J. Kor. Pharm. Sci., Vol. 23, No. 3, S41-S50 (1993)

The Role of Excipients in Iontophoretic Drug Delivery: *In vitro* Iontophoresis of Isopropamide and Pyridostigmine through Rat Skin and Effect of Ion-pair Formation with Organic Anions

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(Received August 12, 1993)

Key words: Iontophoresis; Isopropamide; Pyridostigmine bromide; Quaternary ammonium salt; Ion-pair complex; Counteranions; Sodium ion; Hydronium ion; Permselectivity

ABSTRACT

The iontophoretic delivery across rat skin of quaternary ammonium salts (isopropamide: ISP, pyridostigmine: PS), which are positively charged over a wide pH range, was measured *in vitro*. The study showed that: (a) iontophoresis significantly enhanced delivery of ISP and PS compared to respective passive transport; (b) delivery of ISP and PS was directly proportional to the applied continuous direct current density over the range of $0-0.69$ mA/cm^2; (c) delivery of ISP and PS was also proportional to the drug concentration in the donor compartment over the range of $0-2\times10^{-2}$ M; (d) sodium ion in the donor compartment inhibited the drug transport possibly due to decreasing the electric transference number of the drug; (e) delivery of ISP and PS increased as the pH of the donor solution increased over the pH range 2-7 suggesting permselective nature of the epidermis, and inhibition of the transference number of the drugs by hydronium ion; (f) some organic anions such as taurodeoxycholate, salicylate and benzoate which form lipophilic ion-pair complexes with ISP inhibited the delivery of ISP. The degree of inhibition by the organic anions was linearly proportional to the extraction coefficient (K_e) of ISP from the partition system with each counteranion between phosphate buffer (pH 7.4) and n-octanol. For PS, however, taurodeoxycholate, but not salicylate and benzoate inhibited the iontophoretic delivery. It suggests that not only sodium ion and hydronium ion but also the counteranions which form lipophilic ion-pairs with quaternary ammonium drugs are not favorable components in formulating the donor solution of the drugs to achieve an effective iontophoretic delivery.

Introduction

The transport of ionic and polar solutes across skin is not favored by passive diffusion. One promising technique for increasing the transdermal delivery of ionic solutes is iontophoresis. It increases the transport of ionic drugs with the assistance of an electrical current[1]. It also increases the transport of non-electrolytes by increasing water movement through the skin[2]. The transport of drugs through the skin during iontophoresis has been shown to be dependent on the pH of the donor

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solution[3-6] and the current density[7,8]. Some other factors which influence the ionic circumstances of the drugs such as components of the donor solution (buffer concentration or ionic strength), and the presence of other ions of the same or opposite charge may also affect the transport of drug ions during iontophoresis.

The purpose of this study was to investigate the effect of these factors on the iontophoresis of drug ions. Special emphasis was put on the effect of ion-pair interaction of the drug ion with some counterions in the donor solution. Isopropamide (ISP) iodide and pyridostigmine (PS) bromide, quaternary ammonium salts (QAS), were selected as models of cationic drugs since they are considered completely ionized over wide pH range. This will be a favorable condition in examining the effect of pH of the donor solution on the iontophoresis. As the counterions of QAS, sodium salts of benzoate (BEN), salicylate (SAL) and taurodeoxycholate (TDC) were selected since they form hydrophobic ion-pair complexes with ISP[9].

Materials and Methods

Materials

Isopropamide (ISP) iodide and pyridostigmine (PS) bromide were obtained from Sigma (USA). Sodium salicylate (Na-SAL), sodium benzoate (Na-BEN) and sodium taurodeoxycholate (Na-TDC) were chosen as organic anions and were obtained from Koso Chem. (Tokyo, Japan), Junsei Chem. (Tokyo, Japan) and Sigma Chem. (USA), respectively. Normal saline and gentamicin sulfate were obtained from Choong Wae Pharm. Ind. (Seoul, Korea) and Yuhan Corp. (Seoul, Korea), respectively. All other chemicals including potassium chloride, sodium chloride, hydrochloric acid and ether were of analytical grade.

Preparation of Rat Skin

Abdominal hairs of Male Wistar rats weighing 230-270 g (Experimental Animal Center, Seoul National University) were removed under ether anesthesia using hair clipper with care taken not to affect the integrity of the stratum corneum. Then the rats were sacrificed by injecting air into the femoral vein and full thickness skin was excised by the aid of shaving knife. The skin was stored in aluminum foil at $-20℃$, and was immersed in normal saline (containing 200 ppm of gentamicin sulfate) at $4℃$ for three days prior to each permeation experiment. The hydration over three days was to attain a steady state passive flux of ISP[10]. Gentamicin sulfate was reported not to affect the membrane permeability and to prevent bacterial growth during skin hydration[11]. The skin was then removed of adhering fat and visceral debris by scraping with absorbent cotton, cleaned with deionized water and mounted between the donor and receptor cells of the permeation apparatus.

Set up for in vitro Transport Studies

Valia-Chien diffusion cells (K.C. Scientific Co., Seoul, Korea) with donor and receptor compartments of 10 m*l* maximum volume were used in all the studies. Ag/AgCl electrodes were made from silver wire (99.9% purity, 1 mm diameter, Sang Shin Scientific Co., Seoul, Korea) according to the technique of Burnette and Ongpipattanakul[8]. The tip of each electrode was framed to form a small ring with i.d. of 0.64 cm. The direct current source, which was fabricated in our laboratory, was designed to deliver a constant current between 0 and 2 mA range at $\pm$ 18 volts.

A piece of skin was mounted between the two compartments of the diffusion cell with

dermal side towards the receptor compartment. The surface area of the skin exposed to the solution was 2.16 cm^2. The cells were clamped and immersed in a water bath at 37± 0.5℃. The media of the diffusion cell were stirred at a rate of 600 rpm using magnetic stirrer. The donor and receptor compartments contained 10 m*l* of the respective solution: The receptor compartment was filled with nomal saline in all studies, but the donor compartment was filled with ISP or PS solutions of varying pH and concentrations of the drug, sodium ion and organic anions. The donor solution was prepared by dissolving ISP iodide in Sorensen buffer (pH 7.2). The buffer was prepared by dissolving 2.4 g of sodium phosphate monobasic, 6.629 g of sodium phosphate dibasic and 4.6 g of sodium chloride in deionized water to yield 1 *l*. Sodium concentration of the buffer was approximately 0.113 M.

Anodal iontophoresis was performed by inserting the anode (+, Ag electrode) in the donor compartment and the cathode (−, AgCl electode) in the receptor compartment. The electrodes were positioned 2 cm apart from the skin surface.

Various Factors Affecting the Transport of ISP and PS

Various factors such as electric current density of the system, and the initial pH and composition of the donor solution (concentrations of ISP and PS, sodium ion and counteranions) were examined for their effects on the *in vitro* transport of ISP and PS.

For this purpose, current density (0.0, 0.14, 0.28, 0.46, 0.69 mA/cm^2), pH (2, 3, 4, 5, 6, 7), and concentrations of ISP and PS (5×, 5×, 7×, 10×, 15×, 20×10^{-3} M), sodium ion (0.35, 0.43, 0.66, 1.06 M), and counteranions (0.0×, 15×, 30×, 45×, 60×, 75×10^{-3} M) were varied to see their effects on the transport. The other factors except the selected one were kept constant at current density=0.46 mA/cm^2, [ISP]=15×10^{-3} M, [PS]=38×10^{-3} M, [Na^+] =0.113 M, and pH=7.2.

Sodium concentration was controlled by adding equivalent amount of sodium chloride to the donor solution (Sφrensen buffer) as needed. In the studies on pH effect, pH of the donor solution was controlled by using McIlvaine buffer (phosphate-citrate buffer), and the ionic strength was kept constant at 0.543 by adding appropriate amount of sodium chloride. Effect of counteranions was observed by adding various amount of Na-BEN, Na-SAL or Na-TDC to the donor solution. In this case only, sodium concentration of the donor solution was kept constant at 0.188 M.

Sampling and Assay of ISP and PS

Triple samples were withdrawn at regular time intervals from the receptor compartment (0.2 m*l*) and the same volume was replaced by fresh receptor fluid. ISP concentrations in the samples were assayed by a modified method of Santoro (12). A 0.2 m*l* aliquot of the sample was added to a screw-capped test tube containing 0.6 m*l* saline, 2.0 m*l* of methyl orange buffer (pH 10.2) and 4.0 m*l* of chloroform. After vigorous agitation for about 10 min, two phases were separated by centrifugation at 3000 rpm for about 5 min and a 2.0 m*l*-aliquot of the chloroform layer was added to 0.8 m*l* of 0.5 N HCl in absolute ethanol. Then the absorbance at 525 nm was measured spectrophotometrically. The concentrations of ISP in the samples were calculated from the calibration curve of ISP prepared in the same manner. The calibration curve was linear in the ISP concentration range of 0~20×10^{-3} M.

For the assay of PS, a HPLC method was

used. Aliquots of 50 μl were taken from the receptor compartment and injected into HPLC system. The HPLC system consisted of a precision isocratic pump (Model SP 8810), a C_{18} reversed-phase column (μ-Bondapak, 10-μm silica, 300×3.9-mm id), and a UV absorbance detector (Model 757, Applied Biosystems). The mobile phase was a mixture of 20% acetonitrile in water which contains acetic acid (0.1 w/v%) and hexanesulfonic acid (5 mM). The flow rate of the mobile phase was 1.2 ml/min and the wavelength of the detector was 270 nm. The recovery of PS was more than 90% and the detection limit was 20 μg/ml.

Steady state flux (mg/cm²/h) of ISP or PS was calculated from the slope of the plot between the cumulative amount transported and time. All the data were expressed as mean± SD of the triple determinations.

Results

The cumulative amounts of QAS transported across the skin during passive diffusion and anodal iontophoresis are plotted against time and exemplified for ISP in Fig. 1. The slope of the linear portion of the plot indicates the steady state flux of ISP. The fluxes are expressed as bars in the inset of Fig. 1. The flux during iontophoresis was much greater than that during passive diffusion. For ISP, it was increased by 13-fold from 9.5×10^{-3} mg/cm²/hr (passive diffusion) to 127.0×10^{-3} mg/cm²/hr by iontophoresis at 0.46 mA/cm² and pH 7.2. For PS, it was increased by 41-fold from 3.7×10^{-3} mg/cm²/hr (passive diffusion) to 158.0×10^{-3} mg/cm²/hr by iontophoresis at 0.46 mA/cm² and pH 7.2.

The effect of current density on the transport of QAS is shown for ISP in Fig. 2. The transport flux of ISP and PS increased with increasing current density from 0 to 0.69 mA/cm². Linear relationships were observed between the flux and current density for both ISP and PS.

The transport of QAS at 0.46 mA/cm² and

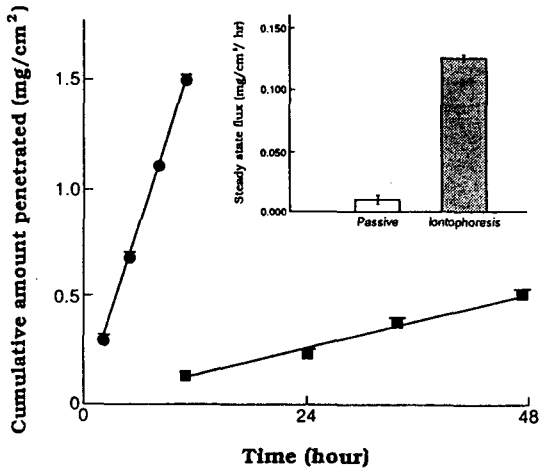

Fig. 1. Plot of mean cumulative amount of ISP permeated *versus* time at pH 7.2 and 15×10^{-3} M of initial ISP concentration during passive diffusion and iontophoresis (0.46 mA/cm²) (n=3). ■: passive diffusion; ●: iontophoresis. The inset shows the steady state flux during passive diffusion and iontophoresis.

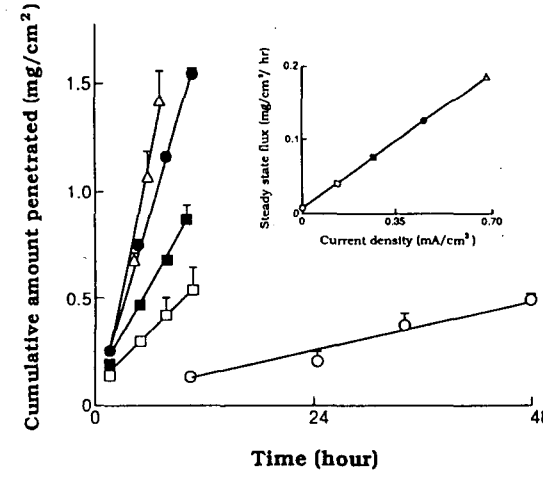

Fig. 2. Effect of applied current densities on the mean cumulative amount, and steady state flux (inset) of ISP permeated at pH 7.2 and 15×10^{-3} M of initial ISP concentration (n=3). ○: 0.0 mA/cm²; □: 0.14 mA/cm²; ■: 0.28 mA/cm²; ●: 0.46 mA/cm²; △: 0.69 mA/cm². The inset shows the plot between steady state fluxes and current densities.

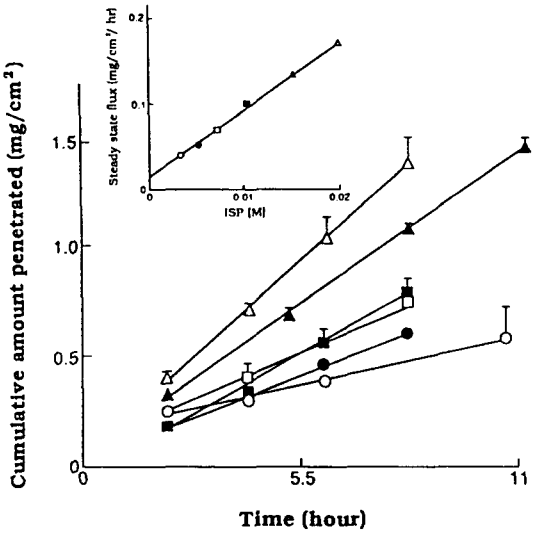

Fig. 3. Effect of ISP concentration on the mean cumulative amount, and steady state flux (inset) of ISP permeated at pH 7.2 and 0.46 mA/cm^2 (n=3). ○: 3×10^{-3} M; ●: 5×10^{-3} M; □: 7×10^{-3}; ■: 10×10^{-3} M; ▲: 15×10^{-3} M; △: 20×10^{-3} M. The inset shows the plot between steady state fluxes and ISP concentrations.

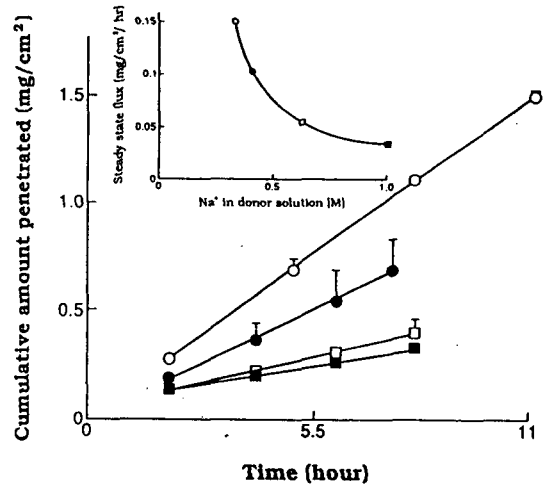

Fig. 4. Effect of sodium concentration in the donor solution (ISP=15×10^{-3} M) on the mean cumulative amount of ISP permeated, and steady state flux (inset) of ISP at pH 7.2 and 0.46 mA/cm^2 (n=3). ○: 0.35 M; ●: 0.43 M, □: 0.66 M, ■: 1.06 M.

pH 7.2 increased as the QAS concentration in the donor solution increased as exemplified of for ISP in Fig. 3. Linear relationships between the flux and QAS concentration over the range $0-2\times10^{-2}$ M were observed.

Fig. 4 shows that the transport of ISP at 0.46 mA/cm^2 and pH 7.2 decreases as the sodium concentration in the donor solution increases. There was an inverse curvilinear relationship between the flux and the sodium concentration. Similar results were also obtained for PS (data are not shown).

Fig. 5-1 shows the effect of pH of the donor solution on the transport of ISP at current density of 0.46 mA/cm^2 and ionic strength of 0.534. The transport increased as the pH of the donor solution increased. The inset in Fig. 5-1 shows two plots simultaneously: fraction ionized of the skin *versus* pH, and ISP flux *versus* pH. Fraction ionized of the skin was calculated theoretically from the Henderson-Hasselbalch equation assuming pKa of the skin is 3.5[13]. Both the flux of ISP and the fraction ionized of the skin increased as the pH of the donor solution increased, but the flux-pH profile was not parallel to the dissociation profile of the skin. As shown in Fig. 5-2, similar results were obtained for PS: both the flux of PS and the fraction ionized of the skin increased as the pH of the donor increased.

Figs. 6-8 indicate that ISP transport is inhibited by the presence of organic anions, TDC, SAL and BEN, in the donor solution. The flux was inversely proportional to the concentration of the anions as is clearly exemplified for TDC (Fig. 6). The inhibition effect of the anions was in the order of TDC≫SAL>BEN. Fig. 9 indicates that PS transport is also inhibited by the presence of TDC. However, SAL and BEN did not affect the transport of PS significantly, which is contrary to the case for ISP.

Discussions

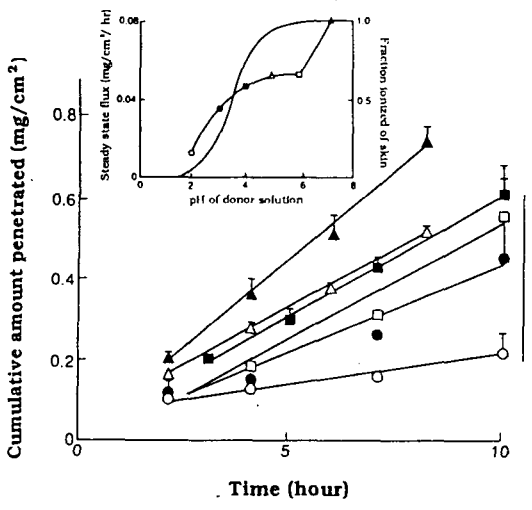

Fig. 5-1. Effect of pH of the donor solution (ISP=15 $\times 10^{-3}$ M) on the mean cumulative amount of ISP permeated, and steady state flux (inset) of ISP at 0.46 mA/cm^2 (n=3). Smooth curve in the inset indicates the fraction ionized of the skin theoretically calculated based on the Henderson-Hasselbalch equation assuming pKa of the skin is 3.5. The pH was controlled by using McIlvain buffer and the ionic strength was kept constant at 0.534. ○: pH 2; ●: pH 3; ■: pH 4; △: pH 5; □: pH 6; ▲: pH 7.

ISP iodide and PS bromide are quaternary ammonium salts which are almost completely dissociated as cations in solution over a wide pH range. Due to the polar characteristics of the ion, passive diffusion of QAS through the skin was small (Fig. 1). The passive diffusion of ISP, however, was known to increase as the skin is hydrated, and to need three days of hydration to reach its steady state[10]. The increase in the passive diffusion during the iontophoresis may lead to misinterpretation of the observed flux data. Thus, all the experiments were performed after three days of hydration of the skin in this study.

The transport was dramatically increased by applying an electric current density of 0.46 mA/cm^2 at pH 7.2: the steady state flux of ISP and PS became more than 13- and 41-fold larger than their respective passive flux. Since

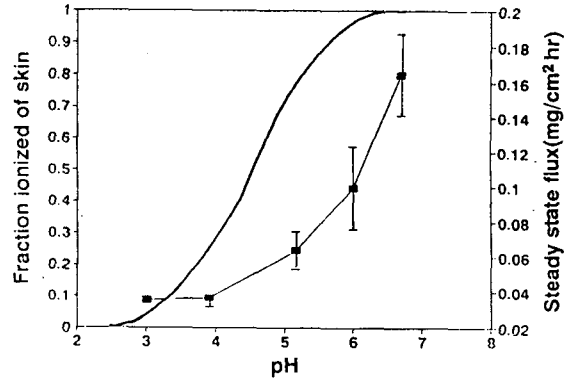

Fig. 5-2. Effect of pH of the donor solution (PS=38 $\times 10^{-3}$ M) on the steady state flux of PS at 0.46 mA/cm^2 (n=3). Smooth curve in the figure indicates the fraction ionized of the skin theoretically calculated based on the Henderson-Hasselbalch equation assuming pKa of the skin is 3.5. The pH was controlled by using McIlvain buffer and the ionic stength was kept constant at 0.534.

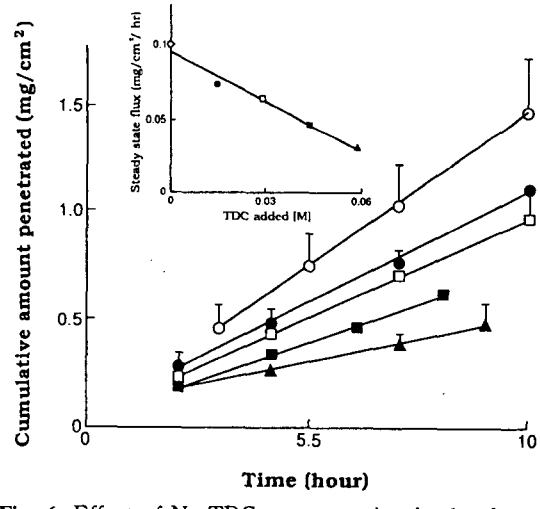

Fig. 6. Effect of Na-TDC concentration in the donor solution (ISP=15$\times 10^{-3}$ M, Na^+=0.075 M) on the mean cumulative amount of ISP permeated, and steady state flux (inset) of ISP at 0.46 mA/cm^2 and pH 7.2 (n=3). ○: 0.0$\times 10^{-3}$ M; ●: 15$\times 10^{-3}$ M; □: 30$\times 10^{-3}$ M; ■: 45$\times 10^{-3}$ M; ▲: 60$\times 10^{-3}$ M.

the permeation study was performed under the steady state passive flux, the increase could be considered to reflect the increase in the iontophoretic transport itself. Fig. 2 shows that the flux increases in proportion to the current

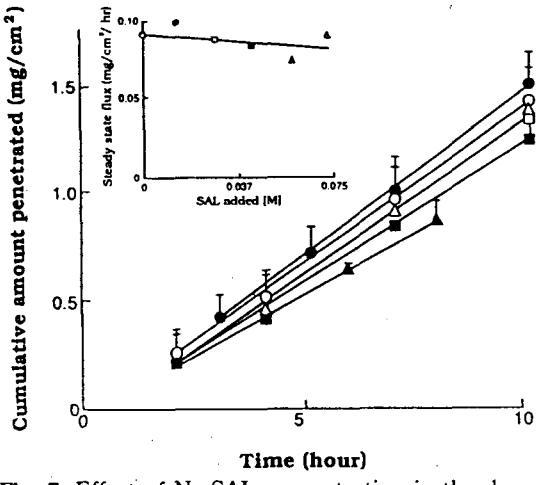

Fig. 7. Effect of Na-SAL concentration in the donor solution (ISP=15×10^{-3} M, Na^+=0.075 M) on the mean cumulative amount of ISP permeated, and steady state flux (inset) of ISP at 0.46 mA/cm² and pH 7.2 (n=3). ○: 0.0×10^{-3} M; ●: 15×10^{-3} M; □: 30×10^{-3} M; ■: 45×10^{-3} M; ▲: 60×10^{-3} M; △: 75×10^{-3} M.

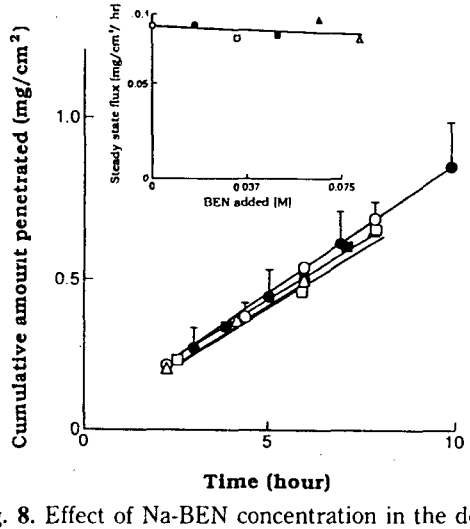

Fig. 8. Effect of Na-BEN concentration in the donor solution (ISP=15×10^{-3} M, Na^+=0.075 M) on the mean cumulative amount of ISP permeated, and steady state flux (inset) of ISP at 0.46 mA/cm² and pH 7.2 (n=3). ○: 0.0×10^{-3} M; ●: 15×10^{-3} M; □: 30×10^{-3} M; ■: 45×10^{-3} M; ▲: 60×10^{-3} M; △: 75×10^{-3} M.

density. The intercept in Fig. 2 which indicates flux by the passive diffusion was comparable to that value in Fig. 1. The flux also increased

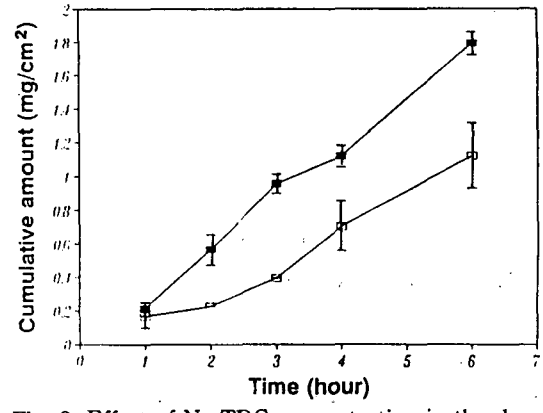

Fig. 9. Effect of Na-TDC concentration in the donor solution (PS=38×10^{-3} M, Na^+=0.075 M) on the mean cumulative amount of PS permeated at 0.46 mA/cm² and pH 7.2 (n=3). ■: 0.0×10^{-3} M; □: 60×10^{-3} M.

in proportion to the concentration of QAS in the donor solution (Fig. 3). Fig. 2 and 3 indicate that the rate of QAS delivery would be controlled easily both by the current density and drug concentration.

It is important to demonstrate the effects of the type and concentration of the salts consisting the donor solution on the drug delivery rate. As exemplified for ISP in Fig. 4, the transport rate of QAS declined almost exponentially with increasing the sodium concentration. It is most likely due to the decrease in the electrical transference number of QAS by the sodium ion added, which is probably attributable to the less diffusivity of ISP and PS ions than that of the sodium ion as discussed for verapamil (14). Electroosmotic volume flow, which is responsible for the enhanced transport of both charged and neutral species via iontophoresis, has also been reported to be inhibited by sodium ion (2, 8, 15). Thus, the decreased electroosmotic volume flow by sodium ion might contribute to the decline of ISP flux (Fig. 4) to some extent. Contrary to the charged ISP, PS and verapamil, the flux of azidothymidine, a nonelectrolyte, across rat skin was increased

by the addition of sodium ion probably due to the convective flow of sodium ion added[16].

The higher flux of ISP and PS with increasing pH of the donor solution from 3 to 7 (Figs. 5-1 and 5-2) may be correlated to the permselective nature of the epidermis[8,14,17]. Since the keratin in the stratum corneum has an isoelectric point of pH 3-4[13], the stratum corneum will be charged more negatively as the pH increases, and thus will become more attractive to positively charged ions like ISP and PS. A similar pH dependency was also observed for the iontophoretic permeation of verapamil[14] and thyrotropin releasing hormone[17]. The pH dependency of the flux, however, cannot be explained satisfactorily by the permselective nature of the skin. If the permselectivity were just a cause of the pH dependency of the flux, the two plots in the inset in Fig. 5-1 must have been parallel, and the flux might have stopped its increase at pH>6, since the skin would be almost completely ionized at pH 5-6. However, the fluxes of ISP and PS continued to increase at pH>6 in this study. Therefore, additional explanations would be necessary.

One probable explanation will be the difference in mobility between H^+ and the drug ion. H^+ has an extremely high mobility in aqueous solutions compared to any other ion[18,19] due to its numerous modes of transport[20]. The electric mobility of H^+ is approx. 7-times higher than that of sodium ion[19]. Thus, as the pH of the donor solutin decreases (as H^+ concentration increases), the transport number of ISP or PS ion through the skin is expected to decrease as a result of competition with H^+ in the transport. And as the pH increases (as H^+ concentration decreases), the competition will decrease and the ISP or PS flux is expected to increase. Change in the diffusion potential with pH, increase in convective coupling at higher pH, and decrease in the amount of current carried by H^+ might also be additional causes of the increased fluxes of ISP and PS with pH as suggested for verapamil[14].

Figs. 6-8 and Fig. 9 demonstrate that not only sodium ion but also some organic anions (TDC, SAL. BEN) inhibit the iontophoretic permeation of ISP and PS. The degrees of inhibition (slope of each line in insets of Figs. 6-8) were linearly proportional to the concentrations of anions added in the case of ISP. Among the anions examined, TDC inhibited most profoundly the flux of ISP followed by SAL and BEN. For the flux of PS, inhibition observed actually only for TDC.

In passive diffusion, some anions might enhance the skin permeation of cationic drugs through forming lipophilic ion-pair complexes with drugs[10]. TDC, SAL and BEN have been reported to form lipophilic ion-pair complexes with ISP[9]. Therefore, the passive diffusion of ISP is expected to be increased by addition of these counteranions. However, the apparent flux of ISP via iontophoresis was decreased in this study by these anions. The flux of PS was also decreased by TDC. It clearly demonstrates that the possible increase in the passive diffusion of ISP or PS through ion-pair formation with counteranions is much less than the decrease in the iontophoretic flux of ISP or of PS by the counteranions. The iontophoretic flux of ISP is linearly proportional to the concentration of unparied ISP (Fig. 3), and the concentration of unpaired ISP decreases in the presence of counteranions[9]. Therefore, the decrease in ISP flux in the presnece of the counteranions is attributable first to the decreased concentration of unparied ISP in donor solution. Similarly, the concentration of unpaired PS must have been decreased by the ion-pair formation with TDC, although the formation have not been confirmed yet.

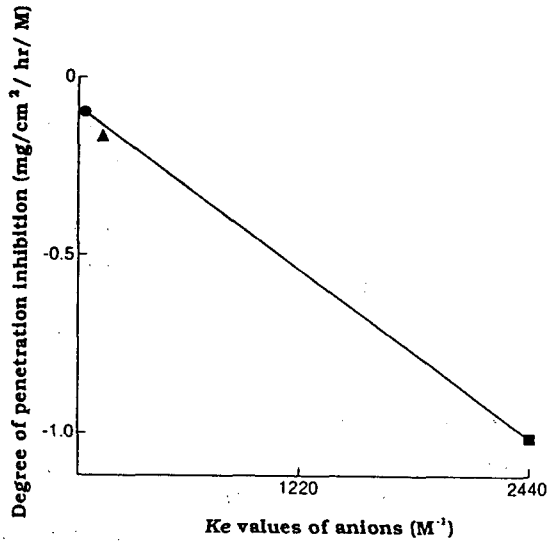

Fig. 10. Relationship between permeation inhibition effect (slopes to the insets of Figs. 6-8) of counteranions against ISP at pH 7.2 and ion-pair extraction constant (K_e). ●: Na-BEN; ▲: Na-SAL; ■: Na-TDC.

In addition to the concentration of unpaired QAS, hydrophobicity of the ion-pair complexes may affect the iontophoretic permeation of QAS. Actually, a linear decrease in the iontophoretic flux with increasing hydrophobicity has been reported for alkanols of various chain length[21] and for amino acids and neutral tripeptides[22]. Therefore, it is of interest to examine how the degree of inhibition of iontophoretic flux is correlated with the unpaired concentration and hydrophobicity of ISP in the presence of the organic counteranions. But it is difficult to calculate separately the unpaired concentration and hydrophobicity of a drug in the ion-pair system[10]. Previously, we have introduced an extraction constant (K_e), which is believed to express both degree of ion-pair formation (or the unpaired concentration) and hydrophobicity of the ion-pair complex[9]. K_e of compound A is defined as:

$$K_e = [AB_o]/[A_w^+][B_w^-] \quad (1)$$

where A_w^+ and B_w^- represent the cation and counteranion in the aqueous phase at partition equilibrium, respectively. Ab_o represents the ion-pair complex of A with counteranion B in the organic phase at the equilibrium. According to the previous report[9], K_e of ISP-TDC, ISP-SAL and ISP-BEN were 2.44×10^3 M^{-1}, 1.37×10^2 M^{-1} and 2.81×10 M^{-1}, respectively when determined from 0.1 M phosphate buffer (pH 7.4)/n-octanol system at 25℃.

Fig. 10 shows the plot of the degree of inhibition of the anions (slope of the lines in insets of Figs. 6-8) against K_e values of the ion-pair complexes. As is clearly shown from the figure, the degree of inhibition was proportional to K_e of the system. Therefor, it could be concluded that K_e values of cationic drugs in the ion-pair system with counteranions can be useful indexes of the flux inhibition. Ion-pair formation has been known to be advantageous for the passive penetration of highly ionized drugs as exemlified for ISP[10]. In iontophoresis, however, it should be kept in mind that counterions as well as the competing ions of the same electrical charge should be avoided to achieve a effective iontophoresis if the drug is likely to form lipophilic ion-pair complexes of large K_e values with the counterions.

Acknowledgment

This study was partly supported by a research grant from the Ministry of Health and Social Affairs of Korea (1991)

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