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Fabrication of microneedle array using LIGA and hot embossing process

Sang Jun Moon, Seung S. Lee, H. S. Lee, T. H. Kwon

Abstract We demonstrate a novel fabrication technology of the microneedle array applied to painless drug delivery and minimal invasive blood extraction. The fabrication technology consists of a vertical deep X-ray exposure and a successive inclined deep X-ray exposure with a deep X-ray mask whose pattern has a hollow triangular array. The vertical exposure makes triangular column array with a needle conduit. With the successive inclined exposure, the column array shapes into the microneedle array without deep X-ray mask alignment. Changing the inclined angle and the gap between the mask and PMMA (PolyMethyl-MetaAcrylic) substrate, different types of microneedle array are fabricated in 750–1000 μm shafts length, 15°–20° tapered tips angle, and 190–300 μm bases area. The masks are designed to 400–600 μm triangles length, 70–100 μm conduits diameter, 25–60EA/5 mm^2 arrays density, and various tip shapes such as triangular, rounded, or arrow-like features. In the medical application, the fabricated PMMA microneedle array fulfills the structural requirements such as three-dimensional sharp tapered tip, HAR (High-Aspect-Ratio) shafts, small invasive surface area, and out-of-plane structure. In the skin test, the microneedle array penetrates back of the hand skin with minimum pain and without tip break and blood is drawn after puncturing the skin. Hot embossing process and mold fabrication process are also investigated with silicon and PDMS mold. The processed tetrahedral PMMA structures are fabricated into the microneedle array by the additional deep X-ray exposure. With these processes, the microneedle array can be utilized as the mold base for electroplating process.

Keywords Drug delivery, Blood extraction, Inclined deep X-ray process, Microneedle array, Hot embossing

1 Introduction

In the transdermal drug delivery and blood extraction applications, the conventional steel needle has been widely used at the medical field. The conventional needle causes pain to patients and is hard to be integrated other medical devices at point-of-care-test fields. The microneedle array overcomes these limitations because minimal invasive area causes less pain and the microneedle array can be integrated to other micro-devices. Recently, A lot of researchers have been trying to develop the fabrication methods of microneedle array with the development of MEMS technology (Liwei Lin et al., 1999). The difficult points of microneedle array fabrication are to form acute three-dimensional tip and long length needle with inexpensive production cost.

The design and fabrication of microneedle array is based on an understanding of the skin structure. Human skin is consists of three layers; epidermis, dermis, and hypodermis in Fig. 1a. In epidermis, outermost skin layer, SC (Stratum Corneum), is composed of keratinized dead cell, scales, which contain no nerves and blood vessels. Its thickness varies with body parts, sex, age, or skin condition. The lower parts of epidermis, SS (Stratum Spinosum) and DP (Dermis Papillae), contain living cell (Champin, R.H. et al., 1992). There are two different ways for transdermal drug delivery and blood extraction. In the formal case, drugs are diffused from SC layer to a blood vessel by the microneedle, which does not cause pain because no nerves are in the layer. In the latter case, blood is extracted from the lower part of epidermis by the capillary force through the microneedle conduits. The minimal invasive microneedle reduces nerve contact area and minimizes the pain. For the application, the back of the hands is more appreciate place to apply microneedle array. Considering skin deformation, microneedle length seems to be limited 300–400? for the former and 700–900μm for the latter, respectively in Fig. 1b. Several conditions are required for fabricating the microneedle array like in Fig. 2 such as acute tip angle control, the robust material to penetrate thick epidermis layer without break, depth control to prohibit the penetration into the dermis, small needle surface to minimize nerve contact, longer needle length to apply for the blood extraction application, and arrayed type needle to find blood vessels.

There are different fabrication processes of the microneedle array as follows; surface- and bulk-micromachining (Liwei Lin et al., 1999; J. G. E. Gardeniers et al., 2002), a reactive ion etching microfabrication (Sebastien Henry et al., 1998; Patrick Griss et al., 2002; Achim Trautmann et al., 2003), polysilicon micromolding (Jeffrey D. Zahn et al., 2000), chemical isotropic etching (Boris Stoeber et al., 2000;Mitsuhiro Shikida et al., 2003), injec-

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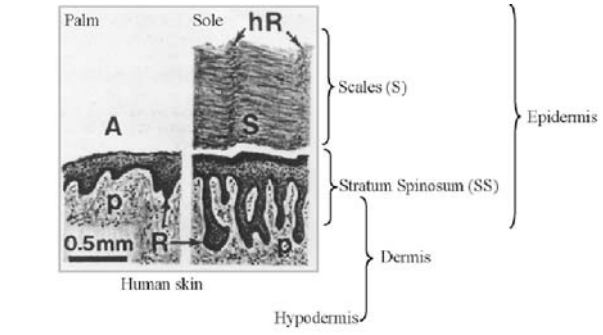
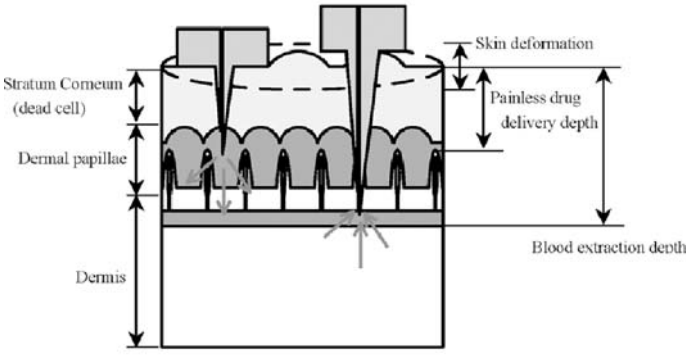


(a) Schematic of the skin structures



(b) The needle penetration depth according to application.

Fig. 1. Skin structures and transdermal application method using microneedle array. **a** Scales (S) and horn ridge (HR) are consisted of keratinized dead cell and no nerve distribution.Sole skin: 1–1.5 mm Palm skin: 0.5–1 mm Abdominal skin: 100–200 μm- Eyelid: 60 μm-. Dermis papillae (DP) and Stratum Spinosum (SS) contains blood vessels and little nerve (small pain). The depth is 1–2 mm. **b** According to the different depth of the skin nerve distribution, the microneedle length is decided for drug delivery and blood extraction. The microneedle penetrates SC only for painless drug delivery by drug diffusion. But for blood extraction, the microneedle reaches to the blood vessel that laid in the dermal papillae or dermis under SC

tion molding and subsequent laser drilling (Ramachandran Trichur et al., 2002), and other molding techniques (Shankar Chandrasekaran et al., 2003; Jung-Hwan Park et al., 2003). The fabrication processes are hard to achieve some requirements of the microneedle array at once. In this paper, we suggest a novel fabrication process that fulfills the overall requirements of microneedle array.

2
Fabrication concept

The LIGA process using the deep X-ray exposure has been conventionally used for the fabrication of the HAR structure devices. The microneedle structure with inclined wall has not been simply fabricated because LIGA process uses the two dimensional vertical deep X-ray exposure method. We suggest the inclined deep X-ray process for making the tapered wall and long shaft structure of the microneedle. The fabrication process consists of a vertical deep X-ray exposure and a successive inclined deep X-ray exposure with a deep X-ray mask whose pattern has a hollow triangular array. The vertical deep X-ray expose makes triangular column array with a microneedle conduit. Inclined deep X-ray exposure process is done by rotating scanner to the direction of theta in the state of being fixed with the deep X-ray mask and the exposed PMMA substrate. With the successive inclined deep X-ray exposure, the triangular column array shapes into the microneedle array without additional deep X-ray mask alignment as depicted in Fig. 3. Unexposed area, which is blocked by

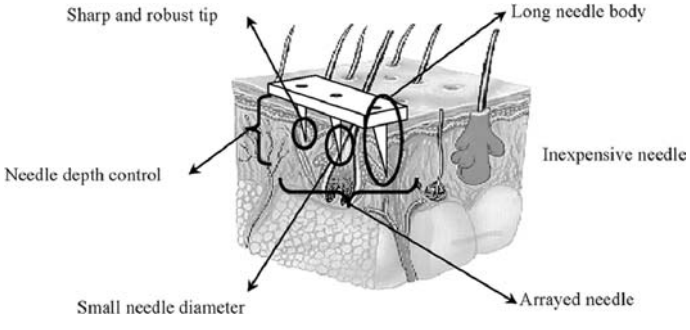


Fig. 2. Schematic view of the microneedle array feature' s requirements for transdermal drug delivery and blood extraction applications. 1. Acute tip angle and robust needle to penetrate thick epidermis without break. 2. Needle depth control to prohibit the penetration into the dermis. 3. Small needle surface to minimize nerve contact. 4. Long needle length enough to contact with blood vessel for the blood extraction. 5. Arrayed feature to find random distributed blood vessel and increase delivery liquid volume. 6. Inexpensive needle fabrication method for one time usage

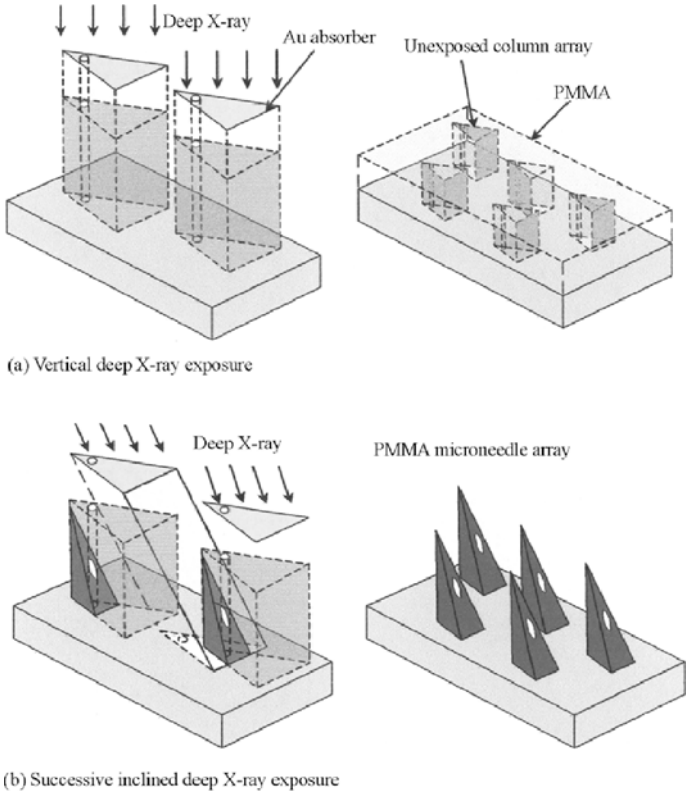


Fig. 3. Conceptual schematic of the microneedle array fabrication using successive inclined deep X-ray exposure process **a** One vertical deep X-ray exposure makes high aspect ratio triangular column array with a microneedle conduit **b** Using successive deep X-ray exposure, the triangular column array shapes into the tetrahedron microneedle array which has sharp point at the a vertex

gold absorber, makes high aspect ratio plane column array which forms needle base shape like hollow triangular column and one side of the sharp tip. With successive second inclined deep X-ray exposure sharp tip and the three-dimensional microneedle structure are made by twice-unexposed area, which is successively shadowed by gold absorber. Therefore, long and sharp tip microneedles are freely constituted by one vertical exposure and one inclined exposure. Changing 2nd X-ray exposure angle, needle tip angle can be controlled to acute or dull shape. Because LIGA process is based on mold fabrication, the fabrication of microneedle array mold is easier and more convenient than other silicon based fabrication. Moreover, good surface roughness can be achieved by high energy X-ray exposure. This is major advantage in LIGA process because this mold base is used for nickel electroplating and successive injection molding process, which requires good surface roughness of the mold insert.

3
Microneedle array design

There are several parameters in microneedle array design; these are deep X-ray exposure angle, deep X-ray absorber thickness, PMMA height, gap between hard X-ray mask and PMMA substrate, microneedle base dimension, needle hole dimension and hard X-ray reflection margin like Fig. 4. Exposure angle and gap

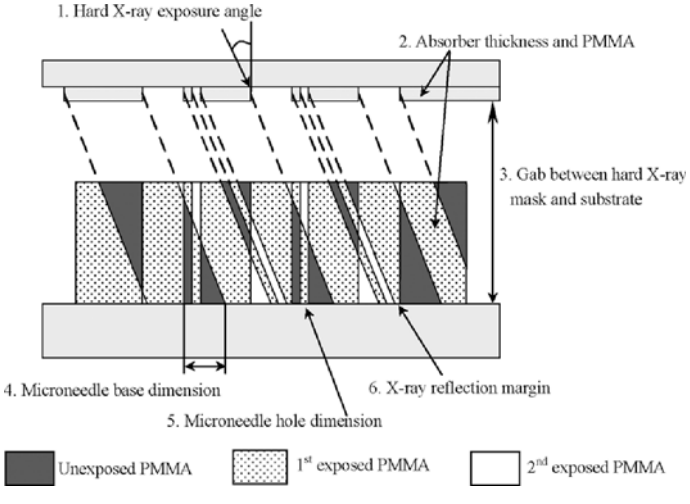


Fig. 4. Design parameters for microneedle array fabrication; 1. Deep X-ray exposure angle determines the needle tip sharpness and base dimension. 2. Gold absorber and PMMA thickness are determined by mask contrast that is the ratio of the dose between top and bottom of the PMMA. 3. Gap between deep X-ray mask and PMMA substrate determines microneedle length and base dimension. 4. Microneedle base dimension is determined by process condition such as PMMA adhesion and aspect ratio. 5. Microneedle hole dimension is suggested by blood cell size and anti-clogging condition. 6. Deep X-ray reflection margin is determined by process condition such as secondary irradiation and successive exposure angle that attacks lower parts of the microneedle array column

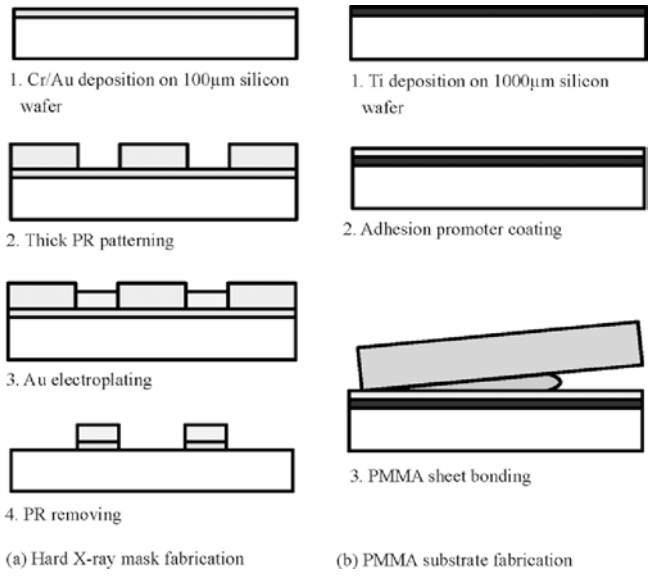


Fig. 5. Deep X-ray mask and PMMA substrate fabrication flowchart

distance between hard X-ray mask and substrate determine needle tip sharpness and length, respectively. Deep X-ray mask absorber thickness is designed by X-ray intensity through the mask membrane and PMMA thickness which determines highest microneedle length. In case of 2 mm thick PMMA and exposure energy over 2.0 GeV, thick gold absorber more than 20 μm are required because of the developing contrast which is dose difference between unexposed upper PMMA surface and exposed bottom PMMA. In general, good surface quality for molding process requires over 100:1 contrast ratio. The gab between hard X-ray mask and PMMA substrate determines the length of microneedle array. The microneedle length is determined by epidermis thickness and flexible skin surface variation, which displacement is about several hundreds of micron ranges. To minimize the pain by sitimulating the nerves, the smaller base dimension less than 200 μm is required but it affects adhesion failure between PMMA and the silicon substrate. Without Fig. 4' s margin requirement, microneedle adhesion is failed by 2nd inclined X-ray exposure during developing because inclined X-ray attacks microneedle base feature under column array. In the suggested design and process, several different needle features can be acquired with the same deep X-ray absorber pattern. This means that microneedle features with different needle efficiencies can be fabricated without deep X-ray mask pattern change. The microneedles, which have different length, sharpness, and shape, are fabricated through the adjustment of the exposure angle and gap distance.

The microneedle array is designed to apply for not only transdermal drug delivery but also blood extraction; Considering with deep X-ray exposure process, developing conditions, and deep X-ray mask design, different types of microneedle array are designed in over 750 μm shafts length, below 20° tapered tips angle, and 300 μm bases area. The masks are designed to 400 μm–600 μm triangles length, 70–100 μm conduits diameter, 25–60EA/5mm^2 arrays density, and various tip shapes such as triangular, rounded, or arrow-like features.

4 Fabrication

Figure 5 describes a deep X-ray mask and PMMA substrate fabrication flowchart, respectively. In the deep X-ray mask fabrication, we use 100 μm thick silicon wafer. Next, chrome and gold is sputtered for electroplating seed layer. Thick Photoresist (AZ9260) is patterned and gold is electroplated over 23 μm thick. In PMMA substrate fabrication, we use 1000 μm thick silicon wafer due to nickel stress during electroplating. Then, adhesion promoter (S1805) and liquid PMMA is coated and cured at 180°C during 1 h. CQ grade PMMA sheet is bonded with MMA solvent.

Fixing with the mask and substrate at a fixure, first vertical deep X-ray exposure is done to 4–5 kJ/cm^3 dose at the bottom of the 1.2 mm thick PMMA. Subsequently, 20° inclined exposure makes the three-dimensional microneedle

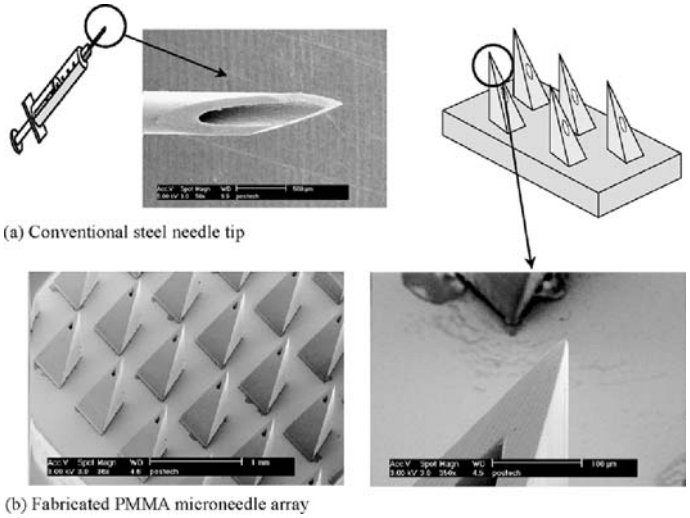


Fig. 6. SEM image of conventional stainless steel needle and fabricated microneedle array

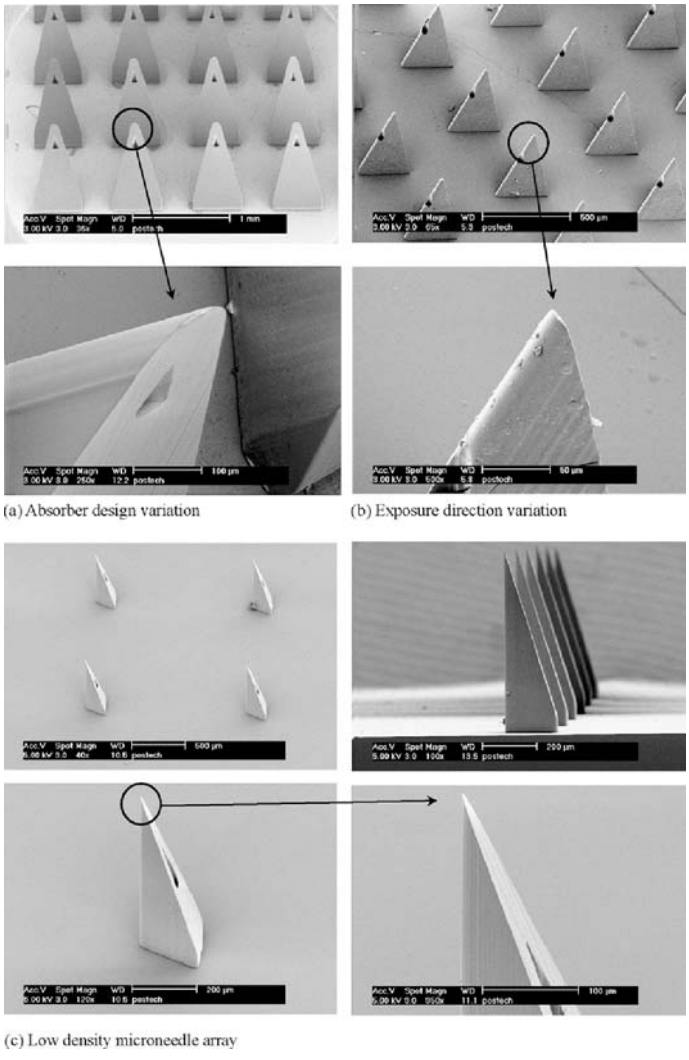


Fig. 7. SEM image of various microneedle array and tip shape: **a** shows the fabricated needle feature by changing the X-ray mask pattern. **b** shows that the needle tip is changed by exposure direction. **c** shows low density microneedle array changed by exposure angle and the X-ray mask pattern

with the same exposure dose. The top dose of the PMMA is about 12–14 kJ/cm^3 after 2nd inclined exposure, because the inclined deep X-ray process uses double exposure process. If top dose is over 15–20 kJ/cm^3, the surface of the top PMMA is boiled to form bubble. Fast developing is needed to prohibit adhesion failure, because of twice exposed area has high dose energy. Exposed PMMA developing takes 3 h in the GG developer with agitation and temperature control (Dong Young Oh et al., 2001).

5
Fabrication results and test

Figure 6a shows the real tip of the steel needle, which made by conventional cutting process. Using inclined deep

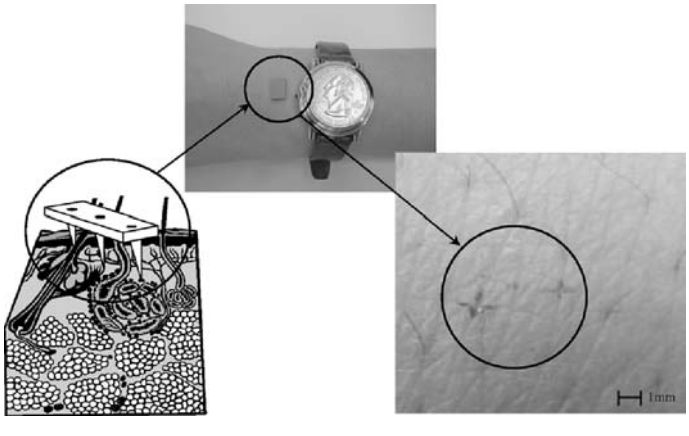


Fig. 8. Skin penetration test using PMMA microneedle array at the hand skin. Three bloodstains show that the fabricated microneedle array penetrates the skin and extracts blood without tip breaks

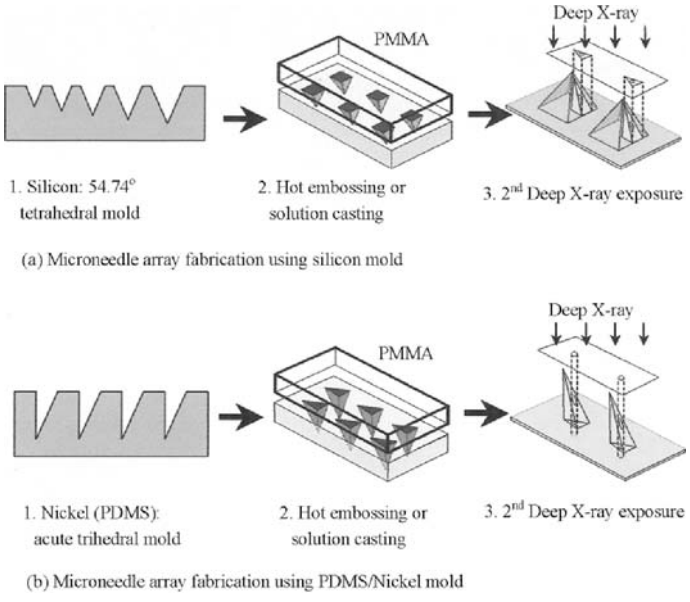


Fig. 9. Schematic of the microneedle array fabrication using hot embossing and successive deep X-ray exposure process

X-ray exposure process, three-dimensional long and sharp tip out-of-plane microneedle array is fabricated. Figure 6b shows SEM image array feature and the close up view of the sloped needle sidewall, which has a pointed edge and a fine wall surface by the process. Furthermore, we fabricate several tip shape and height like Fig. 7. Overall PMMA

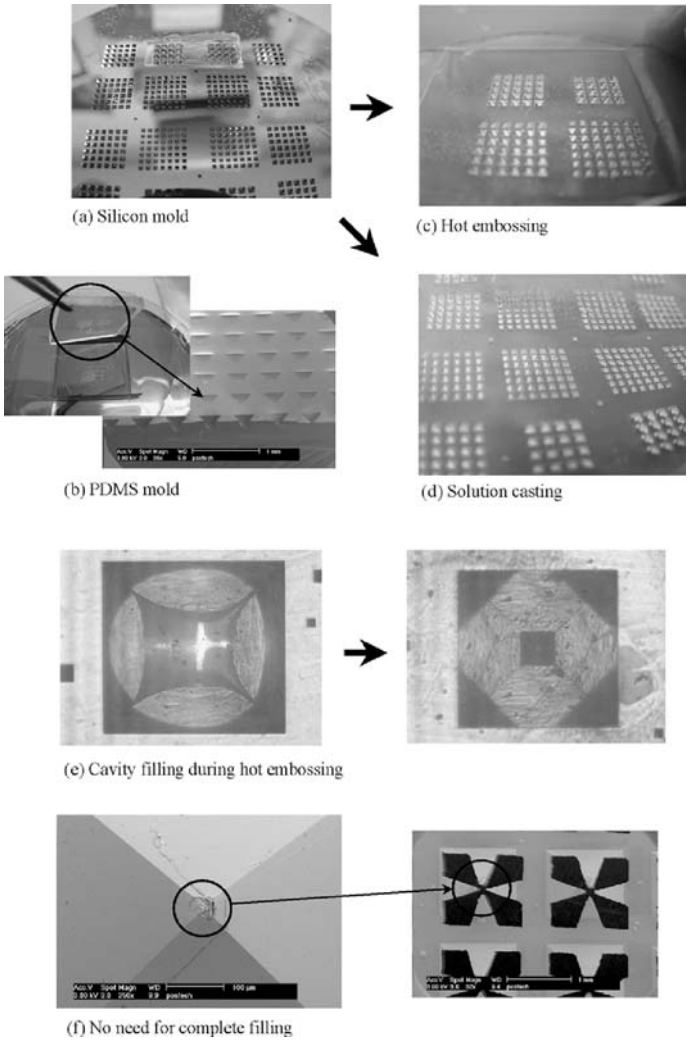


Fig. 10. Fabrication result s of mold processes using hot embossing and solution casting; **c** and **d** show the tetrahedral PMMA structure using hot embossing and solution casting, respectively. **e** show the progress of the PMMA filling during hot embossing. **f** The fabricated microneedle array using the successive deep X-ray exposure does not need to fill the molding cavity because the cavities are removed by successive the deep X-ray exposure

microneedle array density is about 60EA/5mm^2 and 25EA/6mm^2 (Figs. 6b, 7c). We fabricate 4 different types of microneedle tip shape like Fig. 7; base dimension is about 190–400 μm, conduit diameter is about 70–100 μm, tip angle is 15–20°, and microneedle length is over 750–1000 μm. Various tip shapes are fabricated such as triangular, rounded, or arrow-like features. The fabricated microneedle array like Fig. 7b shows less sharp than Fig. 7a. This design is suggested for tip strength and anti-breaking of the tip. SEM image shows that strong tip occupies more base area at the tip edge range, which causes pain. Figure 7c shows low-density type microneedle array for the purpose of reducing penetration force and insertion pain.

The performance of the fabricated microneedle array is tested in order to investigate penetrating capability at the human skin surface like SC. The PMMA microneedle array used in these experiments is 750–900 μm in height, 200–470 μm in base and 750–1500 μm in array space. Two sets of experiment are performed at the two skin spots, which are fingertip and the back of the skin area. The diced microneedle array is inserted into the skin at each place. General skin thickness to the dermis at the hand is about 500–1000 μm. In the first finger tip experiment, the finger skin is so hard and flexible that 750 μm length microneedle is not penetrate dermis layer to extract blood analyte. We think that the skin at the fingertip is more thick and flexible than other skin. Another factor is that surface corrugation prevents blood analyte from extracting during short period by clogging. In case of the upper hand area, microneedle array penetrates skin surface and whole blood analyte is extracted like Fig. 8. Removing of the microneedle array, whole blood analyte is drawn from the back of the skin area to the surface by blood pressure. The puncture of the skin is found to be painless and without any remaining microneedle damage. Figure 8(right) shows three stains of the bloods at the second test spot.

6
Mold fabrication process

We are also investigating mold fabrication proccess in Fig. 9. Fabricated PMMA microneedle array and silicon mold are used for PDMS negative mold or hot embossing mold. Using the mold, PMMA solution casting and hot embossing process are done to make tetrahedral intermediate PMMA structures. Lastly fabricated 3-dimensional PMMA structures are exposed to form needle conduit and outer sharp of the needle body. Fabrication results are in Fig. 10. In case of the hot embossing process, the cavity is not completely filled with PMMA because of atmosphered process condition. Considering fabricated needle structure, it does not problematic because the cavities are removed by successive the deep X-ray exposure.

7
Conclusions

We demonstrate a novel fabrication technology of the microneedle array applied to painless drug delivery and minimal invasive blood extraction. The microneedle base dimension, length, sharpness and position of hole can be defined by the simple mask design, hard X-ray exposure angle, gap between hard X-ray mask and PMMA substrate. Additionally, inclined deep X-ray exposure process does not need alignment with another deep X-ray mask or PMMA substrate to constitute three dimensional needle tip feature.

We fabricate out-of-plane microneedle array with PMMA and investigate the possibility of hot embossing process with successive deep X-ray expoure for the microneedle array fabrication. In the test, the microneedle array penetrates back of the hand skin with minimum pain and without tip break and blood is drawn after puncturing the skin. We will investigate the nickel mold fabrication for mass production of the microneedle array through injection molding and hot embossing process.

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