Quantitative evaluation of electroosmotic transdermal drug delivery via frustoconical porous microneedle

N. Moriyama[1)] , S. Ichinose[2)] , F. Sakai[2)] , G. Wang[2)] , S. Tottori[2)] and M. Nishizawa*[,1)2)]
[1)] Graduate school of Biomedical Engineering, Tohoku University, Sendai, Miyagi, Japan.
[2)] Graduate school of Engineering, Tohoku University, Sendai, Miyagi, Japan.

Keywords: microneedle, iontophoresis, transdermal, drug delivery
Corresponding author*: nishizawa@tohoku.ac.jp

Abstract

Recently, microneedles have attracted attention as a transdermal drug delivery system. However, conventional microneedles are short but sharp, allowing them to penetrate the stratum corneum. This makes them slightly invasive and can sometimes cause discomfort during use. We have developed a less invasive, non-puncture frustoconical porous microneedle. In addition, by generating electro-osmotic flow (EOF) in the charge-modified frustoconical porous microneedles, the synergistic effect of skin stretching by the needles and EOF is expected to deliver more drug faster. In this study, we investigated its efficacy by quantifying the amount of drug in pig skin using High Performance Liquid Chromatography (HPLC). The results showed the effectiveness of the synergistic effects of EOF and the stretching effect by frustoconical porous microneedles.

1. Introduction

Transdermal administration of drugs using microneedles has attracted attention because of its minimally invasive and its ability to avoid the effects of digestive enzymes. We have created a less invasive, non-piercing frustoconical porous microneedle (F-PMN) (Fig.1). F-PMN allows intradermal penetration of drugs by stretching the skin. In addition, by modifying the F-PMN with an electrically charged molecules and applying electricity in the direction of drug penetration, an electro-osmotic flow (EOF) is generated, which can promote intradermal penetration of the drug. F-PMN is expected to enable non-penetrating and highly efficient transdermal drug administration through the synergistic effects of skin stretching and EOF (Fig.2)[1)]. In this study, we loaded a local anesthetic, lidocaine (molecular weight: 234), into F-PMNs and administered it to porcine skin for varying durations of electrical application. Then the pig skin was completely dissolved using proteinase K, and the amount of lidocaine was quantitatively evaluated by HPLC.

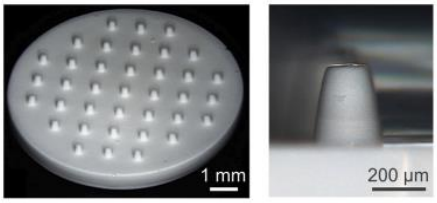

Fig.1 Picture of frustoconical porous microneedle

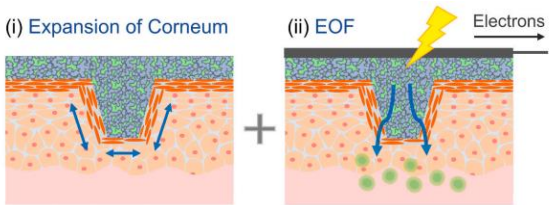

Fig.2 Conceptual illustration of the non-penetrating charge-immobilized F-PMN for EOF-promoted transdermal drug delivery

2. Experiment

The preparation and charge modification of F-PMNs followed the methods established in our

laboratory.[1)] Briefly, Poly-glycidyl methacrylate (PGMA) was used as the substrate and a thin negatively charged film was prepared by graft polymerization of 2-acrylamido-2-methyl-1-propane sulfonic acid (AMPS). For comparison, a plate of the same area without frustoconical needles was prepared by the same procedure. F-PMN and plate were immersed in PBS solutions containing 10% lidocaine overnight to fill the porous structure with lidocaine.

Transdermal delivery experiment into pig skin was performed as shown in Fig.3. Electrical application was at 0.5 mA/cm^2 for 5, 10, 15, and 30 minutes. After administration, pig skin was divided in half and collected in 1.5 mL Eppendorf tubes. Each pig skin was cut into small pieces, to which 600 µL of PBS and 1.5 mg of proteinase K were added and digested at 37°C overnight. The pig skin was then placed at 60°C for about 2 hours to completely dissolve the pig skin. Subsequently, sodium dodecyl sulfate (SDS) was added and micellized, and the solution was centrifuged at 14,000 rpm, 25 minutes. After centrifugation, 500 µL of the solution was centrifuged with a 0.45 µm filtered Eppendorf at 12,000 rpm, 5 minutes. The filtrated solution after centrifugation was collected and detected with HPLC. When making the calibration curve, 600 µL of PBS was converted to a solution of a known concentration of lidocaine.

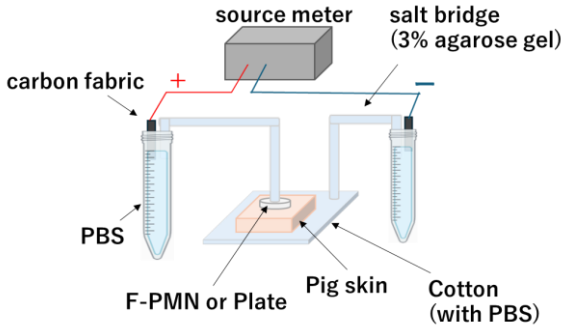

Fig.3 Illustration of the transdermal delivery experiment

3. Results and discussion

The estimated amount of lidocaine in pig skin was highest with F-PMN with current, and the amount that permeated increased with the duration of electrical application (Fig.4). After 30 minutes of applying the lidocaine tape, which is used for treatment, the drug concentration in the skin was approximately 30 µg. Based on these results, a therapeutic effect can be expected in about 5 minutes when F-PMN and EOF are used.

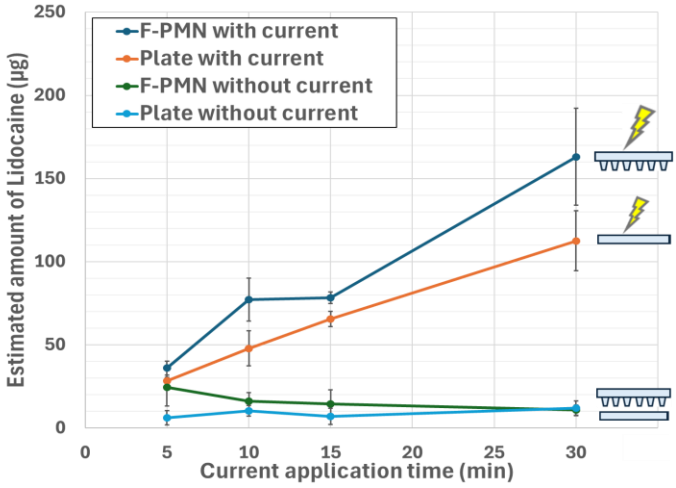

Fig.4 Estimated lidocaine content in the pig skin

4. Conclusions

The quantitative experiments demonstrated that the synergistic effect of F-PMN and EOF enhances transdermal drug delivery. This could serve as the foundation for developing non-penetrating transdermal drug delivery methods. It is anticipated to be applied to a wide range of drugs, particularly those with large molecular weights and protein-based therapeutics in the future.

References

1) D.Terutsuki et al., J. Control. Release., 354, 694(2023).
DOI: 10.1016/j.jconrel.2023.01.055