A model for iontophoresis incorporating the effect of convective solvent flow

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Summary

A model for iontophoretic transport is proposed which incorporates the effects of the applied electric field and the induced convective solvent flow, with a linear term to account for the effect of solvent flow on the permeant flux. The predictions of this model are compared with those of a model without the convective solvent flow term. The new model provides a more detailed framework to decouple and understand the interactions of the applied field and the solvent flow effects. Some interesting features of this model, which are of basic as well as practical significance, are discussed.

Introduction

The Nernst-Planck equation is the most common starting point for the formal description of steady-state diffusion of charged permeants under an electrochemical potential gradient (Schultz, 1980) and has been used to model the iontophoretic transport of drugs across skin (Keister and Kasting, 1986; Kasting and Keister, 1989; Srinivasan et al., 1989a). The Nernst-Planck equation is an example of a single force-flux model, where the flux is assumed to be driven entirely by its conjugate driving force (the electrochemical potential gradient) and non-conjugate flows or forces are neglected. In particular, the coupled transport of a permeant due to convective flow of solvent is assumed to be negligible.

An electrically driven flow of ions across a membrane having a net charge can induce a coupled flow of solvent, called electro-osmosis (Aveyard and Haydon, 1973). Several investigators have presented experimental evidence of iontophoretically induced convective solvent flow (Gangarosa et al., 1980; Pikal and Shah, 1986; Srinivasan et al., 1989b). In particular, it has been shown that the convective solvent flow across net negatively charged membranes is in the direction of the current and consequently can assist the diffusion of a positively charged permeant and impede that of a negatively charged permeant (Mathot et al., 1989; Srinivasan et al., 1989b). For a small positively charged permeant, the convective solvent flow contribution appears to be a second-order phenomenon relative to the effect of

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the applied voltage (Mathot et al., 1989; Srinivasan et al., 1989c). The predictions of iontophoresis models based on the Nernst-Planck equation (without incorporating the solvent flow effect) are in good agreement with experimental observations for a small positively charged solute and higher by a factor of two to three for small negatively charged solutes (Mathot et al., 1989; Srinivasan et al., 1989c). It is not clear whether this asymmetry in the behaviour of positively and negatively charged solutes is due entirely to the convective solvent flow effect.

A model for iontophoretic transport incorporating the effect of the applied electric field and the induced convective solvent flow would provide a more detailed framework for understanding the interactions of the applied field and the induced solvent flow. In this paper, an extension of the Nernst-Planck model for iontophoresis, with a linear term to account for the effect of solvent flow (Schlogl, 1966), is developed and some interesting features of this model are discussed.

Model Development

The steady-state flux J, of a permeant having charge z and diffusion coefficient D, through a porous membrane is given as:

$$J = -D[(dc/dx) + (zFc/RT)(d\psi/dx)] \pm vc,$$
$$(1)$$

where c is the concentration of the permeant, ψ the electric potential at any point x in the membrane, F the Faraday constant, R the gas constant, T the absolute temperature, v the average velocity of the solvent and vc a measure of the transport of permeant resulting from the convective solvent flow. The convective flow in a net negatively charged membrane assists the flux of a positively charged solute and impedes that of a negatively charged solute (Srinivasan et al., 1989b). Therefore, $+vc$ is the correct term to use in Eqn 1 to account for the effect of convective solvent flow on the flux of a positively charged permeant, while the term $-vc$ is the appropriate one for a nega-

tively charged permeant.

For a positively charged permeant, Eqn 1 can be written, in terms of dimensionless variables, as follows:

$$dC/dX + [dV/dX - Pe]C = -M,$$
$$(2)$$

where the dimensionless variables are a dimensionless distance $X = (x/t)$, t being the membrane thickness; a dimensionless electric potential $V = (zF\psi/RT)$, and a dimensionless concentration $C = (c/c_d)$, c_d being the concentration of the permeant at the membrane-donor side interface. The coefficients in Eqn 2 are given by:

$$Pe = (vt/D),$$
$$(3)$$

and

$$M = (Jt/Dc_d).$$

In order to integrate Eqn 2, the electric potential profile within the membrane (dependence of V on X) has to be specified. The simplest and most frequently used assumption is that the electric field within the membrane, dV/dX, is constant (Goldman, 1943). Other assumptions to facilitate the integration of the Nernst-Planck equation are described elsewhere (Schlogl, 1954; Kasting and Keister, 1989). In the present treatment, the constant field assumption will be employed to facilitate the integration of Eqn 2. With this assumption, Eqn 2 becomes a linear, inhomogeneous, first-order, ordinary differential equation with constant coefficients and can be readily solved.

Following the procedure outlined elsewhere (Schultz, 1980; Srinivasan et al., 1989a) and making the appropriate assumptions to eliminate the interface conditions (Schultz, 1980; Srinivasan et al., 1989a), the solution to Eqn 2 (assuming sink conditions on the receiver side) can be readily obtained. It can be rearranged to give an enhancement factor E, which is the ratio of the iontophoretic flux ($J_{\Delta\psi}$) at an applied voltage $\Delta\psi$ across the membrane, to the passive flux (J_o). The enhancement factor best conveys information on the

effect of iontophoresis on the flux of a permeant, and for a positively charged permeant, is given by:

$$E = -K[1 - (Pe/K)] / [1 - \exp\{K(1 - Pe/K)\}], \quad (4)$$

where

$$K = (zF\Delta\psi/RT). \quad (5)$$

For a negatively charged permeant, the enhancement factor is:

$$E = -K[1 + (Pe/K)] / [1 - \exp\{K(1 + Pe/K)\}]. \quad (6)$$

Eqns 4 and 6 give the iontophoretic flux enhancements due to the cumulative effect of the applied voltage across the membrane and the convective solvent flow. The enhancement factor from the Nernst-Planck equation without the convective transport term (Keister and Kasting, 1986; Srinivasan et al., 1989a) can be obtained from Eqn 4 or 6 by setting $Pe = 0$ and is independent of the sign of the permeant's charge.

Fig. 1 shows a plot of the enhancement factor predicted by Eqn 4 as a function of the applied voltage for a monovalent positively charged per-
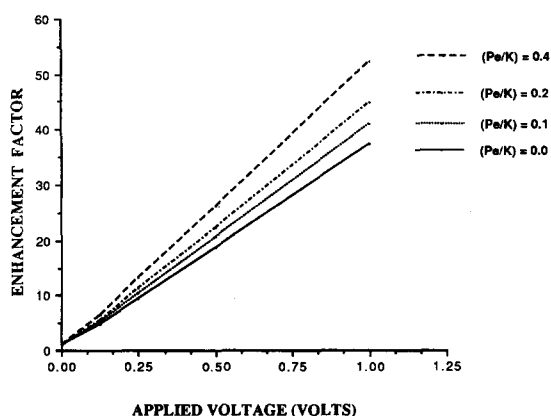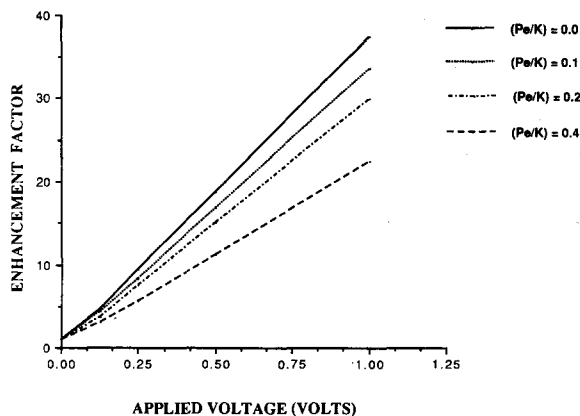

Fig. 2. Relationship between the applied voltage and the enhancement factor for a monovalent negatively charged permeant at 37°C for different values of the parameter (Pe/K), as predicted by Eqn 6.

meant (at 37°C) for different values of the parameter (Pe/K). The solid line (corresponding to $Pe = 0$) is the prediction of the Nernst-Planck equation without the convective transport term. Fig. 2 is the corresponding plot for a monovalent, negatively charged permeant. In Figs 1 and 2, the parameter (Pe/K) is assumed to be independent of the applied voltage (or equivalently, the solvent flow velocity is assumed to be linearly related to the applied voltage) in computing the enhancement factors. The effect of the convective transport term on the enhancement factors for positively and negatively charged solute is symmetric about the solid line if the exponential term in the denominator in Eqns 4 and 6 is much smaller than unity. This is usually the case under most experimental conditions (Srinivasan et al., 1989a).

Discussion

Mechanism of solvent flow

In this model, the convective flow of solvent is assumed to have a contact velocity without any indication as to the nature of, or mechanisms governing the flow. An electric field applied parallel to a charged, solid 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). There is consider-

Fig. 1. Relationship between the applied voltage and the enhancement factor for a monovalent positively charged permeant at 37°C for different values of the parameter (Pe/K), as predicted by Eqn 4.

able experimental evidence to indicate that human skin is negatively charged at physiological pH (Burnette and Ongpipattanakul, 1987); the conduction mechanism in human skin appears to be through aqueous channels or 'pores' (DeNuzzio and Berner, 1988). Therefore, it is reasonable to expect electro-osmosis to be a contributing factor to the observed convective solvent flow during iontophoresis. The primary physico-chemical factors which determine the magnitude of the electro-osmotic velocity are the net charge density of the membrane, the ionic strength and viscosity of the electrolyte, and the magnitude of the applied electric field (Bockris and Reddy, 1970; Aveyard and Haydon, 1973). The charge density is likely to be an intrinsic property of the membrane and depends on its pI and the pH of the electrolyte. The other factors are independently controlled experimental conditions. Additionally, factors such as osmotic pressure differences arising from concentration gradients across the membrane can also induce convective solvent flow. This latter factor can be minimized by proper design of experiments (Srinivasan et al., 1989a).

Influence of permeant size on the solvent flow effect

The dimensionless grouping (vt/D) is known as the Peclet number and characterizes convective mass transport phenomena (Bird et al., 1960). Even in situations where the assumptions in this model are not valid, the effect of the convective flow on mass transport of the permeant will be characterized by the Peclet number. In the expression for the Peclet number (Eqn 3), the numerator is determined entirely by the membrane properties (thickness, charge density) and experimental conditions (electrolyte and electric field strength). The denominator however, is dependent on the molecular size (diffusion coefficient) of the permeant. Therefore, under identical conditions (the same membrane, electrolyte and applied field), the Peclet number will be greater for a larger permeant, because of its smaller diffusion coefficient. Consequently, the effect of the convective solvent flow on the iontophoretic flux is inversely related to the molecular size (diffusion coefficient) of the permeant. For a large, negatively charged permeant such as a polypeptide, the size-dependent

opposing effect of the convective solvent flow may neutralize the influence of the applied electric field. Conversely, for a positively charged permeant, the convective solvent flow may become an increasingly important mechanism of mass transfer relative to the effect of the electric field as the size of the permeant increases.

In experiments with an artificial membrane system, the flux of leuprolide (an LHRH analog, molecular weight = 1209.4, positively charged at pH 7.4) was significantly enhanced by an applied voltage across the membrane system, but the enhancement factors were less than that for a smaller solute of equal charge (Mathot et al., 1989). The flux of a cholecystokinin-8 analog (molecular weight = 1150.7, negatively charged at pH 7.4) did not appear to be enhanced by the applied voltage, whereas that of the small negatively charged (at pH 7.4) butyrate ion was increased by the applied voltage (Mathot et al., 1989).

Decoupling the effects of the electric field and solvent flow

The applied electric field can only influence the flux of charged permeants. The convective solvent flow can affect the flux of any permeant, whether charged or uncharged. By using a neutral probe solute, the effect of the solvent flow alone on the permeant flux during iontophoresis can be determined. For the iontophoresis of the neutral probe solute at the same polarity as for a positively charged solute, the enhancement factor (due only to the solvent flow) can be obtained either by solving Eqn 1 with $z = 0$ or by setting $K = 0$ in Eqn 4 after appropriate rearrangement, and is given by:

$$E = Pe/[1 - \exp(-Pe)]. \tag{7}$$

From the experimentally determined enhancement factor for the probe solute and Eqn 7, the Peclet number can be calculated. If the charge density of the pore wall is known, then the Peclet number under the experimental conditions due to electro-osmosis can be predicted (Bockris and Reddy, 1970; Aveyard and Haydon, 1973). A good agreement between the predicted and experimentally observed Peclet numbers would help establish that

the mechanism behind the induced solvent flow is the phenomenon of electro-osmosis.

If a positively charged solute and the neutral probe solute have approximately the same diffusion coefficient, then under identical experimental conditions, the Peclet number for the two solutes can be assumed to be equal. This assumption is most likely to be valid when the thickness of the electrical double layer at the pore wall is small compared to the pore diameter. When this condition is not met, radial concentration gradients can be quite different for positively and negatively charged permeants due to permselectivity; a neutral solute remains unaffected by permselectivity. Theoretical treatment of this situation is very complex. From the experimentally determined enhancement factor for the positively charged solute and the Peclet number determined from Eqn 7 using the neutral solute, the factor K in Eqn 4 can be calculated. From the magnitudes of Pe and K, the importance of the effect of the convective flow relative to that of the applied field can be quantitatively assessed. By comparing the calculated value of K with that predicted by Eqn 5, the validity of the constant field assumption can be rigorously tested.

The same two-step procedure can also be applied to the combination of a negatively charged solute and a suitable neutral probe solute. The enhancement factor for the neutral probe solute at the same polarity as for the negatively charged solute can readily be obtained by setting $K = 0$ after appropriate rearrangement of Eqn 6.

Concluding Comments

This paper describes a model for iontophoresis incorporating the effect of the applied electric field and the induced convective solvent flow. This model provides a more detailed framework for the elucidation of the interaction between the effects of the electric field and the induced solvent flow on the iontophoretic flux; a technique for decoupling and comparing the relative magnitudes of the two effects can readily be implemented. This model also predicts that the magnitude of the solvent flow effect on the iontophoretic flux is inversely related to the molecular size (diffusion coefficient) of the permeant, becoming increasingly important for high molecular weight permeants such as polypeptides.

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