Permeability enhancement for transdermal delivery of large molecule using low frequency sonophoresis combined with microneedles

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INTRODUCTION

Transdermal drug delivery intends to deliver drug molecules to the blood circulation via percutaneous absorption. However, it is limited by the high resistance of skin towards diffusion of high molecular weight drugs. This is mainly due to the fact that the outer layer of the skin, i.e., the stratum corneum (SC), can prevent diffusion of molecules whose molecular weight is greater than 500 Da [1]. Researches on large molecules delivery become more active and various technologies have been applied to conquer this problem. However, there is no technology can provide satisfactory permeability thereby the problem is still unsolved. The two technologies we used are: (i) sonophoresis which involves use of ultrasound generated cavitation to enhance the permeability of the skin [2]; (ii) microneedles which is used to create micro-cavities in skin while provide painless administration [3]. We report a novel way to combine microneedles with ultrasound. The solid microneedles can create a good porous basis on the skin. It weakens the resistance of the SC layer and exposes parts of the underneath epidermis to the molecule of interest. The ultrasound treatment is then applied on the microneedles pre-treated area to further enhance the skin permeability [4].

MATERIALS AND METHODS

All diffusion experiments are conducted using a Franz diffusion cell system which is commonly used for measuring drug permeability in skin. It was used in this work to determine the permeability. It is consisted of four parts: the water tank, the heater, the magnetic plate and the diffusion cells which are shown in Fig.1.

RESULTS AND DISCUSSION

In all the diffusion experiment, bovine serum albumin (BSA) is used as a model of large molecule. Our results show that the permeability of BSA is increased to 1 \( \mu \text{m/s} \) (Fig.5) with the combination of 1.5 mm microneedles patch and 15 W ultrasound output which is about ten times higher than the permeability obtained in passive diffusion (Fig.2). Diffusion with only microneedles or ultrasound pre-treatment is also tested. The maximum permeability from microneedles (Fig.4) and ultrasound treatment (Fig.3) reached 0.43 \( \mu \text{m/s} \) and 0.4 \( \mu \text{m/s} \), respectively.

CONCLUSIONS

The idea of combining sonophoresis with microneedles patch provides a feasible way for the delivery of large molecules. The permeability of BSA, which has a relatively large molecular weight, is proved to be significantly increased as shown in this study. It also indicates the possibility of transporting large molecules through human skin in future. The combination of microneedles patch and ultrasound may become a painless alternative to the hypodermal injections for delivering large molecules.

REFERENCES