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Interaction of electric field and electro-osmotic effects in determining iontophoretic enhancement of anions and cations

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Summary

The enhanced transport of cations and anions across porous membranes under an applied electric field is found to be asymmetric. This asymmetry may be due to the interaction between the direct effect of the field and convective solvent flow, which has been shown to be directional. The modified Nernst-Planck equations are used to model cation, anion, and neutral solute transport enhancement under an applied electric field. The mechanism of solvent flow is examined via electro-osmotic velocity equations. Uncharged solutes have been used to determine the solvent velocity during iontophoresis. The direct electric field effects on ion transport enhancement were then separated from the convective solvent flow contribution and the asymmetry in cation/anion flux enhancement was assessed. Results of experiments using model charged and uncharged solutes demonstrate the utility of the model and electro-osmosis may be used to explain the cation/anion asymmetry.

Introduction

Iontophoresis is the process of increasing the transport of ions into or through skin by the application of an external electric field across the skin (Keister and Kasting, 1986; Masada et al., 1989; Sims and Higuchi, 1990; Srinivasan et al., 1990). It is a non-invasive technique capable of increasing the transdermal delivery rates of some drugs to therapeutic levels for local and systemic treatment (Sloan and Soltani, 1986; Tyle, 1986).

Recent efforts have been directed at understanding the underlying mechanisms of solute transport during iontophoresis. Several investigators have modeled iontophoresis using the Nernst-Planck equation, which is the starting point for the formal description of ion diffusion under the influence of an electrochemical potential gradient (Schultz, 1980; Masada et al., 1985; Keister and Kasting, 1986; Srinivasan et al., 1990). This model assumes that the iontophoretic flux is driven entirely by the primary or conjugate driving force (the electrochemical potential gradient) and ignores the contributions of secondary effects such as current induced convective solvent flow (Burnette and Marrero, 1986; Mathot et al., 1989; Srinivasan et al., 1989a) and, in biological mem-

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branes, skin permeability increase due to the applied electrochemical potential gradient (Srinivasan et al., 1989a,b; Sims and Higuchi, 1990). As a consequence of these assumptions, this model predicts that the iontophoretic flux enhancement (relative to passive diffusion alone) is independent of the sign of the permeant's charge. This model also predicts that the flux of uncharged solutes should not be affected by iontophoresis.

Transport studies with model cations and anions across hairless mouse skin have shown, however, that the enhancement of cations is much greater than that of anions (Srinivasan et al., 1989b; Sims and Higuchi, 1990). Also, the transport of uncharged solutes in skin was observed to be enhanced during iontophoresis (Gangarosa et al., 1980; Burnette and Marrero, 1986; Burnette and Ongpipattanakul, 1987; Srinivasan et al., 1989a). The increase in flux, relative to passive flux, of the neutral solutes has been interpreted by these authors on the basis of convective solvent flow. The directionality of flow in skin was demonstrated from volume flow studies (Pikal and Shah, 1990) and from iontophoretic transport studies using glucose (Srinivasan et al., 1989a), where the glucose flux was shown to be enhanced when the current was in the same direction as the concentration gradient but inhibited when the current direction was reversed.

To account for convective solvent flow and the asymmetry between cation and anion enhancement, the Nernst-Planck equation was modified by the addition of a linear convective transport term (Srinivasan and Higuchi, 1990). The new model predicts (1) an asymmetry in the enhancement of cations and anions and (2) uncharged molecules are enhanced or retarded depending on the polarity of the applied electric field.

While the modified Nernst-Planck theory predicts the observed trends, it does not address the mechanism(s) governing the convective solvent flow. An electric field applied parallel to a charged surface (such as a pore wall) can induce movement of liquid adjacent to the surface, a process known as electro-osmosis (Aveyard and Haydon, 1973; Hunter, 1981). Skin has been shown to be a net negatively charged membrane (Burnette and Ongpipattanakul, 1987). Thus, it is reasonable to expect electro-osmosis to affect solute transport across skin under an applied electric field. As solvent flow has been shown to be directional, the question of cation/anion enhancement asymmetry may be expected to be due, at least in part, to interaction between the direct effect of the applied electric field and electro-osmotic flow.

Since uncharged solutes are not directly affected by the electric field, the solvent flow velocity may be determined from the iontophoretic enhancement of a neutral molecule. The direct field effects on ion transport enhancement may then be separated from the convective flow contribution. The asymmetry in cation and anion iontophoretic enhancement can then be assessed in light of the directionality of solvent flow. The mechanism of flow may also be investigated using the Helmholtz-Smoluchowski theory for electro-osmosis.

Permeability measurements through hairless mouse skin have been shown to be highly variable (Srinivasan et al., 1989a; Sims and Higuchi, 1990). Additionally, the application of an electric field may alter the stratum corneum permeability (Sims and Higuchi, 1990). In order to eliminate these problems and to elucidate the underlying mechanisms, a model membrane system, the Nuclepore® membrane, has been employed (Mathot et al., 1989). Nuclepore® is a polycarbonate membrane with essentially cylindrical, aqueous filled pores of known dimensions. It has been shown to possess a small, net negative, surface charge (Meares and Page, 1972; Ibanez and Tejerina, 1982; Keesom et al., 1988).

In this paper, glucose is used as a model neutral solute to examine the convective flow contribution to iontophoretic flux enhancement. A method for separating the solvent flow effect from the direct electric field effect on ion transport will be demonstrated. Cation and anion enhancement asymmetry is then examined in the light of interaction between the solvent flow and direct field effects. The mechanism of convective flow is also examined via the Helmholtz-Smoluchowski theory of electro-osmosis. A parallel series of papers show, semi-quantitatively, that a similar approach may be used to understand

iontophoretic transport in human skin (Sims, 1990; Sims et al., 1991a,b).

Model Development

Modified Nernst-Planck equations

The steady-state flux, J, of a permeant having charge z and diffusion coefficient D, through a porous membrane of thickness Δx, is given by (Srinivasan and Higuchi, 1990):

$$J = -D[(dC/dx) + (zFC/RT)(d\psi/dx)] \pm vC \quad (1)$$

where C is the permeant concentration, ψ the electric potential at any point x in the membrane, F the Faraday constant, R the gas constant, T the absolute temperature and v the average solvent velocity. The term vC is a measure of the transport of permeant resulting from convective solvent flow. For a net negatively charged membrane, the convective flow would be expected to assist the transport of a positively charged solute ($+vC$) and impede that of a negatively charged solute ($-vC$) (Srinivasan and Higuchi, 1990). This equation has been solved using the Goldman (1943) assumption of constant electric field within the membrane (Schultz, 1980; Srinivasan and Higuchi, 1990).

An enhancement factor, E, defined as the ratio of iontophoretic flux ($J_{\Delta\psi}$) at an applied voltage $\Delta\psi$ across the membrane, to the passive flux (J_0), can be obtained from Eqn 1 for cations (E_+) and anions (E_-):

$$E_+ = -K[1 - (P_e/K)]/[1 - \exp\{K(1 - P_e/K)\}] \quad (2)$$

$$E_- = -K[1 + (P_e/K)]/[1 - \exp\{K(1 + P_e/K)\}] \quad (3)$$

where

$$K = (zF\Delta\psi/RT) \quad (4)$$

and

$$P_e = (v\,\Delta x/D) \quad (5)$$

Eqns 2 and 3 give iontophoretic flux enhancements due to both a direct field (Nernst-Planck) effect and a solvent flow effect. The Peclet number (P_e) characterizes the effect of convective solvent flow on the flux of the permeant while K involves the direct field effects. Eqn 2 for cation enhancement reflects convective flow from donor to receiver. Similarly, Eqn 3 for anion enhancement reflects flow from receiver to donor. Qualitatively, predictions from Eqns 2 and 3 are consistent with published results for cations and anions (Mathot et al., 1989; Srinivasan et al., 1989b).

Assuming the direct electric field effect applies only for charged permeants, any enhancement in the flux of uncharged solutes can be assumed to be due to convective flow only. The enhancement factor (due only to the solvent flow) can be obtained by taking the limit as K approaches 0 (i.e., $z = 0$) in Eqns 2 and 3 (Srinivasan and Higuchi, 1990):

anode in the donor: $$E = P_e/[1 - \exp(-P_e)] \quad (6)$$

cathode in the donor: $$E = -P_e/[1 - \exp(P_e)] \quad (7)$$

Eqn 6 predicts enhancement factors greater than 1 for the anode in the donor and cathode in the receiver polarity while Eqn 7 predicts $E < 1$ for the opposite polarity. This is consistent with published experimental enhancement values (Mathot et al., 1989; Sims et al., 1989; Srinivasan et al., 1989a).

If a charged solute and a neutral probe solute have approximately the same diffusion coefficient and if the electrical double layer thickness ($1/\kappa$) is small compared to pore dimensions, then under the same experimental conditions, the Peclet number for the two solutes can be assumed to be equal. From the experimentally determined enhancement factor for the charged solute and the

Peclet number determined using the neutral solute, the asymmetry in cation and anion enhancement may be assessed.

Materials and Methods

Materials

Iontophoresis studies were conducted with the following permeants: [3-^{3}H]glucose (specific activity, 13.5 Ci/mmol), [1-^{14}C]mannitol (specific activity 55.0 mCi/mmol), [7-^{14}C]salicylic acid (specific activity 56.1 mCi/mmol) and [1-^{14}C]tetraethylammonium bromide (TEAB) having a specific activity of 3.0 mCi/mmol obtained from New England Nuclear Corporation, Boston, MA. Glucose (MW 180.2) was used as a model uncharged solute to assess the convective flow component of total flux across a membrane. Salicylate (MW 138.1; pK_a 2.97) was used as a model anion and the tetraethylammonium ion (MW 130.3) as a model cation.

Standard phosphate buffered electrolyte solutions (PBS, pH 7.5) were prepared in distilled, deionized water. The ionic strengths used in the studies were 0.001, 0.01, and 0.10 M. The 0.1 M PBS solution was made by dissolving 4.68 g NaCl, 1.63 g $Na_2HPO_4 \cdot 7H_2O$ and 0.14 g $NaH_2PO_4 \cdot H_2O$ per l of buffer. The lower ionic strength solutions were obtained by 10- and 100-fold dilution of the 0.1 M solution to give 0.01 and 0.001 M solutions, respectively. In all cases, NaCl was the dominant salt species. Chemicals were reagent grade and used as received.

Nuclepore ® membranes having pore radii of about 75 Å and a porosity of 0.001 were obtained from Nuclepore Corp., Pleasanton, CA. These membranes have a polyvinylpyrrolidone-coated, polycarbonate backbone and have been shown to have a small, net negative, surface charge density (Meares and Page, 1972; Ibanez and Tejerina, 1982; Keesom et al., 1988).

HPLC analysis

HPLC analysis of glucose was carried out to monitor possible decomposition of glucose during iontophoresis. An Aminex HPX-87H column (Biorad, Richmond, CA) was used and the mobile phase was 0.01 N H_2SO_4 at a flow rate of 0.4 ml/min at 25 °C. Detection was by ultraviolet light at a wavelength of 193 nm.

Iontophoresis apparatus

Membrane transport rates were measured using a four-electrode potentiostat system (JAS Instrumental Systems, Inc., Salt Lake City, UT) which maintains a constant voltage drop across a membrane mounted in a two-chamber diffusion cell. This system has been described in detail elsewhere (Sims, 1990; Srinivasan et al., 1990). Either Pt or Ag-AgCl counter electrodes were used. Ag-AgCl electrodes, prepared by the method of Uzgiris (1980), were used to minimize pH variations. Temperature was maintained at 37 °C by circulating water (Brinkmann RM-6 model circulating bath, American Scientific).

Iontophoresis experiments with Nuclepore ® membranes

Nuclepore ® membranes used in these experiments had a nominal thickness of 6 μm. The resistance of a single membrane was approx. 30 Ω which is of the order of the resistance of the adjacent solution (Srinivasan et al., 1990). To attain an adequate membrane resistance controlled transport, it was found necessary to use 50 Nuclepore ® membranes stacked together. The resistance of this plug was about 1.5 kΩ which is the same order of magnitude as seen with hairless mouse skin (Sims and Higuchi, 1990). This creates a random pore, negatively charged network for diffusion which may be similar to that found in human skin. In Fig. 1 it is shown that the 50 membrane plug maintains a linear current-voltage profile (Ohm's law obeyed) and ensures membrane resistance controlled mass transport. Thus, all Nuclepore ® experiments herein reported were performed using the 50 membrane system.

In each experiment, Nuclepore ® membranes presoaked in PBS were assembled such that there were no air bubbles between individual membranes. The assembled membrane plug was mounted between the half-cells and the Luggin capillaries were inserted. The Luggin capillaries were filled with the same buffer as used in the

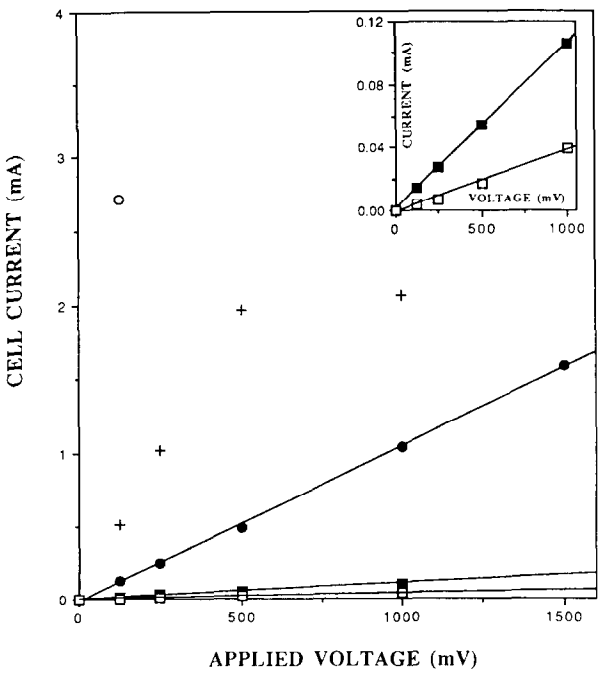

Fig. 1. Cell current as a function of applied voltage for Nuclepore ® membranes. 0.1 M PBS: (○) 1 membrane; (+) 10 membranes; (●) 50 membranes; 0.01 M PBS: (■) 50 membranes; 0.001 M PBS: (□) 50 membranes.

donor and receiver chambers. A 5 ml volume of phosphate buffered saline, pH 7.5, was pipetted into the receiver chamber. Trace amounts of the radiolabeled permeant were pre-mixed in the same PBS solution before pipetting 5 ml of solution into the donor chamber.

A typical experiment involved three stages. Stage I involved the determination of the passive permeability coefficient ($P = P_0$). Samples (1 ml) were withdrawn from the receiver chamber at predetermined time intervals and replaced with fresh buffer each time. For stage II, the four-electrode potentiostat was connected to the diffusion cell system as described earlier (Srinivasan et al., 1990). Usually, permeation runs were carried out consecutively for four different voltages (125, 250, 500, and 1000 mV), for a duration of up to 60 min at each voltage. During each voltage run, 1-ml samples were taken from the receiver chamber at predetermined time intervals and replaced with fresh buffer each time. Also, the current was continually monitored during stage II. The pH of the solution in each chamber was measured before and after each applied voltage period to assure that it remained constant. Also, the receiver chamber was flushed and the donor concentration was checked between the successive increases in applied voltage. At the end of stage II, both chambers were flushed and refilled. Finally, in stage III, the system was again allowed to equilibrate and a second passive permeability coefficient was determined.

The samples were mixed with 10 ml of scintillation cocktail (Opti-Fluor, Packard Instrument Co.) and were assayed on a Beckman Liquid Scintillation Counter, Model LS-7500. The data were plotted as Q, the cumulative disintegrations per min (dpm) transported into the receiver compartment, as a function of time, t. The permeability coefficient, P, was calculated for each of the voltage runs and for the passive permeation stages from:

$$P = [1/(\Delta C \cdot A)](dQ/dt) \qquad (8)$$

where A (0.69 cm^2) is the area for diffusion, ΔC is the concentration difference across the membrane, and dQ/dt is the steady-state slope.

Results and Discussion

Glucose experimental results and calculations

Results of a typical experiment with glucose are presented in Fig. 2. In this experiment, the anode was placed in the donor chamber and the voltages applied in sequence during stage II were 125, 250, 500, and 1000 mV. The slopes (dQ/dt) were determined from such data for both polarities, for each applied voltage, at each ionic strength.

The experimental P values, E values, and Peclet numbers (P_e) for all of the glucose experiments were obtained in the following manner. Eqn 8 was used to calculate the P values and these are tabulated in Table 1. The E values were calculated for each experiment by dividing the P values for each voltage by P_0 (the passive P value), and the averages of these E values are presented in Table 2. Finally, the Peclet numbers were calculated from the E values in Table 2

TABLE 1

Glucose permeability coefficients determined during iontophoresis at 0, 125, 250, 500, and 1000 mV applied voltages as a function of ionic strength, applied voltage drop and polarity

Ionic strength (M)	Passive (P_0) [a]	Permability coefficient (P) ($\times 10^7$) (cm/s) [b]			
		125 mV	250 mV	500 mV	1000 mV
(A) Anode in donor chamber					
0.001	3.1 ± 1.0	7.7 ± 1.5	14 ± 4.1	30 ± 8.6	34 ± 17
0.01	5.1 ± 1.6	14 ± 2.1	23 ± 7.8	54 ± 17	110 ± 16
0.10	2.8 ± 1.7	5.8 ± 4.0	10 ± 9.2	31 ± 21	63 ± 33
(B) Cathode in donor chamber					
0.001	1.8 ± 0.24	0.49 ± 0.23	0.22 ± 0.070	[c]	[c]
0.01	3.2 ± 0.62	1.7 ± 0.79	0.31 ± 0.14	[c]	[c]
0.10	4.7 ± 0.43	2.2 ± 0.14	0.88 ± 0.32	[c]	1.5 ± 0.26

[a] Passive P_0 is the average of stage I and III passive permeability coefficents.
[b] Mean ± S.D.; $n \geq 3$.
[c] Permeability coefficients were indistinguishable from zero.

using Eqns 6 and 7, and these are given in Table 3. The experimental variabilities were generally rather large, and this is reflected in the substantial standard deviations of the P values in Table 1. In most cases, the values for the stage I and stage III passive permeability coefficients in a given experiment were close. Therefore, only the averages of the P_0 values for stages I and III have been listed in Table 1. When, however, these two values in an experiment differed by a factor of two or more, the entire experiment was discarded and not included in calculating the results presented in Table 1.

Tables 1 and 2 clearly show that the two polarities give opposite effects with regard to the influence of the applied voltage. For the anode in the donor side polarity, the E values were always greater than unity and the P values and E values increased essentially linearly with applied voltage. The opposite was true in the case of the anode in the receiver side experiments: the P values and E values decreased with increasing voltage and,

TABLE 2

Enhancement factor (E) for transport of glucose across Nuclepore [®] membranes as a function of applied voltage across the membrane, ionic strength, and polarity

Ionic strength (M)	Enhancement factor (E [a])			
	125 mV	250 mV	500 mV	1000 mV
(A) Anode in donor chamber				
0.001	2.7 ± 0.8	4.9 ± 1.6	11 ± 4.4	22 ± 16
0.01	3.2 ± 1.3	5.1 ± 2.5	9.9 ± 4.1	17 ± 10
0.10	2.1 ± 0.5	3.4 ± 1.1	11 ± 2.4	24 ± 10
(B) Cathode in donor chamber				
0.001	0.29 ± 0.15	0.12 ± 0.023	[b]	[b]
0.01	0.58 ± 0.36	0.10 ± 0.04	[b]	[b]
0.10	0.47 ± 0.04	0.19 ± 0.07	[b]	[b]

[a] Mean ± S.D.; $n \geq 3$.
[b] Permeability coefficients were indistinguishable from zero.

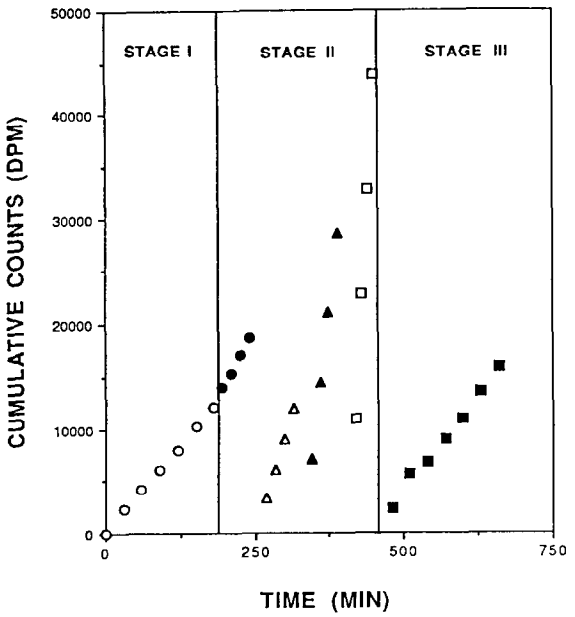

Fig. 2. Results from a typical three-stage glucose permeation experiment using 0.1 M phosphate buffered saline. (○) Stage I passive; stage II: (●) 125 mV; (△) 250 mV; (▲) 500 mV; (□) 1000 mV; (■) stage III passive. The polarity in this experiment was anode in the donor side, cathode in the receiver.

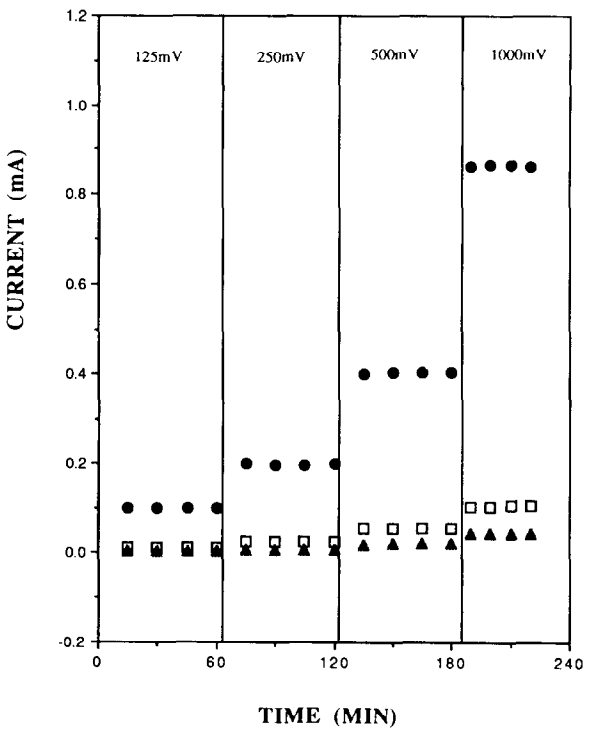

Fig. 3. Current profiles for typical experiments at each ionic strength and applied voltage. (●) 0.10 M PBS; (□) 0.01 M PBS; (▲) 0.001 M PBS.

at the highest voltages (500 and 1000 mV), the P values were indistinguishable from zero.

In one case, 0.1 M PBS and 1000 mV, the average P value ($n = 4$) appeared to be greater than zero (see Table 1). However, an HPLC check indicated that the maximum possible amount of any radiochemical impurity in the receiver chamber at the end of the run would be on the order of 10% which would have been too small to account for the greater than zero P value. It was believed, however, that the greater than zero P value was spurious as later experiments under the same conditions with [^{14}C]mannitol showed zero flux.

Typical current measurements taken during the application of voltage are shown in Fig. 3 for each ionic strength. The current increased linearly with increasing applied voltage and was very constant during the length of each voltage run. These results indicate the Nuclepore ® membrane plug remained unchanged by the applied voltage. Similar studies with human skin have shown non-linear behavior at high voltages (1000

TABLE 3

Peclet numbers (P_e) determined from glucose enhancement as functions of applied voltage drop, ionic strength, and polarity at 37 °C

Applied voltage (mV)	Peclet number (P_e) [a]		
	0.001	0.01	0.10
(A) Anode in donor chamber			
125	2.5 ± 0.8	3.1 ± 1.3	1.8 ± 0.5
250	4.9 ± 1.6	5.1 ± 2.7	3.3 ± 1.1
500	11 ± 4.4	9.9 ± 4.1	11 ± 2.4
1000	22 ± 16	17 ± 10	24 ± 10
(B) Cathode in donor chamber			
125	2.1 ± 0.70	1.1 ± 1.0	1.5 ± 0.10
250	3.3 ± 0.10	3.8 ± 0.60	2.8 ± 0.50
500	[b]	[b]	[b]
1000	[b]	[b]	[b]

[a] Mean ± S.D.; $n \geq 3$.

[b] Permeability coefficients were indistinguishable from zero.

mV), but not at lower voltages of 125 and 250 mV (Sims et al., 1991a,b).

Consistency of the glucose flux enhancements with the Helmholtz-Smoluchowski theory for electro-osmosis

Electro-osmosis has been suggested as a possible mechanism for the convective flow in skin (Burnette and Marrero, 1986; Pikal and Shah, 1990; Srinivasan and Higuchi, 1990). The classical, quantitative theory for electro-osmosis was established by Smoluchowski (1921) for the case when the pore radius (r_0) is much larger than the thickness of the electrical double layer. Using a Boltzmann distribution to describe the charge distribution within the pore and Poisson's equation to relate potential to charge density in the electrical double layer (see, for example, Bockris and Reddy, 1970; Hunter, 1981; Hiemenz, 1986), one may obtain an equation for the flow velocity, v:

$$v = (\epsilon \zeta \boldsymbol{F})/4\pi\eta \qquad (9)$$

where ϵ is the bulk dielectric constant, $\boldsymbol{F}$ is the electric field vector, η the viscosity of the bulk phase, and ζ the zeta potential, which is defined as the potential at the plane of shear of the liquid. Assuming a low surface charge density and neglecting ion-binding reactions, ζ may be approximated by the surface potential, ϕ, (Ottewill et al., 1960; Hunter, 1980; Keesom et al., 1988). The surface charge density, σ, can then be related to the surface potential via:

$$\zeta \approx \phi = 4\pi\sigma/\kappa \qquad (10)$$

κ is the Debye-Hückel reciprocal length and is a measure of the electrical double layer thickness. It is defined as:

$$\kappa = \{[8\pi e^2 IN]/[1000\epsilon kT]\}^{1/2} \qquad (11)$$

where e is the electronic charge, I is the ionic strength of the buffer, N is Avogadro's number, k is the Boltzmann constant and T is the absolute temperature. Substituting Eqn 10 into Eqn 9 and using the constant field assumption of Goldman (1943) results in an electro-osmotic velocity expression:

$$v = (\sigma/\kappa\eta)(\Delta\psi/\Delta x) \qquad (12)$$

Eqn 12 is expected to be strictly valid when $1/\kappa \ll r_0$.

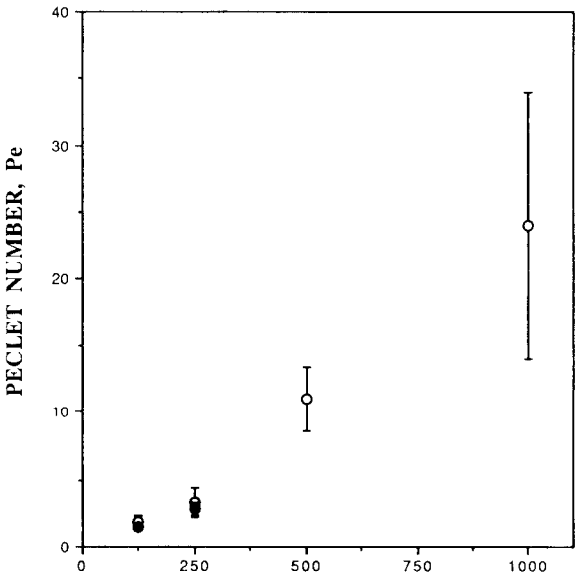

Fig. 4. Peclet number (P_e) determined for glucose in 0.1 M PBS vs the applied voltage drop across the membrane. (○) Anode in the donor side; (●) cathode in the donor side.

In Fig. 4, the P_e values for 0.10 M ionic strength taken from Table 3 are plotted against the applied voltage. Here, $1/\kappa = 10$ Å and, therefore, $1/\kappa \ll r_0$. As can be seen, P_e increases approximately linearly with increasing applied voltage. It is also seen that the Peclet number is independent of polarity. Thus, it appears that the solvent flow velocities determined from glucose transport experiments are consistent with the predictions of the Helmholtz-Smoluchowski theory (Eqn 12).

In Table 4, σ values calculated using Eqn 12 are presented and compared to those reported by Meares and Page (1972). In Meares and Page (1972), σ was determined by electro-osmotic flow studies through large-pore ($r_0 = 0.38$ and 0.26

μm) Nuclepore ® membranes at various ionic strength NaCl solutions. Nuclepore membranes having different pore sizes are manufactured by the same process; therefore, it is reasonable to compare the surface characteristics of the small- and large-pore membranes. In all of the work by Meares and Page, $\kappa r_0 \gg 1$ (see Table 4); however, this is true in the present work only at 0.1 M ionic strength. Despite the differences in experimental methods, it is interesting to note that the σ values calculated from glucose transport experiments are in very good agreement with those obtained from electro-osmotic flow measurements for the case of 0.10 M ionic strength.

For ionic strengths of 0.01 and 0.001 M, the $1/\kappa$ values are about 30 and 100 Å, respectively. For the present study, Eqn 12 is not expected to be valid. However, in Table 4, σ values are presented which have been calculated using Eqn 12 and the glucose transport data. As can be seen, these values are approximately the same order of magnitude as the σ values determined from the study of Meares and Page (1972). Additionally, it is interesting to note (see Table 3) that, for these cases, the P_c values are essentially indistinguishable from those for $1/\kappa \ll r_0$ (the highest ionic strength).

The σ value may be used to estimate the surface potential from Eqn 10. This equation is valid only when $\kappa r_0 \gg 1$ and the surface potential is small; thus, the theory should not be used for the case of 0.001 M ionic strength in small pores ($\kappa r_0 = 0.8$ from Table 4) and, perhaps, even at 0.01 M ionic strength. Rice and Whitehead (1965) have reported an equation for calculating the surface potential when $\kappa r_0 \approx 1$, provided the surface potential is small (≤ 50 mV):

$$\phi = \frac{-4\pi\eta v}{\epsilon} \frac{\Delta x}{\Delta\psi} F(r), \tag{13}$$

$$F(r) = 1 - \frac{2I_1(\kappa r_0)}{\kappa r_0 I_0(\kappa r_0)} \tag{14}$$

where I_n are the zero-order ($n = 0$) and first-order ($n = 1$) modified Bessel functions of the first kind. Table 5 lists the corrected surface potentials for both the present work and that of Meares and Page (1972). When $\kappa r_0 \gg 1$, $F(r)$ tends to 1 and the result is Eqn 10. Thus, the correction factor makes very little difference in the study of Meares and Page and a slight difference for the 0.10 M ionic strength calculation in the present work. There is a 2.5-fold increase in the estimated surface potential at 0.01 M ionic strength but the value is still small. If the potential is calculated for the 0.001 M case, the result is -12.2 mV from Eqn 10 and -178 mV from Eqn 13. Since both equations are valid only in the low potential approximation, it is clear that the above calculations are not correct for the 0.001 M ionic strength. To address the case of $\kappa r_0 < 1$, and ϕ values large compared to (ze/kT), the Poisson-

TABLE 4

Estimates of surface charge density of Nuclepore ® calculated from glucose enhancement compared to the value reported by Meares and Page (1972) as a function of ionic strength

Ionic strength (M)	κr_0		Surface charge density ($\times 10^3$) (C/m^2)	
	Present work	Meares and Page (1972)	Present [a] work	Meares and Page (1972)
0.001	0.8	39 [b]	0.9 ± 0.5	1.27 [b]
0.01	2.4	123 [b]	2.7 ± 0.6	3.24 [b]
0.10	7.7	265 [c]	7.9 ± 2.3	8.4 [c]

[a] Mean ± S.D.; $n \geq 3$; $\epsilon = 78$; $D = 6 \times 10^{-10}$ m^2/s; $\Delta x = 3 \times 10^{-4}$ m; $\eta = 7 \times 10^{-4}$ kg m^{-1} s^{-1}.
[b] $r_0 = 0.38$ μm.
[c] $r_0 = 0.26$ μm.

TABLE 5

Estimates of the surface potential of Nuclepore ® calculated from glucose transport experiments using Eqns 10 and 13 [similar calculations using the data reported by Meares and Page (1972) are also shown]

Ionic strength (M)	Surface potential (mV) using Eqn 10		Surface potential (mV) using Eqn 13 (Rice and Whitehead, 1965)	
	Present work	Meares and Page (1972)	Present work	Meares and Page (1972)
0.001	−12.2	−18.1	−178 ± 83	−19.1
0.01	−11.6	−14.5	−34 ± 17	−14.5
0.10	−11.7	−11.4	−15 ± 4.5	−11.5

Boltzmann and Navier-Stokes equations must be numerically solved to determine the potential, ψ, and velocity as a function of distance, r, from the wall of a cylindrical pore (Sims, 1990; Sims et al., 1991c).

Evaluation of the convective flow contribution to cation and anion transport

Glucose flux enhancement was used to estimate the solvent flow contribution to the transport of ions during iontophoresis. By assuming the diffusion coefficients of model charged solutes are similar to that of glucose, the Peclet number determined from glucose experiments may be used as an estimate of the solvent flow contribution for the charged species. Operationally, this means using Eqns 2 and 3 to predict the enhancement factor for cations and anions, respectively, where the Peclet number determined from the glucose transport experiment is used for both cases. These Peclet numbers were taken from best-fit straight line to the data in Table 3A.

The experimental enhancement factors determined for a monovalent cation (tetracthylammonium ion, TEA^+) and a monovalent anion (salicylate) have been compared to the predictions of Eqns 2 and 3 in each of the three ionic strength buffers in Fig. 5A–C. The Nernst-Planck prediction (without solvent flow) is also shown in each panel of Fig. 5 for comparison.

It is clearly shown in Fig. 5 that the cation and anion behave asymmetrically, i.e. the cation enhancement is above the prediction of the Nernst-Planck theory while the anion enhancement is below the prediction. At the high ionic strengths, both the salicylate and TEA^+ enhancement factors are much better described by the curves which include the solvent flow velocity effects (Fig. 5A, B), especially at the lower applied voltages. The solvent flow at 0.01 and 0.1 M ionic strengths may increase or decrease the flux of the charged solute by as much as 50%. At 0.001 M PBS, the P_0 experiments for salicylate were difficult to carry out due to the very long times to reach steady state (> 24 h) and the reproducibility in the calculated enhancement factor was relatively poor as a result.

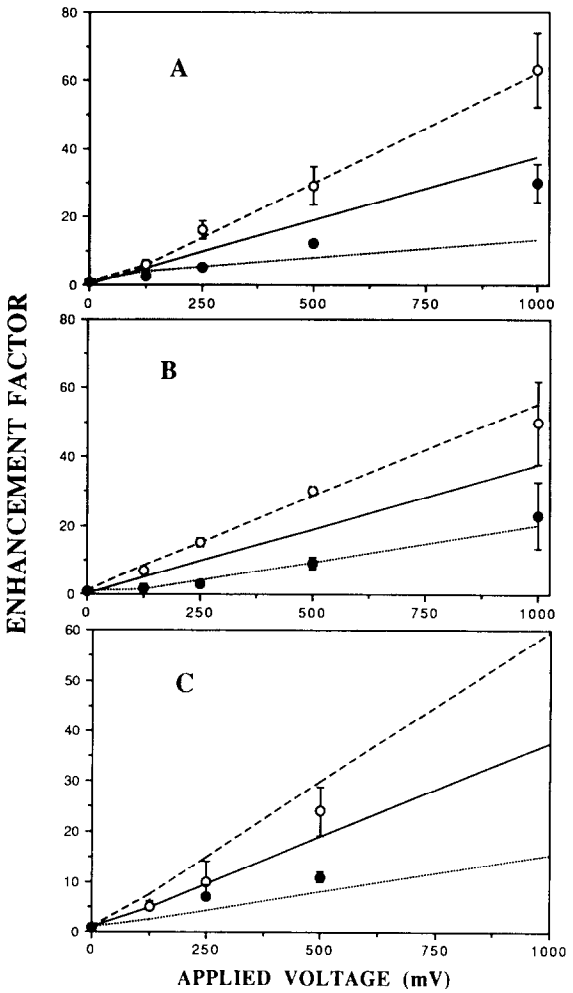

Fig. 5. TEAB (○) and salicylate (●) enhancement factors as a function of applied potential. The solid line is the Nernst-Planck prediction without accounting for convective flow. (- - - - -) Representation of the prediction of Eqn 2 for a monovalent cation and (· · · · · ·) of Eqn 3 for a monovalent anion. (A) 0.1 M ionic strength; (B) 0.01 M ionic strength; (C) 0.001 M ionic strength.

At lower ionic strengths, the theory developed in this manuscript is not applicable; the appropriate theoretical treatment for the low ionic strength case can be found elsewhere (Sims, 1990; Sims et al., 1991c). Additionally, solute dispersion phenomena (Sherwood et al., 1975) may be different for charged and uncharged solutes at low ionic strengths. Therefore, the use of glucose flux enhancement to estimate solvent flow velocity

and using this velocity to predict the enhancement factors for charged solutes may not be strictly valid.

Conclusions

The enhancement of monovalent anions and cations is best described by interaction between convective flow and a direct (Nernst-Planck) effect of the applied field. The equations for electro-osmotic velocity describe the convective flow effect during iontophoresis in high ionic strength buffers which implies electro-osmosis is one mechanism by which convective flow occurs. The proposed theory is able to predict trends in the flux enhancement of uncharged molecules during iontophoresis across microporous membranes.

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