Atom sharp microneedles, the missing link in microneedle drug delivery?

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Introduction
The skin barrier function is a major challenge for delivery of drugs via the skin. Located in the outermost layer of the skin, the stratum corneum (SC) consists of dead cells embedded in lipid regions, only 10–20 µm thick, tough but flexible and elastic. Hypodermic needles penetrate the skin successfully, but nerve rich tissue in the lower skin is penetrated which is simply painful.

Minimally invasive micro-needles provide a reduction of pain sensation. Pain can be eliminated completely when drugs, like vaccines or insulin, are delivered into the dermis, some 0.1 to 1 mm under the stratum corneum. [1]. This shallow penetration is no practice today since hypodermic needles need to have long bevelled tips to ease penetration. Since a significant percentage of the people suffer from needle-phobia, the holy grail is a micro-needle that delivers drugs into the dermis and therefore is not felt (and is not seen either).

Micro-needles are small, and to obtain an acceptable drug flow rates through the inner bores, more needles on a device aerea are used, an approach not used in the needle practice today. Micro-needles have been researched for many decades, however since bulk and surface micromachining of silicon became available during the 1990s and made microstructuring possible, the number of different needle designs increased and real interest rose worldwide [2]. As a result of these fabrication techniques, and the fact that in the early days of micro-needles, needle were designed very short, most designs have been out-of-plane of plane needles. These have been tested in vitro and some on human tissue or in vivo, with various results [3]. Some results have been published [4], but also many results stay unpublished: it has become clear the out-of-plane needles are of use in some application areas, but trouble-free application is not there yet.

The issues with out-of-plane needle designs have not been reported widely. By studying the publications and by interpretation of the results in combination with the various designs, one unresolved issue becomes very clear: sharpness. Since a micro-needle is supposed to be shorter than a hypodermic needle, the insertion in the elastic but tough statum corneum is not straight forward. When length is not compensated by extra sharpness, there simply is no skin penetration. All initial out-of-plane initiatives suffered from this shortcoming, especially since they also were relatively short. Since 2007 some improvements have been reported [5] : It has become clear that lack of sharpness is a key factor for success of microneedles, in combination with longer needles that penetrate the stratum corneum trouble-free. To reach this goal, two different approaches are found in literature : Sharpen the needle [5] or use a procedure or applicator [4]. We've chosen to sharpen the needle.

A more general model on insertion-force and pain sensation in relation to sharpness, penetration depth, needle diameter and material has not been reported widely, although researchers now focus on these issues for their needle designs [6]. These parameters are well known with conventional standardised needles, which they consist of canullas with different point styles. One of the most popular types - minimum pain sensation - are needles with a Lancet tip. Here the lack of ultra sharpness is compensated by the length of the bevel (1,3 mm long for a 30G) or a small opening angle (13 deg bevel average) to penetrates the skin. Shallow drug delivery into the skin is simply impossible here, as is the elimination of pain sensation.

Previously, at University of Twente an innovative out-of-plane needle design was developed [7] in the early 2000’s. Fabrication was based on a combination of dry and wet etching techniques. We have now realised a needle design that combines the ultra sharpness with a short bevel, to enable shallow delivery into the skin. This has been achieved by making use of wet-etching techniques only.

To demonstrate this new needle type, we created solid needles to characterize the penetration, as shown in the pictures below. In the following section we show initial results from in vivo
and in vitro penetration and report on various aspects of these prototypes, like cost, process, penetration, strength.

Out-of-plane versus in-plane needles.
Depending on the drug flow requirements more needles are placed in an array of needles. The assembly of in-plane silicon microneedles into an array of needles is often called difficult and cumbersome. We think this assumption is wrong, since cost and function should be the drivers: in terms of cost it turns out that the most expensive part of a micro-needle is not the hub or the assembly of needles into the hub, it is the size of silicon used, and the more needles are etched out of one silicon wafer, the lower the cost per needle or needle array can be: only the (sharp) needles should to be (expensive) silicon, the rest, including array base and hub, are made of lower cost materials.

MEMS Manufacturing process
Silicon micromachining is semiconductor manufacturing, and the techniques are well known today. The silicon is machined by deposition and etching of materials. Patterns are created by 2D Photolithography [8]. The needle presented here is anisotropically etched in KOH at 70 degrees from <100> silicon wafers and the faces forming the final needle are the <111> planes that remain after etching, since they are the so called ‘slow-etching planes’ in the monolithic silicon crystal. This anisotropic etching process yields near atomic-flat surfaces.

An intersection of two of these non-parallel planes forms a near atom sharp blade, used today for example to create surgical blades with extreme sharpness in silicon [9]. To create the needle we now succeeded to intersect three <111> planes, to form the tip, which therefore also becomes near atom-sharp. The result is a needle that is shaped by the <111> planes and its intersections, and is therefore near atom sharp at all its rims. After etching, it can be assembled and used; it need no sharpening, it is extremely inert and clean and the material’s surface (silicon and silicon native oxide) is extremely pure and inert.

Design
The entire geometry of the atom sharp needles depend on the crystalline orientation of the silicon substrates used and the 2D mask designs for lithography.
This needle uses <100> silicon substrates, which yield a three faced tip and a three faced shaft, where two faces are common. The cross section is triangular everywhere, and constant in size at the shaft, and decreasing to zero towards the tip at the point.
The point has a bevel (openings angle) of 55 degrees, which is given by the intersection of the <111> and <110> crystal plane. It is a result of the silicon crystal orientation used, and cannot be changed.

The result is a needle that resembles a triangular shaped canulla with a bevelled tip at 55 degrees with extreme sharp edges and tip.
The substrate used is 380 micron thick, yielding a maximum base width of 550 micron at the shaft.

Diameter and length
Within a fixed crystalline substrate needle length and width (diameter) are freely chosen without changing the manufacturing process: it is a design freedom in the 2D lithography masks and various lengths and widths are made in one single same manufacturing run.
The current dimensions are the result of the standard available wafer thickness of 400 um. A different substrate thickness yields a different needle diameter.
The needle consists of a shaft with a beveled point. In contrast to the out-of-plane needle design, where the needle length is a result of the etching process, this in-plane needle design defines the shaft length by the mask design.
Needle lengths of 100 micron to 1 mm have been created.

Penetration in vitro
Initial penetration tests have been performed by penetrating through a standard silicone foil of 1 mm thickness. Needles have been used without any coating or siliconization. A 30G, 23.5G
and 21G needle (diameter 0.3, 0.6 and 0.8 mm) have been used for reference purposes, which are coated with silicone oil to reduce friction. [10]. The force increases gradually as the tip starts to penetrate the foil. The maximum penetration force is reached when the shaft enters the foil. The same holds for the reference needles. The maximum force of the atom sharp needle was determined at 83±6 gf. The values for the three reference needles were 46±2 gf, 83±4 gf and 109±7 gf respectively.

**Penetration in vivo**

Initial penetration tests have been performed in life tissue, on various places on the hands and arms. The penetration is inspected through a microscope. The tip of the needle penetrates the skin easily, without pain sensation. Again the force increases to a maximum value when the shaft enters the tissue. Once the tip has cut completely through the tissue, the force decreases as is known from the reference needles. When the shaft enters the tissue, pain sensation is sometimes present, very much depending on the depth and place of penetration. Since the initial needle design chosen is quite large for shallow penetration, the length of only the tip is already 280 micron. Also visual inspection of depth in life skin turns out to be troublesome, so more sophisticated techniques like penetration detection by electrical impedance measurements need to be carried out to quantify the penetration depth / force / pain relation.

Skin is very flexible and tough. Most micro-needle designs today have round or rounded shapes and tips and the penetration of the needle tip and/or shaft through the skin is reached by local rupture of the skin instead of a cut. This might be the reason for penetration forces that are quite high in relation to the small needle dimensions reported [11]. The atom sharp needles, (and the lancet style conventional needles) clearly cut their way into the tissue. This is to be expected because of the triangular needle and atom sharp rims: the cut is a perfect V-shape, a projection of the rims onto the tissue. When using foil instead of tissue the perfect V-shape appears.

**Needle strength and fracture**

Needles have been inspected with a microscope and no deformation or chipping has been observed with multiple use: the sharp rims stay sharp when used in the (relatively soft and flexible) skin, thought to be the effect of the atom sharpness : Along the edges no imperfections exist, not giving rive to any fracture or wear. However, a firm statement on wear cannot be given untill inspection on an atomic scale, and this will to be done by SEM imaging. The Fracture strength has not been quantified, however the needles are strong and have not shown needle fracture during penetration experiments. Some needles have been submitted to high side loads to induce fracture and they fractured at the base, where the shaft is connected to the base, and fracture occurs exclusively along the <111> plane. This corresponds to literature, where silicon’s lowest fracture stress is reported along the <111> plane. ([12] 1 GPa and around 2.2 GPa for the <110> direction). Since silicon is a brittle, fracture needs investigation, especially when needles are smaller, to determine wether various needle designs and geometies might need a coating to resist possible needle fracture [12].

**Conclusions and next steps**

The current needle design yields satisfactory results. Its short bevel of 55 degrees is compensated by the Atom sharp edges and the needle has a penetration force comparable to the best conventional long beveled needles today. It shows superiour cutting properties and no wear. It is made of crystalline silicon, extremely pure, inert and easy to coat with even harder or tougher materials, like silicon oxides and nitrides. Future needle design focusses on smaller geometries, the creation of a hollow bore inside the needle and the assembly of needle arrays.
**Figures & Photos**

Top left: Sketch of needle, consisting of triangular shaft and 55 degrees beveled tip. Top right: Microscope picture of two solid needles. Bottom left and right: SEM photos of bottom and top view of two needles, in which the Atom Sharp edges can be seen. The material around the needles is bulk silicon, from which the needles have been etched.

**References**

[10] BD Microlance 3