Microfabricated Silicon Microneedle Array for Transdermal Drug Delivery

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Abstract. This paper presents developed processes for silicon microneedle arrays microfabrication. Three types of microneedles structures were achieved by isotropic etching in inductively coupled plasma (ICP) using SF$_6$/O$_2$ gases, combination of isotropic etching with deep etching, and wet etching, respectively. A microneedle array with biodegradable porous tips was further developed based on the fabricated microneedles.

1. Introduction
Microfabrication technology, which has traditionally been used to produce microelectronic devices such as microprocessors, has been increasingly applied to machining micro-scale devices, including micropumps, micoreactors, accelerometers and micromirrors. Such devices are commonly referred to as Microelectromechanical systems (MEMS). Microfabricated structures have well controlled features that range in size from millimeter to micrometer because of using the reproductive semiconductor machining processes such as photolithography, wet & dry etching and thin film deposition. BioMEMS, referring to MEMS devices for biological applications, has attracted the attention of researchers during the last decade. Among these microfabricated devices towards diagnostics and therapeutics, microneedles are some of the most important applications for drug and gene delivery.

The transdermal delivery is an alternative way to transport certain drugs, which can not be ideally delivered by pills and hypodermic injection. The barrier in transdermal delivery, poor skin permeability, would be broken down by using of microneedle array to pierce the first layer of skin. The microneedles are used to painlessly deliver big molecular into subcutaneous tissue with the rate at
therapy level by enhancing of skin permeability in transdermal delivery. The earliest silicon microneedle array, fabricated by a reactive ion etching (RIE) process with a chromium mask, could increase the skin permeability by up to four orders of magnitude using a fluorescent dye, calcein [1]. A hollow metal tube array and a hollow metal microneedle array were further demonstrated for transdermal delivery application [2]. These metal microneedles were fabricated by forming polymer or silicon molds and electrodepositing nickel, gold or other metals onto the mold. These hollow microneedles were inserted into human epidermis and were shown to increase skin permeability by up to five orders of magnitude above the assay sensitivity limit. More recently, Park et al developed biodegradable polymer microneedle array using PDMS mold for replication of the microneedles [3]. This polymer microneedle array had the ability to increase skin permeability up to three orders of magnitude in in-vitro experiments; and the microneedle using biodegradable polymer is ideal for clinical applications. Applications of microneedles which were fabricated from metal sheets for in vivo transdermal delivery of drugs such as insulin, oligodeoxynucleotide (ODN) and protein vaccine have been reported. Martanto et al fabricated the solid metal microneedle array by laser-cutting the shape of each needle out of a stainless steel sheet [4]. In this application, an insulin solution was placed on the top of the microneedle array and left in its place for four hours; and a significant effect on blood glucose levels was observed. Other types of metal microneedle arrays with coating of drugs on their surface for in vivo transdermal delivery were etched from titanium sheets or stainless steel sheets. Using these microneedle arrays, Lin et al demonstrated that the ODN delivery flux reached 8.08±0.06 μg/cm²/h; and high-level ODN concentration was found in the deep skin layer [5]. Matriano et al also applied these microneedle arrays to protein vaccine delivery, achieving high delivery rates up to 20 μg in 5s [6].

In our study, dry etching of microneedle in different approach is developed. Isotropic etching in ICP etcher was developed to fabricate microneedle with one step photolithography process. To achieve high height of microneedle, SF₆/O₂ etching combine of BOSCH etching were developed. In addition, KOH wet etching was investigated for fabricating of microneedles. In the follow up research, fabricated microneedle array with biodegradable tips were fabricated for transdermal drug delivery.

2. Microneedles fabrication
The dry and wet etching technologies were investigated for microneedle array fabrication in this study. The thermal silicon dioxide mask patterned in square and dot arrays was used for microneedle fabrication.

2.1. Isotropic dry etching process
Fig. 1 shows the fabricated microneedle array in isotropic etch using SF₆/O₂ gases in STS ICP etcher.

![Figure 1. SEM micrograph of microneedle array fabricated in isotropic etching process](image)
The fabricated results are influenced by the process parameters such as powers, pressure and gas flow. The characterization of isotropic etching for microneedle fabrication has been carried out by the design of experiment (DOE) method [7]. With the characterization results, a variety of microneedle structure can be fabricated. The microneedle arrays with oxide mask is shown in Fig.1 (a) and the result of the mask totally under-etched is shown in Fig.1 (b).

2.2. Combination of isotropic and anisotropic dry etching process
The microneedle array with sharp tips can be fabricated using the isotropic etching, as shown in Fig.1. However, the height of the microneedle highly depends on the pattern dimension of a mask. In our experiments, the maximum height of microneedles is ~120 µm under the square mask with the dimension of 80 µm. To get high aspect ratio microneedle structure, the process, which is combined isotropic etching and anisotropic etching is used to fabrication microneedle. For a square mask of 80 µm in length, a microneedle with ~ 300µm in height was achieved. Figure 2 show the fabricated microneedle arrays using the combined process. The height of microneedles mostly depends on the depth of deep etching process. The time of deep etching in Fig 2 (a) is 40 minutes and in Fig.2 (b) is 100 minutes.

Figure 2. SEM micrograph of microneedle array fabricated in combined process

Figure 3. SEM micrograph of microneedle array fabricated in KOH wet etching process
2.3. Wet etching process
Fig. 3 shows the microneedle fabricated in KOH wet etching process using a square mask. The mask size is 80 µm in length with 150 µm center-to-center distance. The wet etching results highly depend on the crystal plane of silicon. The etching results highly depended on crystal planes as shown in Fig. 3 (a), which shows the microneedle shapes during the KOH etching process. With increased etching time, the top part of the microneedle was etched away, as shown in Fig. 3(b).

3. Microneedle array with biodegradable tips
Furthermore, a process has been developed to fabricate microneedles with macroporous tips. The macroporous silicon is marked as a biodegradable material [8]. Therefore, it has attractive potential application in biological area. Moreover, the porous structure provides an alternated method for drug loading. Fig. 4 illustrates the overall process for porous tips fabrication. Firstly, a silicon nitride layer was deposited onto the fabricated microneedle surface (Fig. 4(b)). Secondly, a thick photoresist was coated to the structural substrate (Fig. 4(c)); and the sample was baked at temperature higher than the photoresist transition temperature to reflow the photoresist from the top of needle. Following the top photoresist etched in RIE with O₂ gas (Fig. 4(d)), the top part and backside silicon nitride layer was removed in RIE using CF₄/O₂ gases (Fig. 4(e)). Finally, a thin gold layer was deposited on the backside of sample. An electrochemical etching process was carried out to generate the porous tip using HF based electrolyte, resulting in the microneedles with porous tips (Fig. 4(f)). Fig. 5 shows the fabricated microneedles with porous tip. It is clear to see the porous structure is formed on the exposed tip part. The porous tip may serve as a tool to load drugs.

![Figure 4. Fabrication schedule of microneedle array with porous tips](image-url)
4. Conclusion

Different microneedles were fabricated by dry and wet etching process. The high aspect ratio needle structure is achieved by combination of isotropic etching and DRIE process in STS ICP etcher. In isotropic dry etching and KOH wet etching process, the height of fabricated microneedle is ~120 µm using the square mask in length of 80 µm. A higher microneedle can be achieved by using large dimension in mask. The process for microneedle with macroporous tips was further developed for transdermal drug delivery. The biodegradable macroporous tips may provide a novel application for drug delivery. The applications of these microneedles will be investigated in transdermal drug delivery. Skin permeability and drug delivery rate will be further measured in the testing experiments for different fabricated microneedles.

References

[1] S.Henry, D.V.McAllister, M.G.Allen and M.R.Prausnitz “Microfabricated microneedles: a novel approach to transdermal drug delivery”, J.Pharm.Sci., Vol 87,922-925,1998
[2] D.V.McAllister, P.M.Wang, S.P.Davis, J-H. Park, P.J.Canetella, M.G.Allen and M.R.Prausnitz, “Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: fabrication methods and transport studies”, Proc.Natl.Acad.Sci. USA Vol.100 13755-13760, 2003
[3] J-H.Park, M.G. Allen and M.R.Prausnitz, “Biodegradable polymer microneedle: fabrication, mechanics and transdermal drug delivery”, J. Contr. Rele., Vol 104, 51-66, 2005
[4] W.Martanto, S.P.Davis, N.R.Holiday, J.Wang, H.S.Gill and M.R.Prausnitz. “Transdermal delivery of insulin using microneedles in vivo”, Pharm. Research, Vol 21, 947-952,2004
[5] W.Lin, M.Cormier, A.Samiee, A.Griffin, B.Johnson, C.Teng, G.E.Hardee and P.Daddon. Transdermal delivery of antisense oligonucleotides with microprojection patch *Pharmaceutical Research* 18 1789-1793,2001
[6] J.A. Matriano, M.Cormier, J.Johnson, W.A.Young, M.Buttery, Knyan and P.E.Daddina, Macroflux microporation array patch technology: a new and efficient approach for intracutaneous immunization *Pharmaceutical Research* 19 63-70,2002
[7] J. Ji, F.E.H Tay. J. Miao and J. Sun, Characterization of Silicon Isotropic Etch by Inductively Coupled Plasma Etcher for Microneedle Arrays Fabrication, iMEMS 2006
[8] L. Buckberry and S. Bayliss Porous silicon as a biomaterial *Materials World* 7 213-215,1999