Development of an Efficient Transdermal Drug Delivery System Using Self-Dissolving Microneedle Arrays Fabricated from Hyaluronic Acid

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We developed novel dissolving microneedle arrays fabricated from hyaluronic acid (HA) as a material and to improve the transdermal absorption of poorly absorbed hydrophilic drugs, including peptide and protein drugs. The length of HA microneedle arrays was 800 μm with a base diameter of 160 μm and a tip diameter of 40 μm. HA microneedle arrays were found to maintain their skin piercing abilities for at least 1 h, even at a relative humidity of 75%. HA microneedle arrays were completely dissolved within 1 h of application to rat skin in vivo. After storing insulin-loaded HA microneedle arrays for a month at -40, 4, 20, and 40ºC, more than 90% of insulin remained in HA microneedle arrays at all temperatures, indicating that insulin is highly stable in HA microneedle arrays at these storage conditions. We also demonstrated that the area under the serum concentration-time curve (AUC) of insulin after application of insulin-loaded HA microneedle arrays was almost equivalent to that after subcutaneous injection in rats, although the plasma concentration profile of insulin after application of HA microneedle arrays exhibited slightly reduced peak plasma concentration (Cmax) and delayed peak plasma concentration time (Tmax) compared to that observed by subcutaneous injection.

In order to further improve the efficacy of HA microneedle arrays, we developed drug tip-loaded HA microneedle arrays. In these tip-loaded HA microneedle arrays, the drug was only localized in the needle tips, which can be penetrated into skin despite skin deformation. We demonstrated that the pharmacokinetics of exendin-4 after application of exendin-4 tip-loaded HA microneedle arrays were almost equivalent to those after subcutaneous injection in rats. In addition, glucose tolerance was improved and the insulin secretion was enhanced after application of exendin-4 tip-loaded HA microneedle arrays, and these effects were comparable to those after subcutaneous injection of exendin-4. These results indicate that the injection-like absorption of exendin-4 was successfully achieved by the application of drug tip-loaded HA microneedle arrays. We also found the efficient transdermal delivery of poorly absorbed hydrophilic drugs such as bisphosphonate and sumatriptan using these HA microneedle arrays for the treatment of osteoporosis and migraine headaches, respectively. These findings indicate that our microneedle arrays are promising transdermal formulation for delivering poorly absorbed hydrophilic drugs, including peptide and protein drugs.