

Quadruplets-Microneedle Array for Blood Extraction

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ABSTRACT

A novel fabrication of painless microneedle array using Synchrotron Radiation lithography with PMMA (Polymethylmethacrylate) is presented in this paper. The microneedles were shaped by Plain-pattern to Cross-section Technique (PCT). 4 patterns of X-ray mask were investigated and tested then the optimal one has been selected. The 1024(32x32) quadruplets-needles are consisted in 1x1 cm² chip. The crown-shaped structure with 4 tips microneedle can be usehd without the consideration of holes for blood extraction. The tip-size in nano-scale has also been approached. Fabrication of the PMMA microneedle is applicable for LIGA technique. The electroplating of metal and injection of a plastic material can be done for batch production.

Keywords: microneedle array, blood extraction, PMMA, X-ray lithography

1. INTRODUCTION

In biomedical application, the sharp tips, high strength and bio-compatible microneedles are required. PMMA is a material which can be safely used with human skin since it is not a brittle material, alike silicon. The High-Aspect-Ratio MicroStructure(HARMS) has been shaped by synchrotron radiation Lithography. Using the standard deep X-ray lithography exposing on an X-ray resist layer, the 2.5-dimension microstructure can be fabricated. However, the resulting side wall is usually vertical. In order to reach the 3-dimension microstructure, Plain-pattern to Cross-section Technique(PCT) was investigated. The structure has been resulted in the arbitrary shaped wall[1]. In addition, sharp microneedle tip is the key of reducing the skin damage from piercing reaction[2,3]. Also the needle with sharp tip can smoothly penetrate to the skin at the correct position[4]. Nanoscale microneedle tip-size has also been achieved. Recently, a microneedle array has been fabricated using PCT method originated in Ritsumeikan University, Japan[5]. The previous work has presented single-tip microneedle arrays whilst the shape was simple and difficult to use for a blood extraction[6]. However, a method of approaching arbitrary structure was developed and now applied to the novel design in this work.

2. X-RAY MASK PATTERNS

Four patterns of X-ray mask have been investigated. The double right triangles, u-shape triangle, double trapezoids, and u-shape trapezoid as seen respectively in Fig. 1(a) to 1

(d), were used as X-ray absorber patterns for fabrication of PMMA microneedle array.

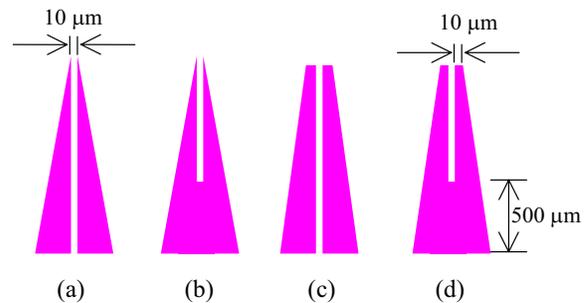


Fig.1 The four shapes of X-ray mask patterns used for X-ray lithography.

Figure 2(a) shows the dimension of a double right triangle pattern. In this figure, 32 patterns of 1500 μm -height with 300 μm -pitch are consisted in a row. The base of each pattern is 100 μm . Figure 2(b) shows the actual X-ray mask which is made by using UV lithography. X-ray absorber has been made of 3.5 μm -thick Au. The membrane is polyimide. Figure 2(c) is the closed up image of the tips of the mask pattern. For the other dimensions being unstated here are similar with the sample pattern.

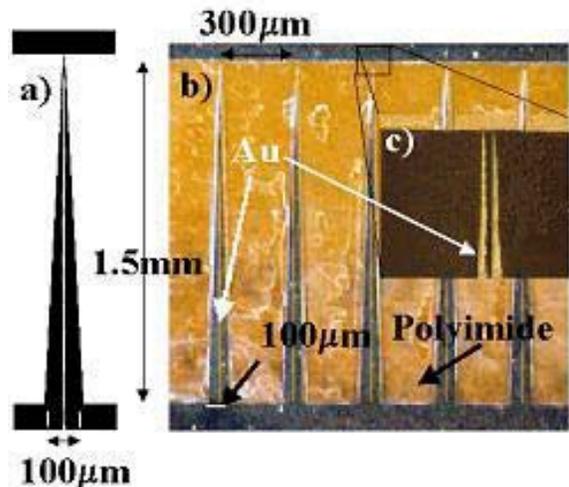


Fig. 2 The dimension of each right triangles pattern(a) the actual X-ray mask (b) and the closed up image of the tips.

3. FABRICATION TECHNIQUE

PCT Technique is a new method for fabricating 3-dimensional structures whose cross-sections are similar to the two-dimensional patterns on X-ray mask. A PMMA substrate is moving repeatedly with the scanning stage while X-ray is exposed through the X-ray mask. Figure 3 shows a simple schematic of PCT steps. The horizontal movement(x-direction) of the work stage forms the three-dimensional structures and gradually enlarges the exposed area of the PMMA. Since the X-ray absorption profiles in the PMMA depend on window spaces of absorber on the X-ray mask, the cross-section patterns in the PMMA forms similar structures to X-ray mask patterns whilst resulted in three-dimension. The exposed depth in the PMMA depends on X-ray dosage and the absorption coefficient of the PMMA mixture. Depth of the pattern after development can be controlled by exposure time and scanning speed. During the fabrication of microneedle, PMMA must be exposed twice by SR light source. The second X-ray exposure is done after PMMA substrate has been rotated 90° from the first exposure position.

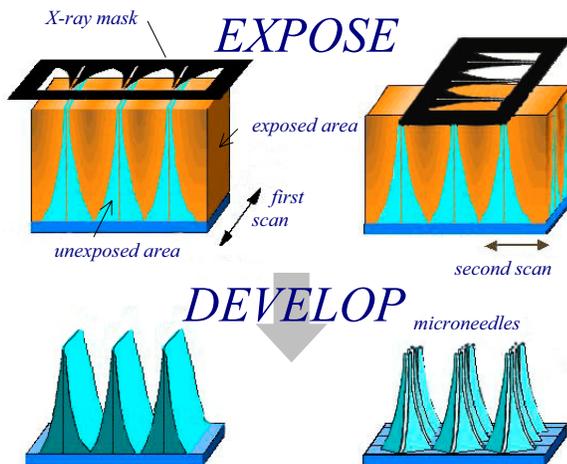


Fig.3 Twice scanning X-ray exposures by moving stage, so called PCT

Using four types of the masks suggested above, the PMMA was exposed through the masks with BL-13 of synchrotron radiation source AURORA at SR center, Ritsumeikan University, Japan. The wavelength of the SR light was between 0.15 to 0.73 nm. The applied electron energy and the maximum storage current of AURORA in the experiment were 575MeV and 300mA respectively. The exposure environment was fixed to Helium gas at 1 atm. The data of deposited doses against the processed depths on the resist collected 6 times in each experiment is shown in Fig. 4. The experiment started from a short exposure time at 60 min. At the lower deposited dosage (below 0.02 A.h.), the processed depth tends to increased uniformly to the dosage. However, at the higher deposited dosage (above 0.02 A.h.), the processed depth starts to be exponentially respecting to the dosage. The selected exposure dosage for one directional scan during the fabricate of micro needle array was about 0.06 A.h. The

exposed PMMA structures appear after developing by GG developer at 37°C for 3.5 hours.

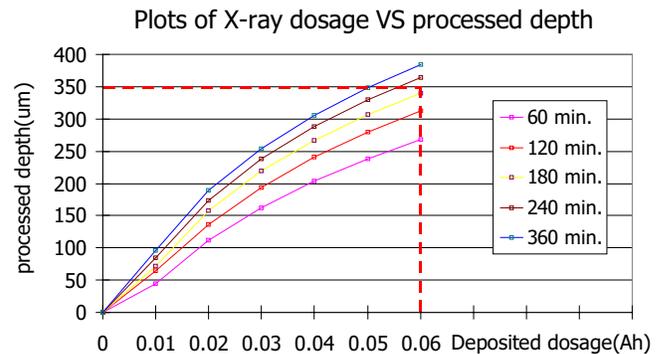


Fig. 4 The deposited dosage data against the processed depths of PMMA resist at the exposure times varied from 60 min. to 360 min.

4. PRINCIPLE OF THE MICRONEEDLE

The skin was flaring while piercing the microneedle. By the capillary force, blood can be extracted and kept after flowing to the grooves. Figure 5 shows the schematic diagram of blood extraction process. The quadruped grooves enhance the area of storing blood after penetrating the microneedle to skin.

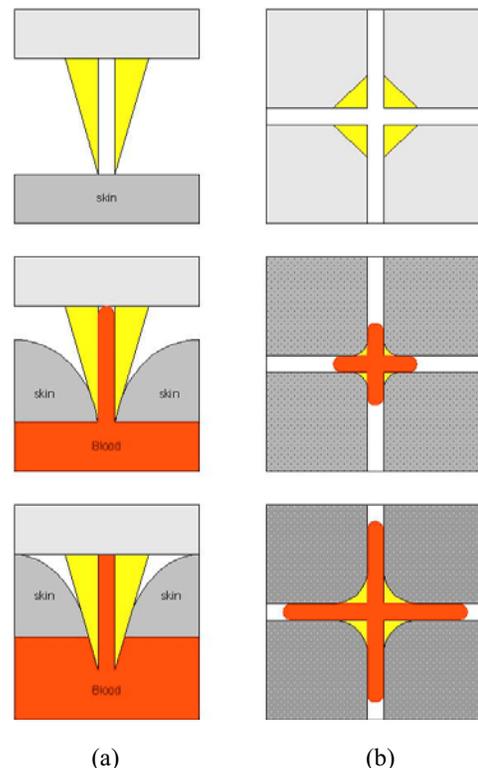


Fig.5. Schematic of blood extraction process. The cross section(a) and top view (b) of microneedle during the penetration

In order to consider the length dependent on the groove size the capillary equation is shown in equation (1).

$$\text{Capillary effect} \quad r = 2\gamma\cos\theta / \rho gh \quad (1)$$

r is the gap between parallel grooves, h is the capillary height, θ is the angle of edge of blood surface against a groove wall and γ is the surface tension. Value of r must be as small as possible yet the volume of blood contained in the needle grooves is enough for a medical test.

5. EXPERIMENTAL RESULTS

The experiment has been done firstly with both trapezoid patterns. The results are shown in Fig. 6. The microneedles exposed from double trapezoids pattern(Fig. 6(a)) are more useful than one exposed from u-shaped trapezoid pattern (Fig. 6(b)) since flow channel in the grooves is connected to the middle of the quadruplets. The blood can be extracted and kept inside the groove. However, the structures were found that each spike was slim and weak.

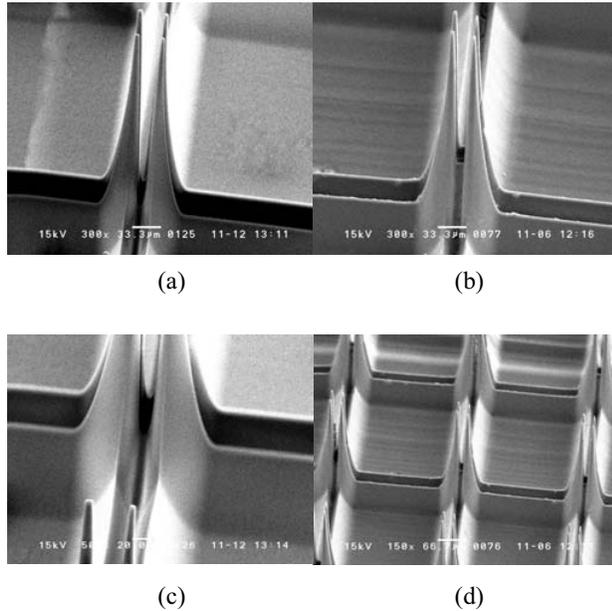


Fig. 6 SEM photographs of fabricated microneedles. The pattern used were, double right triangles(a) and u-shape triangle(b). The close up image of double right triangles(c) and array of u-shape triangle(d).

In order to be applicable for a safe use, the mask patterns, therefore, have been changed to be the triangle pattern. Using both double right triangles and u-shape triangle gave very sharp tips in nanoscale. Figure 7(a) is SEM photographs of microneedle array fabricated by triangle patterns and Fig. 7(c) shows the tip-size is about 300 nm. Thus, the best X-ray mask pattern for fabricating quadruplets microneedle array for safe use has been selected to be the double right triangle.

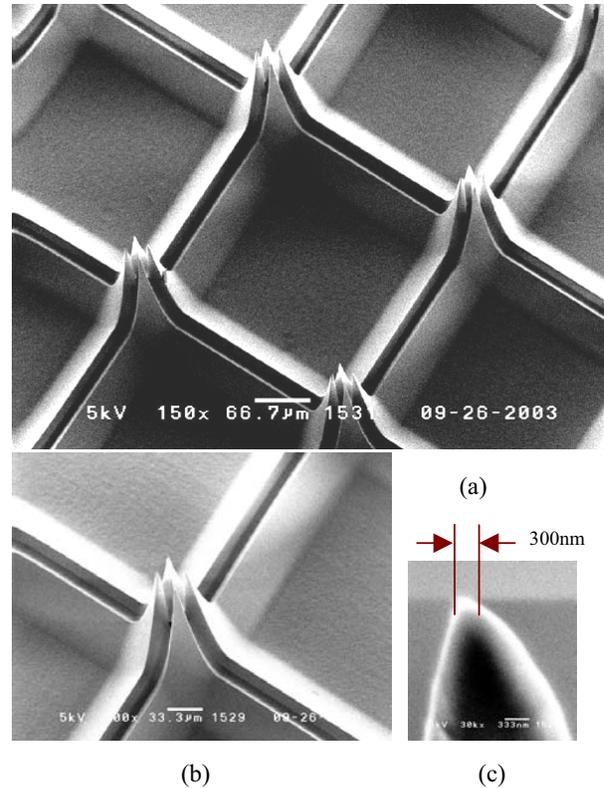


Fig. 7. SEM photographs of fabricated microneedles by . The triangle patterns. The array of microneedle(a), close-up image of a microneedle(b) and close-up image of the needle tip

6. DISCUSSION

A test of the microneedle array has been done with a thin piece of chicken meat. Aniline blue solution(Wako chemicals, Japan) was used as the test-liquid since it has the similar viscosity as blood and the blue color can be simply observed. The test was done by dripping several drops of Aniline to a container and put the piece of thin chicken meat(slices less than 0.3mm.) on the liquid surface. After that, press the microneedle array from the back so that the needles could penetrate the meat. The result of testing is shown in Fig. 8 and Fig. 9. In each microneedle, Aniline was kept in the middle, between each spike. However, liquid still did not flow along the grooves. The cause might be from the pressure of liquid that was free in lateral directions but the interface between the chicken meat and the container. After pressing the array, liquid was spread out of the testing area to the rest of the container. This problem may be solved by using a thin tube with applied pressure to the liquid flowing inside the tube or test with an alive animal by an assist of medical doctor or licensed person. Figure 9 shows the chicken meat after flared by microneedles. It could be seen that all the needles have been pierced through the meat without any part broken. The holes left on the meat were found to be as big as the microneedle base(100µm).

Liquid is kept between each spike

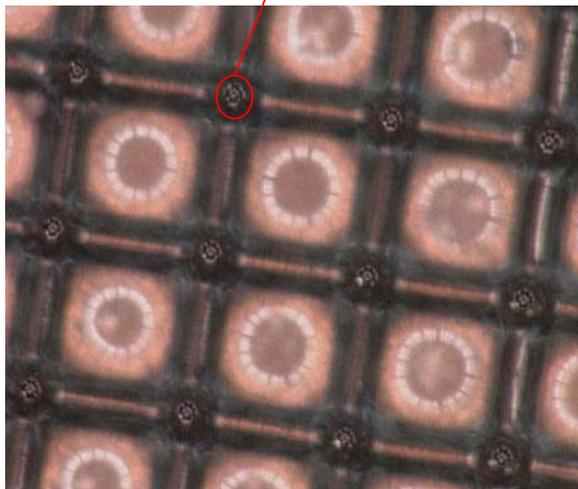


Fig 8. The array of microneedle after insertion through chicken meat. The liquid was kept between each spike by capillary force.

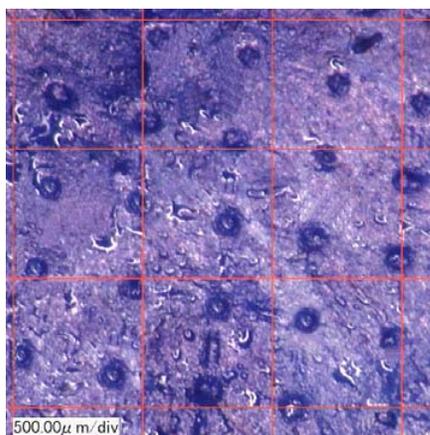


Fig.9. A photograph of chicken meat taken by an optical microscope after flaring by the microneedles.

7. CONCLUSION

The alternative way of using microneedles without holes to get the blood sample has been introduced. The optimum mask pattern was investigated. In this work, the double right triangle is suggested. The tip-size of less than 300nm of the microneedle was achieved. The PMMA microneedle structures can be used as molds for further LIGA process (electroplating and plastic injection) in order to reduce the cost of batch fabrication. Although the process is uncomplicated, the experience for mask design and dosage

control for each experiment is necessary. The dosage chart has to be changed from time to time due to the life cycle of X-ray. Since the fabrication of each array is expensive, the number of sample arrays is limited. Only few tests have been done. Also the Aniline is a poison if the intake quantity is high. However, the test of microneedle on a tube of liquid with applied pressure will be tried in order to prove that quadruplets microneedle can be used in substitution of the microneedle with hole.

8. ACKNOWLEDGEMENT

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