Abstract

Mold-less microneedle fabrication for pre-loading drug

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The microneedle technology gets high attention in transdermal drug delivery systems (TDDS) research due to the limitations in the oral and parenteral drug delivery systems. Herein, the photolithography microneedle fabrication method, mold-less, has been employed to overcome the limitation of other fabrication methods. It takes less than 5 minutes for each fabrication process that includes adjusting the length and shape of microneedle by varying the time for UV irradiation and the pattern micro-windows on the photomask that is suitable to produce for industrial scale. Four-point star-shaped microneedles are fabricated via a photolithography process, and sulfobetaine (SPB) monomer is combined with dextran-glycidyl methacrylate/acrylic acid (Dex-GMA/AAc) to form the hydrogel network. The toxicity study shows that the Dex-GMA/AAc/SPB polymer can be considered as extremely biocompatible. The microneedle itself exhibits high drug loading capacity, high-efficiency drug release, and inhibits protein aggregation. The acrylated epoxidized soybean oil (AESO) sheet, microneedle substrate, shows a clear and flexible property and non-absorb drug during the drug loading process; when the microneedle patch is applied on the skin, it also curves along the surface that demonstrating its ability to be easy to apply to any body part. A pre-drug loading platform is designed for the advanced features of the microneedles that provide an effective option for administering therapeutic drugs.

The rhodamine B drug loading and releasing models show that the microneedle can load drug up to 8μg on one microneedle patch and release up to 80% of loading in 6h, with only 41 needles. The microneedle has the potential for chemical drug delivery due to its propensity for greater loading and releasing efficiency in microneedle applications. The Dextran-FITC diffusion represented that the molecular drug weight lower than 10 kDa can absorb/diffuse into the center of the microneedle. The Dextran-FITC showed a fast release and diffusion into the artificial skin in a short period.

The protein delivery shows some limitation of protein loading and releasing at low pH, but at pH 7.4, protein releases show higher efficiency suitable for transdermal drug delivery, owing to the presence of pH 7.4 in the interstitial fluid. The Lactate dehydrogenase (LDH) enzyme activity study illustrates that the poly-SPB side chains in the Dex-GMA/SPB/AAc hydrogel inhibit protein aggregation while loading enzyme into the microneedle according to having a higher enzyme kinetic activity than Dex-GMA/AAc hydrogel that do not have the poly-SPB side chains even under external stress, releases the proteins in their native state (without activity loss). A ThT assay determining the fibril formation in human insulin indicates that the human insulin-loaded Dex-GMA/AAc and Dex-GMA/SPB/AAc effectively suppress the formation of fibrils in human insulin under the dry condition and high-temperature condition that presented only 25% and 20% aggregation, respectively. The combination of hydrogel microneedle and poly-SPB side chains has a potential for biopharmaceutical transdermal drug delivery, especially protein base drug that increases the efficiency bioavailability.

Keywords: microneedles, photolithography, transdermal drug delivery, zwitterionic polymers, protein aggregation