The application of microneedles fabricated by diffraction ultraviolet (uv) lithography

by

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Abstract

This report summarizes a series of research results based on UV-light microneedles manufacturing technology. The content can be divided into three parts: Discussing the effect of wavelength on UV lithography microneedle fabrication results, a fabrication process of a wound patch that includes an array of light-focusing microneedle and self-actuatable and light-filtering hydrogel, and fabrication of hollow microneedle and hollow-well microneedle.

UV diffraction lithography has been introduced as a rapid and batch-friendly microneedle fabrication method. The shape and aspect ratio can be defined by masks with variable patterns. The shape of the UV light source is changed through the mask, and different patterns are mapped on the photosensitive material layer so as to make various 3d structures. In this manufacturing process, we found that the wavelength of the light source can affect the experimental results. Therefore, the research began by testing the relationship between wavelength and the shape of microneedles fabricated by UV lithography. After that, I joined the MAP (Microneedle-array patch) project. In this project, all the microneedles we used were fabricated by UV lithography. As mentioned above, the MAP project is trying to develop a wound-healing microneedle array that loads 9 solid microneedles. Solid microneedles are only one type of microneedle. In order to increase the functionality of the microneedles array, we also Explore the method of fabricating hollow-well microneedles.

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Introduction

Microneedle is a kind of micro structure with wide application prospect. Its hypoallergenic and painless characteristics have attracted attention in medical beauty and epidermal injection. However, microneedles also have some disadvantages, such as high cost and tedious preparation process. Recently diffraction ultraviolet (UV) lithography process was reported to be a rapid, scalable microneedle fabrication process that can achieve moderate height to base aspect ratio (< 3) [1]. The principle of the microneedle forming was extensively discussed in the previous report. In brief, light diffraction occurs when collimated UV light passes through micro patterns; the intensity distribution of the diffracted UV light behaves like a Gaussian distribution. Given that a photosensitive resin was coated in the described scenario, the crosslinked resin would form a microlens shape. The microlens innately converged the following UV light, which ultimately transformed into a microneedle. Previously, the shape of the microneedle was primarily determined by the UV light intensity, exposure time, micro-pattern size, and shape. In this report, we further explore the capability of the diffraction UV lithography process by investigating the effect of UV light wavelength to the shape of the microneedle. We found that the short wavelength such as 375 nm light source resulted a very different shape of the microneedle to the ·long wavelength, such as 425 nm. We investigated the wavelength ranging from 375 nm to 460 nm, measured the light absorbance via various photosensitive resin thicknesses, and correlated to the microneedle shapes. We formulated those parameters to predict the microneedle height. Microneedles with various shapes and heights were fabricated using different wavelengths with a constantly applied intensity, including a conical shape, a bell-tip on top of the conical shape, and a second harmonic structure on top of the conical shape in the height range of 450 micron to 2 millimeters. The above research results have also been applied in the MAP project. Phototherapy, such as low-level laser (or light) therapy and photodynamic therapy has been commonly used for wound treatment [2]. However, the human skin naturally acts as a barrier to the electromagnetic wave, which highly attenuates the intensity of the ultraviolet (UV) light that reaches to the desired site. Long-term and large area of UV exposure are typically not recommended as it could cause permanent damage to the DNA of the host cells [3]. The MAP project proposes a wound patch that incorporates an array of light focusing microneedles with self-actuatable and light filtering hydrogels inside a transdermal patch as the overall housing as shown in Figure 1. To preserve the light intensity, the microneedles array was

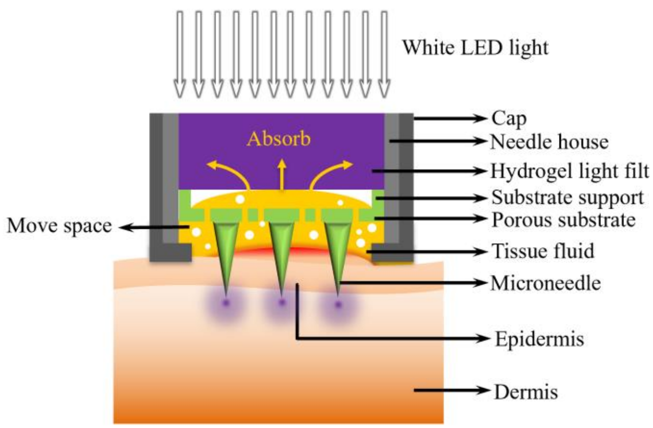

Figure 1: Drawing of wound patch on skin.

fabricated via a diffraction UV lithography method, which was reported to be capable of forming translucent microneedles using 3D printing resin [4]. The microneedles were formed on top of a microporous substrate to allow unobstructed flow through the substrate. On the other hand, the hydrogel contributes to the actuation and light-filtering functions of the system. The microneedles used in the MAP project are solid microneedles. The following research objective is to develop more microneedle types. Thus, we can adjust the product function in the future.

This report will mainly focus on the process of developing hollow-well microneedles, the fabrication of hollow microneedles will be discussed too. The hollow-well microneedle is a solid microneedle incorporated with a pocket structure at the tip for drug reserve. Compared with ordinary coated solid microneedles, this reservoir structure can significantly increase the drug dose a single microneedle can deliver [5]. Storing drugs in the reservoir, rather than coat on the surface of the microneedles, could also help alleviate the problem of high drug loss in existing coated microneedles. Due to its simple, fast, and scalable manufacturing capabilities, the hollow well microneedles can be manufactured in less than 30 minutes from start to finish. The proposed hollow well microneedles demonstrate the feasibility of improving the performance of coated microneedles by enhancing transdermal drug delivery.

Fabrication and Result

Study of Wavelength Variation for UV Diffraction Lithography

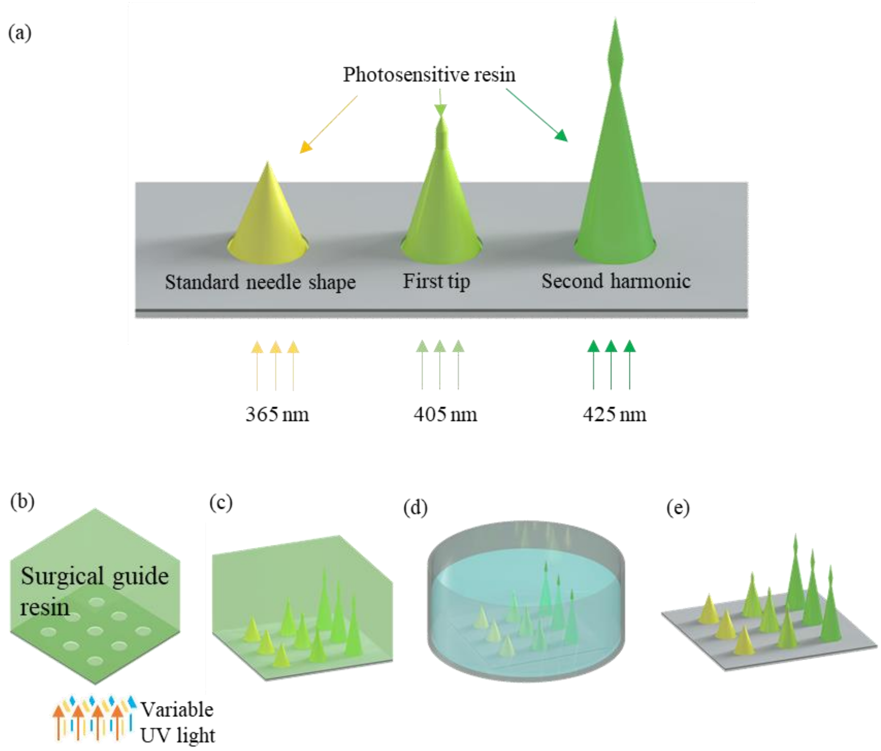

Figure 2. The conception figure and fabrication process. (a) The conception of microneedle. (b) exposure UV light on the sample from bottom. (c) Different wavelength will result variable height. (d) Develop in isopropanol. (e) The result of fabrication

As showing in figure 2(b) to figure 2(e), to test that the wavelength of UV light can influence the aspect ratio, fabrication of multiple wavelength microneedle is necessary. A photomask with 3x3 circle photopatterns was designed. A certain amount of surgical guide resin was dispensed on the photomask. A wavelength adjustable UV light source was set under the photomask directly. Variable wavelength UV light will be used to exposure the set. When the UV light cross though the photo pattern, the unique diffraction behavior will form microneedles. When the beam cross the resin, the center of the beam becomes the most intense region. This will cause result that the central resin will be crosslinked faster. A structure similar to a lens will be formed. When a light beam passes through a convex lens, it is refracted twice on the edges of the lens and concentrates on a point on the central. The central intensity will be more robust, and the crosslink speed will be faster. A needle shape can be formed in this light behavior. The shape and heights of microneedles will be different based on the different wavelengths. After our experimental certification, 425nm has been identified as the wavelength that can form the highest needle. Once we finished the exposure, the photomask with microneedle on it will ·be put into isopropanol to wash it. In this step, the liquid state resin will be washed away, and the microneedles will be visible. The different wavelengths were tested to verify the relationship between wavelength and transmission through the photosensitive resin as more transmitted light energy was presumably propagated further, thereby, the taller microneedle. A piece of glass was set under a UV intensity meter directly. An inch of square glass was set on the sliced glass. The space between the intensity meter and the sliced glass is minimal. A UV LED light source is set under the sliced glass. The intensity meter data is recorded when the UV LED turns on. By reading the intensity meter, the transmission of the UV light at various wavelengths through the tested resin is described as shown in Figure 3(a).

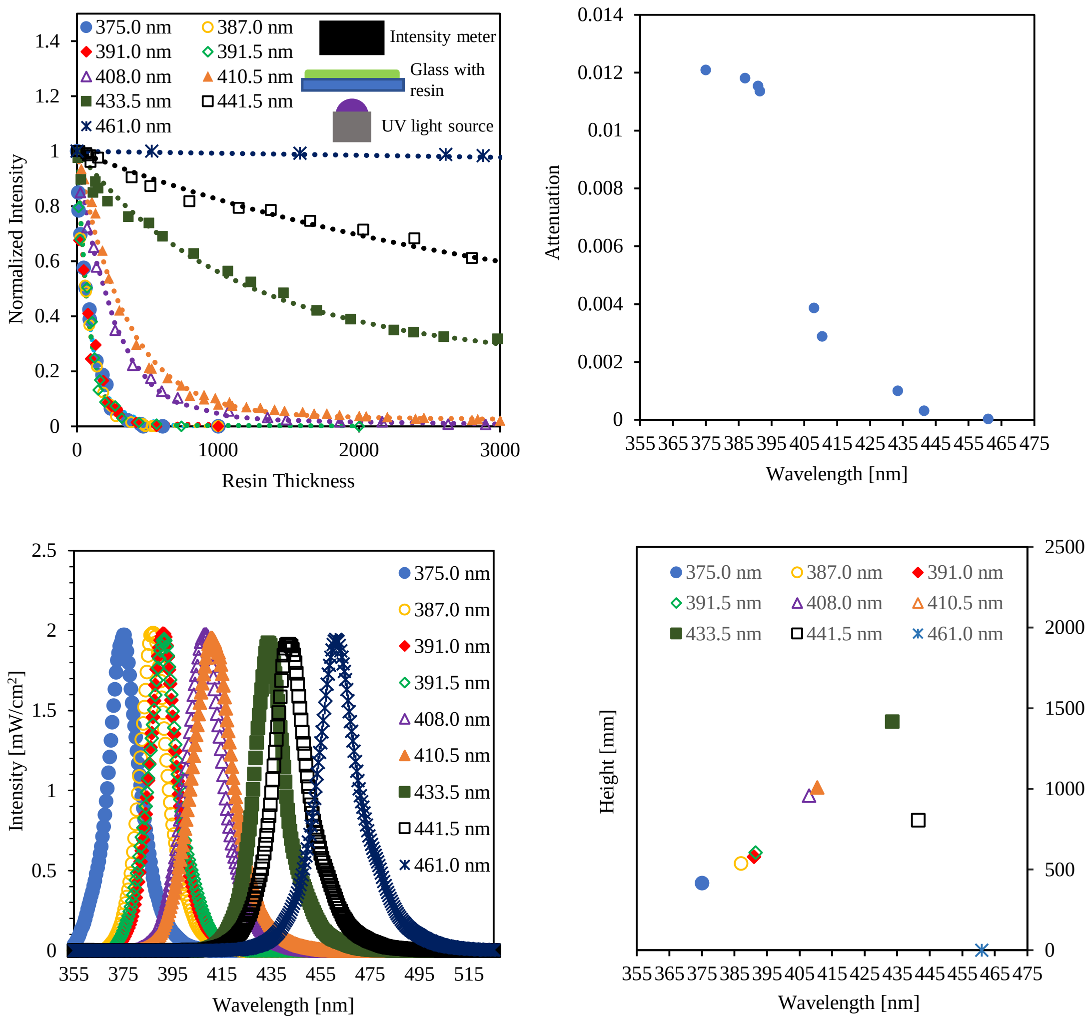

Figure 3. (a) The normalized intensity versus resin thickness. (b) Attenuation factor versus wavelength. (c) The normalized intensity for variable wavelength. (d) Needle height versus wavelength.

The attenuation factors are shown in Figure 3(b). The equation below can present the relationship between wavelength and transmission.

$$T = Y_0 - \frac{V_0}{K}(1 - e^{-K \cdot z})$$

Which T is the transmission ability of this wavelength, Y0 is the normalized initial intensity, V0 is experimentally verified constant to define span of the transmission, K is the attenuation factor of the medium based on wavelength and z is the thickness of the medium.

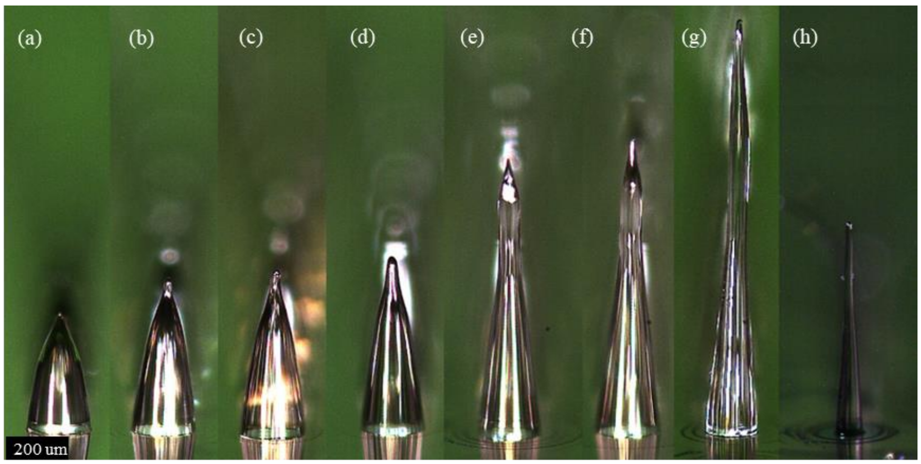

Figure 4. The result of microneedle fabricated under variable wavelength UV light

Figure 4 shows the result of microneedles fabricated under variable wavelengths. The experimental results clearly show that the height of the microneedles formed under the short-wave UV light is lower, and the height of the microneedles is higher and higher with the increase of the wavelength. However, when the wavelength reached 425nm, increasing the wavelength of the light source instead caused the height of the microneedles to decrease. It can be concluded that for surgical guide resin, the highest microneedles can be formed by a light source with a wavelength of around 425nm. At the same time, we also found that compared with the microneedles made under low wave light, the physical rigidity of microneedles made at 425nm and 440nm is weaker, which is easy to break during the mechanical test. In order to confirm the pressure that different shapes of microneedles can withstand, we performed force tests. A single microneedle was tested using a commercial force meter. The microneedle was settled under the force gauge, and the force meter was programmed to compress the microneedle at a 1.2 mm/min speed. The underside diameter of the microneedle is uniformed to 300 microns. Figure 5 shows the force test for microneedles fabricated under three different wavelengths. The results showed that as the shape of the microneedles became elongated, the stability decreased. The best

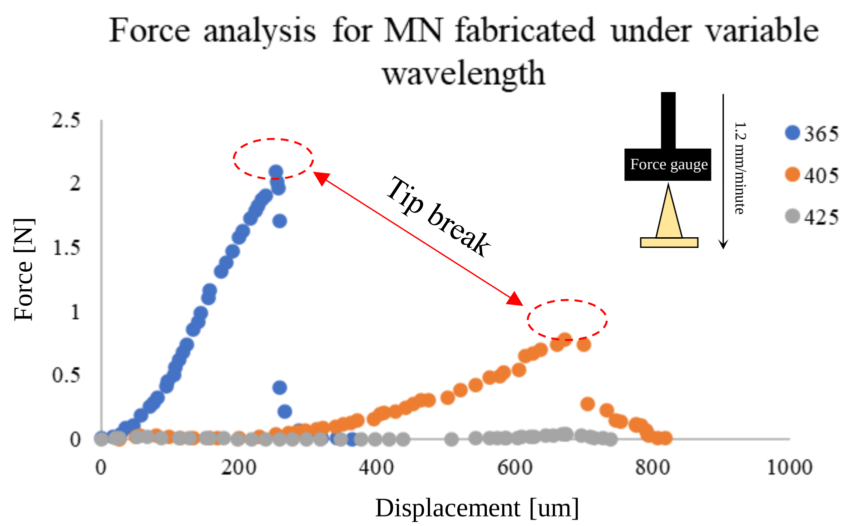

Figure 5. The force analysis for microneedles that are fabricated by different wavelengths

microneedles at 365nm could withstand 2N of force, while those at 425nm could withstand 0.14N. For the high aspect ratio microneedles, we can increase the underside diameter or make a sharper tip to increase the possibility of penetrating the skin's surface.

The MAP projects

The hydrogel was fabricated by mixing 1 part of gelatin powder with 10 parts of deionized (DI) water and two drops of the color dye. The mixture was allowed dry naturally until a 190 µm thin film was obtained. The assembly of the transdermal patch is depicted in Figure 6. Starting from the bottom, a transparent patch was vacuum-molded, and a 3D-printed microneedle house was placed inside the patch. The dyed hydrogels were placed separately inside each house, followed by the microneedles, then firmly enclosed with a 3D-printed cap.

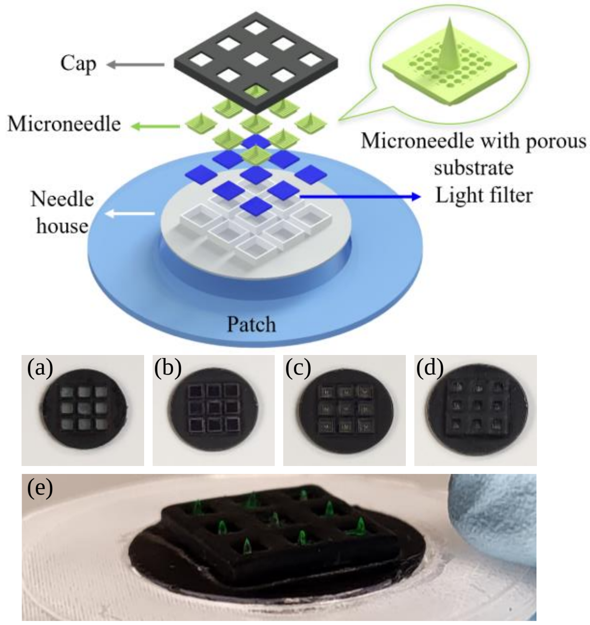

Figure 6: The assembly of wound patch.

Figure 7 shows the actuation of the hydrogel with 10 µL of DI water applied to the microneedle. The displacement increased linearly in the first 200 seconds, then gradually slowed down as the volume of the DI water was reduced due to absorption and evaporation.

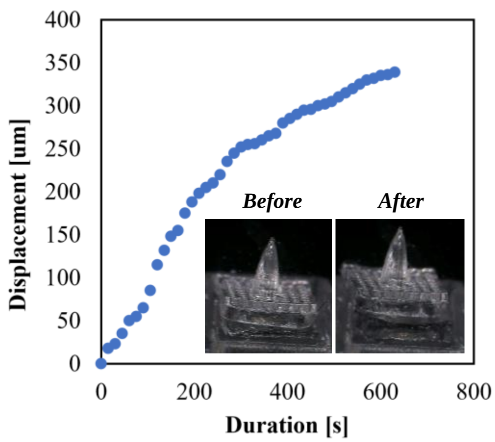

Figure 7: Displacement characteristic of the hydrogel.

The measurement was terminated at 600 seconds with a final displacement of 339 µm. Figure 8 shows a complete force analysis throughout the swelling and shrinking process of the hydrogel.

10 μL of DI water was dropped onto the microneedle, and the microneedle was immediately placed under a force gauge to measure the exerted force.

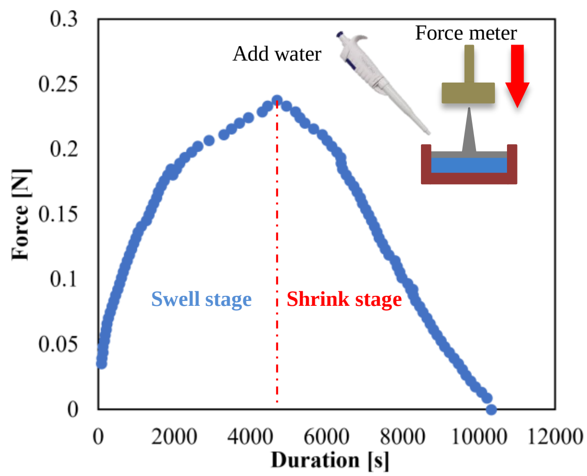

Figure 8: Force analysis of hydrogel swelling and shrinking processes.

The exerted force increased linearly in the first 200 seconds and gradually slowed down, then reached its maximum force of 0.25 N at 4700 seconds. After that, the microneedle slowly released the pressure from the force gauge through evaporation, and a complete release was

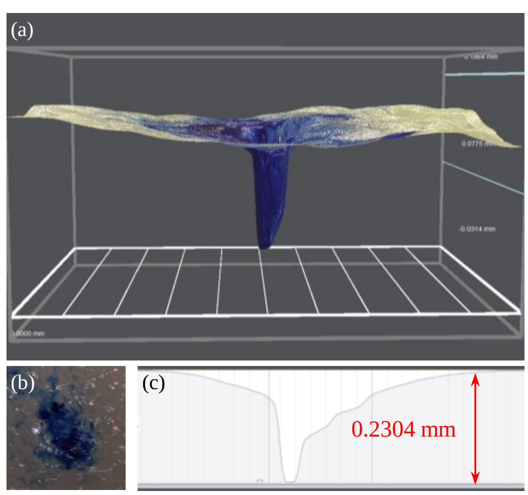

Figure 9: 3D topology of pig skin insertion test result.

observed at 10330 seconds. The microneedle was assessed with an insertion test on a pigskin; the result is shown in Figure 9. The 3D topology of the insertion site was captured using a digital optical microscope. Figure 10 shows the light-filtering function of the hydrogel, suggesting that a certain portion of wavelength can be filtered from the spectrum by using different color dyes to acquire the desired wavelength for phototherapy.

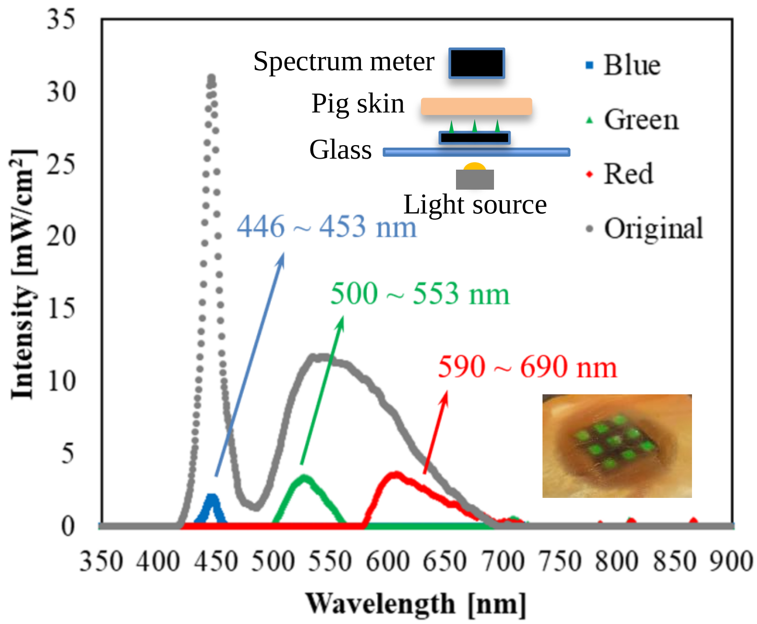

Figure 10: Light filtering result of color dyed hydrogel.

Study of Hollow well microneedle

The image (Fig. 11) shows how hollow-well microneedles are made. The process involves coating a photomask with a special resin and using lithography and wet etching processes to create a ring-shaped pattern on the mask. The coated photomask is then exposed to UV light twice: first from the bottom to the top to form the outer shell of the microneedle, and then from the top to the bottom to create the hollow well inside. A narrow-band ultraviolet light emitting diode (UV-LED) exposure system is used during the process to ensure a smooth surface. The sample is then developed in isopropanol for 2 minutes and baked for 1 minute at 70°C to create the concave shape due to the capillary effect. After the second UV exposure, the

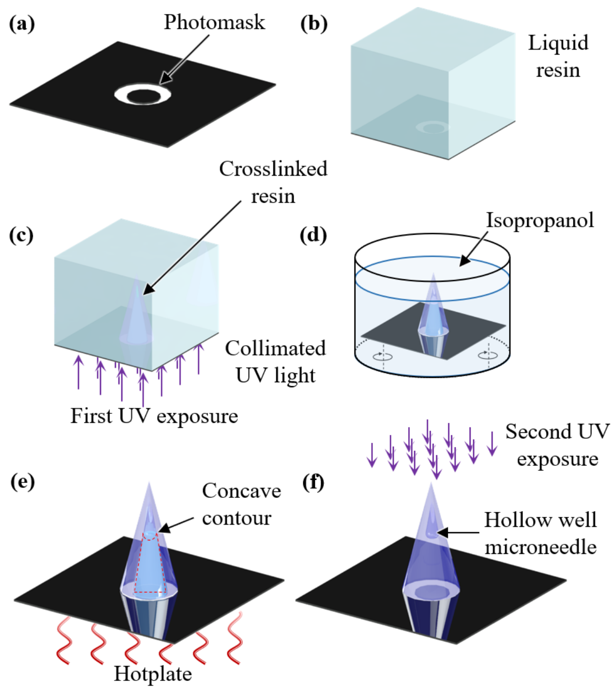

Figure 11. The fabrication process of the hollow-well microneedle. (a) Photomask. (b) Photosensitive resin coating. (c) First UV exposure. (d) Resin development. (e)Thermal treatment to form concave contour. (f) Second UV exposure and complete.

hollow-well microneedle fabrication is complete.

The shape and size of the hollow-well microneedles can be controlled by varying the photomask pattern used during fabrication. Fig. 10 shows three different designs of the microneedles: center-well, side-well, and dual-well microneedles. The center-well microneedle shown in Fig. 10 (a) has a ring-shaped pattern in the center of the photomask, which creates a hollow well at the center of the microneedle tip. The outer diameter of the pattern is 300 µm, while the inner diameter is 180 µm. The UV exposure during fabrication is constant over the translucent region of the pattern, which ensures a uniform growth of the outer shell around the center axis of the microneedle. However, the diameter of the aperture at the tip of the microneedle is smaller than the inner diameter of the pattern due to the converging effect of the

UV light. This effect reduces the size of the opening. The fabrication process used to create microneedles was demonstrated to be versatile by creating a side-well microneedle and a dual-well microneedle. To create the side-well microneedle, the position of the inner pattern was shifted 25 µm from the center, resulting in uneven growth of the outer shell and creating a wider region that formed the sharp tip and a narrower region that formed the opening of the reservoir. The resulting microneedle had a height of 700 µm and an oval-shaped opening with a long side of 100 µm and a short side of 70 µm. The dual-well microneedle was achieved by increasing the number of inner patterns, resulting 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 simultaneously allow two drug delivery types. The proposed technology can enable the fabrication of a greater number of wells on the microneedle to apply various drugs with varying release times. However, increasing the number of wells may result in mechanical instability, so

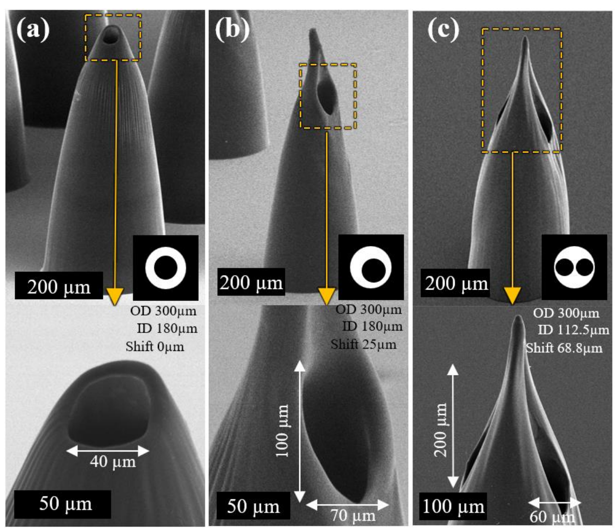

Figure 12. SEM images of the hollow-well microneedles fabricated with three photomask designs. (a) Center-well, (b) side-well, (c) dual-well (upper) and close-up (lower).

the design and fabrication process should be validated carefully.

A drug delivery analysis was conducted to compare the drug delivery efficiency of a conventional transdermal patch, a coated microneedle, and a hollow-well microneedle. The result shown in Figure 12. The candidates were pre-coated with blue tissue dye and applied onto a pig cadaver skin for passive diffusion. The conventional transdermal patch was allowed to diffuse for 30 minutes and had a maximum diffusion depth of 180 μm. The pre-coated microneedle and hollow-well microneedle had the same height of 700 μm and were dip-coated into the tissue dye at the same time. After one minute of diffusion, both microneedles were inserted approximately 400 μm deep into the skin. However, wider dye dispersion was observed at the inserted site of the hollow-well microneedle, indicating a larger drug-loading dosage for each administration.

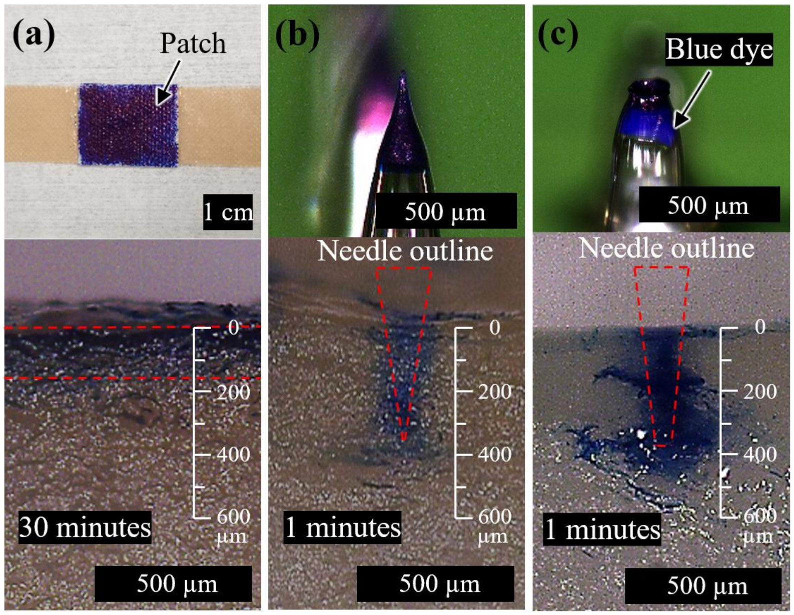

Figure 13. Drug delivery analysis on pig cadaver skin. Blue tissue dye coated (a) patch, (b) solid microneedle, (c) hollow-well microneedle (upper) and drug dispersion result (lower).

Conclusion

This report addresses lithography-based one-step microneedle fabrication, and the influence of different wavelengths light sources on the microneedles aspect ratio is discussed emphatically. Compared to traditional microneedle fabrication, this method can save much time, and do not need expensive equipment or complicated process. Based on the diffraction of light, we use a mask with a circular pattern and a UV light source to make microneedles. Compared with other methods, this method can produce microneedles quickly and in large quantities. To control the height and shape of the microneedle further accurately, we began to study the influence of different wavelengths of UV light on the shape of the microneedle. By setting a control group, higher microneedles could be formed under the same intensity of long-wave UV light. At the same time, we also recorded the penetration ability of resin with different wavelengths between 365nm and 460nm. The calculation formula of the ferment factor is summarized. In the MAP project, we designed the parts and structure of the microneedle patch and studied the most appropriate proportion of hydrogel. The finished product was manufactured, and skin piercing experiments and natural light filtration tests were performed. Proved the feasibility of the project. The proposed microneedles in the hollow well microneedle project have a pocket structure at the top that acts as a drug repository, providing greater drug-loading capacity than traditional microneedles. Mechanical tests show that the microneedle has excellent mechanical strength, which can withstand up to 2.0N force without deformation, and can adhere to the matrix even after 10.6 N compression. The drug administration analysis showed that compared with the traditional transdermal patch and coated microneedles, the hollow hole microneedles had the highest administration efficiency. Diffraction UV lithography shows great potential for the preparation of various types of microneedles, including the proposed hollow microneedles, as well as solid and hollow microneedles. Its versatility, reliability, and scalability make it superior to other microneedle manufacturing methods.

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