

Through-Hole Microneedle Fabricated by Alignment X-ray Lithography

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Abstract

A sharp-tip microneedle array with through-hole has been fabricated. The work has solved the limitations of fabrication by X-ray lithography: vertical side-wall and the alignment between 2 patterns since the fabrication of through-hole required an additional alignment technique. A portable alignment tool with precision-control by digital microscope has been designed. The accuracy of hole-alignment at $\pm 3\mu\text{m}$ was observed. The study is based on geometrical design of X-ray mask patterns and experiments. We have fabricated 4 single-tip microneedle arrays by synchrotron radiation (SR) X-ray lithography with additional PCT (plain-pattern to cross-section transfer) technique. The following process is, to align holes in 4 different locations. In addition, the 2nd X-ray exposure for through-hole was performed. The optimization of hole-location is beneficial since the hole centrally located to the needle-tip has raised a trouble of corking skin into the hole. The liquid or blood, thus, can not go through the hole and made microneedle useless. The problem has been suppressed by the technique described in this paper. The array of microneedle with nanoscaled sharp-tip can be used for multi-purpose of bio-medical MEMS application.

1. Introduction

Microneedles have been generally considered for serving an application of Bio-medical MEMS, e.g. drug delivery system, blood extraction system. Therefore, a hole or a liquid channel for liquid flow is required. For decades, the methods of through hole fabrication of microneedle were found as; excimer laser[1], plasma etching[2,3], and inclined X-ray lithography[4]. All the above methods require a precise alignment. Generally, the alignment work for X-ray lithography causes difficulty on matching the center for perforating. It is apparently impossible by hand-adjustment. So far, the difficulty was taken into account, we, consequently designed pen-type microneedle that can be used for blood extraction without the requirement of a hole[5] as shown in Fig. 1. However, the use of quadruplets-microneedle is nearly impossible for drug delivery system since there is no connecting path to an external pumping system.

Microneedles with through holes are required in most bio-medical MEMS applications and some fluidic MEMS applications. According to the consideration of multi-functional use, we, therefore, made another design of microneedle with an exertion of the portable alignment tool that can be temporarily assembled onto the resist stage of X-ray exposure chamber. The simple and low-cost alignment tool was designed and resulted in the accuracy of $\pm 3 \mu\text{m}$. The fabricated microneedle has $40\mu\text{m}$ -diameter and $200\mu\text{m}$ in length. The 1024 PMMA microneedles constructed on a $1 \times 1 \text{ cm}^2$ array chip can be used for multi-functional Bio-medical MEMS purposes either drugs delivery or blood extraction.

For decades many researchers have put their efforts to miniaturize needles for drug delivery or blood extraction system as the smaller, the painless. Main objections are, material properties, bio-compatibility and the most recently interesting problem is liquid-block by corking skin into the hole during the insertion. The material properties other than the strength and the bio-compatibility will not be discussed here since there have been heretofore sufficient papers described about the benchmarking of materials. Moreover, our fabrication method is LIGA(Lithography, Electroforming, and Molding) which the materials are selectable after manufacturing the mold. Thus, the geometrical study on original microneedle structure has attracted our attention in order to develop an operative mold afterward.

2. Experimental

The fabrication technique employed in this work is one of the advanced X-ray lithography. The extension of 2.5 dimensional structures to 3 dimensional structures has been successfully approached by several additional processes, e.g. moving mask[6], and PCT(Plain-pattern to Cross-section Transfer) Technique which has been discussed by S. Sugiyama et al.,[7]. The two-dimensional pattern is resulted in three-dimensional structure whilst similar cross-section. Several types of PMMA(poly-methyl-methacrylate) microneedle array have been fabricated.

The brief description of PCT process is as following. The vertical movement of the resist stage forms microstructures and gradually enlarges the exposed area of the PMMA. Double exposures with perpendicularly scanning-directions form lateral axes-symmetric structures. The X-ray absorption profiles in the PMMA is dependent to the area of absorber on X-ray mask(Au), the cross-section of patterns on X-ray mask formed similar structure on PMMA whilst resulted in 3-dimension. The exposed depth in PMMA depends on X-ray dosage and the absorption coefficient of the PMMA sheet. The X-ray dosage required for the structure of $300 \mu\text{m}$ -depth is at 0.42 A.h. The developing time is 180 minutes at 37°C . The GG developer (60 vol% 2-(2-butoxy-ethoxy) ethanol, 20% tetra-hydro-1, 4-oxazine, 5 vol% 2-amino-ethanol-1 and 15 vol% water) was used. The exposure chamber of PCT process has been located at Beamline-13 (BL-13) of synchrotron radiation compact source AURORA at

SR center, Ritsumeikan University, Japan. The exposure environment was covered with Helium gas at 1 atm. The wavelength of SR light at AURORA is between 0.15 - 0.73 nm. The applied electron energy and the maximum storage current in the experiment were 575 MeV and 300 mA.

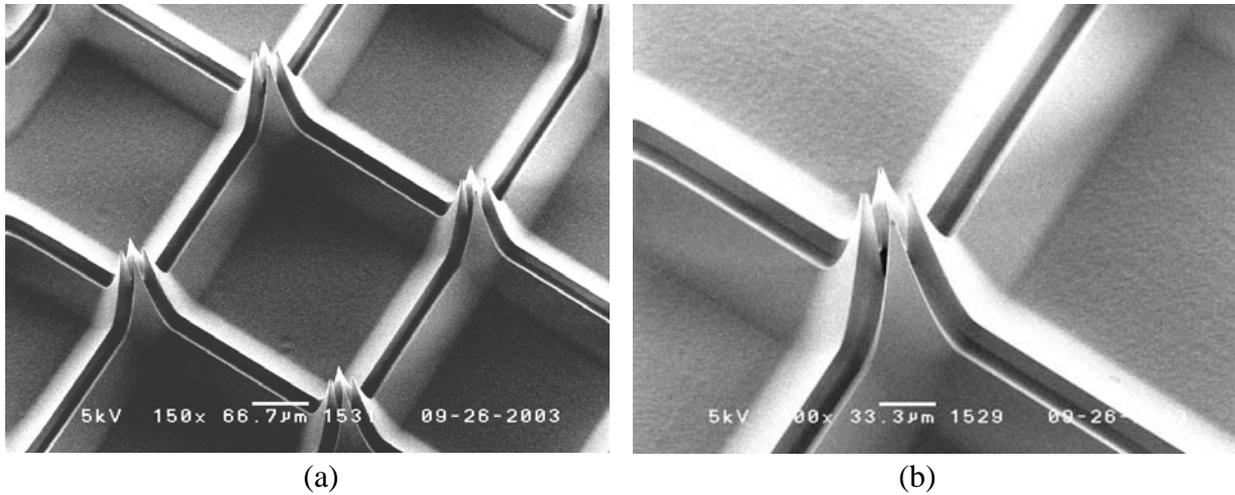


Fig.1 SEM photos of (a) quadruplets-PMMA microneedle array and (b) close-up photo of a quadruplets-microneedle.

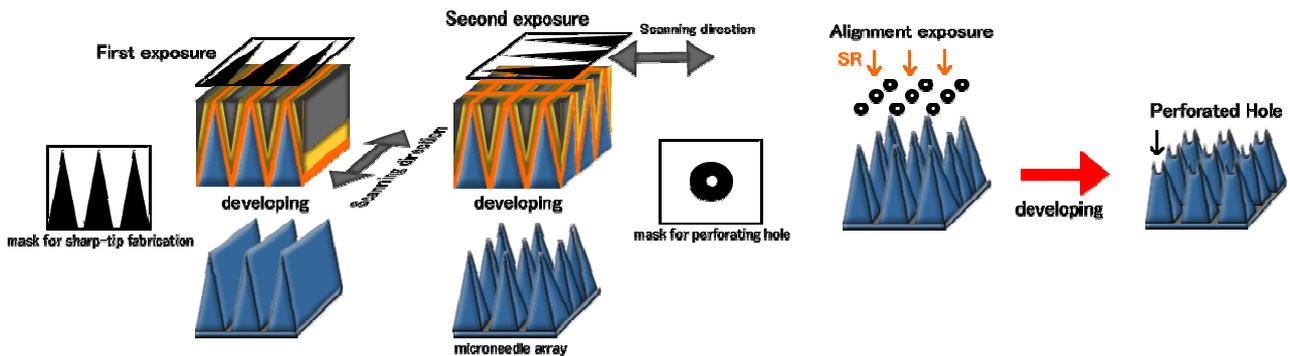


Fig. 2. PCT process following by alignment exposure (from left to right)

3. Alignment Design and Requirements

After twice exposures through isosceles-triangle mask by PCT technique and developing, the resist with single-tip microneedle array was fixed onto the alignment stage following by placing the X-ray mask above the resist. The third exposure was done through hole-pattern mask. The process diagram is shown in Fig. 2. The alignment tool employed in this work is shown in Fig. 3. Due to the relatively light weight and low-cost, manual alignment tool was made by aluminum to be assembled on resist stage of the X-ray exposure chamber. The tool consists of four stages; X, Y, Z, and θ . During the alignment process, a digital microscope (KEYENCE, VH-8000) was used with the frame set (mesh-scale menu) shown on the monitor Figure 4(a) and 4(b) show the frames containing hole-mask pattern and single-tip microneedle respectively. After aligning, the focus in between PMMA and mask confirms the right position as shown in Fig. 4(c). The gap between mask and resist was left at approx. 1 mm. in order to secure the mask membrane from scratching with resist. However, the zero-gap is possible after the X, Y and θ stages have been locked. Alignment of the hole mask-pattern and

microneedle inside a frame can ensure that the center of hole-pattern and the area that perforation required, e.g. tip of the microneedle are precisely matched. Moreover, the perforating holes are not prerequisite to be only at the center of microneedle. Firstly, we have fabricated the hole through the center of microneedle-tip. The type of microneedle causes the problem of blood corking since the skin will easily block the hole. The solution is to move the hole away from the center. Therefore, we have tried again two experiments according to the two specifications in Table 1. After the alignment process has been completed, the alignment tool, resist and X-ray mask is then assembled to the resist stage in the exposure chamber of Beamline-6 (BL-6) of the AURORA.

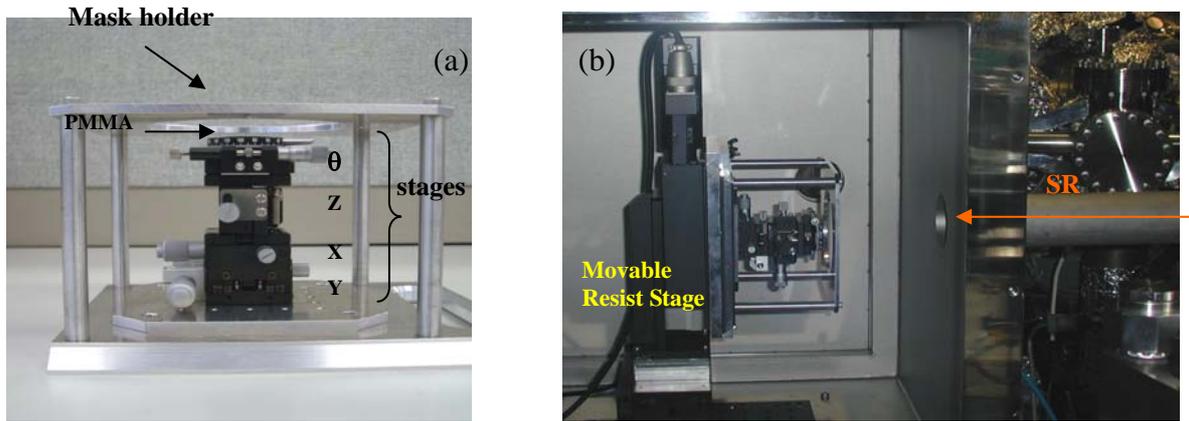


Fig. 3. (a) The portable alignment tool and (b) exposure chamber BL-6

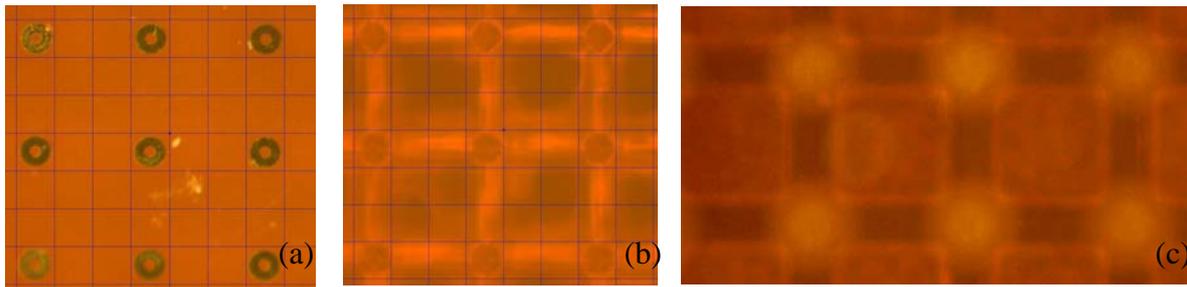


Fig.4 Alignment of tip and second X-ray mask pattern. (a) focus at X-ray mask, (b) focus at PMMA and (c) focus at between mask and PMMA.

Cases	PCT mask	hole mask	Alignment
Spec. 1		 (centered)	 50 μm horizontally from center hole mask
Spec. 2		 (30 μm away from center)	 50μm vertically from center

Table 1. Two alignment specifications. Top-view sketch of single-tip microneedle :

4. Experimental Result

The results from experiments in Table 1. are shown in Fig. 5. The types of microneedle are suitable for blood extraction system since the tip is sharp enough to reach the inner layer of skin where plenty of capillaries located. Moreover, the consideration of cost reduction has been taken into the account. By reducing the PCT-2nd scanning step while the size of microneedle-base has also been reduced to 100 μm, the results were relatively similar by both cases. The experiments have been done by two different processes of PCT exposure. Table 2. shows the experiment design and results. The pitch is 300 μm and more than a thousand microneedles were fabricated in a square centimeter-chip of PMMA. The first experiment employs twice scanning PCT and the holes aligned to 20μm away from the microneedle tips. The second experiment is single scanning PCT following by the holes aligned at 20μm away from the tips. The microneedles from both experiments show that although twice PCT scanning resulting as a sharper tip of microneedle, the single PCT scanning is also sufficient for utilization in bio-medical application whilst the X-ray dosage reduced from 0.84 to 0.42 A.h. The cost decreased about US\$250 per an exposure.

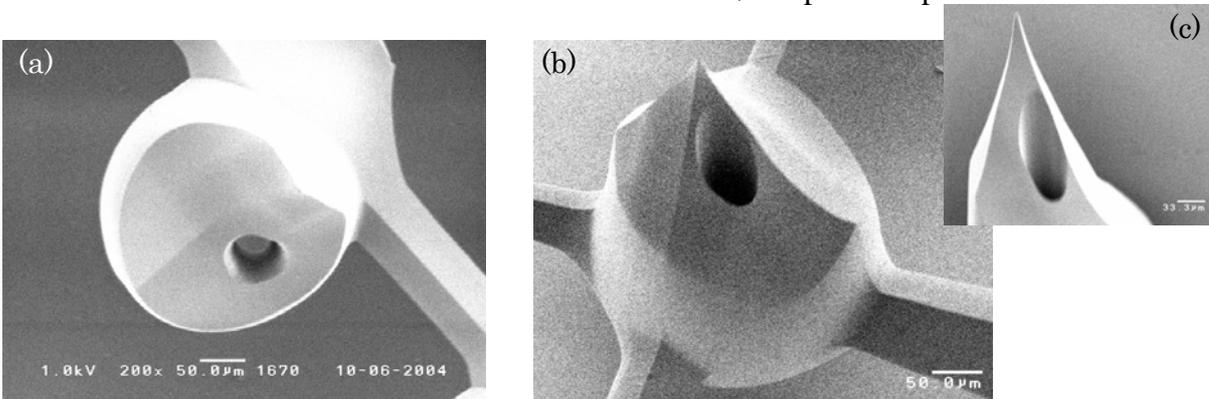


Fig. 5. The results from experiments in Table 1. (a) specification 1 and (b) specification 2 and (c) close-up vertically of the microneedle in (b)

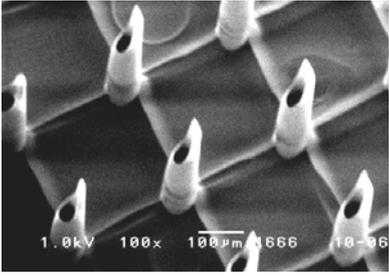
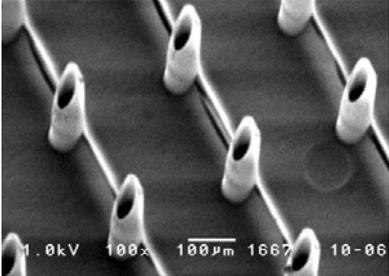
PCT 1 st scan	PCT 2 nd scan	SEM photo of results
√	√	
√	X	

Table 2. Results from reducing steps of PCT before the alignment-exposure.

5. Conclusion

The work reported in this paper is a solution for solving two troubles of microneedle fabricated by X-ray lithography. The enhancement of vertical side-wall to sloped side-wall structure by PCT technique has been suggested. The other difficulty was the through-hole fabrication onto three-dimensional structure. Although the alignment facilities are available commercially, the cost is relatively expensive and importable. We, therefore, applied a simple, low cost and portable alignment tool for the accuracy of $\pm 3 \mu\text{m}$ which is sufficient for aligning our structure. The experimental results from X-ray lithography at AURORA, synchrotron radiation storage ring, Ritsumeikan University were given and the experiment of single scanning PCT and hole aligning $20 \mu\text{m}$ away from the tip of microneedle has been selected to be further replicated since it is lower cost. The through-hole exposure was done in order to make a fluid connection to an external pumping system. The fabricated microneedle array on $1 \times 1 \text{ cm}^2$ chip of PMMA consists microneedles with $250 \mu\text{m}$ in length and $40 \mu\text{m}$ of hole-diameter that prevents the clogging problem of blood since the diameter of white blood cell is approx. more than $20 \mu\text{m}$. The microneedle fabricated by using triangular mask is suggested to be used in drug delivery system since it is not recommended to penetrate the skin as deep as the inner layer. The problem is the strength of the microneedle-tip. During a penetration test, some of microneedle tips were broken, up to 30% of the array. However, we have reported the replication process that the material for injection into the mold can be selected. Therefore, the injection-trials of many plastic materials will be required so that the highest strength and bio-compatible plastic will be found for a practical use. Moreover, the experiments using pentagonal mask with various hole-locations have also been reported. For pentagonal mask, the very sharp-tip of microneedle was achieved at about 300 nm. It is noted that, the pentagonal mask requires twice scanning PCT. The microneedles fabricated by pentagonal mask were designed to serve either drugs delivery or blood extraction system.

References

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