Evaluation of in Vitro and in Vivo Transdermal Absorption of Solifenacin Succinate

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Solifenacin (Sol), an antimuscarinic agent has been widely used for the treatment of overactive bladder. Transdermal formulations can be administered without water as well as absorbed slowly into the blood over a long period of time. The aim of this study was to develop cream and tape formulations of Sol, and evaluate the transdermal permeation and absorption of the drug from the two formulations in vitro and in vivo, respectively. In the preparation of cream formulation, Sol succinate was dissolved in purified water, and the mixture was added to the hydrophilic cream. In the tape formulation, Sol succinate was dissolved in a solvent with propylene glycol, diisopropanolamine, triethyl citrate, and EUDRAGIT E100. The dissolved solvent was poured onto a polyethylene film. Cream (5%) and tape (15%) formulations demonstrated high skin permeability. Addition of an adsorption enhancer (N-methyl-2-pyrrolidone) did not further increase the level of skin permeability. In subsequent in vivo experiments in rats, both the cream and tape formulations led to slow absorption of Sol into plasma, with increased t1/2 compared with oral administration. Plasma Sol concentrations peaked 24 h after transdermal application and the drug was still detectable in plasma 72 h after application. Additionally, the cream (5%) and tape (15%) formulations resulted in a higher area under the plasma concentration vs. time curve from 0 to 72 h (AUC0–72) compared with oral formulation (30 mg/kg). In conclusion, significant in vitro permeability and in vivo absorption of Sol from the transdermal formulations were observed.

Key words overactive bladder; solifenacin succinate; transdermal formulation; in vivo transdermal absorption; half-life; QOL

Introduction

Overactive bladder (OAB) is defined as a symptomatic syndrome characterized by urinary urgency. The symptoms of OAB resemble those associated with the lower urinary tract, and are accompanied by frequent urination and nocturia, with a profoundly negative effect on the QOL of those affected. According to recent epidemiological studies, OAB symptoms are recognized in Japan in about 15% of the adult population. Similarly, OAB affects 17% of the population in the United States. Muscarinic receptor antagonists (antimuscarinic agents) are recommended for the treatment of OAB and have been widely used. Solifenacin is an antimuscarinic agent with greater selectivity for the urinary bladder than for salivary glands compared with other antimuscaric drugs such as tolterodine, oxybutynin, darifenacin, and atropine, and may consequently provide symptomatic benefit in the treatment of OAB with reduced incidence of dry mouth. Vesicare® (Astellas Pharma, Inc., Tokyo, Japan), solifenacin succinate, was approved for the treatment of OAB in Europe in 2004, in U.S.A. in 2005, and in Japan in 2006, and has subsequently been used widely in those regions. Compared with other antimuscaric agents, Vesicare® is associated with high levels of persistence following initial prescription; however, the drug is only available as an oral formulation, which is problematic for patients who have difficulty swallowing tablets. In addition, some patients are reluctant to take the drug with water due to the risk of subsequent urinary urgency.

A method to overcome the limitations of the tablet formulation is to develop a transdermal administration system for solifenacin. In addition, transdermal formulations are expected to result in the slow absorption of the drug into blood over an extended period of time, which could further reduce the incidence of side effects and the number of administrations compared with the oral formulations. In fact, the efficacy and safety of transdermal formulations of antimuscaric agents have been evaluated and commercialized for the treatment of OAB. For example, GELNIQUE® and Oxytrol® were approved in 1975 and 2003, respectively, in the U.S.A. and Neoxi TAPE® was approved in 2013 in Japan. Therefore, transdermal formulations of solifenacin may have efficacy and further improve the QOL for patients who have difficulty swallowing tablets.

In this study, we prepared cream and tape formulations containing solifenacin succinate with the aim of developing transdermal formulations for the treatment of OAB as alternatives to oral formulations. The in vitro permeability and in vivo transdermal absorption of the formulations were evaluated.

Experimental

Materials Solifenacin succinate (Shanghai PI Chemicals Ltd., China) used in this study was purchased from Nippon Fine Chemical Co., Ltd. (Tokyo, Japan). Vesicare® 5 mg tablets (Astellas Pharma Inc.) were used as commercially available solifenacin succinate tablets. Isostearyl alcohol (Kokyu Alco-
hol Kogyo Co., Ltd., Chiba, Japan), propylene glycol (Kanto Chemical Co., Inc., Tokyo, Japan), propylene glycol monocaprylate (Nikko Chemicals Co., Ltd., Tokyo, Japan), isopropyl myristate (FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan), N-methyl-2-pyrrolidone (FUJIFILM Wako Pure Chemical Corporation), and liquid paraffin (Maruishi Pharmaceutical Co., Ltd., Osaka, Japan) were purchased for use in the experiments. All other reagents used for the study were special grade products.

**Solubility of Solifenacin Succinate**  Solifenacin powder was prepared by grinding Vesicare® tablets and then used to evaluate the solubility of solifenacin succinate. Solifenacin powder, which corresponds to 25 mg solifenacin succinate, was added to 5 mL of phosphate buffered saline (PBS at pH 4, 7 or 8), isostearyl alcohol (IAL), propylene glycol (PG), propylene glycol monocaprylate (PGM), isopropyl myristate (IPM), N-methyl-2-pyrrolidone (NMP), and liquid paraffin (LP). Each mixture was stirred for 1 min with a vortex mixer, sonicated for 30 min, then stored overnight (for 16–20 h) at 30°C. After that, the suspension was centrifuged at 3000 rpm for 20 min and the supernatant was filtered through a 0.45 µm syringe filter (Toyo Roshi Kaisha, Ltd., Tokyo, Japan) to obtain a filtrate for use as a solifenacin solution. The concentration of solifenacin was measured using HPLC.

**Preparation of Solifenacin Creams**  Solifenacin cream formulations (SC-1 to SC-8, 0.5–15%) were prepared as shown in Table 1. Solifenacin succinate was dissolved in purified water, then mixed with a hydrophilic cream (Mylan Co., JP, Tokyo, Japan), which is an emulsion vehicle, containing 25% white petrolatum, 20% stearyl alcohol, 12% PG and 4% polyoxyethylene hardened castor oil. For SC-8, NMP was added to the hydrophilic cream, which had been mixed with the solifenacin solution. Finally, purified water in which sodium hydroxide (FUJIFILM Wako Pure Chemical Corporation) was dissolved was mixed to obtain the cream formulations at pH 8.0 ± 0.1.

**Preparation of Solifenacin Tapes**  Solifenacin tape formulations (ST-1 to ST-6, 2–20%) were prepared as shown in Table 2. Solifenacin succinate, PG, diisopropanolamine (Tokyo Chemical Industry Co., Ltd., Tokyo, Japan), triethyl citrate (Tokyo Chemical Industry Co., Ltd.), EUDRAGIT® E100 (Evonik Industries, Essen, Germany), and NMP were weighed as shown in Table 2, and then dissolved in solvents containing acetonitrile, ethanol, and isopropanol. The dissolved solvents (4.3 g) were poured onto a polyethylene film (120 cm²) and dried for 20 min to obtain solifenacin tapes (2.5 mg of formulation/cm²). In the evaluation of the effects of the amount, the solvents (4.3, 8.6, 17.2 g) were poured onto the films (120 cm²), and the amount of 2.5, 5, and 10 mg of formulation/cm², respectively, were yelloled.

**In Vitro Skin Permeation Study of Solifenacin Solutions, Creams, and Tapes**  An in vitro skin permeation test was conducted using Franz-type diffusion cell (effective diffusional area: 3.14 cm² receptor volume:17 mL). Skin was carefully peeled from the ears of a <6-month-old pig (Tokyo Shibaura Organ, Tokyo, Japan) using a scalpel to separate adipose tissue. The skin was stored at −20°C. For in vitro experiments, the pig skin was thawed at room temperature and placed on the Franz receptor cell with the stratum corneum facing upwards, in an unoccluded condition. The receptor cell (dermis side) was filled with PBS at pH 7.4, stirred with a magnetic stirrer bar, and maintained at 37°C in order to hold the temperature on the stratum corneum surface at 37°C.

Solifenacin solutions were prepared in PBS (at pH 4, 7, and 8 in PBS) by adding 25 mg of solifenacin powder to 5 mL of PBS. Solifenacin solutions were prepared in the permeation enhancer (LP, IPM, IAL, PGM, NMP, and PG) by adding 250 mg of solifenacin succinate to 4700 mg of each perme-

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### Table 1. Composition of Cream Formulations Containing Solifenacin Succinate

| Ingredients                  | SC-1 | SC-2 | SC-3 | SC-4 | SC-5 | SC-6 | SC-7 | SC-8 |
|------------------------------|------|------|------|------|------|------|------|------|
| Solifenacin succinate        | 0.50 | 1.00 | 3.00 | 5.00 | 7.00 | 10.00| 15.00| 5.00 |
| Hydrophilic cream            | 85.85| 85.85| 85.85| 85.85| 85.85| 85.85| 81.85| 85.85|
| Sodium hydroxide             | 0.09 | 0.15 | 0.45 | 0.70 | 0.95 | 1.30 | 1.96 | 0.90 |
| Purified water               | 13.56| 13.00| 10.70| 8.45 | 6.20 | 2.85 | 1.19 | 0.25 |
| NMP                          | —    | —    | —    | —    | —    | —    | —    | 8.00 |
| Total                        | 100  | 100  | 100  | 100  | 100  | 100  | 100  | 100  |

NMP, N-methyl-2-pyrrolidone.

### Table 2. Composition of Tape Formulations Containing Solifenacin Succinate

| Ingredients                  | ST-1 | ST-2 | ST-3 | ST-4 | ST-5 | ST-6 |
|------------------------------|------|------|------|------|------|------|
| Solifenacin succinate        | 2.0  | 5.0  | 10.0 | 15.0 | 20.0 | 5.0  |
| Propylene glycol             | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 | 10.0 |
| Diisopropanolamine           | 0.4  | 1.0  | 2.0  | 3.0  | 4.0  | 1.0  |
| Triethyl citrate             | 29.2 | 28.0 | 26.0 | 24.0 | 22.0 | 20.0 |
| EUDRAGIT® E100               | 58.4 | 56.0 | 52.0 | 48.0 | 44.0 | 56.0 |
| NMP                          | —    | —    | —    | —    | —    | —    |
| Total                        | 100  | 100  | 100  | 100  | 100  | 100  |

NMP, N-methyl-2-pyrrolidone.
ation enhancer and 50 mg of disopropanolamine. Then, the solifenacin solutions were applied to the stratum corneum side as an infinite condition to keep the drug concentration in the donor constant at 3.14 cm².

Solifenacin cream (SC-1 to SC-8) and tape (ST-1 to ST-6) formulations were used in the in vitro study to evaluate the effects of different concentrations of solifenacin, the amount of each formulation, and permeation enhancers on skin permeation. The cream formulations were applied to the stratum corneum at the amount of 2, 5, and 10 mg of formulation/cm². The tape formulations were applied at the amount of 2.5, 5, and 10 mg of formulation/cm².

Following application of the samples to the stratum corneum for 2, 4, 6, 8, 10, and 24 h, 1.5 mL of the receptor solution was collected from the sampling port of the Franz and the same amount of PBS (pH 7.4) at 37°C was added to the receptor cell.

**Measurement of Solifenacin** The amount of solifenacin was determined by HPLC, which consisted of a pump (LC10ADvp, Shimadzu Corporation, Kyoto, Japan), an UV detector (SPD-10AVp, Shimadzu Corporation), and a separation column (CAPCELL PAK C18 MGII, 3 μm, 150 mm × 3 mm i.d., Shiseido Company, Limited, Tokyo, Japan), integrated with Labsolutions software (LCsolutions® v1.25, Shimadzu Corporation). The column temperature was set to 40°C, and a mobile phase composed of 5 mM sodium octane sulfonate (Tokyo Chemical Industry Co., Ltd.) and 0.1% phosphoric acid in acetonitrile/water (45:55) was used. The flow rate was set at 0.5 mL/min and the detection was based on UV absorbance at 210 nm.

**Oral Administration of Solifenacin Succinate** An aqueous solution of solifenacin succinate was administered orally to male rats at a dose of 30 mg/kg. Blood was taken from the jugular vein at 0.5, 1, 2, 4, 6, 8, and 24 h after administration. Animals were fasted from the day before the administration date and feeding was resumed 6 h after administration. Plasma was collected by centrifugation then stored at −20°C. After the experiment, the rats were euthanized. All the in vivo experiments were conducted with the approval of the Institutional Animal Care and Use Committee of the University of Shizuoka.

**In Vivo Transdermal Absorption Experiments for Solifenacin Creams and Tapes** On the day of the experiment, 8-week-old male Sprague-Dawley rats (Japan SLC Co., Shizuoka, Japan) were anesthetized with pentobarbital and shaved with a hair clipper to prevent the back from being damaged. The solifenacin cream (SC-4, 5%) and tape (ST-4, 15%) formulations were applied to 20 cm² (5 cm × 4 cm) of the shaved back. The doses of both formulations were 2 and 10 mg of formulation/cm² for SC-4, which were corresponded to 7.0 and 34.8 mg of solifenacin succinates/kg body weight, and 2.5 and 5 mg/cm² for ST-4, which were corresponded to 26.1 and 52.2 mg of solifenacin succinates/kg body weight. Then, blood was collected from the jugular vein under anesthesia at 0.5, 1, 2, 4, 6, 8, 24, 48, and 72 h after application. Plasma was collected by centrifugation and then stored at −20°C.

**Measurement of Solifenacin Concentration in Plasma** Plasma samples were added to methanol, centrifuged to remove the protein, and then filtered (0.45 μm). The plasma concentrations of solifenacin in the in vivo experiments were determined by LC-MS/MS. LC-MS/MS was performed in an API 4000 Q-TRAP® (Applied Biosystems, CA, U.S.A.) equipped with HPLC. The target compound was cationized by the electrospray ionization method, the ionization potential was 4.5 kV, and the ion source temperature was 450°C. Using the multiple reaction monitoring method, the mass-to-charge ratio was set to 364.2/110.1 m/z (Q1/Q3). Data were collected with Analyst® 1.5 software (Applied Biosystems). For HPLC analysis, Prominence UFLC (Shimadzu Corporation) and CAPCELL PAK C18 MG III (5 μm, 150 × 2 mm i.d., Shiseido Company, Limited) were used and the column temperature was set at 40°C. A mobile phase consisting of solvent A (0.1% formic acid) and B (acetonitrile containing 0.1% formic acid) was delivered in a gradient from 65% of A and 35% of B over 3 min. This was held at 10% of A and 90% of B for 4 min, and then at 65% of A and 35% of B for 5 min. The flow rate was 0.2 mL/min.

**Data Analysis** For in vitro skin permeability tests, the apparent steady-state permeation flux (J) was calculated using the cumulative amount of solifenacin and the least-squares method using the solver function of Microsoft® Excel 2010.

The pharmacokinetic parameters of the drugs were estimated by noncompartmental analysis. The maximum concentration in plasma (Cmax) and time to reach Cmax (Tmax) were used as the observed data. The half-life (t1/2) during the log-linear terminal phase was calculated from the elimination rate constant determined by linear regression analysis, and the area under the plasma concentration versus time curve (AUC0–t) was obtained by the trapezoidal rule until 72 h.

Statistical analysis was performed by Dunnett’s multiple comparison test using GraphPad Prism software (version 5.0, GraphPad, CA, U.S.A.). The data were expressed as the mean ± standard deviation (S.D.). Statistical significance was accepted at p < 0.05.

**Results**

**Solifenacin Concentration and J for the Test Solution**

As shown in Table 3, the concentration of solifenacin succinate in PBS ranged from 1.60 mg/mL at pH 8 to 2.94 mg/mL at pH 4. Figure 1 shows time profiles for cumulative amount of sorifenacin after the application of PBS at pH 4, 7, and 8 in the in vitro permeation study. The cumulative amount of the drug appeared from 4 to 6 h, and the apparent steady-state permeation flux (J) was calculated based on the cumulative permeated amount at 24 h. The J for PBS was 0.24 μg/cm²/h.

| Solvent | Concentration (mg/mL) | J (μg/cm²/h) |
|---------|-----------------------|-------------|
| PBS (pH 4) | 2.94 ± 0.15 | 0.24 ± 0.15 |
| PBS (pH 7) | 2.92 ± 0.78 | 4.71 ± 1.97 |
| PBS (pH 8) | 1.60 ± 0.02 | 7.23 ± 1.05 |
| IAL | 1.62 ± 0.37 | 3.35 ± 2.77 |
| PG | 2.49 ± 0.26 | 0.06 ± 0.06 |
| PGM | 2.42 ± 0.21 | 0.23 ± 0.05 |
| IPM | 0.77 ± 0.02 | 2.88 ± 0.48 |
| LP | 2.51 ± 0.08 | 0.58 ± 0.30 |
| NMP | 3.09 ± 0.69 | 10.35 ± 3.80 |

Each value represents the mean ± standard deviation (S.D.; n = 3–4). PBS, phosphate-buffered saline at pH 4, 7, and 8; IAL, isooctyl alcohol; PG, propylene glycol; PGM, propylene glycol mononitrile; IPM, isopropyl myristate; LP, liquid paraffin; NMP, N-methyl-2-pyrrolidone.
at pH 4 and 7.23 µg/cm²/h at pH 8. Since $J$ for solifenacin succinate was highest at pH 8, the alkalinity of the cream and tape formulations was adjusted for further studies. As shown in Tables 1, 2, in subsequent studies, sodium hydroxide was added to the solifenacin cream formulations, and iminodipropanol was added to the solifenacin tapes.

**In Vitro Permeation of Solifenacin in Cream and Tape Formulations**

Figure 2 shows the permeation of solifenacin at various concentrations following the application of 2 mg/cm² cream and 2.5 mg/cm² tape. $J$ for the cream formulations increased up to 3%, ranging from 1.08 to 1.40 µg/cm²/h for SC-3, -4, -5, -6, and -7, with no significant difference observed above 3% of solifenacin succinate (SC-3). In contrast to the cream formulations, the $J$ for tape formulations increased up to 20% of solifenacin succinate (9.38 µg/cm²/h for ST-5).

Figure 3 shows the amount of the SC-4 containing 5% of solifenacin succinate and ST-4 containing 15% of solifenacin succinate on in vitro skin permeation. $J$ tended to increase as the amount of formulation increased; however, the trend was different between the two formulations, with a larger increasing trend observed with SC-4 compared with ST-4.

**Effect of NMP on Skin Permeation by Solifenacin**

As shown in Table 3, NMP resulted in the highest concentration and $J$, thus, NMP was selected for further evaluation of in vitro skin permeation in the cream and tape formulations. However, as shown in Fig. 4, NMP had no effect on the in vitro skin permeation observed. Thus, we used SC-4 and ST-2, which do not contain NMP for the subsequent in vivo study.

**Oral Administration of Solifenacin Succinate**

Figure 5 shows the plasma concentration versus time profile of solifenacin after oral administration. The plasma concentration peaked (11.1 ng/mL) 1 h after administration and solifenacin was eliminated from the blood 24 h after administration. The pharmacokinetic parameters are summarized in Table 4.

**In Vivo Transdermal Absorption of Solifenacin SUccinate**

Figure 6 shows the plasma concentration versus time profile following cream (SC-4) and tape (ST-4) application. The plasma concentration increased with both formulations and peaked 24 h after application [2.5 ng/mL for SC-4 (2 mg/cm²), 9.7 ng/mL for SC-4 (10 mg/cm²), 1.0 ng/mL for ST-4 (2.5 mg/cm²), and 4.9 ng/mL for ST-4 (5 mg/cm²)], then slowly decreased. Solifenacin was detected 72 h after application of the cream and tape formulations (1.0 ng/mL for SC-4 (2 mg/cm²), 5.8 ng/mL for SC-4 (10 mg/cm²), 0.8 ng/mL for ST-4 (2.5 mg/cm²), and 2.2 ng/mL for ST-4 (5 mg/cm²)). With both formulations, the plasma concentration profile was dose-dependent.

Pharmacokinetic parameters are summarized in Table 4. The $t_{1/2}$ for SC-4 and ST-4 ranged from 35.4 to 45.3 h and from 46.6 to 52.0 h, respectively. The $t_{1/2}$ for oral administration was 3.60 h. The $T_{max}$ ranged from 20.4 to 22.4 h for SC-4 and from 24 to 33.6 h for ST-4. The $T_{max}$ for oral formulation was 1.30 h. The $C_{max}$ ranged from 2.78 to 10.00 ng/mL for SC-4 and from 1.11 to 4.93 ng/mL for ST-4. The $C_{max}$ for oral administration was 11.6 ng/mL. The $AUC_{0–72}$ ranged from 122 to 536 h·ng/mL for SC-4, which was approximately 1.7–7.4-times higher than that for oral administration (72.3 h·ng/mL), and from 57.4 to 233 h·ng/mL for ST-4, which was approximately 0.7–3.2 times compared to that for oral administration.

**Discussion**

In this study, we aimed to develop the transdermal formula-
tions for solifenacin succinate as alternative formulations to oral formulation. First, we have evaluated the effect of pH on the in vitro permeation of solifenacin through the skin by using PBS with different pH, and the pH 8 showed the highest, although the concentration was the lowest at pH 8. Since the solifenacin is a weak basic of $pK_a = 8.5$, and its dissociated state differs depending on the pH in the drug products, the ionized fraction of solifenacin increases as the pH of the drug product decreases. In addition, the stratum corneum, which is the main barrier for drug permeation into the blood streams,

![Fig. 3. In Vitro Skin Permeability of Various Amounts of Solifenacin in Cream (SC-4, A) and Tape (ST-4, B) Formulations](image)

Solifenacin cream (SC-4) and tape (ST-4) formulations were applied to the stratum corneum in the Franz-type diffusion cell at 2, 5, and 10 mg/cm² and 2.5, 5, and 10 mg/cm², respectively. The apparent steady-state permeation flux ($J$) was calculated using the cumulative amount of solifenacin. Each column represents the mean ± S.D. ($n = 3–4$).

![Fig. 4. Effect of N-Methyl-2-pyrrolidone (NMP) on the in Vitro Skin Permeation of Solifenacin in Cream (SC-4) and Tape (ST-2) Formulations](image)

NMP were applied to the stratum corneum in the Franz-type diffusion cell at 2 and 2.5 mg/cm², respectively. The apparent steady-state permeation flux ($J$) was calculated using the cumulative amount of solifenacin. Each column represents the mean ± S.D. ($n = 3–4$).

![Fig. 5. Plasma Concentration versus Time Profile of Solifenacin after Oral Administration](image)

An aqueous solution of solifenacin succinate was orally administered to rats at 30 mg/kg. Each point represents the mean ± S.D. ($n = 4$).

![Fig. 6. Plasma Concentration versus Time Profile of Solifenacin after Application of Cream (SC-4, A) and Tape (ST-4, B) Formulation](image)

Solifenacin cream (SC-4) and tape (ST-4) formulations were applied to shaved areas of 20 cm² (5 × 4 cm) on the backs of rats. The solifenacin cream (SC-4, 5%) and tape (ST-4, 15%) formulations were applied to 20 cm² (5 × 4 cm) of the shaved back. The doses of both formulations were 2 and 10 mg of formulation/cm² for SC-4, which were corresponded to 7.0 and 34.8 mg of solifenacin succinate/kg body weight, and 2.5 and 5 mg/cm² for ST-4, which were corresponded to 26.1 and 52.2 mg of solifenacin succinate/kg body weight. Each point represents the mean ± S.D. ($n = 5$).
has high hydrophobicity and generally allows hydrophobic drugs to permeate the skin. Therefore, at pH 8, the J for solifenacin was higher in due to an increase in the non ionized fraction of solifenacin, compared to pH 4 and 7. Indeed, the permeability coefficient estimated from J and solifenacin concentrations in PBS (Table 3) was approximately 56-fold larger at pH 8 compared to pH 4 (0.08 vs. 4.5 × 10⁻⁴ cm/h, respectively). Thus, we adjusted the alkalinity of the cream and tape formulations for further studies.

Next, we prepared cream and tape formulations, evaluated the concentration of solifenacin succinate in each formulation, and the amount of formulation through in vitro studies. Sodium hydroxide was added to cream formulations to adjust the pH to alkaline, and hydrophilic cream containing PG and white petroleum, was used as a general cream base. PG, which was used as a moisturizer, penetrates the skin and increases water content, while white petrolatum creates a membrane on the skin and prevents water vaporization. Disopropylamine was added to tape formulations to adjust the pH to alkaline. PG, EUDRAGIT®E100 was used as a general plaster and tri-ethyl citrate was used as a general plasticizer.

In this study, the J for tape formulations increased up to 20% of solifenacin succinate, although the J for cream formulations was saturable above 3% of the drug. According to Higuchi’s equation, if activity of the drug is maximal, the J is dependent on the activity coefficient in the skin barrier. Thus, this equation suggests that the thermodynamic activity of solifenacin increased with an increase in the concentration of the drug in the tape formulation, which is similar to the occlusive condition. However, after the application of cream formulations, the water in the creams would get evaporated. It is speculated that the decreased amount of water in the cream formulation could result in decreased solubility of solifenacin and increased activity of the drug.

Permeation enhancers are used in transdermal formulations of several drugs to promote skin permeation, providing a combination-dependent synergistic effect. In our study, we investigated in vitro skin permeation using NMP, which presented the highest solubility among the permeation enhancers used in the solubility study. However, as shown in Fig. 4, the permeation enhancers had no effect on in vitro permeation. Low concentration (8%) of NMP, which is based on the previously used concentration in formulations, in the cream and tape formulations did not enhance permeation. In addition, the J of solifenacin was high and a significant enhancement of NMP was not observed. Therefore, NMP was not used as a permeation enhancer in the formulation for the in vivo studies.

For the in vivo transdermal study, the drugs were administered orally at 30 mg/kg for comparison. Since the in vivo transdermal studies showed that the plasma concentration with the cream and tape formulations was comparable to that obtained following oral administration, it is expected that by using the cream and tape formulations, solifenacin will be absorbed into the blood circulation through the skin to levels with pharmacological effects. In in vivo pharmacokinetic studies, rats have been frequently used. In addition, it has been reported that rat skin could be useful for in vitro studies of human skin permeation, although some differences between rats and humans, such as skin barrier, blood flow, and metabolisms of solifenacin, exist.

Transdermal application of the cream and tape formulations resulted in a larger T_max compared with oral administration. In addition, the peak to trough ratio was lower than that observed with oral administration. Therefore, the cream and tape formulations may reduce side effects related to the anticholinergic activity of the drug, such as acute urinary retention, which might be due to the rapid increase in plasma concentration observed following oral administration. Furthermore, these formulations resulted in a larger J compared with oral administration and was detected 72 h after application. Sustained plasma concentrations following application of the cream and tape formulations could reduce the frequency of administration (for example, every 3 d), leading to reduced stress for patients. Plasma solifenacin concentrations following application of the cream (10 mg/cm²) and tape (5 mg/cm²) formulations increased to 9.7 and 4.9 ng/mL, respectively. These values were comparable to the those reported in clinical studies using oral tablets.

In this study, the application area was 20 cm², which can be altered for clinical use as necessary. Indeed, for Oxytrol, an antimuscaric drug commercially available in the U.S. for the treatment of OAB, the average area of application is 39 cm². Therefore, it is possible that the cream and tape formulations of solifenacin succinate are able to achieve sufficient plasma concentrations when applied for clinical use, although the skin permeability of drugs in animals does not necessarily correlate with that in humans.

**Conclusion**

In a rat in vivo transdermal study, application of solifenacin via cream and tape formulations resulted in slow absorbance.
into the blood over an extended period of time, and the plasma concentration was maintained at a level comparable to that observed in clinical studies using oral tablets. Therefore, it is possible that cream and tape formulations of solifenacin succinate can achieve sufficient plasma concentration when applied for clinical use.

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Conflict of Interest MY and RM are employees of Astellas Pharma Inc. (Tokyo, Japan) and Shiseido Co., Ltd. (Tokyo, Japan), respectively. SU, YK, ST, and NN report no conflict of interest.

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