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Systemic delivery of artemether by dissolving microneedles

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ABSTRACT

Dissolving microneedles (DMNs) based transdermal delivery is an attractive drug delivery approach with minimal invasion. However, it is still challenging to load poorly water-soluble drugs in DMNs for systemic delivery. The aim of the study was to develop DMNs loaded with artemether (ARM) as a model drug, to enable efficient drug penetration through skin for systemic absorption and distribution. The microconduits created by microneedles were imaged by confocal laser scanning microscopy (CLSM), and the insertion depth was suggested to be about 270 μm. The maximum amount of ARM delivered into skin was 72.67 ± 2.69% of the initial dose loaded on DMNs preparation. Pharmacokinetics study in rats indicated a dose-dependent profile of plasma ARM concentrations, after ARM-loaded DMNs treatment. In contrast to intramuscular injection, DMNs application resulted in lower peak plasma levels, but higher plasma ARM concentration at 8 h after administration. There were no significant difference in area under the curve and bioavailability between DMNs group and intramuscular group ($P > 0.05$). Pharmacodynamics studies performed in collagen-induced arthritis (CIA) rats showed that ARM-loaded DMNs could reverse paw edema, similar to ARM intramuscular injection. In conclusion, developed DMNs provided a potential minimally invasive route for systemic delivery of poorly water-soluble drugs.

1. Introduction

Transdermal drug delivery as a non-invasive route is an attractive alternative to parenteral drug delivery. In the meanwhile, the enzymatic degradation in the gastrointestinal and liver related to oral delivery can be avoided by transdermal delivery. However, the potent barrier of the uppermost layer of the skin, the stratum corneum, hampers a board range of molecules permeating across the skin (Prausnitz, 2004; Prausnitz and Langer, 2008). To overcome this barrier, microneedles (MNs) consisting of micron-scale needles have been developed as a minimally invasive, potentially painless strategy to breach the stratum corneum barrier function (Kim et al., 2012; Tuan-Mahmood et al., 2013). There are different types of microneedles, including solid microneedles, hollow microneedles, coated and dissolving microneedles (van der Maaden et al., 2012). Among them, dissolving microneedles (DMNs) have the unique advantages that they have no risk of leaving harmful material in the skin and do not generate sharp needle waste. Moreover, the low cost and mild preparation conditions of DMNs make industrialization easier to achieve. Therefore, DMNs attracted numerous attentions in the recent years. A large variety of drugs, such as alendronate (Katsumi et al., 2012), ibuprofen sodium (McCrudden et al., 2014), leuprolide acetate (Ito et al., 2011), insulin (Donnelly et al., 2012; Ito et al., 2010; Ling and Chen, 2013), low molecular weight heparin(Ito et al., 2008), human growth hormone, desmopression (Fukushima et al., 2011), exenatide (Zhu et al., 2014) and vaccines (Qiu et al., 2015; Sullivan et al., 2010) were delivered using DMNs.

As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water-soluble. Approximately 40% of new pharmacologically active lipophilic compounds are poorly water-soluble (Dahan and Hoffman, 2008). Despite the large number of compounds developed for DMNs based (trans)dermal delivery, most of the compounds are hydrophilic, relatively little attention has been paid to hydrophobic compounds. A model hydrophobic dye, Nile red, was pre-formed in poly-lactide-co-glycolic acid (PLGA) nanoparticles (Donnelly et al., 2010). Then DMNs were prepared from aqueous blends of copolymers and Nile red-loaded PLGA particles. Local delivery of

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Nile red was observed in excised porcine skin using the DMNs. However, the amount of lipophilic dye delivered into skin was too small to be of practical concern. Another attempt for DMNs mediated lipophilic drug delivery was conducted on all-trans retinoic acid (ATRA) (Hiraishi et al., 2013a,b). Local delivery of ATRA was realized in hairless mice for seborrheic keratosis. However, further investigation of systemic delivery was not performed. Ito et al. evaluated the effect of lipophilicity on the bioavailability (BA) of drugs after administration by DMNs (Ito et al., 2012). BA decreased from 95.1% to 38.4% as the log P value of drugs increased from −1.95 to 1.73. However, it has to be noticed that, in this study drugs were simply mixed with the aqueous chondroitin sulfate solution. The poor BA of lipophilic drugs might be due to the simple formulation design. As we know, DMNs are typically made of water-soluble materials, such as chitosan (Chen et al., 2012), carboxymethyl cellulose (Lee et al., 2011; Lee et al., 2008; Raphael et al., 2010), sodium hyaluronate (Hiraishi et al., 2013b; Liu et al., 2014), chondroitin sulfate (Ito et al., 2011; Ito et al., 2010) (Fukushima et al., 2011), polyvinylpyrrolidone (Guo et al., 2013; Sullivan et al., 2010; Sullivan et al., 2008), polyvinyl alcohol (Wendorf et al., 2011), silk (Tsioris et al., 2012) and poly (methylvinylether maleic anhydride) (McCrudden et al., 2014) (Garland et al., 2012) (Gomaa et al., 2012). Compared to hydrophilic drugs, there is a worse dispersion of hydrophobic drugs in the aqueous solution of water-soluble materials. From above, novel formula design and detail study are needed to investigate the possibility of loading poorly water-soluble drug into DMNs for systemic delivery.

The aim of this work was to develop DMNs loaded with a poorly water-soluble drug for systemic delivery. Artemether (ARM) was selected as the model drug with high lipophilicity (Log $P = 3.5$) (Mazzone et al., 2014) and poor water solubility (0.018 μg/mL in distilled water containing 1% sodium lauryl sulfate). The oral formulation of ARM is rapidly but incompletely absorbed whereas parenteral oily formulation leads to pain on injection and poor patient compliance (Karbwang et al., 1997). In our study, ARM-loaded DMNs were prepared followed by characterization of mechanical property, insertion depth and drug loading capacity. And then, the dissolution of DMNs in rat skin and in vitro transdermal drug delivery after DMNs application was investigated. Finally, the in vivo pharmacokinetics and effect of ARM protected against collagen-induced arthritis in rats after DMNs application were examined.

2. Materials and methods

2.1. Materials and subjects

Oligomeric sodium hyaluronate (HA-Oligo) was obtained from Bloomage Freda biopharm Co., Ltd. (Shandong, China). Polydimethylsiloxane (PDMS, Sylgard 184) was purchased from Dow Corning (USA). Artemether (ARM), dihydroartemisinin (DHA) and artemisinin (ART) were all bought from Chongqing Huali Wulingshan Medicine Co., Ltd. (China). Acetonitrile, methanol, ethanol and calcein were purchased from sigma (USA). Ammonium acetate was obtained from Dikma Technologies Inc. (China).

Male Wistar rats (6 weeks old, 180–220 g), were purchased from Beijing Xinglong Experimental Animals Ltd., Co. (China). All rats were housed under pathogen-free condition. All animal experiments were conducted following the Guide for the Care and Use of Laboratory Animals (Eighth edition, 2011).

2.2. Fabrication of microneedle master structure and inverse mold

Microneedle master structure was manufactured by micro-milling. As shown in Fig. 1A, the microneedle master, smooth with sharp tips, was made of stainless steel. The master structure consists of 169 (13 × 13) pyramidal microneedles. Each microneedle is a pyramid with 380 μm in base length and 680 μm in height. The inverse Polydimethylsiloxane (PDMS) mold was made by casting the mixture of dimethyl siloxane and initiator onto the microneedle master structure.

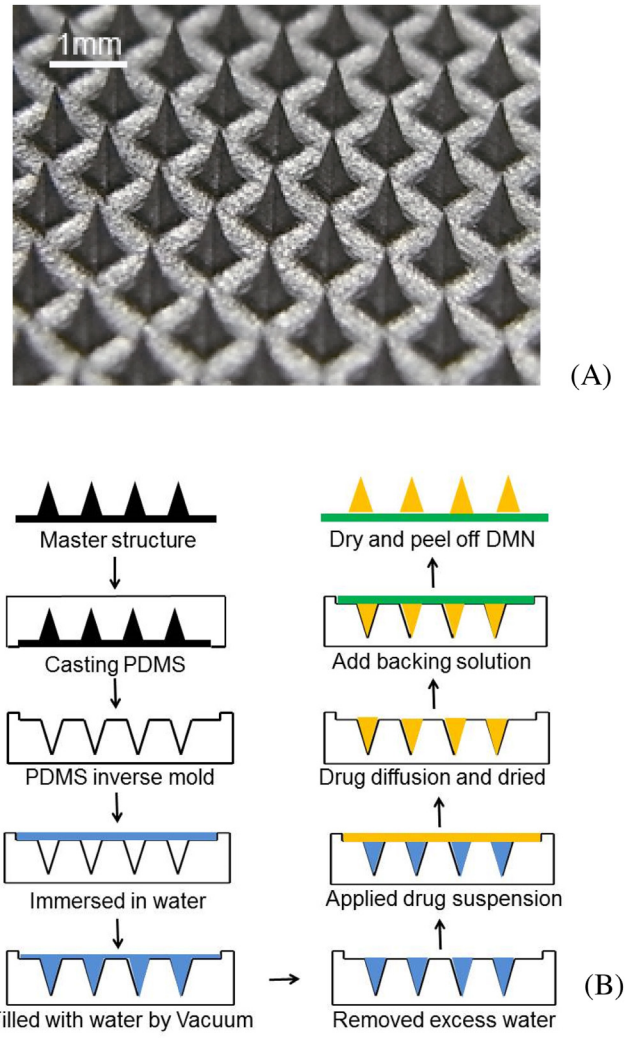

Fig. 1. (A) Microneedle master structure fabricated by electrical discharge machining technology. (B) Preparation scheme of ARM-loaded DMNs.

2.3. Fabrication of dissolving microneedles

Oligo-HA was used as the polymer base of the DMNs in our study. HA is normally used as a common ingredient in skin care products with high biocompatibility. Hirobe et al. (2013) reported that application of HA-based microneedles in human subjects for 6 h caused slight erythema in a few subjects. And most reactions disappeared within 30 days. Severe systemic adverse events were not observed. It indicated HA-based DMNs could be safely applied to the human skin. In our study, the repeated use might cause deposition of HA in skin. However, considering the relatively small molecular of oligo-HA, the possibility of deposition was lower than regular HA.

Since ARM was almost insoluble in water, it was challenge to incorporate it uniformly into water soluble materials. Hence, aqueous solution of HA-oligo, and calcein (1 mg/ml) if added, and ethanol solution of ARM were mixed to form a suspension for