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Microfabricated Microneedles for Transdermal Drug Delivery

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I. INTRODUCTION

Drug delivery technologies strive to balance the ability to deliver drugs effectively with the ability to do so in a patient-friendly manner [1,2]. Injection or infusion through a hypodermic needle is the gold standard for effective delivery, since large amounts of drug of any size can be administered with controlled kinetics. However, the pain and inconvenience of needles have motivated alternative drug delivery approaches, such as transdermal drug delivery. By transporting drug across the skin either by passive diffusion or combined with chemical, electrical, ultrasonic, or other enhancers, transdermal delivery provides controlled release of drugs from a patient-friendly patch [3,4]. However, this approach is severely limited, because the skin's great barrier properties prevent most drugs from crossing skin at therapeutic rates.

To achieve a better balance between efficacy and convenience, we and others have proposed a hybrid of the hypodermic needle and transdermal patch through the use of microscopic needles that can deliver drugs effectively (like a hypodermic needle) and, because their small size makes them painless, are well tolerated by patients (like a transdermal patch) [5]. Although this idea received attention already in the 1970s [6], the technology needed to make microneedles became available only recently.

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The microneedle concept employs an array of micron-scale needles that is inserted into the skin sufficiently far that it can deliver drug into the body, but not so far that it hits nerves and thereby avoids causing pain. An array of microneedles measuring tens to hundreds of microns in length should be long enough to deliver drug into the epidermis and dermis, which ultimately leads to uptake by capillaries for systemic delivery [3,4]. When microneedle arrays are inserted into the skin, they can create conduits for transport across the stratum corneum, the outer layer of skin that 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. This is similar to conventional transdermal patch delivery, except the rate-limiting barrier of the stratum corneum is circumvented by the pathways created by microneedles.

Small microneedles can also be painless if designed with an understanding of skin anatomy. Human skin is made of three layers: stratum corneum, viable epidermis, and dermis [7]. 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, dermis forms the bulk of skin volume and contains living cells, nerves, and blood vessels. Therefore, microneedles that penetrate skin slightly more than 10–15 μm deep should provide transport pathways across the stratum corneum, but do so painlessly since microneedles do not reach nerves found in deeper tissue. Moreover, if microneedles do penetrate deeper into the skin, their odds of hitting a nerve should be reduced owing to their small diameter.

Needles of micron dimensions can be made using microfabrication technology, which is the same technology used to make integrated circuits [8]. In this microfabrication approach, silicon, metal, polymer, or other materials are exposed to masking steps, which define the shape of structures to be created, and chemical etching steps, which sculpt the material into the prescribed shapes. 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.

II. FABRICATION OF MICRONEEDLES

To test the hypothesis that very small needles could increase skin permeability in a painless manner, we first fabricated solid, silicon microneedles. Silicon was employed because it is the most commonly used material in the microelectronics industry and solid needles were made because their fabrication was simpler than hollow ones. Subsequently, we made needles out of other materials—notably metal—and then developed techniques to make microneedles that are hollow.

A. Microfabrication of Solid Silicon Microneedles

As a first prototype, we made small arrays of microneedles using a novel deep plasma etching technique based on the black silicon method [9]. Performed in a microelectronics cleanroom, this technique involves first depositing onto a silicon wafer a chromium mask, which defines the location and size of the microneedles. Then, in a reactive ion etcher, the silicon is chemically etched away preferentially at locations not covered by the mask. By adjusting the ratio of the SF_6 to O_2 in the etching plasma, the amount of "underetch" (i.e., etching underneath the protective mask) can be manipulated and thereby the needles' aspect ratio and sharpness can be controlled. The technique creates arrays of microneedles such as those shown in Figure 1, b and c.

These microneedles have two important structural features. First, they have extremely sharp tips (radius of curvature < 1 μm) that facilitate easy piercing into the skin. Second, they are approximately 150 μm long. Because the skin surface is not flat due to hair and dermatoglyphics (i.e., tiny wrinkles), 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 fabrication technique can easily be modified to make longer or shorter needles if needed.

These microneedles are orders of magnitude smaller than conventional needles. To illustrate this point, Figure 1a shows a conventional 26-gauge hypodermic needle and Figure 1b shows an array of microneedles at the same magnification.

B. Microneedles Made from Other Materials

Because silicon is the most common material used for microfabrication techniques, it was the material our first studies used. However, we prefer to use other materials, such as metals, which are stronger and have a record for safe use in humans. To demonstrate the feasibility of making microneedles from other materials, we made a mold of silicon microneedles and then filled the mold with metal (NiFe) by electroplating. The mold was made of polymeric photoresist (SU-8) and provided the inverse structure of the needles. Comparing the original silicon needles to the metal needles created with the mold showed that the metal needles were essentially identical replicas (data not shown). We have also employed a similar approach involving a mold to make microneedles out of polymers.

C. Microfabrication of Hollow Microneedles

There may be some advantages to delivering drugs through hollow microneedles, rather than solid ones. To make hollow microneedles, we electroplated a thin

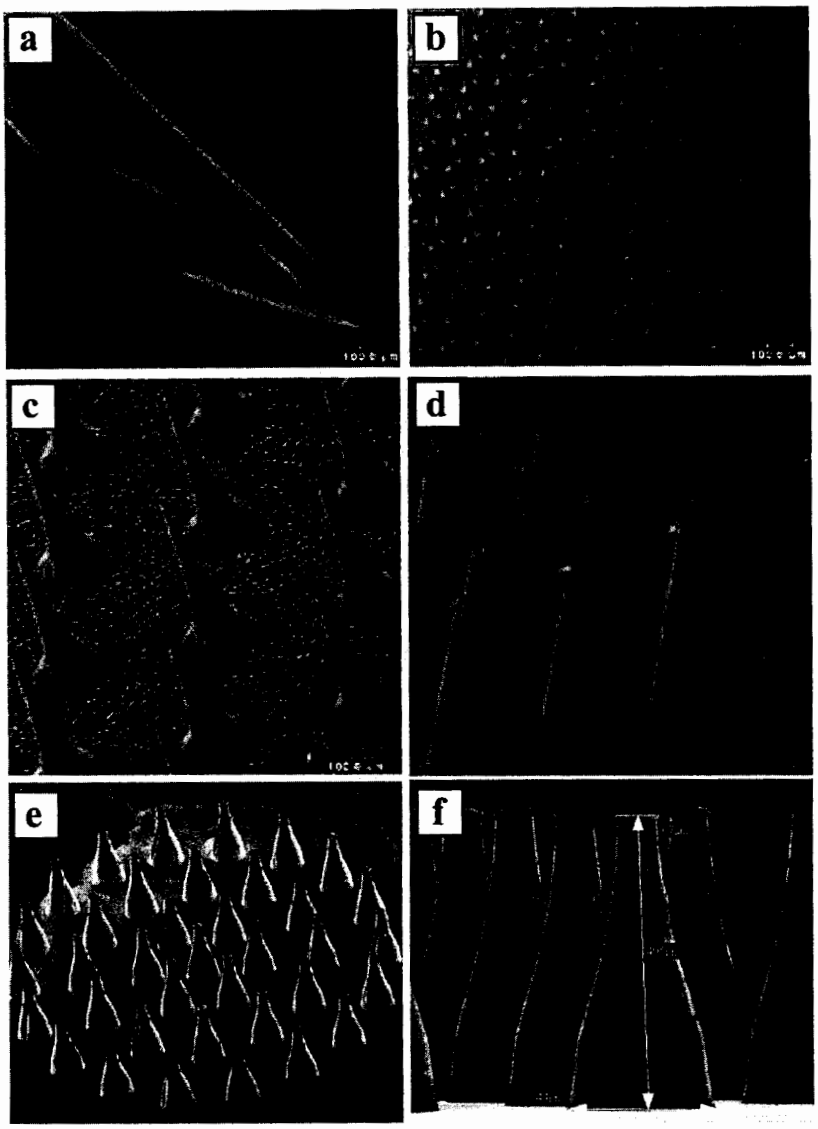

Figure 1 Scanning electron microscopy images of microneedles. (a) The tip of a conventional 26-gauge hypodermic needle is shown at the same magnification as (b) a portion of an array of microneedles. Images at greater magnification show (c) solid silicon microneedles (~150 μm tall) and (d) hollow metal microtubes (~150 μm tall). An array of somewhat larger microneedles (~500 μm tall) is shown at (e) lesser and (f) greater magnification. Reproduced from Refs. [10, 12] with permission.

coating of metal (NiFe) onto the inner surface of molds similar to those made for solid metal needles, which left a thin metal shell in the shape of a needle [10], as shown in Figure 1, d–f. Testing of these prototype hollow needles indicated that they are mechanically strong enough to pierce skin and permit the passage of fluids, as described below.

III. TESTING OF MICRONEEDLES

One of the most important potential advantages of microneedles is the prospect that they can deliver drugs without the pain typically associated with conventional hypodermic needles. To test this possibility, we inserted arrays of 400 solid silicon microneedles (Fig. 1c) into the forearms of human volunteers [11]. The microneedles could be easily inserted into the skin (data not shown). Moreover, insertion of microneedle arrays was never reported as painful (Fig. 2). Sensation caused by microneedles was statistically indistinguishable from pressing a

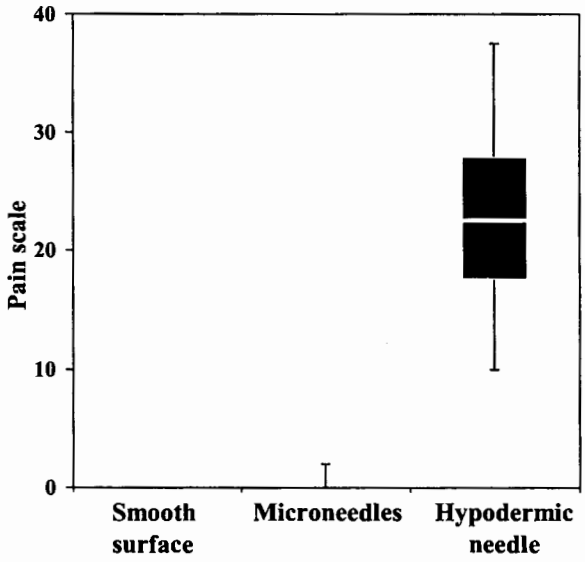

Figure 2 Box plot showing visual analog pain scores from a blinded comparison between (i) a smooth silicon surface, (ii) a 400-microneedle array (Fig. 1c) and (iii) a 26-gauge hypodermic needle (Fig. 1a) inserted into the forearm of human subjects. For each treatment, the fifth, twenty-fifth, fiftieth, seventy-fifth, and ninety-fifth percentiles are shown. Microneedles were reported as being painless. (Reproduced from Ref. [11] with permission.)

smooth surface against the skin. In contrast, pain caused by a hypodermic needle was substantially greater than pain from microneedles. The skin into which microneedles had been inserted was visually inspected after the study. No redness or swelling was observed, suggesting that the microneedles had not caused damage or irritation. None of the subjects reported adverse reactions.

Another potential advantage of using microneedles is the ability to deliver large molecules across the stratum corneum. In vitro experiments using human cadaver epidermis mounted in standard diffusion chambers showed significant enhancement in rates of transdermal transport for a broad range of compounds. For example, calcein is a small, hydrophilic molecule (623 Da) representative in size of many conventional drugs. Without microneedles, skin permeability to calcein was undetectable, whereas insertion of microneedles into skin increased skin permeability by more than 3 orders of magnitude above the detection limit (Fig. 3) [9]. Insertion and subsequent removal increased skin permeability by more than 4 orders of magnitude.

Similar results were observed for transdermal delivery of insulin (6 kDa) and bovine serum albumin (66 kDa) (Fig. 3) [12]. Transport of polymeric nanoparticles was also observed at significant rates through skin permeabilized by needles inserted and then removed. Such large permeabilities to insulin, BSA, and nanospheres is remarkable, since until recently the skin was considered impermeable to macromolecules.

A similar in vitro experiment was performed to mimic extraction of molecules of interest from the skin. In this case, calcein solution was placed on the opposite side of the skin from the microneedle arrays in the same diffusion cell configuration described above. Similar increases in skin permeability were observed for the "extraction" of calcein as for its delivery (data not shown). These results could be important for minimally invasive methods of interstitial fluid sampling of interest for glucose monitoring of diabetics and other applications.

Hollow microneedles offer the opportunity to diffuse drug molecules or even flow drug solutions through needle bores. To demonstrate this possibility, we measured the flow rate of water though a 100-microneedle array as a function of pressure (Fig. 4). Flow rates of tens of milliliters per minute were measured at pressures of just a few psi, which are comparable to flow rates and pressures applied by hand to hypodermic needles attached to syringes.

IV. REGULATORY ISSUES

Microneedles used for drug delivery will be subject to approval by the U.S. Food and Drug Administration and its counterpart organizations in other countries. Specific registration issues for a particular microneedle product will depend partly

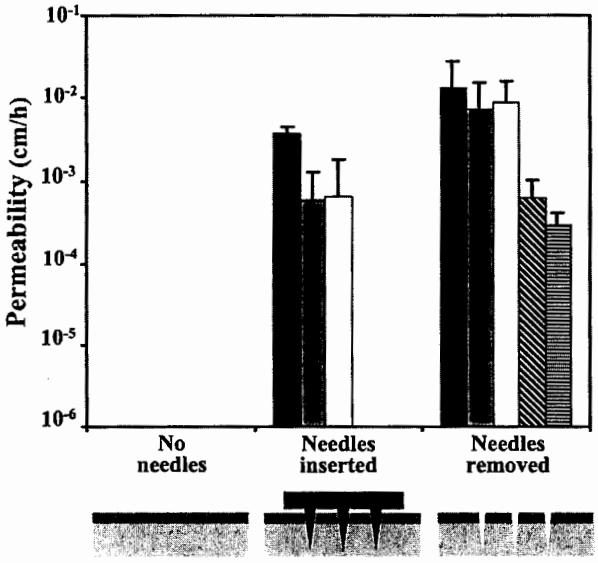

Figure 3 Skin permeability to calcein (black), insulin (gray), bovine serum albumin (white), 50-nm nanospheres (diagonal stripes), and 100-nm nanospheres (horizontal stripes) in vitro. Permeability is shown for intact skin (always below detection limit), skin with an array of 400 solid microneedles (Fig. 1c) inserted and left in the skin, and skin with an array of 400 solid microneedles inserted and then removed from the skin. Small molecules, proteins, and even nanospheres can be transported across skin using microneedles.

on properties of the microneedle device, but probably to an even greater extent on the nature of the compound, its therapeutic category and whether it is administered via a rapid single-use injection or a slow, long-term infusion. Because no drug to date has been directly delivered to the superficial layers of skin for systemic uptake, regulatory bodies may view microneedles as a new route of delivery. However, the transport route employed by microneedle-assisted delivery and conventional transdermal patch delivery have some similarities.

Both safety and efficacy studies will be expected for registration of a microneedle product and even the use of microneedles as a general injection device will have to be studied and possibly approved on a drug-by-drug basis. Particular attention needs to be paid to possible sensitization responses to drug or formulation excipients administered into skin using microneedles. Because microneedles breach the stratum corneum barrier, a sterile and pyrogen-free device and formulation may be required.

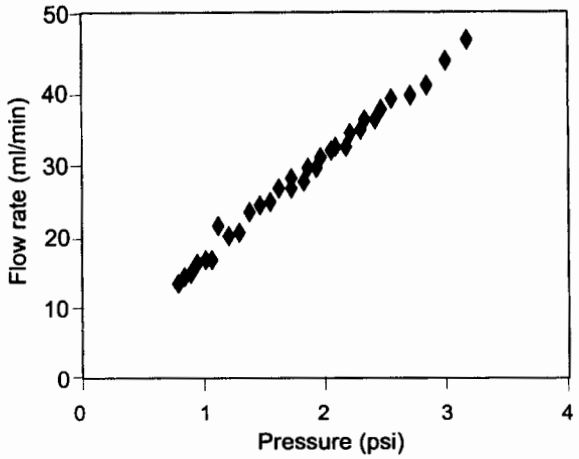

Figure 4 Flow rate of water through an array of 100 hollow microtubes (Fig. 1d) as a function of pressure. Very small pressures, e.g., a few psi, are sufficient to flow water through arrays of microneedles at rates of many milliliters per minute.

V. TECHNOLOGY POSITION AND FUTURE DIRECTIONS

A. Comparison with Hypodermic Needles and Transdermal Patches

Microneedles have many of the advantages of both conventional needles and transdermal patches. Capturing the effectiveness of hypodermic needles, microneedles create transport pathways sufficiently large to deliver small drugs, macromolecules, and even drug-loaded nanoparticles into and across the skin. Capturing the user-friendliness of transdermal patches, microneedles are short and thin, which means they should be painless and can be incorporated into a small, wearable device.

The drugs that can be delivered using microneedles may have many of the restrictions imposed by hypodermic needles and transdermal patches. For example, highly irritating formulations generally cannot be injected subcutaneously or intramuscularly and probably cannot be administered using microneedles either. Also, transdermal formulations administered at high concentrations within skin can stimulate sensitization reactions to drugs and excipients. Because microneedles deposit drug formulations near the epidermis-dermis junction, where immune-responsive cells reside [7], it is likely that the microneedle delivery route will also be limited to nonimmunoreactive compounds and formulations. How-

ever, this limitation may present an opportunity for delivery of vaccines [13], which may elicit improved immune responses when administered with microneedles. Moreover, some dermatological applications [7] and gene therapy applications [14] may also benefit from having direct access to the epidermis-dermis juncture.

B. Microneedle Application Scenarios

Microneedle arrays could be used for short-term delivery in a manner similar to conventional injection. The advantage of microneedles is that they could provide that injection painlessly. However, this may not be the area in which microneedles have the most impact. It is unlikely that microneedles will be able to rapidly deliver large volumes of drug solution into the spatially confined skin. Moreover, direct access to the bloodstream is difficult with microneedles, making rapid infusion problematic. However, for those applications where smaller volumes can be delivered over longer periods of time (i.e., more than a few seconds) and the pain-free and other advantages of microneedles are important, short-term delivery with microneedles should be an attractive method.

Drug delivery over hours to days is where microneedles have the potential to make the greatest impact. By adding microneedles to a device similar to current transdermal patches, large and hydrophillic drugs like insulin or heparin could be delivered continuously across the skin in the same way that small, hydrophobic drugs like nicotine are currently administered from patches. When coupled with additional driving forces using a pump or iontophoresis, delivery rates could be increased and even modulated according to a preprogrammed schedule or in response to input from the patient or health care worker.

In addition to drug delivery for therapeutic purposes, microneedles may also be useful for pain-free extraction of interstitial fluid for diagnostic purposes. For example, it has already been demonstrated that the glucose content of interstitial fluid can be correlated to systemic glucose levels [15]. Thus, if microneedles can be used to extract interstitial fluid, they can be an important tool for the diagnostic industry for measurement of solutes.

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REFERENCES

1. R Langer. Drug delivery and targeting. Nature 392:5–10, 1998.
2. K Park. Controlled Drug Delivery: Challenges and Strategies. Washington, DC: American Chemical Society, 1997.
3. MR Prausnitz. Reversible skin permeabilization for transdermal delivery of macromolecules. Crit Rev Ther Drug Carr Syst 14:455–483, 1997.
4. EW Smith, HI Maibach. Percutaneous Penetration Enhancers. Boca Raton, FL: CRC Press, 1995.
5. DV McAllister, MG Allen, MR Prausnitz. Microfabricated microneedles for gene and drug delivery. Annu Rev Biomed Eng 2:289–313, 2000.
6. MS Gerstel, VA Place. Drug delivery device. US patent 3,964,482, 1976.
7. RH Champion, JL Burton, FJG Ebling. Textbook of Dermatology. London: Blackwell Scientific, 1992.
8. WR Runyan, KE Bean. Semiconductor Integrated Circuit Processing Technology. New York: Addison-Wesley, 1990.
9. S Henry, DV McAllister, MG Allen, MR Prausnitz. Microfabricated microneedles: a novel method to increase transdermal drug delivery. J Pharm Sci 87:922–925, 1998.
10. DV McAllister, F Cros, SP Davis, LM Latta, MR Prausnitz, MG Allen. Three-dimensional hollow microneedle and microtube arrays. Proc Transduc 99:1098–1101, 1999.
11. S Kaushik, AH Hord, DD Denson, DV McAllister, S Smitra, MG Allen, MR Prausnitz. Lack of pain associated with microfabricated microneedles. Anesth Analg 92: 502–504, 2001.
12. D McAllister, S Kaushik, P Patel, J Mayberry, M Allen, M Prausnitz. Solid and hollow microneedles for transdermal protein delivery. Proc Int Symp Control Rel Bioact Mater 26:192–193, 1999.
13. MF Powell. Drug delivery issues in vaccine development. Pharm Res 13:1777–1785, 1996.
14. JA Wolff. Gene Therapeutics: Methods and Applications of Direct Gene Transfer. Boston: Birkhäuser, 1994.
15. J Tamada, S Garg, L Jovanovic, K Pitzer, S Fermi, R Potts. Noninvasive glucose monitoring: comprehensive clinical results. Cygnus Research Team. JAMA 282: 1839–1844, 1999.