Improvement of Transdermal Delivery of Insulin Using Novel Microneedle Arrays Fabricated from Hyaluronic acid

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ABSTRACT SUMMARY

The aim of the present study was to develop novel insulin-loaded microneedle arrays (MNs) fabricated from hyaluronic acid (HA), and characterize their applicability in the transdermal delivery of insulin. The transdermal absorption of insulin from MNs was examined via an in vivo absorption study in diabetic rats. We found that insulin administered via MNs was almost completely absorbed from the skin into the systemic circulation, and that the hypoglycemic effect of insulin-loaded MNs was almost similar to that of the subcutaneous injection of insulin.

INTRODUCTION

Recently, attention has been paid to the possibility of using MNs in delivering insulin into the skin. As a novel and minimally invasive approach, MNs are capable of creating superficial pathways across the skin for small drugs, macromolecules, nanoparticles, or fluid extractions to achieve enhanced transdermal drug delivery. In previous attempts at MN-aided insulin delivery, hollow and solid MNs have been shown to enhance skin permeation of insulin via in vitro and in vivo studies. However, the use of MNs is associated with a number of problems.

On the other hand, hyaluronic acid (HA), which is normally used as a common ingredient in skin care products, was found to produce MNs with high biocompatibility and resistance to deformation. The resulting MNs were strong enough to reliably pierce into skin, dissolved, and rapidly released the contained drug into the skin. Furthermore, the absence of a heating step and organic solvents during fabrication proved to be a notable advantage in preserving the stability of incorporated drugs, such as insulin.

Therefore, in the present study, we developed novel insulin-loaded MNs fabricated from HA. We also assessed the ability of these MNs in transdermally delivering insulin to diabetic rats in vivo.

EXPERIMENTAL METHODS

MNs were fabricated via micromolding technologies, with HA as the base material, and then, were loaded with 0.13, 0.25, and 0.44 U of bovine insulin. The fabrication process of MNs can be considered as transcription from the micromould with needle-shape in place.

Prior to experimentation, diabetic rats were fasted for 14 h, while being provided water ad libitum. All animals were anesthetized via an intraperitoneal injection of 35 mg/kg of pentobarbital sodium, and the abdominal region was carefully shaved. Then, 0.13, 0.25, and 0.44 U insulin-loaded MNs were applied onto abdominal skin and fixed with tape. Blood samples were collected from jugular vein after the administration and centrifuged at 10,000 rpm for 5 min to immediately separate the plasma. Plasma glucose levels were determined via a glucose CII-Test kit (Wako Pure Chemical Industries, Ltd.; Osaka, Japan). Plasma insulin concentrations were measured via an insulin-EIA Test kit (Wako Pure Chemical Industries, Ltd.; Osaka, Japan).

RESULTS AND DISCUSSION

A scanning electron micrograph of a section of MNs fabricated from HA is presented in Fig. 1. The resulting tapered-cone MNs were uniform in size with sharp tips. Each needle was approximately 800 μm in height, with a diameter of 160 μm at the base and 40 μm at the tip, and an interspacing of 600 μm between the rows of needles. There were approximately 190
needles in a circular area with a diameter of 10 mm.

The cumulative release of insulin from insulin-loaded MNs was determined via an *in vitro* release study (Fig. 2). At the start of the experiment, MNs were readily dissolved and insulin was rapidly released from the MNs at a relatively constant rate. In the present study, the majority of the insulin was released within 1 h, suggesting that the release of insulin is very rapid from MNs.

![Fig. 2 The cumulative release of insulin from insulin-loaded MNs](image)

The effects of various doses of insulin on changes in plasma glucose levels of diabetic rats after treatment with insulin-loaded MNs are studied. A significant and dose-dependent hypoglycemic effect was observed after treatment with insulin-loaded MNs of varying doses in comparison to the control (Fig. 3). We also directly measured plasma insulin concentrations following the treatment of diabetic rats with insulin-loaded MNs. It was found that, in comparison to the control, there was a significant and dose-dependent increase in plasma insulin concentrations after treatment with insulin-loaded MNs (Fig. 3). These findings suggest that insulin is being absorbed from the MNs via the skin, and that the novel MNs system is effective in the transdermal delivery of insulin.

![Fig. 3 Plasma glucose levels and insulin concentration after the application of insulin-loaded MNs to the skins](image)

We also evaluated the skin damage after the application of MNs to the skin by measuring the transepidermal water loss (TEWL) of rat skins. A significant increase in TEWL was observed after the application of MNs. However, this parameter recovered back to baseline within 24 h after the removal of MNs. These findings indicate that the skin damage induced by the MNs was reversible.

**CONCLUSION**

The present study demonstrated that the novel insulin-loaded MNs fabricated from HA is safe and possesses self-dissolving properties. Moreover, transdermal delivery of insulin was successful via the novel HA MNs. Therefore, these findings indicate that the novel MNs are a very useful alternative method for delivering insulin from the skin into the systemic circulation without any serious damage to skin.

**REFERENCE**