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Spin coating of polymer solution on polydimethylsiloxane mold for fabrication of microneedle patch

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ABSTRACT

Since 1990 s, research and development of microneedles (MNs) for transdermal drug delivery (TDD) have been receiving great attention. Among various kinds of MNs, the dissolvable polymer MNs provide several attractive merits such as biocompatibility, biodegradability, and active and controlled release of drugs. Currently, the widely practiced approaches, *i.e.* evaporation and centrifugation, suffer from either relatively long processing time or tedious procedure. This project aims to develop and validate a new method, *i.e.* spin-coating process, to fabricate polymer MNs in a relatively simple and fast manner. First, the polydimethylsiloxane (PDMS) daughter mold replicated from the MNs array was used and bonded to the cleaned glass slide. The assembly was then placed on the spin coater, followed by dispensing the polymer solution and switching on the spin coater. It was found that, addition of trace amount of bovine serum albumin (BSA) in the polymer solution will facilitate formation of polymer film on PDMS surface by spin coating. Moreover, with the simple setup and procedures, the dissolvable polymer MNs with needle height up to 300 μm can be obtained.

1. Introduction

Transdermal drug delivery (TDD) is a new path for drug administration and has been gaining more and more attention in recent years [1–3]. Compared to the oral path drug administration, TDD offers several advantages such as preventing the drug from degradation in the gastrointestinal tract, first-pass effects of the liver and sustaining therapeutic drug level [4]. The non-invasive drug delivery, lower risk of infection and better patient compliance even makes TDD superior to the conventional intravenous injection. The main barrier for TDD is the *Stratum corneum* layer (about 20 μm) and viable epidermis layer (about 300 μm) of human skin which provide protection from the external impurities. There are two main strategies used to overcome the skin barrier [5–7]. One is the chemical treatment where the physical properties of lipid bilayer are changed reversibly by chemical compounds like sulfoxides, azones, pyrrolidones, alcohols, alkanols, *etc.* [5] The other is the physical treatment (*e.g.* electroporation [6], iontophoresis [7], ultrasound technique [8], photoacoustic methods [9] and microneedles [11]) where the reversible pinholes are created to allow the molecular drug to penetrate skin barrier into human systemic circulations and, thus, it prevents the risk of extra chemical compounds involvement. Among these techniques used in the physical treatment, exploitation of microneedles (MNs) provides extra benefits such as ease of administration and system integration, being painless and no need of expensive equipment. Different methods have been proposed to fabricate MNs using various materials such as silicon [10–13], metal [14–16], photoresist [17,18] and polydimethylsiloxane (PDMS) [19]. However, direct usage of the MNs made of these materials poses some serious concerns like the risk of residual fragment remained in the human body, production of biohazardous sharp waste or lacking sufficient mechanical strength. The polymeric materials, especially the biodegradable and biocompatible polymers, offer attractive merits

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such as the added functionality, active and controlled release, improved resistance to shear-induced breakage, cost effectiveness, sufficient mechanical strength and additional safety [20,21]. Although various fabrication techniques have been proposed and demonstrated [17,12–27], casting in conjunction with vacuum and centrifugation are two widely practiced approaches [28–30]. The substantially long drying time in the casting process will be detrimental to MNs-related product manufacturing while the repetitive procedures in the centrifugation process and the maximum footprint of the MNs restricted by the diameter of centrifuge tube [28,31] jeopardize its potential application in MNs production.

In this study, we proposed and demonstrated that the polymer MNs can be fabricated by spin coating process. Fabrication of silicon mold having the MNs with different shapes and aspect ratios was described and the effect of different processing parameters on formation of polymer MNs such as solution property, solution concentrations, spin rates and aspect ratios of the funnel-like cavities on the PDMS daughter mold were discussed.

2. Materials and methods

2.1. Materials

Poly(dimethyl siloxane) (PDMS) (Sylgard 184) was purchased from Dow Corning. 6 inch silicon wafer was purchased from Guv Team International Co. Ltd., Taiwan. Polyvinylpyrrolidone (PVP; MW = 360,000) and bovine serum albumin (BSA; 66.5 kDa) were purchased from Sigma-Aldrich (St. Louis, MO, USA). The photoresist (AZ-5214E), hydrofluoric acid, acetone, isopropyl alcohol, hexamethyldisilazane, BOE and Caro acid were provided by National Nano Devices Laboratories, Taiwan. The plastic microneedle patch with 600 μm was purchased from 3 M (St. Paul, MN, USA).

2.2. Fabrication of silicon microneedle mold

The silicon wafer was used to fabricate the microneedle (MN) mold. It was first immersed in Caro acid (H_2SO_4: H_2O_2 = 3:1) at 120 °C for 10 min to remove the organic residue on the wafer, followed by hydrofluoric acid at 20 °C for 1 min to remove the native oxide layer. Then the silicon wafer was cleaned by acetone, isopropyl alcohol and copious amount of DI water for 3 times. It was subsequently blown dry with nitrogen gas and placed on the 110 °C hot plate for 5 min. The as-cleaned silicon wafer was deposited with 2-μm thick SiO_2 through plasma-enhanced chemical vapor deposition (Plasmalab System 100, Oxford, UK) and went through the standard photolithographic process to yield the patterned photoresist array of circles with 80 (or 600) μm in diameter and 150 (or 700) μm center-to-center distance. The patterned silicon wafer was then immersed in the buffered oxide etch (BOE), followed by plasma etching away the photoresist and the SiO_2 array of circles on the wafer was obtained to serve as the etching mask.

The silicon wafer with the SiO_2 etching mask was further diced into 3 × 3 cm^2 chips, which were placed in the Plasmalab System 100 to undergo inductively coupled plasma-reactive ion etching (ICP-RIE) process. Either one-step or two-step process was adopted. For the one-step process, the silicon chip was simply placed in the etching chamber to be isotropically etched. For the two-step process, the silicon micropillars were first formed by anisotropic etching, followed by isotropic etching to obtain the microneedles. The gas flow rates for O_2 and SF_6 range from 0 to 30 and 25 to 100 sccm, respectively. The RF power and the ICP power were between 1–4 and 1100–1350 W, respectively. The operating temperature was set at −110 °C and the chamber pressure was 10 mTorr. It is worthy of mentioning that, due to the thickness of the silicon wafer, the height of the MNs as fabricated is usually less than 300 μm.

2.3. Fabrication of PDMS microneedle mold

For MNs with needle height larger than 300 μm, etching of PDMS micropillars can be exploited and found elsewhere [19]. In brief, array of cylindrical holes was created on polymethylmethacrylate (PMMA) by computer numerical control machining. The base of PDMS and the curing agent were mixed at the ratio of 10:1, followed by de-gasing, pouring the mixture onto the PMMA substrate with the array of cylindrical holes and placing in the 65 °C oven for 4 h. The PDMS micropillars were peeled from the substrate and immersed in the etchant to undergo the etching process. The PDMS MN mold was obtained after approximately 30 min. Note that the needle height of the PDMS MNs can be adjusted according to the dimensions of the micropillars. In this study, an array of PDMS micropillars with 400 μm in diameter, 400 μm in height and 1000 μm in center-to-center spacing was used, which underwent the etching process to yield an array of PDMS MNs with needle height approximately 300 μm.

2.4. Fabrication of PDMS daughter mold

To obtain the PDMS daughter mold, the mixture of the base and curing agent was poured either onto the silicon MN mold, 3 M microneedle patch or PDMS MN mold with surface modification [19], followed by placing in the 65 °C oven for 4 h. The PDMS daughter mold was then peeled off from the mother mold and cut into the size of 2 × 2 cm^2 for subsequent spin-coating process.

2.5. Spin-coating process for fabrication of polymer microneedles

The PDMS daughter mold was attached to the glass slide and the assembly was mounted onto the spin coater (GSSP-02A, Hung Yao Instruments Co., Taiwan). The concentrations of polyvinylpyrrolidone (PVP) solution ranging from 10 to 30 wt% (w/v) were prepared by dissolving the PVP powder in DI water with addition of different amount of BSA (0–0.5 wt% (w/v)). The solution was then dispensed on top of the PDMS daughter mold, followed by spin coating with the rotation speed ranging from 100 to 2000 rpm (from 1 to 400 g) for 1 min. The PDMS daughter mold with the spin-coated polymer was left dry at the ambient condition for 1 day.

2.6. Sample characterization

The microneedles were examined using either scanning electron microscope (SEM) (Hitachi S-3000H or JEOL JSM-6700F) or the optical microscope. To measure the thickness of PVP film, the sample was treated with liquid nitrogen, followed by cutting the sample and measuring the cross section of the film by SEM.

2.7. Skin insertion test

Optical coherence tomography (OCT) was used to evaluate the skin insertion and can be found elsewhere [32]. In brief, the force of approximately 10 N per patch was applied for 10 min without peeling off and an optical coherence tomography (OCT) system was used with a MEMS-based swept source for visualizing a series of polymer MN arrays. The center wavelength of the swept source (HSL-20, Santec Corp., Japan) is located at 1310 nm with a scanning spectral range of 105 nm. The A-mode scanning rate and the output power can reach the values of 100 kHz and 30 mW, respectively. With an A-scan rate of 100 kHz, the frame rate can achieve 100 frames per second, in which each frame consists of 1000 A-scans. The insertion and creation of pores following the application by the PVP MNs to porcine cadaver skin at a force of 9.8 N per patch for 10 min was investigated using an OCT