ULTRA-RAPID MICROFABRICATION OF HOLLOW-WELL MICRONEEDLES BY DIFFRACTION ULTRAVIOLET (UV) LITHOGRAPHY

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Abstract— **This paper presents the fabrication of one-of-a-kind hollow-well microneedles using unique diffraction UV lithography. The microneedles incorporated a small pocket (well) at the tip for the drug reservoir, which enables unprecedentedly effective drug delivery than a traditional solid microneedle coated with a drug. The hollow-well microneedles were fabricated via diffraction UV lithography, which resulted in high aspect ratio microstructures. A batch microfabrication of the proposed diffraction lithography was successful by demonstrating over the 50 hollow-well microneedles on the single substrate. A mechanical test was performed on a hollow-well microneedle to determine its viability for skin penetration. The drug delivery of the hollow-well microneedle was investigated using pigskin. When compared to the typical drug-coated solid microneedle, the dispersed blue colored drug markings showed a substantial improvement.**

Keywords—microneedle, diffraction UV lithography, hollow-well, reservoir, dip-coating, photosensitive resin

INTRODUCTION

Microneedle has expanded the practicality of transdermal patches by improving the drug delivery capability through the skin [1]. As a result, microneedle-related research topics have received increasing attention in the past two decades [2], especially in drug delivery system [3]. Coated microneedle, in particular, has shown some unique advantages over other types of microneedles. Unlike solid microneedle, which typically requires a two-step poke and applies process, pre-coated microneedle one-step administration feature maximizes the user compliance and the convenience, especially in the cosmetical application [4]. Biodegradable or dissolvable microneedle has been mainly used in cosmetics and pharmaceutical applications as it carries a relatively larger capacity in compared to coated microneedle, avoids waste of drugs unlike solid microneedle, and omits the need for an external pressure pump to enable drug delivery like hollow microneedle. However, dissolvable microneedle's mechanical properties vary as the capsulated drug type or fraction changes, which limits the availabilities of drugs [4]. Contrary to dissolvable microneedle, coated microneedle's mechanical properties remain unchanged regardless of the coated drug. In contrast to hollow microneedles, which are typically associated with a sophisticated fabrication process and high cost, dissolvable microneedle's relatively simple and straight forward fabrication process has shown greater feasibility for manufacturing over hollow microneedle [5]. In addition, various coating methods has been explored including dip-coating, drop-coating, immersion coating, gas jet drying, spray coating, electrohydrodynamic atomization (EHDA) process, and piezoelectric inkjet printing [4], [5], which enables a broad spectrum of materials and applications. Studies have reported successful delivery using a coated microneedle for gene therapy [6], vaccines [7], chitosan [8], hormones [9], cytokines [10], and insulin [11].

Its minimal invasive and convenient nature has proven to be a good replacement for a conventional hypodermic needle, which has been associated with painful and invasive administration [1]. However, several challenges still persist and prevent the popularization of drug delivery using coated microneedle in clinical practices. Low drug loading capacity, poor control of drug delivery, and low molecular weight drugs have been the major limitations of coated microneedle [12]. Inspired by these challenges, we have developed a novel hollow-well microneedle, which contains an innate well-type reservoir at the needle tip or body for larger drug loading capacity and wider drug availabilities, as shown in Fig. 1. The proposed hollow-well microneedle was fabricated based on the diffraction ultra-violet (UV) lithography process, which is a versatile fabrication method that has been used to fabricate solid and hollow microneedles with various aspects ratios [13]–[15]. Using a ring-shaped micropattern, the back-side UV exposure crosslinks a liquid-state photosensitive resin. The ring-shaped micropattern photomask is defined by translucent outer and opaque inner patterns. The outer shell first defines the overall microneedle shape. The resin residue that remains uncured inside the microneedle's hollow is then cured by second UV exposure from the topside, which forms a small pocket at the tip. The drug reservoir can be located while evading the tip by offsetting the inner pattern. It is also possible to realize multiple wells by increasing the number of inner patterns, which can be utilized for drug delivery with temporal control, a broader selection of drugs, or a higher dose. Due to its simple, rapid, and scalable fabrication capability, a hollow-well microneedle fabrication takes less than 30 min from start to finish. The proposed hollow-well microneedles indeed show the feasibility of improving the performance of coated microneedles due to enhanced drug delivery capability for transdermal application.

FABRICATION PROCESS

Fig. 2 illustrates the fabrication process of hollow-well microneedles, which includes a single resin coating, a partial

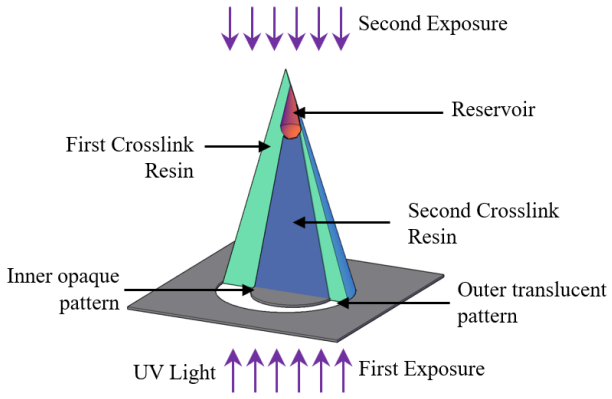

Figure 1. Conceptual drawing of the hollow-well microneedle.

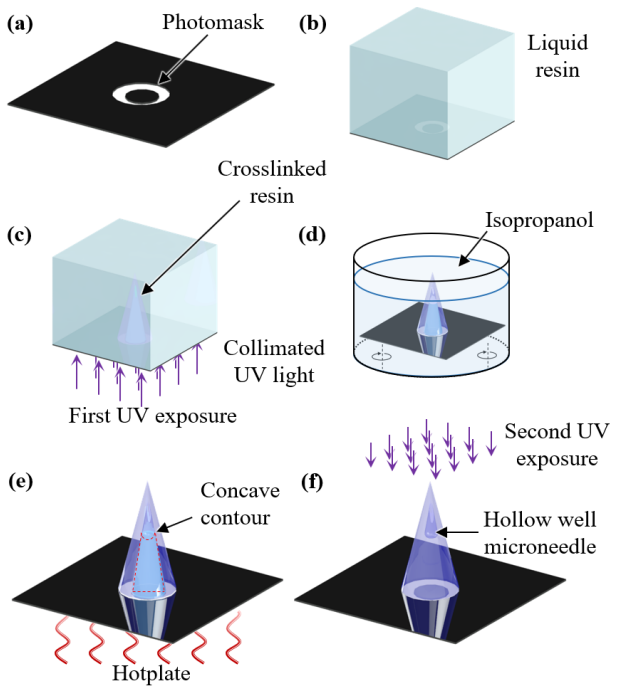

Figure 2. Fabrication process of the hollow-well microneedle. (a) Photomask. (b) Photosensitive resin coating. (c) First UV exposure. (d) Resin development. (e)Thermal treatment to form concave contour. (f) Second UV exposure and complete.

development, and two steps of UV exposure processes. A photomask with a ring-shaped micropattern was prepared using a mask writer (SF-100 XPRESS, Scotech Co., Ltd.) on a chromium coated glass (soda-lime glass, Telic company) through lithography and wet etching processes. The photomask was used as the substrate and coated with photosensitive resin (Surgical guide resin, Formlabs Inc.). The first UV exposure was performed with a bottom-top direction through the micropattern to crosslink the resin and form the outer shell of the hollow-well microneedle while leaving the center uncrosslinked. A narrow band ultraviolet light emitting diode (UV-LED) exposure system [16] was used during the process to produce smooth microneedle surface [17]. The sample was developed in isopropanol for 2 minutes with moderate swirling. The sample was baked for 1 minute at 70°C to create the concave shape due to the capillary effect. Second top-bottom UV exposure was followed to crosslink the uncured resin for the well formation, completing the hollow-well microneedle.

RESULTS

Since the photomask pattern defines the geometry of the microneedle, various varieties of hollow microneedles were fabricated by varying the position and quantity of the interior pattern. Fig. 3 presents the hollow-well microneedle prototype using three different photomask designs, including the center-well microneedle, side-well microneedle, and dual-well microneedle. Fig. 3(a) shows a 700-µm tall and 300-µm wide center-well microneedle that was fabricated using a photomask with a center-aligned ring-shaped pattern as shown in the inset of Fig. 3(a). The micropattern has outer and inner diameters of 300 µm and 180 µm, respectively. As previously stated, the outer pattern dictates the overall shape of the microneedle, whilest the inner pattern specified the opening location

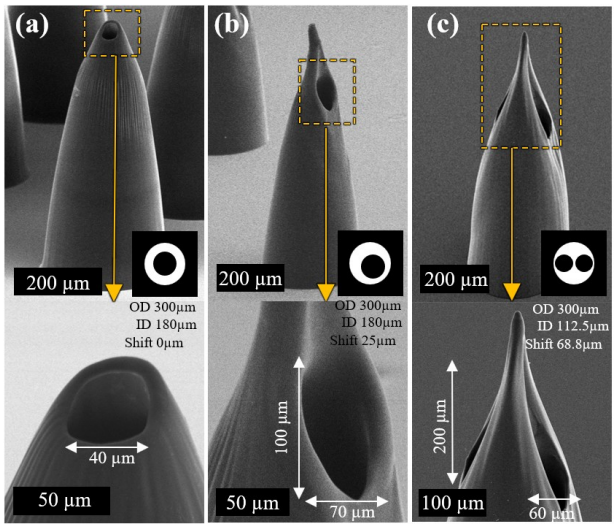

Figure 3. SEM images of the hollow-well microneedles fabricated with three photomask designs. (a) Center-well, (b) side-well, (c) dual-well (upper) and close-up (lower).

and reservoir size. Since the micropattern was designed to be symmetrical around the center of the photomask, the UV exposure remains constant over the translucent region of the micropattern, which allows a uniform growth of the outer shell of the microneedle to form around the center axis with a hollow-well located at the center of the microneedle tip. The diameter of the aperture at the tip of the microneedle, on the other hand, was measured to be 40 µm, which is significantly less than the diameter of the inner pattern. This is due to the outer shell converging effect that was caused by the diffraction of the UV light, which as a result, reduced the size of the opening.

To demonstrate the versatility of the fabrication process, the side-well microneedle was fabricated as shown in Fig. 3(b). By shifting the inner pattern, the position of the reservoir can be relocated to enable the sharp tip. In this scheme, the size of the outer and inner patterns was kept the same as the center-aligned pattern, but the position of the inner pattern was shifted 25 µm from the center. This created an unbalanced UV exposure over the translucent region and uneven growth of the outer shell. The wider region formed the sharp tip due to the converging effect while the narrower region formed the opening of the reservoir, which completed the side-well microneedle with a height of 700 µm and an oval-shaped opening with a long side of 100 µm and a short side of 70 µm. Similarly, a dual-well microneedle was achieved by increasing the number of inner patterns as demonstrated in Fig. 3(c). The size of the inner pattern was reduced to 112.5 µm, and both were shifted 68.8 µm from the center to accommodate an additional inner pattern. This resulted in a slimmer oval-shaped opening with a long side of 200 µm and a short side of 60 µm. The height of the microneedle was 700 µm with a diameter of 300 µm. The dual-well microneedle was developed to improve drug loading capacity or allow two types of drug delivery at the same time. The proposed diffraction lithography technology enables the fabrication of a greater number of wells on the microneedle for the application of various drugs with varying release times. However, because increasing the number of wells in the microneedle may result in mechanical instability, the design and fabrication process should be validated as well.

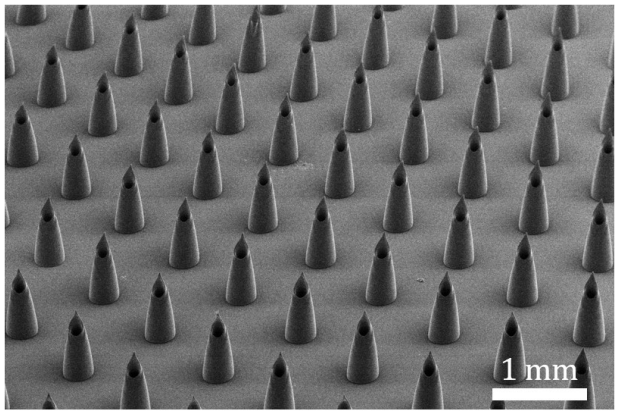

Figure 4. SEM of hollow-well microneedle array.

Fig. 4 shows a scanning electron microscope (SEM) image of a microneedle array with a 300-µm diameter and 700-µm height, indicating high uniformity and reliability of the batch fabrication. 400 hollow-well microneedles were successfully fabricated in this fabrication; however, due to the SEM's screen capture size, over 50 hollow-well microneedles were presented. Up to 3,600 microneedles on a 20×20 mm^2 substrate have been fabricated for higher drug loading capacity using the same fabrication process, without sacrificing the fabrication speed.

To verify the feasibility of the hollow-well microneedle, we conducted a mechanical test on a single hollow-well microneedle using a commercial force gauge (FC200, Torbal Inc.). The microneedle was mounted under the force gauge and the force gauge was programmed to compress the microneedle at a speed of 1.2 mm/min. Fig. 5 shows the mechanical test result of the hollow-well microneedle. Unlike a typical solid microneedle with a tip, which generates a sudden decline of force when the tip breaks [18], the tested microneedle projected a gradual increment of force with a slight change of slope at 2.0 N, indicating the deformation of the

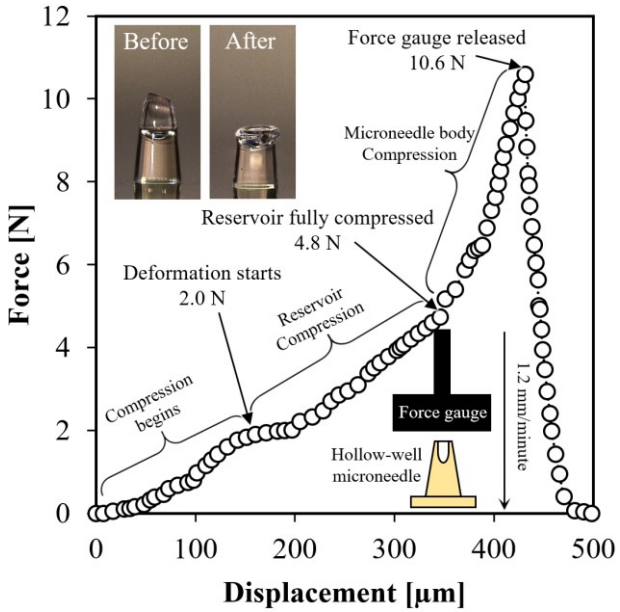

Figure 5. Mechanical test result of the hollow-well microneedle.

reservoir started. After that, the force gauge experienced a linear increment of force until 4.8 N before experiencing another change of slope, this indicates that the reservoir was fully compressed at 4.8 N. The force gauge was allowed to compress the microneedle until it passed the safety limit of the force gauge (10.6 N) and was commanded to release the pressure. The result shows that the hollow-well microneedle was exceptionally sturdy even with an empty reservoir equipped. Note that the presented force-displacement graph shows the tested result of a single microneedle, the tested microneedle remained intact on the substrate after experiencing up to 10.6 N of compression. The result has shown the feasibility and functionality of the hollow-well microneedle for safe transdermal applications.

A drug delivery analysis was conducted to compare the drug delivery efficiency of a conventional transdermal patch, coated microneedle, and hollow-well microneedle. All candidates were pre-coated with blue tissue dye prior to the applications. The candidates were allowed for passive diffusion after being applied onto a common pig cadaver skin, the result is shown in Fig. 6. A conventional transdermal patch was allowed a longer diffusion time of 30 minutes and was measured to have a maximum diffusion depth of 180 µm as shown in Fig. 6(a). The pre-coated microneedle and hollow-well microneedle were characterized to have the same height of 700 µm to eliminate the effect of insertion depth to the area of diffusion. Both microneedles were dip-coated into the tissue dye at the same time and allowed diffusion for 1 minute as shown in Fig. 6(b) and (c). As can be seen in the result, both microneedles were inserted equally deep into the skin at approximately 400 µm, but wider dispersion of dye was observed at the inserted site of the hollow-well microneedle, confirming a larger drug loading dosage for each administration.

CONCLUSIONS

This paper introduces rapid microfabrication of hollow-well needles based on diffraction UV lithography. The proposed microneedle equips a pocket structure (well) at the top of the microneedle that serves as a drug reservoir. The reservoir offers a larger drug loading capacity, which allows a larger volume of drugs

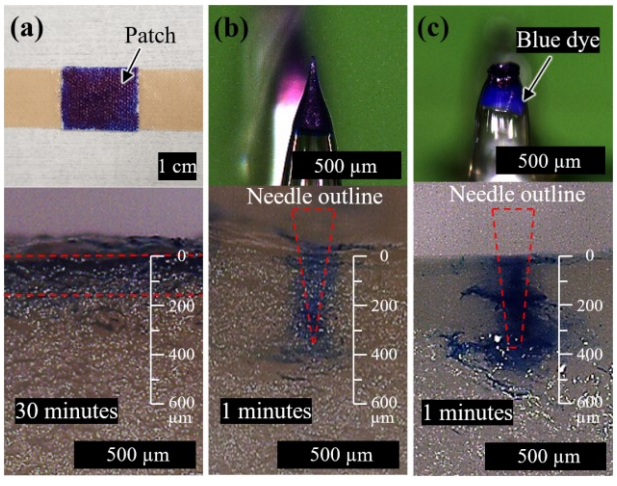

Figure 6. Drug delivery analysis on pig cadaver skin. Blue tissue dye coated (a) patch, (b) solid microneedle, (c) hollow-well microneedle (upper) and drug dispersion result (lower).

to be delivered by each microneedle. The reservoir also enables a broader spectrum of drugs that were not available for the surface coating to be delivered through the transdermal system. We demonstrated the fabrication process of the hollow-well microneedles was achieved through a relatively simple setup and processes including UV lithography and time-controlled development to form the well structure of the microneedle. In addition, various types of hollow-well microneedle can be easily fabricated using the same process with only slight changes on the photomask. Center-well microneedle was presented for maximizing the drug loading capacity, side-well microneedle was introduced to enable a sharp tip for smooth skin insertion, and dual-well microneedle was presented for delivery of two drugs through a single administration. A 20×20 large-scale microneedle array was demonstrated within a single fabrication process, confirming the manufacturing feasibility. To verify the practicality of the hollow-well microneedle, a mechanical test was conducted and showed the microneedle could withstand up to 2.0 N before deformation and remained intact to substrate after 10.6 N of compression, denying the risk of fracturing and buckling during skin insertion. Lastly, a drug delivery analysis was performed to compare the drug delivery efficiency with the conventional transdermal patch, typically coated microneedle and the proposed hollow-well microneedle. The results have shown that hollow-well microneedle released the largest volume of the drug under the same circumstances. Diffraction UV lithography has shown great potential in fabricating various types of the microneedle, including the proposed hollow-well microneedles as well as the previously presented solid and hollow microneedles. Its versatility, reliability, and scalability in fabricating microneedle have shown great advantages over other microneedle fabrication methods. The proposed hollow-well microneedle has demonstrated outstanding performances, which shows great potential in the transdermal application.

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