European Journal of Pharmaceutics and Biopharmaceutics 83 (2013) 224–233

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Spatially discrete thermal drawing of biodegradable microneedles for vascular drug delivery

Chang Kuk Choi [a], Kang Ju Lee [a], Young Nam Youn [b], Eui Hwa Jang [b], Woong Kim [a], Byung-Kwon Min [a], WonHyoung Ryu [a,*]

[a] School of Mechanical Engineering, Yonsei University, Seoul, Republic of Korea
[b] Division of Cardiovascular Surgery, School of Medicine, Yonsei University, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 30 July 2012
Accepted in revised form 25 October 2012
Available online 29 November 2012

Keywords:
Microneedles
Drug delivery
Vascular tissue
Thermal drawing
Biodegradable polymers

ABSTRACT

Spatially discrete thermal drawing is introduced as a novel method for the fabrication of biodegradable microneedles with ultra-sharp tip ends. This method provides the enhanced control of microneedle shapes by spatially controlling the temperature of drawn polymer as well as drawing steps and speeds. Particular focus is given on the formation of sharp tip ends of microneedles at the end of thermal drawing. Previous works relied on the fracture of polymer neck by fast drawing that often causes uncontrolled shapes of microneedle tips. Instead, this approach utilizes the surface energy of heated polymer to form ultra-sharp tip ends. We have investigated the effect of such temperature control, drawing speed, and drawing steps in thermal drawing process on the final shape of microneedles using biodegradable polymers. XRD analysis was performed to analyze the effect of thermal cycle on the biodegradable polymer. Load–displacement measurement also showed the dependency of mechanical strengths of microneedles on the microneedle shapes. *Ex vivo* vascular tissue insertion and drug delivery demonstrated microneedle insertion to *tunica media* layer of canine aorta and drug distribution in the tissue layer.

1. Introduction

Microneedles have demonstrated enhanced efficacy by delivering various therapeutic compounds through skin barriers with advantages such as self-administration, pain-free injection, and enhanced safety [1–3]. Microneedles have typically been fabricated using metals, ceramics, or polymers. Ceramic or metal microneedles have been fabricated by chemical etching or laser cutting [4–9]. On the other hand, polymer microneedles were generally constructed by casting polymer melt or solution in micro-molds [10–14]. However, negative cavities of micro-molds have relatively low aspect ratios (depth over area) that limit the creation of microneedles with high aspect ratio.

Recently, a thermal drawing method was developed to create hollow metal [15] or solid polymer microneedles with high aspect ratio [16,17]. In this method, heated polymer is vertically drawn by a metal pillar structure at a controlled speed. After a cooling step, the neck is fractured by fast drawing, and microneedle structure is formed. Closer investigation into the apex of microneedles fabricated in this way reveals that the fracturing step results in rather flat or elongated apex. Such uncontrolled tip geometry seriously limits the insertion capability of microneedles into target tissues. However, despite the recent development of thermal drawing processes for microneedles, relatively less attention was paid to how sharp tips can be formed when the thermal drawing process is used for microneedle fabrication.

Synthetic biodegradable polymers such as poly (lactic acid) (PLA), poly (glycolic acid) (PGA), or their copolymers, poly (lactic-co-glycolic acid) (PLGA) have been popular for the fabrication of medical implants, drug delivery systems, and tissue scaffolds [18–20]. Biodegradable polymers have also been employed in microneedle fabrication by micro-molding or casting [10–13]. Microneedles made of biodegradable polymers can be left in human body and deliver drugs over an extended period of time depending on their degradation speed and delivery mechanisms. When such biodegradable devices are fabricated by thermal processing, it is important to confirm that the original physical and chemical properties of the materials remain unchanged. In particular, crystallization during thermal processing or hydrolysis from the exposure to humidity due to sudden temperature change during a thermal cycle can easily change the critical properties of biodegradable polymers such as degradation time, molecular weight, and mechanical strength. When thermal drawing is used to fabricate biodegradable microneedles, it inevitably exposes biodegradable polymers to a thermal cycle. The effect of the thermal cycle on the property of biodegradable polymer needs to be monitored before and after the process.

* Corresponding author. School of Mechanical Engineering, Yonsei University, Seoul 120-749, Republic of Korea. Tel.: +82 2 2123 5821.
E-mail address: whryu@yonsei.ac.kr (W. Ryu).

0939-6411/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejpb.2012.10.020

Microneedles have mainly been used to deliver therapeutic molecules through skin as mentioned previously. Our recent work showed the potential of microneedles for drug delivery to vascular tissues to treat atherosclerosis or intimal hyperplasia [17]. Cuff-shaped devices containing an array of microneedles were fabricated and tested *in vivo* for the perivascular delivery of model drugs to the internal layers such as *tunica adventitia* and *media*. Among many challenges, it was the most critical to have microneedles that could penetrate the vascular tissues at a minimal force. The insertion capability was strongly dependent on the strength and tip shape of microneedles. However, regardless of the convenience of the thermal drawing method to fabricate high aspect ratio microneedles, the mechanism of sharp tip formation and the shape optimization for strength improvement were not studied in detail.

In this report, we introduce spatially discrete thermal drawing (SDTD) process to fabricate biodegradable microneedles with sharp tip ends for vascular drug delivery. In this process, temperatures of the top and bottom sides of microneedles are controlled separately to allow for more precise modulation of the shape of microneedles including tip geometry. Configuration of an SDTD system is explained in detail and the operation steps are discussed. Then, the formation of microneedle tips is investigated under various thermal boundary conditions, and the dependency on drawing speeds is also discussed. First, standard "cold drawing fracture (CDF)" mechanism is demonstrated, and the resulting shape is discussed. This neck fracture method produces either a flat tip end or an elongated tip depending on the fracture speed. To avoid the formation of such less ideal geometry for microneedle tips, heating from micro-pillars, is demonstrated and analyzed as an improved way to form the sharp apex of microneedles. As an alternative way to adjust the tip shape of microneedles, post-annealing is employed, and the effect on the final shape is analyzed. Furthermore, in order to investigate the effect of thermal processes on PLGA, X-ray diffraction (XRD) analysis was performed, and the results were discussed. Using the SDTD process, microneedles of two different shapes (slender and bullet-shaped microneedles) were fabricated, and their mechanical strengths were measured and compared for their insertion into vascular tissues such as artery and vein *ex vivo*.

2. Materials and methods

2.1. Materials

Biodegradable polymers, 90/10PGLA (M_w = 268,267 Da) and 30/70PGLA (M_w = 69,900 Da), were generously donated by Samyang Corporation, Republic of Korea. 50/50PLGA (5050 DLG 1A, M_w = 5.7 kDa) was purchased from Lakeshore Biomaterials, Birmingham, AL. Dimethyl sulfoxide (product no. D0457, DMSO) and rhodamine B (product no. R0050, RB) were purchased from Samchun Chemical Inc., Republic of Korea. Stainless steel pillar array structures were fabricated by electrical discharge machining (EDM). Each pillar had the height of 300 μm and the diameter of 300 μm. The pillars were formed in a 3 × 3 array.

2.2. SDTD system

A SDTD system was custom-built and comprised of a heating/cooling substrate (aluminum), a micro-pillar (stainless steel), and a stereo microscope (Fig. 1). The temperature of the heating/cooling substrate was controlled in a range between a room temperature and 200 °C by a temperature controller. The cooling of the substrate was controlled by water cooling system. The substrate was moved manually at a minimum step of 2 μm using a micro-manipulator. A micro-pillar was linked to an automatic micro-z-stage and moved up and down at a preset speed. A separate thermal controller was connected to the micro-pillar to adjust the temperature of the micro-pillar between a room temperature and 260 °C.

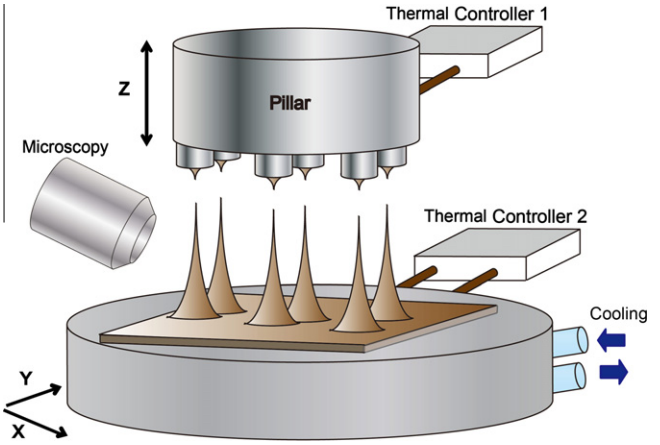

Fig. 1. Schematic diagram of spatially discrete thermal drawing system. The system is comprised of a bottom substrate, micro-pillar, and stereo microscope. Temperatures of bottom substrate and micro-pillar are separately monitored and controlled. Heat is applied by resistive heater units, and cooling of bottom substrate is regulated by water cooling system. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.3. Microneedle fabrication

Microneedles were fabricated using either conventional thermal drawing or SDTD process comprised of three steps. In thermal drawing, first, PLGA film on a bottom substrate was heated up to 135 °C, and then, micro-pillar is lowered down to make a contact on the heated PLGA. The PLGA is gradually drawn vertically by the micro-pillar until a neck is formed. Then, the bottom substrate is quenched below the glass transition temperature (T_g) of PLGA. After the drawn polymer is solidified, rapid lifting of micro-pillar breaks the neck, and microneedles are formed. On the other hand, in SDTD, after drawing step, bottom substrate is quenched, but the micro-pillar remains heated at 135 °C or higher temperature. Continuous heating form the pillar side separates the neck of drawn polymer due to "surface energy minimization" rather than mechanical breakage in the thermal drawing process.

2.4. Tissue insertion test

Abdominal aorta was harvested after Mongrel dogs were sacrificed. The harvested vessels were fixed in a custom jig for insertion testing. Microneedles were gradually lowered down by a micromanipulator until the insertion occurs. After the insertion test, the vascular tissue samples were sectioned transversely and fixed in 10% neutral buffered formalin. The fixed specimens were embedded and sectioned with paraffin. The sections were stained with hematoxylin and eosin (H&E) for histopathological imaging. Fluorescent images were obtained with a standard filter set for RB. The images were analyzed using a computer-assisted image analyzer program (DP Controller, OLYMPUS). All animal experiments were performed in accordance with the "Guide for the Care and Use of Laboratory Animals" of Yonsei laboratory animal research center and a protocol (no. 2011-0070) approved by Institutional Animal Care and Use Committee.

2.5. SEM and XRD analysis

SEM images were taken using Hitachi S-4300 after samples were sputter-coated with Pt. XRD analysis was performed to