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Rapid implantation of dissolving microneedles on an electrospun pillar array

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ABSTRACT

Dissolving microneedles (DMNs), designed to release drugs and dissolve after skin insertion, have been spotlighted as a novel transdermal delivery system due to their advantages such as minimal pain and tissue damage, ability to self-administer, and no associated hazardous residues. The drug delivery efficacy of DMNs, however, is limited by incomplete insertion and the extended period required for DMN dissolution. Here, we introduce a novel DMN delivery system, DMN on an electrospun pillar array (DEPA), which can rapidly implant DMNs into skin. DMNs were fabricated on a pillar array covered by a fibrous sheet produced by electrospinning PLGA solution (14%, w/v). DMNs were implanted into the skin by manual application (press and vibration for 10 s) by tearing of the fibers hung on the 300-μm pillars. Separation of DMNs from the fibrous sheet was dependent on both pillar height and the properties of the fibrous sheet. After evaluation of the implantation and dissolution of DMNs with diffusion of red dye by taking cross-sectional images of porcine skin, the hypoglycemic effect of insulin loaded DEPA was examined using a healthy mouse model. This DMN array overcomes critical issues associated with the low penetration efficiency of flat patch-based DMNs, and will allow realization of patient convenience with the desired drug efficacy.

1. Introduction

A microneedle, which is a micro-scale needle, was invented to overcome the disadvantages of traditional hypodermic needles, such as pain and tissue damage [1–3]. In particular, dissolving microneedles (DMNs), in which drugs are encapsulated in a biodegradable polymer matrix, are designed to release drugs and dissolve after skin insertion [4,5]. Polymer and drugs are absorbed by the body with minimal invasion, and can be self-administered safely without the help of trained experts [6,7]. In addition, solidified drugs in DMNs are stable, because most drugs are less reactive in solvent-minimized conditions [8–10]. DMNs are therefore considered an effective transdermal drug delivery system.

To deliver DMNs into skin, an adhesive patch is usually used to support the DMNs during skin insertion and to keep the DMNs attached to the skin for dissolution [11–14]. However, because of the unevenness of the skin surface and skin elasticity, complete insertion of DMNs into the skin is often difficult, which can result in incomplete delivery of the encapsulated drugs in the DMNs [15,16]. Furthermore, extended application times are required for this patch-based system, which may result in inconvenience to the patient.

To overcome incomplete drug delivery, two-layered DMNs, in which drugs are only encapsulated into the tip of DMNs, have been developed [13,17,18]. Because the encapsulated drugs are located only in the tips of the DMNs, complete delivery of loaded drugs is possible, even in cases of incomplete skin insertion of the DMNs. However, a waiting period is still required for dissolution of the DMNs after patch attachment in this two-layered system due to the nature of patch-based DMN delivery. If the DMNs separated rapidly from their base, this sticky patch system would not be needed for DMN delivery. Following this rationale, a rapidly dissolvable microneedle patch with a water-soluble polyvinylpyrrolidone (PVP) supporting substrate was introduced to replace the adhesive patch [19]. In this system, a drop of water is dripped on the PVP membrane to dissolve and wipe off the PVP membrane after skin insertion to rapidly separate DMNs from the substrate and eliminate patch attachment during dissolution of DMNs. Although rapid

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separation of DMNs is possible in this water-soluble patch system, and no adhesive patch is required, incomplete insertion of the DMNs remains an issue. The water used to dissolve the water-soluble patch may also dissolve parts of the DMNs not completely inserted into the skin, which would result in removal of the drugs rather than absorption of the drugs into the skin. DMNs on a metal shaft like an arrow were introduced to enhance simultaneously the penetration and dissolution of DMNs [20,21]. Arrowhead-like DMNs were fully embedded in the skin, successfully addressing the problem of incomplete insertion associated with traditional patch-dependent DMN delivery. The issue of an extended period of time required for DMN application, however, was not solved.

As briefly reviewed, rapid separation of DMNs with complete insertion is the ultimate goal to establish a reliable drug delivery using DMNs; however, no novel DMN delivery system that satisfies the two requirements of complete insertion and rapid administration has been developed to date.

In this paper, we achieved rapid implantation of DMNs by fabricating DMNs on an electrospun pillar array (DEPA) that allowed rapid separation of DMNs from the pillar array by tensile breakage of a fibrous sheet. The porous structure of the fibrous sheet and the pillar array allowed rapid separation of the DMNs from their substrate and complete skin insertion, resulting in rapid implantation of the DMNs. Separation of the DMNs from the pillars and dissolution and diffusion of the implanted DMNs and their contents into the skin were observed by applying the DEPA to porcine skin. The hypoglycemic effect of insulin loaded DEPA was examined *in vivo* using a healthy mouse model. Development of this DEPA will facilitate intradermal delivery of pharmaceuticals using DMNs without the need for a patch system.

2. Materials and methods

2.1. Preparation of polymer solutions for electrospinning

Polyvinyl alcohol (PVA, 30–70 kDa), polyvinyl pyrolidone (PVP, 360 kDa), and polyethylene oxide (PEO, 600 kDa) were electrospun as hydrophilic polymers. Poly D, L-lactide-co-glycolide (PLGA, 50–70 kDa), polyurethane (PU), and polycaprolactone (PCL) were electrospun as hydrophobic polymers. PVA and PEO were dissolved in distilled water at 85 °C and 45 °C, respectively. PVP and PLGA (85:15, PLG:PLA) were dissolved in ethyl alcohol and 1,1,1,3,3,-Hexafluro-2-propanol, respectively. To dissolve PU and PCL, a 1:1 mixture of N, N-dimethlyformamide (DMF) and tetrahydrofuran (THF), and DMF and dichloromethane (DCM) were used. All polymers and their solvents were purchased from Sigma Aldrich, Korea.

2.2. Fabrication of fibrous sheets by electrospinning

Polymer solutions were fabricated into fibrous sheets by electrospinning onto a collector [22–27]. Polymer solution in a 21-gauge stainless steel needle was positioned vertically 90 mm above the collector connected to a high voltage supply (ESN-HV60, NanoNC Co., Korea). Electrospinning was carried out at room temperature at different voltages (6.0–12.0 kV) and flow rates (0.2–2 mL/h) for each polymer solution. Electrospun fibrous sheets and their diameters were observed by Field emission scanning electron microscopy (FESEM, JEOL-7001F, Japan).

2.3. Properties of electrospun fibrous sheets

2.3.1. Contact angle of HA droplets on fibrous sheets

Hyaluronic acid (HA, 29 kDa, Soliance, France) dissolved in distilled water (30%, w/v) was used as a matrix material for DMNs. HA solution (2 mg) was dispensed to form droplets by a dispenser (Musashi Co., Japan). The affinity between HA droplets and the six fibrous sheets of PVA, PVP, PEO, PLGA, PU, and PCL at concentrations of 3, 7, 6, 12, 8, and 15% (w/v) was analyzed by observing the contact angle and shape of the HA droplets. Contact angle and shape of the HA droplets formed on each fibrous sheet were observed at room temperature with 40% humidity using an optical microscope (Samwon Co., Korea).

2.3.2. Tensile analysis of fibrous sheets

The tensile behavior of hydrophobic fibrous sheets was analyzed with a force analyzer (Universal testing machine, Zwick Roel). Specimens (PU 20%, PCL 20%, and PLGA 14% w/v) were electrospun to fabricate a uniform fibrous sheet on a silicon wafer (70 mm diameter, EMPAK) with a circular hole 10 mm diameter at the center. The fibrous sheet over the hole was then compressed vertically at a velocity of 10 mm/min with a 3.8 mm-diameter cylindrical moving probe. The force sensed by the probe was collected to construct force–distance curves.

Tensile tests of PLGA fibrous sheets were conducted by the force analyzer to observe the tensile strengths of rectangular specimens (100 mm × 500 mm) with different fiber diameters and sheet thicknesses [28,29]. Electrospinning time and concentration of PLGA were adjusted from 2 to 5 min and 14–20% (w/v) to produce fibrous sheet of various thicknesses and fiber diameters. Tests were conducted for five samples, and average values are reported. All tests were performed at room temperature.

2.4. Electrospinning of PLGA on pillar arrays

PLGA solution (14%, w/v) was electrospun for 2 min on different height (100, 300, and 500 μm) pillar arrays with a diameter of 600 μm. Metal pillars with different heights were imaged by an optical microscope before and after electrospinning, and the fibrous sheets electrospun on the pillar arrays were imaged by FESEM.

2.5. Fabrication of HA DMNs on PLGA electrospun pillar arrays

To visualize the implantation of HA DMNs and diffusion of their ingredients, red edible dye (Cheonwoo Food Manufacturer, Korea) was mixed with HA 30% (w/v) solution for a final concentration of 1% (w/v). Red HA solution was dispensed on the top of the PLGA electrospun pillars by applying a pressure of 0.180 MPa for 0.110 s using a dispenser. HA droplets were placed in contact with a polydimethylsiloxane (PDMS) slab and elongated by 1.7 mm at a rate of 0.5 mm/min to shape microneedles. Air was blown at 0.015 MPa for 200 s to solidify the shaped HA DMNs by using a draw and blowing machine (in-house design). Fabricated microstructures were observed by optical microscopy.

2.6. Implantation and dissolution of the DEPA on skin

Separation of DMNs from the pillars was analyzed using red HA DMNs fabricated on PLGA electrospun 3 × 3 pillar arrays with different heights (0, 100, 300, and 500 μm). DMNs fabricated on various pillar arrays were inserted into the sub-cutaneous fat of shaved porcine skin for 10 s with compression and shear forces induced by a manual press and vibration, respectively. Images of the DEPAs after insertion were taken using an optical microscope. Furthermore, cross-sectional images of porcine skin with implanted red HA DMNs were taken at 0, 30 min, 1 h, 3, and 6 h after insertion.

2.7. In vivo efficacy test of the DEPA for insulin delivery

The *in vivo* insulin delivery of DEPA was evaluated using male C57BL/6 mice (7–8 weeks old, OrientBio). Mice were anesthetized