A fabrication method of microneedle molds with controlled microstructures

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A B S T R A C T

Microneedle (MN) offers an attractive, painless and minimally invasive approach for transdermal drug delivery. Polymer microneedles are normally fabricated by using the micromolding method employing a MN mold, which is suitable for mass production due to high production efficiency and repeat-using of the mold. Most of the MN molds are prepared by pouring sylgard polymer over a MN master to make an inverse one after curing, which is limited in optimizing or controlling the MN structures and failing to keep the sharpness of MNs. In this work we describe a fabrication method of MN mold with controlled microstructures, which is meaningful for the fabrication of polymer MNs with different geometries. Laser micro-machining method was employed to drill on the surface of PDMS sheets to obtain MN molds. In the fabrication process, the microstructures of MN molds are precisely controlled by changing laser parameters and imported patterns. The MNs prepared from these molds are sharp enough to penetrate the skin. This scalable MN mold fabrication method is helpful for future applications of MNs.

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1. Introduction

Microneedles (MNs) are micro-scale needles that could pierce into epidermis of skin [1,2], in which micro channels are created and enable drug penetrate stratum corneum barrier and diffuse into the subcutaneous tissues [3]. Advantages associated with microneedle based drug delivery include: avoiding drug degradation in stomach, liver and metabolism like oral administration [4], increased patient compliance due to minimal pain and damage to the skin and reduction of multiple dosing regimes [5,6], as well as reduced medical waste for the environmental protection [1].

The application of MN technique for the insulin [7,8] and vaccine [9,10] delivery via transdermal system has been studied since the late of 1990s for its painless [3,11], usability and acceptability for self-vaccination [6,12]. Current MN products have the following basic types: solid MN for skin pre-treatment to increase skin permeability [10,13], coated MN enable drug on the needle's surface released in the skin [14,15], hollow MN for drug infusion into the skin [16,17], and dissolving MN encapsulated drug and dissolve into skin and release drugs after insertion [18,19], swelling MNs enable drug delivered through MN matrix from an upper drug-loaded reservoir [20,21]. The first generation of MNs were made from silicon [4,22], metals [4,10,23] or organic materials, while in recent years,

various kind of polymers materials including degradable polymers such as PLA [24], PLGA [25], PVA [26,27], PEG [20], PVP [28], CMC [29], silk [30,31], and chitosan [32] and non-biodegradable polymers SU-8 [6,24], PMMA [33,34], PS [13] have been used to prepare MNs. Since many kinds of materials could be used to prepare MNs, fabrication methods of that are varied. Silicon MNs have been fabricated using deep reactive ion etching [22], wet etching [35,36] and dry etching methods [22]. Metallic MNs have been fabricated using three-dimensional laser ablation, laser cutting, and wet etching and metal electroplating methods [3,4,37]. Fabrication method of polymer MNs involve micro-molding [26,30,38], UV photolithography [6,20,24] and drop drawing method [8,18]. Polymer solution or melt micro-molding using MN mold is commonly employed in preparation of polymer MN, including casting, hot embossing, injection molding [1,27].

MN mold-based fabrication method is suitable for mass production due to high production efficiency and repeat-using of the mold. Most common MN molds are reverse-molded from a maser MN arrays using polydimethylsiloxane (PDMS) [26,32]. Briefly, the PDMS is mixed in a 10:1 *v*/v ratio of prepolymer to curing agent, and is degassed in an 800 Mb vacuum for half an hour. Poured over the master micro-needle arrays before curing at 90 °C for 5–6 h. Resultant cured mold with inversed patterns is peeled away from the master arrays. As well known, the geometries have great influence on the properties of MN [39–41], especially for the fabrication process of polymer MNs. In the case of height of MN, smaller height will cause less pain and hurt to the skin, while reduce the pierce property of MN and drug loading. Larger height will take more pain and hurt, but it does help to increase

the pierce property and drug loading, which is important for drug delivery [42]. Therefore, it is meaningful to develop a scalable MN mold fabrication method with controlled microstructure for various MN applications. However, the reverse process of mold described above may influence the sharpness of MNs more or less, and it is unfavorable to achieve the control of microstructures and mass production using this two-step process of MN mold. In this work we report a method to prepare MN mold with controlled microstructures using laser-based technique, which has been used in the manufacture of MNs [27,43].

2. Materials and method

2.1 Materials

PDMS (polydimethylsiloxane/sylgard) was purchased from Dow Corning (Wiesbaden, Germany).PVA (polyvinyl alcohol, 75% hydrolyzed, MW approximately 2000) was purchased from Acros Organics (New Jersey, USA). Sucrose (MW approximately 324.3) was purchased from Tokyo Chemical Industry Company (Tokyo, Japan). PLA (polylactic acid, 50–60 kDa) and Sulforhodamine B was purchased from Lakeshore Biomaterials (Birmingham, AL).

2.2 Fabrication of MN molds using different laser parameters

Unlike reverse molding method mentioned previously, in this work, we fabricate PDMS MN molds in one step by drilling on the surfaces of 2-mm-thick PDMS sheets with laser beam, as shown in Fig. 1. First, to obtain a PDMS sheet with uniform thickness, the PDMS was mixed in a 10:1 v/v ratio of prepolymer to curing agent and degassed in an 800 Mb vacuum for half an hour, followed by curing into a customized mold with smooth surfaces curing at 60 °C for 5 h, and then resultant PDMS sheets were peeled away from the mold (Fig. 1A). Furthermore, we employed a laser engraving machine (VLS3.50, 50 W, Universal Laser System, USA) to emitting a carbon dioxide laser beam to drill on surface of PDMS sheets and generated micro-cavities (Fig. 1B). The focus length of lens is 1.5 in. and the diameter of focal spot is 75 μm. In this process, different patterns could be designed in CAD files and imported into laser engraving machine, and the laser parameters can also be controlled by computer.

Laser power and speed are important influential factors for the microstructures of MN molds. In this work, to explore the effect of laser power on the microstructures of MN mold, using point as laser engraving patterns, we fixed the laser speed at 50% while the laser power was set to 10 groups varying from 5% to 95% (the full power value is 50 W) with length step of 5%. Similar, to get the relationship between laser speed and the microstructures of MN mold, using point as laser engraving patterns, the laser power was fixed at 20% while the laser speed was set to 10 groups varying 5% to 95% with length step of 5%. According to the laser parameters above, MN molds with
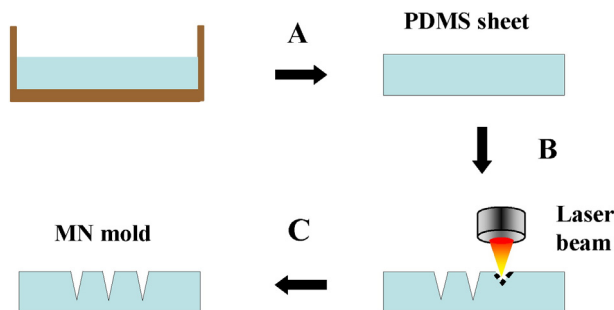

Fig. 1. Schematic fabrication process of PDMS MN mold using the laser-drilling method. (A) The PDMS prepolymer was mixed with curing agent and poured in to a mold, curing at 60 °C for 5 h to get a PDMS sheet with 2 mm in thickness. (B) Laser beam is employed to drill on the surface of PDMS sheets. (C) PDMS MN mold with micro-cavities was obtained.

different microstructures was fabricated using the method described previously.

1. 2.3 Fabrication of MN molds using different imported patterns

Besides the laser parameters as described above, the microstructures of MN mold were also influenced by the imported patterns in the laser engraving machine. To explore the effect of imported patterns on the geometries of MN, we designed six pattern models and matching laser parameters (Table 1), including point (model 1), circle (model 2 and 3) and helix arrays (model 4, 5 and 6). When the element imported patterns were circles, to explore the effect of diameter of circle on the microstructures, we designed model 2 and 3, in which the diameters of circle are 0.04 mm and 0.08 mm respectively. Similarly, to explore the effect of diameter and number of turns of helix, we designed model 4–6 with number of turns of 3, 6 and 3 respectively. Moreover, the diameters of the helix base in model 4, 5 are both 0.08 mm, while the diameter of helix base in model 6 is 0.10 mm. We also designed model 1 with point as patterns for comparison. According to the patterns and parameters in Table 1,six different MN molds were prepared using laser drilling method as described in Fig. 1.

2.4 Fabrication of PLA/PVA MNs

To compare the differences of the microstructures of these MN molds, PLA solid MNs and PVA dissolving MNs were prepared using the molds prepared in this work according to the method described in Fig. 2. For the PLA MNs, briefly, PLA solid particles were firstly put on the mold (Fig. 2A1) and heated at 200 °C to fill the cavities in the MN mold (Fig. 2B1). Then the melted PLA was pressed with a steel sheet to make a flat backing surface of a MN patch when the bubbles in the melted PLA was disappeared (Fig. 1C1). The resultant PLA solid MNs were obtained after de-molding process (Fig. 1D1). For the PVA MNs, briefly, the MN mold was filled with drug solution under vacuum (Fig. A2). Residual drug solution was removed from the surface and dried under vacuum (Fig. 2B2). PVA solution blended with sucrose (used as stabilizer) was cast onto the mold (Fig. 2C2). The cavities of mold were filled by polymer solution under vacuum (Fig. 2D2). PVA MNs were freeze-dried and peeled away from the mold (Fig. 2E2). In the fabrication of drug-loaded PVA MNs, 1 mg/ml Sulforhodamine B solution was used as model drug. To prepare 30 wt% PVA solution, 9 g PVA and 6 g sucrose were dispersed in 15 ml DI water and heated at 60 °C for 2 h.

2.5 Skin penetration tests of MNs

To evaluate the insertion capability of the MNs prepared from the molds described in this work, we selected 6 kinds of PLA MNs with different geometries for porcine skin penetration tests. Porcine skin was used as the skin model and Sulforhodamine B was used as the model drug. First, the MN arrays were fixed on a simple push dynamometer and pressed by hand onto the porcine skin in a vertical direction using a force of approximate 10 N. Subsequently, a drop of 1 mg/ml drug solution was applied onto the area where MN arrays treated. After 5 min, drug solution was removed from the surface of skin, and then the skin was washed three times with 70% ethanol and then observed under an optical microscope immediately.

3. Result and discussion

3.1 Effect of laser parameters on microstructures

In this work, we fabricated PDMS MN molds using a laser engraving machine emitting a carbon dioxide laser beam to drill on surface of PDMS sheets and generated micro-cavities, where the body of MN was formed. The drilling process can be described as that, the sylgard