Acta Biomaterialia xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Acta Biomaterialia

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

Full length article

Rapidly separating microneedles for transdermal drug delivery

Dan Dan Zhu [1], Qi Lei Wang [1], Xu Bo Liu, Xin Dong Guo *

Beijing Laboratory of Biomedical Materials, College of Materials Science and Engineering, Beijing University of Chemical Technology, Beijing 100029, PR China

ARTICLE INFO

Article history:
Received 28 January 2016
Received in revised form 12 May 2016
Accepted 2 June 2016
Available online xxxx

Keywords:
Microneedle
Quick separation
Biodegradable
Drug delivery

ABSTRACT

The applications of polymer microneedles (MNs) into human skin emerged as an alternative of the conventional hypodermic needles. However, dissolving MNs require many minutes to be dissolved in the skin and typically have difficulty being fully inserted into the skin, which may lead to the low drug delivery efficiency. To address these issues, we introduce rapidly separating MNs that can rapidly deliver drugs into the skin in a minimally invasive way. For the rapidly separating MNs, drug loaded dissolving MNs are mounted on the top of solid MNs, which are made of biodegradable polylactic acid which eliminate the biohazardous waste. These MNs have sufficient mechanical strength to be inserted into the skin with the drug loaded tips fully embedded for subsequent dissolution. Compared with the traditional MNs, rapidly separating MNs achieve over 90% of drug delivery efficiency in 30 s while the traditional MNs needs 2 min to achieve the same efficiency. With the *in vivo* test in mice, the micro-holes caused by rapidly separating MNs can heal in 1 h, indicating that the rapidly separating MNs are safe for future applications. These results indicate that the design of rapidly separating dissolvable MNs can offer a quick, high efficient, convenient, safe and potentially self-administered method of drug delivery.

Statement of Significance

Polymer microneedles offer an attractive, painless and minimally invasive approach for transdermal drug delivery. However, dissolving microneedles require many minutes to be dissolved in the skin and typically have difficulty being fully inserted into the skin due to the skin deformation, which may lead to the low drug delivery efficiency. In this work we proposed rapidly separating microneedles which can deliver over 90% of drug into the skin in 30 s. The *in vitro* and *in vivo* results indicate that the new design of these microneedles can offer a quick, high efficient, convenient and safe method for transdermal drug delivery.

1. Introduction

Transdermal drug delivery is an attractive approach for the delivery of therapeutic agents because it can avoid the emotional trauma and pain associated with injections, reduce the risk of needle-stick injuries, increase patient compliance, improve bioavailability, and reduce overall doses [1–3]. Conventional plaster patches can provide steady, controlled drug delivery [4], however, it generally takes several hours for people wearing the patches to slowly administer drugs [5]. Moreover, only a limited number of molecules have been successfully delivered transdermally to date due to the existence of stratum corneum [6]. Thus, various approaches such as chemical enhancers, electricity, and ultrasound are being explored to improve the transdermal drug delivery by disrupting the stratum corneum structure [7–9]. However, these methods generally require skin permeabilization before the drug patch application, resulting in the difficulties in practice and limited success [10]. A new approach to transdermal drug delivery that acts as a bridge between the user-friendliness of patches and the broad effectiveness of hypodermic needles has recently received much attention [11]. Needles of microns dimensions arose at the moment as a minimally invasive alternative to increase skin permeability and enhance transdermal drug delivery [12]. In the past years, some kinds of microneedles (MNs) were developed and used for transdermal drug delivery, such as solid MNs for tissue pretreatment, drug-coated MNs, hollow MNs, and dissolving MNs [13,14].

Solid MNs, usually fabricated from silicon [15] or metal [16,17], are used to pretreat the skin to make micro channels facilitating the permeation of drug into the skin [18]. Metal MNs coated with

* Corresponding author.
E-mail address: xdguo@buct.edu.cn (X.D. Guo).
[1] They contributed to the work equally.

http://dx.doi.org/10.1016/j.actbio.2016.06.005
1742-7061/

drug have been used to administer macromolecular drugs such as parathyroid hormone [19], influenza vaccine [20] and other compounds [21]. Dissolution of the drug coated on the tip of MNs in the skin takes a number of minutes, after which the metal MNs are discarded as biohazardous sharp waste [22]. In addition, the fabrication process of coated MNs are complicated and the amount of drug coated onto the MNs tips are difficult to be precisely controlled, which may lead to improper drug administration [23].

Alternatively, dissolving MNs made completely out of water-soluble and biodegradable polymer that encapsulates the drug are designed as an improvement over coated MNs because after the dissolution there will leave behind no sharps waste. Traditional MNs are usually fabricated by using micromolds filled with drug solutions and polymer/sugar gels, followed by drying and stripping [24–30]. However, dissolving MNs usually require many minutes to dissolve in the skin and typically have difficulty being fully inserted into skin limited by the mechanical weakness of water-soluble excipient and the skin deformation under tension [31]. The incomplete dissolution of the MNs could induce low drug delivery efficiency and the waste of drug [32,33]. Also, people will take many minutes or even hours [34] to wear MN patches to ensure the full drug release, which leads to the inconvenient application of the dissolving MNs. To address these issues, separable arrowhead MNs were proposed with a dissolving pyramid-shaped MN on the top and a metal shaft on the bottom [35]. This metal shaft served as a structural support which can overcome the skin deformation and separate from the arrowhead pyramidal MN within seconds when inserted into skin.

In this study, we present rapidly separating MNs combining the good water solubility of polymer dissolvable MNs and the good mechanical property of polymer solid MNs instead of metal materials, which can be expediently fabricated and eliminate non-biodegradable waste. The rapidly separating MN mounts a water-soluble MN encapsulating drug onto an insoluble solid polymer MN, which served as mechanically strong spacer that overcomes skin deformation during MN insertion. When fully embedded into the skin, the dissolving drug-loaded MNs can be completely exposed in body fluid environment and contacted with skin's interstitial fluid. Once the polymer gels in the connection of dissolving MNs and solid MNs dissolved (within seconds), the solid MNs on the patches can be easily peeled off against skin. And the time required to administer drug will be greatly shortened compared to the traditional dissolving MNs. After separation, the remaining solid MNs on the patch can be safely discarded without the need for biohazardous waste disposal systems. In addition, both of the upper water-soluble MN and supporting solid polymer MN were fabricated using mold casting method, which was simple and helpful to provide a promising mass production for the future application MNs.

2. Materials and methods

2.1. MN mold

Rapidly separating MNs consist of two parts, the polymer dissolving MNs encapsulating drug and the solid polymer MNs served as the strong spacer, which can facilitate the full insertion of the upper dissolving MNs. To fabricate rapidly separating MNs, a polydimethylsiloxane (PDMS, Sylgard 184, Dow Corning, Midland, MI) mold was firstly fabricated using laser and molding techniques to generate a 5×5 array of conical MN cavities [36]. The cavities for dissolving MNs was 600 μm in deep and 300 μm in diameter at the base and tapered to a tip of 15 μm in width. For solid MNs, the cavities measured 550 μm in length, 250 μm in diameter at the base, and 10 μm in width at the tip. The center-to-center spacing between cavities was 750 μm.

2.2. Preparation of MN matrix

To avoid producing biohazardous waste, materials for the MN bases and drug-loaded tips were prepared from biodegradable polylactic acid (PLA) (3051D), which was mechanically robust for skin insertion. Sulforhodamine B (Molecular Probes, Eugene, OR) was used as the model drug. To encapsulate the drug in the tip of dissolving MNs, a polymer matrix solution were then prepared. Briefly, a mixture of polyvinyl alcohol (PVA) (MW2000 Da, ACROS Organics, Geel, Belgium) and sucrose (Sigma-Aldrich, St Louis, MO) at a weight ratio of 8:6 was dissolved in DI water with heating at 90 °C for 6 h, and then cooled to room temperature (RT) to obtain a 48% (w/w) PVA/sucrose gel.

2.3. Fabrication of rapidly separating MNs

Molten PLA was cast onto the PDMS mold under vacuum at −85 kPa for 2 h at 200 °C to fabricate the solid MN bases. The PLA MNs were then cooled to room temperature and removed from the mold for further use. A casting process was used to prepare the upper drug loaded dissolving MNs. Briefly, the sulforhodamine B solution (1 mg/ml) was applied to the PDMS mold surface under vacuum at −85 kPa for 5 min. residual drug solution on the mold surface was removed by pipetting and saved for later use. The drug solution loaded in the mold cavities was then dried at room temperature under vacuum at −85 kPa for 20 min. The PVA/sucrose gel was then cast onto the mold under vacuum at −85 kPa for 30 min at room temperature. Residual gel on the mold surface was cleaned and a PLA solid MN array was aligned manually with gentle force applied backing against the mold. After the alignment, the whole system was freeze-dried (Boyikang freeze dryer, VFD-1000, Beijing) using the following program: the samples were frozen at −40 °C for 1 h, and then vacuumed at −101 kPa at −40 °C for 12 h, 0 °C for 1 h, and 25 °C for another 12 h. Finally, the dried rapidly separating MN array was gently peeled out of the mold and examined using a stereomicroscope (SZX7, Olympus, Japan).

2.4. Mechanical performance test

Mechanical failure tests of rapidly separating, traditional and solid PLA MNs were measured by a displacement-force test machine (Mark-10, Force Gauge Model, USA). Briefly, single MN was attached to the rigid stainless steel station, and the sensor probe pressed the MN at a speed of 0.1 mm/s for a transverse force application. The displacement-force test machine recorded the transverse force required to move the probe as a function of distance. Both the needle force and displacement were continuously measured until the MN was broken. After each test, the MN was visually inspected and imaged under a microscope to confirm that the MN had deformed and failed.

2.5. In vitro skin penetration

To evaluate the *in vitro* skin insertion capability of rapidly separating MNs, sulforhodamine B loaded MN patches were inserted with IACUC approval into porcine cadaver skin (Pel-Freez, Rogers, AR) using an in-house made applicator. Before insertion, porcine cadaver skin was processed by removing hair using a razor and subcutaneous fat using a scalpel. Then the MN patch was manually pressed against the skin and then embedded for a specific time to enable the separation by dissolution. After insertion, the patch was peeled off. The histological sections of the skin were then excised and observed. To determine the insertion depth, the skin samples

Please cite this article in press as: D.D. Zhu et al., Rapidly separating microneedles for transdermal drug delivery, Acta Biomater. (2016), http://dx.doi.org/10.1016/j.actbio.2016.06.005