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Rapid fabrication of microneedles using magnetorheological drawing lithography

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ABSTRACT

Microneedles are micron-sized needles that are widely applied in biomedical fields owing to their painless, minimally invasive, and convenient operation. However, most microneedle fabrication approaches are costly, time consuming, involve multiple steps, and require expensive equipment. In this study, we present a novel magnetorheological drawing lithography (MRDL) method to efficiently fabricate microneedle, bio-inspired microneedle, and molding-free microneedle array. With the assistance of an external magnetic field, the 3D structure of a microneedle can be directly drawn from a droplet of curable magnetorheological fluid. The formation process of a microneedle consists of two key stages, elasto-capillary self-thinning and magneto-capillary self-shrinking, which greatly affect the microneedle height and tip radius. Penetration and fracture tests demonstrated that the microneedle had sufficient strength and toughness for skin penetration. Microneedle arrays and a bio-inspired microneedle were also fabricated, which further demonstrated the versatility and flexibility of the MRDL method.

Statement of Significance

Microneedles have been widely applied in biomedical fields owing to their painless, minimally invasive, and convenient operation. However, most microneedle fabrication approaches are costly, time consuming, involve multiple steps, and require expensive equipment. Furthermore, most researchers have focused on the biomedical applications of microneedles but have given little attention to the optimization of the fabrication process. This research presents a novel magnetorheological drawing lithography (MRDL) method to fabricate microneedle, bio-inspired microneedle, and molding-free microneedle array. In this proposed technique, a droplet of curable magnetorheological fluid (CMRF) is drawn directly from almost any substrate to produce a 3D microneedle under an external magnetic field. This method not only inherits the advantages of thermal drawing approach without the need for a mask and light irradiation but also eliminates the requirement for drawing temperature adjustment. The MRDL method is extremely simple and can even produce the complex and multiscale structure of bio-inspired microneedle.

1. Introduction

A microneedle is a needle-like structure with its diameter in the size order of micron and a length of up to 1000 μm [1,2]. A microneedle can easily penetrate the skin to pass the barrier of the stratum corneum, the outermost layer of the skin, without causing pain or bleeding owing to its small diameter and height. The microneedle offers the possibility of a minimally invasive transdermal interaction with the biological system under investigation. Therefore, microneedle, bio-inspired microneedle, and microneedle array have shown great potential in several biomedical fields, such as transdermal delivery of drugs and compounds (e.g., insulin, proteins, vaccines, DNA, antibodies, and antibacterial agents) [3–8], collection of blood and dermal interstitial fluid [9,10], transdermal biosensing (e.g., glucose, alcohol, biomarkers, and ion detection) [11,12], tissue adhesives [13], brain-computer interface [14], and bio-signal monitoring (e.g., electromyography (EMG), electrocardiography (ECG) and electroencephalography (EEG)) [15,16].

Various processes have been reported for the fabrication of microneedles. Typically, the subtractive process is employed to fabricate microneedles, in which the 3D structure of the micronee-

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dle is selectively carved out of a 2D substrate. Lithography with wet or dry etching is one of the most popular processes for the fabrication of silicon and glass microneedles [17,18]. However, it requires sophisticated equipment located in clean rooms and produces toxic waste, which is inconvenient, complex, expensive, and eco-unfriendly. Electroplating [19,20], laser cutting [21], wire-electrode cutting [22], and micromachining [23] have been adapted to fabricate metal microneedles. However, they are costly, have poor efficiency, and are not suitable for mass production. Traditional subtractive processes are limited to flexible structural microneedles. The micromolding method has been employed to fabricate most polymer microneedles owing to its potential for up-scaling production, characterized by multiple costly and time-consuming steps, such as master preparation, mold fabrication, polymer filling, and microneedles separation [13,24–26]. Additive processes, such as 3D printing [27], droplet-born air blowing [28], electro-drawing [24], and thermal drawing [29], can also form 3D structures of polymer microneedles from droplets or 2D surfaces. 3D printing is flexible and allows personalized customization. However, the resolution of 3D printing is low, and the resulting microneedles have millimeter-scale lengths and tip diameters of about 100 μm [27]. Droplet-born air blowing, in which a polymer droplet is shaped into a microneedle through air blowing, involves gentle fabrication conditions without the use of UV irradiation or heat [28]. It has good productivity and has been even commercialized [30]. Electro-drawing, in which droplets are self-assembled into the 3D structures of microneedles by the electrohydrodynamic force, is free of molding and contact. Thermal drawing, in which the thermosetting polymer is drawn directly from a 2D solid surface to produce a 3D microneedle, is a maskless method that does not use light irradiation. However, the above drawing processes suffer from the limitations of relatively difficult operation in the lab and usually fabricate microneedles from the 2D flat substrates [24,31]. Therefore, challenges still remain for the rapid and easy fabrication of microneedles with a low cost. Furthermore, most researchers have focused on the biomedical applications of microneedles but have given little attention to the optimization of the fabrication process.

Here, we propose a novel magnetorheological drawing lithography (MRDL) method to efficiently fabricate microneedles, bio-inspired microneedles, and microneedle arrays. In the proposed technique, a droplet of curable magnetorheological fluid (CMRF) is drawn directly from almost any substrate to produce a 3D microneedle under an external magnetic field. The method not only inherits the advantages of thermal drawing without the need for a mask and light irradiation but also eliminates the requirement for the drawing temperature adjustment. Therefore, the MRDL method is extremely simple and can even produce the complex and multiscale structure of bio-inspired microneedle. In this study, the mechanism of the MRDL method for microneedle formation was experimentally and theoretically investigated. The fabricated microneedle was characterized, and its mechanical performance was measured. Finally, a microneedle array and a bio-inspired microneedle were fabricated to demonstrate the feasibility and flexibility of the MRDL method.

2. Experimental

2.1. Preparation of CMRF

A CMRF was specifically prepared to form microneedles with the MRDL method. A curable liquid (epoxy/novolac resin), curing agent (modified aliphatic amine), and magnetic particles (iron powder with an average diameter of 1 μm) at a mass ratio of 3:1:3 were uniformly mixed for 10 min using an ultrasonic oscillator. The mixture was pre-polymerized at a temperature of 80 °C for 3 min. Finally, the CMRF was prepared. The physical properties, chemical formulas, and poly-condensation equation of the epoxy/novolac resin and the modified aliphatic amine are listed in Table S1. The specific parameters of the iron particles are provided in Table S2. The magnetic hysteresis loop of the CMRF was measured using a vibrating sample magnetometer (7410, Lake Shore, USA) and its relative permeability was calculated, as shown in Fig. S1.

2.2. Fabrication of microneedle

A custom-made automatic setup was developed for the fabrication of microneedles with the MRDL method, as shown in Fig. S2. Cylindrical NdFeB permanent magnets were employed to produce an external magnetic field. A copper pin with a diameter of 0.7 mm was chosen as a drawing pillar. A 30-nL hemispherical CMRF droplet dipped and suspended on the tip of pillar was driven toward the substrate. The droplet was compressed on the top surface of the substrate, held for 300 ms, and drawn back at a speed of 1 mm s^{-1} and deposited a liquid microneedle on the substrate under the external magnetic field. This fabrication process was digitally controlled using custom-made software based on Visual Basic. This formation process of the liquid microneedle was monitored by an optical microscope. The liquid microneedle was maintained under an external magnetic field and was pre-baked by hot air blowing at a temperature of 95 °C for 5 min. The pre-baked microneedle was further solidified in an oven at a temperature of 100 °C for 1 h.

The magnetic field distributions of five typical states during the MRDL process were analyzed with COMSOL Multiphysics, as shown in Fig. S3. The morphology of the microneedle, bio-inspired microneedle, and microneedle array were observed by an SEM (JSM-6380LA, JEOL, Japan) and an optical microscope. The key geometry parameters of the microneedle, including the height and tip radius, were analyzed with a Digimizer (V4.0, Med-Calc Software, Republic of Korea) using the captured images.

2.3. Penetration and fracture performance

Mechanical loading equipment was developed to perform the penetration and fracture experiments, as shown in Fig. S4. Fresh rabbit skin was prepared for ex vivo skin penetration and transdermal drug delivery experiments. A New Zealand rabbit (male, 3 months old, 3.0 kg) was purchased from the XinHua experimental animal farms (Huadu District, Guangzhou City, China). All procedures were performed in strict accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The protocol was approved by the Institutional Animal Care and Use Committee (IACUC), Sun Yat-sen University (Approval Number: IACUC-DD-16-0901). The rabbit was sacrificed using pentobarbital through intravenous injection. The hair was removed from the skin, and the skin was cut into squares of size 20 mm × 20 mm and average thickness 2.5 ± 0.1 mm.

The procedures of the penetration performance experiment were as follows: (1) A microneedle was bonded on the probe of a force transducer. A piece of fresh rabbit skin was fixed on the fixture using pins under a relative humidity of 80%. (2) Insertion stage: the microneedle was driven toward the fresh rabbit skin by a linear motor with a loading displacement of 1.5 mm and velocity of 0.1 mm s^{-1}. (3) Relaxation stage: the linear motor was stopped when the loading displacement reached 1.5 mm and held at that position for about 1 s. (5) Pull stage: the microneedle was pulled upward from the rabbit skin using the linear motor at a velocity of 0.1 mm s^{-1} and an unloading displacement of 3.5 mm. (6) The force and displacement were synchronously recorded.

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