# DISSOLVABLE-TIPPED, DRUG-RESERVOIR INTEGRATED MICRONEEDLE ARRAY FOR TRANSDERMAL DRUG DELIVERY

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## ABSTRACT

This paper presents a dissolvable-tipped, drug-reservoir integrated microneedle array for transdermal drug delivery. The hydrogel-based dissolvable tips are formed in a reusable polydimethylsiloxane (PDMS) mold, and then contact-transferred onto a microtube array with drug-surrogate pre-filled reservoirs incorporated into each microneedle. The microtube array is fabricated by a single photolithography process using a gray-tone mask. After insertion into an agarose gel, the water-soluble tips effectively dissolve within a minute to expose each reservoir, and the pre-filled drug-surrogate successfully diffuses. A preliminary tissue penetration test shows mechanical stability of the dissolvable tipped microneedle and feasibility of drug delivery as well as safe prevention of the proposed microneedle from possible reuse.

## INTRODUCTION

Microneedles are attractive tools for transdermal drug-delivery and vaccination due to their potential for simple and rapid administration, reduced pain over intramuscular and hypodermic injections, and efficacious drug and antigen delivery [1, 2]. While many microneedle-based prototypes have demonstrated successful drug delivery as well as the promise of self-administration [1, 3], challenges such as the mass-production of micro-sized features and sharpness, limited drug volume delivery, and controlled, safe, and single-use simple administration remain. In order to address these manufacturing and safety challenges, our microneedle device expands upon previous designs by incorporating high throughput dissolvable-needle micromolding paired with single-stage micro reservoir photo-patterning.

The micro-tube array incorporated in this design can permit relatively large volumes and macromolecular payloads, and the individualized nature of the tube reservoirs allows simultaneous delivery of multiple drugs. The microneedle dissolvable tip geometries are determined by a pre-fabricated mold, which not only reduces manufacturing complexity, but ensures consistent tip sharpness and aspect ratio. The dissolvable needles also confer several administration and safety advantages. Following insertion into the skin, the dissolvable tips are absorbed into surrounding tissue, leaving no sharp or biohazardous waste materials remaining after use. This alleviates device disposal concerns and more importantly prevents reuse [4].

Given the expected handling, storage, and use of this device, the condition of the drug within the device is also a concern. Exposure to warm or humid environments can alter the drug condition, affecting effectiveness or even safety. In addition to dissolving in skin, the water-soluble polymer needle tips act as a quality control measure, as they irreversibly deform or liquefy when exposed to certain environments, making the device unusable. With this multi-purpose design feature, safe and reliable self-administration with minimal or no medical training may be enabled.

Figure 1 depicts the proposed microneedle array, which consists of reservoirs storing a drug, a substrate for mechanical support, and contact-transferred water-soluble polymer tips.

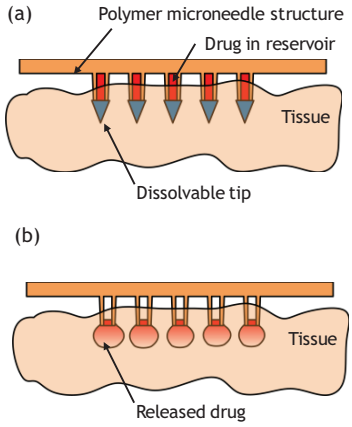


**Figure 1.** (a) Schematics of the microneedle array, consisting of reservoirs storing a drug, a substrate for mechanical support, and dissolvable tips. (b) Illustration of drug release after tips dissolving in a tissue.

In this paper, the proposed microneedle array fabrication process using photolithography and replica molding is outlined. The fabrication process utilizes an SU-8 epoxy for a structural material and water-soluble polymer for dissolvable sharp tips. Delivery of a drug-surrogate from the drug-reservoir in the microneedle to a target is also demonstrated to evaluate the proposed drug delivery mechanism.

## FABRICATION

### Gray-tone Mask Design

To accomplish a single-step photolithography process to define the substrate and reservoir integrated

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microtube array, a gray-tone or variable thickness chromium (Cr) mask [5] was constructed. The gray-tone areas on a mask, depending on Cr thickness, provide a specific transmission of ultra-violet (UV) light compared to near complete transmission through glass or blocked transmission through thick chrome. Regions of negative photoresist exposed to limited UV doses will cross-link from the exposed surface to a diminished depth, allowing control in patterning variable-height structures.

A 50mm×75mm glass substrate with sputterer-deposited stepwise Cr thicknesses is used as a photolithography mask to characterize the gray-tone mask process. A soft-baked 1mm-thick SU-8 on another glass substrate is exposed to UV light through the stepwise gray-tone mask. A total dose of 4200mJ/cm$^2$ is delivered. After post exposure bake (PEB) and development, the thickness of the cross-linked SU-8 epoxy layer is measured with a digital vernier caliper. The translucent Cr layer reduces UV transmission exponentially. The developed SU-8 layer thickness decreases linearly, and can be effectively predicted based on UV exposure dosage.

The transmitted UV light (365nm, I-line) intensity through gray-tone areas and the thickness of an SU-8 2025 epoxy as a function of mask Cr thickness is shown in figure 2. From this result, a 25nm-thick "gray" chromium layer is chosen to define a 400µm-thick SU-8 substrate of the microneedle array.

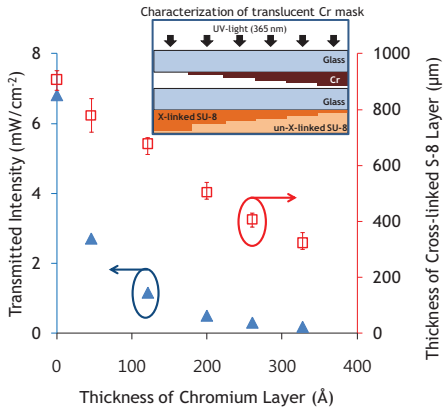


**Figure 2.** Characteristics of a gray-tone mask process. Measured transmitted intensity of UV light through a translucent chromium layer (▲) and thickness of a crosslinked SU-8 layer (□) are plotted using the exposure scheme shown in the inset schematic.

**Fabrication Microtube Array and Dissolvable Tips**

Previously developed process conditions for a high aspect ratio SU-8 structure and a reusable PDMS mold with concave pyramidal trenches are utilized for the drug-reservoir integrated microtubes and the dissolvable tips mold, respectively [6]. Figure 3 shows schematics of fabrication method of microtubes and dissolvable tips. A 1mm-thick SU-8 layer is cast on a 50mm×75mm glass substrate by weight, and then soft-baked on a 95°C hotplate for 24 hours. The SU-8 layer is patterned using the gray-tone mask and an UV exposure dosage of 4000mJ/cm$^2$. The UV light passes through the transparent patterns to the SU-8 layer without reduction to crosslink the microtube walls. The UV light passing through the translucent Cr layer defines the thinner base substrate of the microneedle array, due to the reduction of light intensity in this region. After PEB and development of the SU-8 layer, a three dimensional microneedle structure with a substrate and with drug-reservoirs is achieved. Due to diffraction and refraction of UV light through the Cr mask and the glass substrate, transparent ring patterns produce tapered pillar structures in high aspect ratio SU-8 structures [7]. This tapered shape helps the fabricated microneedle array to be easily aligned with the dissolvable tips in the PDMS molds for contact transfer.

The reusable PDMS mold for the dissolvable microneedle tips is fabricated by an inclined rotational photolithography process [6-8], and is filled with a water-soluble polymer as shown in figure 3(b). After gentle casting of the water-soluble polymer on the PDMS mold, a backside vacuuming technique [6] is used to eliminate trapped air bubbles inside of the PDMS mold. Excessive polymer on the PDMS surface is removed using a PDMS block [9].

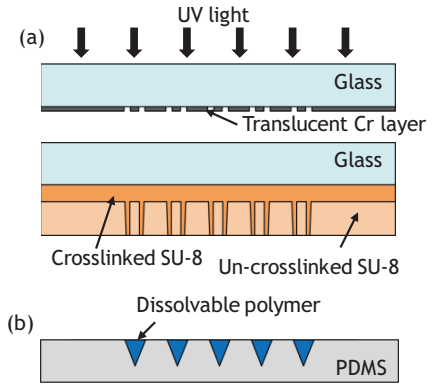


**Figure 3.** (a) Schematic of fabrication process for drug-reservoir integrated microneedles using a gray-tone mask. (b) Schematic of a reusable PDMS mold of trenches for sharp tips, which is filled with a dissolvable polymer.

**Device Assembly**

The microneedles with integrated drug-reservoirs before and after filling a drug-surrogate (FD&C red #40 solution) are shown in Figure 4(a) and 4(b), respectively. The trenches of the PDMS mold are filled with a mixture of polyvinyl alcohol (PVA), polyvinyl-pyrrolidone (PVP), and water with a weight ratio of 3:2:4. The water-soluble tips, which

are dyed with an FD&C blue #1 solution for visibility, are transferred to the microneedles as shown in figure 4(c). The SU-8 pillar structure is aligned and lightly pressed on the PDMS mold before the filled polymer dries. After water content of the polymer mixture is fully evaporated at room temperature for 24 hours, the polymer forms a structural shape of tips, which is transfer-molded from the PDMS mold. Due to slight shrinkage of the dried polymer, the tips on the microneedle structure are easily separated from the PDMS mold.

The total height of a fabricated microneedle including 244μm-high dissolvable tip is approximately 711μm. The bottom width of a pillar is 500μm, and the top width is about 230μm. The width of a pyramidal tip is about 380μm, which is wider than the top width of a pillar. The narrower pillar top fits into the slope of the tip mold, which simplifies alignment, since it acts as a mechanical stopper.

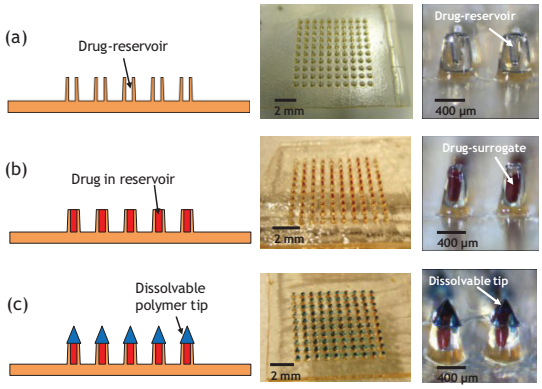


**Figure 4.** The fabricated microneedle array. (a) Before and (b) after filling reservoirs with a drug-surrogate. (c) Blue-dyed dissolvable tips are contact-transferred onto the drug-reservoirs.

## EVALUATION

### Drug-release Demonstration

In order to demonstrate the insertion of the microneedle array and the delivery of a drug-surrogate, an 1.2wt.% agarose gel is prepared. The test demonstrates the successful delivery of a drug-surrogate into the tissue-like agarose gel as shown in figure 5. A block of the agarose gel is placed on the microneedle array and pushed gently until tips are inserted into the gel. The blue-dyed water-soluble tips dissolve within one minute after the insertion, and then the stored red-dyed drug-surrogate diffuses steadily over two hours into the gel as shown in figure 5(b) and 5(c), respectively. After two-hours of dye diffusion, most reservoirs in the microneedle array are empty except for a few with residue at the bottom.

The drug-reservoirs of the developed microneedle array contain the red-dyed drug-surrogate, and release it by diffusion. To understand the diffusion kinetics of this drug delivery system, images of the agarose gel during the diffusion process are obtained through a microscope as a function of time. The area of red-dyed surrogate seen through the agarose gel is calculated using image processing software, and then normalized to the total dyed area of two-hour diffusion as shown in figure 6. The blue color corresponds to dissolution of the water-soluble tips from the initial state. After the tips dissolve, red color starts to appear within one minute, as red-dyed surrogate diffuses steady into the gel. In the first 15 minutes following insertion, the calculated increment ratio of the red-dyed area starts from $1.68\times10^{-4}$ $cm^2/s$, and then reduces to $9.76\times10^{-6}$ $cm^2/s$, as adjacent red spots merge together.

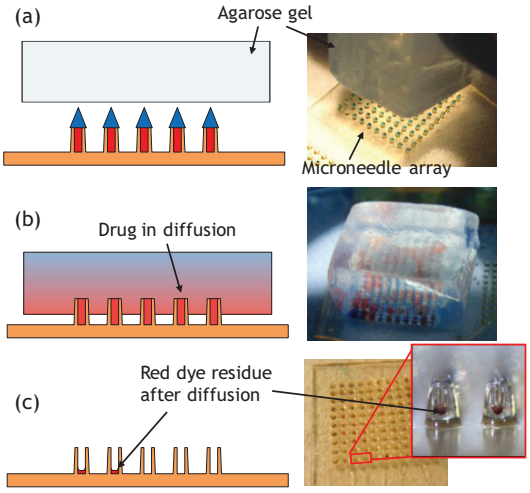


**Figure 5.** (a) A microneedle array to be inserted into agarose gel. (b) The water-soluble tips dissolve after insertion within a minute, and then drug-surrogate stored in reservoirs diffuse into gel. (c) The microneedle array following 2 hours of dye delivery into gel.

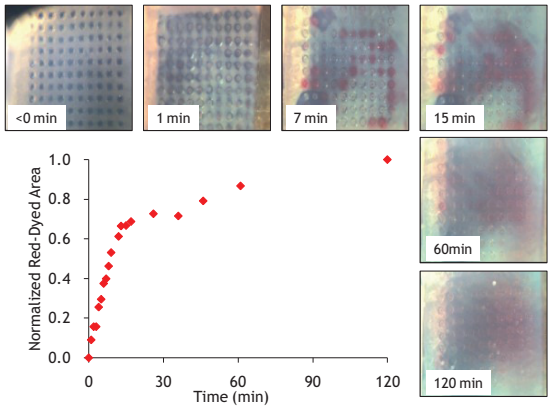


**Figure 6.** Diffusion kinetics of drug release into the agarose gel by the dissolvable-tipped microneedle array using diffusion of red-dyed surrogate.

**Tissue Penetration Test**

A chicken leg is used for a preliminary penetration experiment of the microneedle array. The 10×10 microneedle array, filled with red-dyed drug-surrogate, is manually inserted into the chicken leg muscle, and held for three minutes. After removing the microneedle array from the leg, the image of the administrated site is taken. Holes penetrated by sharp tips on microneedles, and red-dyed spots diffused from drug-reservoirs are shown in figure 7(a). All of the microneedle tips dissolve, but approximately 50% of microneedles produce holes on the fascia which surrounds and protects the muscle, and 35% of microneedles deliver the drug-surrogate successfully into the muscle. This could result from non-uniform pressure to the microneedle substrate when manually pushing the microneedle onto the curved tissue, or reduced delivery time. Another insertion test is performed by using the same used microneedle array without sharp tips. Although pressed marks are shown in figure 7(b), the marks disappear after shape recovery by tissue tension. A few points of the muscle are stained with a diffused red-dye without penetration. The microneedle is not able to penetrate a tissue after a single use, which prevents possible reuse.

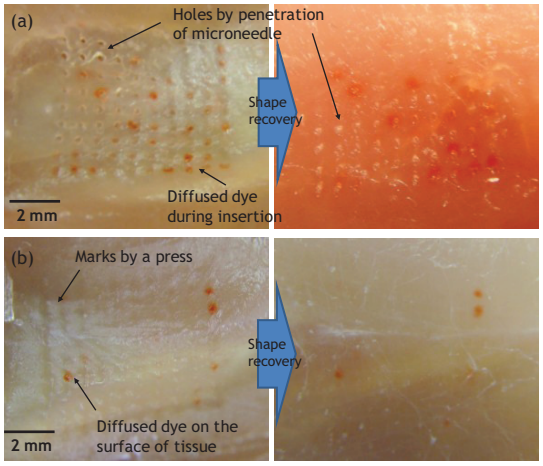


**Figure 7.** Insertion test of developed microneedle array into a chicken leg muscle. (a) Holes caused by penetration of microneedle tips maintain after shape recovery by tissue tension. (b) Insertion test with the used microneedle array. Pressed marks disappear after shape recovery.

## CONCLUSION

The dissolvable-tipped microneedle array, which is composed of a drug-reservoir integrated polymer structure and water-soluble sharp tips, was fabricated, and its use was demonstrated. The substrate and pillars of the microneedle array were defined in a single photolithography process using a gray-tone mask. The dissolvable tips of the mixture of PVA and PVP were successfully molded and contact-transferred to the drug-surrogate filled microtubes. The total height of the fabricated microneedle, including 244μm-high dissolvable tip, was around 711μm. The drug-reservoir integrated microneedle array successfully delivered its contents into both agarose gel and tissue. Prevention of reuse of the microneedle arrays was demonstrated due to the one-use nature of the sharp, dissolving microneedle tips.

## ACKNOWLEDGEMENT

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