Optimization of Dissolving Microneedle Delivery System through Simplifying Fabrication and Investigating Drug Release

Qingqing Wang, Xin Pan, Ying Huang, Chune Zhu, Min Huang, Peiqing Liu, Chuanbin Wu

School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou, P R China
cbwu2000@yahoo.com

ABSTRACT SUMMARY
A feasible method was established to simplify and diversify the fabrication process of dissolving microneedle arrays. Two representative sharps, a stable hydrophilic model drug, and several dissolving polymers were selected to prepare microneedle arrays. Investigation on factors influencing the drug release and permeation was carried out to determine the optimal sharp and structural material for establishing a base preparation. Further research will focus on dissolving microneedles for delivery of hydrophilic biomacromolecular drugs.

INTRODUCTION
Combining the efficient delivery of injections, the safety, patient compliance of the patch, and the low manufacturing cost, the dissolving microneedle arrays offer a novel, unlimited potential approach for transdermal delivery of biological macromolecular drugs and vaccines. Numerous researches have been carried out on dissolving microneedle arrays since the first trial ten years ago. However, the studies were focused on formation of needles and drugs delivered. Most of the master molds were produced by lithographic and laser etching technologies which were complex, expensive, imprecise, and incapable for heteromorphosis mold. As an emerging delivery system, the dissolving microneedle arrays undoubtedly require further studies to develop a versatile basis for property characterization and influencing factor investigation.

In this study, fabrication of master mold was simplified and the factors influencing the drug delivery from dissolving microneedle arrays were investigated.

EXPERIMENTAL METHODS
To make microneedle arrays, various polymeric materials were dissolved into deionized water and filled into the polydimethylsiloxane (PDMS) female mold of the master mold produced by micromilling technology. Centrifugation was employed to ensure the filling of micro cavities, followed by drying overnight in an oven.

Venlafaxine Hydrochloride (VH) was used as a hydrophilic model drug to evaluate the release properties of the microneedle arrays with different sharps and structure materials. Drug glue solution was produced by adding the structure material into drug solution at varying ratios (1:1, 1:2, 1:3) and swelling overnight. The blank glue solution was prepared by replacing drug solution with deionized water.

The sharps of obtained microneedles were observed and measured by optical microscopy and their mechanical properties were tested by compression force and skin insertion experiments.

The drug loading and dissolution profiles were tested in a vial that contained 10 ml of pH 5.8 PBS under magnetically stirring at 250 rpm and temperature of 37 °C. The microneedle arrays floated on the solution by adhering to a coverslip using the Sotch® restickable strip. The concentration of VH in the receptor medium was determined by HPLC.

RESULTS AND DISCUSSION
Two master molds in different sharps (type A and B) were produced by micromilling technology, which was good for fine processing especially for heteromorphosis mold that was hardly produced by lithographic and laser etching technologies.

Based on material screen, Povidone (PVP) and Dextran (Dex) were selected as the microneedle materials for the further
characterization due to their excellent mouldability. The prepared microneedles had the cone sharp about 800 μm in height and 300 μm in base diameter for type A, and the cone-cylinder sharp about 300 μm in height of cone-segment, 500 μm of cylinder-segment and 200 μm in base diameter for type B. The two types of arrays had the same total volume according to the design (Figure 1).

![Type A and Type B microneedle arrays](image1)

Figure 1. Sharps of dissolving microneedle arrays.

Compression force and skin insertion tests indicated that the failure force of the type A-PVP microneedles was about 2.2 N per needle, which was 30 fold of the force needed to insert microneedles into the excised rat skin. The microneedle arrays made of Dex performed better in permeating the miniature pig skin than those made of PVP as indicated by the pinhole counts in Figure 2. There was no significant decrease in the pinhole numbers as the ratio of Dex/drug changed from 1:1 (Dex-11) to 1:3 (Dex-13), suggesting little influence of Dex/drug ratio to the array penetration.

![Pinhole Counts](image2)

Figure 2. Number of Pinholes created in miniature pig skin by microneedle arrays (n=3).

For the same type of sharps, microneedle arrays made of Dex showed faster release than those made of PVP. For the same material PVP, type B arrays with smaller base diameter accelerated the drug release (Figure 3). Both structure materials and sharps affected the release rate.

![Cumulative Release](image3)

Figure 3. Cumulative release of VH from microneedle arrays with different sharps and structure materials (n=3).

Figure 4a indicated that Dex/drug ratio in microneedles had little effect to the release rate of VH, but the cumulative release amount increased obviously with the reducing of Dex content (Figure 4b). This can be explained by the drug loading in microneedle arrays, which was dependent on the total volume of microneedles and the concentration of drug glue, and thus was influenced by contents of both drug and structure material. As a relatively greater variation in pinhole numbers was observed for Dex-13 arrays, Dex-12 with the Dex/drug ratio of 1:2 was chosen as the optimal formulation for microneedle arrays.

![Cumulative Release Rate and Amount](image4)

Figure 4. Cumulative release rate (a) and amount (b) of VH with different Dex/drug solution ratios (n=3).

**CONCLUSION**

Micromilling technology was employed to simplify the preparation of the master mold for microneedles. Microneedle arrays with type B sharp showed faster drug release. Dex with the Dex/drug solution ratio of 1:2 was selected as the optimal structure material because of its excellent penetration capacity in miniature pig skin and enhanced cumulative permeation of drugs.

**REFERENCES**