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Transdermal iontophoresis of sodium nonivamide acetate. IV. Effect of polymer formulations

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Abstract

The patch or semisolid dosage form is more applicable than solution as a transdermal iontophoretic delivery system to be administered clinically. Therefore the effect of iontophoresis for sodium nonivamide acetate (SNA) from various polymer formulations was investigated by using an in vitro permeation study. The cumulative amount–time curves were suitable to fit by a zero-order equation which indicated a steady-state permeation rate or sustained release effect could be achieved from polymer hydrogels. The permeability coefficient of SNA from polyvinylpyrrolidone (PVP) or hydroxypropylcellulose (HPC) were similar and showed the highest penetration capacity among six individual polymers. In order to develop optimal devices for clinical utilization, blends of two polymers as binary system formulations were prepared in order to attain acceptable bioadhesion and viscosity. The binary cellulose–PVP formulations apparently improve the mechanical characteristics of hydrogel. Moreover, the flux of SNA from these binary systems increased in the order of methylcellulose (MC) + PVP < hydroxypropyl methylcellulose (HPMC) + PVP < HPC + PVP, which was consistent with the rank order of the SNA permeability coefficient from three individual cellulose derivatives. After the examination of pH shift during iontophoresis, HPMC could provide a sufficient buffer capacity to stabilize the pH value of the donor in an electrical field. Isopropyl myristate showed an enhancing iontophoretic flux of SNA after pretreatment with skin, possibly due to the ability of water accumulation in the skin reservoir. However, Azone showed no or negative effect on iontophoretic transport of SNA. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Sodium nonivamide acetate; Transdermal iontophoresis; Polymer; Hydrogel

1. Introduction

Sodium nonivamide acetate (sodium *N*-nonanoyl vanillyl-4′-*O*-acetate (SNA)) is a recently designed derivative of capsaicin which was

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synthesized from nonivamide (Fang et al., 1995). SNA showed a higher antinociceptive potency than did capsaicin or indomethacin, by 1.75- and 27.50-fold, respectively (Chen et al., 1992). In our previous investigations, SNA was shown to have potential for extensive use in clinical therapy, as applied by the transdermal route, as it does not cause pungent skin sensation or burning pain which had been found with capsaicin (Fang et al., 1996a, 1997b). SNA becomes an ionized molecule because of the removal of sodium salt at appropriate pH. So transdermal iontophoresis is suitable for SNA to enhance its penetration capacity (Fang et al., 1996b,c, 1997a).

When the transdermal iontophoretic delivery system is administered clinically, the patch or semisolid dosage form may be more applicable than solution. However, most researches which are related to transdermal iontophoresis focus on the discussion of aqueous solution. To hold promise for further in vivo application, the polymer is added into vehicle to form a hydrogel matrix in this present study. Polymer delivery systems have been developed with the capability of controlling the release rate of a drug over a long period of time (Langer et al., 1985). Furthermore, there is always a great volume of water employed in gel formulation which exhibits a high electrical conductivity. Formulation of hydrogels can be adjusted for optimal penetration of drugs into the skin. In this study, various polymer formulations were investigated for in vitro permeation studies. The pH value and viscosity of vehicles were also determined, since this is the most widely utilized method for the characterization of polymer (Mitchell et al., 1993). Many polymers offer good release rate for drugs; however, the mechanical characteristics of these polymers are often inadequate. In order to overcome this pharmaceutical deficiency, well-characterized polymeric combinations can provide different gel structure and viscoelastic behavior (Cascone et al., 1995; Kim and Fassihi, 1997). Accordingly one polymer was blended, in different ratios, with another one to attain adequate release rate and viscosity for SNA.

An extensive application area may be needed for a therapeutic effect, and this may prevent good patient acceptance and compliance (Kondo and Sugimoto, 1987). One of the ways to reduce device size is to incorporate penetration enhancers which will improve the permeation characteristic of the skin (Hadgraft, 1996). Moreover, the combination of enhancers and iontophoresis would moderate the iontophoretic regimen required to achieve target flux, thus improving the tolerability of skin (Srinivasan et al., 1990). After a series of investigations in this present study, polymer formulations with good release properties and mechanical characteristics may be obtained to offer a basis for further clinical study of transdermal iontophoresis of SNA.

2. Materials and methods

2.1. Materials

Polyvinylpyrrolidone (PVP; MW 360000), hydroxypropyl cellulose (HPC), methylcellulose (MC; 350–550 cps), pectin and polyvinyl alcohol (PVA; $n = 1750$) were supplied by Tokyo Kasei (Japan). Hydroxypropyl methylcellulose (HPMC; Metolose®; 4000 cps) was obtained from Shin-Etsu (Japan). Chitosan was purchased from Fluka (USA). Plastoid® (hydrophilic polyacrylate) was obtained from Rohm (Germany). Isopropyl myristate was from Wako (Japan). Azone (99% in purity) was a gift kindly supplied by the School of Chemistry, Kaohsiung Medical College, Taiwan. The synthetic procedure of SNA had been performed in our laboratory and reported earlier (Fang et al., 1995). All other chemicals and solvents were of analytical grade.

2.2. Preparation of hydrogels

A 5% w/v polymer was added into citrate–phosphate buffer, pH 4.2 (McIlvaine) to give a total volume of 100%. The ionic strength of buffer was 0.06 M. SNA was incorporated into the base to give a concentration of 200 μg/g (0.02%). The pH of the polymer formulation was adjusted with either 1 M NaOH or 1 M HCl to pH 4.2. The hydrogel formulation were performed for in vitro experiment after 48 h of preparation, since the

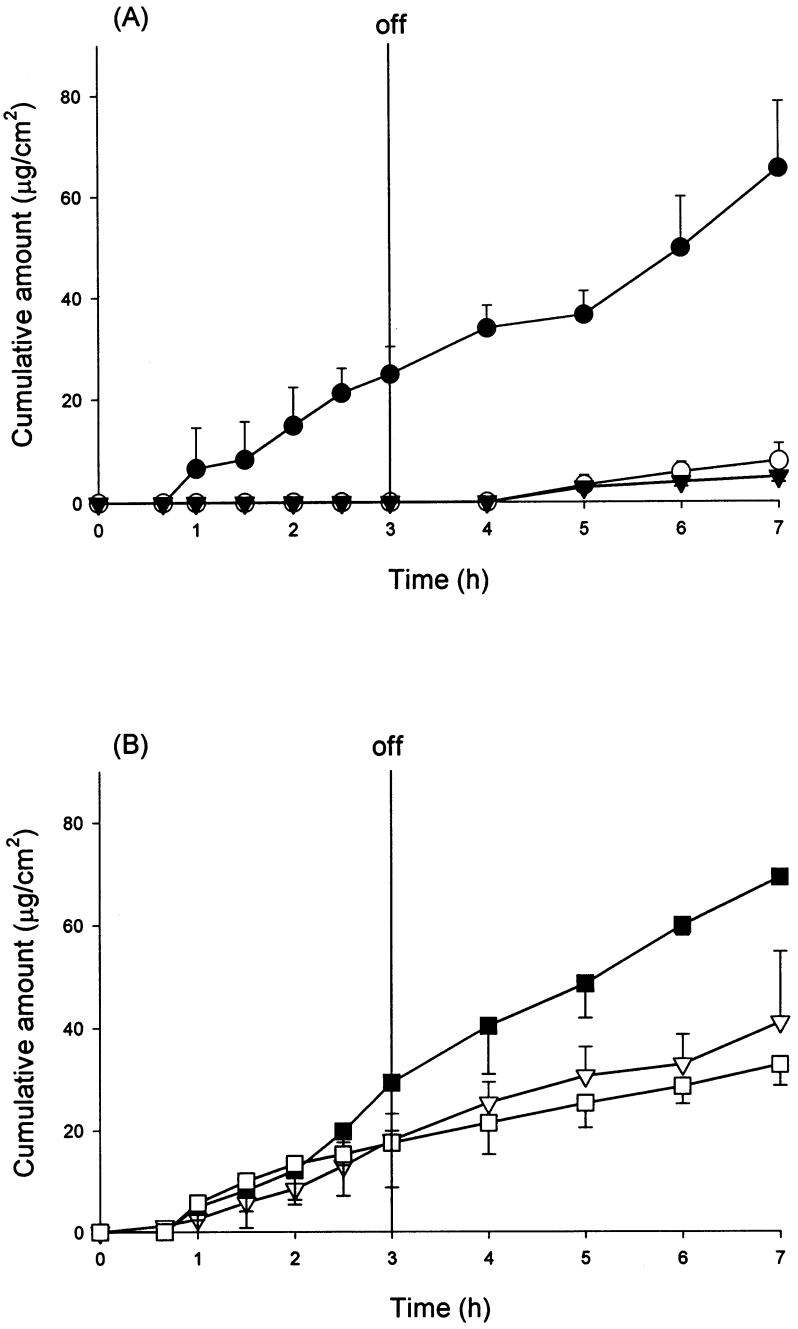

Fig. 1. Cumulative amount of SNA detected in the receptor compartment vs time following iontophoresis from various polymer vehicles: (●) PVP; (○) chitosan; (▼) Plastoid®; (▽) HPMC; (■) HPC; (□) MC. All data represent the means of three experiments ± S.D.

Table 1
Effect of various polymer solutions (5%, w/v) in donor on the viscosity and iontophoretic penetration of SNA at pH 4.2

Polymers	Final pH of donor	Viscosity ($cps \times 10^3$)	Permeability coefficient $\times 10^3$ ($1/cm^2$ per h)
PVP	5.36	8.92 ± 0.78	5.85 ± 1.19
Chitosan	4.22	102 ± 17	—[a]
Plastoid®	4.25	35.2 ± 3.1	—
HPMC	4.75	108 ± 12	4.03 ± 1.36
HPC	4.85	34.2 ± 6.1	6.97 ± 0.36
MC	4.50	91.8 ± 8.8	2.89 ± 0.37

Each value represents the mean $\pm$ S.D. ($n = 3$). PVP, polyvinylpyrrolidone; HPMC, hydroxypropyl methylcellulose; HPC, hydroxypropyl cellulose; MC, methylcellulose.
[a] The data points are not sufficient to compute the permeability coefficient.

viscosity and clarity would attain the highest value after this period (Martin et al., 1983).

2.3. Instruments and in vitro permeation procedures

The in vitro permeation procedures of iontophoresis were determined using horizontal glass diffusion cells. The abdominal skin of excised Wistar rats was used as the model membrane. The hair of the abdominal skin was shaved using an electric clipper. The skin pieces were soaked in the receptor buffer solution for 45 min prior to being placed in the cells. The receptor phase, containing 8 ml of 0.06 M McIlvaine buffer, pH 7.4, was used. The available diffusion surface area was 0.785 cm^2. A pair of platinum wires, having an effective length of 15 mm (99.99% purity, 0.5 mm in diameter), used as electrodes, were immersed in the cell with the anode in the donor and the cathode in the receptor. The electrode polarity was reversed for anion iontophoresis. The electrodes were connected to a current power supplier (Yokogawa, Model 7651, Japan). Current density of 0.5 mA/cm^2 was applied to stimulate the penetration of SNA in experiments.

The experiments were agitated by a magnetic stirrer at 600 rpm. The 200-μl samples were withdrawn from the receptor at regular intervals and immediately replaced by an equal volume of fresh receptor solution. The samples were assayed by HPLC as described previously (Tsai et al., 1994).

Table 2
Effect of various polymer solutions (5%, w/v) on the stratum corneum–polymer solution partition coefficient

Polymers	Partition coefficient
—[a]	32.6 ± 24.31
HPMC	17.23 ± 5.32
HPC	23.47 ± 4.90
MC	11.31 ± 3.69

Each value represents the mean $\pm$ S.D. ($n = 3$). HPMC, hydroxypropyl methylcellulose; HPC, hydroxypropyl cellulose; MC, methylcellulose.
[a]pH 4.2 buffer solution without polymers.

2.4. Pretreatment procedure of penetration enhancer

The 8 ml of enhancer solution, including isopropyl myristate or Azone, was deposited onto the stratum corneum surface after mounting the rat skin between the two half-horizontal glass diffusion cells. Skin samples were pretreated with the test enhancers for 12 h. After the duration of pretreatment, the enhancer solution was removed, and the skin was rinsed twice with 5 ml McIlvaine buffer, pH 7.4, and then wiped off using a paper tissue. The donor cell was replaced by a new one and the permeation experiment was then conducted.

2.5. Viscosity measurements

Measurements of viscosity were carried out on hydrogels before and after the performance of the in vitro permeation study. Tests were maintained at 37°C in a cone-and-plate viscometer

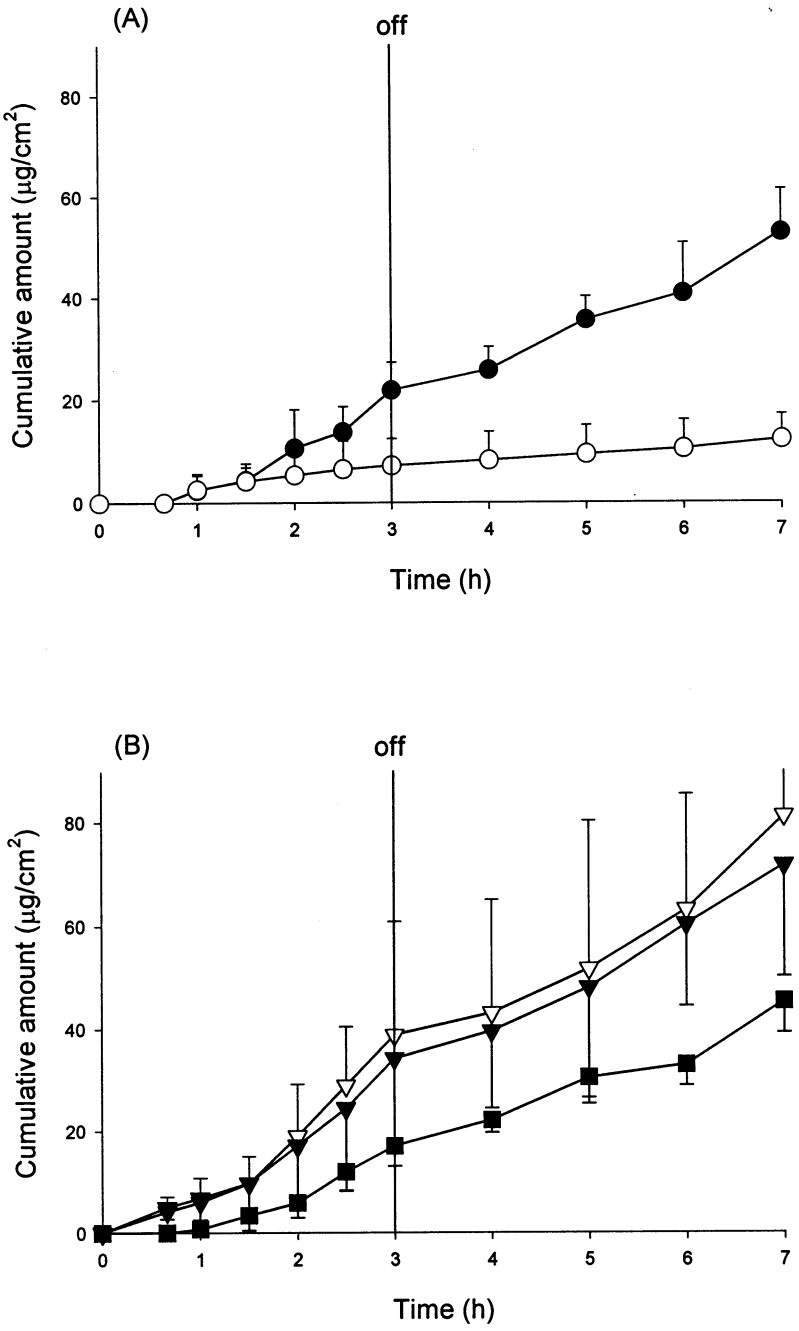

Fig. 2. Cumulative amount of SNA detected in the receptor compartment vs time following iontophoresis from various binary polymer systems: (●) PVA + PVP; (○) HPMC + pectin; (▲) HPMC + PVP; (▽) HPC + PVP; (■) MC + PVP. All data represent the means of three experiments ± S.D.

Table 3
Effect of various 5% binary polymer solutions and ratios in donor on the viscosity and iontophoretic penetration of SNA at pH 4.2

Polymers	Ratios	Final pH of donor	Viscosity (cps $\times 10^3$)	Permeability coefficient $\times 10^3$ ($1/cm^2$ per h)
PVP + PVA	1:1	4.69	36.0 ± 3.7	5.11 ± 0.73
HPMC + pectin	1:1	4.32	61.2 ± 8.9	1.02 ± 0.41
MC + PVP	1:1	5.54	68.2 ± 14.4	4.44 ± 0.61
HPMC + PVP	1:1	4.76	69.0 ± 7.1	5.40 ± 1.79
HPMC + PVP	1:3	4.66	36.0 ± 4.9	4.77 ± 0.48
HPMC + PVP	3:1	4.40	75.2 ± 8.6	2.82 ± 0.96
HPC + PVP	1:1	5.39	35.2 ± 9.6	7.38 ± 1.78
HPC + PVP	1:3	4.77	14.4 ± 2.6	5.40 ± 1.16
HPC + PVP	3:1	4.89	29.2 ± 9.7	7.67 ± 0.43

Each value represents the mean $\pm$ S.D. ($n = 3$). PVP, polyvinylpyrrolidone; PVA, polyvinyl alcohol; HPMC, hydroxypropyl methylcellulose; HPC, hydroxypropyl cellulose; MC, methylcellulose.

(Brookfield, Model DV-2, USA). Reading was carried out 30 s after measurement was made, when the level had stabilized.

2.6. Determination of stratum corneum–polymer solution partition coefficient

The method used to assess the stratum corneum–polymer solution partition coefficient was based on the previous study (Williams and Barry, 1991). Dry stratum corneum of rat was weighed and hydrated in 0.002% (w/v) aqueous sodium azide solution. After 72 h the samples were floated flat onto tissue paper, blotted dry, reweighed and equilibrated with the SNA buffer solution, pH 4.2, with 5% (w/v) polymer for 24 h. Then the samples were blotted dry, solubilized and the drug determined by HPLC. The partition coefficient was calculated by dividing the concentration of SNA in stratum corneum by that in solution with polymer.

3. Results and discussion

3.1. Effect of various polymer hydrogels

The current was set to 0.5 mA/cm^2, which has been reported in the literature to be the maximum acceptable current producing minimal skin damage and irritation (Brand and Iversen, 1996). The profile of cumulative amount–time curves for six single polymer formulations of SNA is shown in Fig. 1. All formulations were prepared at a same pH value of 4.2 to minimize the pH effect. After the performance of the in vitro permeation study, the pH of donor was increased because of the production of OH^- ions at the cathode, as depicted in Table 1. This is a common phenomenon with platinum electrodes. However, platinum wires are still selected for this present experiment since they do not precipitate ions, as Ag/AgCl electrodes do. Besides, they can be utilized immediately without any oxidation-reduction pretreatment. Accordingly, platinum electrodes are the convenient choice for the iontophoretic delivery system. Although the pH drifts produced by chitosan and Plastoid® were negligible, the penetration capacities of SNA from both polymers were relatively low. On the other hand, a series of cellulose polymers maintained sufficient buffer capacity and showed moderate SNA flux as compared with PVP. For cellulose polymers, the penetration capacity was directly related to the pH shift between initial and final pH values in the in vitro permeation experiment.

Viscosity is the most widely utilized method for the characterization of polymer structure, although it is not sufficiently comprehensive for full determination of gel strength (Wakerly et al., 1997). Basically, as shown in Table 1, the permeability coefficient of SNA increased following the

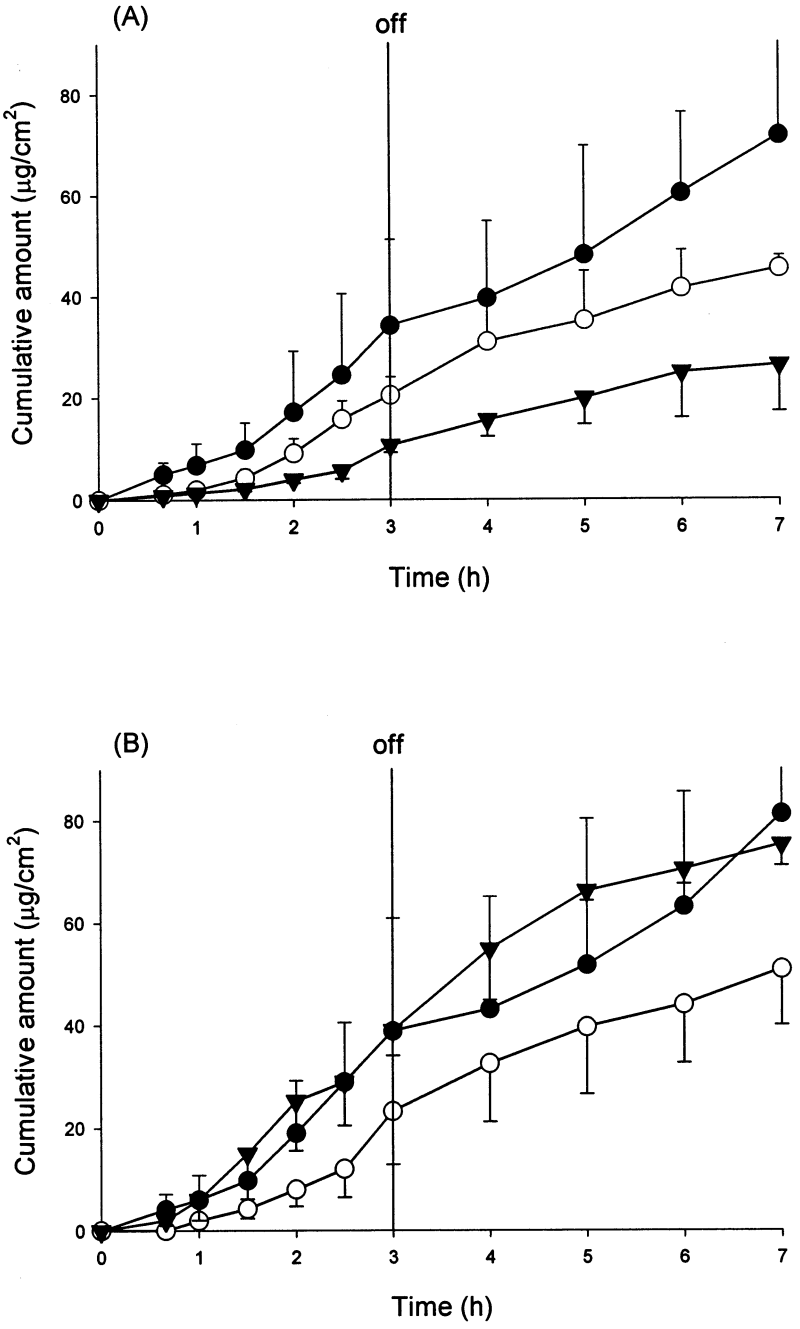

Fig. 3. Cumulative amount of SNA detected in the receptor compartment vs time following iontophoresis from various binary polymer systems with various ratios: (●) 1:1; (○) 1:3; (▼) 3:1. (A) HPMC + PVP; (B) HPC + PVP. All data represent the means of three experiments ± S.D.

Table 4
Effect of various percents of polymer solutions in donor on the viscosity and iontophoretic penetration of SNA at pH 4.2

Polymers	Percent (%)	Final pH of donor	Viscosity (cps $\times 10^3$)	Permeability coefficient $\times 10^3$ (1/cm^2 per h)
PVP	2.5	4.86	8.28 ± 3.27	6.68 ± 0.44
	5.0	5.36	8.92 ± 0.78	5.85 ± 1.19
	10.0	5.41	18.6 ± 3.5	4.23 ± 0.55
HPMC+PVP (1:1)	2.5	4.76	46.6 ± 7.7	2.58 ± 0.84
	5.0	4.76	69.0 ± 7.1	6.65 ± 1.79
	10.0	4.27	87.2 ± 10.1	5.25 ± 0.56

Each value represents the mean $\pm$ S.D. ($n = 3$). PVP, polyvinylpyrrolidone; HPMC, hydroxypropyl methylcellulose; HPC, hydroxypropyl cellulose; MC, methylcellulose.

decrease of polymer viscosity, with the exception of that of the Plastoid® formulation. This result is similar to our previous study, that an increase in the viscosity resulted in a decrease in the formulation conductivity (Fang et al., 1996c). Therefore, drug diffusion through the hydrogel matrix may be a rate-determining step, as the viscosity plays an important role in controlling the release of drug into receptor (Ho et al., 1994).

The slopes of the resulting linear plots were computed. From these slopes, the flux (μg/cm^2 per h) was calculated. The curves were suitable to fit using a zero-order equation. This means a steady-state permeation rate of SNA could be achieved from polymer hydrogels. Accordingly a controlled drug delivery may be observed for SNA from a polymer matrix, since sustained release of drugs has been focused on the development of systems which result in either zero-order release or a drug-release profile which is a simple function of time (D'Emanuele, 1996). Although the current was cut off after 3 h of application, SNA molecules continuously permeate through the skin even after terminating the current density, as shown in Fig. 1. One explanation for this observation is the existence of a drug reservoir in the skin (Lelawongs et al., 1990). Thus, after iontophoretic treatment, the flux should still be greater than that of passive diffusion until a sufficient amount of the drug has desorbed from the skin. Another explanation is the alteration of the nature of the skin. The presence of an electrical field may provide sufficient heat to make conformational changes in the lipid bilayer, increasing the fluidity of the stratum corneum (Lashmar and Manger, 1994). Such conformational changes may not be immediately reversible after termination of current density, and this alteration could yield some changes in skin permeability (Chien et al., 1989; Srinivasan et al., 1989). The current-induced change in the intrinsic permeability of skin, from which the tissue cannot recover, is relatively apparent in the in vitro status (Santi and Guy, 1996). Moreover, the fact that the reduction in the resistance of skin, which produces membrane change, was also reported recently to result in continuous penetration after iontophoretic treatment (Kasting and Bowman, 1990; Inada et al., 1994).

The penetration capacity of SNA is found to be influenced by various vehicles, as shown in Table 1. The permeability coefficient of SNA from hydrogels prepared with PVP or HPC was similar, and showed the highest penetration capacity among six polymers. SNA showed a supersaturated state because of the concentration (0.02%) in formulations. So, precipitation (crystallization) was observed during experiment. PVP and HPC are both excellent crystal growth retardants for some drugs which would stabilize the supersaturated solutions (Megrab et al., 1995). Antinucleant polymer slows the transformation of drugs from a high-energy state to a crystalline form. The adsorption of polymer on the hydrophobic surface of crystals has been well discussed with regard to the stabilization of suspensions, which results in the increase of the thermodynamic activity of drugs. Thus, the transport of SNA was enhanced in PVP and HPC formulations, since membrane transport

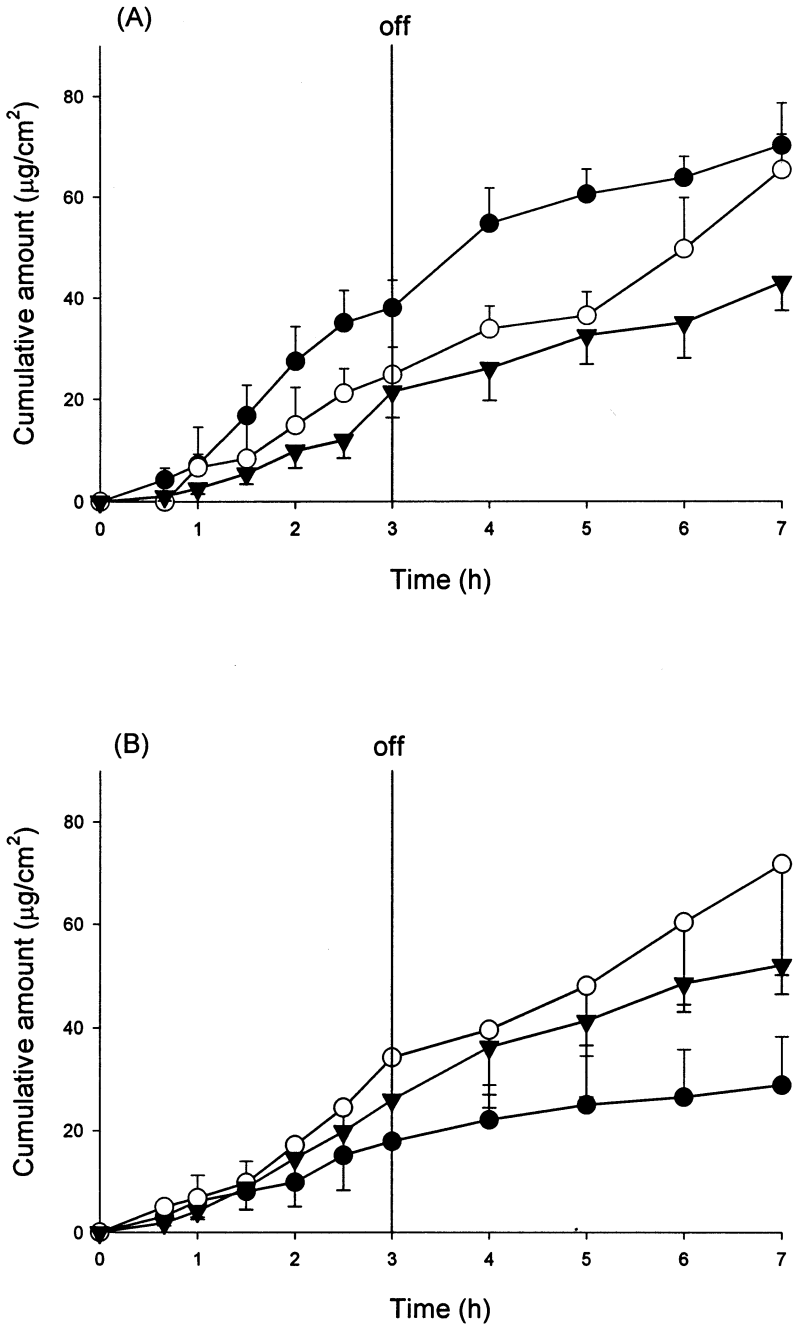

Fig. 4. Cumulative amount of SNA detected in the receptor compartment vs time following iontophoresis from various polymer formulations with various polymer concentrations: (●) 2.5%; (○) 5.0%; (▼) 10.0%. (A) PVP; (B) HPMC + PVP (1:1). All data represent the means of three experiments ± S.D.

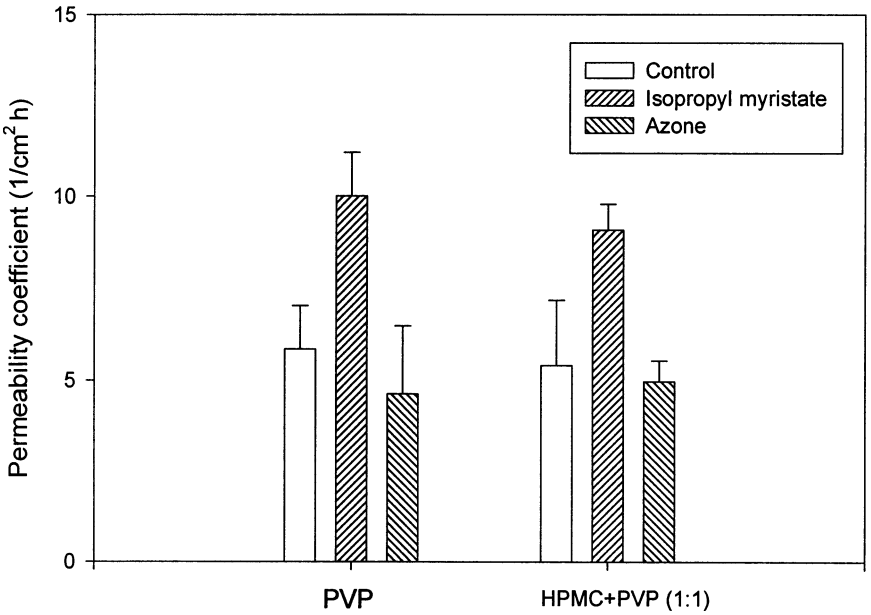

Fig. 5. Iontophoretic flux of SNA from PVP and HPMC + PVP (1:1) formulations pretreated with isopropyl myristate or Azone. All data represent the means of three experiments ± S.D.

is directly proportional to the thermodynamic activity of a permeant in a vehicle.

Judging from the derivatives of cellulose, the flux increased in the order of MC < HPC (Fig. 1B). According to the theory of partitioning (Okabe et al., 1992), the difference in the polymer–stratum corneum partition coefficients would have consequences for the uptake into the stratum corneum. As the hydrophilicity of cellulose derivatives show a trend of MC < HPC (Narasimhan and Peppas, 1997), the partition coefficients of SNA would be expected to favour the stratum corneum in the same order. As shown in Table 2, the result of SNA stratum corneum–polymer solution partition coefficient increases in the order of MC < solution without polymer as expected. The fluxes of SNA from two ionizable polymers, chitosan and Plastoid®, are negligible, as shown in Fig. 1. Chitosan, a water-soluble cationic polysaccharide, may form the ion pair or complex with SNA in the formulation, resulting in a lower iontophoretic flux. Moreover, the addition of chitosan always reduces the amount of drug released (Munjeri et al., 1997). Plastoid® is a commercially available polymer solution composed of polyacrylate. Since polyacrylate shows anionic characteristics which are the same as Carbopol 940® gel (polyacrylic acid), it would compete with SNA molecules resulting in the reduction of current density carried by SNA (Fang et al., 1996c). For this reason, to maintain good penetration capacity of drugs, ionizable polymers should be avoided for transdermal iontophoretic delivery.

3.2. Effect of binary polymer hydrogels

In the development of topical dosage devices, several desirable attributes that contribute to the patient compliance and clinical efficacy of the product may be defined. These include optimal mechanical properties, good bioadhesion and acceptable viscosity. However, optimal properties cannot simply be achieved for single polymer. So the blends of two or more polymers as drug delivery vehicles are necessary to attain more suitable transdermal devices. A series of binary polymer systems was prepared to perform in vitro permeation experiments and determine the mechanical property of viscosity. PVA and PVP were

mixed to prepare a binary vehicle since a successful patch, Nitrodur®, composed of these two polymers, is commercially available. Another binary vehicle of HPMC and pectin was also evaluated according to previous research (Kim and Fassihi, 1997). Although SNA molecules showed a high permeability coefficient from PVP hydrogel, the viscosity of PVP was the lowest among six polymers. Furthermore, the mucoadhesive force of PVP is also lower as compared with other polymers (Doelker, 1987). Therefore cellulose polymers, such as MC, HPC or HPMC, were blended with PVP, which has not only the highest viscosity of cellulose derivatives (as shown in Table 1), but also the ability to adhere to the skin (Jones et al., 1997).

The blends of two polymers at a ratio of 1:1 in an in vitro penetration of SNA were carried out, and the result is shown in Fig. 2. As with the single-polymer hydrogels, the flux of binary systems could also be described fairly well by a zero-order kinetic profile. There was no significant difference (t-test, $p > 0.05$) between the flux of PVA + PVP and that of PVP formulation, indicating similar characteristics between PVA and PVP. The penetration capacity of SNA from the mixture of HPMC + pectin was relatively lower than those of the other binary vehicles, as demonstrated in Table 3. Pectin is an anionic polymer, which could compete with SNA, resulting in the reduction of SNA permeation during iontophoresis. Moreover, cationic ions in buffer bound to the anionic polyelectrolyte, such as pectin, produce the complexing and inhibit the thermodynamic activity of vehicle (Takahashi et al., 1978). Accordingly, although there have been some successful polymer formulations for drugs developed and commercially available, one cannot simply substitute one drug for another in a given system. Each drug requires a dosage form specifically designed to fit its properties.

As shown in Fig. 2B, the flux of SNA from cellulose–PVP hydrogels increases in the order of

MC + PVP < HPMC + PVP < HPC + PVP,

which is consistent with the rank order of SNA flux from three cellulose derivatives. As expected, the viscosity and permeability coefficient of MC + PVP and HPMC + PVP were situated between the values of two individual polymers and moderate mechanical property and penetration capacity were consequently obtained. On the other hand, there were no significant differences (t-test, $p > 0.05$) for viscosity and SNA flux between HPC + PVP and HPC formulations. Moreover, the pH shift after in vitro iontophoresis was identical between HPC + PVP (1:1) and PVP. This demonstrates the mechanical properties and thermodynamic activity of HPC, as well as the buffer capacity of PVP, were retained in the binary system of HPC + PVP hydrogel.

Studies of various ratios of HPMC + PVP and HPC + PVP, used in hydrogels as donor vehicles, were conducted for in vitro iontophoretic delivery and the results are shown in Fig. 3. It can be seen in Table 3 that increasing the HPMC content of HPMC + PVP hydrogels would increase the viscosity. The flux of SNA was reduced as the HPMC content was increased to 75%. No significant difference (t-test, $p > 0.05$) was observed between the permeability coefficients of 25 and 50% HPMC formulations, although the 50% HPMC combined with 50% PVP formulation showed the highest permeation of SNA. Thus, 50% HPMC may act as a maximum proportion to achieve effective iontophoretic transport, since the higher proportions may restrict the penetration capacity. For HPC + PVP formulations of various ratios, the permeability coefficient of SNA increased following the increase of proportion of HPC. The viscosity of this binary vehicle showed suitable values which were situated between the viscosities of the two individual polymers.

3.3. Effect of polymer concentration

For a specific dose of drug, varying the polymer concentration is probably the most efficient way to adapt the release characteristics of the formulation to a specific criterion. Individual PVP and binary HPMC + PVP formulations were selected for the evaluation of various polymer concentrations on viscosity and permeability coefficient of SNA, as shown in Table 4 and Fig. 4. The viscosity increases gradually with polymer concentration, as expected. As shown in Fig. 4A, iontophoretic permeation of SNA decreases with increase in the

amount of PVP in the gels. So it was considered that PVP in hydrogel functioned as a diffusion barrier for the drug. This is a general rule for increasing the proportion of hydrophilic polymer, which would cause a more rigid structure of gels and decrease the rate of drug release (Doelker, 1987). Another possible reason is that an increase in the viscosity results in a decrease in the solution conductivity, and the permeability coefficient of drug is decreased as a result (Fang et al., 1996c). A different phenomenon was observed for HPMC + PVP, suggesting mechanisms other than those found in PVP formulations occurred. The 5.0 and 10.0% blend polymers released significantly more SNA than the 2.5% formulation. It is our opinion that the increase of polymer concentrations also decreases the proportions of buffer solution, which results in the reduction of the current density carried by the buffer species. An additional observation was that a 10.0% HPMC + PVP mixture showed a sufficient buffer capacity, because of the minor pH shift from 4.20 to 4.27 after iontophoretic treatment. HPMC but not PVP may have an important role in this effect according to the minor pH shift of all formulations containing HPMC (Tables 1–3).

3.4. Effect of pretreatment by penetration enhancers

Combination of enhancers with iontophoresis not only slows down the process of polarization of skin, but also reduces the possibility of skin damage. Thus, two lipophilic enhancers (isopropyl myristate and Azone) were pretreated with skin for 12 h and then used for in vitro iontophoretic delivery. The effect of isopropyl myristate is thought to involve direct interaction of the ester with the skin (Inagi et al., 1981). Pretreatment of the skin with isopropyl myristate dose alters the barrier property of skin, so that subsequently applied iontophoresis elicits a greater transport of SNA from both PVP and HPMC + PVP formulations, as shown in Fig. 5. The mechanism for the effective iontophoretic flux of isopropyl myristate could be due to the fact that isopropyl myristate retards the rate of loss of water from the skin, resulting in a higher cumulative amount of water in the epidermis which was proved by determining transepidermal water loss (TEWL) (Dempski et al., 1965; Fang et al., 1997a). Subsequently this ability to hold water in the skin would increase the conductivity of skin and the iontophoretic permeation of the drug (Rao and Misra, 1994).

Azone is a non-polar material which dramatically affects the lipid structure of skin. However, there is either no or a negative effect on the iontophoretic transport of SNA after pretreatment of Azone, as shown in Fig. 5. According to the previous research (Chow et al., 1984), penetration retardation is observed after an 8-h exposure of Azone to skin. The same phenomenon may occur for SNA after 12 h pretreatment due to the interaction of Azone with the skin component or the coexistence of SNA and Azone in the skin.

4. Conclusions

Transdermal iontophoretic delivery offers a strong penetration capacity for SNA from polymer hydrogels. For individual polymer formulations, in general, the flux of SNA increased following the decrease of viscosity due to the conductivity change. The fact that PVP and HPC are both excellent crystal growth retardants, which would stabilize the supersaturated solutions, resulted in the highest flux of SNA among six polymer formulations. The flux of cellulose derivatives increased in the order of MC < HPC, which was related to the theory of partitioning. For binary systems of polymer, optimal mechanical properties and penetration capacity of SNA could be attained. In the study of effect of polymer concentrations, PVP in hydrogel functioned as a diffusion barrier for SNA, resulting in the decrease of flux following the increase of PVP concentrations. However, a binary system of HPMC + PVP hydrogel showed different mechanisms other than those in PVP formulation, which may be the influence of the competitive ion effect of buffer species. Skin pretreated by isopropyl myristate increased the cumulative amount of water in skin, resulting in an increase of skin conductivity and iontophoretic flux of SNA. On the other hand, Azone showed no or negative effect on SNA penetration during iontophoresis, which sug-

gested that a transport impedance occurred after exposure of Azone on skin. After a series of transdermal iontophoretic studies on polymer hydrogels, it is suggested that ionizable polymers should be avoided for iontophoretic delivery so as to maintain good penetration capacity of SNA. Moreover, that the fluxes of SNA from hydrogels were all suitable to fit using a zero-order equation indicates that a steady-state permeation rate of SNA may be achieved and, thus, also the sustained release effect. This present study is holds promise for the further clinical study of iontophoretic regimens of SNA from polymer hydrogels.

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