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

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Transdermal drug delivery (TDD) method can avoid the gastrointestinal and liver metabolism and, it has been considered as an alternative to oral drug delivery [1]. But TDD is often limited by the resistance of the skin towards molecular diffusion. The outer layer of the skin, which is called the stratum corneum (SC), can prevent diffusion of substances whose molecule weights are greater than 500 Da [2]. Sonophoresis is a technology that uses ultrasound to enhance the permeability of the skin. However, in the delivery of large molecules, ultrasound cannot seem to provide an efficient enhancement of the molecular diffusion without generating pain sensation. In that case, ultrasound treatment must be kept in a safe range while other method is involved to cooperate with sonophoresis [3]. Microneedles array is employed to create pores and loosen the structure of SC layer. Subsequently, optimised ultrasound treatment can be applied on the skin target area whereby micro-jet can be introduced by inertial cavitation to further increase the permeability [4]. To explore the feasibility of this option, bovine serum albumin (BSA) which has molecular weight over 60,000 Da has been chosen as a model drug for permeation study. In vitro porcine skin is used for the diffusion studies, which is mounted on Franz diffusion cells. The permeability experiment for passive diffusion and 1200µm and 1500µm long microneedles pre-treatment have been done [5]. Some of the typical results are shown in Fig. 1 and Fig. 2. All the microneedles pre-treatment is done under 1 MPa pressure for 10min and the experiment is continued for 5 hours. The maximum permeability is found to reach 0.43 µm/s at 30 min when using the 1500 µm microneedles. It shows 4 times higher permeability as compared to that of the passive diffusion at the same time point. Fig. 2 shows the permeability results of microneedles combined with ultrasound. The highest permeability occurs when using 1500 µm microneedles pre-treated the skin sample for 10min then applying 15 W ultrasound for another 10min. The permeability reaches 1 µm/s which is doubled in comparison to 1500 µm microneedles alone. The results indicate that using ultrasound cavitation effect after the microneedles pre-treatment can increase the permeability of the large molecule through skin sample which reveals a better prospect of transdermal drug delivery technologies. It also suggests in the transportation of large molecules, the stratum corneum may not be the only barrier. The ultrasound cavitation not only disrupt the stratum corneum but also increases the penetration depth of the microneedles pre-treated area which means it may also help the drug molecules to pass through the underneath skin layers easier.

Fig.1 Microneedles pre-treatment for 10 min with 1200 µm and 1500µm compare to passive diffusion

Fig.2 Different ultrasound output power with 10 min treatment time combined with 1.2 mm and 1.5 mm microneedles patch

References