A NOVEL METHOD OF MICRONEEDLE ARRAY FABRICATION USING INCLINED DEEP X-RAY EXPOSURE

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Abstract. We report a novel fabrication method for the microneedle array with a 3-dimensional feature and its replication method; “Hot-pressing” process with bio-compatible material, PLLA (Poly L-Lactide). Using inclined deep X-ray exposure technique, we fabricate a band type microneedle array with a single body on the same material basement. Since the single body feature does not make adhesion problem with the microneedle shank and basement during peel-off step of a mold, the PMMA (Poly-Methyl-MethAcrylate) microneedle array mold insert can be used for mold process which is used with the soft material mold, PDMS (Poly-Di-Methyl-Siloxane). The side inclined deep X-ray exposure also makes complex 3-dimensional features by the regions which are not exposed during twice successive exposure steps. In addition, the successive exposure does not need an additional mask alignment after the first side exposure. The fabricated band type microneedle array mold inserts are assembled for large area patch type out-of-plane microneedle array. The bio-compatible microneedle array can be fabricated to the laboratory scale mass production by the single body PMMA mold insert and “Hot-pressing” process.

1. Introduction

The several fabrication methods for the microneedle array were introduced at journals and other conferences [1-15]. Generally the microneedle array was fabricated by silicon itself [2, 6, 7, 9, 10, 14, 15], metal or polymer material [1, 3-5, 8, 11-13] for fabricating microneedle array mold insert. The fabrication methods are limited to 2-dimensional features for a needle shank and a tip feature. For extending the mold inserts fabrication process to a mold process for a polymer microneedle array replica, more complex microneedle design is required for the molding and de-molding steps [4, 8, 10-13]. The major issues of the microneedle array fabrication are related with 3-dimensional feature formation for its tip shape, shank design related with strength and replication. As the design freedom of the microneedle geometry increase, the more the strength of the microneedle array during the administration can be robust [5] and the more the application field of microneedle can be extended [12]. With the silicon material at the previous work, the process does not have much freedom for the 3-dimensional shank shape since they generally used reactive ion etching and wet etching which etches the material in the fixed direction [2, 10]. Using photo-resist patterning process [1], the microneedle array can be formed by mask features and characteristics of the UV-light [8, 13]. However, in the process, the microneedle shank features are limited in 2.5-dimention because of one directional
exposure and penetration characteristic of the UV-light. For changing the shank and tip feature which are required for the special application such as biopsy tool [12], the UV-exposure process can not be applied for the special feature of the microneedle shank.

In case of photo-resist such as SU-8 and PMMA which is used for LIGA process, those also need a substrate for photo-resist handling and free standing features at the conventional vertical exposure step. The high aspect ratio microneedle array structure causes the adhesion problem between the silicon substrate and polymer because the structure has small area for the adhesion during developing step. The process also causes the adhesion problem in case the replication mold insert are used for a soft molding process using PDMS. This paper will introduce a simple fabrication method for eliminating the adhesion problem and the shape limitation for its various applications. The replication methods reported here differ from previous works in the specific method of the mold insert fabrication and in the replication process.

2. Batch fabrication of the band type out-of-plane PMMA microneedle array mold insert

2.1. Fabrication concept of a band type out-of-plane microneedle array.

A conceptual schematic view of the inclined side deep X-ray exposure step is shown in figure 1. The deep X-ray light source, PLS (Pohang Light Source, Pohang, Korea; http://pal.postech.ac.kr) have 2.5GeV energy and 150mA beam current. The power can be used for penetration over 10mm thick PMMA by 24hours exposure. For the process efficiency of the exposure and the feature size of gold absorber, a 5mm thick PMMA sheet is used for exposure. It determines the band thickness of the out-of-plan type microneedle array. The deep X-ray mask, gold absorber on the 500µm thick silicon blank is fixed at 50mm×50mm×5mm PMMA sheet with gab formed by a machined steel spacer. After the deep X-ray mask and the PMMA sheet are fixed with designed gab, the successive two side deep X-ray exposures make each side feature of the microneedle shaft by the twice unexposed area. The side deep X-ray exposure method does not limit 3-dimensional features of the microneedle comparing with the previous work. By controlling the exposure angle, PMMA sheet thickness, triangular pattern density and the gab between gold mask, the exposed feature can be changed according to an application requirement.

In addition, the exposure method eliminates the adhesion problem between the exposed microneedle structures and the basement which supports the needle shanks because it makes a...
substrate and a needle features all at once unlike the previous works. Moreover, the basement thickness and needle height can be changed by controlling basement line in the pattern of the deep X-ray mask. Since the PMMA sheet and the deep X-ray mask are fixed during the successive deep X-ray exposure shown in figure 1, the align problem for the each side of the shank features does not occur.

2.2. Fabrication of PMMA microneedle array mold inserts.

For exposure of the 5mm thick PMMA sheet, the gold absorber thickness should over 45µm to increase dose contrast up to 100:1. The dose contrast is defined by the ratio of the top PMMA dose at which the deep X-ray penetrates silicon substrate only and top PMMA dose through the gold absorber. The bottom dose at the PMMA sheet surface in the opposite direction of the exposure side is calculated to 2KJ/cm³ which is generally used for threshold dose for developing PMMA with the GG developer (volume ratio of 60:20:5:15 for di(ethylene glycol)butyl ether : morpholine : ethanolamine : DI). The dose can be reduced compare with general LIGA process which uses over 3KJ/cm³ for PMMA development at the bottom side because of double side development. Since two successive exposures accumulate more doses at the top of the exposure side, the total does should be under 15KJ/cm³. With the poor convection of air cooling system and higher dose than a limit surface dose level, the front surface of the PMMA sheet turn to boil and the exposure process fail. In case of 5mm thick PMMA, the exposure time takes over 12hours for one side of PMMA sheet. After the 1st inclined exposure, the mask and PMMA sheet rotates with respect to scanner’s z-axis by automatic motor control. After the whole exposure steps, the PMMA sheet is released from the mask jig fixture and each strips are developed at the same time. The developing time is less than conventional LIGA processes because each sides of the sheet are develop at once. Since the strips move around by the stirring flow during the development, both sides of the strips are not patterned by the deep X-ray exposures. After rinsing with diluted GG-developer (volume ratio of 80:20 for di(ethylene glycol)butyl ether : DI) and DI water, each strip structures are dry out with N₂. Finally the end sides of the needle strips are cut by dicing saw to assemble each strip.

Figure 2. Fabrication flow chart for laboratory scale mass production of PLLA microneedle array

(a) Assemble PMMA microneedle array band
(b) PDMS negative mold fabrication
(c) Demolding PDMS negative mold
(d) "Hot-press" for PLLA microneedle array

Figure 2. Fabrication flow chart for laboratory scale mass production of PLLA microneedle array
3. Fabrication of the soft mold with PDMS

The fabrication process of the microneedle array replication is schematically shown in figure 2. The exposed PMMA sheet is developed in GG developer during 8 hours at 35°C. After dicing step, each PMMA strips are assemble on a petri-dish with AZ5214 photo-resist. For drying the bonding polymer, the assembly put in a convection oven during 1 hour at 60°C. Using the assembled PMMA microneedle array mold insert, a negative feature mold is made by PDMS. Purring the PDMS mixture (weight ratio of 10:1 for base and curing agent, SYLGARD 184, Dow corning®) to the Petri-dish, the negative mold was formed in the convection oven after 4 hours at 65°C. The hardened PDMS is peeled off by the hand. From the edge of the PDMS, the 5 mm thick mold is peeled off gently. After peeling off the PDMS mold, no breakage of the needle tip end is observed. As the figure 3 setup, “Hot-pressing” process with bio-degradable material PLLA (from HONAM PETROCHEMICAL, Korea; http://www.hpc.co.kr) makes the final microneedle array using the negative PDMS mold. The pressing force is 100 N at temperature 140°C of the heat block as shown in figure 3. Each process variables are measured by LVDT and load-cell. Since the flexible PDMS mold is deformed during “Hot-pressing” process, the small feature size of the needle can be formed without a cavity. However the needle feature did not change after cooling and de-molding because of the shrinkage of the PDMS during cooling process. After cooling process to the ambient temperature, the upper press plate is released. According to the pressure force and gab thickness adjustment with the side Teflon sheet and LVDT, the basement of the microneedle is changed. The PLLA microneedle array with the thin basement sheet is gently peeled off by the hand. Because of the PDMS shrinkage after cooling, the PLLA microneedle array is demolded naturally.

Figure 3. Laboratory scale “Hot-pressing” machine
4. Mold fabrication results with soft material (PDMS)

Figure 4(a) shows a picture of assembled 3D PMMA microneedle array mold insert strips fabricated by the inclined side deep X-ray exposure process. Each strip has different geometry such as needle density, shank height, and tip feature. These strips also have a single body shape which is made by the same material PMMA with microneedle basement and shank as shown in figure 4(a). To control of the microneedle basement height, thin layer of the PDMS is poured and cured. After silanization process on to the surface of the PDMS and PMMA during 3 hours in the vacuum chamber, the negative shape of PDMS mold can be easily released. The SEM image of the released PDMS mold is shown in figure 4(b). The PDMS mold dimension is that the shank length is 223µm and the width is 21µm as shown in figure 4(b). Its shape has the rounded shank toward the tip which helps de-molding process without sticking and tip broken at the PDMS mold.

Figure 5 shows the PLLA microneedle array fabricated by “Hot-pressing” process. Enlarged SEM image of the microneedle shows 40µm width rectangular needle shanks spread with 80µm space density. Because of the mold flexibility, each microneedle was not bent after manual peeling process like shown in figure 5(a). According to the application, the transdermal drug delivery system, the microneedle density can be controlled by the process parameters such as mask, gap and exposure angle. As densify the microneedle array, as increase punctual sites and insertion force during administration. Figure 5(b) shows enlarged figure of the 3-dimensional features at tip point and shank. It shows the tip radius is about 10µm and shank has rounded feature into the basement direction. Since the PLLA microneedle array is dissolved at the body after administration, the array can be used at bio-application field without remaining of debris which is harm to body.

Figure 6 shows the various microneedle array types and its size. Small feature size with respect to the conventional steel needle shown in figure 6(a) reduces pain during the transdermal application. By the combination of the PDMS soft mold and “Hot-pressing” process, taller microneedle array which has high aspect ratio up to 10:1 can be molded than the conventional replication process like figure 6(b). As the side inclined deep X-ray exposure helps the design freedom of the microneedle array shank features, rounded pyramidal feature of the microneedle can be fabricated, which enhances melting polymer filling and de-molding process during “Hot-pressing” process. As shown in figure 6(b), the fabricated PLLA microneedle tip has sufficient sharp tip radii for the transdermal or mezzo-therapy application to puncture epidermis layer without tip breakage.
6. Conclusions
The large area out-of-plane type microneedle array is fabricated using the inclined side deep X-ray exposure, PDMS molding, and “Hot-pressing” process with bio-compatible material (PLLA). The PMMA microneedle array mold insert for soft molding is assembled for large area patch-type microneedle array. Introducing new exposure technique and assemble process for the fabrication of the large area microneedle array, the out-of-plane type microneedle array which have three dimensional features are successfully fabricated. Moreover, the technique can help molding process be easy as increasing the design freedom of the microneedle geometry comparing with the methods of the conventional microneedle fabrication. The “Hot-pressing” process with soft mold (PDMS) is introduced for the laboratory scale mass fabrication of the large area PLLA microneedle array. Using the fabrication method, the mass fabrication of microneedle array can be achieved with easier manner than the conventional silicon process. We are currently applying the fabricated microneedle array in the special application field such as mezzo-therapy tool and patch-type drug delivery system.
Acknowledgments
This research was funded by the Center for Ultramicrochemical Process Systems (CUPS) sponsored by KOSEF. The author also thanks the staff in 9C LIGA beam line, Pohang Light Source (PLS), Korea for their assistance on the fabrication process. Experiments at PLS were supported in part by MOST and POSTECH.

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