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Fabrication and characterization of dissolving microneedle arrays for improving skin permeability of cosmetic ingredients

Yonghun Park [a], Kyu Sik Kim [b], Minsub Chung [a], Jong Hwan Sung [a,**], Bumsang Kim [a,*]

[a] Department of Chemical Engineering, Hongik University, Seoul 04066, Republic of Korea
[b] Mizon, 40-20, Gajangsaneopseobuk-ro, Osan-si, Gyeonggi-do 18103, Republic of Korea

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ABSTRACT

Delivery of sufficient amounts of cosmetic ingredients through the skin is a big challenge in the cosmetic industry, since the stratum corneum, the outer layer of the skin, acts as a barrier against external substances. One of the methods to solve this problem is using microneedles. In this study, a laser-writing process is described for fabricating a polydimethylsiloxane mold for microneedles, which is a very simple and efficient method compared to the conventional photolithography technique. Using this polydimethylsiloxane mold, it was possible to fabricate a dissolving sodium hyaluronate microneedle array with consistent shapes and sizes. Amylopectin was used to tailor the properties of the microneedles, such as mechanical strength and solubility. When amylopectin content in the needle increased, the mechanical strength of the needle increased but the dissolution rate of the microneedles decreased. Using the microneedle array, significant enhancement in the skin permeability of niacinamide and the anti-oxidant activity of ascorbic acid after crossing the skin was observed. These results indicate that the microneedle array developed in this study has the potential to be used in cosmetics by being combined with conventional cosmetic patches.

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Introduction

Recently, various functional ingredients have been introduced into a number of cosmetic products due to consumer demand for more effective cosmetics that improve not only the appearance of the skin but also the health of the skin [1–3]. However, the effectiveness of traditional methods in administering cosmetic ingredients to the skin, such as creams and patches, is limited because the stratum corneum of the skin provides a significant barrier to the transport of those ingredients into the body. The stratum corneum is the outermost nonviable layer of the skin, which is the actual physical barrier to most external substances that come in contact with the skin [4]. One of the techniques for overcoming the inefficient skin penetration of cosmetic ingredients is the use of microneedles to temporarily compromise the skin barrier layer. Microneedles are micron-scale needles that are designed to pierce across the stratum corneum and into the epidermis and/or superficial dermis to deliver compounds into the skin for local or systemic administration. Microneedles can be categorized into four types depending on how they work, which are (a) poke and flow type using hollow microneedles, (b) poke and patch type, (c) coat and poke type, and (d) poke and release type [5]. Early research work was focused on the poke and flow type, which is similar to conventional injection needles. Hollow microneedles are fabricated and drugs to be delivered are injected through the hollow openings of the microneedles. This method allows efficient and continuous drug delivery through the skin, but the fabrication process is relatively difficult. In addition, continuous drug delivery through this type of microneedle requires additional devices, and there is a risk of fractured pieces remaining inside the skin tissue [6]. The poke and patch type microneedles are applied onto the skin and removed to create small holes in the skin, and then drugs are applied directly or in the form of a patch [7,8]. In the case of the coat and poke type microneedles, drugs are coated on the surface of the microneedles and delivered through the skin when the microneedles are inserted into the skin [9]. These two types are relatively easy to fabricate and require less training for self-administration but are fabricated from

* Corresponding author at: Department of Chemical Engineering, Hongik University, Wausan-ro 94, Mapo-gu, Seoul 121-791, Republic of Korea
Tel.: +82 2 320 3009.
** Corresponding author at: Department of Chemical Engineering, Hongik University, Wausan-ro 94, Mapo-gu, Seoul 121-791, Republic of Korea
Tel.: +82 2 320 3067.
E-mail addresses: jhsung22@hongik.ac.kr (J.H. Sung), bskim@hongik.ac.kr (B. Kim).

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undissolvable materials, thus the issue of fractured microneedles still remains. Poke and release type microneedles are fabricated from biodegradable and biocompatible materials, such as hyaluronic acid, carboxymethyl cellulose, and poly(lactic-co-glycolic acid). Drugs to be delivered can be encapsulated inside the material and released when the microneedles are dissolved in the skin. Since these microneedles are made from biocompatible and biodegradable materials, they are free from the risk of fractured needles remaining in the body. Encapsulating drugs inside the microneedle also offers the advantage of enhancing the stability of the drugs [10]. Additionally, the rate of drug release can be controlled by adjusting the degradation rate of the microneedles.

The goal of this study was to develop a transdermal delivery system of cosmetic ingredients with a microneedle array that completely dissolves and is resorbed by the skin. This microneedle array would be assembled into patches, which offers simplicity of use and low cost, similar to conventional cosmetic patches, which would have a significant impact on microneedle applications for the cosmetic industry. In addition, we report a laser-writing technique for the rapid fabrication of the dissolving microneedle array instead of the photolithography technique, which is the general method for fabricating the mold for the microneedle array. Self-dissolving microneedle arrays containing cosmetic ingredients were made with sodium hyaluronate (SH) as a base matrix and amylopectin (AP) was used to control the properties of the microneedles such as mechanical strength and solubility. Niacinamide and ascorbic acid were used as model cosmetic ingredients and their *in vitro* skin permeation through the skin was determined with porcine skin and a Franz diffusion cell.

Experimental

Materials

Niacinamide, amylopectin (AP), L-ascorbic acid, and 2,2-diphenyl-1-picrylhydrazyl (DPPH) were purchased from Sigma–Aldrich Chemical Co. Sodium hyaluronate (SH, molecular weight = 1,900,000–3,200,000) and polydimethylsiloxane (PDMS) were obtained from Sungwon Pharmacopia Co. and Dow Corning Corporation, respectively.

Fabrication of mold using laser-writing process

The PDMS mold for the microneedle array was prepared using a programmable CO_2 laser writer (PL-40K, Korea stamp) according to previously reported methods [11,12]. Briefly, PDMS substrate was prepared by mixing polymeric PDMS solution and hardener. This PDMS pre-solution was poured on a flat surface, and then kept in a vacuum desiccator to completely remove blisters. Finally, the substrate was heated to be hardened in a dry oven at 72 °C for 2 h to achieve a hardened PDMS sheet. Laser beams were then shot at the flat PDMS sheet to create an array of cone-shaped holes. The size and shape of the holes could be adjusted by manipulating the parameters in the operating software for the laser writer. An array of 12 by 12 cone-shaped holes with a depth of 800–900 μm and diameter of 400 μm in the PDMS sheet was made and this PDMS mold was cleaned in an ultrasonic cleanser with 70% ethyl alcohol.

Fabrication of SH microneedle array

SH was dissolved in deionized water at 3% (w/v) concentration and the solution was poured onto the PDMS mold, previously fabricated by the laser writer. After placing in a desiccator, the SH solution on the mold was degassed under vacuum to completely fill the holes of the mold. After degassing for 180 min, the SH microneedle array was dried in an oven at 50 °C for 15 h and then the array was separated from the mold after drying. 0.1 g of niacinamide or ascorbic acid were mixed with 30 ml of microneedle pre-solution to prepare the microneedle arrays containing niacinamide or ascorbic acid, respectively.

Characterization of SH microneedle

The mechanical strength of the microneedles was determined by investigating the deformation of the microneedles after applying a load to the microneedles perpendicularly. A flat glass plate was placed on the tip of microneedles and various loads were placed on the glass plate. After applying the designated load, the length change of the microneedles was observed with a microscope. Two types of solubility of SH microneedles were examined. First, the water solubility of the needle was tested by immersing the needle portions of the microneedle array in 5 ml of phosphate buffered saline (PBS, pH 7.0) and the remaining length of microneedles was measured using microscopy. Second, the *in vitro* dissolution rate of the microneedle was determined by inserting the microneedle array into the porcine skin and examining the remaining length of the microneedles.

In vitro *skin permeation experiment with niacinamide*

An *in vitro* skin permeation experiment with niacinamide was carried out using Franz diffusion cells (FCDV-15, Labfine) and porcine skin (Medikinetics) with a thickness of 1.7–2.0 mm and a size of 2 × 2 cm^2. A diffusion cell consisted of a donor chamber and a receptor chamber with the skin positioned between the chambers. The absorption surface area of the skin was 0.785 cm^2 and the receptor chamber was filled with 5 ml of PBS. After equilibration of the porcine skin with the receptor phase, the dissolving microneedle array containing niacinamide was applied to the surface of the skin. The receptor fluid was maintained in contact with the underside of the skin from the time of application until the end of the experiment when the receptor fluid was collected. The diffusion cell and skin were maintained at a constant temperature of 36 °C. The receptor fluid was continuously agitated with a magnetic stirrer at 500 rpm. After 24 h, the sample solution was taken from the receptor chamber and the niacinamide concentration was measured using HPLC (Agilent 1260, Agilent). The HPLC was operated with an Agilent Zorbax Eclipse XDB (C18, 4.6 mm × 250 mm, 5 μm) column, a mobile phase of 75% 0.05 M KH_2PO_4 solution and 25% methanol, and the UV detection wavelength at 263 nm. For control experiments, the same amount of niacinamide that was encapsulated in the microneedle array, was directly applied on the skin and the permeated concentration of niacinamide was measured using the same HPLC conditions.

In vitro *skin permeation experiment with ascorbic acid*

To determine the skin permeation of ascorbic acid, the antioxidant activity after skin permeation was measured by DPPH assay. The assay method was based on previously published papers [13,14]. The microneedles containing ascorbic acid were applied on the porcine skin in the Franz diffusion cell as previously mentioned. After 24 h, 100 μL of the solution in the receptor chamber was collected and mixed with 100 μL of 0.1 mM DPPH solution. The concentration of DPPH solution was measured by reading the absorbance at a wavelength of 517 nm. For control experiments, the same amount of ascorbic acid that was encapsulated in the microneedle array was directly applied on the skin, and the antioxidant activity was measured using the same method. Antioxidant activity was calculated using the following equation.

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