

Transdermal Delivery of Sodium Nonivamide Propionate by Iontophoresis

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The aim of this study was to investigate the transdermal iontophoresis of a newly designed capsaicin derivative, sodium nonivamide propionate (SNP). The iontophoretic permeation of SNP from various pH buffers increased following the decrease of pH values. This trend was consistent with that of sodium nonivamide acetate (SNA) which is another synthetic analogue of capsaicin. However, the iontophoretic permeability of SNP was much lower than that of SNA. SNP was also delivered iontophoretically from hydrogel formulations. It is suggested that ionizable polymers should be avoided for iontophoretic delivery to maintain good penetration capacity of drugs. Both nonionic cellulose polymers of methylcellulose (MC) and hydroxypropyl methylcellulose (HPMC) showed higher iontophoretic flux for SNP than the others did. Furthermore, the flux of SNP leveled off with an increase in the amount of polymers in hydrogel, indicating that the viscosity of vehicles plays an important role in the permeation of SNP. Comparing the various iontophoretic application modes, the discontinuous on/off cyclic mode showed higher penetration capacity than did the continuous mode although they possessed the same electrical energy. Moreover, the desorption time of SNP from skin was approximately 20 min which was longer than that of SNA.

Key words transdermal iontophoresis; sodium nonivamide propionate; hydrogel

Sodium nonivamide propionate (sodium *N*-nonanoyl vanillylamide-4'-*O*-propionate; SNP, C₂₀H₃₀NO₅Na) is a recently designed derivative of capsaicin which is synthesized by alkylation of the phenolic hydroxyl group of nonivamide with β -bromopropionic acid in the presence of sodium hydroxide.¹⁾ SNP reveals marked antinociceptive activity without producing the overt pungent sensation and irritation that have been found in capsaicin. This suggests that SNP can be extensively used in clinical therapy because of the lack of pungent pain to improve patients' compliance. The antinociceptive potency of SNP evaluated by ED₅₀ value is 13.2 and 1.4 times than that of indomethacin and capsaicin respectively.²⁾ Furthermore, the acute toxicity test in mice indicates that SNP is comparatively less toxic than capsaicin.¹⁾ The poor antinociception after oral dosing of capsaicin derivatives is reported due to the first-pass metabolism.^{3,4)} Accordingly, transdermal delivery is a more suitable choice for SNP to achieve better bioavailability.

Our previous studies investigated transdermal delivery of sodium nonivamide acetate (SNA) *via in vitro* iontophoretic enhancement.⁵⁻⁷⁾ The difference in structure between SNA and SNP is that the ether-linked group of phenol is acetate and propionate respectively. The aim of this present study was the investigation of *in vitro* transdermal iontophoresis of SNP for comparison with that of SNA studied previously. Moreover, various formulations and application modes were utilized to maximize or optimize the iontophoretic permeability of SNP. The excised Wistar rat skin was used as the model membrane since the flux of SNA through this skin was more similar to that through human skin.⁸⁾ Accordingly, the rat skin was also used for the skin barrier of SNP because of the structural similarity of the two analogues and the possibility of comparing their penetration capacity in the same status.

MATERIALS AND METHODS

Materials Carbopol 940[®] was obtained from B. F. Goodrich

Co. (U.S.A.). Tween 20[®] and propylene glycol were obtained from Merck Co. (Germany). Methylcellulose (MC), carboxymethyl cellulose sodium (CMC) and nonivamide (NVA) were purchased from Tokyo Kasei Ind. Co. (Japan). Hydroxypropyl methyl cellulose (HPMC) was obtained from Shin-Etsu Co. (Japan). The synthetic procedure of SNP was performed in our laboratory according to the method of Yang *et al.*²⁾ All other chemicals and solvents were of analytical grade.

Instruments and *in Vitro* Permeation Procedures The *in vitro* permeation procedures of iontophoresis were determined using a pair of horizontal glass diffusion cells. The method for determining transdermal iontophoresis of SNP was that used previously.⁵⁾ Briefly, the donor compartment of the cell was filled with 8 ml of 0.06 M buffer solution or 8 g of hydrogel base containing 200 μ g/ml SNP. The receptor phase containing 8 ml of 0.06 M, pH 7.4 McIlvaine buffer was used. The ionic strength of buffer was adjusted as reported.⁹⁾ A pair of platinum wires having an effective length of 15 mm (99.99% purity, 0.5 mm in diameter) and used as electrodes was immersed in the solution or gel with the cathode in the donor and anode in the receptor respectively.

Effect of Donor pH Value The effect of pH value on the flux of SNP was determined using pH values of 4.2, 5.6, 7.0 and 8.0 while the ionic strength of donor solution was adjusted to 0.06 M. Current densities of 0, 0.2, 0.5, and 1.0 mA/cm² were applied in a continuous mode respectively.

Iontophoresis of SNP from Hydrogel Bases Various hydrogel formulations including Carbopol 940[®], MC, CMC and HPMC were incorporated with SNP to perform the *in vitro* iontophoretic delivery. Various concentrations of cellulose derivatives were also prepared for the following experiments. The preparation method of these formulations was the same with the previous paper.⁶⁾

Optimization of Iontophoretic Application Modes Four studies were conducted at a fixed current density of 0.5 mA/cm² from pH 4.2 buffer solution and 5% MC hydrogel formulation. In the first study, current was continuously

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applied for 3 h, and then was cut off. In the second study, current was discontinuously applied for a 20:10 min on/off cycle. In the third study, a discontinuous application was conducted for a 20:20 min on/off cycle. In the fourth study, the discontinuous application was a 20:30 min on/off cycle. Total current density application time was 3 h for these four experiments.

Analytical Methods The SNP content of the various samples was analyzed by an HPLC system consisting of a Waters Model M-45 HPLC pump, a Waters 715 sample processor and a Waters 470 fluorescence detector. A 12.5 cm long, 4.0 mm inner diameter stainless steel column with RP-18 column (Merck) was used. An automated integrator system (Hewlett Packard 3395) was used to detect the area under the curve. The SNP sample was mixed with a suitable amount of nonivamide as the internal standard. The mobile phase consisting of 50% pH 4.0 buffer and 50% acetonitrile was used at a flow rate of 1.0 ml/min. The column effluent was passed through the fluorescence detector set at an excitation wavelength of 280 nm and an emission wavelength of 310 nm. The retention time of SNP and NVA were found to be 4.1 and 5.4 min, respectively.

RESULTS AND DISCUSSION

Effect of Donor pH Value The SNP transdermal permeation with or without current density was carried out at pH of 4.2, 5.6, 7.0 and 8.0 as shown in Fig. 1. There were no cumulative amounts of SNP detected for passive diffusion during 6 h at any pH. The permeation of SNP was greatly enhanced after application of iontophoresis. Moreover, the number of SNP molecules passing through the skin increased with an increase of current strength as expected. The iontophoretic flux was found to be pH dependent and showed a trend of pH 4.2 > pH 5.6 > pH 7.0 > pH 8.0, which was consistent with the trend of SNA.⁵ The chemical structure of SNP is carboxylate salt, the pK_a of the corresponding carboxylic acid should be in the range from 3 to 5. This molecule will be neutral at pH below pK_a and ionized at higher pH. The iontophoresis was basically more effective at pH values where the drug was primarily ionized.¹⁰ Nevertheless, the exact opposite result was observed in this experiment. The skin has a minimum charge density at a pH value of 3–4 which is the isoelectric point of keratin. When the pH approximates this value, skin becomes positively charged and favors the delivery of negatively charged drug. So the iontophoresis favoring SNP at lower pH values resulted in the higher iontophoretic flux of SNP. Another explanation might be the direction of electro-osmotic flow produced by iontophoresis. The electro-osmotic flow is usually from anode to cathode which is an unfavorable factor for SNP.¹¹ The current-induced electro-osmotic flow of water across skin increased following the increase of pH.¹² Such a mechanism could explain the decrease in SNP flux with pH increased.

Comparison of the iontophoretic flux between SNA and SNP at various donor pH values showed the permeability of SNA to be significantly lower than that of SNP (3.58–16.19 fold) during iontophoresis.⁵ The determination of solubility and *n*-octanol/water partition coefficient showed SNP to be more hydrophobic than SNA.¹³ The difference between the iontophoretic permeability of these two analogues can be

explained by the free volume model theory.¹⁴ The ion sphere mobility has been assumed to be proportional to the fractional volume of the space that is accessible to the ion sphere.¹⁵ So the iontophoretic permeation of an ion solute has been shown to be directly related to the molar volume of the solute. The molar volume of an ion is related to its molecular weight.¹⁴ Accordingly, a solute with lower molecular weight shows high electrophoretic mobility. This is consistent with the previous study that iontophoretic delivery is theoretically inversely related to the molecular weight of a series of derivatives.¹⁶

Transdermal Iontophoresis of SNP from Hydrogels

When the transdermal iontophoresis is administered clinically, the semisolid dosage form may be preferable to the solution. The hydrogel provides a fast release of drug. Moreover, there is a great volume of water employed in hydrogel formulation which exhibits a high electrical conductivity. For these reasons the iontophoretic delivery of SNP from gel bases were developed. The various Carbopol 940[®] formulations and cellulose hydrogels at proximate viscosities were prepared for transdermal iontophoresis to exclude the effect of viscosity on drug delivery.⁶ As shown in Fig. 2, the iontophoretic flux of SNP from Carbopol 940[®] and CMC hydrogels is lower than that from MC and HPMC hydrogels. Carbopol 940[®] (polyacrylic acid) and CMC are both anionic polymers. Partial current would be carried by the anionic polymers resulting in the reduction of current density carried by SNP. It is therefore suggested that ionizable polymers be avoided for iontophoretic delivery to maintain good drug permeability.

The iontophoretic flux of SNP from MC and HPMC hydrogels was even higher than that from buffer solution at the same current density, because polymers are certainly more lipophilic or oil-like than water.¹⁷ MC and HPMC may increase the solubility of SNP in formulations resulting in the enhancement of permeability. Moreover, the lipophilicity of MC is higher than that of HPMC which results in higher SNP flux from MC hydrogel.¹⁸ Another possible reason that cellulose exhibits a high capacity of SNP permeation is its ability to retard the crystallization. Cellulose derivatives are antinucleating polymers which would stabilize the supersaturated solutions resulting in an increase in thermodynamic activity of a drug.¹⁹ Further study is needed to determine this mechanism, however.

Effect of Polymer Concentration For a specific dose of drug, varying the polymer concentration is probably the most efficient way for the formulation to adapt the release characteristics to a specific criterion. MC and HPMC were selected for evaluation of various polymer concentrations on SNP iontophoretic permeation (Fig. 3). The flux of SNP decreased with an increase in the amount of both polymers in the hydrogels, and it was interpreted that both substances in hydrogel functioned as a diffusion barrier for SNP. This is a general rule for increasing the proportion of hydrophilic polymer would cause more rigid structure of hydrogels and decrease drug release rate.²⁰ Another mechanism is that an increase in the viscosity results in a decrease in the vehicular conductivity, so the iontophoretic permeation of drug is also decreased.²¹ Moreover, it is our opinion that the increase of polymer concentration simultaneously decreases the proportion of water in the vehicle, resulting in the reduction of con-

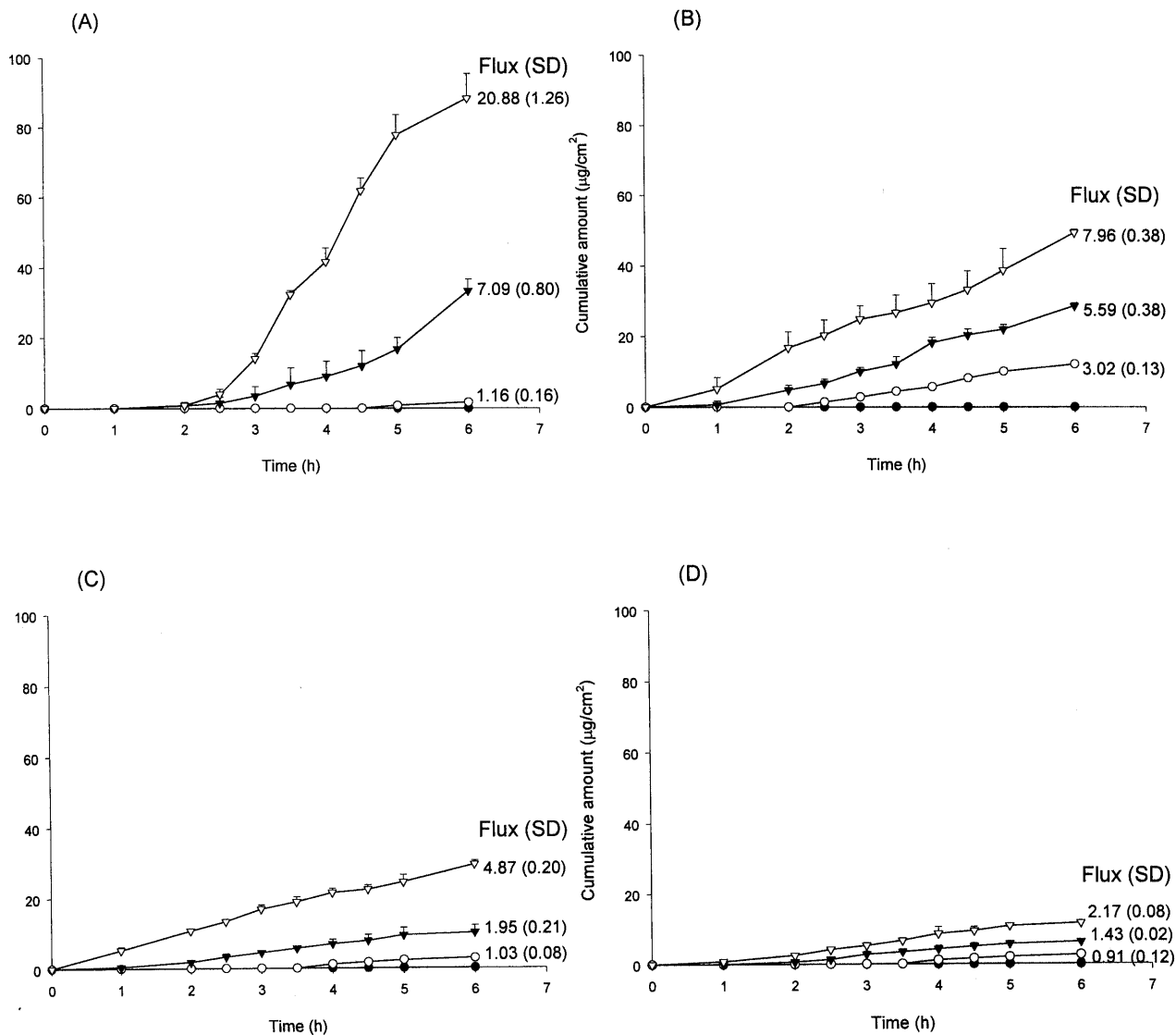


Fig. 1. Cumulative Amount of SNP Detected in the Receptor Compartment versus Time Following Iontophoresis at Various Donor pH Values
 ●, 0 mA/cm²; ○, 0.2 mA/cm²; ▼, 0.5 mA/cm²; ▽, 1.0 mA/cm²; (A) pH 4.2, (B) pH 5.6, (C) pH 7.0, (D) pH 8.0 Points and vertical bars represent means and S.D., respectively (n=3).

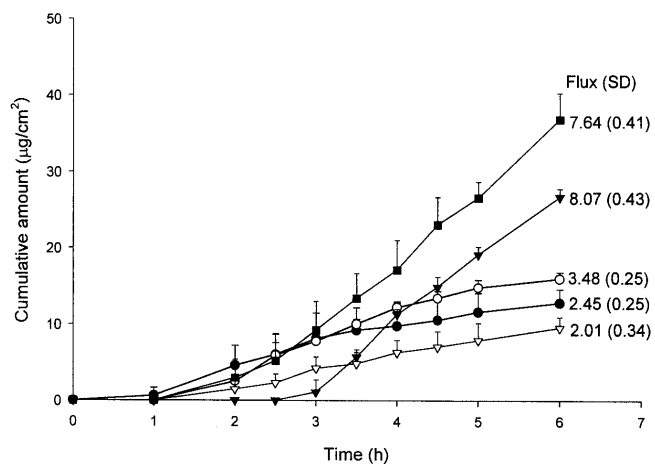


Fig. 2. Cumulative Amount of SNP Detected in the Receptor Compartment versus Time Following Iontophoresis at Various Gel Formulations
 ●, C940+Tween 20; ○, C940+PG; ▼, MC; ◻, CMC; ■, HPMC, Carbopol 940® (0.3%), propylene glycol (4.0%), MC (6.0%), CMC (4.5%), HPMC (5.0%). Point and vertical bars represent means and S.D., respectively (n=3).

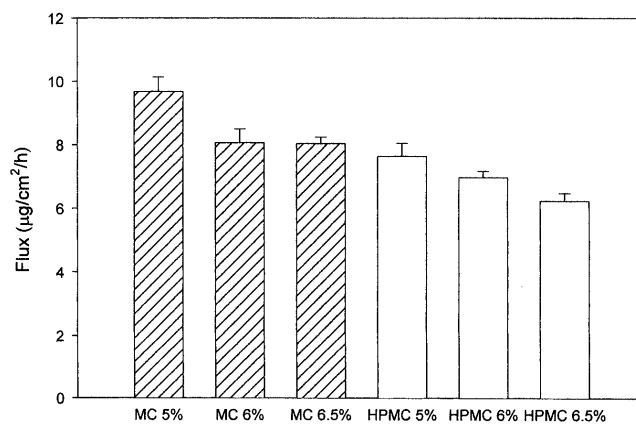


Fig. 3. Flux of SNP from Cellulose Gel Formulations at Various Cellulose Concentrations during Transdermal Iontophoresis
 Point and vertical bars represent means and S.D., respectively (n=3).

Table 1. Effect of Various Current Application Modes at 0.5 mA/cm² on The AUC_{0-6h} ($\mu\text{g}/\text{cm}^2$) of SNP from Solution and Cellulose Gel Formulations

Application mode	Formulation	
	pH 4.2 buffer solution	MC hydrogel
Continuous	3.12±0.42	7.91±0.31
20:10 min on/off	4.36±0.71	7.68±0.34
20:20 min on/off	6.02±0.76	8.58±0.21
20:30 min on/off	2.73±0.29	5.14±0.64

Each value is the mean±S.D., n=3.

ductivity of a formulation.

Effect of Various Application Modes during Iontophoresis Four modes of iontophoresis were used to maximize the permeability of SNP, including the 3 h continuous mode, 20:10 min on/off cyclic mode, 20:20 min on/off cyclic mode and 20:30 min on/off cyclic mode. The AUC (area under the curve) of the flux (dQ/dt) to time profile of the iontophoretic permeation was calculated as the level of permeation capacity. As shown in Table 1, the AUC of discontinuous modes of 20:10 and 20:20 exhibits a higher value than the continuous mode. This is due to the intensity of the effective current of discontinuous mode across skin not decaying exponentially as a function of iontophoretic treatment duration, as observed in the continuous mode.^{22,23)}

Judging from the AUC of three cyclic application modes, the 20:30 discontinuous mode showed the lowest value. During the current-off period, the permeant is desorbing from the skin until the emptying of drug reservoir inside the skin.²⁴⁾ Accordingly, the desorption time of SNP from skin after current-off requires about 20 min since the longer period of current-off time (30 min) causes the reduction of AUC . This desorption time of SNP was longer than that of the 10 min period of SNA,⁶⁾ confirming a slower diffusion and higher lipophilicity of SNP than SNA as noted previously.

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