Arrays of Hollow out-of-Plane Microneedles for Drug Delivery

Boris Stoeber, and Dorian Liepmann

Abstract—Drug delivery based on MEMS technology requires an invasive interface such as microneedles, which connects the microsystem with the biological environment. Two-dimensional arrays of rigid hollow microneedles have been fabricated from single-crystal silicon using a combination of deep reactive ion etching and isotropic etching techniques. The fabricated needles are typically 200 µm long with a wide base and a channel diameter of 40 µm. The fabrication process allows creating either blunt needles or needles with sharp tips. Their shape and size make these needles extremely suitable for minimally invasive painless epidermal drug delivery. MEMS technology allows for batch fabrication and integration with complex microsystems. Fluid has been successfully injected 100 µm deep into sample tissue through arrays of microneedles. Needle breakage did not occur during this procedure. Experiments have shown that the modified Bernoulli equation is a good model for liquid flowing through the narrow microneedle lumen.

Index Terms—Arrays of hollow out-of-plane microneedles, bioMEMS, drug delivery, microfluidics.

I. INTRODUCTION

Historically needles have been made from hollow steel with a sharpened tip. Needle diameters typically range from 0.4 mm to 3.4 mm. Because of their size, hypodermic needles have generally been used to deliver a drug relatively deep into the body targeting muscles, blood vessels, or subdermal fat. A few compounds are delivered into the skin using hypodermic needles, for example reaction tests for allergies or tuberculosis. A consistent method for drug delivery into the epidermal skin layer would open new pathways for drug administration allowing well known and novel therapeutic agents to be administered in a non-traditional way. In this paper we present microneedles fabricated in standard MEMS technology that are specifically designed for epidermal drug delivery.

Microneedles have the form of a needle, lancet or thorn-like mechanical structure with at least one dimension of their shaft much smaller than 500 µm. Microneedles have been an active area of MEMS research since the early 1990s and have been fabricated from different types of materials and in different shapes. Their most common purpose is to act as an interface between a microsystem and an organism such as the human body. Injection or withdrawal of fluids with such needles can then be applied to drug delivery or bioassay [1]. As part of a drug delivery system microneedles will need to provide the fluid passage for the drug into the required location in the human body.

Fig. 1 shows the concepts of epidermal drug delivery, where a needle penetrates only the outermost layer of the skin, the stratum corneum. The drug is then injected through the needle into the viable epidermis, from where it diffuses into the blood vessels of the deeper dermal skin layer. Only very few nerve endings are located in the epidermis [2], [3] so that only little or no sensation of pain may be associated with an epidermal injection.

Microneedles for epidermal drug delivery have to be sharp so that they can easily break the stratum corneum. However, because the mechanical properties of the human skin are not sufficiently known or consistent, an exact requirement for the sharpness of the needles cannot be formulated at this point. The target injection site for epidermal drug delivery is the viable epidermis, which is typically located between 20 µm and 100 µm underneath the skin surface [4]. Since the skin is very flexible [5], it can be assumed that the entire needle shaft will not penetrate the skin. The shaft should therefore be longer than 100 µm. The microneedles should not break during an injection. The critical load for typical applications are lateral forces resulting in a bending moment on the needle shaft, which induces the maximum stress concentration at the base of a needle with a straight shaft. This is especially important for MEMS-based microneedles made from brittle materials that could exhibit catastrophic failures, i.e. break.
compared to steel, which is ductile and will only bend. Arranging needles in an array allows injection into a wider distributed area than in the case of a single needle or a single row of needles. Therefore, a relatively low flow resistance for flow through the needle lumens and a better liquid absorption by the tissue may be achieved using a needle array. In addition, a large number of needles increases the redundancy of the drug delivery system making it less vulnerable to failure of individual flow passages due to clogging from tissue trapped in a needle lumen during insertion into the skin. However, if the needles are placed too close together, a bed-of-nails effect can result in the needles pushing the skin down uniformly without penetrating it.

II. MICRONEEDLES

Different shapes of microneedles have been developed in MEMS technology using a variety of different materials. Microneedles can be divided into two principal groups based on their general design. In-plane needles have shafts that are parallel to the substrate plane. The shafts of out-of-plane needles are perpendicular to the substrate surface, so that multiple needles can be fabricated in two-dimensional arrays. Solid needles have been developed with in-plane [6], [7] and with out-of-plane design [8]–[15] as electrode arrays or to puncture human skin. Epidermal drug delivery requires hollow needles to deliver drugs into a specific depth in the skin. In-plane designs [16]–[22] generally result in only one row of needles, which does not allow for drug distribution over a large area of skin. Brazzel et al. have suggested that two-dimensional needle arrays can be fabricated by stacking several individual rows of hollow in-plane needles [20]. However, from a technological viewpoint it is more convenient to pursue out-of-plane needle concepts to obtain large arrays of microneedles.

Table I gives an overview of the typical characteristics of the hollow out-of-plane microneedles reported in the literature to date. The surface area of the needle tips and the cross-sectional area 10 µm below the tips give an impression of the sharpness of the needles, where a sharp needle has a small tip surface area and the needle shaft does not widen abruptly. The data for the lumen opening measured from the tip gives information on how far a needle needs to be inserted before the lumen opening reaches the tissue and at which needle depth the opening is entirely inserted.

The electroplated thin-walled structures by McAllister et al. [23] and by Kobayashi and Suzuki [24] are much less sharp than all the other reported hollow out-of-plane microneedles. In addition, the fabrication process demonstrated by Kobayashi et al. [24] typically allows for generation of individual microneedles at a time and not for large arrays.

The SiO₂ microcapillaries presented by Chun et al. [25] were developed for injection of genetic material into individual cells. They are very sharp, but the needle length is limited by the achievable aspect ratio of a DRIE step into silicon.

The single-crystal silicon needle arrays developed by Griss and Stemme [26] and by Gardeniers et al. [27] are extremely sharp, and their design makes them very robust. However, their fabrication processes require that the lumen openings are located too far away from the needle tip. Thus, the needles need to be inserted much deeper into the skin than 100 µm. Therefore, these microneedles are not ideal for epidermal drug delivery.

The hollow single-crystal silicon out-of-plane microneedles with pointed tips developed by Stoeber and Liepmann [28] are fairly sharp. The lumen opening is located right underneath the needle tip and their wide and rounded base makes them extremely robust. They have been designed specifically for epidermal drug delivery and will be discussed in this paper. Successful painless drug delivery with these needles into the upper layer of the skin has been reported elsewhere [29].

**TABLE I**

<table>
<thead>
<tr>
<th>Needle Reference</th>
<th>Typical Properties of Hollow Out-of-Plane Microneedles</th>
</tr>
</thead>
<tbody>
<tr>
<td>McAllister et al. [23]</td>
<td>Lumen diameter [µm] 55 (at tip)</td>
</tr>
<tr>
<td>Chunn et al. [25]</td>
<td>Outer needle dimension</td>
</tr>
<tr>
<td>Stoeber et al. [28]</td>
<td>Tip [µm] 75</td>
</tr>
<tr>
<td>Kobayashi et al. [24]</td>
<td>Base [µm] 300</td>
</tr>
<tr>
<td>Griss et al. [26]</td>
<td>Needle length [µm] 500</td>
</tr>
<tr>
<td>Gardeniers et al. [27]</td>
<td>Cross-sectional area at tip [µm²] 44000</td>
</tr>
<tr>
<td></td>
<td>10 µm below [µm²] 4800</td>
</tr>
<tr>
<td></td>
<td>Lumen opening from tip [µm] 0 - 0</td>
</tr>
<tr>
<td></td>
<td>Array size</td>
</tr>
<tr>
<td></td>
<td>Needle material</td>
</tr>
<tr>
<td></td>
<td>(Ni, Ni/Fe)</td>
</tr>
</tbody>
</table>

| Chunn et al. [25]                | 3                                                    |
| Stoeber et al. [28]              | 40                                                  |
| Kobayashi et al. [24]            | 50                                                  |
| Griss et al. [26]                | 60                                                  |
| Gardeniers et al. [27]           | 70                                                  |
|                                 | 10                                                   |
|                                 | 160                                                  |
|                                 | 200                                                  |
|                                 | 2000                                                |
|                                 | 100                                                 |
|                                 | 50                                                  |
|                                 | 100 - 160                                           |
|                                 | 60 - 190                                            |

Most values are based on estimations.
III. DESIGN OF ARRAYS OF POINTED HOLLOW OUT-OF-PLANE NEEDLES

Fig. 2 shows the fabrication concept for arrays of hollow out-of-plane microneedles suitable for drug delivery and bioassay. The lumen of a hollow needle is etched through the bulk material using an anisotropic etching technique such as DRIE, as shown in Fig. 2a. Underetching of a mask is then used to define the outer shape of the needle (Fig. 2b). Even though other shapes are possible, the needle geometries in the further discussion will be limited to circular cross-sections for both the fluid channel and microneedle. When the mask center is aligned with the channel center, the resulting needle will have a flat top (Fig. 2c). Sharp needles can be fabricated by off-centering the mask and the channel by a small distance $\delta$ (Fig. 2d). In both cases, the inside of the needle lumen must be protected during the etch steps that form the outer shape of the needles. The wall thickness of both needle designs is smallest at the needle tip from where it increases along the shaft to its maximum at the needle base. The wall thickness at the needle tip can be as small as zero; the thickness is controlled by the amount of horizontal underetching of the corresponding mask. The wide base of the shaft makes these needles very strong against bending moments in all directions, which has been a problem for in-plane needles [19].

If the circular mask will be underetched using a perfectly isotropic etching step, it needs to have a diameter of more than twice the needle height. Thus the number of needles per unit area is limited by this mask structure and the isotropy of the etch step where the masks of neighboring needles cannot overlap. For example, the maximum density per unit area for 200 $\mu$m long needles with a lumen diameter of 40 $\mu$m is therefore 640 $\text{cm}^{-2}$. Instead of using a perfectly isotropic etch for the outer shape of the needles etching more vertically than sideways produces more slender needles so that a closer spacing of needles is possible. Since the backside of the silicon plate carrying the needles is flat, except for the lumen openings, it offers many possibilities for easy integration with microfluidic systems using a simple bonding process.

![Fig. 2 Design of 2 needles: a) vertically etched lumens; b) needle shape generated through underetching of a mask; c) symmetric needles obtained through overlaying the center lines of a and b; d) pointed needles, where the center lines of the lumens a and the outer shapes b are dislocated by the distance $\delta$.](image-url)
IV. FABRICATION OF POINTED HOLLOW OUT-OF–PLANE MICRONEEDLES

Silicon was chosen as material for the microneedles because of the availability of silicon wafers and the processing tools. In addition, available microfabrication capabilities make it possible to integrate a range of sensors and devices on the back of the silicon needles.

The fabrication process for single crystal silicon needles is sketched out in Fig. 3. First, a double-sided polished wafer is coated with silicon dioxide. After a photolithography step, the silicon dioxide on the backside of the wafer is patterned for the 40 µm wide lumens using a Lam 590 plasma etcher with a CF$_4$:CHF$_3$:He (90:30:120 sccm) plasma at 2.8 Torr with 850 Watts and an electrode gap of 3.8 mm. This etch mask is subsequently used to etch the channels with the Bosch process [30] in a Surface Technology Systems ICP (inductively coupled plasma) etching tool, where the plasma is generated with a coil power of 600 Watts. 7 seconds long deposition cycles with 85 sccm C$_4$F$_8$ at 18 mTorr are followed by 9 seconds of 130 sccm SF$_6$ plasma at 32 mTorr with a directive platen power of 12 Watts. The DRIE is stopped on the front side oxide layer or close to it after about 4 h 20 min. A deposition of silicon nitride in a SiCl$_2$H$_2$:NH$_3$ (100:25 sccm) atmosphere at 140 mTorr and 835°C provides a protective layer for subsequent etch steps (step 4 of Fig. 3). At this point the front side of the wafer is still flat, which facilitates photolithography on this face, while care has to be taken during mask alignment to the structures etched from the backside in order to achieve the correct offset $\delta$ for the desired needle shape. The photolithography step is followed by a Lam 590 plasma etch with the same process parameters as before to pattern the silicon dioxide and silicon nitride on the front side of the wafer with 425 µm large circles for the following isotropic etching steps. First, an isotropic silicon plasma etch is performed in the ICP tool with 130 sccm SF$_6$ at 32 mTorr and a platen power of 600 Watts and a platen power of 10 Watts. This process has a relative high etch rate (1.67 µm/min), but results in high surface roughness of the slopes in the underetched regions. The following isotropic wet chemical etching step smoothens the surface of the silicon at a low etch rate (1500 Å/min) using a HNO$_3$:$H_2$O:$HN_3$F (126:64:5 ml) bath at room temperature. While silicon dioxide has a high selectivity to bare silicon for the plasma etch, its selectivity is poor for the wet chemical etch. In this case, silicon nitride is a good mask material, and the silicon nitride coating in the channels protects their walls. Alternatively, a non-isotropic plasma etch can be chosen in order to achieve needles of different shapes such as a higher aspect ratio. In either case the etch mask is anchored on its backside to the silicon nitride passivation of the lumen, which prevents detachment of the mask before the desired tip shape is reached during etching. In a final step, the remaining silicon dioxide and silicon nitride are removed in concentrated hydrofluoric acid.

Fig. 3 Process flow for the fabrication of hollow out-of-plane microneedles.

Fig. 4 shows a single symmetric needle that is 200 µm high with a channel diameter of 40 µm. The sharp needles shown in Fig. 4b and 4c are obtained by dislocating the centerlines of the channels and of the circular etch mask for the isotropic etch step by $\delta = 20$ µm in step 5 of Fig. 3, as discussed above. The distance between needles in the array is 750 µm. For both designs, the uniformity across a wafer has been very high, and a yield for individual needles on a 4” wafer of close to 100% has been achieved. Fig. 5 shows a 25G5/8 hyperdermic steel needle and hollow microneedles for size comparison. 25G5/8 needles have an outer diameter of 0.53 mm.

V. TESTING OF SILICON MICRONEEDLES

A. Liquid Injection through Microneedles

It has been shown that a significant enhancement of drug delivery into the upper skin layer of human volunteers can be achieved without the sensation of pain using the pointed microneedles [29]. Goal of the following investigation is to determine the location and distribution of the injected liquid in a sample tissue and to relate it to the needle geometry. For this purpose, a silicon plate with an array of 8 200 µm long pointed needles is mounted to the end of a plastic syringe shaft as shown in Fig. 6. Using the regular plunger, injection can be performed in a conventional manner, with the only difference that it occurs through the microneedles instead of a steel needle.

Skinless chicken breast has been chosen as a sample tissue to test the injection capability of the pointed needles with this setup because the bright color of this tissue makes it easy to identify the injection site visually for positioning during imaging. The skin of a piece of chicken breast that does not
surround the entire piece is typically not very firm, so that its mechanical properties are expected to be very different from human skin. Therefore, no experiments have been carried out using chicken breast with skin. Even though skinless chicken breast is not a perfect model for human skin as it lacks a layer comparable to the stratum corneum we consider it a good model tissue for liquid injection experiments. The fresh skinless chicken breast has been used as purchased. The dye Lucifer Yellow has been utilized as a fixable fluorescent tracer, which covalently combines with proteins [31], so that only little diffusion of the dye occurs after injection into the tissue. A small amount of blue ink has been added to the fluorescent dye for easier visual location of the injection site.

Fig. 4 SEM images of microneedles fabricated using the process outlined in Figure 3. The needles are approximately 200 µm high with a lumen diameter of 40 µm: (a) a symmetric needle, (b) a sharp needle with a pointed tip, (c) an array of sharp needles. The distance between needles in the array is 750 µm. The centerlines of the lumens and of the masks for the isotropic etching step in (b) and (c) were dislocated by 20 µm.

Confocal microscopy has been performed with a Zeiss 510 UV/Vis Confocal Microscope to detect the injected dye in planes parallel to the tissue surface in different depths. The recordings shown in Fig. 7 reveal that the sample fluid has been successfully delivered up to almost 100 µm into the tissue, which is the desired depth for epidermal drug delivery as argued in the introduction. These pictures also show that the dye has not been injected in a symmetric fashion around the point of needle insertion. The asymmetric shape of the needle, which has its lumen opening on one side of the needle shaft results in dye injection in one distinct direction away from the needle. Furthermore, it can be assumed that the insertion depth of the lumen opening into the soft tissue is 25 µm, since the maximum dye concentration occurs at this location. From there the pressure of the injection must have

Fig. 5 A 25G5/8 steel needle (diameter: 0.53 mm) next to 4 single crystal silicon out-of-plane needles.

Fig. 6 Setup for an injection experiment. A silicon plate with an array of 8 200 µm long sharp needles is mounted to the tip of a conventional plastic syringe.
driven the liquid deeper into the tissue, because diffusion of
the dye in tissue is negligible.

At the arms and the upper human body, the epidermal skin
layer is typically about 100 µm thick. Most nerve endings
occur underneath the epidermis, while the injection
documented in Fig. 7 occurred less deep, which explains why
injections with these needles do not stimulate the nerve
endings [29].

An important design requirement for these needles is that they
do not break during insertion into tissue. The needle shown in
Fig. 8 was pressed 10 times onto human skin in vivo with a
vertical force of 10 N. According to a recent study of
microneedle insertion force into human skin as a function of
the tip surface area [32] this is more than 10 times the typical
insertion force for such a needle. The experiment has been
repeated with a second needle, where a force of 20 N was
applied 10 times at an angle of 45° relative to the axis of the
needle shaft from different azimuthal directions. No visible
damage occurred in either experiment, which indicates that
needles in the current design are strong enough to withstand
the forces associated with a typical biomedical application.
Clinical studies by R. Sivamani et al. [29] have shown that
these needles can be used to significantly enhance epidermal
drug delivery with no sensation of pain experienced by the
human volunteers.

B. Characteristics of Liquid Flow through Microneedle Arrays

A complete description of liquid flow through these needles
during an injection would have to include in vivo effects such
as the liquid absorption in the epidermis. The motion of the
fluidized drug in the skin will be hindered due to the presence
of cell structures, so that highly non-linear effects such as
saturation can be expected. Preliminary experiments for liquid
injection into cadaver skin illustrate this problem [29]. A fluid
mechanical description of the skin has not been established
yet, and it will require extensive research. A complete fluid
mechanical characterization of these needles in the skin will
have to be performed through experiments. The present flow
characterization will therefore be limited to the fluid
mechanics of liquid flow through needle arrays using water as
a model liquid.

It will be assumed that the distance between needles is large
enough so that fluid flowing through one needle should not
influence the fluid dynamic behavior of fluid through a
neighboring needle. The pressure drop \( \Delta p \) as a function of
flow rate \( q \) for an individual needle as shown in Fig. 9 has
been modeled with the modified Bernoulli equation [33],

Fig. 7 Horizontal cuts obtained through confocal microscopy reveal that the
fluorescent marker Lucifer Yellow has been injected about 100 µm deep into
chicken tissue using a pointed needle with the setup shown in Fig. 6.

Fig. 8 A pointed single crystal silicon needle as shown in Fig. 4b before (top)
and after (bottom) 10 insertions into human skin using a force of 10 N. The
needle has not been damaged.
\[ \Delta p = \mu \frac{128 q L}{\pi D^4} + \rho \frac{8(K_1 + K_2)}{\pi^2 D^4} q^2, \] (1)

which is generally used to describe fluid flow through macroscopic piping systems.

Fig. 9 The parameters for fluid flow at a volumetric flow rate \( q \) through a needle lumen of circular cross section with diameter \( D \) and length \( L \), causing the pressure drop \( \Delta p = p_1 - p_2 \).

Standard macroscopic values for a square edged inlet \((K_1 = 0.5)\) and for an exit \((K_2 = 1.0)\) that represent the inertial minor losses of piping systems [33] were chosen to model the flow characteristics of the \( L = 550 \mu m \) long microneedle lumen. The density and viscosity of water were assumed as \( \rho = 1000 \text{ kg/m}^3 \) and \( \mu = 1.006 \cdot 10^{-3} \text{ Pa s} \) respectively. Gravitational forces were ignored in the calculations because they were negligible during the flow experiments. These forces will also be relatively small during an actual application of microneedles.

The volumetric flow rate of water through a silicon plate with microneedles is set with a syringe pump (Cole-Parmer 40900-20). The resulting pressure drop \( \Delta p \) across the array of microneedles can be determined from the gauge pressure measured upstream from the microneedles \( p_1 \) using a commercially available piezoresistive pressure sensor (Honeywell 26PC Micro Switch series), assuming that the pressure downstream from the needles \( p_2 \) stays constant.

A total of 30 measurements per data point were collected in 3 cycles ramping the flow rate through 8 parallel needles up to 5000 \( \mu l/min \) and back down to 0 \( \mu l/min \). The mean values of these measurements represented by the circles in Fig. 10 deviate by only 2% from the theoretical result obtained from the modified Bernoulli equation (1), which is represented by the solid line.

Fig. 10 Pressure drop \( \Delta p \) as a function of flow rate \( q \) through one needle for an array of 8 needles; theory [-], measurements [o].

The maximum Reynolds number \( \text{Re} = 330 \) for these experiments justifies the assumption of laminar flow made for the friction factor in the modified Bernoulli equation (1). An experimental relation for the entrance length

\[ L_E = (0.59 + 0.055 \text{Re}) D \] (2)

of laminar flow entering a circular pipe has been given in [34]. For the two highest flow rates, \( q = 625 \mu l/min \) & 500 \( \mu l/min \), used in this experiment, the associated entrance lengths, \( L_E = 750 \mu m \) & 600 \( \mu m \), exceed the lumen length \((L = 550 \mu m)\), so that the Hagen-Poiseuille flow cannot fully develop within the lumen. However, the majority of the inertial pressure drop in a channel occurs right at the entrance [35]. Therefore, ignoring the fact that the flow exits the lumen before being fully developed only induces a negligible inaccuracy in the calculation of the pressure drop. Hence, the Bernoulli equation (1) is a good model for flow through microscopic channels such as the lumen of a microneedle as shown by the good match between the experimental results and the theoretical values in Fig. 10. This flow characterization has been performed for symmetric needles. Similar results are expected for pointed needles, where the coefficient for the minor losses at the channel exit \( K_2 \) will have to be modified.

VI. CONCLUSION

A fabrication process for hollow single-crystal silicon out-of-plane microneedles has been presented. It has been demonstrated that the manufactured needles are effective for shallow injections into biological tissue, so that these needles might be useful for painless epidermal drug delivery. However, more knowledge of skin properties such as the mechanical resistance and compliance of the skin and the flow
resistance for liquid flow into the tissue are necessary to optimize the needle design. Furthermore, it has been shown that the Bernoulli equation is a good model for liquid flow through microchannels such as the microneedle lumens.

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REFERENCES


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