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RESEARCH ARTICLE

Two-layered dissolving microneedles for percutaneous delivery of sumatriptan in rats

Yukako Ito[1], Sumie Kashiwara[1], Keizo Fukushima[2], and Kanji Takada[1]

[1]*Department of Pharmacokinetics, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto, 607–8412, Japan and* [2]*Department of Clinical Pharmacokinetics, Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Minatojima, Chuo-ku Kobe, Japan*

Abstract

A novel transdermal delivery of sumatriptan (ST) was attempted by application of dissolving microneedle (DM) technology. Dextran DM (d-DM) and hyaluronate DM (h-DM) were prepared by adding ST solution to dextran solution or hyaluronic acid solution. One DM chip, 1.0×1.0 cm, contains 100 microneedle arrays in a 10×10 matrix. The mean lengths of DMs were 496.6±2.9 μm for h-DM and 494.5±1.3 μm for d-DM. The diameters of the array basement were 295.9±3.9 μm (d-DM) and 291.7±3.0 μm (h-DM), where ST contents were 31.6±4.5 μg and 24.1±0.9 μg. These results suggest that ST was stable in h-DM. Each DM was administered to rat abdominal skin. The maximum plasma ST concentrations, C_{max}, and the areas under the plasma ST concentration versus time curves (AUC) were 44.6±4.9 ng/ml and 24.6±3.9 ng · h/ml for h-DM and 38.4±2.7 ng/ml and 14.1±1.5 ng · h/ml for d-DM. The bioavailabilities of ST from DMs were calculated as 100.7±18.8% for h-DM and 93.6±10.2% for d-DM. Good dose dependency was observed on C_{max} and AUC. The stability study of ST in DM was performed for 3 months under four different conditions, −80, 4, 23, and 50°C. At the end of incubation period, they were, respectively, 100.0±0.3%, 97.8±0.2%, 98.8±0.2%, and 100.7±0.1%. These suggest the usefulness of DM as a noninvaisive transdermal delivery system of ST to migraine therapy.

Keywords: Dissolving microneedles, array chip, sumatriptan, bioavailability, transdermal delivery, rats

Introduction

Migraine is a common multisymptom disorder that can severely impact the daily activities of migraineurs, which may be due to the severe pain, nausea, vomiting, and long duration of attacks if left untreated[1]. As a selective agonist at the vascular 5-hydroxytryptamine-1 (5-HT_{1D}) receptor, sumatriptan (ST) was developed as an acute treatment of migraine[2]. When migraine attack occurs, rapid onset of the action of ST is necessary[3, 4]. However, the oral preparation, a tablet, cannot elucidate quick pharmacological activity of ST. In addition, migraine episode often associates with nausea and vomiting[5], rendering intake of the oral ST preparation difficult for patients. A recent study of the bioavailability (BA) of ST from oral, intranasal, and suppository administrations revealed that the BA of ST was low (14.3% for oral tablet, 15.8% for nasal spray, and 19.2% for suppository) compared to the subcutaneous administration of ST[6]. To solve the low-BA problem of ST, a new administration route such as transdermal[7, 8], pulmonary, and buccal[4] administration has been studied. Duquesnoy et al.[9] performed a clinical pharmacokinetic study of a single dose of ST following 25 mg oral, 25 mg rectal, and 20 mg intranasal administrations. Consequently, the BA values of ST from oral and nasal preparations are approximately 15%, and subcutaneous injection preparation presents the problem of giving pain to the patients. Development of nonoral and noninvaisive delivery system to treat migraine could therefore address several limitations to current treatment options.

Transdermal drug delivery systems (TDDS) have produced many commercial preparations. In fact, TDDS has the following advantages over the traditional

Address for Correspondence: Yukako Ito, Department of Pharmacokinetics, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607–8412, Japan. E-mail: yukako@mb.kyoto-phu.ac.jp; Sumie Kashiwara, Keizo Fukushima, and Kanji Takada, Yukako Ito, Department of Pharmacokinetics, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607–8412, Japan. E-mail: takada @mb.kyoto-phu.ac.j

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pharmaceutical preparation like tablet and capsule: (i) no first-pass effects of the liver associated with oral delivery; (ii) little or no degradation by hydrolytic enzymes compared to that in the GI tract; (iii) little or no pain compared to subcutaneous injection; (iv) better convenience of administration than intravenous injection; (v) better and more continuously controlled delivery rate than that of oral or subcutaneous sustained-release preparations; and (vi) easy removal if side effects appear. Although transdermal iontophoresis has been proposed[10, 11], there are still many difficulties of low permeability to the skin due to the barrier function of stratum corneum.

Recent advances in microfabrication technology have made it possible to prepare microneedles, which have a possible application as novel TDDS. Since the first publication by Henry[12], microfabrication techniques for the production of silicon, metal, glass, and polymer microneedle arrays with micrometer dimensions have been reported[13–16]. The microneedles are either solid or hollow and have a geometrical shape. Microneedle TDDS are roughly defined using a micron-size needle preparation through and by which the drug is administered percutaneously. Microneedle TDDS are classified as follows: (i) extremely small needles through which a drug solution can be injected into the skin, (ii) metallic and/or silastic microneedles onto which a surface drug is coated, (iii) metallic and/or silastic microneedles with which conduits (micropores) are made on the skin and drug solution is applied after removing the microneedles, and (iv) dissolving microneedles (DMs) made of water-soluble biopolymer like chondroitin sulphate and dextran, in which drug molecules are formulated as a solid dispersion. Our previous studies suggest that macromolecules such as insulin[17, 18], erythropoietin (EPO)[19, 20], interferon[21], and recombinant human growth hormone[22] were well absorbed through rat skin by DMs. The usefulness of DMs was proposed as a new TDDS for peptide/protein drugs having poor membrane permeability. Similarly, ST was applied to DM for the purpose of overcoming the low bioavailability as a new TDDS.

In this study, ST was formulated into DM. Sodium hyaluronate and dextran were selected as the base of DM from the standpoint of safety, hardness, and ease of production of microneedles. Hyaluronic acid[23] and dextran[24,25] are polysaccharides that exist in the body. Dextran DM (d-DM) and hyaluronate DM (h-DM) were evaluated as a new transdermal DDS of ST by measuring the BA values of ST after the percutaneous administration to rats.

Materials and Methods

Materials

Imigran® nasal solution was obtained from GlaxoSmithKline plc. (Tokyo, Japan). Sodium hyaluronate, FCH-60, was obtained from Kibun Chemifa Co. Ltd. (Tokyo, Japan). Dextran (MW = 50–70 kDa) and methylene blue (MB) and polyethylene glycol 400 (PEG) were obtained from Nacalai Tesque Inc. (Kyoto, Japan). All other materials were of reagent grade and were used as received. Male Wistar Hannover rats used in the study were obtained from SLC Japan Inc. (Hamamatsu, Japan). A standard solid-meal commercial food (LabDiet®; SLC Japan Inc., Hamamatsu, Japan) was used. All other materials used were of reagent grade and were used as received.

Preparation of DM patches

As shown in Figure 1, DM patch was fabricated in a same method with Takada[26]. To produce the hyaluronate microneedles, 500 mg of sodium hyaluronate was dissolved with 13 ml of distilled water and 135 mg of the obtained gel was mixed well with 10.0 µl of Imigran and 1.0 µl of 50.0 w/v% MB suspension. For dextran microneedles, 100 mg of dextran was dissolved with 40.0 µl of Imigran, 5.0 µl of 10.0 w/v% MB suspension, and 0.15 ml of distilled water. The obtained drug glue was mixed well. After the drug glue was degassed under reduced pressure, it was dispensed into a mould containing 100 inverted cone-shaped wells, each with area of 1.0 cm^2. Each well was 500 µm deep, with 300 µm diameter at its top. The mould was covered with a 300 g steel plate; then the drug glue was filled into the wells. After the plate was removed, glue made of either 15 mg of chondroitin sulphate or 15 mg of dextran and 25 ml of distilled water was painted over the mould. It was then dried under the pressure of the stainless steel plate for 3 h. Thereafter, the plate was removed and a DM patch was obtained by detaching it with a supporting material, the base shown in Figure 2.

Preparation of ST solution for intravenous injection experiment

The Imigran nasal solution was diluted with saline and solution for an intravenous injection study; 50.0 µg/ml was obtained.

Microscopic observation of DM

A DM patch containing ST and MB was observed using a digital videomicroscope (VH-5500; Keyence Co., Osaka, Japan) under normal light.

Drug content in DM patch

ST was extracted from DM patches with 1.0 ml of 0.1 mM phosphate buffer, pH 7.4; a 100 µl aliquot was used for the isocratic HPLC assay described below.

Stability experiment

The DM patches were kept for 3 months under four different conditions: –80, 4, 23, and 50°C. Thereafter, ST was extracted from the patches with 10 ml of phosphate buffer, pH 7.4. The ST contents were measured using isocratic HPLC method.

In vivo absorption experiments in rats

Male Wistar Hannover rats, 294–328 g, were anaesthetized by intraperitoneal injection of sodium pentobarbital, 50 mg/kg. One group consisted of 3–4 rats. At 5 min

before drug administration, 0.25 ml blank blood samples were obtained from the left jugular vein with a heparinized syringe. The hair on the abdominal region was removed using a shaver (ES7111; Panasonic Inc., Osaka, Japan). One chip or half-chip of the DM was inserted to the skin by pressing the base with two fingers for 3 min with no treatment. At 2, 5, 10, 15, 20, 30, 45, 60, and 90 min after administration, 0.25 ml blood samples were collected from the left jugular vein. By centrifuging at 12,000 rpm for 10 min at 4°C using a centrifuge (Kubota 1700; Kubota Corp., Tokyo, Japan), 100 µl of the plasma sample was obtained. The resultant plasma samples were stored at –80°C until analysis.

For the intravenous infusion experiment, the ST solution was infused for 15 min into the right jugular vein of the anaesthetized rats at the dose of 50.0 µg/kg. After a 0.25 ml blank blood sample was obtained from the left jugular vein, additional blood samples of 0.25 ml were obtained at 2, 5, 10, 15, 20, 30, 45, 60, 90, and 120 min using a heparinized syringe. After centrifugation, a plasma sample was obtained. All these plasma samples were kept in a deep freezer at –80°C until analysis.

Isocratic HPLC and LC/MS/MS assay methods for ST

The samples obtained from drug content and stability studies were measured using an isocratic HPLC method reported previously[10]. Then, 100 µl of ST sample was injected onto a HPLC system (LC-10A; Shimadzu Corp., Kyoto, Japan) equipped with a UV detector (SPD-10A; Shimadzu Corp.), and a reversed phase column (Chemcosorb 5-ODS-UH, 4.6 × 250 mm; Chemco Scientific Co. Ltd., Osaka, Japan). The mobile phase was a mixture of 0.5 M ammonium acetate buffered pH 5.0 with formic acid and acetonitrile (85:15, v/v). The flow rate was 1.0 ml/min and the column temperature was 50°C. ST was detected at 282 nm wavelength.

The plasma samples obtained from *in vivo* absorption experiment were measured using the LC/MS/MS method with some modification[27]. Briefly, the extraction of ST from plasma sample was conducted using liquid–liquid extraction method as follows; aliquots of 100 µL sample in a 1.5 ml microcentrifuge tube were added to 250 µl of acetonitrile and vortexed vigorously for 15 s. Then 1 ml of diethyl ether was added to the tube, vortexed for 30 s, and centrifuged at 12,000 × *g* for 10 min. The aqueous phase

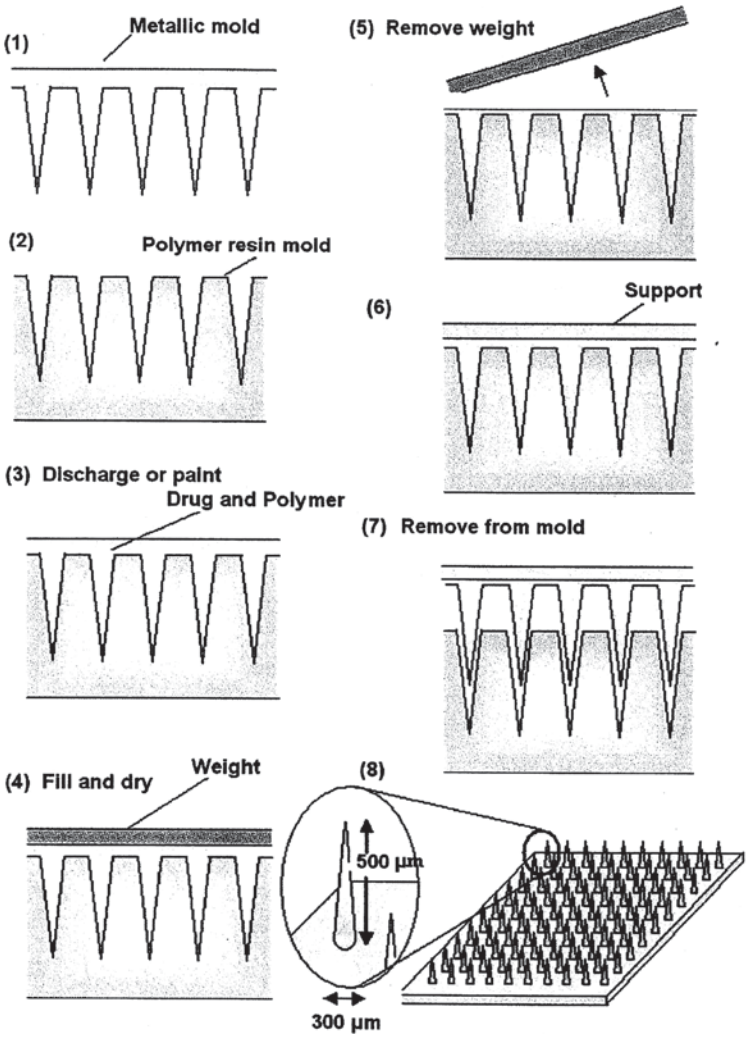

Figure 1. Fabrication process of self-dissolving microneedle patch.

was frozen in a cold bath at −10°C and the ether phase was transferred to HPLC sample vials. The organic phase was evaporated to dryness at 70°C in a water bath with an air draught. The residues were reconstituted with 100 µl of the mobile phase as described below; then 30 µl was injected into the following LC/MS/MS system, which consisted of an API 3200 triple quadrupole mass spectrometer equipped with turbo ion spray sample inlet as an interface for electrospray ionization (ESI), an analyst workstation (Applied Biosystems, CA, U.S.A.), a micropump (LC-10AD; Shimadzu Corp., Kyoto, Japan), and an automatic sample injector (AS8020; Tosoh Corp., Tokyo, Japan). The mobile phase, 10 mM ammonium acetate buffered pH 5.0 with formic acid and acetonitrile (10:90, v/v), was degassed and pumped through an ODS column (2.1 mm i.d. × 100 mm, 3 µm size, Quicksorb; Chemco Scientific, Co. Ltd., Osaka, Japan) at a flow rate of 0.2 ml/min. The column temperature was maintained at 25°C. The transitions of m/z 296→58 were optimized for the following conditions. Ionization occurred *via* the turbo ion spray inlet in the positive ion mode. The flow rates of nebulizer gas, curtain gas, and collision gas were set, respectively, at 8.0, 8.0, and 2.0 l/min. The ion spray voltage and temperature were set, respectively, at 5 kV and 500°C. The declustering potential, the entrance potential, the collision energy and the collision cell exit potential were set respectively to 29.0, 8.0, 39.0, and 2.0 V.

Pharmacokinetic analysis

Pharmacokinetic parameter values were calculated using a noncompartment analysis method. The maximum drug concentration, C_{max}, and the time to reach maximum concentration, T_{max}, were determined from the authentic plasma drug concentration versus time data. The area under the plasma drug concentration versus time curve, AUC, after percutaneous administration or intravenous injection was calculated using the linear trapezoidal rule up to the last measured drug concentration, $C_{p(last)}$, and was extrapolated to infinity by addition of the correction term $C_{p(last)}/k$, where k was the terminal elimination rate constant. The bioavailability (BA) of ST from the DM patch was calculated using the following equation, where AUC_{patch} and $AUC_{i.v.}$ were AUCs obtained after percutaneous administration and iv infusion of ST of which the doses were $Dose_{i.v.}$ and $Dose_{patch}$, respectively.

$$BA\,(\%) = (AUC_{patch}/AUC_{i.v.}) \times (Dose_{i.v.}/Dose_{patch}) \times 100$$

The area under the first-moment curve to the last measured plasma concentration, AUMC, was also calculated using the linear trapezoidal rule and the addition of the concentration term after the last measured point (t_{last}) to infinity, namely, $t_{last} \times C_{p(last)}/k + C_{p(last)}/k^2$. The mean residence time (MRT) was calculated using AUMC/AUC.

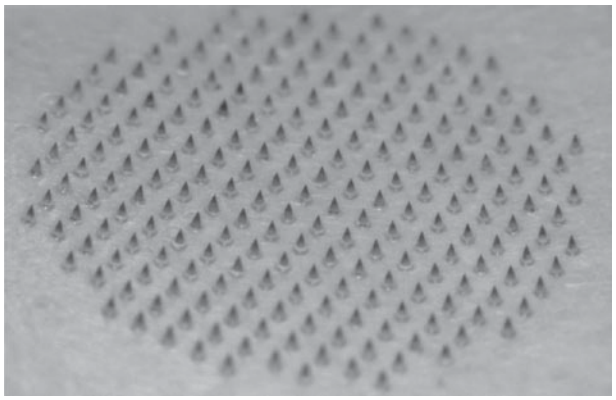

Figure 2. Image of h-DM patch before administration.

Statistics

All values are expressed as their mean ± S.E. Differences were inferred as statistically significant for $p < 0.05$ (Student's unpaired t-test).

Results and discussions

Physicochemical properties of the prepared DMs were studied using DMs of two types: h-DM and d-DM. The length of h-DMs was 496.6 ± 2.9 µm. That of d-DMs was 494.5 ± 1.3 µm. The diameters of the basements were 295.9 ± 3.9 µm for d-DMs and 291.7 ± 3.0 µm for h-DMs. The length of drug loaded spaces were 311.6 ± 10.3 µm (h-DM) and 267.7 ± 15.3 µm (d-DM). To study the uniformity of ST content in DMs, the ST contents in 1 chip of DM were measured as 31.6 ± 4.5 µg for h-DM and 24.1 ± 0.9 µg for d-DM.

The absorption efficiency of ST from DMs was studied in rats. Figure 3 shows the plasma ST concentration versus time curves after administrations of 1/2-chip and 1-chip of h-DM to the rats. Plasma ST concentrations increased rapidly after percutaneous administrations of h-DM, decreased gradually thereafter and disappearing within 1.5 h. The C_{max}s of ST were 19.8 ± 4.0 ng/ml for the 1/2-chip study and 44.6 ± 4.9 ng/ml for the 1-chip study. Pharmacokinetic parameter values were calculated using the non-compartment analysis method: the results are shown in Table 1. The bioavailability

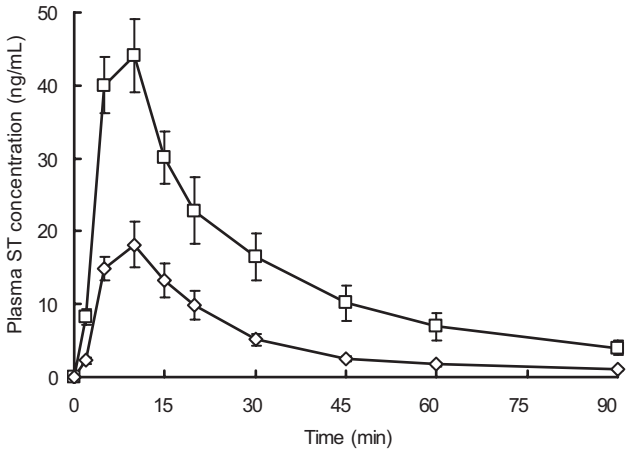

Figure 3. Plasma ST concentration-time curves after percutaneous administration of (□) one and (◇) half h-DM chip to rats. One h-DM chip contains 31.6 ± 4.5 µg of ST. Each point represents the mean ± S.E. of 3–4 experiments.

(BA) values were 77.7 ± 13.9% for the 1/2-chip h-DM study and 100.7 ± 18.8% for the 1-chip h-DM study. In addition, Figure 4 shows the plasma ST concentration versus time curves after administrations of 1/2-chip and 1-chip of d-DM to rats. The C_{max}s of ST were, respectively, 16.0 ± 1.1 ng/ml for the 1/2-chip study and 38.4 ± 2.7 ng/ml for the 1-chip study. Pharmacokinetic parameter values are shown in Table 2. The BA values were 92.3 ± 7.9% for the 1/2-chip d-DM study and 93.6 ± 10.2% for the 1-chip d-DM study. Consequently, plasma ST concentrations increased rapidly after the administrations of both h-DM and d-DM to the rat skin and decreased thereafter gradually and disappeared within 1.5 h. The T_{max} values of ST after percutaneous administrations of h-DM and d-DM were, respectively, 0.13 ± 0.02 h and 0.08 ± 0.00 h. To characterize the pharmacokinetic profiles of ST from h-DM and d-DM, MRT was calculated after percutaneous administration of DMs to rats. The results are shown in Table 3. The MRT values were, respectively, 0.67 ± 0.05 h and 0.59 ± 0.02 h for h-DM and 0.54 ± 0.02 and 0.61 ± 0.07 h for d-DM. The T_{max} values were 0.13 ± 0.02 and 0.13 ± 0.02 h for h-DM and 0.08 ± 0.0 and 0.09 ± 0.01 h for d-DM. Because h-DM showed more long-acting characteristics in the rat plasma than d-DMs after percutaneous administration to the rat abdominal skin, long-term stability study of ST was performed using h-DM. The h-DMs were incubated for 3 months under four different conditions, –80, 4, 23, and 50°C. At the end of incubation period, ST was extracted from each h-DM and ST content was measured using HPLC. Table 4 presents the results. Comparison to the ST content in h-DMs after 3 mo at –80°C, supported calculation of the fraction of remaining of ST in h-DMs incubated under other temperature conditions. They were, respectively, 97.8 ± 0.2%, 98.8 ± 0.2% and 100.7 ± 0.1% at 4, 23, and 50°C. These results suggest that ST was stable in h-DM.

In the *in vivo* absorption experiment, h-DM and d-DM were administered to the rat abdominal skin. The T_{max} values of ST after percutaneous administrations of h-DM and d-DM were 0.13 ± 0.02 h and 0.08 ± 0.00 h. Considering the T_{max} values obtained at approximately 1.5 h after the administrations of ST oral tablet, 20–100 mg, to healthy male adult patients[28,29], and approximately 30 min obtained after the administrations of ST nasal spray, 20 mg[30], it was inferred that ST was absorbed immediately into the systemic circulation after percutaneous administrations of DM, resulting in the rapid appearance of its pharmacological action. Iontophoretic delivery like Zelrix™ or other patches was also applied for longer-acting therapy.[10, 31] However, two DMs – h-DM and d-DM – showed different plasma ST concentration versus a time profile obtained after percutaneous administrations to rats. Although DMs having the same shape and size were administered, the release rate and absorption rate of ST

Table 1. Pharmacokinetic parameters of ST after percutaneous administration of h-DM to rats.

Formulation	Dose (μg/kg)	C_{max} (ng/mL)	$AUC_{0\ to\ \infty}$ (ng·h/mL)	BA (%)
½ Chip	35.1 ± 2.8	19.8 ± 4.0	8.4 ± 1.7	77.7 ± 13.9
1 Chip	79.6 ± 4.7	44.6 ± 4.9	24.6 ± 3.9	100.7 ± 18.8

Note: C_{max}: maximum plasma ST concentration. AUC0^co: area under the plasma ST concentration-time curve. BA: bioavailability. Each value shows the mean ± S.E. (n = 5–6).

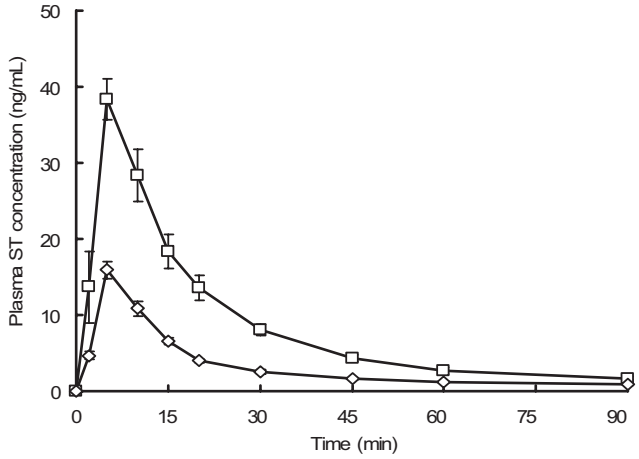

Figure 4. Plasma ST concentration-time curves after percutaneous administration of (□) one and (◇) half d-DM chip to rats. One d-DM chip contained 24.1 ± 0.9 μg of ST. Each point represents the mean ± S.E. of 3–4 experiments.

Table 2. Pharmacokinetic parameters of ST after percutaneous administration of d-DM to rats.

Formulation	Dose (μg/kg)	C_{max} (ng/mL)	$AUC_{0\ to\ \infty}$ (ng·h/mL)	BA (%)
½ Chip	19.0 ± 1.1	16.0 ± 1.1	5.4 ± 0.5	92.3 ± 7.9
1 Chip	49.3 ± 3.7	38.4 ± 2.7	14.1 ± 1.5	93.6 ± 10.2

Each value shows the mean ± S.E. (n = 6–7).

Table 3. Comparison of the pharmacokinetic parameters of ST between two kinds of DMs after percutaneous administration to rats.

Formulation	Dose (chip)	T_{max} (h)	MRT (h)
h–DM	1	0.13 + 0.02 *	0.67 + 0.05 *
	½	0.13 + 0.02	0.59 + 0.02
d–DM	1	0.08 + 0.00	0.54 + 0.02
	1/2	0.09 + 0.01	0.61 + 0.07

Note: T_{max}: the time when plasma ST concentration reaches to its maximum value. MRT: the mean residence time of ST. Each value shows the mean ± S.E. (n = 5–6).
*p < 0.05 compared to d-DM.

Table 4. Stability of ST in DM after 3 months.

Temperature	% Remaining of ST after 3 months
–80°C	100.0 ± 0.3
4°C	97.8 ± 0.2
23°C	98.8 ± 0.2
50°C	100.7 ± 0.1

Note: Each value represents the mean ± S.E. (n = 6).

from DMs were affected by the polymer used as the DM base. Hyaluronic acid is composed of aminosugar, while dextran is highly water-soluble and includes only sugar. Therefore, h-DM easily dissolves after insertion into the skin epidermis. The possibility exists that we can control the plasma ST concentration versus time profile by selecting the appropriate base polymer. When a base polymer with a high rate of dissolution after insertion into the skin is used, we might obtain rapid induction of the analgesic effect and disappearance of associated symptoms. Furthermore, when a base polymer that dissolves slowly is used, the duration of pharmacological activity is thought to increase, perhaps preventing the headache recurrence. Consequently, additional ST loading will be unnecessary.

The BA values of ST obtained after the administrations of 1 chip of h-DM and d-DM were 100.7 ± 18.8% and 93.6 ± 10.2%. By considering the BA value of ST after oral administration to human volunteers, approximately 14%, and that after intranasal administrations, approximately 16%[9], we might state that DM have considerably improved the BA of ST. That is, DM can deliver the formulated ST with high efficiency, thereby decreasing the cost of the therapy. In addition, administration of DM to the patients causes neither fear nor pain as given by self-injection similarly to insulin. In this case, patients used DM with ease. Results show that DM will be a useful dosage form for patients who have troubles with intake of the oral preparation, tablets, which cause nausea and vomiting associated with the attack of migraine. Consequently, the BA values of ST from oral and nasal preparations are less than 15%, and subcutaneous injection preparation presents the problem of giving pain to the patients. DM is approved for improvement of BA of ST. Similarly with macromolecules like peptide/protein drugs having poor membrane permeability, the possibility was suggested that DM was applied to a low molecular-weight organic compound as a new TDDS.

Conclusion

For a novel migraine therapy, two types of DMs, h-DM and d-DM, having hyaluronic acid and dextran as their respective bases were evaluated in the *in vivo* rat experiment. ST was formulated into h-DM and d-DM. The BA values of ST after the percutaneous administration to rats were considerably improved in place of oral or intranasal preparations. That is, DM can deliver the formulated ST with high efficiency, thereby decreasing the cost of the therapy. Sodium hyaluronate and dextran were selected as the base of DM from the standpoint of safety, hardness, and ease of production of microneedles. Moreover, plasma ST concentration versus time profiles showed good dose dependency. The possibility that DM was applied to not only macromolecules such as peptide/protein drugs but also a low molecular-weight organic compound like ST was obtained. Therefore, DM would be useful over a wide range of molecules as a new TDDS.

Declaration of interest

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