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Microneedles for transdermal drug delivery

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Abstract

The success of transdermal drug delivery has been severely limited by the inability of most drugs to enter the skin at therapeutically useful rates. Recently, the use of micron-scale needles in increasing skin permeability has been proposed and shown to dramatically increase transdermal delivery, especially for macromolecules. Using the tools of the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials. Most drug delivery studies have emphasized solid microneedles, which have been shown to increase skin permeability to a broad range of molecules and nanoparticles in vitro. In vivo studies have demonstrated delivery of oligonucleotides, reduction of blood glucose level by insulin, and induction of immune responses from protein and DNA vaccines. For these studies, needle arrays have been used to pierce holes into skin to increase transport by diffusion or iontophoresis or as drug carriers that release drug into the skin from a microneedle surface coating. Hollow microneedles have also been developed and shown to microinject insulin to diabetic rats. To address practical applications of microneedles, the ratio of microneedle fracture force to skin insertion force (i.e. margin of safety) was found to be optimal for needles with small tip radius and large wall thickness. Microneedles inserted into the skin of human subjects were reported as painless. Together, these results suggest that microneedles represent a promising technology to deliver therapeutic compounds into the skin for a range of possible applications.

Keywords: Microfabrication; MEMS; Transdermal drug delivery; Injection; Skin mechanics; Pain

Contents

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1. Introduction

When oral administration of drugs is not feasible due to poor drug absorption or enzymatic degradation in the gastrointestinal tract or liver, injection using a painful hypodermic needle is the most common alternative. An approach that is more appealing to patients, and offers the possibility of controlled release over time, is drug delivery across the skin using a patch [1,2]. However, transdermal delivery is severely limited by the inability of the large majority of drugs to cross skin at therapeutic rates due to the great barrier imposed by skin's outer stratum corneum layer.

To increase skin permeability, a number of different approaches has been studied, ranging from chemical/lipid enhancers [3,4] to electric fields employing iontophoresis and electroporation [5,6] to pressure waves generated by ultrasound or photoacoustic effects [7,8]. Although the mechanisms are all different, these methods share the common goal to disrupt stratum corneum structure in order to create "holes" big enough for molecules to pass through. The size of disruptions generated by each of these methods is believed to be of nanometer dimensions, which is large enough to permit transport of small drugs and, in some cases, macromolecules, but probably small enough to prevent causing damage of clinical significance.

An alternative approach involves creating larger transport pathways of microns dimensions using arrays of microscopic needles. These pathways are orders of magnitude bigger than molecular dimensions and, therefore, should readily permit transport of macromolecules, as well as possibly supramolecular complexes and microparticles. Despite their very large size relative to drug dimensions, on a clinical length scale they remain small. Although safety studies need to be performed, it is proposed that micron-scale holes in the skin are likely to be safe, given that they are smaller than holes made by hypodermic needles or minor skin abrasions encountered in daily life [9].

Although the microneedles concept was proposed in the 1970s [10], it was not demonstrated experimentally until the 1990s when the microelectronics industry provided the microfabrication tools needed to make such small structures. Since the first studies of transdermal drug delivery in 1998 [11], there has been rapidly increasing interest in the field, with most activity in the microfabrication community to develop novel needle fabrication technologies and the drug delivery industry to develop microneedles for pharmaceutical applications.

2. Transdermal drug delivery using microneedles

The overarching motivation for microneedles is that they can provide a minimally invasive means to transport molecules into the skin. Guided by this goal, a number of specific strategies have been employed to use microneedles for transdermal delivery. Most work has focused on making microscopic holes in the skin by inserting solid microneedles made of silicon or metal. The "poke with patch" approach uses microneedles to make holes and then apply a transdermal patch (or some prototype) to the skin surface. Transport can occur by diffusion or possibly iontophoresis if an electric field is applied. Another approach is "coat and poke," where the needles are first coated with drug and then inserted into the skin. There is no drug reservoir on the skin surface; all the drug to be delivered is on the needle itself. A variation on this second approach is "dip and scrape," where microneedles are first dipped into a drug solution and then scraped across the skin surface to leave behind drug within microabrasions created by the needles.

Hollow microneedle designs and methods have also been studied using an approach more reminiscent of an injection than a patch. Although harder to make and use, hollow needles facilitate active fluid flow through the needle bore and into the skin, which can

lead to much faster rates of delivery that can be modulated over time.

Following is a summary of the literature on the use of microneedles for transdermal delivery of drugs, proteins, genetic material, and vaccines. It emphasizes work that has been published and directly addresses drug delivery. This review does not include the dozens of conference abstracts from the microfabrication community that focus on novel needle fabrication technology without examining the performance of those needles to deliver drugs into skin. Similarly, it does not include the apparently extensive, unpublished work of companies developing microneedles for transdermal drug delivery.

2.1. Solid microneedles

Solid microneedles can be used to create micron-scale holes in the skin through which molecules can more easily transport. The first microneedle arrays reported in the literature were etched into a silicon wafer and developed for intracellular delivery in vitro by Hashmi et al. [12]. These needles were inserted into cells and nematodes to increase molecular uptake and gene transfection. Shortly after this work was published, microneedles were developed for transdermal delivery applications, which have been shown to insert into skin and thereby deliver a variety of different compounds in vitro and in vivo.

2.1.1. First studies of transdermal delivery

Henry et al. [11] conducted the first study to determine if microneedles could be used to increase transdermal drug delivery. An array of solid microneedles was embedded in cadaver skin, which caused skin permeability to a small model compound, calcein, to increase by three orders of magnitude. Increased transport was interpreted to occur through leakage pathways between the needles and skin. After removing the needles, thereby unplugging the holes they created, skin permeability increased by another order of magnitude.

In a follow-up study, McAllister et al. [13] studied permeability of cadaver skin to a range of different compounds and found that insulin, bovine serum albumin, and latex nanoparticles as large as 100 nm in diameter could cross the skin after treatment with microneedles. Mathematical modeling of the data indicated that transport of these compounds was by simple diffusion.

In these studies, microneedles were made from a silicon wafer using lithography and reactive ion etching. As shown in Fig. 1a, the resulting needles formed a 20-by-20 array, where each needle measured 80 μm at the base and tapered to a height of 150 μm with a radius of curvature at the tip close to 1 μm.

The significance of these studies is that they demonstrate increased transdermal transport using microneedles and show that skin permeability can be increased by orders of magnitude. They also present detailed information on methods to fabricate needles suitable for transdermal drug delivery.

2.1.2. Oligonucleotide delivery: “poke with patch”

Extending in vitro findings to the in vivo environment, Lin et al. [14] used microneedles either alone or in combination with iontophoresis to deliver 20-mer phosphorothioated oligodeoxynucleotides across the skin of hairless guinea pigs. Using a sandwich design, microneedle arrays were inserted into the skin (“poke”) and covered with an oligonucleotide-loaded gel, which sometimes had an iontophoretic electrode on top (“patch”). Insertion of microneedles during iontophoresis increased transdermal flux by 100-fold relative to iontophoresis alone. In the absence of iontophoresis (i.e. passive diffusion), microneedles also increased transdermal delivery relative to intact skin. Histological examination of the skin revealed high levels of oligonucleotide delivered 700–800 μm deep into the skin using microneedles. In contrast, delivery without microneedles showed lower concentrations with only superficial transport into skin. Additional studies showed that increasing donor concentration, current density and time (up to 24 h) all increased the amount of drug delivered using microneedles. A related study further demonstrated microneedle-enhanced delivery of desmopressin and human growth hormone using a similar approach [15].

The needles used in this study—termed “microprojection arrays”—were etched from stainless steel or titanium sheets. Each needle measured 430 μm in height and made up an array of 480 needles in an area of 2 cm^2 (similar to those shown in Fig. 1c).

The significance of this study is that it demonstrates microneedle-based delivery in vivo and examines the effects of some formulation variables. The highest

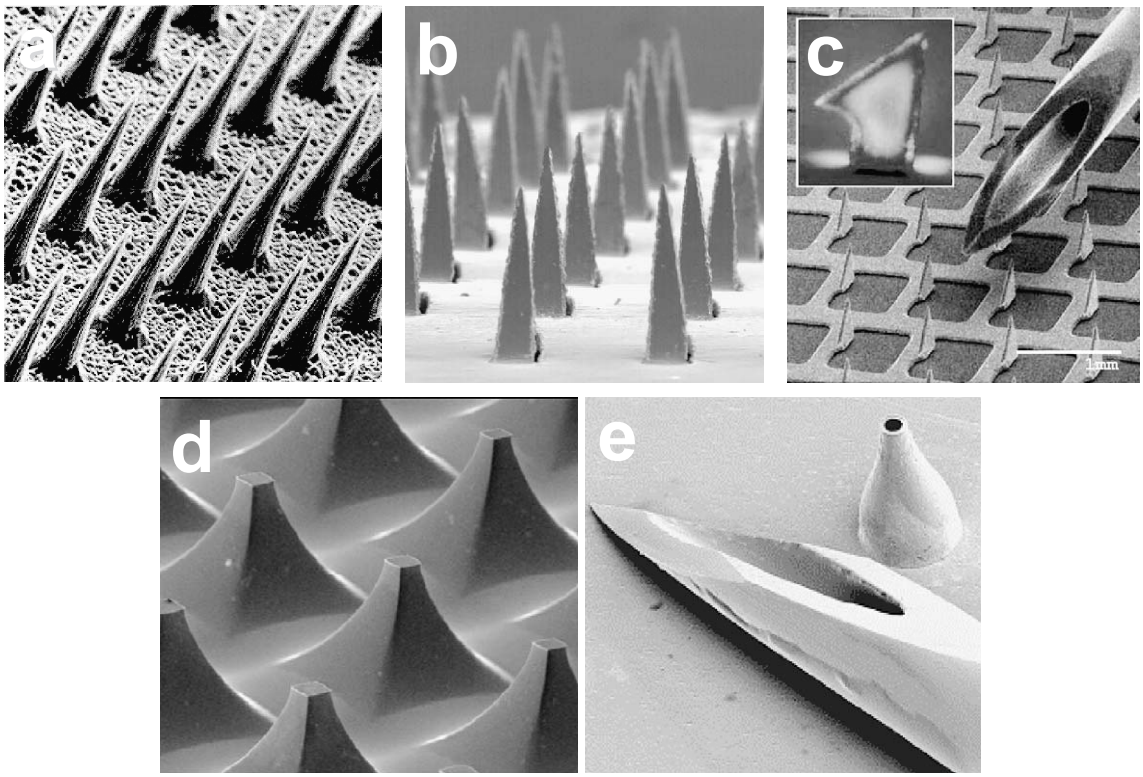

Fig. 1. Images of microneedles used for transdermal drug delivery. (a) Solid microneedles (150 μm tall) etched from a silicon wafer were used in the first study to demonstrate microneedles for transdermal delivery. (b) Solid microneedles (1000 μm tall) laser-cut from a stainless steel sheet were used to deliver insulin to diabetic rats. (c) Solid microneedles ("microprojection array", 330 μm tall) acid-etched from a titanium sheet were coated with protein antigen for vaccine delivery in vivo; similar needles were used to deliver oligonucleotides in vivo. (d) Solid microneedles ("microenhancer array", 200 μm tall) chemically etched from a silicon wafer were dipped in plasmid DNA solution for vaccine delivery in vivo. (e) Hollow microneedles (500 μm tall) formed by electrodeposition of metal onto a polymer mold were used for needle insertion and fracture force measurements. Images were adapted and reproduced with permission from (a) Ref. [11], (b) Ref. [16], (c) Ref. [17], (d) Ref. [18] and (e) Ref. [22].

delivery rate achieved was 16 mg/day, which may be sufficient for future therapeutic applications of oligonucleotides.

2.1.3. Insulin delivery: "poke with patch"

Using solid microneedles of a different design, Martanto et al. [16] delivered insulin to diabetic hairless rats in vivo. Microneedle arrays were inserted into the skin using a high-velocity injector and shown by microscopy to embed fully within the skin. A solution of insulin was placed on top of the microneedle array and left in place for 4 h. Over this time period, blood glucose levels steadily decreased by as much as 80%. Insulin placed on the skin surface without microneedles as a negative control did not have significant effects. Increasing the donor solution insulin concentration or decreasing the microneedle insertion time both resulted in larger drops in blood glucose levels.

This study employed arrays with 105 needles measuring 1000 μm in length with a 75×200 μm cross section at their base and tapering to a sharp tip (Fig. 1b). These arrays were fabricated by laser-cutting the shape of each needle into a stainless steel sheet and then bending each needle at 90° out of the plane of the sheet.

The significance of this study is that it demonstrates pharmacological efficacy of a bioactive drug (i.e. reduction of blood glucose level by insulin in a diabetic animal) using microneedles.

2.1.4. Protein vaccine delivery: "coat and poke"

Matriano et al. [17] examined the use of microneedles to deliver ovalbumin as a model protein antigen coated onto the needle surface. Microneedles were prepared with a dry-film coating of antigen and then inserted into the skin of hairless guinea pigs in vivo using a high-velocity injector. Insertion depth was shown to average 100 μm, with 300 μm as the maximum depth. A range of doses was given by varying the antigen solution concentration coated onto the needles and the number of needles used. Antigen release from the needle surface was found to occur quickly, where up to 20 μg could be released within 5 s. Using a prime-plus-boost protocol, antibody responses were found to be similar for microneedle delivery and intradermal injection, and up to 50-fold greater than subcutaneous or intramuscular injection of the same antigen doses. The greater immune responses to the two intracutaneous delivery methods is proposed to be caused by the presence of antigen-presenting Langerhans cells in the basal epidermis. Coating microneedles with both antigen and a glucosaminyl muramyl dipeptide adjuvant increased antibody responses further. A related study also demonstrated delivery from microneedles coated with desmopressin [15].

The microneedle arrays (i.e. microprojections) used in this study were acid-etched from a titanium sheet and measured 330 μm in length. Array size was either 1 or 2 cm^2 with a needle density of 190 needles per cm^2, as shown in Fig. 1c.

The significance of this study is that it demonstrates protein antigen delivery to generate an antibody response using microneedles. It also establishes the feasibility of using a dry-coat method to deliver compounds from microneedles.

2.1.5. DNA vaccine delivery: "dip and scrape"

Mikszta et al. [18] studied delivery of naked plasmid DNA into skin using microneedles. The arrays were dipped into a solution of DNA and scraped multiple times across the skin of mice in vivo to create microabrasions. Expression of a luciferase reporter gene was increased up to 2800-fold using microneedles compared to topical application alone. Using plasmid DNA encoding hepatitis B surface antigen, microneedle delivery induced immune responses that were stronger and less variable compared to hypodermic injection and required fewer immunizations for full seroconversion.

Unlike microneedles used previously, this study used blunt-tipped microneedles measuring 50–200 μm in length over a 1 cm^2 area (Fig. 1d). These "microenhancer arrays" were etched from silicon wafers using lithography and potassium hydroxide etching.

The significance of this study is that it demonstrates DNA vaccine delivery to generate an immune response using microneedles. It also establishes the feasibility of using blunt-tipped microneedles to scrape the skin for increased delivery.

2.2. Hollow microneedles

In contrast to the solid microneedles discussed above, microneedles containing a hollow bore offer the possibility of transporting drugs through the interior of well-defined needles by diffusion or, for more rapid rates of delivery, by pressure-driven flow. A variety of hollow microneedles have been fabricated, but only limited work has been published on their possible use to deliver compounds into skin.

McAllister et al. [13] used single glass microneedles inserted into the skin of diabetic hairless rats in vivo to deliver insulin during a 30-min infusion. This study demonstrated up to a 70% drop in blood glucose level over a 5-h period after the insulin was administered. These needles were fabricated using a micropipette puller and beveler with a tip radius of 60 μm and were inserted into the skin to a depth of 500–800 μm. This study demonstrates microneedle-based drug injection into the skin.

In related studies, Stoeber and Liepmann [19] demonstrated injection into chicken thigh in vitro using microneedle arrays. Chen and Wise [20] used microneedles to inject chemical stimuli into brain tissue in vivo. Smart and Subramanian [21] used single microneedles to extract nanoliter quantities of blood from the skin to measure glucose levels.

3. Mechanics of microneedle insertion into skin

Most studies of microneedles have addressed methods of fabrication and assessed drug delivery capabilities. The mechanics of microneedle insertion have

received only limited attention, but are critically important to practical applications. Only microneedles with the correct geometry and physical properties are able to insert into skin. Some needle designs require only insertion by hand, whereas others benefit from high-velocity insertion, as mentioned above. When the force required for insertion is too large, needles can break or bend before insertion occurs.

These issues have been explicitly addressed by Davis et al. [22], who measured the force required for fracture, the force required for insertion, and their ratio (termed the margin of safety) as a function of needle geometry and physical properties. In this study, individual hollow metal microneedles were used (Fig. 1e) with tip radii of 30–80 μm, wall thicknesses of 5 μm to solid tips (equivalent to 58 μm wall thickness) and constant length of 500 μm.

To determine the effect of microneedle geometry on the force of insertion, individual microneedles were inserted into the skin of human subjects while recording the force and displacement of the needle, as well as monitoring skin resistance (which was used to indicate needle insertion into the skin). Forces of insertion varied from 0.1 to 3.0 N (i.e. 10–300 g) and showed an approximately linear dependence on the area of the needle tip. Insertion force was found to be independent of wall thickness; thin-walled hollow needles and solid needles with the same outer tip radii required the same force of insertion. This indicated that skin was insufficiently flexible to dimple into the needle bore.

To determine the effect of microneedle geometry on the force of fracture, individual microneedles were pressed against a rigid surface until they fractured. Over the range considered, measured fracture forces were between 0.5 and 6 N. Fracture force increased strongly with increasing wall thickness and increased weakly with increasing wall angle, but was independent of tip radius. These results agreed with analytical and finite element modeling.

The ratio of the fracture force to the insertion force can be considered the margin of safety; values greater than one identify needles that will insert into skin without breaking. Almost all needles tested had margins of safety greater than one and some were greater than ten. The largest margin of safety was achieved using needles with small tip radius (to facilitate insertion) and large wall thickness (to provide strength).

4. Lack of pain caused by microneedles

Microneedles are of interest primarily because they offer the promise of painless drug delivery. Because the skin's stratum corneum barrier has no nerves, skin anatomy provides the opportunity to pierce needles across the stratum corneum without stimulating nerves. In current practice, there is no evidence of microneedles penetrating just 10–20 μm across stratum corneum without entering the viable epidermis, where nerves are found. Instead, microneedles are inserted at least into the epidermis and sometimes into the superficial dermis, as discussed above. Nevertheless, microneedles are still reported as painless, probably because their small size reduces the odds of encountering a nerve or of stimulating it to produce a painful sensation.

Kaushik et al. [23] carried out a small trial to determine if microneedles are perceived as painless by human subjects. Microneedle arrays (Fig. 1a) were inserted into the skin of 12 subjects and compared to pressing a flat surface against the skin (negative control) and inserting a 26-gauge hypodermic needle into the skin surface (positive control). Subjects were unable to distinguish between the painless sensation of the flat surface and that caused by microneedles. All subjects found the sensation caused by the hypodermic needle to be much more painful. Other studies have also reported that microneedles were applied to human subjects in a painless manner [18,21].

5. Conclusion

A review of the literature shows that microneedles can be fabricated by a number of different methods to yield a variety of needle sizes, shapes and materials. Solid microneedles have been shown to increase transdermal delivery by "poke with patch," "coat and poke," and "dip and scrape" methods, and hollow microneedles have been shown to microinject into skin. Therapeutic responses have been achieved in vivo following delivery of proteins, DNA and vaccines. Proper needle design can assure insertion into the skin that prevents needle fracture or patient pain. These studies suggest that microneedles may provide a powerful new approach to transdermal drug delivery.

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