Research paper

Tip-loaded dissolving microneedles for transdermal delivery of donepezil hydrochloride for treatment of Alzheimer’s disease

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A B S T R A C T

Donepezil hydrochloride (DPH) is often used in the treatment of Alzheimer’s disease. A new treatment method was developed by encapsulating high DPH content in the tips of dissolving microneedles for rapid, transdermal delivery of a predetermined dose of DPH. The microneedles were prepared by a micromolding method using a hydroxy-propyl-methyl-cellulose (HPMC)-ethanol/water mixture (80:20, v/v) for the tips and carboxy-methyl cellulose (CMC)-water for the base of the needles. The micromolding method involved centrifuging a DPH-HPMC-ethanol/water mixture at 10°C to obtain tips with sufficient mechanical strength. To test their mechanical strength, microneedles with different DPH content were inserted into porcine skin. Then the amount of DPH encapsulated in the microneedles was measured using high-performance liquid chromatography. The efficiency of administering DPH tip-loaded microneedles was investigated using four administrations of a pharmacokinetic test: (1) two oral administration groups (283 μg/kg and 692 μg/kg) and (2) two microneedle administration groups (283 μg/kg and 692 μg/kg). High DPH content (up to 78%, w/w) was encapsulated in the microneedle tips without serious loss of mechanical strength by using a mixture of hydroxy-propyl-methyl-cellulose (HPMC) and ethanol/water mixture (80:20, v/v). Because of the distribution of DPH in the tissue, 95% of the DPH was delivered into porcine skin after 5 min of insertion. As measured by Cmax and AUC, transdermal delivery of DPH tip-loaded microneedles was more effective compared to oral administration of the same dose of DPH. Transdermal delivery could replace oral administration of DPH.

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1. Introduction

Alzheimer’s disease (AD) is a chronic neuro-degenerative disorder that induces the symptoms of memory loss, disinhibition, loss of motivation, and problems with language [1–3]. The pathogenic mechanisms of AD are still not entirely clear. However, the reduced synthesis of the neurotransmitter acetylcholine is one cause of AD [4,5]. Acetylcholinesterase (AChE) hydrolyzes the acetylcholine, and the inhibitors of AChE have demonstrated functionality in the symptomatic treatment of AD. Therefore, AChE inhibition has been reported as a critical method for the effective treatment of AD by increasing the availability of acetylcholine in the brain regions and decreasing the availability of beta amyloids [6]. Different classes of AChE inhibitors, including tacrine, donepezil, rivastigmine, galantamine, xanthostigmine, para-aminobenzoic acid, coumarin, flavonoid, and pyrrolo-isoxazole analogs, have been developed for the treatment of AD. Among them, donepezil hydrochloride (DPH) is the second FDA-approved anti-AD drug and is considered a safe and well-tolerated drug for AD patients [7,8]. DPH has a very long half-life, indicating that it is ideal for convenient once-daily dosage [3,8–10]. DPH has been administrated orally, but this method often leads to adverse gastrointestinal effects, including nausea, diarrhea, and vomiting. To avoid these drawbacks, transdermal administration of DPH has been studied and may have advantages compared to oral administration, especially in the elderly [11,12]. When patients have a chronic neurological disorder, transdermal delivery allows for the circumvention of their unwillingness or inability to swallow medicine, and they do not have to remember to take their medication or carry pills. The molecular weight (MW) and the LogP of donepezil hydrochloride are 415.96 and 4.27, respectively [12]. The number of H-bond acceptors and H-bond receptors are 4 and 0, respectively [37]. None of the parameters violated the Rule of Five for good absorption and permeation of drug [38]. However, the MW of DPH is close to the cutoff of MW (500), and the LogP of DPH is close to cutoff of LogP (5). In addition, because DPH is a

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hydrophilic molecule with a molecular weight of 415.96, its skin permeability is too low to achieve sufficient transdermal flux [13,14]. One study [15] sought to increase skin permeability by solubilizing DPH in propylene glycol containing fatty acid, but this method showed only a small increase in skin permeability. This study also showed this method required lengthy adhesion on the skin to satisfy DPH dosing requirements. To overcome the limitation of transdermal drug delivery, microneedle systems were introduced [16–20]. Dissolving microneedles have been devised to entirely dissolve in the skin and thereby leave behind no biohazardous sharps tips after use [21–24]. These microneedles are usually made of biocompatible and water-soluble materials, such as cellulose derivatives and sugars. Drugs are encapsulated inside the dissolving microneedles for release into the skin. Another study showed that dissolving microneedles could be used to treat AD by vaccine delivery of amyloid β into the skin [25].

In the present study, DPH was encapsulated in tips of dissolving microneedles and delivered through the skin for the first time. The study also presented an optimal formulation for encapsulating high DPH content in the microneedle tips in order to obtain a satisfactory clinical application of DPH. DPH tip-loaded microneedles were prepared based on an ethanol/water mixture, and the drug delivery properties of DPH tip-loaded microneedles were studied. Also, the pharmacokinetic properties of transdermal delivery were compared with those of oral administration. Fig. 1 illustrates the scheme of inserting and dissolving DPH tip-loaded microneedle into the skin. Fig. 1(a) shows a DPH tip-loaded microneedle after insertion into the skin. Fig. 1(b) shows the dissolution in skin and systemic delivery of DPH into the blood capillaries. Thus, we believe that transdermal delivery of DPH tip-loaded microneedles is an excellent tool for treatment of AD.

2. Materials and methods

2.1. Materials and animals

Donepezil hydrochloride (DPH) was obtained as a gift from Yu-Han Pharm. Co. Ltd. Hydroxy-propyl-methylcellulose (HPMC, MW 10kD) was obtained from Shin-Etsu Chemicals (Tokyo, Japan). Carboxy-methyl-cellulose (CMC, MW 250kD) and Nile Red were purchased from Sigma-Aldrich (St. Louis, MO). Fresh porcine skin was purchased from CRONEX (Seoul, South Korea).

2.2. Solubility of DPH in water and ethanol/water mixture

DPH solubility in distilled water (D.I. water) and in an ethanol/water mixture (80:20, v/v) was determined at room temperature. To reach equilibrium, an additional amount of DPH was added to D.I. water and to the ethanol/water mixture and mixed by vortexing for 2 h. The equilibrated sample was centrifuged at 1942g for 10 min to remove the undissolved DPH. The supernatant was analyzed at a wavelength of 268 nm using a UV-spectrophotometer (S-3100, Scinco, South Korea).

2.3. Preparation of DPH tip-loaded dissolving microneedles

Two types of solvent (D.I. water and ethanol/water mixture) were used to prepare DPH tip-loaded microneedles. HPMC was dissolved in D.I. water and an ethanol/water mixture (80:20, v/v) up to 5% (w/w) to obtain an HPMC solution. Then DPH was added to the HPMC solution to make 4.9%, 9.8%, 14.9%, and 20% DPH-HPMC solutions. A control group with no DPH-HPMC solution was also prepared. 300 μl of DPH-HPMC solution at the various concentrations was added to fill the 100 microneedle cavities (600-μm height and 250-μm base; Fig. 2(a)) in the poly-dimethyl-siloxane (PDMS) mold. As shown in Fig. 2(b), the mold was placed in a vacuum chamber (Belart, Wayne, USA) for 10 min at room temperature. Then the mold was placed in a centrifuge (Combi, Hanil Science Industry, South Korea) and centrifuged (90° angle, 1942g, 10°C) for 20 min to fill the microneedle cavities in the mold. The residual DPH-HPMC solution on the mold was removed (Fig. 2(c)) and centrifuged again for 10 min at 10°C for drying (Fig. 2(d)). CMC gel (0.15 g of 20%, w/w) without DPH was placed on the mold (Fig. 2(e)) and the sample was centrifuged for 5 h to obtain dried microneedles (Fig. 2(f)). The final DPH tip-loaded microneedles are shown in Fig. 2(g). Nile Red is used as a model drug to confirm the location of the drug in the microneedles. Nile Red tip-loaded microneedles were prepared from an ethanol/water mixture (80:20, v/v) using the same procedure. Final samples were dissolved in D.I. water, and the content of DPH in the microneedles was measured using high-performance liquid chromatography (Agilent 1200 series, USA). Chromatography was used on Zorbax C18 (4.6 × 250 mm, 5 μm, Agilent Technologies, USA). The mobile phase was a mixture of methanol/0.098 M buffered phosphate/triethylamine = 50/50/0.5 (v/v/v). Chromatography was conducted at 25°C using a 1.0 ml/min flow rate and a 90 min run time. Injection volume was 20 μl and ultraviolet detection was at 268 nm.

2.4. Insertion test of DPH tip-loaded microneedles

To examine the successful insertion into the skin of tip-loaded microneedles, three arrays of 100 microneedles with five different amounts of DPH (0%, 52%, 69%, 78%, 84% [w/w]) in the tips, respectively, were pushed into the full thickness of porcine skin with a strength of 50 N for 10 s. Then the pierced skin was stained with Trypan Blue (Sigma-Aldrich) for 10 min. Excess dye was removed.
The number of stained holes was counted in each stratum corneum using an optical microscope (sv-35, Sometech, South Korea). The skin was evaluated for the appearance of blue dots on the skin. (a) Pour the 300 µl of DPH solution onto the mold. (b) Vacuuming to fill solution in the microwells evenly and additional centrifuging to pack the solution in the microwells. (c) Remove the excess solution remaining on the mold. (d) Centrifugation and drying. (e) Pour the high-concentration gel without the donepezil hydrochloride (DPH) on the mold. (f) Centrifugation and drying. (g) Peel off the microneedle.

and the skin was evaluated for the appearance of blue dots on the stratum corneum using an optical microscope (sv-35, Somotech, South Korea). The number of stained holes was counted in each of the three arrays.

2.5. Drug delivery property of DPH tip-loaded microneedles

The amount of DPH delivered into the skin was measured regarding insertion duration. DPH tip-loaded microneedles were applied to the skin for 5 min with 50 N of compression (HAP-0015, Hana tech, South Korea) at 32 °C and then, for good adhesion, were affixed with a dermaplast band aid (HARTMANN, Germany) at 32 °C for a predetermined time after the compression device was removed. Samples were removed from the skin at 5, 15, 30, and 60 min and dried in a desiccator (Dry keeper, Sanplatec Corp., Japan) for 24 h. Dried samples were dissolved in D.I. water and 60 min and dried in a desiccator (Dry keeper, Sanplatec Corp., Japan) for 24 h. Plasma samples were obtained by centrifuging. After oral administration, blood samples were collected using the same method at identical periods. All animal protocols were performed in accordance with Yu-Han Experiment Guidelines and approved by the Animal Care Committee. Pharmacokinetic parameters were calculated by non-compartmental analysis using Phoenix WinNonlin 6.3 software (Certara, St. Louis, MO).

2.6. Pharmacokinetic study of DPH tip-loaded microneedles

Twenty rats were divided into four groups of five rats each: (a) two groups received oral administration of DPH and (b) two groups received microneedle administration. 8 weeks old SD rats, 260 ± 15 g, were anesthetized by inhalation of isoflurane, and the back hair of the rats was removed with a shaver. For the two groups receiving oral administration, the drug was inserted into the stomach using oral gavage. One group received 2 ml of solution with 283 µg/kg of DPH, and the other group received 2 ml of solution with 692 µg/kg of DPH. For the two groups receiving microneedle application, one group had microneedle arrays containing 283 µg/kg of DPH inserted into the back, and the other group had microneedle arrays containing 692 µg/kg of DPH inserted into the back. During insertion, the base of the needle was attached to the skin with support from a dermaplast band aid. To prevent the needle’s base from vertical movement, a clip was applied for the first 5 min. After the clip was removed, the band aid remained for an additional 55 min. After microneedle administration, 200 µl of blood was collected from the jugular vein at 0.5, 1, 2, 3, 4, 6, 10, and 24 h. Plasma samples were obtained by centrifuging. After oral administration, blood samples were collected using the same method at identical periods. All animal protocols were performed in accordance with Yu-Han Experiment Guidelines and approved by the Animal Care Committee. Pharmacokinetic parameters were calculated by non-compartmental analysis using Phoenix WinNonlin 6.3 software (Certara, St. Louis, MO).

2.7. Measurement of DPH content in plasma

The DPH content in plasma was measured using liquid chromatography–mass spectrometry (LC/MS/MS). The LC/MS/MS analysis was performed using an Agilent 1100 series system (Agilent Technologies, USA) with an auto-injection system connected to a 4000Q TRAP LC/MS/MS system (Applied Biosystems) equipped with an electrospray ionization (ESI) source. The separation was achieved using INNO ODS C18 (50 × 2.0 mm LD, 5.0 µm). The system delivered a constant flow of 300 µl/min, and the mobile phase consisted of acetonitrile/water/formic acid = 600/400/1 (v/v/v). The volume of injection was 5 µl. A standard calibration procedure was performed. A standard amount of DPH (5.5 mg) was dissolved in 50 ml of methanol to prepare 100 µg/ml of stock solution. Working solutions of 4, 10, 20, 100, 200, and 10,000 ng/ml were prepared by serial dilution. 10 µl of working solution were mixed with 190 µl of rat blank plasma to obtain 0.2, 0.5, 1, 5, 10, and 50 ng/ml of DPH plasma standards. To acquire DPH standard samples, 10 µl of Oxybutynin HCl and 1 µg/ml of acetonitrile were added, and 100 µl of acetonitrile sample was vortexed for 1.5 min and centrifuged at 18,138g for 3 min at 4 °C. Then supernatant solution was injected. The area under the peak from the standard samples was utilized to obtain the calibration curve. The measurement was repeated three times for experimental accuracy. To determine DPH in plasma, 50 µl of plasma obtained from rats was treated with the same protocol of calibration.

3. Results and discussion

3.1. Solubility study of DPH in water and ethanol/water mixture

The saturated solubility of DPH in water and in an ethanol/water mixture (80:20, v/v) solution was 120.47 ± 2.27 mg/ml and 223.36 ± 7.44 mg/ml, respectively. HPMC was selected as the microneedle material because, in addition to its good biocompatibility, it dissolves both in the ethanol/water mixture and in water [26]. Microneedle tips were made of HPMC with molecular weight below 40 kDa can be cleared from the body of 10 kDa. Dissolvable and non-biodegradable polymer segments with molecular weight below 40 kDa can be cleared from the body by renal excretion [39,40]. In clinical use, tip-loaded microneedles can be disposed safely because tips are dissolved after insertion into the skin. DPH is a hydrophilic form of donepezil, but it showed higher solubility in the ethanol/water mixture (80:20, v/v) than in water. Tip-loaded microneedles were prepared using a solvent casting method, and the solubility of the drug and matrix material
3.2. Fabrication of tip-loaded microneedles

Master structures were fabricated and copied using micromolding to produce replica microneedle arrays for tip-loaded microneedles. The resulting 10 × 10 array contained 100 microneedles with center-to-center spacing of 850 μm of tips made of HPMC-DPH and a base substrate made of CMC measuring 0.75 cm × 0.75 cm × 0.05 cm. Compared to a previous water-based molding process [27–29], the ethanol/water mixture evaporated more quickly. Thus, the HPMC-DPH-ethanol/water mixture filled in the cavities evenly using vacuuming at first, followed by centrifugation. During the centrifugation, the temperature affected the evaporation rate to solidify the microneedle tips, which would result in a porous structure and loss of mechanical strength. While a temperature of 25 °C was shown the porous structure in the microneedle tips due to the fast evaporation rate as shown in Fig. 3(a), a temperature of 10 °C showed the complete structure of microneedle tips without the pore, because of slower evaporation rate than that of a temperature of 25 °C (Fig. 3(b)). Therefore, a low temperature of 10 °C was maintained during centrifugation to prevent sudden solidification of the microneedle tips. The base was prepared from a CMC aqueous gel because of the low solubility of DPH in this aqueous gel described in Section 3.1. This prevented diffusion of DPH into the base during process. To apply our preparation method of donepezil-tip loaded microneedles to the conventional solvent casting-molding method used for mass production, addition of a partially low temperature process is necessary to fill microneedle cavities with the ethanol solution.

When tip-loaded microneedles were prepared with a water-based solution containing HPMC-DPH-water, as shown in Fig. 4 (a) and (c), the surface of the microneedle tips was very rough and domain separation was found. However, when the tips were prepared with a HPMC-DPH-ethanol/water mixture (80:20, v/v), the domain separation and rough surface were not found, as shown in Fig. 4(b) and (d). There was obvious difference in surface roughness and domain separation by solubility of DPH in water and ethanol/water mixture (80:20, v/v). We selected HPMC-DPH-ethanol/water mixture (80:20, v/v) solution for tips in microneedle to avoid the loss of mechanical strength and low encapsulated content of DPH. Loss of mechanical strength of the microneedles and failure in microneedles insertion by domain separation are discussed in Section 3.3. When manufacturing DPH tip-loaded microneedles, it is important that productions batches maintain uniformity of geometries and of the amount of drug loaded in the tips. Proper

Fig. 3. Optical microscopic image of DPH tip-loaded microneedles prepared at (a) 25 °C and (b) 10 °C during centrifugation.

Fig. 4. Optical microscopic image of DPH tip-loaded microneedles prepared from (a) D.I water, (b) ethanol/water mixture (80:20, v/v), and SEM image of DPH tip-loaded microneedles prepared from (c) D.I water and (d) ethanol/water mixture (80:20, v/v).
As shown in Fig. 5(a) and (b), the model drug Nile Red was distributed in the tips of the microneedles but was not found in the base when Nile Red tip-loaded microneedles were prepared from an HPMC-Nile Red-ethanol/water mixture and CMC-water mixture. Nile Red was selected as a model drug because it had good solubility in the ethanol/water mixture and had the fluorescence. The model drug could be encapsulated in the tips by utilizing the solubility of cellulose and the drug in ethanol/water mixture and water.

The tip-loaded dissolving microneedle system needs a sterilization process in order to be suitable for clinical use. In previous study, microneedles were sterilized using ethylene oxide gas or gamma radiation [41,42]. A sterilization process for DPH tip-loaded microneedles needs to be considered for clinical use in order to provide effective treatment as well as to ensure the economy and convenience of the process.

3.3. Characterization of insertion of DPH tip-loaded microneedles

The insertion of DPH tip-loaded microneedles was investigated as a function of the content of DPH. Microneedles prepared from five different HPMC-DPH solutions (0%, 4.9%, 9.8%, 14.9%, 20%) corresponded to 0%, 52%, 69%, 78%, 84% DPH in the tips, respectively, after the drying process. Porcine skin was used for mechanical test of DPH tip-loaded microneedles because its structure and mechanical properties are similar to those of human skin [30–32]. The successful insertion of tip-loaded microneedles was evaluated by applying microneedles with DPH on porcine skin as shown in Fig. 6. The mechanical strength of the polymer composite structure depends on the content of the composite material in the polymer matrix. The mechanical strength was determined by the high molecular weight material of HPMC, and the content of the DPH with low molecular weight is critical for successful insertion without mechanical failure. When the insertion test was performed with tip-loaded microneedles with 52% and 69% (w/w) of DPH content, the microneedles were inserted into skin successfully as shown in Fig. 6(a) and (b). However, tip-loaded microneedles with more than 78% (w/w) of DPH content began to be inserted only partially as shown in Fig. 6(c) because the increased DPH content reduced the mechanical strength of the microneedles. In addition, the use of a water solvent decreased the success of insertion above 52% (w/w) of DPH content as shown in Fig. 6(d). This is because of domain separation caused by the lower solubility of DPH in water.

3.4. Determination of DPH delivered into the skin

The amount of DPH delivered into the skin layer was measured as function of insertion time. The morphological change of DPH tip-loaded microneedles is shown in Fig. 7. Most of the tips, except the part corresponding to 35% of microneedle height, did not remain in the skin for 5 min (Fig. 7(a)). Morphological changes in DPH tip-loaded microneedles did not appear after 15 min of insertion time. Also, the amount of DPH delivered was not different after 5 min of insertion time as shown in Fig. 8. Over 95% of DPH was delivered within 5 min of insertion, and all tips with DPH were fully dissolved in the skin within 15 min. More than 15 min of insertion time will be required to fully dissolve the microneedle tips, resulting in efficient delivery of DPH. Most DPH was located near the apex of the microneedle tips and was delivered within 5 min. By loading the drug in the tips, a predetermined amount of drug could be delivered into the skin quickly. Obtaining feedback about microneedle insertion is important to assure delivery of right drug dose. A recent study introduced feedback about the use of pressure film [43]. The integration of such sophisticated technology can improve the use of microneedles. The use of an applicator also can improve the uniformity of microneedle penetration depth.

3.5. Pharmacokinetic study of DPH tip-loaded microneedles

To investigate transdermal absorption of DPH tip-loaded microneedles, a pharmacokinetic study was performed with normal SD rats. DPH was administered to two groups of rats using tip-loaded microneedles. One group received 692 µg/kg (179.9 µg) and the other group received 283 µg/kg (73.6 µg) of DPH. The content of DPH in the two arrays of microneedles applied to the two rat groups amounted to about 15% and 6% (w/w), respectively, of the total content in an array of 100 microneedle tips. The plasma profiles and relevant pharmacokinetic parameters after oral administration and microneedle administration are shown in Fig. 9. A low oral dose (283 µg/kg) did not show a clear pharmacokinetic profile. The C_max value was dependent on the delivered dose of DPH. DPH tip-loaded microneedles (692 µg/kg) had T_max and C_max values of 0.8 h and 9 ng/ml, respectively. Compared with oral administration of the same dose of DPH, C_max of DPH tip-loaded microneedles was four times that of oral administration and AUC of DPH tip-loaded microneedles was three times that of

Fig. 5. (a) Optical microscopic image of an array of Nile Red tip-loaded microneedles and (b) fluorescence microscopic image of one Nile Red tip-loaded microneedle.
oral administration. Compared to previous pharmacokinetic data on dissolving microneedles, $T_{\text{max}}$ of 0.8 h was later than those of 0.25 h (exenatide, HA) [33], 0.25 h (hGH, dextran and chondroitin) [34]. When considering MW of drug and solubility of needle material in water, there was difference in $T_{\text{max}}$ between this study and that in a previous study. However, this result was comparable with those of other dissolving microneedle studies [35,36]. The relative bioavailability of microneedle administration showed a higher value than that of oral administration. In the case of 692 μg/kg of administration, the bioavailability of microneedle administration was 2.4 times higher than that of oral administration.

In the pharmacokinetic study, a total of 179.9 μg of DPH (69% w/w), corresponding to 692 μg/kg, was encapsulated in the tips of 100 microneedles, which were placed on a 0.49 cm² square plate. The amount of drug delivered can be increased in three ways: (1) by encapsulating more DPH in the microneedles, (2) by increasing microneedle density, and (3) by enlarging the size of the patch. When the maximum amount of DPH is encapsulated (78%) and needle density is the same as that of the microneedle

Fig. 6. Optical micrograph of porcine skin pierced by an array of tip-loaded microneedles with DPH content of (a) 52% and (b) 69% (w/w) subsequently exposed to Trypan Blue dye. (c) The change in the ratio of the number of holes generated by microneedles prepared using ethanol/water mixture (80:20, v/v) regarding the content of DPH. (d) The change in the ratio of the number of holes generated by microneedles to the number of microneedles prepared using water solvent regarding the content of DPH.

Fig. 7. SEM image of morphological change in DPH tip-loaded microneedles regarding insertion into porcine skin at (a) 5 min, (b) 15 min, (c) 30 min, and (d) 60 min. DPH content of 69% (w/w) was encapsulated in tips of microneedles prepared from an HPMC-DPH-ethanol/water mixture solution.

Fig. 8. Profile of amount of DPH delivered into porcine skin (in vitro) as function of insertion duration at 32 °C.
system described in this article, the size of the patch should be approximately 5.7 cm² to satisfy the human oral dose requirement of 11 mg/60 kg. However, the AUC of DPH tip-loaded microneedles was three times that of oral administration. Thus, a 1.9 cm² tip-loaded microneedle patch with 78% DPH content can deliver the same dose as that delivered by conventional oral administration.

4. Conclusion

The ACh inhibitor DPH was loaded in the tips of dissolving microneedles for transdermal delivery of the correct dose of DPH. DPH tip-loaded microneedles were prepared using a micromolding method based on an HPMC-ethanol/water mixture and CMC-water. High DPH content was successfully loaded in tips of microneedles by using an HPMC-ethanol/water mixture (80:20, v/v). Up to 78% DPH (w/w) content could be encapsulated in the tips with sufficient mechanical strength for successful insertion into the skin. High DPH content was critical for clinical use of tip-loaded microneedles. DPH content of 78% in 100 microneedles tips, placed on a 0.49 cm² plate, provided the possibility of clinical application of DPH. Because DPH was located only in the microneedle tips, most of the DPH was delivered into the skin within 5 min after insertion. $C_{\text{max}}$ increased by the increase in the amount of DPH in tip-loaded microneedles, and $C_{\text{max}}$ of DPH tip-loaded microneedles was four times that of oral administration with the same dose of DPH. Administered with tip-loaded microneedles with high DPH content could replace oral administration of DPH, a second FDA-approved anti-AD drug. Tip-loaded DPH microneedles have the advantage of transdermal drug delivery of DPH by brief administration to the rat, J. Drug Metab. Toxicol. (2012).

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