Development, Strength and Functional Evaluation of Plastic Microneedle Array Fabricated by Injection Molding

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We hereby fabricated the microneedle arrays whose dimensions of 300 μm in height, 100 and 150 μm in diagonal lengths of bottom surface and with densities of 900 and 4,400 needles / cm^2 by injection molding. The resist patterns were pre-formed by three-dimensional fine manufacturing with movable resist during the exposure in LIGA process. Polylactic acid was used for microneedle arrays in consideration of the prospective medical use in transdermal methods and the like. Our study was to evaluate the material filling of the needle tips and dermal penetrability. The flexibility of the needle tips was also tested by the force added to the tips, and its result was compared with the analysis of flexibility by CAE; computer aided experiment. The resin filling did not reach to the deepest point of the Ni stamper, and the filling remained within the range of 12 to 17 μm in diameter. However, the penetration rate on pig skin with the density of 900 needles / cm^2 resulted in the range of 60 to 80%, and this result represented the satisfactory capability of dermal penetration in spite of the previously described needle tip dimensions of microneedle array. Closely resembling needle flexibility to its analysis proved that CAE analysis on the strength of microstructures was well effective.

Keywords : Microneedle array, Plastic injection molding, Polylactic acid, LIGA process, Plane-pattern to Cross section Transfer, Material filling, CAE analysis

1. Introduction

Microneedle array on which needles of several hundreds μm in height are formed in high density, several hundreds to thousands / cm^2 , are available in transdermal method, a medication method that has been a focus of attention in medicine, and has been recognized as an easier and more effective method than oral medication or injections.

Microneedle arrays for transdermal purposes must be fabricated with harmless materials to human body. Moreover, the material should be decomposed to harmless substances and be dissolved within the body in case of any damages on needles within or under the skin.

One of the materials that meet the requirement is Polylactic acid (hereinafter referred to as PLA), a biodegradable polymer that has been used in medicine.

Plastic molding is an effective in manufacturing technology for mass-production with its cycle time, the time required to produce a product, of few seconds to several tens of seconds, which is remarkably shorter compared with the one in the other manufacturing methods.

As represented by DVD, It is also capable of accurately transferring microstructures as small as the dimensions of sub- μm order.

In $\mu\text{-TAS}$ 2002, several tens of microneedles, made of Cyclic olefin copolymer (COC) and Polymethyl methacrylate (PMMA) with needles of 110 μm in diameter at front ends were reported to have penetrated the parafilm of 200 μm in thickness⁽¹⁾. This study focused on the biological safety and penetrability against skin as well as the effectiveness of medication, and aimed tried to fabricate microneedle arrays, using PLA, with high penetrability and the maximum density of 4,400 needles / cm^2 .

PLA was injected into a mold with Ni stamper mounted on its cavity. The Ni stampers of the microneedle arrays were fabricated in electroforming by transferring the resist patterns formed in Plane-pattern to Cross section Transfer (hereinafter referred to as PCT)⁽²⁾ in LIGA process⁽³⁾. After the confirmation of the sharpest figure at the tip that can be fabricated, the microneedle arrays were tested on their dermal penetrability to evaluate the capability of functions as needles. Furthermore, an accurate estimation of the strength by CAE analysis is crucial in the efficient prototype designing. This study verified by comparing the values of actual test and the estimated values in the analysis to prove a multi-purpose structure-analyzing program is well capable of streamlining the process by accurately estimating the influences on a needle tip by a force provided from above.

2. Figures of Microneedle Arrays

The prototypes of microneedle arrays with three different specifications were designed and fabricated in this study.

The specifications are as shown in Table 1.

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Table 1. Specification of microneedle arrays fabricated

Type	Needle height	Width (bttm.)	Aspect ratio	Figure	Density
1	300μm	200μm	1.5	Pyramid	900/ cm ²
2	300μm	100μm	3	Pyramid	900/ cm ²
3	300μm	100μm	3	Pyramid	4,400/ cm ²

3. Formation of Microstructure on PMMA Resist

As shown in Fig. 1, the resist is set closely under the X-ray mask and is exposed to X-ray as it slides in a reciprocate movement parallel to the mask. This sliding movement and the changes in the range of X-ray exposed through the opening of the mask create time difference in exposure time, consequently distributing X-ray absorbance two-dimensionally on to the resist in the vertical direction.

Fig. 1. The overview of PCT

This distribution of X-ray absorbance enabled to form a latent picture of laid triangular prisms as shown in Fig. 1. Later, in the second exposure, latent picture of pyramids were formed with their peaks pointing above, by sliding the resist perpendicularly to the sliding direction in the first exposure with the mask pattern turned 90 degrees from the initial setting. The X-ray absorbers were fabricated on the membrane made of SiC, etc. First the UV resist was fabricated by UV lithography where no X-ray absorber was required. Second, Au was plated 3.5 μm thick as X-ray absorbers were on the membrane, where no UV resist was formed.

The mask patterns were initially designed with their X-ray absorbers in the shape of isosceles triangles. However, after development in UV lithography, the peaks of the triangles were not successfully etched and they remained round and dull.

This result had lead to the mask pattern of parallelograms. The parallelograms were made by, first, dividing the isosceles triangles at their centerlines, creating pairs of symmetrical triangles. Then these triangles were rejoined with one of the sides reversed upside down to form parallelograms. This mask with the pattern of parallelograms, could maintain the distribution of light exposure to the resist equally to the one with the isosceles triangles, and yet, enabled the formation of sharp angled peaks on the resist⁽⁴⁾.

The needle height, which is largely affected by the exposure amount, was targeted at 300 μm in this study, using 0.96 Ah of light exposure from the light source, Synchrotron radiation, 575 MeV, at Ritsumeikan University, and GG developer for the

development at the temperature of 37 °C for 6hours.

The followings are the SEM photos of PMMA structures, Fig. 2 and 3 for microneedle array type 1, Fig. 4 and 5 for type 2, and Fig. 6 and 7 for type 3.

Fig. 2. PMMA structure of type 1

Fig. 3. Enlarged photo of Fig. 2

Fig. 4. PMMA structure of type 2

Fig. 5. Enlarged photo of Fig. 4

Fig. 6. PMMA structure of type 3

Fig. 7. Enlarged photo of Fig. 6

The stamper was fabricated by electroforming the resist-made microneedle array with nickel after the formation of an electrically conducting layer.

4. Fabrication by Plastic Injection Molding

4.1 PLA(Polylactic Acid) PLA is a biodegradable plastic that is environmentally friendly. It is made of polymerized lactic acid, produced through lactic fermentation of carbohydrate, which is extracted from plants. It is recommended that biodegradable materials should be selected for plastic microneedle arrays, which cannot be reused on hygienic grounds. Furthermore, it is required that the material be decomposed to harmless substances and dissolved within the body. PLA was selected thereby, as a polymer to meet the requirement of biodegradability, in vivo degradability and biocompatibility⁽⁵⁾.

In consideration of the prospective medical use, and requirement of compressive strength, flexural strength as well as the heat resistance for dermal penetration, crystalline PLA in the L-form was selected as L-form is the same form of lactic acid in human body.

4.2 Test To fill the resin in the needle tips, the microneedle arrays were molded using an experimental design (Taguchi method)⁽⁶⁾⁽⁷⁾ to narrow down the optimum molding conditions such as injection speeds, pressures and temperatures⁽⁸⁾, which was to minimize the diameter of the needle tip.

As shown in Fig. 8, in the evaluation of material filling, the diameter of the needle tip was referred to as the distance between breaking point on both sides, where the outlines on both sides of the material separate from the ones of mold cavity.

Before evaluation, the surface was coated with commercially available epoxy resin in liquid form. The epoxy resin was, then, sliced after solidification, and polished prior to the observation under optic microscope. Despite the tapered figure of the needles, which appears to cause no damages on needles as to release them by enabling a smooth mold release, the presence of any damages and deformation was searched under an electronic microscope.

Fig. 8. Diameter of a needle tip

4.3 Evaluation of the Result

(1) Material filling

Fig. 9 to 14 are the SEM photos of molded PLA microneedle arrays type 1 to type 3.

Fig. 9. PLA microneedle array type 1

Fig. 10. Enlarged photo of Fig. 9

Fig. 11. PLA microneedle array type 2

Fig. 12. Enlarged photo of Fig. 11

Fig. 13. PLA microneedle array type 3

Fig. 14. Enlarged photo of Fig. 13

The needle tips of the molded microneedle arrays in Fig. 9 to 14 are dull compare to the ones on resist in Fig. 2 to 7.

The tapered figures of the needles allowed the smooth mold release, and no damages or deformation was observed under electronic microscope.

Table 2 shows the measured tip diameters of needle tips on resist, Ni stamper and needles molded from PLA.

Table 2. Needle tip diameter

	Type 1.	Type 2.	Type 3.
Resist	$\leq 3\mu\text{m}$	$\leq 3\mu\text{m}$	$\leq 1\mu\text{m}$
Ni stamper	—	—	$\leq 1\mu\text{m}$
Molded product (PLA)	15 - 17 μm	15 - 17 μm	12 - 14 μm

To confirm the fact, the Ni stamper was sliced to see its cross sectional figure.

Fig. 15 is the cross sectional photo of needle portion in Ni stamper type 3, matched with the cutout cross sectional picture of the molded microneedles. The dark part shows the hollow portion, and shaded part shows the cross section of molded microneedles.

Fig. 15. Matched cross-section photo of Ni stamper and molded needles of type 3

As shown in Fig. 15, the shape of sub μm needle tip shown in Fig. 7 was successfully transferred to the Ni stamper, maintaining the needle tip figure on resist during electroforming.

During the molding process, mold cavity was depressurized by vacuum pump to effectively ventilate the air within the cavity and the gases produced by molten resin, and the air in the substrate of the needles was released followed by the mold structure design as resin flowing in. However the deepest portions could not be filled up with resin. It could be presumed, then, air in the portions could not be released smoothly because the corn figure holes of the stamper was deep, and their deepest tips were extremely thin. Creating high vacuum within the cavity in order to increase the filling rate of the material would result in longer molding cycle, consequently ruining the effect of depressurization by generation of more gas inside, heat deterioration as well as degradation of resin within the cylinder. Therefore, the resin must be filled with depressurization at the level of which would not affect the cycle time rather than pursuing to achieve high vacuum within the mold cavity.

With this view, the injection pressure was examined. The necessary pressure for the air compression was estimated,

supposing that the air under the atmospheric pressure should have captured and compressed to the volume of the hollow portion within the mold cavity where the material filling would be incomplete due to the disability of ventilation. The volume of a needle on microneedle array type 3 was approximately $338,000 \mu\text{m}^3$, and $8,590 \mu\text{m}^3$ for the incomplete filling portion. The temperature was then estimated by referring to one of the defect causing phenomena in injection molding called “Burning”.

“Burning” is a defect-causing phenomenon in which generated heat through the adiabatic compression of the captured air within the mold cavity burns and carbonizes a portion of the molded product. Since the tip of the molded needles were not burned, the temperature of the compressed air in the hollow portion was estimated to be below 600°C .

Using the formula of Boyle-Charles’s law, the required pressure to compress the air in the needle portion of the cavity at the atmospheric pressure to the volume of the incomplete filling portion, generating the temperature of 600°C , was calculated as follow.

$$\begin{aligned} P_2 &= (P_1 \cdot V_1 \cdot T_2) / (V_2 \cdot T_1) \\ &= (0.101 \cdot 338,000 \cdot (600 + 273)) / (8,590 \cdot (40 + 273)) \\ &= 11.1 \text{ MPa} \end{aligned}$$

As the calculation shows, it only required 11.1 MPa at maximum to compress the air to the volume of the incomplete filling portion. However, the required pressure to fill the cavity was 34.3 MPa, triple of the pressure required to compress the air to the volume.

Upon this result, it was presumed that incomplete material filling in the needle tip portion of the cavity should be attributed to the viscosity of the resin and its flow resistance rather than the remaining air within the cavity.

In general, the viscosity of resin is $10,000 \text{ Pa s}$, 10^7 times higher compared with the water viscosity of 0.001 Pa s . When resin is injected from the center of the flow path, it flows spreading towards the inner wall of the cavity forming skin layer, the outer layer of the resin, which is solidified by touching the wall. This skin layer, functioning as the insulator, maintains the fluidity of the resin within the cavity. Because due to the fact that the molten resin instantly solidifies as it hits the inner wall of the cavity, the material filling in the deepest portion of the circular corn figure, just like a needle which has larger surface area for its volume, was difficult in plastic molding.

However, in the test of penetrability with pigskin, the penetration ratio (penetrated holes / number of needles) of microneedle array type 1 showed the result of over 60 %, and over 70% for type 2. As the results show, these microneedle arrays can function as needles in spite of their current figures.

5. CAE Analysis

5.1 Flexural Test and CAE Analysis It is crucial to accurately estimate the necessary strength of the needles by CAE analysis to efficiently design the prototype. In molding of thin-walled product, the strength is reinforced, if using a material in which the molecule has better orientation as the shear stress, gained during the flowing in the cavity, increases the rate of skin layer with better orientation of molecules.

On the other hand, the strength tends to be weakened if a material, which is high in degree of crystallinity, is used as the short solidification time in molding of thin-walled product inhibits the sufficient crystallization.

In a case of a figure such as the microneedles molded from PLA in this study, a question arose to be answered whether or not the strength of the figure was accurately analyzed and verified in the computer-aided experiment.

CAE analytic values were compared with the test results to evaluate their accuracy, using a structure-analyzing program.

5.2 Methods and Conditions of Flexural Test and Analysis

1) Flexural Test

As shown in Fig. 16, the strength and displacement of the needles were measured by tilting them in the angle of 30° , and by bending them with the contact of rigid plane indenter at constant load-velocity.

The test was conducted on microneedle arrays type 1 and 2. For each type 10 needles were selected randomly.

The test on type 3 was omitted on the grounds that the figure of the needle on the pattern was the same as the one of type 2.

The test conditions are as shown in Table 3.

Fig. 16. Flexural test model

Table 3. Flexural test conditions

Type	No.1	No.2
Load-velocity	10mN/s	3mN/s
Applied force	50mN	30 mN

2) CAE analysis

3-D flexural analysis was conducted, using a structure- analyzing program. The model of needle for analysis was a needle picked up from a microneedle array, sliced in a half at the symmetrical line.

The needle was tilted in the angle of 30° from the horizontal line, and bent by a force from above with rigid plane indenter.

The end surface of the beam was completely fixed as the force was supplied to the tip, fixing the surface of the cross section at the symmetrical line, where the needle was sliced in half, in its perpendicular direction.

The physical values of the PLA used in calculation are shown in Table 4.

Table 4. Physical properties of PLA

	Young's modulus [GPa]	Poisson's ratio
PLA	3.0, 3.3, 3.6	0.33

As stated previously the dimension of needles were thinner than the other products of molding, therefore the analysis was

conducted for three patterns, the modeling needle and two others in their Young's modulus of $\pm 10\%$.

Following the test, two sizes of needles were measured in the CAE analyses.

5.3 Result and Evaluation The graphs in Fig. 17 and 18 show the test results and CAE analytic values by plotting the force provided on to the needle tips and their displacement. The solid line represents the CAE analytic values, and dotted line for the test results.

As the graphs show, the CAE analytic values were well within the range of the fluctuations in test results, thus the close resemblance of CAE analytic value to the test results were confirmed.

Fig. 17. Analytic values and test results of type 1

Fig. 18. Analytic values and test results of type 2

The fluctuations in the test results were attributed to the measuring conditions rather than the fluctuations in the figures of each needle. In a test to detect minimal force in mN order, such as the one in this study, the result was largely affected by physical element such as position, minimal wind, thermal expansion, flexure and frictions.

In addition, the dimension of the needle used in the CAE analysis and the physical values of PLA were those of the models. The analysis excluded all the local radiuses as well. Nevertheless table 5 shows the displacement when 8 mN of force was provided the needle from microneedle array type 1, and 4 mN for type 2. As the table shows, it is considered that the estimated values of CAE analysis did show close resemblance to the test results.

This study only analyzed flexibility of the needle, excluding yield stress and plastic modification. However, Von Mises stress

was detected as the force to yield the subject was supplied, and its analytic values also closely resembled the results in the test.

Table 5. Comparison of analytic values and test results

	Analytic value		Test result	
	Force	Displacement	Force	Displacement
Type 1	8.0mN	6.6 - 8.3 μ m	8.10mN	7.3 - 11.9 μ m
Type 2	4.0mN	8.0 - 10.5 μ m	4.05mN	8.8 - 13.6 μ m

The force supplied in this analysis was in the range of 0 to 20mN. However, the analytic values based upon the forces exceeding these values, over 14mN type 1 and 6mN for type 2, were not significant.

Fig. 19 shows the displacement distribution in microneedle array type 1 with a force of 15 mN, and 5 mN for type 2 in Fig. 20.

Fig. 19. Displacement distribution in type 1

Fig. 20. Displacement distribution in type 2

6. Conclusion

Injection molding using molds, fabricated by Plane-pattern to Cross section Transfer in LIGA process, was conducted to produce microneedle arrays with their dimensions of 300 μ m in height, 100 and 150 μ m in diagonal lengths of bottom surface and with densities of 900 and 4400 needles / cm^2 .

In consideration of prospective medical use, Polylactic-L-acid was selected as the material to meet the requirement of biodegradability, in vivo degradability and biocompatibility.

As for the transferability, the diameters of needle tips in the range of sub μ m to 3 μ m on the resist were accurately transferred on to the Ni stamper, however the needle tip diameters remained within the range of 12 to 17 μ m when molded, due to the difficulty in complete filling of the cavity. It was presumed that the incomplete filling of the resin should be attributed to the flow resistance gained by resin viscosity rather than the remaining air within the cavity. Yet, the microneedle arrays showed over 60 % of penetrability for type 1, and over 70% for type 2 in the test with pigskin. Thus, these microneedle arrays were proven to function as needles des in spite of the current needle tip figure.

The relation between the force and displacement was plotted after the flexural test, and the flexibility estimated by CAE analysis was found to be well within the range of the fluctuation in the test result.

From all these findings from this study stated above, the possibility in practical application of microneedle arrays, fabricated in the plastic-injection molding using Polylactic acid, as well as the effectiveness of CAE analysis in streamlining prototype designing were affirmed.

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