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Microneedles and transdermal applications

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With the limitations of oral drug delivery and the pain and needle phobias associated with traditional injections, drug delivery research has focused on the transdermal delivery route. A formidable barrier to transdermal drug delivery is the stratum corneum, the superficial layer of the skin. In the last 10 years, microneedles were proposed as a mechanical tool to pierce through the stratum corneum, in order to create drug delivery channels without stimulating underlying pain nerves. Since then, the field of microneedles has rapidly evolved to spawn a plethora of potential transdermal applications. In this review, the authors provide an overview of the progress in microneedle research and design, and the advancements that have been made in employing this technology for transdermal applications.

Keywords: gene therapy, injection, microneedles, skin, stratum corneum, transdermal drug delivery, vaccines

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1. Introduction

The oral route – the choice for most drugs taken by patients – comes with limitations on bioavailability, due to exposure to stomach acid, poor absorption rates in the gastrointestinal tract and first-pass hepatic metabolism. As an alternative drug delivery route, needles are useful because they can avoid these limitations of oral delivery. However, needles are painful and many people have a fear of them. Furthermore, they are more difficult to use in a long-acting continuous drug input system outside of the hospital. As a result, research into alternate transdermal drug delivery technologies have intensified (reviewed in [1]).

One focus of transdermal drug delivery (TDD) research has centred on the microneedle. Microneedles are miniature needles fabricated from lithographic techniques that have been designed to penetrate the stratum corneum (outer most skin layer) and enter the epidermis of the skin, yet avoid nerve endings that reside in the underlying dermis. This has been confirmed in several clinical studies [2-4]. As a result, microneedles offer a painless way to puncture through the stratum corneum. Expectedly, there are many possible applications that are under study at present, including targeted gene delivery, vaccinations, drug injections and fluid extraction.

2. Microneedle designs

Microneedles have been fabricated in a variety of designs, but come in two basic forms: in-plane and out-of-plane (Figure 1). In-plane microneedles are formed so that the needle is parallel to the fabrication surface; out-of-plane microneedles are formed such that the needles are perpendicular to the fabrication surface. Out-of-plane microneedles can be further subdivided into solid and hollow microneedles. The distinction between the two is that the hollow microneedles contain a conduit within the needle to allow for fluid passage, which the solid microneedles do not contain. A comparison between in-plane and out-of-plane

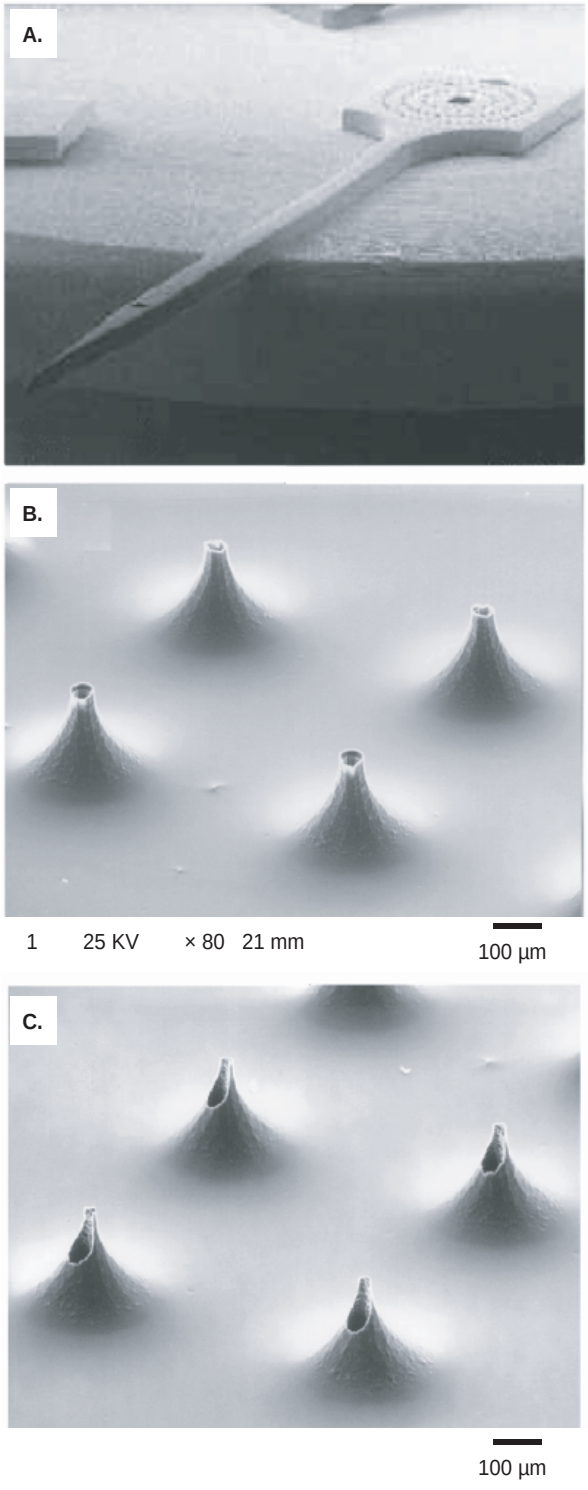

Figure 1. A. In-plane microneedles. B. Symmetrical out-of-plane hollow microneedles. C. Asymmetrical out-of-plane microneedles.

Adapted from SIVAMANI RK, STOEBER B, WU GC *et al.*: Clinical microneedle injection of methyl nicotinate: stratum corneum penetration. *Skin Res. Technol.* (2005) **11**(2):152-156, with permission from Blackwell Publishing.

microneedles is shown in Table 1. Reed and Lye provide an extensive review of the fabrication processes used in the development of in-plane and out-of-plane microneedles [5].

2.1 Microneedle fabrication material

The first microneedle devices were fabricated from silicon [6,7], but many other materials are now being used to manufacture microneedles. Although short-term biocompatibility studies have shown that silicon does not cause irritation in animals [8], portions of the silicon microneedle can potentially break off, due to silicon's brittle characteristics, and stay embedded in the epidermis. Long-term studies of silicon in the skin have not been performed, but there are rare reports of silicon-related granulomas, with a latency ranging from months to years [9]. For superficially penetrating microneedles, the renewing epidermis may shed broken pieces of silicon. On the other hand, silicon that breaks off deeper penetrating microneedles, such as fluid sampling microneedles, could possibly enter the dermis due to external mechanical forces, potentially resulting in prolonged silicon implantation. Furthermore, silicon is expensive and it would be more cost-effective to make microneedles out of other materials [10]. So far, microneedles have also been fabricated out of glass [11-13], titanium [14,15], metal [16], polymers [12,17-20], and sugars [3]. Glass microneedles also have the potential to break off in the skin, and although they are suitable for preliminary studies of feasibility and injection characteristics [12], it would be more desirable to use polymers and sugars, as they can biodegrade in the skin with time. On the other hand, polymer and sugar microneedles require more complex fabrication schemes than their silicon and glass counterparts.

2.2 Microneedle insertion and flow rates

It is essential that design parameters of the microneedle allow for efficient insertion and a high breaking-force:insertion-force ratio. Microneedle insertion force is linearly related to the needle tip interfacial area, and these insertion forces are low enough to allow for successful insertion by hand [21]. Furthermore, the ratio of breaking force to insertion force was found to be greater than one, favouring insertion over microneedle breakage. Vibratory actuation [22] and a jagged side design mimicking a mosquito proboscis [23] have been used to further improve in-plane microneedle insertion. Even though microneedles must pierce through 15 – 20 µm of stratum corneum before reaching the epidermis, microneedles need to be fabricated to much greater lengths due to the skin's elasticity [24].

Once the microneedle is in the skin, shear forces play an important role in microneedle breakage; it is no surprise that an increase in microneedle wall thickness leads to a decrease in the microneedle breaking force [21,24]. The use of arrays can help spread the surface forces between the microneedles in the array. Therefore, in-plane microneedles are at a disadvantage, as it is harder to fabricate a planar array, as opposed to a linear array. As a result, these microneedles will be exposed to higher individual microneedle shear forces and be more susceptible to breakage. Lin and Pisano showed

Table 1. Microneedle designs.

Microneedle Design	Advantages	Disadvantages
In-plane microneedles	Better control of design as all lithography is on the same plane Can be more easily integrated with sensors and pumps	Harder to develop an array of parallel microneedles Difficulty in array development exposes each microneedle to higher shear and breaking forces
Out-of-plane solid microneedles	Easier to fabricate arrays Can be coated with drugs or antigens for vaccination Can be left in place for slow release drug delivery	Cannot be used for slow infusion of drugs Cannot be used to extract fluid for analysis Pre-coated microneedles are able to deliver a limited dosage
Out-of-plane hollow microneedles	Easier to fabricate arrays Can be used for infusions Can be used to extract fluids for analysis (e.g., glucose) Can be integrated with microchips for infusion or withdrawal of fluid (more complex than with the in-plane microneedles)	More complex fabrication process Harder to integrate microchips and pumps into design

that in-plane microneedles were capable of repeated insertions into porterhouse steak without breaking [25]. It is of note that in an *in vivo* insertion, the microneedles are likely to experience greatly increased shear forces, due to movement and skin elasticity. In contrast, out-of-plane microneedles have an advantage in resisting breakage, as they can be fabricated into planar arrays, with the caveat that there must be enough spacing between each microneedle to avoid decreases in insertion efficiencies due to a 'bed of nails' effect [24,26].

With the exception of solid out-of-plane microneedles that have no conduit for fluid flow, the fluid flow characteristics of in-plane and hollow out-of-plane microneedle are important for drug delivery. In-plane microneedles with larger tip opening diameters require less pressure to deliver a particular flow rate of fluid [13], and conically shaped out-of-plane microneedles create a pressure gradient that increases flow efficiencies [27]. In contrast to cylindrically shaped out-of-plane microneedles, where fluid flow depends on the microneedle length, Martanto *et al.* showed through mathematical modelling that flow in tapered out-of-plane microneedles was not dependant on microneedle length [27]. This provides two advantages: first, the length of the microneedle can be dictated by the epidermal anatomy rather than be limited by microneedle length. Secondly, tapered microneedles can penetrate the stratum corneum more easily and would require reduced insertion forces compared with cylindrical microneedles.

The design and placement of the orifice in hollow out-of-plane microneedles influence the microneedle's propensity to clog upon insertion into tissue. Microneedles with their orifice placed symmetrically along the plane of insertion, had reduced fluid delivery efficiency compared with microneedles that had their orifice offset from the midline axis [4] (Figure 1). In order to reduce this, several unique fabrication designs placed the fluid delivery path away from the insertion point of the microneedle [28,29]. Distinct from clogging of the needle, skin compression opposed fluid flow out of the microneedles due to increases in flow resistance [4,30] and partial retraction of microneedle improved flow rates *in vitro* [31] and *in vivo* [32].

2.3 Microneedle applications

2.3.1 Out-of-plane solid microneedles

Solid microneedle arrays were first used as a patch to create tiny holes in the stratum corneum and therefore create transport pathways for drug solutions and increase stratum corneum permeability [7]. This system was shown to be able to successfully transport insulin in human cadaver skin [12] and in rats [33]. In order to better control and define the drug delivery transport rates, newer solid microneedles were coated with drug solutions prior to insertion. This scheme was used to deliver desmopressin into guinea-pigs after a 5-min application of a desmopressin-coated metal microneedle array [15]. More recent designs include fabrication of microneedles with porous tips that can potentially serve as a reservoir bay for drugs [34], and the fabrication of microneedles that includes loading of drugs into the tip during the fabrication process (Figure 2) [19] .

Microneedles have also been designed with drugs that are dispersed into the microneedle during the fabrication process, where the drug is slowly released as the microneedle degrades in the skin. Miyano *et al.* fabricated a dissolving sugar microneedle and suggested that sugar microneedles could be loaded with insulin or DNA material for release after insertion [3]. Dissolving polymer microneedles have been inserted into rats and mice to slowly release erythropoietin [20] and insulin [35].

Solid out-of-plane microneedles have also been used for gene therapy and vaccination studies. Disruption of the

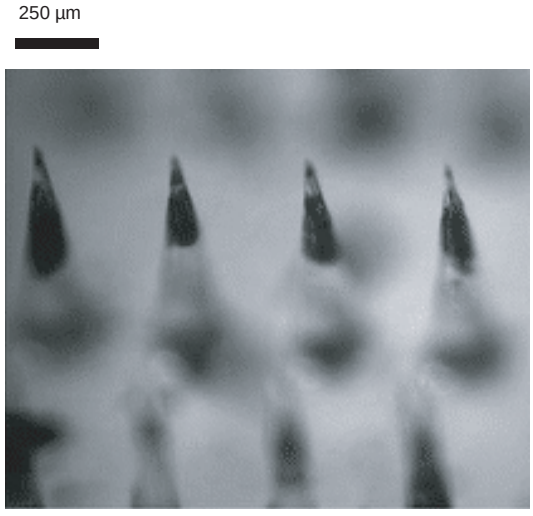

Figure 2. Polymer tapered-cone microneedles made of poly-lactide-co-glycolide and encapsulating calcein within their tips.

Adapted from MILLARD DR JR, MAISELS DO: Silicon granuloma of the skin and subcutaneous tissues. *Am. J. Surg.* (1966) **112**(1):119-123, with permission from Springer.

stratum corneum was shown to create holes in epidermal sheets that were large enough to allow for passage of pDNA material through the microneedle pores [36]. Indeed, microneedle insertion forms conduits through the stratum corneum and allows topical penetration and expression of plasmid DNA *ex vivo* in human skin [37,38] and *in vivo* in mice [39].

Microneedle vaccinations were proposed as a potential vaccination route due to the presence of Langerhans cells in the epidermal layers. These cells are efficient antigen-presenting cells that can elicit an immune response and have been the focus of several TDD vaccination studies (reviewed in [40]). Microneedle vaccinations have become more tangible, with one of the first microneedle studies showing successful immunisation against the hepatitis B surface antigen through plasmid-based delivery in mice [39]. In fact, microneedle delivery was more efficient in producing antibodies against anthrax and hepatitis B in comparison with intramuscular and intranasal antigenic delivery routes [39,41]. In these studies, the microneedles created pores in the stratum corneum and then the antigenic solution was topically applied. However, a recent study has shown efficient immunisation by coating microneedles with the antigenic material prior to insertion into skin [42]. Microneedles delivered ~ 50% of their coated drug load, and the elicited immune responses in guinea-pigs were dependant on the loading dose but independent of the depth of delivery, the microneedle density or the area of application. Interestingly, coated microneedle vaccination produced a greater immune response than intramuscular injection, which was in agreement with earlier studies [39,41]. More information about the field of transdermal vaccinations can be found in a detailed review by Giudice and Campbell [43].

2.3.2 *Out-of-plane hollow microneedles*

The fabrication of hollow microneedles opened new frontiers in TDD, including the possibility of bolus and continuous drug delivery therapies. On the other hand, development and usage of hollow microneedles have their own set of obstacles, including more complex fabrication processes and issues with clogging and flow efficiencies. Stoeber and Liepmann reported the first *in vitro* hollow silicon microneedle array based injections with an injection depth of 100 µm [44]. Subsequent studies showed that single, glass microneedles developed from micropipette techniques were capable of penetrating and injecting below the stratum corneum [12]. It was found that during insertion, the tissue developed considerable resistance to flow during compression and retraction, and vibration of the microneedle array greatly improved injection efficiencies [30-32]. Successful *in vivo* insulin injections to lower blood glucose have been performed in rats [12,16,28], and Gardeniers *et al.* reported that microneedle array injection of insulin was comparable to subcutaneous insulin injection [28]. A recent study with blunt hollow microneedles found that the microneedles were unable to inject insulin into rats [26], underscoring the need for tapered microneedles for effective stratum corneum penetration. Controlled clinical trials in humans showed that microneedles improved transdermal penetration of methyl nicotinate and that microneedles with an asymmetrical conduit were more efficient in transdermal delivery than microneedles with a symmetrical conduit [4]. Subsequent tape-stripping injection studies have suggested that microneedles enhanced transdermal penetration by delivering under the stratum corneum rather than delivering into the stratum corneum [45]. The authors are not aware of any studies that have investigated long-term drug injections with out-of-plane hollow microneedle arrays.

Several recent studies have adapted hollow microneedles for interstitial fluid and blood collection. Tsuchiya *et al.* describe a glucose detection system where a single microneedle has been attached to a piezoelectric microactuator for indentation into skin and extraction of blood at the rate of 2 µl/min for analysis [14]. In another study by Mukerjee *et al.*, arrays of microneedles were fabricated such that inserted microneedles extracted epidermal interstitial fluid based on capillary action and shunted the fluid to a glucose sensor for *in situ* measurement [46].

2.3.3 *In-plane microneedles*

In-plane fabrication of microneedles has afforded a greater ability to integrate microfluidics and electrodes into the body of the microneedle [8,47,48]. With this design, pumps can be fabricated for pumping and extraction, coupled with *in situ*

fluid analysis (reviewed in [49]). Microfluidics have been incorporated with glass in-plane microneedles to control injection volumes to < 1 nl *in vitro* [13], but these integrated devices have not been tested in tissue injection studies. Oka *et al.* designed a jagged microneedle based on the mosquito proboscis anatomy for blood extraction, and incorporated a reservoir for holding the extracted blood [23]. More complex detection schemes have also been developed where the extracted fluid components can be selectively analysed based on molecular weights [48]. Although planar arrays of microneedles are difficult to fabricate [5], linear arrays of in-plane microneedles have been developed [50,51] for fluid analysis and extraction. A more detailed review of in-plane fabrication methods is provided by Reed and Lye [5].

3. Conclusions

Over the past 10 years, microneedles have evolved from a science of fabrication into a science of clinical promise. As more creative fabrication techniques emerge, there has been a drive to move away from silicon towards more biocompatible materials. The initial development of microneedle to puncture and painlessly create transport pathways through the stratum corneum has expanded to include direct drug infusion, vaccination, gene therapy and fluid detection systems.

There is much work to be done before microneedles are accepted for wide use in patient care, but novel designs are addressing these issues. Unique microneedle designs have reduced clogging rates. Greater control over fluid flow characteristics has been achieved through the integration of pumps. Microfluidic and self-contained *in situ* analysis systems reflect progress in the development of integrated microneedle systems. It is hoped that as microneedle research continues to progress, clinical acceptance of microneedles will be achieved in the near future.

4. Expert opinion

The drive for research into TDD reflects the growing need to develop clinical alternatives to the currently used oral and traditional needle delivery routes. Microneedles have emerged with significant potential to revolutionise the way that drugs are delivered into the body. Other TDD techniques such as iontophoresis, liposomal transport, injection jets and electroporation also bypass or disrupt the stratum corneum barrier to enhance penetration, but microneedles possess several significant advantages. Microneedles create larger transport pathways to allow for the delivery of larger drugs such as insulin. In addition, there is the potential for controlled, continuous release by integration of microfluidics with hollow microneedles. Microneedles also possess more versatility than other TDD modalities. Solid microneedles have been used to increase skin permeability to subsequently administered drug patches. They are coated with drugs for vaccinations and gene therapy applications, and can be created in dissolving forms for slow release of drugs. In fact, a recent study with desmopressin-coated solid microneedles showed that the average bioavailability of desmopressin injected through coated microneedles was 79% [15]. Hollow microneedles have been used for bolus injections, extraction of interstitial fluid and blood for subsequent analysis, and have the potential for continuous drug injection with onboard microcircuitry.

However, there are obstacles that will be important points of investigation as microneedle research continues to advance. The process of pre-loading drugs into the tips or the body of dissolving microneedles requires that the loaded molecules or peptides remain stable through the microneedle fabrication process. More studies will be needed to determine which drugs or vaccines will be suitable for this type of delivery, as opposed to injection through hollow microneedles, which would expose drugs or vaccines to milder conditions. *In vitro* studies have shown that when solid microneedles are inserted and then removed, skin permeability remains elevated for at least 5 h [7]. However, it remains to be determined how long the microneedle created pores remain open *in vivo* with or without skin occlusive patches. This will be important knowledge as longer pore closure times will lead to a greater chance of infection. Almost all recent *in vivo* reports focus on the short-term insertion and removal of microneedles, and no studies, to our knowledge, have analysed the effects of leaving microneedles inserted for long periods of time. The potential for infections and microneedle failure will need to be addressed in future long-term studies.

Nevertheless, microneedles can dramatically transform several areas of drug delivery. Microneedles offer a revolutionary solution over exisiting diabetic treatment regimens. One can envision a microneedle patch in the future that is able to measure glucose levels and then send a signal to an onboard microchip that can trigger the controlled release of an appropriate amount of insulin. Such a device could potentially automate the system much like an artificial pancreas and afford better control of blood glucose levels. This has many public health implications, including the delay of the onset of severe diabetes-related pathology such as cardiovascular disease, retinopathy and nephropathy. Several recent studies have shown that microneedles can be used for fluid extraction and measurement of glucose levels, but another obstacle lies herein that must be addressed in the coming years. In order to avoid pain during microneedle extraction, only the fluid from the epidermal layers should be extracted; this will be interstitial fluid rather than blood, as there are no vessels in the epidermal layers. Therefore, accurate algorithms will need to be developed to relate the blood glucose to the interstitial fluid glucose levels, and these algorithms can be quite complex, with many parameters [52]. As future studies move toward a more clinical approach, assessment of the validity of these algorithms will be paramount before initiating broad patient trials. Another area for future research will be to find ways to create a detection/delivery patch that integrates detection microneedles

with delivery microneedles. This answer may lie in coupling in-plane microneedles for detection with hollow out-of-plane microneedles for drug infusion, and future research will shed light on the possibilities.

The potential impact of creating microneedle gene therapy and vaccination systems is tremendous. This review has shown that microneedle vaccinations may be more effective than intramuscular injections and this can have a global public health impact. Microneedle vaccinations would be painless and would not require special training, unlike intramuscular injections. Furthermore, the painless aspect of the vaccine is likely to be met with more acceptance and increased vaccination compliance rates. In addition, the simplicity of administering such a vaccine would make it more accessible in poorer parts of the world, as a volunteer could be quickly trained and therefore a trained health professional would not be required. The cost of fabricating microneedles was much more expensive when silicon was the only possible fabrication surface, but the recent development of polymer-based microneedles make cost-effective mass production more possible. Before these future potentials can be realised, it will be important to further investigate which vaccines can be suitably coated or fabricated onto a microneedle. Further study of vaccination efficiencies will be needed through *in vivo* animal experiments, with progression to clinical testing.

In summary, this an exciting time for microneedle research, and there are many potential applications on the horizon. Taken together, this embryonic field offers promise. Clinical execution will benefit from the cooperation of experienced scientists combining pharmacokinetics, engineering and dermatology.

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