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PERCUTANEOUS ABSORPTION OF CAPSAICIN AND ITS DERIVATIVES

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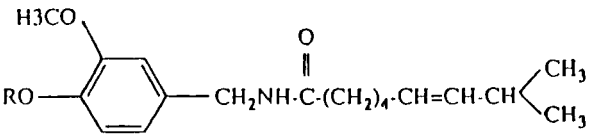
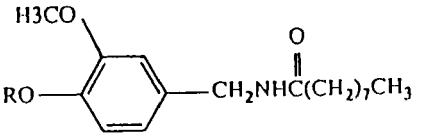
ABSTRACT

Nonivamide (NVA), sodium nonivamide acetate (SNA) and sodium nonivamide propionate (SNP) are analogues of Capsaicin (CAP). The structure and pungent property of NVA are similar to CAP. The solubilities of SNA in different pH value buffer solution were higher than that of NVA and CAP. For the NVA and SNA, the n-octanol/buffer partition coefficients decreased with increasing pH value. The fluxes of CAP and its analogues were determined using excised rat skin and the effect of pH was also investigated. The flux of NVA and SNA mixture was higher than individually NVA or SNA, and the ratio of 70:30 was a better choice. Sodium lauryl sulfate (SLS), an anionic surfactant, had significant effect on SNA skin permeation.



Capsaicin (CAP)



Nonivamide (NVA)	R: - H
SNA	R: -CH_2COONa
NVAA	R: -CH_2COOH
SNP	R: -CH_2CH_2COONa
NVP	R: -CH_2CH_2COOH

FIGURE 1

Chemical structures of CAP, NVA, SNA, NVAA, SNP and NVP.

INTRODUCTION

Capsaicin (CAP, Figure 1), the pungent principle of most Capsicum species, is a potent sensory stimulating agent, acting on cardiovascular, respiratory and nervous systems[1,2]. Further actions of CAP were reviewed by Virus and Gebhart[3]. Although the pharmacological activity of topical application appear to be of potential clinical significance[4,5], many CAP-type substances are

found to produce pain sensation and the therapeutic use of CAP entails some difficulties.

Inasmuch as CAP extracted from natural sources has unsaturated side chain leading to addition reaction and expensive prices, its practical application is unsuitable. Several analogues of CAP have been sythesized[6-8], and some of them have been evaluated for pharmacological activities[9,10]. Of these analogues, Nonivamide (NVA, Figure 1) was found to have a pharmacological profile similar to that of CAP[9,11]. NVA has been used as a substitute for CAP in experimental study.

In order to attenuate the untoward effects and increase the solubility of NVA, a number of analogues of NVA have been synthesized. Sodium nonivamide acetate (SNA, Figure 1) and Sodium nonivamide propionate (SNP, Figure 1) were synthesized by modification of the phenolic hydroxyl group of NVA. The analogues revealed marked a potent antinociceptive activity without overt pungent sensation and irritation[12,13,14].

The purpose of the present study is to establish the drug solubility, the partition coefficient between n-octanol and water and the flux of NVA and its analogues. These data are particularly helpful in the development of transdermal drug delivery system.

MATERIALS

CAP was products of Sigma Co.(U.S.A.). NVA, bromoacetic acid and β-bromopropionic acid were obtained from Tokyo Chemical Industry Co. (Japan). SNA and SNP were synthesized according to Yang et al[13]. All other chemicals were reagent grade and were used as received.

METHODS

SOLUBILITY MEASUREMENTS

The solubilities of CAP, NVA, SNA and SNP in different pH value solvent systems were determined by addition of excess amount of the drug to the appropriate solvent (pH 5, 6, 7, 7.4, 8) at 25 ± 1℃. These suspensions were shaked for 24 hr at which time the samples were centrifuged (3000 rpm, 10 min). The concentration of CAP, NVA, SNA and SNP in the supernatant were separately measured using HPLC.

PARTITION COEFFICIENTS

The n-octanol/water partition coefficients of CAP, NVA, SNA, SNP, Nonivamide acetate (NVAA) and Nonivamide propionate (NVP) were determined in different pH value buffer solution at room temperature. The various aqueous phases were buffered to pH 4, 4.2, 4.4, 4.6, 4.8, 5, 6, 7, 7.4 and 8 with sodium phosphate. Equal portions (2ml) of n-octanol saturated with buffer and different pH value buffer solution were poured into the reservoir of the MIXXOR (Genex Co. U.S.A.). The MIXXOR, a separatory cylinder, consists of a graduated glass mixing chamber, into which fits a glass piston containing an axial channel. Slowly move the piston up and down forcing the liquid through the axial channel to cause intimate mixing of the two phases in a highly efficient transfer operation. After twenty strokes of the MIXXOR, the aqueous phase was collected and centrifuged (3000 rpm, 10 min). The aqueous phase was analyzed by HPLC.

IN VITRO PERMEABILITY STUDIES

The diffusion cell, similar to the Franz horizontal diffusion assembly[15], was used for the permeability ex-

periments with rat skins. The rats (200-250g) were sacrificed in an ether chamber, and an approximately 9 cm^2 area of full-thickness skin was excised from the shaved abdominal site. The skin was mounted and clamped between the receptor cell and donor cell with the furry side facing donor side.

The receptor phase was approximately 15 ml of the alcohol-pH 7.4 buffer (1:1) solution. The donor phase prepared by suspending excess drug in the appropriate solvent systems (pH 4.2, 4.8, 5, 6, 7, 7.4, 8) was also approximately 15 ml containing an enhancer or no enhancer. The temperature of the cell was maintained at 37 ± 0.5℃ by thermostatically controlled water which was circulated through a jacket surrounding the cell body. Samples (0.5 ml) were removed from the receptor phase at regular intervals and replaced by a fresh alcohol-pH 7.4 phosphate buffer solution. The samples were assayed using HPLC.

The amount of the drug diffused through the skin was plotted as a function of time and a linear regression analysis was used to determine the flux of the drug for each formulation.

CHROMATOGRAPHIC ANALYSIS

The HPLC analyses were performed on a Waters system (U.S.A.) consisting of a Model M-45 pump, a Model 470 Fluorescence detector, a Model 715 Ultra WISP sample processor and a Model 740 Data Module integrator. The column was a 125x4 mm i.d. LiChroCART 250-4 C18 (Merck). The mobile phase consisted of an acetonitrile-pH 4 buffer solution (38:62, v/v) mixture. The operating temperature was ambient, and the flow rate was 1.0 ml/min with absorbance monitoring at an excitation wavelength of 250 nm and an emission wavelength of 310 nm.

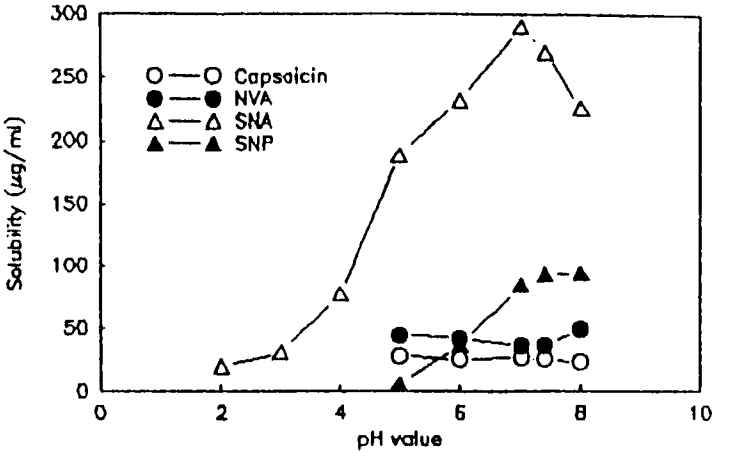


FIGURE 2

Solubility of CAP and its analogues in different pH value buffer solution.

RESULTS AND DISCUSSION

The solubilities of CAP and its analogues at 25℃ in different pH value buffer solution are shown in Figure 2. The solubilities of CAP and NVA were similar and independent on the pH value. Conversely, the increase in solubilities of SNA and SNP was dependent on the pH value of solvent. For the SNA, solubility increased with increasing the pH value of solvent and the highest solubility was achieved at pH 7.0.

Table 1 records the partition coefficients of CAP and its analogues. For the NVA and SNA, the n-octanol/buffer partition coeffecients decreased with increasing pH value and was significantly different at pH above 5 and 4.4, respectively.

TABLE 1. Partition coefficients of CAP and its analgues

Compounds	pH 4.2	pH4.8	pH 5.0	pH 6.0	pH 7.4	pH 8.0
CAP	---*	---*	---*	---*	---*	---*
NVA	---*	---*	77.96	36.96	29.93	27.86
SNA	---*	43.93	18.99	2.05	0.48	0.29
NVAA	---*	---*	54.27	1.60	1.50	1.05
SNP	---*	---*	385.90	213.09	6.65	4.21
NVP	---*	---*	---*	---*	---*	---*

* Compound 100% in octanol phase (oil phase).

The fluxes of CAP and its analogues through excised rat skin from various pH value buffer solution are shown in Figure 3. The fluxes of CAP were similar to NVA and ranged between 7 and 11 $\mu g/cm^2/hr$. The effect of pH value on the fluxes was probably not sensitive. The low pH value of the aqueous donor phase (pH 4.2) led to slightly higher flux relative to pHs in the range 5-8. From Figure 3, it was also evident that the fluxes of SNA and SNP were considerably less than that of CAP or NVA. According to the pH-partition hypothesis when drugs permeate predominantly lipophilic biologic membranes by passive diffusion, the unionized species permeates more compared to the ionized species because of its higher membrane partitioning[15]. For the SNA, sodium salt of nonivamide acetate, solubility was higher than that of CAP or NVA. On the contrary the flux of SNA was dramatic decreased and slightly higher than that of SNP in various pH value buffer solution.

To further examine the effect of ionized and unionized species on drug flux, NVAA and NVP were synthe-

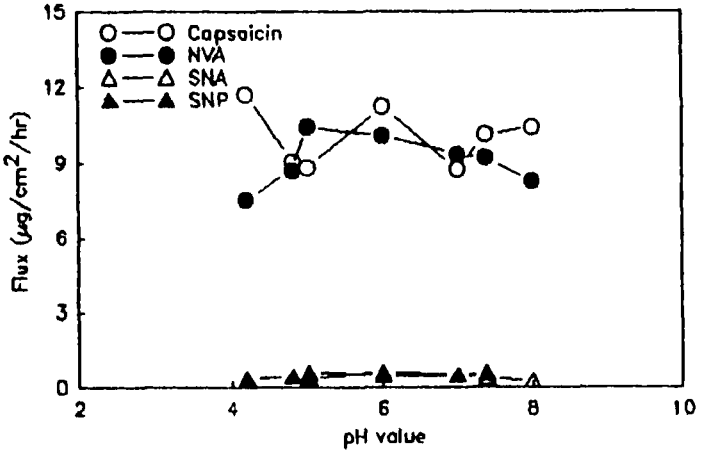


FIGURE 3

Effect of pH value on flux of CAP and its analogues.

sized in this study. The fluxes of NVAA compared to SNA is shown in Figure 4. Except for pH 4.2, no significant difference was observed between NVAA and SNA. The similar result in NVP and SNP (Figure 5) was found which confirms the better permeation of unionized species.

Mixtures of NVA and SNA were also tested and the individually fluxes of NVA and SNA through rat skin using the different ratio mixtures are shown in Figure 6. The flux of NVA increased from a steady-state value of about 9.23 μg/cm²/hr up to 17.97 μg/cm²/hr when the weight percentage of NVA in the mixture was added from 40% to 80%. The flux of SNA was increased to about 1.26 μg/cm²/hr when the ratio of NVA:SNA was 70:30. From these results, the flux of NVA and SNA mixture was higher than individrally NVA or SNA, and the ratio of 70/30 was abetter choice.

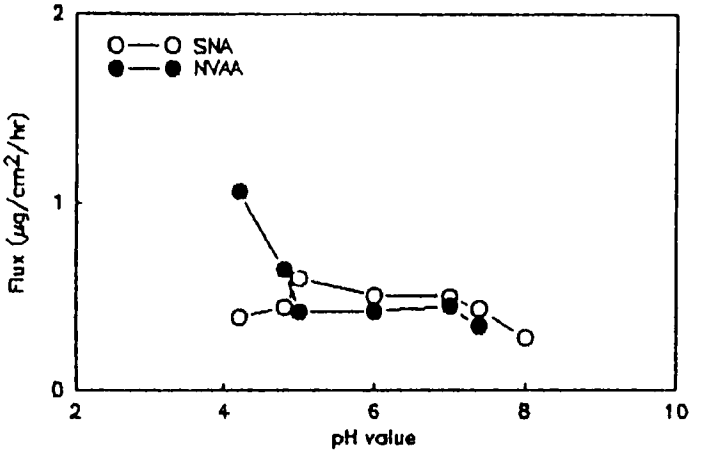


FIGURE 4

Effect of pH value on flux of SNA and NVAA.

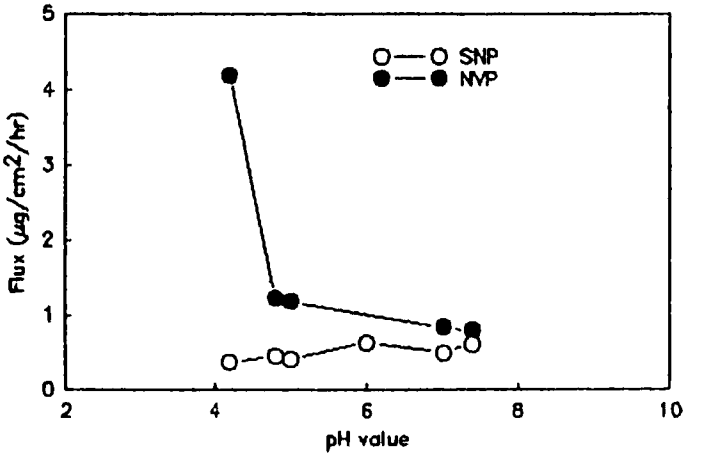


FIGURE 5

Effect of pH value on flux of SNP and NVP.

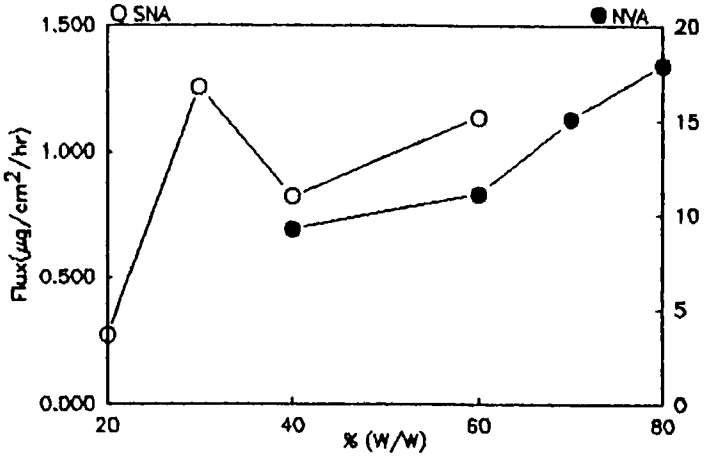


FIGURE 6

Effect of mixtrue ratio of NVA and SNA on flux of NVA and SNA.

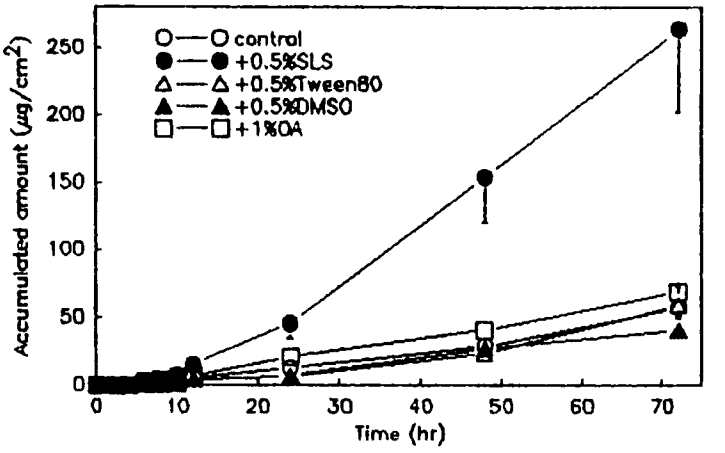


FIGURE 7

Effect of enhancers on the permeation of SNA.

In order to increase the flux and permeable amount of SNA, four compounds were evaluated as permeation enhancers for SNA: sodium lauryl sulfate(SLS), polysorbate 80 (Tween 80), dimethyl sulfoxide (DMSO) and oleic acid (OA). The effect on SNA permeability of adding enhancer in the pH 4.2 buffer solution is shown in Figure 7.

The greatest increase in flux was achieved with SLS which was 4.9 times higher than that of the control group, whereas the Tween 80, DMSO and OA caused no change. The flux of SNA in presence of different concentrations of SLS was also tested. The result indicates that 1% SLS may be a better choice for SNA. Lower flux observed at higher concentration of SLS is most likely due to micellar trapping of the drug. It has been reported[17] that dilute solute solutions of ionic surfactants may alter the physical state of the skin reversibly and thus promote passage of charge hydrophilic substance. The mechanism appears to be related to the tendency of these molecules to bind to epidermal protein and disrupt their long range order[18].

The physicochemical properties and results of in vitro permeable informations offer the foundation of transdermal delivery system for CAP and its analogues.

ACKNOWLEDGMENTS

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