Microfabricated Microneedles: A Novel Approach to Transdermal Drug Delivery

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Abstract □ Although modern biotechnology has produced extremely sophisticated and potent drugs, many of these compounds cannot be effectively delivered using current drug delivery techniques (e.g., pills and injections). Transdermal delivery is an attractive alternative, but it is limited by the extremely low permeability of skin. Because the primary barrier to transport is located in the upper 10–15 μm of skin and nerves are found only in deeper tissue, we used a reactive ion etching microfabrication technique to make arrays of microneedles long enough to cross the permeability barrier but not so long that they stimulate nerves, thereby potentially causing no pain. These microneedle arrays could be easily inserted into skin without breaking and were shown to increase permeability of human skin in vitro to a model drug, calcein, by up to 4 orders of magnitude. Limited tests on human subjects indicated that microneedles were reported as painless. This paper describes the first published study on the use of microfabricated microneedles to enhance drug delivery across skin.

Introduction

The development of more sophisticated drugs has demanded the need for more sophisticated methods to deliver those drugs. Conventional drug delivery techniques using pills and injections are often not suitable for new protein-based, DNA-based, and other therapeutic compounds produced by modern biotechnology.[1−3] An attractive alternative method of delivery involves drug administration across the skin. This approach avoids degradation in the gastrointestinal tract and first-pass effects of the liver associated with oral delivery as well as the pain and inconvenience of intravenous injection.[4−6] Moreover, it offers the possibility to continuously control the delivery rate, in contrast to conventional methods which deliver a large, discrete bolus.

Despite its many potential advantages, transdermal drug delivery is severely limited by the poor permeability of human skin; most drugs do not cross skin at therapeutically relevant rates. A number of methods have been developed to increase rates of transdermal transport with varied levels of success. Chemical enhancers can increase permeability of skin to small molecules but also trigger skin irritation or other safety concerns which limit their use.[5] Iontophoresis employs an electric field to drive ionized molecules across skin by electrophoresis and nonionized molecules by electroosmosis.[7] Despite concerns about skin irritation, iontophoresis may be useful to deliver some peptides and small proteins. Recently, physical methods to transiently increase skin permeability using electroporation[8] and ultrasound[9] have shown promise for delivery of both small drugs and macromolecules. However, more work, especially clinical studies, are needed to fully assess their potential impact.

In this study, we present a novel approach to transdermal drug delivery which dramatically enhances transport of molecules across skin. We have used standard microfabrication techniques to etch arrays of micron-size needles into silicon. When these microneedle arrays are inserted into the skin, they create conduits for transport across the stratum corneum, the outer layer of skin which forms the primary barrier to transport. Once a compound crosses the stratum corneum it can diffuse rapidly through deeper tissue and be taken up by the underlying capillaries for systemic administration. In addition, for reasons described below, microneedle arrays could create these transport conduits without causing pain. This type of approach has been proposed before in patents,[18,19] but, to our knowledge, has not before been demonstrated in the scientific literature.

The design of microneedles which painlessly permeabilize skin is based on an understanding of skin anatomy. Human skin is made of three layers: stratum corneum, viable epidermis, and dermis.[10] The outer 10−15 μm of skin, called stratum corneum, is a dead tissue that forms the primary barrier to drug transport. Below lies the viable epidermis (50−100 μm), a tissue containing living cells and nerves, but no blood vessels. Deeper still, the dermis forms the bulk of skin volume and contains living cells, nerves, and blood vessels. Therefore, microneedles which penetrate the skin just a little more than 10−15 μm should provide transport pathways across the stratum corneum, but do so painlessly since the microneedles do not reach nerves found in deeper tissue.

Microneedles were made using microfabrication technology, which is the same technology used to make integrated circuits.[11] An advantage of this approach is that microfabrication readily makes structures of micron dimensions in a way that is easily scaled up for cheap and reproducible mass production. In addition to extensive work using microfabrication for nonbiological purposes, this technology has been used for biological applications to fabricate two-dimensional arrays of electrodes used to excite neurons and record their activity[12,13] and three-dimensional arrays of pyramidlike structures to facilitate transfection of microorganisms.[14] To adapt this technology for transdermal drug delivery, we created three-dimensional arrays of sharp-tipped microneedles of approximately 150 μm in length.

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Materials and Methods

Microneedles—A deep reactive ion etching process was used to microfabricate the needles for this study. In this process, a chromium masking material is deposited onto silicon wafers and patterned into dots which have a diameter approximately equal to the base of the desired microneedles. The wafers are then loaded into a reactive ion etcher and subjected to a carefully controlled plasma based on fluorine/oxygen chemistries to etch very deep, high aspect ratio valleys into the silicon. Those regions protected by the metal mask remain and form the microneedles.

Definition and Deposition of Mask—⟨100⟩-oriented, prime grade, 450−550 μm thick, 10−15 Ω-cm silicon wafers (Nova Electronic Materials Inc., Richardson, TX) were used as the starting material. The wafers were cleaned in a solution of 5 parts by volume deionized water, 1 part 30% hydrogen peroxide, and 1 part 30% ammonium hydroxide (J. T. Baker, Phillipsburg, NJ) at approximately 80 °C for 15 min, and then dried in an oven (Blue M Electric, Watertown, WI) at 150 °C for 10 min. Approximately 1000 Å of chromium (Mat-Vac Technology, Flagler Beach, FL) was deposited onto the wafers using a DC-sputterer (601 Sputtering System, CVC Products, Rochester, NY). The chromium layer was patterned into 20 by 20 arrays of 80 μm diameter dots with 150 μm center-to-center spacing using the following lithographic process. A layer of photosensitive material (1827 photoresist, Shipley, Marlborough, MA) was deposited onto the chromium layer covering the silicon wafers. A standard lithographic mask (Telic, Santa Monica, CA) bearing the appropriate dot array pattern was positioned on top of the photoresist layer. The wafer and photoresist were then exposed to ultraviolet (UV) light through the mask by means of an optical mask aligner (Hybralign Series 500, Optical Associates, Inc., Milpitas, CA). The exposed photoresist was removed by soaking the wafers in a liquid developer (354 developer, Shipley, Marlborough, MA) leaving the desired dot array of photoresist on the chromium layer. In a subsequent step, the wafers were dipped into a chromium etchant (CR-75; Cyantek, Fremont, CA) that etched the chromium that had been exposed during the photolithography step, leaving dot arrays of chromium (covered with photoresist) on the surface of the silicon wafer. Finally, the photoresist still present on the chromium dots was removed by soaking the wafers in acetone (99.5%; J. T. Baker). The chromium dots formed the masks needed for fabrication of the microneedles.

Fabrication of Microneedles—Microneedles were fabricated using a reactive ion etching technique based on the Black Silicon Method developed at the University of Twente.[15,16] The patterned wafers were etched in a reactive ion etcher (700 series wafer/batch Plasma Processing System, Plasma Therm, St. Petersburg, FL), with means for ensuring good thermal contact between the wafers and the underlying platen (Apiezon N, K. J. Lesker, Clairton, PA). The wafers were etched using the following gases and conditions: SF_6 (20 standard cubic centimeters per minute) and O_2 (15 standard cubic centimeters per minute) at a pressure of 150 mTorr and power of 150 W for a run time of approximately 250 min. These conditions caused both deep vertical etching and slight lateral underetching. The regions protected by the chromium masks remained and formed the microneedles. Etching was allowed to proceed until the masks fell off due to underetching, leaving behind an array of sharp silicon spikes. By controlling the ratio of flow rates of the SF_6 and O_2 gases used to form the plasma, the aspect ratio of the microneedles could be adjusted.

Skin Experiments—Experiments on skin were designed to assess the mechanical properties of microneedles and to determine their ability to enhance transdermal transport. Microneedle mechanical strength was tested by inserting microneedles into skin and then removing them for analysis by microscopy. Microneedle enhancement of transdermal drug delivery was investigated by measuring the effects of microneedles on skin permeability to calcein, a model drug. All experiments were performed at room temperature (23 ± 2 °C).

Skin Preparation—Human skin was obtained from autopsy and plastic surgery procedures and stored at −80 °C until use (FZU-13; Thermotron Industries, Holland, MI). All experiments used epidermis (i.e., stratum corneum and viable epidermis) which was isolated from dermis using a standard heat separation technique.[4] Following common practice, we used only the epidermis for transdermal transport experiments, because (a) the primary barrier to transport is the epidermal stratum corneum and (b) the inclusion of dermis provides an artifactual reservoir and binding site for drug which has crossed epidermis, since most drugs in vivo would be taken up by capillaries found near the dermal−epidermal junction.[4−6]

Mechanical and Piercing Properties of Microneedles—To determine if microneedles could pierce skin without breaking, arrays of microneedles were pressed into epidermis using a force of about 10 N applied with a small wooden probe (2 mm in diameter; Baxter Healthcare, Round Lake, IL). To better simulate the in vivo mechanical environment, the dermis was placed below the epidermis as a supporting cushion. After the microneedles were inserted, the epidermis and microneedles were inspected by light (StereoZoom 7; Bausch & Lomb, Rochester, NY) and/or scanning electron (S-800, Hitachi, Tokyo, Japan) microscopy.

Transdermal Transport Experiments—To test the ability of microneedle arrays to enhance transport across skin, epidermis was mounted in vertically oriented Franz permeation chambers (FDC-100 no. 20; Crown Glass Co. Inc., Somerville, NJ). The donor compartment (facing the upper or stratum corneum side of epidermis) was filled with 10^{-3} M calcein (a fluorescent dye; Sigma, St. Louis, MO) in phosphate buffered saline (PBS; pH 7.4; Sigma). The receiver compartment (facing the lower side of epidermis) was filled with PBS and stirring was maintained (magnetic stirrer; Barnstead/Thermolyne, Dubuque, IA).

In a typical experiment, the passive permeability of unaltered skin was measured over a 1 h period and verified to be less than approximately 1×10^{-6} cm/h to ensure that the skin was not damaged. Then a microneedle array was inserted into the skin, and calcein permeability was measured over a second 1 h period. Finally, the microneedles were removed, and permeability was measured for at least one more hour. In some experiments, the microneedle array was only left in for approximately 10 s, in which case no permeability measurement was made during needle insertion. Permeabilities were determined by removing samples from the receiver compartment and measuring calcein fluorescence with a spectrofluorimeter (QM-1; Photon Technology International, South Brunswick, NJ). For unaltered skin, permeability measurements were made on the basis of the full skin surface area exposed to the donor solution (0.79 cm^2). Permeabilities for skin pierced by microneedles were made on the basis of only the skin area covered by the microneedle array device (0.0915 cm^2). This is justified because under permeabilized conditions, almost all transport occurs through that small area under the array; the rest of the skin area does not contribute significantly to the permeability.

Results and Discussion

To determine if microfabricated microneedles could be used to enhance transdermal drug delivery, we made arrays of microneedles using a deep plasma etching technique, tested their ability to penetrate skin without breaking, and measured the changes in transdermal transport which resulted.

Arrays of microneedles were fabricated, as shown in Figure 1. These microneedles have two important features. First, they have extremely sharp tips (radius of curvature < 1 μm; Figure 1b) which facilitate easy piercing into the skin. Second, they are approximately 150 μm long. Because the skin surface is not flat due to dermatoglyphics (i.e., tiny wrinkles) and hair, the full length of these microneedles will not penetrate the skin. That which does penetrate should insert deep enough to cross the stratum corneum barrier but not so deep to hit nerves found in deeper tissue. The microfabrication technique can easily be modified to make longer or shorter needles if needed.

After making microneedles of the desired dimensions, we tested their ability to pierce skin without breaking. Insertion of the arrays into skin required only gentle pushing (estimated to be approximately 10 N, which is about the force needed to push an elevator button). Inspection by light and electron microscopy showed that more than 95% of microneedles within an array pierced across the stratum corneum of the epidermis samples

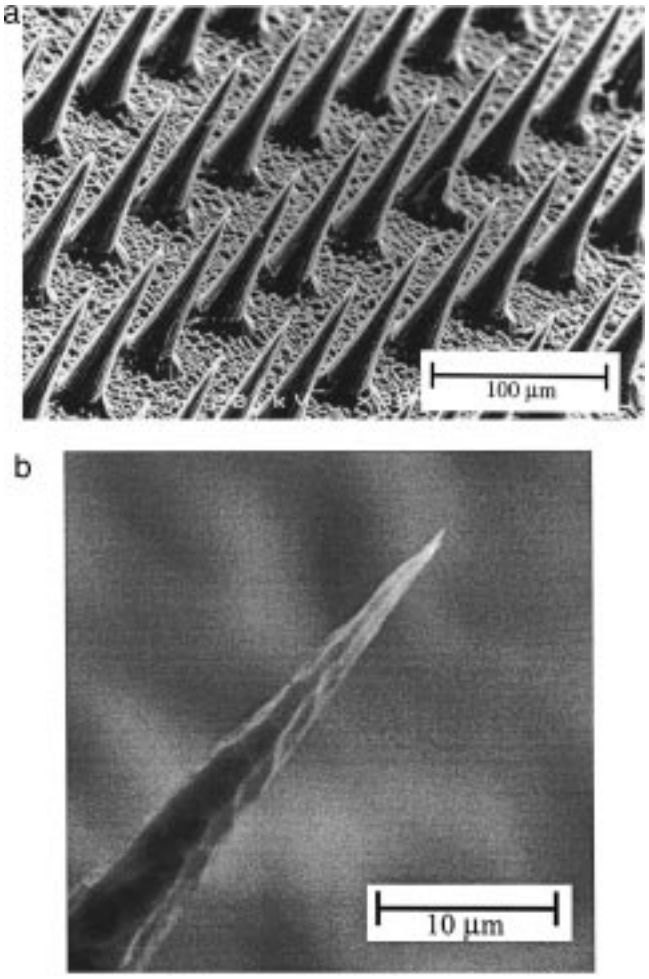

Figure 1—Scanning electron micrographs of microneedles made by the reactive ion etching technique. (a) A section of a 20 by 20 array of microneedles. (b) Close-up view of a microneedle tip. Microneedles are uniform in size and sharp at their tips, which is important for easy insertion to a desired depth in skin.

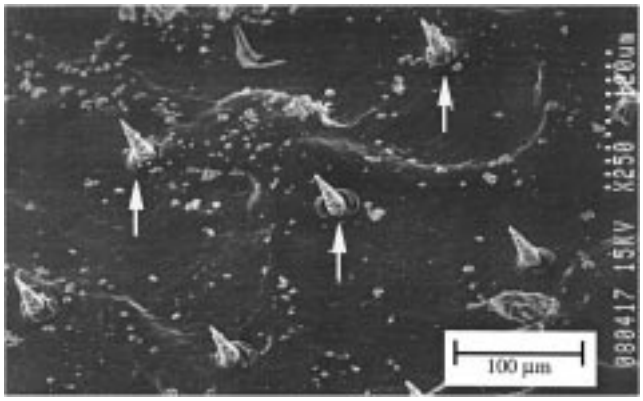

Figure 2—Microneedle tips inserted across epidermis. An array of microneedles was inserted into the stratum corneum side of human epidermis. The underside of the epidermis is shown, indicating that the microneedles penetrated across the tissue and that the tips were not damaged. Arrows indicate some of the microneedle tips.

(Figure 2). Moreover, all but a few percent of the microneedles remained fully intact. On those very few which broke, only the top 5−10 μm was damaged. Microneedle arrays could also be removed without difficulty or additional damage, as well as reinserted into skin multiple times.

To quantitatively assess the ability of microneedles to increase transdermal transport, we measured calcein

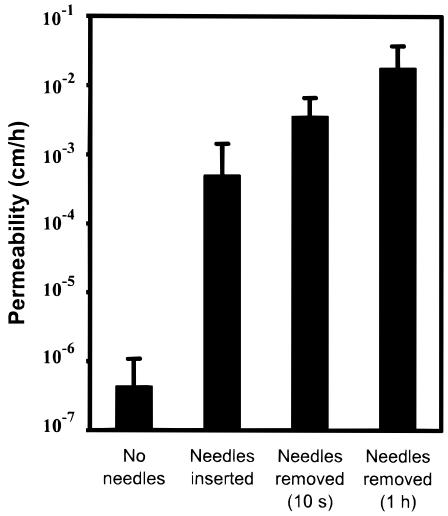

Figure 3—Permeability of human skin treated with different microneedle protocols in vitro. Increases of 3 to 4 orders of magnitude were observed for microneedles (1) inserted and left in skin, (2) inserted for 10 s and then removed, and (3) inserted for 1 h and then removed. Such large increases in skin permeability have the potential to significantly increase the number and types of drugs which can be delivered across the skin. Each data point represents the average of 7 to 9 experiments. Standard deviation bars are shown.

permeability of human epidermis with and without inserted microneedle arrays. Calcein crosses skin very poorly under normal circumstances and therefore represents an especially difficult compound to deliver. As expected, passive permeability of calcein across unaltered skin was very low, indicating that the epidermis samples were intact (Figure 3). Moreover, in control experiments where bare pieces of silicon with no microneedles etched into them were pressed against the skin, skin permeability was not affected (data not shown).

Insertion of microneedles into skin was capable of dramatically increasing permeability to calcein (Figure 3). When microneedles were inserted and left embedded in the skin, calcein permeability was increased by more than 1,000-fold. Insertion of microneedles for 10 s, followed by their removal, yielded an almost 10000-fold increase. Finally, insertion of a microneedle array for 1 h, followed by its removal, increased skin permeability by about 25000-fold. Permeabilities for skin with microneedles inserted and then removed are higher than for skin with microneedles remaining embedded probably because the microneedles themselves or the silicon plate supporting the array may block access to the microscopic holes created in the skin. Light microscopy showed that the holes which remained in the skin after microneedles were removed were approximately 1 μm in size (data not shown).

Increased skin permeability appeared to occur rapidly after microneedle insertion and to be maintained for hours in vitro. Skin permeability measurements were made once every hour. Elevated permeability was always seen during the first hour after microneedle insertion and remained at approximately the same level for as much as 5 h (data not shown); longer experiments were not performed. Although reversibility was not seen, and would not be expected in vitro, holes created by microneedles in vivo are likely to reseal, although the kinetics of resealing are presently unknown.

To supplement in vitro experiments which showed that skin permeability can be significantly increased by microneedles, preliminary results were obtained from studies with human volunteers, for which informed consent and IRB approval have been secured. They indicated that

microneedles could be easily inserted into the skin of the forearm or hand (data not shown). Moreover, insertion of microneedle arrays was never reported as painful, but sometimes elicited a mild "wearing" sensation described as a weak pressure or the feeling of a piece of tape affixed to the skin. Although transport experiments were not performed in vivo, skin electrical resistance was measured before and after microneedle insertion. Microneedles caused a 50-fold drop in skin resistance in vivo, a drop similar to that caused by the insertion of a 30-gauge "macroneedle" (data not shown). Inspection of the site immediately after microneedle insertion showed no holes visible by light microscopy; no erythema, edema, or other reaction to microneedles was observed over the hours and days which followed. This indicates that microneedle arrays can permeabilize skin in human subjects in a nonpainful and potentially safe manner.

To put these results in perspective, approaches which increase transdermal transport by more than 1 or 2 orders of magnitude are rarely seen in drug delivery research.[1−6] Therefore, the ability of microneedles to increase transdermal transport by more than 4 orders of magnitude has the potential to make great impact. Because the increased permeability results from the creation of micron-sized holes in the stratum corneum, it is likely to be applicable for a broad range of compounds, including macromolecules. This is in contrast to, for example, chemical enhancement techniques, which are often specific to certain classes of drugs and are unable to significantly increase transport of macromolecules.[4−6]

Conclusion

In this study, we explored a novel approach to enhancing transdermal drug delivery using an array of microneedles to pierce the skin and thereby provide conduits for drug transport in a potentially nonpainful manner. These microneedles did not break when inserted into the skin and were capable of increasing skin permeability by as much as 4 orders of magnitude. Preliminary tests in human subjects confirmed that skin could be permeabilized without causing pain. The microfabrication technique used to make microneedles is relatively simple and therefore amenable to inexpensive mass production for future applications. This approach has the potential to significantly increase the number and types of drugs which can be delivered across the skin.

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