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Ciprian Iliescu

Institute of Bioengineering and Nanotechnology, Singapore, ciliescu@ibn.a-star.edu.sg

Bangtao Chen

Institute of Bioengineering and Nanotechnology, Singapore

Jiashen Wei

Institute of Bioengineering and Nanotechnology, Singapore

Zhilian Yue

Institute of Bioengineering and Nanotechnology, Singapore, zyue@uow.edu.au

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Abstract

The paper presented an enhancement solution for transdermal drug delivery using microneedles array with biodegradable tips. The microneedles array was fabricated by using deep reactive ion etching (DRIE) and the biodegradable tips were made to be porous by electrochemical etching process. The porous silicon microneedle tips can greatly enhance the transdermal drug delivery in a minimum invasion, painless, and convenient manner, at the same time; they are breakable and biodegradable. Basically, the main problem of the silicon microneedles consists of broken microneedles tips during the insertion. The solution proposed is to fabricate the microneedle tip from a biodegradable material - porous silicon. The silicon microneedles are fabricated using DRIE notching effect of reflected charges on mask. The process overcomes the difficulty in the undercut control of the tips during the classical isotropic silicon etching process. When the silicon tips were formed, the porous tips were then generated using a classical electrochemical anodization process in MeCN/HF/H₂O solution. The paper presents the experimental results of in vitro release of calcein and BSA with animal skins using a microneedle array with biodegradable tips. Compared to the transdermal drug delivery without any enhancer, the microneedle array had presented significant enhancement of drug release.

Keywords

delivery, insights, drug, microfabrication, transdermal

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TRANSDERMAL DRUG DELIVERY: MICROFABRICATION INSIGHTS

Ciprian Iliescu, Bangtao Chen, Jiashen Wei, Zhilian Yue

Institute of Bioengineering and Nanotechnology 31 Biopolis Way, The Nanos, #04-01, Singapore 138669

E-mail: ciliescu@ibn.a-star.edu.sg

Abstract—The paper presented an enhancement solution for transdermal drug delivery using microneedles array with biodegradable tips. The microneedles array was fabricated by using deep reactive ion etching (DRIE) and the biodegradable tips were made to be porous by electrochemical etching process. The porous silicon microneedle tips can greatly enhance the transdermal drug delivery in a minimum invasion, painless, and convenient manner, at the same time; they are breakable and biodegradable. Basically, the main problem of the silicon microneedles consists of broken microneedles tips during the insertion. The solution proposed is to fabricate the microneedle tip from a biodegradable material – porous silicon. The silicon microneedles are fabricated using DRIE notching effect of reflected charges on mask. The process overcomes the difficulty in the undercut control of the tips during the classical isotropic silicon etching process. When the silicon tips were formed, the porous tips were then generated using a classical electrochemical anodization process in MeCN/HF/H₂O solution. The paper presents the experimental results of *in vitro* release of calcein and BSA with animal skins using a microneedle array with biodegradable tips. Compared to the transdermal drug delivery without any enhancer, the microneedle array had presented significant enhancement of drug release.

Keywords: Microneedles, biodegradable, transdermal delivery.

1. INTRODUCTION

Transdermal delivery is an attractive method to deliver drugs or biological compounds into human body, for its distinct advantage of eliminating pain and inconvenient intravenous injections. However, the efficiency of transdermal delivery is greatly limited by the poor permeability of the hard layer of skin at the stratum corneum (SC) which is the outmost layer of skin that forms the primary transport barrier [1]. The rate of transdermal drug diffusion also depends in part on the size and hydrophilicity of the drug molecules, which usually takes a long time, up to hours or days, and it may not be convenient or practical for clinical application. Due to this fact, only small doses (<10 mg/day) of lipophilic and low-molecular weight drugs (< 500 Da) can be successfully delivered via transdermal method [2]. A number of methods have been developed in order to improve drug

transport across the skin, methods that include mechanical [3] or chemical enhancers [4], iontophoresis [5], electroporation [6] and sonophoresis [7].

The solid microneedle array, first reported by Henry et al in [8], was used as a mechanical enhancer to improve the drug penetration through the skin. In this technique, micro-sized needles protrude through the primary biological barrier of TDD, the stratum corneum, yet without affecting the dermis layer that contains nerves and blood vessels, thus avoiding pain and bleeding (shown in Figure 1). Moreover, the microneedle arrays have the advantage of a uniform delivery of the drug. Because these devices are fabricated using microfabrication technology, they can be easily scaled up for cheap and reproducible mass production. So far, a wide variety of microneedles fabricated from different materials has been reported. Arrays of hollow out-of-plane silicon microneedles were presented in [9] by Stoeber and Liepmann, while microneedles with biodegradable tips (mesoporous silicon) were reported in [10]. Other materials were explored as well: polysilicon [11], and even polymers [12, 13]. Metal microneedles have also been targeted for transdermal drug delivery mainly due to their good mechanical properties and biocompatibility [14, 15]. *In vitro* and *in vivo* (on diabetic mice) studies demonstrate the delivery of insulin [16, 17]. Lin et al [18] used microneedles to deliver 20-mer phosphorothioated oligodeoxynucleotides across the skin of hairless guinea pigs. In [19] Matriano et al demonstrated the delivery of ovalbumin as a model protein coated onto a needle surface. Recently, “dissolving microneedles” were reported, i.e. microneedles which encapsulate the drug to be delivered and which slowly dissolve within the skin [20].

Basically, the microneedles are fabricated by silicon with MEMS technologies. The various shapes and profiles of silicon microneedles, either hollow or solid needles, can be fabricated using the DRIE process [21-23].

Fig. 1. Microneedles can create pathways into the skin for drug delivery and are painless due to their size

However, due to the high-aspect-ratio needle structure and fragility of silicon, these microneedles have some several shortcomings. The main problem of the silicon microneedles is that it breaks easily during the insertion process into the skin (Figure 2), and this increases the possibility of an infection. The solution proposed here is to fabricate the microneedles tip from a biodegradable porous silicon material. This porous silicon is well-known as nano-structured silicon and good for biological applications because of its bioactive and biodegradable properties [24-25]. The microneedles have been fabricated to have macro porous tips by using electrochemical etching process. These porous tips may break off after the drug delivery process and be allowed to remain in the skin, as it can be easily biodegraded within 2 to 3 weeks.

Fig. 2. SEM image showing the tip of a broken microneedle after insertion into a pig skin.

Here we report the development of silicon microneedles array with biodegradable tips. The silicon microneedles array was fabricated by using notching effects of reactive ion etching

(RIE). The macroporous tips were fabricated using a classical anodization process in MeCN/HF/H₂O solution. The microneedles array was tested *in vitro* with an animal skin model by using a comparative study (bare skin diffusion and diffusion through the microneedle array). Calcein (molecular weight of 623 Da) and bovine serum albumin (BSA) - molecular weight of 66.430 kDa were investigated in the drug delivery. The drug release profile was characterized using UV spectra detection, and the results showed that microneedles can enhance the calcein release rate by 5 times compared to conventional transdermal drug delivery methods without enhancers. Similarly, the enhancement factors of microneedle array for BSA were 7 times compared to the bare diffusion rate.

2. DESIGN AND FABRICATION

The micro-sized needles are designed to penetrate the primary biological barrier of stratum corneum and the epidermis but without penetrating into the dermis layer that contains nerves and blood vessels, thus avoiding pain and bleeding. In our application, we chose to fabricate the microneedle arrays from silicon, making use of microfabrication techniques, mainly due to simplicity of the fabrication process. The microneedles are out-of-plane, 100 μm high, and arrayed in a 30×30 matrix on a $12 \times 2 \text{ mm}^2$ silicon chip. Since the stratum corneum of skin has a depth of 10~20 μm , and epidermis has a variable depth of 50~100 μm , the penetrating length of the microneedles is preferred to be around 100 μm .

Furthermore, in order to have an easy penetration into the skin, the microneedles should have a high aspect ratio. The fabrication of the microneedles was realized using an optimized SF₆/O₂ RIE process. By controlling the two gas flow rate, the microneedles were fabricated with an aspect ratio of 3:1 (height: width of the needle base) [26]. The isotropic profile of the microneedles was fabricated using two effects: flowing of thick photoresist mask and notching effect of the reflected charges on mask. It is a well-known property of the thick photoresist that it reflows when it is heated at 120 °C [27]. The modification of the vertical wall of the patterned photoresist can reflect the charges (ions and radicals) during the RIE process and in this way generates the etched profile under the oxide

mask. This phenomenon has also been reported for the Bosch process [28].

Fig. 3. Notching effect of reflected charges on mask.

Fig. 4. SEM image with released microneedles.

Figure 3 is an example of the notching effect of reflected charges on the mask where ions and radicals with high energy are reflected by the oblique profile of the photoresist and generate an increased etching under the mask. The process eliminates the difficulty in the undercut control of the tips during the classical isotropic silicon etching process. Also, the end of the process can be very easily monitored using the video-camera of the “End Point Detection System” of the deep RIE tool. Once the required shape of the tip is achieved, the square shape of the mask is modified and we could observe the different rectangular shapes that correspond to the projection of the tiled square mask on the monitor. An SEM image that illustrates the released microneedles at the masking layer is presented in Fig. 4.

The main steps of the fabrication process of the microneedles are presented in Fig. 5. A 4” silicon wafer with <100> crystallographic orientation, n-type 1~10 ohm-cm was initially cleaned in

piranha solution (H_2SO_4 : $\text{H}_2\text{O}_2 = 2:1$) at 120°C for 20 minutes and then rinsed in DI water and spun dried (Fig. 5a). On the silicon wafer a $0.5\ \mu\text{m}$ -thick SiO_2 was deposited at 300°C , from SiH_4 and N_2O , at a pressure of 700 mTorr and a power of 300 W using STS-PECVD equipment (Fig. 5b). A photoresist mask using AZ9260 positive photoresist (from Clariant), with a thickness of $8\ \mu\text{m}$, was used for the patterning of the SiO_2 -PECVD layer (Fig. 5c). The pattern is transferred to the SiO_2 layer using a RIE etching system with CHF_3 : He gases on RIE dielectrics Adixen AMS100 (Figure 5d). After the patterning of the oxide layer, the tips were generated using an isotropic RIE process (Fig. 5e and 5f) with SF_6/O_2 in an ICP DRIE system. The process was optimized for a better control undercut, and with a depth-to-width aspect ratio of 3:1 [26]. A SEM image with the needles is presented in Fig. 6.

Fig. 5. Fabrication process of nanotips: a) silicon wafer, b) PECVD SiO_2 , c) photoresist mask d) etching of SiO_2 , e) plasma etching in SF_6 , f) release of nanotips

Fig. 6. SEM picture of the fabricate microneedle.

3. FABRICATION PROCESS OF THE BIODEGRADABLE TIPS

After the fabrication of the silicon microneedles array, the following target was to develop an anodization process that allows the conversion of a single crystal silicon material of the tip into a porous structure. In order to achieve this, the “body” of the microneedles must be protected with a Si_3N_4 layer, releasing only the tip to be exposed during the anodization process. The main steps of the porous tips fabrication are shown in Fig. 7.

Fig. 7. Fabrication process flow for the porous tips: (a) LPCVD Si_3N_4 deposition, (b) photoresist coating, (c) photoresist reflowing and O_2 plasma, (d) Si_3N_4 etching in RIE and photoresist removal, (e) Al deposition (back of the wafer), (f) anodization.

After cleaning, a 500 nm Si_3N_4 layer was deposited on the microneedles surface in PECVD

reactor [29, 30] (Figure 7a). With relatively good results, also PECVD SiC [31, 32] can be used for the needles covering. A thick layer of photoresist AZ9260 was spun twice on the surface of the microneedles, followed by baking at 120 °C for 15 min (Figure 7b). Due to the flowing effect, the photoresist covering the tips of the needles was much thinner than those at the body and at the bottom. Thus the photoresist on the tips of the microneedles was cleaned/removed in an O_2 plasma etching process in RIE System (Fig. 7c). In this way only the top part of the needle is free of photoresist and the Si_3N_4 layer on the microneedle tips can be removed using a RIE process (CHF_3/He chemistry) – Fig. 7d. The Si_3N_4 layer, from the backside of the wafer, was also removed using a similar RIE process. On the back of the wafer, an aluminum layer was sputtered in order to achieve a good electric contact for next electrochemical process (Fig. 7e). Then the porous silicon was generated only on the tip of the microneedle using a classical anodization process, while as the needle body was protected by the remaining Si_3N_4 layer (Fig. 7f). Fig. 8 shows the experimental setup of the anodic electrochemical etching process [33]. The Pt electrode was used as the cathode and silicon wafer as anode. A DC power of 36~72 V was used as the source. The used electrolyte was a mixture of acetonitrile (MeCN) and diluted hydrofluoric acid (HF). The mixture has two compounds of $\text{MeCN} : \text{HF}(4\text{M}) : \text{H}_2\text{O} = 92\% : 4\% : 4\%$ by weight. The electrochemical anodization process was carried out at a current intensity of $10 \text{ mA}\cdot\text{cm}^{-2}$ for 30 min. Fig. 9 shows a SEM picture of the porous silicon tip after the anodization process.

Fig. 8. Schematic view of the electrochemical anodization process.

Fig. 9. SEM picture of the porous silicon tip.

4. DRUG DELIVERY USING MICRONEEDLES ARRAY WITH BIODEGRADABLE TIPS

4.1 Skin model

The microneedle array was applied to the in vitro transdermal drug delivery model using pig skin. Pig skins were used in the experiment due to their similar physiological properties with the human skin. All animal procedures were performed in compliance with relevant regulations approved by the Institutional Animal Care and Use Committee of National University of Singapore. For the pig skins preparation, the skin were excised from the pig immediately after the pigs were sacrificed. The excised skins were fixed on top of plastic foam with the epidermis layer facing up. The adhering fat and other visceral debris in the skin were then carefully removed. The underlying subcutaneous fat was gently scraped off until the skin was about 1 mm thick. The prepared skins were washed, wrapped in aluminum foil, and stored at -80°C .

4.2 In vitro delivery testing setup

A Franz diffusion cell (Logan Instruments Corp., Somerset, NJ) was used for the in vitro drug release. The pig skin was removed from the refrigeration chamber 1 hour before each experiment and mounted onto a Franz diffusion cell, with the stratum corneum side facing to the donor compartment. The microneedle array was then pressed onto the surface of the skin, and held by the donor compartment. The donor and

receiver compartments were then clamped together. The receiver compartment was filled with phosphate buffered saline (PBS) solution while the temperature of water bath was maintained at 37°C . Figure 10 illustrates the experimental setup. For a better comparison, the drug release experiments were carried out in four parallel sessions: using passive diffusion through the skin, using the microneedles array.

Fig. 10. Illustration of the in vitro transdermal delivery with the microneedles enhancer.

4.3 Materials for testing

The drugs tested in the experiments were calcein (at a concentration of 10^{-3} mol/l, or 623 Da) and bovine serum albumin (BSA, molecular weight 66430 Da) with the concentration of 10^{-3} mol/l. The permeability and transport of calcein across the skin was detected using UV-visible spectrophotometry (Agilent 8453 UV-vis system). The excitation wavelength of calcein was set to 480 nm. The same method was employed for BSA detection, but excitation wavelength in this case was 280 nm.

4.4 Experimental results of calcein and BSA delivery

Microneedles were inserted into the pig skin to generate conduits or microchannels for the transport of drugs across the stratum corneum. Once the delivery compound crosses the stratum corneum, it diffuses rapidly through the deeper tissue and is taken up by the underlying capillaries for systemic administration. The drug release profiles from the two kinds of transdermal delivery were compared and the results are shown in Fig. 11. The skin permeability of calcein was greatly enhanced to 5-6 times with microneedles,

compared to the passive transdermal delivery without microneedles. In other words, the total drug release with passive diffusion in 24 hours can be delivered in 7 hours with microneedles. Similarly, the drug release profiles from the two kinds of transdermal delivery were compared and the results are shown in Fig. 12. The skin permeability of BSA with microneedles was enhanced by ~7 times compared to the bare skin diffusion. This enhancement was attributed to the microchannels and pathways in the skin tissue created by the microneedles, which greatly increased the permeability of the skin.

Fig. 11. Calcein release profile with pig skin.

Fig. 12. BSA release profile with pig skin.

5. CONCLUSIONS

The microneedles array with biodegradable porous silicon tips for transdermal drug delivery was fabricated using micromachining technologies. The high aspect ratio of these needles was obtained with reflow of photoresist and the notching RIE process. The microneedle tips fabricated are macroporous and biodegradable and this is achieved by using the

electrochemical anodization process. The transdermal drug delivery experiments showed that the microneedles can greatly enhance the skin permeability for better drug transport. The results indicate the feasibility of microneedles as a more effective transdermal drug delivery system with significant clinical potential.

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