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Investigation on fabrication process of dissolving microneedle arrays to improve effective needle drug distribution

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ABSTRACT

The dissolving microneedle array (DMNA) offers a novel potential approach for transdermal delivery of biological macromolecular drugs and vaccines, because it can be as efficient as hypodermic injection and as safe and patient compliant as conventional transdermal delivery. However, effective needle drug distribution is the main challenge for clinical application of DMNA. This study focused on the mechanism and control of drug diffusion inside DMNA during the fabrication process in order to improve the drug delivery efficiency. The needle drug loading proportion (NDP) in DMNAs was measured to determine the influences of drug concentration gradient, needle drying step, excipients, and solvent of the base solution on drug diffusion and distribution. The results showed that the evaporation of base solvent was the key factor determining NDP. Slow evaporation of water from the base led to gradual increase of viscosity, and an approximate drug concentration equilibrium was built between the needle and base portions, resulting in NDP as low as about 6%. When highly volatile ethanol was used as the base solvent, the viscosity in the base rose quickly, resulting in NDP more than 90%. Ethanol as base solvent did not impact the insertion capability of DMNAs, but greatly increased the *in vitro* drug release and transdermal delivery from DMNAs. Furthermore, the drug diffusion process during DMNA fabrication was thoroughly investigated for the first time, and the outcomes can be applied to most two-step molding processes and optimization of the DMNA fabrication.

1. Introduction

Microneedles are designed to penetrate through the stratum corneum into the epidermis but not to pierce the dermis layer which harbors sensory nerve endings (Donnelly et al., 2010). Therefore, microneedles can enhance the transport of drug across the skin in a manner of painless or minor pain (Bariya et al., 2012). Being as efficient as hypodermic injection and as safe and patient compliant as conventional transdermal delivery, the microneedles offer a novel, unlimited potential approach for transdermal delivery of biological macromolecular drugs and vaccines (Kim et al., 2012). Generally, there are four strategies to fabricate microneedles from silicon, metals, ceramics, polymers, and other materials (Kim et al., 2012) for transdermal drug delivery (van der Maaden et al., 2012): (1) 'poke and flow' for hollow microneedles by delivering drug through the hollow needles; (2) 'poke and patch' for silicon or metal solid microneedles by piercing through the skin and creating microchannels for administrating a medicated preparation; (3) 'coat and poke' by piercing the skin with drug coated solid microneedles; and (4) 'poke and release' for dissolving microneedles made from polymers or polysaccharides by releasing the encapsulated drug during the dissolution of microneedles.

Numerous researches have been conducted on dissolving microneedle arrays (DMNAs) since the first trial ten years ago (Bediz et al., 2013; Ito et al., 2006; Ke et al., 2012; Lee et al., 2011a,b; Miyano et al., 2005; Ryan et al., 2012; Sullivan et al., 2010; Tsioris et al., 2012; Yang et al., 2012). The most common fabrication method for DMNAs is micromoulding (Donnelly et al., 2011; Ito et al., 2010; Ke et al., 2012; Lee et al., 2008; Tsioris et al., 2012), which includes the production of mold and the molding of microneedles from dissolving materials.

High-temperature molding (Donnelly et al., 2009; Miyano et al., 2005), UV photo-polymerization curing (Sullivan et al., 2008), and aqueous solution casting (Donnelly et al., 2011; Ito et al., 2010;

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Sullivan et al., 2010) have been used for molding microneedles from dissolving materials. These processes involved radiation source, polymerizing reagents, or elevated temperatures, which could impair the stability of biomacromolecular drugs and cause skin irritation (Donnelly et al., 2010; Kim et al., 2012). Therefore, most DMNAs were recently produced by filling the mold with aqueous blend of drug and excipients and then drying under mild temperatures. The typical process includes pouring the polymer solution into female molds (Lee et al., 2008; You et al., 2011), filling the microcavities of the mold under centrifugation (Donnelly et al., 2011; Lee et al., 2008), vacuum (Chu et al., 2010; Sun et al., 2013; You et al., 2011) or pressure (Ito et al., 2012), and finally drying under ambient conditions, centrifugation, or pressure.

For DMNA, drug is delivered through dissolving of the needles that pierce into the skin (Sullivan et al., 2008), hence only the drug encapsulated in the needle portion can be efficiently delivered and the drug in the base may be wasted. An idea DMNA should exclusively contain drug in the needles (Chu et al., 2010).

Various methods were reported (Ito et al., 2011; Lee et al., 2008; Ling and Chen, 2013; Moga et al., 2013; Park et al., 2007) to fabricate DMNA with medicated needles and blank base. A general method used in many researches (Lee et al., 2011a,b; Ling and Chen, 2013; Naito et al., 2012) is two-step molding (Fig. 1), in which a drug-containing solution was cast for needles and a drug-free solution was molded for the base. However, this fabrication process may create a drug concentration gradient between the needle portion and the base, which will induce drug diffusion from the needles to the base (Ritger and Peppas, 1987a,b) and change the drug distribution in DMNA. Unfortunately, the ultimate drug content in needle portion of DMNA was rarely measured in the previous studies (Ito et al., 2012; Ling and Chen, 2013; Naito et al., 2012; Sullivan et al., 2008) or only indicated by the change of color tracer (Chu et al., 2010; Sullivan et al., 2008). And the distribution of color tracer was seriously influenced by polymer concentration in the casting solution (Chu et al., 2010).

Drug diffusion would not only reduce the effective drug loading in DMNAs and cause drug waste, but more seriously, it would cause indeterminacy of drug loading in the DMNA and lead to serious problems in manufacture and clinical application. To deal with the drug diffusion, air bubble was introduced at the bottom of the needle during fabrication, keeping drug at the needle tip (Chu et al., 2010). However, it was reported the presence of bubbles decreased the mechanical strength of the microneedles (Chu et al., 2010).

By far, preparation of an optimized DMNA with controlled drug distribution and adequate mechanical strength is still a challenge. Accurate drug positioning in DMNA is the foundation for precise quantification and effective utilization of drug, but the research attempt was hindered due to the complexity of drug distribution process during DMNA fabrication. Therefore, this study focused on the drug migrating behaviors inside various DMNAs during the molding process and determination of the key factors influencing the drug distribution in DMNAs.

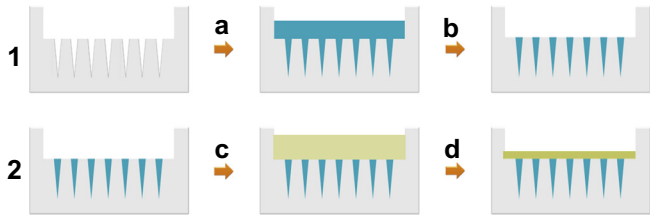

Fig. 1. Schematic of two-step molding process for dissolving microneedle arrays (DMNAs). (a) Filling the female mold with a drug-containing solution; (b) removing residual solution from the surface; (c) casting a drug-free solution on the mold; and (d) solidification under mild conditions to form DMNAs.

2. Material and methods

2.1. Materials

A series of polyvinyl pyrrolidone (PVP) (PVP K30, PVP K90) were obtained from BASF (Ludwigshafen, Germany). Dextran (Dex) was purchased from Aladdin (Shanghai, China). Metoprolol tartrate (MT) was obtained from Hanfang pharm. co. (Guangzhou, China). Fluorescein isothiocyanate (FITC), bovine serum albumin (BSA) and Trypan blue were purchased from Sigma–Aldrich (St Louis, MO, USA). Polydimethylsiloxane (PDMS, Sylgard 184 Silicone Elastomer Kit) was obtained from Dow Corning (Midland, MI, USA). All other materials were of reagent grade and used as received.

2.2. Fabrication of molds

A brass master mold of 100 (10 × 10) conical microneedles with 300 μm in base diameter, 800 μm in height, and 900 μm tip-to-tip space was made using micromilling technique, which was managed by computer aided manufacturing (CAM) according to the precision design drawing using computer aided design (CAD).

Female molds were made from PDMS by exactly inversely replicating the master structures. This was done by pouring defined amount of PDMS monomer and curing agent mixture (10:1 w/w) over the brass master mold and allowing the polymer to cure at 80 °C for 2 h. The obtained PDMS molds were repeatedly used to make DMNAs.

2.3. Preparation of medicated matrix material for needle portion of DMNAs

Deionized (DI) water was used as the solvent of the needle portion in view of the drug stability. Metoprolol tartrate (MT) with the molecular weight of 684.82 was used as a hydrophilic model drug because it is very soluble in water and freely soluble in alcohol. MT (12.5 mg and 2.5 mg) was dissolved in 50 μl of DI water to form drug solutions MT-h and MT-l with higher and lower drug content respectively. NaN_3 (0.05% w/v) was added as the preservative and biocide. Then the polymeric excipient (12.5 mg) was added in the drug solution and the mixture swelled overnight to form medicated needle solution. Several biocompatible and biodegradable polymeric materials such as Dextran, PVP K30, and PVP K90 were used as needle excipients.

Bovine serum albumin (BSA) with the molecular weight of about 66 kDa was used as the model protein to study the migration of macromolecular drug inside DMNAs. For content determination, BSA was fluorescently labeled with FITC using the method described in the literature (Zou et al., 2007). Dry powder of FITC-labeled BSA (FITC-BSA) was obtained through lyophilization. Following the above procedure, FITC-BSA-h/Dex glue with high concentration of FITC-BSA (12.5 mg) and excipient Dex was prepared.

2.4. Preparation of blank matrix material for base portion of DMNAs

DI water and ethanol were employed as solvents with different solvation properties and volatility to prepare the base blank matrixes. PVP K30 and PVP K90 with different molecular weights were dissolved in the solvents to form base solutions.

Base solutions K90 W and K90E were prepared by adding PVP K90 (50 mg) into 150 μl of DI water and ethanol respectively and swelling overnight. Similarly, more PVP K90 (100 mg) was added to make more viscous base solutions K90 W-h and K90E-h, and PVP K30 was used similarly to prepare base solution with lower molecular weight.