Regular Article

Improvement of Transdermal Delivery of Sumatriptan Succinate Using a Novel Self-dissolving Microneedle Array Fabricated from Sodium Hyaluronate in Rats

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Received July 9, 2014; accepted December 14, 2014

The purpose of the present study was to develop an alternative transdermal formulation containing sumatriptan succinate (SS) for the treatment of migraine. Novel self-dissolving SS-loaded microneedle arrays (MNs) were fabricated from sodium hyaluronate and their efficacy for transdermal delivery of SS was characterized. The resulting MNs maintained their skin piercing abilities for at least 30 min after being placed at a high relative humidity of 75%. Rapid release of SS from the MNs was also observed in vitro. Optical coherence tomography images demonstrated that MNs were able to successfully pierce into rat skin without any bending or cracking, and needles were completely dissolved within 1 h. MNs significantly increased transepidermal water loss; however, skin barrier function gradually recovered to control levels within 24 h, in contrast to the skin damage observed after tape stripping treatment. These findings indicated that the micropores created by MNs quickly resealed, and that the skin damage was reversible. Furthermore, a dose-dependent plasma concentration of SS was obtained after transdermal delivery using SS-loaded MNs in rats. Absorption of SS delivered by MNs was similar to that observed after subcutaneous injection and was associated with high bioavailability (ca. 90%), which was much higher than that produced by oral administration. These findings suggested that application of SS-loaded MNs to the skin provided an effective alternative approach to enhance the transdermal delivery of SS without serious skin damage, and would be likely to improve patient compliance.

Key words microneedle; sumatriptan succinate; sodium hyaluronate; transdermal drug delivery; transdermal absorption; absorption enhancement

Migraine is a chronic, intermittent neurologic disease characterized by episodes of headache and usually associated with nausea, vomiting, and sensitivity to light, sound and head movement; symptoms that typically last for 4–72 h.1) The mainstay of acute migraine treatment are the so-called “triptans.” Sumatriptan succinate (SS), a selective serotonin (5-hydroxytryptamine; 5-HT) agonist at 5-HT1B and 5-HT1D receptors, is the most frequently prescribed triptan drug for migraine therapy.2)

SS has been commercialized for administration by oral formulation, nasal spray, subcutaneous injection, and iontophoresic delivery. Unfortunately, oral and intranasal SS administration routes are associated with low bioavailability (BA, 15% and 17%, respectively), due to pre-systemic metabolism and incomplete absorption.3,4) Subcutaneous SS administration results in much higher BA (97%); however, from the patient’s perspective, this is often the least desirable option because of a reluctance to self-inject and the occurrence of administration site skin reactions.5) Transdermal administration offers a convenient means to overcome these limitations, as it allows drug permeation across the skin and into the systemic circulation. This route avoids SS degradation in the gastrointestinal tract and via hepatic first-pass metabolism, while providing controlled drug delivery and good patient compliance. However, the stratum corneum is a tough barrier composed of the outermost layer of skin which significantly limits the transdermal absorption of hydrophilic or high molecular weight drugs.6) In particular, SS has high hydrophilicity (log PPH 7.4 = −0.86) and it is difficult to deliver therapeutically effective amounts of drug by passive diffusion across the skin using reasonably sized patches.7) Recently, an iontophoresis transdermal system, Zecuity® (NuPathe Inc., Conshohocken, PA, U.S.A.), has been developed and made commercially available.8) Overall, iontophoretic delivery seems to have several benefits over passive delivery of SS. However, this system requires a sophisticated electronic device and application site skin reactions may occur.9) Therefore, in order to suppress these adverse effects, while sustaining the therapeutic efficacy of SS, a more effective alternative drug delivery method is needed to exploit the advantages of parenteral and transdermal drug delivery.

In recent years, microneedle arrays (MNs) have received much attention as a novel, minimally invasive approach. These micron-sized needles disrupt the stratum corneum and create micro-scale pathways that can increase the transdermal transport of drugs.10) These needles are sufficiently long to breach the skin barrier and increase drug transport, yet are sufficiently short to avoid stimulating skin nerves. Therefore, these needles are painless, in contrast to hypodermic needles.11) MNs have been applied to the delivery of many types of compounds, ranging from low molecular weight drugs to proteins, vaccines, plasmid DNA, as well as the influenza virus. Additionally, they have been fabricated from a wide range of materials, including silicon, metals, and polymers.12–16) Qiu et al. increased the skin penetration of docetaxel by applying elastic liposomes to skin that had been pretreated with silicon-based MNs.16) Other research groups employed metal-based MNs,
coated with DNA using a water-soluble formulation.\textsuperscript{15} However, these types of MNs are limited by their expensive material costs or an undesirable two-step administration process. In addition, choosing silicon or metals as the basal material raises safety concerns, since MNs can be accidentally broken and may remain in the skin after application.

To overcome these shortcomings and limitations, MNs fabricated from biodegradable polymers and water-soluble carbohydrates have been developed recently.\textsuperscript{17–21} These MNs were completely degraded or dissolved in the skin interstitial fluid, thereby releasing their encapsulated drug. Nevertheless, the development of dissolving MN systems presents many obstacles. For example, fabrication of MNs at high temperatures can reduce the activities of their heat-sensitive cargoes, such as peptides and proteins.\textsuperscript{17,18,21} In addition, carbohydrate-based MNs deformed readily under relatively humid conditions, which negatively affected the mechanical strength of the needles.\textsuperscript{20,21}

We have previously prepared sodium hyaluronate-based MNs encapsulating insulin, alendronate, and fluorescein isothiocyanate-labeled dextran (FD4), and improved transdermal delivery of these model compounds.\textsuperscript{13,22,23} Sodium hyaluronate is a component of skin tissue and is hydrophilic in nature; it has high biocompatibility and is commonly present in cosmetics. These findings indicated that our developed MN would provide a promising delivery system, with high efficacy and safety. The present study aimed to develop a self-dissolving MN system fabricated from sodium hyaluronate and containing SS for the treatment of migraine. The effect of SS-loaded MN hygroscopy on their mechanical strength was measured. Skin penetration characteristics and subsequent dissolution of the MNs after application onto rat skin were evaluated using optical coherence tomography (OCT). To assess the disruption and recovery of skin barrier function after administration of MNs, transepidermal water loss (TEWL) was measured. Additionally, we also investigated the in vivo transdermal absorption of SS from MNs, in comparison with that observed after subcutaneous (s.c.) injection or oral administration.

**MATERIALS AND METHODS**

**Materials** SS was purchased from Viwit Pharmaceutical Co., Ltd. (Shanghai, China). Sodium hyaluronate (Japanese Pharmacopoeia [JP] grade) was purchased from Kikkoman Biochemifa Company (Tokyo, Japan). l-(-)-Tartaric acid was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). Acetonitrile and ammonium dihydrogen phosphate were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All other chemicals and reagents were of analytical reagent grade.

Male Wistar rats (8 weeks old, 250–270 g) were purchased from Shimizu Laboratory Supplies Co., Ltd. (Kyoto, Japan). All experiments were performed in accordance with the guidelines of the Animal Ethics Committee at Kyoto Pharmaceutical University.

**Fabrication of MNs** Dissolving MNs containing SS or blue dye were fabricated by micromolding technologies with sodium hyaluronate as the base material. In brief, 10% sodium hyaluronate was obtained by thorough mixing with distilled water. Either SS or blue dye solution, dissolved in 3% tartaric acid, was added to the sodium hyaluronate solution and uniformly mixed. A small aliquot of the resulting solution was carefully cast in micromolds and dried in a desiccator at room temperature. After drying the micromolds completely, a polyethylene terephthalate adhesive tape was attached to the base plate for reinforcement. The SS- or blue dye-loaded MNs were obtained by peeling the mold off and cutting to a circular area with a diameter of 10 mm using a punch. Placebo MNs were also fabricated in the same manner, without any model component (SS or blue dye).

**Measurement of the Mechanical Failure Force and Hygroscopy of SS-Loaded MNs** The mechanical failure force of SS-loaded MNs was measured using a texture analyzer (SV-52N-50, Imada Seisakusho Co., Ltd., Aichi, Japan). A single MN array was attached to a lower test station, and the upper cylindrical movable probe then pressed the MNs at a speed of 1.0–1.5 mm/min. The maximum force applied before immediate force drop was measured as the force of needle failure. Before and after the failure force test, all needles were examined by stereoscopic microscopy (M205 C, Leica Microsystems Ltd., Wetzlar, Germany).

To determine the hygroscopy of SS-loaded MNs under high moisture conditions, the arrays were stored in a desiccator containing a saturated solution of sodium chloride to achieve a relative humidity of 75%. MNs were removed at predetermined intervals, and their water content was measured using a moisture analyzer (MS-70, A&D Co., Ltd., Tokyo, Japan). In addition, the mechanical failure force of the moisture-conditioned MNs was also determined.

**In Vitro Release of SS from SS-Loaded MNs** MNs were placed in 5 mL phosphate-buffered saline (PBS, pH 7.4) and maintained at 32°C throughout the test period, while stirring with magnetic bars at 100 rpm. At predetermined intervals, 0.5 mL of supernatant was withdrawn and replaced with an equal volume of fresh PBS. The concentration of SS was analyzed by HPLC (Hitachi L-7000, Kyoto, Japan) with a UV detector (Hitachi L-7405) and a reverse phase C18 column (4.6 mm×250 mm, Shiseido Co., Ltd., Tokyo, Japan). The mobile phase consisted of acetonitrile and 0.5 mM ammonium dihydrogen phosphate solution, pH 3.3 (5:95), at a flow rate of 1.0 mL/min. The column temperature was 40°C and the detection wavelength was 228 nm.

**Assessing Dissolution of MNs Following Inserting into Rat Skin Using OCT** The penetration characteristics and subsequent in-skin dissolution of MNs after application onto rat skin in vivo, were observed using OCT. Rats were anesthetized via an intraperitoneal injection of 40 mg/kg pentobarbital sodium and their abdominal hairs were carefully shaved using electric clippers and a razor 24 h prior to the experiment. Just before treatment, healthy rats without signs of scratches or illness were chosen. MNs were applied into the skin by an applicator. The applicator can apply MNs into the skin with a defined force (15 N/cm²), and the force is enough for the insertion of MNs into the skin. Upon application of the MNs, the skin treated sites were immediately observed using a GaNymede model OCT microscope (Thorlabs GmbH, Munich, Germany) at indicated time intervals.

**Determination of TEWL after Application of MNs** Rats were anesthetized via intraperitoneal injection of 40 mg/kg pentobarbital sodium and their abdominal hair was carefully shaved using electric clippers and a razor 24 h prior to testing. Just before treatment, healthy rats without signs of

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scratches or illness were chosen. Animals were acclimatized to the ambient room temperature (25°C) and relative humidity (50%) for 30 min. TEWL values for rat skin were measured using a Tewameter (TM 300, Courage and Khazaka Electronic GmbH, Cologne, Germany), where a probe was applied to the skin. Three circular areas were marked on the shaved abdominal area of every rat and measured without any treatment (control group), after treatment with MNs (SS-loaded MN group), and after tape stripping (tape stripping group). Tape stripping was achieved by applying circular adhesive celophane tape (10 mm in diameter) to the stratum corneum surface of the skin. Each skin section was stripped sequentially with 15 pieces of adhesive tape. TEWL values represented the mean readings for 20 s before the measurements were automatically stopped. The values were recorded before and after each treatment at predetermined time intervals over a period of 24 h in all groups.

Recovery of Micropores Created by Insertion of MNs into Rat Skin Rats were anesthetized via intraperitoneal injection of 40 mg/kg pentobarbital sodium and their abdominal hair was carefully shaved using electric clippers and a razor 24 h prior to the experiment. Just before treatment, the shaved skins were closely examined to ensure their integrity, in case any damage had occurred during handling, healthy rats without signs of scratches or illness were chosen. MNs containing 5% blue dye were then applied to the rat skin and left in place for 24 h in vivo. Before and after treatment, the rat skin surface was observed over a period of 24 h using a Dermatoscope (Dermashot-Scope, Fineopto Co., Ltd., Tokyo, Japan).

In Vivo Transdermal Absorption Study Prior to administration, rats were fasted for 12 h, with water ad libitum. All animals were anesthetized via intraperitoneal injection of 40 mg/kg pentobarbital sodium. Prior to transdermal medication, the abdominal hair was carefully shaved using electric clippers and a razor. The following groups of animals were studied before and after drug administration. 24) (1) SS intravenous (i.v.) group, where SS solution (5.0 mg/kg in PBS, pH 7.4) was injected intravenously into the jugular vein using a hypodermic needle; (2) SS s.c. group, where SS solution (5.0 mg/kg) was injected subcutaneously into abdominal skin; (3) SS oral group, where SS solution (5.0 mg/kg) was administered orally using an intragastric needle; (4) MNs + SS solution group, where placebo MNs were applied onto abdominal skin and removed 5 min later, then a piece of cotton (diameter 10 mm) saturated with SS solution (5.0 mg/kg) was applied onto the treated skin site; (5) SS-loaded MNs group, where MNs containing three different amounts of SS (2.4, 5.0, and 9.6 mg/kg) were prepared and applied to abdominal skin, then fixed with gum tape. Blood samples (0.5 mL) were collected from the jugular vein at 5, 15, 30, 60, 90, 120, 180, 240, 360, and 600 min after administration in all groups. Blood samples were immediately centrifuged at 12 000 rpm (11 10 g) for 5 min to separate plasma. The plasma samples were stored at −50°C until analysis.

Plasma Sample Extraction Procedure The plasma samples obtained as described above were treated and analyzed according to the following methods. Plasma samples (100 µL) were mixed with 1 mL acetonitrile and vortexed for 1 min to precipitate protein. After centrifugation at 12 000 rpm (11 10 g) for 5 min, the clear supernatant layer was collected and evaporated using a centrifugal concentrator (VC-36 N, TAITEC Co., Ltd., Saitama, Japan) to remove organic solvents. The dried residue was reconstituted with 150 µL PBS (pH 7.4) and centrifuged before being injected into the HPLC system described above.

Pharmacokinetic Analyses The maximal plasma drug concentration (C max) and the time to maximal plasma drug concentration (T max) were determined directly from the individual plasma concentration–time profiles. The area under the plasma concentration–time curve (AUC) for 0–10 h was calculated by the linear trapezoidal rule method. Absolute BA was calculated according to the following equation:

\[
BA(\%) = \left( \frac{AUC_{MN} \times \text{Dose}_{iv}}{AUC_{iv} \times \text{Dose}_{MN}} \right) \times 100
\]

Where AUC MN and AUC iv indicated the AUCs after applying SS-loaded MNs and after i.v. injection of SS, respectively. The BA for other administration routes was calculated using the same method.

Statistical Analyses Statistical analyses were performed using GraphPad Prism software (GraphPad Software Inc., San Diego, CA, U.S.A.). Student’s unpaired t-tests were used for comparisons between groups. Results are presented as mean values ± standard error (S.E.). In all cases, p < 0.05 was considered to be statistically significant.

RESULTS

Fabrication of MNs There were approximately 500 needles in a circular array with a diameter of 10 mm. Needles were tapered cone-shaped, and of uniform size with sharp tips. Each needle was about 800 µm in height, with a diameter of 110 µm at the base and 25 µm at the tip. Rows of needles were 350 µm apart.

Mechanical Failure Force and Hygroscopy of SS-Loaded MNs Figure 1A shows the force-displacement curve of MNs under an axial load. Upon needle failure, the force declined suddenly, and the point before the sudden decrease was interpreted as the needle failure force. The failure force of the SS-loaded MN array was approximately 21 N. As shown in Fig. 1B, before the failure force test, the needles were straight taper and no deformation. After the failure force test, all needles were deformed with almost the same tip bending of 45°, along with a displacement of approximately 200 µm.

To evaluate the effect of hygroscopy on mechanical strength, the water content of MNs maintained at a relative humidity of 75% was measured. As shown in Fig. 1C, the mean water content of MNs before storage was 4.5%, and this value gradually increased to 10.0% within 4 h. It appeared that the absorption of moisture became saturated after 4 h. As expected, the mechanical strength of the MNs declined as their water content increased (Fig. 1D). When the water content increased to 10.0%, the failure force decreased to approximately 11.7 N per array. However, further experiments showed that our MNs possessed sufficient strength to penetrate the skin if the failure force was ≥ 16 N per array (data not shown), indicating that MNs maintained their insertion ability for at least 30 min, even at a relative humidity of 75%.

In Vitro Release of SS from MNs Figure 2 shows the cumulative release of SS from dissolving MNs under perfect sink conditions. The MNs dissolved rapidly and almost all of
the formulated SS was released within 1 h, indicating that the MNs were water soluble and that they released SS rapidly.

**In Vivo** Dissolution of MNs Following Inserting into Rat Skin

The representative cross-sectional two-dimensional (2D) images of the *in situ* dissolution of SS-loaded MNs following application onto rat skin were shown in Fig. 3. Needles appeared to successfully pierce into rat skin without any bending or cracking. Furthermore, needles were reduced in length by approximately 50% within 15 min, and were completely dissolved by 1 h. These findings showed that our novel MNs fabricated from sodium hyaluronate were easily dissolved upon application onto skin.

**Assessment of Rat Skin Barrier Function Using TEWL**

Damaged skin shows high TEWL, while intact and healthy skin has very low TEWL values. To evaluate the skin barrier function following application of SS-loaded MNs or tape stripping, rat skin TEWL was measured before and immediately after removal of the arrays at the indicated time intervals for up to 24 h (Fig. 4). The mean TEWL of untreated skin was $6.2 \pm 0.3 \text{ g/h \cdot m}^2$. TEWL values significantly increased ($p < 0.001$) and peaked ($47.6 \pm 1.8 \text{ g/h \cdot m}^2$) immediately after application of MNs and after tape stripping ($p < 0.001$, $68.8 \pm 8.9 \text{ g/h \cdot m}^2$), compared with the control group. However, the mean TEWL values then gradually decreased back to baseline ($p > 0.05$) within 24 h after removal of MNs. Conversely, there was no significant reduction in the mean TEWL values of the tape stripping group within the time frame of the experiment; these remained at $43.3 \pm 7.6 \text{ g/h \cdot m}^2$, even after 24 h. These findings suggested that MNs pierced the skin successfully, caused less disruption than tape stripping, and that the MN-associated reduction in skin barrier function was reversible.

**In Vivo Recovery of Micropores after Applying MNs to Rat Skin**

As shown in Fig. 5, micropores were created in rat skin after application of MNs. The skin surface was observed before treatment, and immediately after removal of MNs at 0, 1, 4, and 24 h. The injection sites were stained by the blue
dye released from the MNs and the blue dots therefore corresponded to the needle injection sites. It was also evident from Fig. 5 that micropores created by MNs gradually resealed over time; the blue color diffused quickly and had disappeared from the skin by 24h after removal. Taken together, these results indicated that the creation and recovery of micropores were consistent with the changes in TEWL values.

**In Vivo Transdermal Absorption of SS Delivered by MNs** The mean plasma concentration–time profiles for SS after administration by a range of methods are presented in Fig. 6. As shown in Fig. 6A, SS rapidly disappeared from the blood circulation after its i.v. injection. After oral administration, SS was rapidly absorbed from the gastrointestinal tract with a \( C_{\text{max}} \) of 0.2±0.1 \( \mu \)g/mL at a \( T_{\text{max}} \) of 26.3±3.8 min. In contrast, there was only a small spike in plasma SS concentration in the MNs+SS solution group, compared with the levels achieved using SS-loaded MNs and s.c. injection (Fig. 6B). A significant and dose-dependent increase in plasma SS concentration was observed after treatment with SS-loaded MNs. The peak plasma SS levels were reached within an hour and ranged from 1.0±0.7 \( \mu \)g/mL to 4.0±0.5 \( \mu \)g/mL as the dose increased from 2.4 to 9.6mg/kg.

The pharmacokinetic parameters after administration of SS via different routes were calculated and are summarized in Table 1. There were significant differences between the BA (\( p<0.001 \)) values after transdermal administration of SS-loaded MNs vs. oral administration. The BA of SS after treatment with different doses of SS-loaded MNs ranged...
from $87.6\pm14.3\%$ to $90.4\pm10.3\%$. In addition, very low AUC ($2.6\pm0.6\mu g\cdot min/mL$) and BA ($0.8\pm0.3\%$) values were achieved in the MNs+SS solution group. As we expected, SS was sufficiently absorbed from skin into the systemic circulation after treatment with SS-loaded MNs, and the use of MNs dramatically improved the BA of SS, as compared with oral administration. Additionally, the pharmacokinetic parameters of the SS-loaded MNs were similar to those observed after s.c. injection. Therefore, these findings indicated that the absorption and delivery of SS administered using SS-loaded MNs were almost comparable to those achieved by s.c. injection.

**DISCUSSION**

Passive transdermal delivery of SS is severely limited by the inability of this drug to cross the stratum corneum barrier. Recently, the use of MNs to increase skin permeability by creating micro-scale pathways across the skin barrier has been proposed as a novel drug delivery method that combines the advantages of transdermal delivery and hypodermic needles. In the present study, sodium hyaluronate was used to produce a self-dissolving MN array for enhancing the transdermal delivery of SS. As sodium hyaluronate is a skin tissue component, it is considered safe for this biomedical application. We found that the SS-loaded MNs were biocompatible, sufficiently strong to reliably pierce the skin, and produced a similar level of SS absorption and delivery as that achieved by s.c. injection.

Due to the hydrophilicity of sodium hyaluronate, our fabricated MNs might easily absorb moisture under conditions of high humidity, which could affect needle morphology and/or strength. We therefore evaluated the effect of hygroscopy on the mechanical strength of SS-loaded MNs. Compared with the earlier studies, our present study employed high density SS-loaded MNs (500 needles/array). Moreover, the present study paid more attention to the evaluation of the moisture absorption speed of our MNs at a high wet environment, and then mechanical strength of the moisture-conditioned MNs was accordingly measured to obtain a specific needle soften trend, providing an useful reference for the practical application. It was found that the MNs maintained their skin piercing capability for up to 30 min after being placed at a high relative humidity of 75%. Moreover, the structure of MNs did not change during the 24 h experimental period. These findings indicated the feasibility of practical application of these MNs. Our sodium hyaluronate based MNs therefore had an advantage over previously reported dissolvable MNs. For example, MNs fabricated from galactose by Donnelly et al. rapidly deformed in conditions exceeding humidity of 43%, and completely dissolved within 1 h at a relative humidity of 75%.

OCT is a non-destructive optical imaging technique which allows acquisition of 2D or 3D image data in situ and in real time, up to a depth of 2 mm below the surface of the tissue. Recently, OCT has been as a valuable tool to evaluate the penetration characteristics, and subsequent in-skin dissolution kinetics of MNs after application onto skin. In the present

**Fig. 5. Microscope Images of the Rat Skin Surface before and after Insertion of Microneedle Arrays (MNs) Containing 5% Blue Dye in Vivo at the Indicated Time Intervals**

Bars=400 $\mu m$. 
study, we observed that the needles were totally dissolved after *in vivo* application onto rat skin by 1h, indicating that our sodium hyaluronate fabricated MNs had self-dissolving properties. It was also noted that almost all of the formulated SS was released from the MNs within 1h *in vitro*, indicating that these MNs were speedily and completely dissolved in aqueous solution. These findings suggested that the MNs were biocompatible and SS was rapidly released from the arrays both *in vitro* and *in vivo*. The results further demonstrated that these self-dissolving MNs, with tapered cone-shape geometry, possessed enough mechanical strength to puncture the stratum corneum layer, and that a length of 800 µm was sufficiently long to deliver SS into the dermis. These results were well consistent with the research of Hiraishi *et al.*, who demonstrated that the model antigen fluorescein isothiocyanate-labeled-ovalbumin (FITC-OVA) was gradually delivered from the epidermis to superficial dermis after applying the FITC-OVA-loaded self dissolving MNs to the mice skin. Further, following the dissolution of MNs, the drug permeation pathways created by insertion of MNs gradually resealed over time because of the elastic nature of skin.

To evaluate the integrity of the stratum corneum barrier and skin permeability, TEWL values were measured after application of MNs and after tape stripping treatment. We found that although TEWL immediately increased after application of MNs, the values were lower than those observed after tape stripping treatment. Furthermore, TEWL gradually recovered back to baseline levels within the experimental period after MN treatment, implying that the micropores created by MNs were subsequently closed. In contrast, no significant recovery

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**Table 1. Pharmacokinetic Parameters of Sumatriptan Succinate (SS) after Intravenous (i.v.), Oral, Subcutaneous (s.c.) and Transdermal Administration in Rats**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Dose (mg/kg)</th>
<th>$C_{\text{max}}$ (µg/mL)</th>
<th>$T_{\text{max}}$ (min)</th>
<th>$AUC_{0-10\text{h}}$ (µg·min/mL)</th>
<th>BA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS i.v.</td>
<td>5.0</td>
<td>—</td>
<td>—</td>
<td>328.5±25.7</td>
<td>—</td>
</tr>
<tr>
<td>SS oral</td>
<td>5.0</td>
<td>0.2±0.1</td>
<td>26.3±3.8</td>
<td>67.3±5.5</td>
<td>20.5±3.8</td>
</tr>
<tr>
<td>SS s.c.</td>
<td>5.0</td>
<td>3.9±0.3</td>
<td>15.0±0.0</td>
<td>306.4±9.5</td>
<td>93.3±7.6</td>
</tr>
<tr>
<td>SS-loaded MNs 2.4</td>
<td>2.4</td>
<td>1.0±0.7</td>
<td>75.0±8.7</td>
<td>138.1±24.0</td>
<td>87.6±14.3***</td>
</tr>
<tr>
<td>SS-loaded MNs 5.0</td>
<td>5.0</td>
<td>2.4±0.2</td>
<td>67.5±7.5</td>
<td>295.1±3.6</td>
<td>89.8±2.1***</td>
</tr>
<tr>
<td>SS-loaded MNs 9.6</td>
<td>9.6</td>
<td>4.0±0.5</td>
<td>52.5±6.7</td>
<td>570.3±18.9</td>
<td>90.4±10.3***</td>
</tr>
<tr>
<td>MNs+SS solution</td>
<td>5.0</td>
<td>0.03±0.02</td>
<td>22.5±4.3</td>
<td>2.6±0.6</td>
<td>0.8±0.3</td>
</tr>
</tbody>
</table>

Results are presented as the mean±S.E. of at least four experiments. ***p<0.001, compared with oral administration.

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**Fig. 6.** Plasma Concentration–Time Profiles of Sumatriptan Succinate (SS) (A) after Intravenous (i.v.) Injection, Oral Administration, Application of SS Solution Following Pretreatment with Microneedle Arrays (MNs+SS Solution); (B) after Subcutaneous (s.c.) Injection, and after Treatment with Three Dosages of SS-Loaded MNs

Results are presented as the mean±S.E. of at least four experiments.
in TEWL was seen after tape stripping. These findings corroborated those of previous reports. In addition to an increase in TEWL, these findings suggested that the MNs effectively pierced the skin, consistent with the OCT data.

To vividly observe resealing of micropores created after application of MNs, we recorded the surface of the treated skin. This revealed that the small pores rapidly resealed over time, and had almost entirely disappeared within 24h. This finding was highly consistent with the results obtained from TEWL measurement. The increases in TEWL values corresponded to pore creation, while decreases in TEWL could be attributed to effective pore resealing. Zhou et al. previously reported that MNs induced much less skin damage than a 25-G hypodermic needle. Therefore, these results demonstrated that skin puncture by the dissolving MNs caused only slight skin damage, which was reversible in vivo.

Various transdermal systems were developed to achieve SS delivery via the skin, instead of more traditional formulations. In addition to in vitro and preclinical studies, Pierce et al. reported an iontophoretic transdermal technology for the acute treatment of migraine, where the \( T_{\text{max}} \) was approximately 2h and serum SS concentration was maintained approximately 2h and serum SS concentration was maintained. However, this delivery system had disadvantages, including local reactions at the application site that could result in pruritus or pain. Compared with these previous studies, the present study demonstrated that SS could be delivered into the systemic circulation effectively and painlessly using SS-loaded MNs fabricated from highly biocompatible sodium hyaluronate, thus resulting in good patient compliance. The transdermal absorption of SS after application of the MNs was almost equivalent to that observed after s.c. injection. High SS absolute BA (approximately 90%) was obtained after the application of SS-loaded MNs, which was much higher than that produced by oral administration.

It was apparent that SS-loaded MNs had advantages over the traditional passive patch system, since they could overcome the stratum corneum barrier by inserting into the skin and could effectively improve the transdermal delivery of SS, these findings suggested that novel MN-mediated system was the optimal method for transdermal SS delivery. In addition, it was also demonstrated that only a marginal plasma concentration was achieved by application of SS solution to MNs pretreated skin. This may reflect the rapid closure of the small pores created by MNs, as confirmed by the TEWL and micropore recovery experiments above. Therefore, the delivery of SS gradually reduced over time and most of the SS was trapped in the stratum corneum. However, further studies are required to clarify this finding.

We observed no significant differences in the pharmacokinetic characteristics of the SS-loaded MN group and the s.c. injection group using the same doses of SS, suggesting that SS-loaded MNs delivered similar amounts of SS as s.c. injection. Additionally, BA has an obvious impact on pharmacological benefit. Previous studies suggested that higher BA and faster absorption may correspond to improved clinical benefit. Furthermore, in addition to the in vivo animal experiments, our preliminary in vitro human cadaver study demonstrated that the novel sodium hyaluronate MN delivery system was an excellent candidate for delivering SS to migraine patients, while avoiding the pain associated with use of hypodermic needles.

CONCLUSION

A new transdermal delivery system for SS using novel self-dissolving MNs fabricated from sodium hyaluronate was successfully developed. The novel SS-loaded MNs possessed suitable hygroscopy, drug release profiles and dissolution properties. The skin disruption caused by MNs was reversible. Moreover, the delivery of SS achieved by MNs was almost equivalent to that observed after s.c. injection, and was considerably higher than that associated with oral administration. Taken together, these findings indicated that this SS-loaded MN transdermal delivery system provides a very useful alternative means to deliver this compound and represents a promising approach to improving its therapeutic effects and patient compliance.

**Conflict of Interest** The authors declare no conflict of interest.

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