Expert Opinion

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Microporation applications for enhancing drug delivery

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Microporation involves the creation of micron-sized micropores or microchannels in the skin which can then allow the transport of water soluble molecules and macromolecules. Technologies which can create these microchannels in the skin include mechanical microneedles, thermal or radiofrequency ablation and laser ablation. These technologies will open a new frontier for the delivery of biopharmaceuticals, as these hydrophilic macromolecules cannot be delivered via the skin passively. Companies which are developing these technologies are discussed, along with potential hurdles to commercialization related to the elasticity of skin, immunogenicity issues, pore closure kinetics, or microneedle material and geometries. In spite of the obstacles, these technologies look very promising and are likely to revolutionize transdermal drug delivery in the near future. Bioavailability considerations and the potential use of inexpensive coated microneedles for mass immunizations are also discussed.

Keywords: laser ablation, microneedles, microporation, radiofrequency ablation, thermal ablation, transdermal delivery

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1. Introduction

The transdermal patches currently on the market are limited to the delivery of small, potent and lipophilic drug molecules such as clonidine, estradiol, fentanyl, granisetron, methylphenidate, rivastigmine, rotigotine, selegiline, nicotine, nitroglycerin, oxybutynin, scopolamine and testosterone. Patches with an estrogen/progestogen combination for birth control and lidocaine patches for topical use are also available. The horizon of transdermal delivery can be expanded to the delivery of therapeutic proteins and small water soluble drugs using new physical enhancement technologies such as iontophoresis, electroporation, phonophoresis, jet-propelled particles and various microporation technologies [1-5]. Microporation involves the creation of micron-sized micropores or microchannels in the skin which can then allow the transport of water soluble molecules and macromolecules. These water soluble molecules do not normally pass through the skin. Microporation technologies can significantly expand the scope of transdermal delivery, since many of the biotechnology-derived pharmaceuticals happen to be hydrophilic molecules which cannot be formulated into a passive conventional patch.

Microporation has been described recently as one of the few third generation enhancement strategies which will have significant impact on medicine [6]. Microporation technologies involve a temporary physical disruption of the skin barrier and are considered to be 'minimally invasive'. The micropores created in the skin are superficial, typically breaching the stratum corneum in localized areas of the micropores and reaching into the epidermis. Nerve endings reside in the papillary (upper) dermis alongside capillaries and lymphatic vessels. Therefore, these technologies are painless when properly designed. Microporation of skin can

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be achieved by a variety of technological approaches such as mechanical microneedles, thermal/radiofrequency ablation, laser ablation or miscellaneous approaches discussed later in this review. Once these pathways are created in the skin, drug molecules of any size and even small particles can be delivered through these pathways. This article provides an up-to-date overview of skin microporation, including an expert opinion section and discussion of delivery of particulates, hurdles to regulatory approval and our current understanding of pore closure.

2. Mechanical microneedles and their applications

This section will discuss the literature relevant to the fabrication of microneedles and especially applications of microneedles to drug or vaccine delivery. However, it should be noted that microneedles also have various other applications in medicine that are not discussed here. An array of microscopic needles can be used to create pathways of micron dimensions in the skin. It has been reported that the insertion of microneedles into the skin is not painful [7-9]. Human volunteers have reported that a microstructured array having more than 1200 microprojections of about 250 µm height were not painful upon insertion (3M Brochure on *Microstructured transdermal systems for intradermal vaccine and drug delivery*). In another recent study, human subjects were asked to score pain on a 0 – 100 scale and reported a microneedle insertion pain score of 6 ± 5, as compared to 24 ± 16 for injection by a hypodermic needle used as a positive control. This study used a patch having 5 × 10 arrays of 620 µm long stainless steel needles and also demonstrated systemic delivery of a hydrophilic drug, naltrexone. Naltrexone was not detected in plasma when delivered from untreated skin but was delivered via microporated skin, with steady state plasma concentrations achieved within 2 h of patch application and maintained for at least 48 h [10]. Yet another recent study in 18 human volunteers reported that microneedle insertion was painless and caused only minimal irritation which lasted less than 2 h [11].

The pathways created in the skin by microneedles are large relative to drug dimensions and therefore allow the transport of drug molecules of any dimensions. However, these aqueous microchannels may better allow the delivery of hydrophilic drug molecules and delivery can be increased by increasing the solubility of drug in the vehicle [12]. A recent study has used an immunohistochemical staining technique to demonstrate the diffusion of antibodies across microchannels created in the skin by microneedles [13]. Delivery of insulin by microneedles has been reported by several investigators [9,14-17]. Vaccine [18-20] and gene delivery [21-23] through these pathways has also been reported. However, the pathways are still much smaller than holes made in skin by hypodermic needles [24,25]. Nevertheless, even particles can be delivered through these microchannels [26]. Coulman *et al.* have recently demonstrated the delivery of 100 nm negatively charged nanoparticles into human skin [27]. We have found that 2.0 µm sized FluoSpheres® (carboxylate modified microspheres; FluoSpheres, Invitrogen, CA, USA) could be delivered into skin treated with maltose microneedles (500µm), as monitored by confocal microscopy. Delivery to a depth of ~ 110µm from the surface of the skin was observed (**Figure 1**).

2.1 Mechanisms of drug delivery by microneedles

Broadly speaking, drugs may be delivered using microneedles by a variety of mechanisms: i) by directly coating the drug onto solid microneedles; ii) by delivering the drug via hollow microneedles; iii) by incorporating the drug inside the microneedles during fabrication (for microneedles that dissolve in the skin upon insertion); or iv) diffusion of the drug through microchannels created in the skin by solid microneedles.

Direct coating on microneedles is generally used for vaccines or very potent drugs since only a very small quantity of drug can be coated onto the microneedles. This is generally not a problem for vaccine delivery since only miniscule amounts of antigen are needed to generate an immune response. Since microneedle arrays do not penetrate the skin to their full length, coatings should be applied to the tip or upper part of the microneedles. Coatings are usually applied by dipping microneedles in a drug formulation at the desired concentration, viscosity and surface tension to provide reproducible drug loading. Widera *et al.* coated titanium microneedles with a model antigen by applying the coating only to the tip of the microneedles. Higher loading dose was obtained by multiple coatings by repeatedly immersing the microneedles into the coating solution with a drying time of 5 sec between coatings [19]. Other investigators have further optimized the dip coating process to uniformly coat both hydrophilic and hydrophobic molecules onto microneedles. Coatings of calcein, vitamin B, bovine serum albumin, plasmid DNA, model proteins and that of modified vaccinia virus and 1 – 20 µm microparticles on microneedles have been demonstrated [28,29].

Hollow microneedles have a conduit within the needle and drug solution can be delivered via hollow microneedles using a driving force such as pressure or iontophoresis. Hollow silicon microneedles with a pore diameter of about 3 µm [30] to 20 µm [31] have been described. Roxhed *et al.* have recently described a microneedle-based patch having 400 µm long hollow silicon microneedles with an integrated liquid reservoir. The reservoir is covered by a composite that heats up and expands when a small current is passed through lithographically defined heaters on its printed circuit board (**Figure 2**) [9]. Others have also described hollow silicon microneedles with an integrated microfluid chip that has been tested by injecting Rhodamine B dye into 1% agarose gel through the microchannels of the integrated microneedle [31] or by their ability to extract interstitial fluid from skin [32]. One potential hurdle to delivering a drug solution via

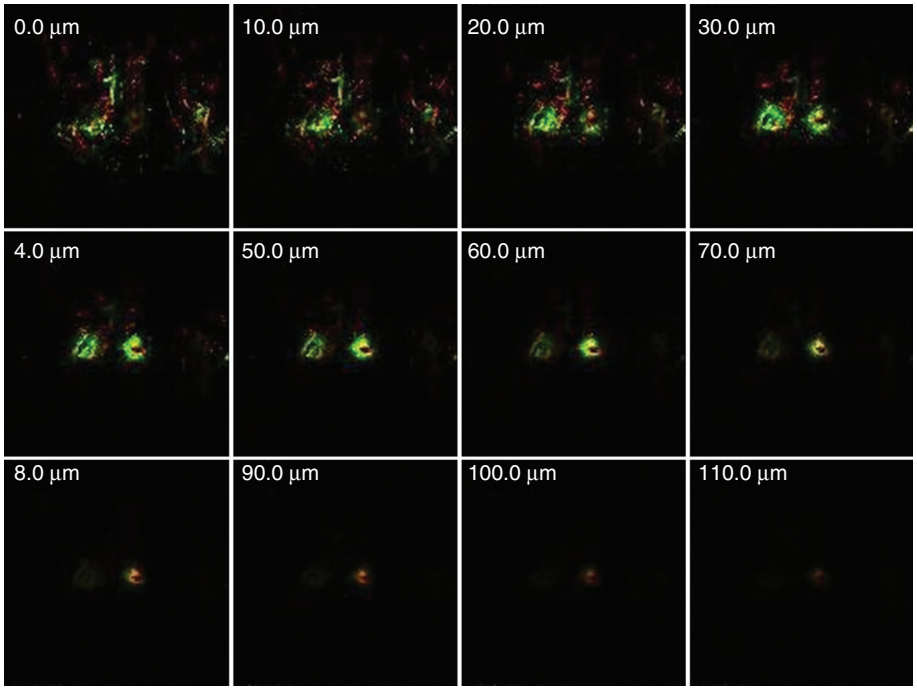

Figure 1. Permeation profile of calcein and 2.0 µm sized FluoSpheres® (carboxylate-modified microspheres) across maltose microneedles (500 µm) treated hairless rat skin, as monitored in two microchannels by confocal microscopy using dual dye imaging. The green fluorescence indicates the permeation profile of calcein; red fluorescence indicates the permeation profile of the FluoSpheres®; and the areas where both the dyes are present are indicated by yellow. Both the dyes permeated up to a depth of ~ 110 µm from the surface of the skin (Kalluri and Banga, unpublished data).

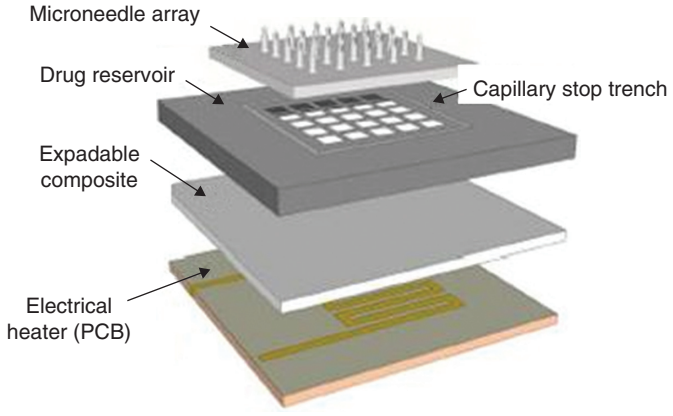

Figure 2. Exploded view of the microfabricated drug delivery system.
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hollow microneedles is the limitations to the volume of solution that can diffuse through the skin, although recent technologies such as recombinant human hyaluronidase [33] can help by breaking down hyaluronic acid to create space in the matrix of tissues such as skin. Drug molecules as large as 200 nm may then diffuse freely through the extracellular matrix, which recovers its normal density within about 24 h. Other approaches to overcome flow resistance in dense dermal tissue to allow microinfusion of small fluid volumes via hollow microneedles include partial retraction of the microneedles after insertion [34-36]. Hollow microneedles can also be potentially used to extract interstitial fluid from the skin to monitor drug levels in the body or to monitor endogenous compounds for diagnostic applications [32]. A recent study has suggested that hollow microneedles can be packaged with drugs and then sealed to preserve the stability of the drug. The drug will then be released at the time of use by several possible mechanisms to break the seal, for example, a 170 nm thick gold membrane breaking when the microneedles are inserted into skin tissue [37].

Drugs can also be delivered by incorporation into self-dissolving microneedles, for example, insulin-loaded microneedles have been prepared by using dextrin as the base [14]. Solid microneedles can also be used to create microchannels in the skin first and then a drug solution is placed on the microporated skin after the microneedles have been withdrawn. The drug then diffuses through the micropores. This approach generally results in a low bioavailability, relative to subcutaneous injection. However, by using a patch with a dry formulation, bioavailability can be increased.

2.2 Types of microneedles and applications

Microfabrication technologies have made possible the design and production of microneedle arrays [38-40]. Microneedles were primarily made of silicon when this field evolved for drug delivery applications about 10 years ago, but fabrication of silicon microneedles requires expensive microfabrication techniques and clean room processing. Furthermore, these needles may break off in the skin due to the brittle nature of silicon, or silicon grains from needles could remain behind in the skin after the needles are removed. Any such residue would be small and the skin is constantly regenerated, but nevertheless it will need to be addressed. This may be particularly true for hollow silicon microneedles as they may be mechanically less robust. However, Wu *et al.* have reported that primary skin irritation tests indicate that silicon microneedles or their extractable chemicals caused no irritation [41]. Unlike silicon, metal and polymer microneedles can be made by low cost manufacturing methods and may be more acceptable from a regulatory perspective. Currently, microneedles made of metal, polymers, or sugars are more commonly being developed for potential commercialization. Metallic microneedles can be made by laser patterning of needle structures onto a metal surface, followed by raising the microneedles out of plane. Polymer microneedles can be made by micromolding techniques utilizing microfabricated silicon microneedles as a primary template [42] and they can also be made hollow [43].

Microneedles that dissolve in the skin, for example those made of maltose, have also been investigated. These microneedles can be made by molding at very high temperatures and may be relatively inexpensive to produce [44]. The materials used are generally quite inert and these microneedles will thus also be attractive from a regulatory approval perspective. Kolli and Banga have used these maltose microneedles to create microchannels in the skin which were then characterized by methylene blue staining, SEM, transepidermal water loss (TEWL) and confocal microscopy studies. The microchannels were observed to be about 55 µm in diameter and uptake of calcein by these microchannels was uniform as measured by pore permeability index values. Flux of nicardipine HCl across microporated skin was 7.05 µg/cm^2/h as compared to 1.72 µg/cm^2/h for untreated skin [45]. These maltose microneedles have also been used to demonstrate transdermal delivery of methotrexate [46] and therapeutic antibodies [13].

Ito *et al.* used three thread-forming polymers – dextrin, chondroitin sulfate and albumin – to make microneedles containing erythropoietin. Upon percutaneous administration to mice, the bioavailability was 82.1, 59.7 and 78.6%, respectively, and C_{max} appeared at around 8 h [47]. Lee *et al.* [48] have described a fabrication process for making dissolving microneedles made of carboxymethylcellulose or amylopectin based on casting a viscous solution in a microfabricated mold during centrifugation. A viscous solution was first made by concentration of a dilute solution by evaporation under vacuum or by heating. The solution was then cast into micromolds and dried at 37°C under centrifugation, which compressed the mold contents and minimized void formation. Microneedles fabricated from the biodegradable polymer poly-lactide–co-glycolide have also been reported [49,50].

Zosano Pharma is developing metallic microneedles (Macroflux® microprojection arrays) by creating precision microprojections on a thin titanium sheet [18]. Zosano's PTH [1-35] microneedle patch for osteoporosis [51] has completed Phase II clinical trials (**Table 1**). Zosano Pharma has reported that titanium microneedles coated with model antigen ovalbumin produced an immune response in hairless guinea pigs that was dose-dependent but largely independent of depth of delivery, density of microneedles, or area of application. Microneedles of 225 – 600 µm with an array density of 280 or 1314 microneedles were used in this study. All microneedles penetrated at least the first 90 µm of the skin [18,19]. 3M is developing microstructured transdermal systems (MTS) in solid (sMTS) or hollow (hMTS) design in a variety of different shapes and sizes. In one configuration, pyramidal projections of about 250 µm were developed. These microneedles are typically less than 500 µm and are applied with an applicator device with proper force to ensure that the microneedles are able to penetrate the skin to the

Table 1. Various microporation technologies in development.

Microporation principle	Technology/company	Technology details	Product pipeline
Laser microporation	P.L.E.A.S.E.® / Pantec Biosolutions AG LAD / Norwood Abbey	Laser ablation of the skin using an erbium:YAG laser, emitting light at 2.94 µm Laser ablation of skin	Preclinical work in diabetes, pain, vaccine and *in vitro* fertilization therapeutic areas Norwood Abbey has introduced a device called Epiture Easytouch™ to allow the application of OTC 4% lidocaine cream to achieve dermal anesthesia in 5 min
Thermal microporation	PassPort™ / Altea Therapeutics	An array of metallic filaments attached to a conventional patch are activated by a handheld applicator by a single pulse of electrical energy. This energy is converted to thermal energy which ablates the stratum corneum under each filament to create micropores. The patch is then folded over to apply the drug to the microporated skin	Clinical studies are underway for the delivery of basal insulin, hydromorphone HCl, fentanyl citrate and apomorphine HCl. Preclinical studies have also demonstrated delivery of several drugs including interferon-α, hepatitis B antigen and parathyroid hormone
Radiofrequency microporation	ViaDerm / TransPharma	A high frequency AC current is passed through a densely spaced array of microelectrodes placed on the skin to create localized ablation of cells within milliseconds to create RF-microchannels, with a typical depth of less than 100 microns, and covering less than 1% of the treated area	Clinical studies have been done for the delivery of hPTH (1-34), human growth hormone and insulin. Preclinical studies have demonstrated delivery of granisetron hydrochloride, diclofenac sodium, plasmid DNA and nanoparticles
Microneedles*	Microstructured Transdermal Systems (MTS) / 3M	Microneedles in various shapes and sizes, with the current emphasis on solid (sMTS) coated biocompatible polymeric microneedles for vaccine delivery	Preclinical studies have been conducted with ovalbumin, tetanus toxoid, human growth hormone and naloxone
	Macroflux® Technology / Zosano	Macroflux Technology creates micropores using precision microprojections on a thin titanium screen. Drugs may be dry-coated on the microprojection array for bolus delivery into the skin	A PTH (1-34) patch for osteoporosis has completed Phase II clinical trials successfully
	DrugMAT and VaxMAT / TheraJect, Inc. MicroCor™ / Corium	Self-dissolving microneedle arrays made from various GRAS materials Microstructure arrays fabricated from flexible polymers or other materials using a continuous embossing process that allows for reproducible, low cost and high volume production	Preclinical work reported with PTH (1-84), lidocaine, influenza and acne treatment ‡
	MicroPyramid platform / NanoPass in conjunction with Silex Microsystems	Silicon solid or hollow microneedles manufactured by MEMS technology, with sharp tip diameters of less than 1 µm	‡

*Other companies/institutes with microneedle technology include Apogee Technology, Becton Dickinson, Elegaphy, Imtek, ISSYS, Kumetrix, Norwood Abbey, Valeritas and Zeopane.

‡Undisclosed preclinical or clinical studies; technology available for contract manufacturing.

desired depth. Using a polycarbonate array containing over 1000 microstructures in a patch, they were able to penetrate to a depth of about 120 µm when tested in domestic swine and hairless guinea pigs. Under extreme pressure, these microstructures will bend but not fracture or break, thereby providing safety for use. Pharmacokinetic profiles following sMTS delivery of naloxone HCl were comparable to those following subcutaneous (s.c.) injection, with respect to C_{max} and bioavailability. Similarly, intradermal infusion of human growth hormone through hMTS provided pharmacokinetic profiles comparable to those following s.c. injection, with respect to C_{max} and bioavailability. Liquid formulation up to 1 ml could be infused in less than 15 min via hollow plastic microstructures with minimal discomfort or side reactions [52-54]. Hollow microneedles have been reported to deliver a lipophilic drug past the stratum corneum in humans [55].

2.3 Importance of microneedle geometry

The geometry of the fabricated microneedles is also very important as it controls the insertion characteristics and even drug delivery. It is important that there must be enough spacing between individual microneedles in an array as a very high microneedle density may lead to a 'bed of nails' effect [25,56], whereby the microneedle array will deform the elastic skin but not penetrate into the skin. Davis *et al.* [57] have reported from studies in human subjects and human cadaver skin that over the range of microneedle geometries they investigated, forces required for inserting microneedles into the skin varied from about 0.1 to 3 N, which is low enough to allow insertion by hand. Insertion force was found to vary linearly with the interfacial area of needle tip. The margin of safety, defined by the ratio of fracture to insertion force, was greater than one and increased with increasing wall thickness and decreasing tip radius. These parameters are helpful to design microneedles with the desired mechanical properties. A radius of curvature which is less than 10 µm at the tip is required to enable the microneedles to easily penetrate the skin by hand. In a more recent study, octagonal pyramid-shaped 150 µm silicon microneedles were inserted in skin by an applicator using a force of 2 N. The needle tip was less than 1 µm wide and the microneedles had a cone angle of 38° and a base length of 100 µm. After reuse over 100 times, no fracture or damage of the microneedles was observed [41]. Verbaan *et al.* have also reported that for short (< 300 µm) microneedles, the use of an applicator may be required to overcome the elasticity of the skin. They found that an electrically driven applicator facilitated their microneedle arrays to penetrate dermatomed human skin *in vitro* [58].

As discussed, these microneedles must have a sharp tip to be able to penetrate the skin. Hollow silicon needles with a tip radius < 100 nm have been reported. These needles also have side-openings to avoid clogging from or coring of tissue during insertion [9]. Microneedle length is also important for insertion characteristics, drug delivery and perception of pain. Oh *et al.* have reported that delivery of the hydrophilic molecule calcein (622.5 Da) across skin was enhanced about fivefold with 500 µm microneedles as compared to about threefold with 200 µm microneedles. Delivery was also increased as microneedle density increased from 45 to 154 per sq cm. Polycarbonate microneedle arrays were used in this study [59]. However, this may not always be the case. Widera *et al.* have reported that the immunization response to ovalbumin-coated microneedles was similar for the same dose delivered by three different (225, 400 and 600 µm) microneedle lengths [19].

2.4 Pore closure

Following the creation of micropores in the skin, the TEWL values go up while the skin resistance drops. For example, following the creation of micropores, the TEWL values in guinea pigs increased from 4.0 to 36.1 $gh^{-1}m^{-2}$ [60]. Similarly, microneedles have been reported to cause a 50-fold drop in skin resistance [7]. These values can be monitored to track the recovery of skin following microporation. A near sustained delivery of an oligonucleotide has been reported for 24 h and the authors suggested that the skin pathways created by microprojections remain open throughout this 24 h period [61]. Using TEWL, fluorescence imaging and methylene blue staining, we have shown that pores stay open if they are occluded by covering with an occlusive film or by being exposed to water or any solution/buffer, irrespective of pH. Some decrease in the pore permeability index values was observed, but the pores were still open at 24 h when occluded [62]. We have also shown that pores were still open when monitored for up to 72 h under occlusive conditions and then close within 2 – 3 h of microporation when not occluded (unpublished data). This turns out to be great finding, as this essentially means that pores stay open when a patch is placed on microporated skin and then close quickly once the patch is removed. However, the mechanism of pore closure is still not well understood. Occlusion is known to disrupt the recovery of the barrier function of skin and produce major changes in the skin physiology [63,64]. However, the relatively quick closure of pores after removal of occlusion needs further investigation.

3. Thermal and radiofrequency ablation and applications

Exposure of skin to short, high temperature pulses can cause structural disruption and removal of stratum corneum by locally ablating the stratum corneum without significantly heating or damaging the deeper tissues. This can create micron-size microchannels in the skin similar to those created by microneedles, but, unlike microneedles, which create such channels by cutting a pathway in the skin, thermal ablation does so by decomposition and vaporization of stratum corneum in a localized area [65]. These micropores are temporary, since the layers of stratum corneum are

continuously being replaced through the natural process of desquamation.

Altea Therapeutics (Tucker, GA, USA) is using the thermal ablation technology to develop a single use disposable patch to be used with a reusable handheld applicator [66]. An array of electrically resistive filaments are applied to the skin surface and when a short controlled pulse of electric current is passed through the filaments, they heat up to transfer thermal energy to the skin to ablate localized areas of the skin to create micropores. Badkar *et al.* have used this technology to deliver interferon α-2b through microporated skin. It was shown that interferon could not be delivered through intact skin or even with iontophoresis, but was only delivered when these micropores were created in the skin [67]. In another study, a 10 – 100-fold greater cellular and humoral immune response has been reported following topical application of an adenovirus vaccine to thermally micro-porated mice skin as compared to intact skin [68]. Thermal microporation conditions can be adjusted to create micropores which may typically be 50 – 200 µm in width and 30 – 50 µm in depth. Clinical studies are underway for delivery of basal insulin, hydromorphone HCl, fentanyl citrate and apomorphine HCl (**Table 1**). In a study in human diabetic subjects, it has been shown that thermal microporation also has potential use in diagnostics to develop an alternative method to blood glucose monitoring via finger stick, based on sampling of skin interstitial fluid to track blood glucose levels [69].

Another technology, based on radio frequency ablation, is similar to thermal ablation and has been adapted from medical technology, where it is used to remove small tumors by placing a probe inside the tumor. It is being developed by TransPharma Medical for skin microporation and uses an electric current in the radio frequency (100 – 500 kHz) range applied to a closely spaced array of microelectrodes placed on the skin surface. This high frequency causes ionic vibrations within the skin cells, which in turn leads to localized heating and cell ablation. This technology, termed ViaDerm™, has been shown to generate 144 microchannels over a 1.4 cm^2 area in full thickness human skin, with each microchannel being about 50 µm in length and 30 – 50 µm at its widest aperture. These microchannels allowed the transport of gene therapy vectors and 100 nm diameter nanoparticles to the viable regions of the skin [70] and have also been shown to deliver granisetron hydrochloride and diclofenac sodium [71].

Levin *et al.* have used this technology to deliver human growth hormone (22 kDa) across microchannels created in skin by radio frequency ablation. Using printed patches with a thin uniform layer of protein in dry form, a high bioavailability of 75 or 33% (relative to s.c. injection) was achieved in rats or guinea pigs, respectively. This relatively high bioavailability was attributed to the formation of a high localized concentration of hGH *in situ* by the dissolution of water soluble hGH from the printed patch by the fluid coming from the microchannels created in the skin. This is followed by diffusion across a large concentration gradient to result in a profile similar to s.c. injection, but with a somewhat higher T_{max} that represents the time required for the dissolution and diffusion of hGH. A dose-dependent increase in delivery was observed in C_{max} and AUC up to a dose of 300 µg hGH per 1.4 sq cm patch area [60]. The high bioavailability observed in this study for a delivery of a large protein molecule is encouraging, especially considering that only 1% of the treated skin area was microporated, with a microchannel density of 200/sq cm. TransPharma Medical and Teva Pharmaceuticals of Israel are co-developing a patch for delivery of human growth hormone by radiofrequency ablation for growth hormone deficiency. TransPharma is also co-developing (with Eli Lilly) hPTH [1-35] product for the treatment of osteoporosis, which is currently in Phase II clinical testing [72].

4. Laser ablation, other approaches and applications

Medical lasers have been used in recent years for cosmetic and reconstructive surgery. Laser-based technologies can also be used for skin microporation, by specifically exciting water molecules on the skin surface; the resulting superheating of water on a microsecond scale causes an explosive evaporation which in turn creates microchannels. Pantec Biosolutions AG (Ruggell, Liechtenstein) is developing a handheld laser device, P.L.E.A.S.E.® (Painless Laser Epidermal System) which can create micropores in the skin by using an erbium:YAG laser (**Figure 3**). This laser emits light at 2940 nm, corresponding to main water absorption peak, allowing the creation of micropores (150 – 200 µm in diameter) with minimal heat transfer to the surrounding tissue. By controlling the laser pulse settings, the depth of these micropores can be controlled in the 100 – 200 µm range. When used in human subjects, the slight to moderate erythema observed returned to baseline reading by day 5 of treatment and TEWL returned to baseline levels by day 3 of treatment [73,74]. Norwood Abbey (Victoria, Australia) is also developing laser assisted drug delivery (LAD) technology and has introduced a device called Epiture Easytouch™ to allow the application of over-the-counter (OTC) 4% lidocaine cream to achieve dermal anesthesia in 5 min. Photomechanical (stress or pressure) waves generated by high power pulse lasers at 694.3 nm have also been investigated for transdermal delivery [42].

Some other technologies can also be possibly used for skin microporation, but they have received limited attention at this time and will not be discussed at length in this review. For example, it has been suggested that use of 20 kHz ultrasound at an intensity around 20 W/cm^2 (higher than normally used in sonophoresis) can actually create pores in the stratum corneum, and allowed particles up to 25 µm to diffuse through the epidermal layers. This sonomacroporation seems to result from acoustic cavitation [75]. It has also been reported that

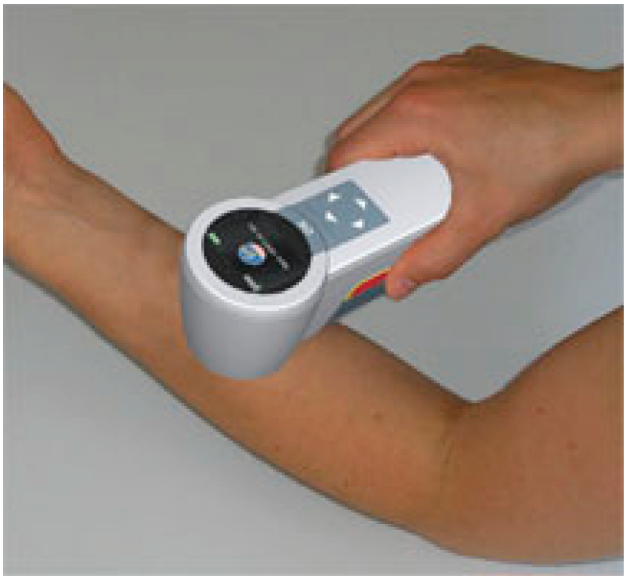

Figure 3. A handheld laser device, P.L.E.A.S.E.® (Painless Laser Epidermal System), being used to create controlled aqueous micropores in the epidermis.
Reproduced from [87] with permission.

microconduits can be rapidly and painlessly created in the skin via micro-scissioning by 25 µm inert sharp sided (aluminum) particles impacting the skin in a flow of accelerated gas through the aperture in a mask held against the stratum corneum [76].

Other skin abrasion techniques have also been used, although these may not be considered microporation in the true sense. Iomai has used skin abrasion techniques and is in Phase II trials with heat-labile enterotoxin of *E. Coli* for traveler's diarrhea [6]. Microdermabrasion is another technique that uses tiny crystals (typically aluminum oxide) to impact the skin under negative pressure to partially or completely remove the stratum corneum. It is widely used as a cosmetic procedure but is now also being investigated as a drug delivery method. However, microdermabrasion may not be a true microporation technology in the sense that it is not creating micropores in the skin.

Fang *et al.* have delivered 5-aminolaevulinic acid by erbium:YAG laser and microdermabrasion across pig skin. As the treatment duration with microdermabrasion increased from 0 to 10 sec, the thickness of stratum corneum decreased linearly from 9.36 to 2.05 µm. For laser, an ablation threshold of about 1.4 J cm^{-2} was observed and also higher energies did not always result in more enhancement [77].

5. Combination approaches

Microporation technologies are also being investigated in combination with other enhancement strategies to enable or enhance drug delivery through the skin. One such technique is iontophoresis, which applies a small amount of current to deliver charged molecules across the skin [78]. Several companies are actively developing iontophoresis technology. A partial list includes Alza, Empi, Iomed, Vyteris, Travanti Pharma and Transport Pharmaceuticals. However, iontophoretic delivery is limited to delivery of drug molecules up to a size of about 10 kDa, although it may be possible to deliver insignificant amounts of much larger molecules [79]. In contrast, microporation technologies create large transport pathways in the skin and there is no size limit to what drug molecules can be dissolved through these pathways. Iontophoresis can be very helpful to drive ionized drug molecules across the pathways created by microporation technologies.

Using an integrated microprojections array system, it was shown that the delivery of a 20-mer oligonucleotide across hairless guinea pig skin was enhanced 10-fold by applying a current of 0.1 mA/sq cm for 4 h. The stainless steel microprojection arrays used had a length of 430 µm and a density of 240/sq cm [61]. Similarly, it has been reported [80] that iontophoresis significantly enhanced the flux of FITC–dextrans across microneedle-treated skin as compared to treatment by microneedles alone or iontophoresis alone. The lag time of delivery increased from 0.36 to 2.82 h as the molecular weight of FITC–dextran increased from 3.8 to 200 kDa. Badkar *et al.* have reported a twofold increase in the dose of interferon delivered when iontophoresis was applied to microporated skin [67]. Vemulapalli *et al.* have reported a synergistic 25-fold enhancement in delivery of methotrexate across skin when iontophoresis was combined with microneedles, as measured in the dermis by microdialysis [46]. A combined use of elastic liposomes and microneedles for delivery of docetaxel as a model drug has also been reported. Elastic liposomes were able to enhance delivery as compared to passive delivery and combination with microneedles enhanced delivery further *in vitro* across rat and porcine skin using 150 µm long microneedles [81].

6. Expert opinion

Skin microporation technologies will open a new frontier for delivery of biopharmaceuticals, as these hydrophilic macromolecules cannot be delivered via the skin passively. This exciting technology has gained increasing attention in recent years since a microneedle-based patch is expected to be very simple, and does not need any power supply or advanced microelectronics, unlike some other delivery systems. Skin microporation may be considered a minimally invasive technology which can be broadly divided into two categories: i) microneedle technology; and ii) other technologies which include thermal microporation, laser ablation and miscellaneous approaches to create microchannels in the skin. There is considerable interest in both approaches to skin microporation.

Several companies/institutes, including Apogee Technology, Becton Dickinson, Corium (acquired technology from Procter & Gamble), Debiotech, Elegaphy, Imtek, ISSYS, Kumetrix, 3M, Nanopass, Norwood Abbey, Silex Microsystems, Theraject, Valeritas (a subsidiary of BioValve), Zeopane and Zosano (formerly Macroflux, an Alza spin-off) are exploring microneedles for drug delivery. In addition, academic groups like Georgia Tech, MIT and the transdermal delivery laboratory at Mercer University are actively pursuing research in the applications of microneedles to drug delivery. In addition, several universities and National Science Foundation (NSF)-funded nanofabrication facilities are actively investigating and developing fabrication methods for making microneedles from a variety of materials. This good collaboration between engineering and biological sciences is helping to go beyond fabrication methods to discovering new applications. However, at this time, only very few companies have the capability of scaling up operations for commercialization of microneedle technology. Among these are Becton Dickinson, 3M and Zosano Pharma.

Coated microneedles are very promising, but the maximum dose that may be coated or encapsulated on a microneedle array may be around 1 mg or even less, limiting applications to vaccine delivery or delivery of very potent drugs such as desmopressin, interferon or erythropoietin [50,82]. A microneedle-based influenza vaccine product from Sanofi Pasteur and Becton Dickinson has completed Phase III clinical studies and is submitted for registration in Europe. This product utilizes a microinjection system with one tiny microneedle for intradermal delivery and is in that sense different from microneedle array patches in development having up to several hundred microneedles (typically 100 – 500 microns each) in the patch. Microneedles can be mass produced at very low cost and this, coupled with the feasibility of using coated microneedles for immunizations, will be one of the drivers of this technology in the coming years.

Several companies are exploring other technologies for skin microporation such as thermal ablation (Altea Therapeutics), radiofrequency ablation (TransPharma) and laser ablation (Pantec Biosolutions AG and Norwood Abbey). These technologies are discussed in **Table 1**. Bioavailability similar to s.c. delivery has been reported in the literature for the delivery of human growth hormone by radio-frequency ablation, using printed patches with powder formulation [60]. This is very encouraging and in the not too distant future, several biotechnology-derived products may be marketed for delivery via microneedle-based skin patches.

The recent economic slowdown may delay advancements in this exciting technology, but not for too long. The slowdown on Wall Street is causing drug delivery companies to rethink the Speciality Pharma model and return to their roots of what they do best, that is, focus on the drug delivery technology. FDA approval of microneedle patch will require studies to prove that the creation of microchannels in the skin does not pose safety (e.g., infection) risks, although early human studies seem to suggest that the procedure is safe for long-term use. However, it is still anticipated that any commercially produced microneedles will have to be sterile. A better understanding of the kinetics of pore closure and factors affecting pore closure is required. Also, coated microneedles must release the coated drug into the skin in a reasonable time period, typically within a few minutes. FDA may also need data to show lack of immunogenicity when protein drugs are being administered via the skin [79]. In contrast, immunogenicity is desired when a protein or other antigen is intended to be a vaccine application. Skin has a rich population of Langerhans cells in the epidermal layers and is therefore an attractive target for immunization. Microporation technologies can deliver the antigen in close proximity to these antigen presenting cells and lower doses may be required as compared to injectable formulations. Coated microneedles for vaccination can be produced at low cost and do not need any special training for administration, unlike hypodermic needles. This could be very promising for mass immunization programs. The depth of needle penetration may also be important to immunogenicity considerations. Avoiding variable delivery will be important and more work needs to take place on the design of applicators which can insert microneedles into the skin to reduce variability and allow penetration of smaller microneedles into the skin by reducing considerations related to elasticity of skin, which produces some deformation around the insertion site, which in turn reduces the insertion depth of microneedles. Applicators may also be helpful to ensure that all microneedles enter the skin to a similar depth, although some microneedle patches may just be inserted by finger or thumb pressure. Keeping the skin under tension may decrease skin deflection and therefore help to increase insertion depth. Microneedle geometry will also play a role and is being investigated. Despite the hurdles, FDA approval of microneedle technologies is likely since microneedles bear a close analogy to the widely used hypodermic delivery systems and offer several advantages, including low or no risk of needle stick injuries and allowing precise penetration depths with no trauma to the tissue. Dermaroller, a cosmetic/medical device with microneedles, is already available for direct application to the face followed by the application of cosmeceuticals. In its most common form, it has 192 microneedles in eight rows on a roller with a needle length of 130 μm. It has also been recently reported to be promising for drug delivery applications [83].

Recently, there have been many deaths associated with fentanyl patches due to increased delivery under heat, and other safety issues with marketed patches such as those relating to adhesive failure [84-86]. These considerations may also be important for microneedle patches and any additional safety considerations will need to be addressed. However, one advantage of microporation technologies may be that the microchannels created in the skin are generally hydrophilic, partly due to the presence of interstitial fluid. This can allow

the use of a soluble salt form of the drug, which is less likely to form a depot and the resulting problems. The salt form is also less likely to have significant passive permeation, thereby reducing the risk of accidental overdosage.

In summary, although microporation technologies have not fully matured yet and there are potential hurdles to overcome, they are very promising and are likely to revolutionize transdermal drug delivery in the near future. Several products are in clinical trials using microporation technologies and a product has also been approved using laser microporation (**Table 1**).

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