddona, P. E., et al. 2001 Device for enhancing transdermal agent flux. Patent (serial number *U.S. 6,322,808* B1).

Treffel, P., Panisset, F., Humbert, P., et al. 1993. Effect of pressure on in vitro percutaneous absorption of caffeine. *Acta. Derm. Venereol (Stockh).* 73:200–202.

Tsai, J. C., Guy, R. H., Thornfeldt, C. R., et al. 1996. Metabolic approaches to enhance transdermal drug delivery. 1. Effect of lipid synthesis inhibitors. *J. Pharm. Sci*. 85:643–648.

Turner, N. G., Kalia, Y. N., and Guy, R. H. 1997. The effect of current on skin barrier function in vivo: recovery kinetics post iontophoresis. *Pharm. Res*. 14:1252–1255.

Tyle, P. 1986. Iontophoretic devices for drug delivery. *Pharm. Res*. 3:318–326.

Vanbever, R., Langers, G., Montmayeur, S., and Préat, V. 1998. Transdermal delivery of fentanyl: rapid onset of analgesia using skin electroporation. *J. Control. Rel*. 50:225–235.

Varvel, J. R., Shafer, S. L., and Hwang, S. S., et al. 1989. Absorption characteristics of transdermally administered fentanyl. *Anaesthesiology* 70:928.

Venkatraman, S., and Gale, R. 1998. Skin adhesives and skin adhesion 1. Transdermal drug delivery systems. *Biomaterials*, 19:1119–1136.

Vyteris Wesite. 2005. Retrieved on 31 January 2005 from the World Wide Web: http://www. vyteris. com/index. html

Wang, Y., Allen, L. V., Li, C., and Tu, Y. 1993. Iontophoresis of hydrocortisone across hairless mouse skin: investigation of skin alteration. *J. Pharm. Sci*. 82:1140–1144.

Wang, Y., Thakur, R., Fan, Q., and Michniak, B. 2005. Transdermal iontophoresis: Combination strategies to improve transdermal iontophoretic drug delivery. *Eur. J. Pharm. Sci.* 60:179–191.

Weaver, J. C., Vaughan, T. E., and Chizmadzhev, Y. A. 1999. Theory of electrical creation of aqueous pathways across skin transport barriers. *Adv. Drug. Del. Rev*. 35:21–39.

Whittington, R., and Faulds, D. 1994. Hormone replacement therapy: I. A pharmacoeconomic appraisal of its therapeutic use in menopausal symptoms and urogenital estrogen deficiency. *Pharmacoeconomics* 5:419–45. Review. Erratum in *Pharmacoeconomics* 1995 8:244.

Williams, A. C., and Barry, B. W. 2004. Penetration enhancers. *Adv. Drug Del. Rev.* 56:603–618.

Yang, S. I., Park, H. Y., Lee. S. H., et al. 2004. Transdermal eperisone elicits more potent and longer-lasting muscle relaxation than oral operisone. *Pharmacology* 71:150–156.

Yano, T., Nagakawa. A., Tsuji. M., and Noda. K. 1986. Skin permeability of various non-steroidal anti-inflammatory drugs in man. *Life Sci*. 39:1043–1050.

Yazdanian, M. 1994. Effect of freezing on cattle skin permeability. *Int. J. Pharm*. 103:93–96.

Yuzhakov, V. V., Sherman, F. F., Owens, G. D., and Gartstein, V. 2001. Apparatus and method for using an intracutaneous microneedle array. Patent (serial number *U.S. 6,256,533*).

Zars Website. 2005. Retrieved on 31 January 2005 from the World Wide Web: http://www. zars. com/

Zhang, L., Hofmann, G. A., and Rabussay, D. 2001. Electrically assisted transdermal method and apparatus for treatment of erectile dysfunction. Patent (serial number *U.S. 6,266 560*).

Zhang, L., Nolan, E., Kreitschitz, S., and Rabussay, D. P. 2002. Enhanced delivery of naked DNA to the skin by non-invasive in vivo electroporation. *Biochim. Biophys. Acta* 1572:1–9.