Epidermal Iontophoresis: I. Development of the Ionic Mobility-Pore Model

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Purpose. An integrated ionic mobility-pore model for epidermal iontophoresis is developed from theoretical considerations using both the free volume and pore restriction forms of the model for a range of solute radii (r_j) approaching the pore radii (r_p) as well as approximation of the pore restriction form for $r_j/r_p < 0.4$. In this model, we defined the determinants for iontophoresis as solute size (defined by MV, MW or radius), solute mobility, solute shape, solute charge, the Debye layer thickness, total current applied, solute concentration, fraction ionized, presence of extraneous ions (defined by solvent conductivity), epidermal permselectivity, partitioning rates to account for interaction of unionized and ionized lipophilic solutes with the wall of the pore and electroosmosis.

Methods. The ionic mobility-pore model was developed from theoretical considerations to include each of the determinants of iontophoretic transport. The model was then used to reexamine iontophoretic flux conductivity and iontophoretic flux-fraction ionized literature data on the determinants of iontophoretic flux.

Results. The ionic mobility-pore model was found to be consistent with existing experimental data and determinants defining iontophoretic transport. However, the predicted effects of solute size on iontophoresis are more consistent with the pore-restriction than free volume form of the model. A reanalysis of iontophoretic flux-conductivity data confirmed the model's prediction that, in the absence of significant electroosmosis, the reciprocal of flux is linearly related to either donor or receptor solution conductivity. Significant interaction with the pore walls, as described by the model, accounted for the reported pH dependence of the iontophoretic transport for a range of ionizable solutes.

Conclusions. The ionic mobility-pore iontophoretic model developed enables a range of determinants of iontophoresis to be described in a single unifying equation which recognises a range of determinants of iontophoretic flux.

KEY WORDS: iontophoresis; ionic mobility; free volume model; Debye layer; pore.

INTRODUCTION

Iontophoresis can be defined as the migration of a solute, either charged or uncharged, across a membrane under the influence of an electrical potential gradient. It has been shown to be effective in the enhancement of penetration of many drugs delivered by the transdermal route. This method of administration of drugs is dependent on many factors, including the nature and magnitude of the electric field applied and the compositions of donor and receptor solutions (1–6). Our group has suggested that conductivity of a solute in an aqueous solution is the best predictor of extraneous ion effects on the iontophoresis on both cations (7) and anions (8). Gangarosa et al. (3) had also previously suggested that the iontophoretic transport of a number of solutes may also be related to the conductivity of those solutes in aqueous solutions.

The relationship between solute molecular structure and iontophoretic transport is less well understood. Siddiqui et al. (4), in studying the relationship between the fraction change in flux of an ionized solute and solute structure, concluded that MW did not appear to be a determinant of the iontophoretic delivery of weak electrolytes. However, Roberts et al. (5), in a reanalysis of this and other published iontophoretic data concluded that the logarithm of the iontophoretic flux could be related to the MW of a solute with a slope of 0.003. The molecular size dependence of iontophoretic transport (5) has been confirmed with a larger number of solutes (9–10). In these studies, they examined the extent to which the solute structure-iontophoretic permeability relationship could be described by a Stokes-Einstein, free volume or pore restriction model of iontophoretic transport. The radius of the pore restricting transport appears to be in the order of magnitude of 10^{-9} m and has been confirmed by a number of other independent studies (9,11–12).

In this study, we were particularly interested in developing a solute structure-epidermal transport model further to account for a range of determinants of iontophoretic transport including (i) the solute ionic mobility within the "aqueous" solution within the pore and in the donor solution, (ii) the effect of the pore size restriction on solute iontophoretic transport, (iii) the competition of the donor and receptor solution ions and (iv) the effect of partial solute ionization. This paper develops the model and then examines the determinants of transport for individual solutes where ionic mobility and size are constant parameters. The accompanying paper (13) applies the model across a range of local anesthetics where both ionic mobility and size vary but other parameters can be kept constant.

THEORETICAL SECTION

The total flux of a solute j through the epidermis $J_{j,total,epi}$ by iontophoresis is given by the sum of the passive diffusion flux through the epidermis $J_{j,passive,epi}$ (mainly through the intercellular lipids for uncharged lipid solutes) and that through pores by iontophoresis $J_{j,iont,overall}$, assuming that the molecules of solute passing through these two pathways do so independently:

$$J_{j,total,epi} = J_{j,passive,epi} + J_{j,iont,overall} \quad (1)$$

Given that $J_{j,passive,epi}$ can be determined independently in the absence of iontophoresis for any set of conditions, this work has focused on the determinants of $J_{j,iont,overall}$ recognising that $J_{j,iont,overall}$ is defined through a rearrangement of eq. 1 as $J_{j,total,epi} - J_{j,passive,epi}$ and both $J_{j,total,epi}$ and $J_{j,passive,epi}$ can be determined independently.

The total flux observed for the jth mole of a partially ionized solute in an *individual uncharged pore* during iontophoresis, $J_{j,pore,overall}$ is given by (9):

$$J_{j,pore,overall} = J_{j,passive,pore}(x) + J_{j,iont,pore}(x) \pm J_{j,convective,pore}(x)$$

$$= D_{j,pore}\left[-\frac{\partial C_{j,p}}{\partial x} + \frac{C_{j,p} f i_{j,p} z_j F}{RT} E\right] \pm (1 - \sigma_j) v_p C_{j,p} \quad (2)$$

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where $J_{j,passive,pore}(x)$, $J_{j,iont,pore}(x)$ and $J_{j,convective,pore}(x)$ is flux due to passive diffusion, iontophoresis and convective flow at position x in the pore, respectively, $D_{j,pore}$ is the diffusion coefficient in the pore, $C_{j,p}$ is the concentration of the solute in the pore, $fi_{j,p}$ is the fraction of solute ionized in the pore, z is the charge of the solute j in the pore, F is Faraday's constant, R is the gas constant, T is the absolute temperature, E is the electrical field strength, σ_j is the reflection coefficient term and v_p is the velocity of convective water flow.

When $J_{j,passive,pore} << J_{j,pore,overall}$, eq. 3 can be used to define the total iontophoretic flux across a unit membrane area, $J_{j,iont,overall}$:

$$J_{j,iont,overall} = J_{j,iont,pore} \pm J_{j,convective,pore}$$
$$= D_{j,pore} f_{pore} \frac{C_{j,p} fi_{j,p} z_j F}{RT} E \pm (1 - \sigma_j) v_m C_{j,p} \quad (3)$$

in which f_{pore} is the area of all pores per unit area of membrane and v_m is the velocity of water flow across the membrane ($f_{pore}\ v_p$).

We now express eq. 3 in terms of the equivalent terms in bulk solution, recognising that (i) the ratio of diffusion coefficient in the pore to diffusion coefficient in the bulk solution $D_{j,pore}/D_{j,solution} = PRT_j/\Re_{pore}$ where PRT_j is a pathway restriction term, defined as a measure of hindrance factors for movement of solutes in cylindrical pores, in pore transport (14) and $\Re_{pore}$ is a dimensionless resistance parameter which is related to tortuosity, viscosity in membrane pathway relative to bulk solution and the effects of electrical charge on solute mobility, electrical field, and other undefined factors (for ease of analysis, $\Re_{pore}$ is assumed to be independent of nature of ions present), (ii) the mobility of solute j in solution is given by $\mu_j = D_j/RT$, (iii) $E = I_T/k_{skin}$ (6) and (iv) assuming $C_{j,pore} = C_{j,s}$ and $fi_{j,p} = fi_{j,s}$ where $C_{j,s}$ is concentration of solute j in solution and $fi_{j,s}$ is the fraction ionized in solution. Eq. 3 can then be reexpressed as:

$$J_{j,iont,overall} = \left[\frac{\mu_j f_{pore} F fi_j z_j I_T PRT_j}{\Re_{pore} k_{skin}} \pm (1 - \sigma_j) v_m \right] C_{j,s} \quad (4)$$

where I_T is the total current density and k_{skin} is the total conductance of the membrane.

The conductance of the membrane k_{skin} can be expressed as:

$$k_{skin} = F \sum_j \left(\frac{f_{pore}\ \mu_j PRT_j}{\Re_{pore}} \pm (1 - \sigma_j) \frac{v_m}{E} \right) C_j z_j fi_j \quad (5)$$

The conductance in the skin is largely determined by the flux of small ions. When the PRT_j for these small ions is assumed to approach 1 with the ion flux contribution due to electroosmotic flow (v_m) being much less than that due to electrokinetic transport, eq. 5 can be approximated as:

$$k_{skin} \approx \frac{F f_{pore} \sum_j C_j \mu_j z_j}{\Re_{pore}} \quad (6)$$

Recognising that the j ions present in the skin arise from m cations entering the skin from compartment 1 through cathodal iontophoresis and n anions entering from the other compartment through anodal iontophoresis then:

$$k_{skin} \approx \frac{F f_{pore}}{\Re_{pore}} \left(\sum_m C_m \mu_m z_m + \sum_n C_n \mu_n z_n \right) \quad (7)$$

Although Roberts et al. (5) used a form of eq. 7 to describe data reported by Bellantone et al. (2) and other workers, Phipps & Gyory (6) have suggested that ion-ion interactions may be significant. Yoshida and Roberts (7–8) have suggested that conductivity better reflects effective ion concentrations, and hence, the use of conductivity in this analysis. If the conductivities of the solutions with the anode $k_{s,a}$ and cathode $k_{s,c}$ are assumed to be equally determined by the conductivities of the anions and cations present, then:

$$k_{skin} = \frac{f_{pore}}{\Re_{pore}} \left(\tfrac{1}{2} k_{s,a} + \tfrac{1}{2} k_{s,c} \right) \quad (8)$$

Combining eq. 4 and 8 yields:

$$J_{j,iont,overall} = \left(\frac{2 \mu_j fi_j F z_j I_T\ PRT_j}{k_{s,a} + k_{s,c}} \pm (1 - \sigma_j) v_m \right) C_j \quad (9)$$

The iontophoretic flux $J_{j,iont}$, of the jth ion can also be expressed in terms of the conductivity k_{jw} in water, by substituting $\mu_j = k_{j,w}/(FC_j z_j)$ in eq. 9.

Accordingly, the membrane pathway restriction term PRT_j is given as the constant A by Yoshida & Roberts in relating iontophoretic flux to solute and solution conductivities (7–8).

Membrane Pathway Restriction of Iontophoretic Transport

Iontophoretic transport of solutes through the epidermis is restricted to a number of pores, both through appendages and through the intercellular regions of the stratum corneum (15). Yoshida & Roberts (9–10) have proposed that solute flux is limited by solute size due to a pathway restriction in transport. Two of their pathway restriction models are considered further here: (i) the free volume model (PRT_j^{FV}), in which there is a limited space where molecules can jump into, in transport through the pores and (ii) pore-restriction model (PRT_j^{PR}) where there is steric hindrance in entry into the pore and in movement through the pore due to friction with the pore wall (see Fig. 1). In the free volume model, the pathway restriction term is defined by the negative exponent of the ratio of the solute molecular volume MV to an effective average "cage" volume (V_{av}^i):

$$PRT_j^{FV} = exp\left(-\frac{MV}{V_{av}^i} \right) \quad (10)$$

In epidermal iontophoretic transport, V_{av}^i is approximately 155 cm^3/mol (9–10).

A modified Renkin equation was proposed for a pore-restriction iontophoretic transport (9–10):

$$PRT_j^{PR} = [1 - \lambda_j]^2 [1 - 2.10\lambda_j + 2.09\lambda_j^3 - 0.95\lambda_j^5] \quad (11)$$

where λ_j is the ratio of solute radius r_j to pore radius r_p. The most appropriate solute radius r_j to be used in PRT_j^{PR} is the Stokes-Einstein radius which is defined as $kT/6\pi\eta D_j$ where k is Boltzmann's constant, T is absolute temperature, η is the viscosity of solution in which the solute has a diffusion coefficient D_j. Yoshida & Roberts (9) initially estimated a pore radius

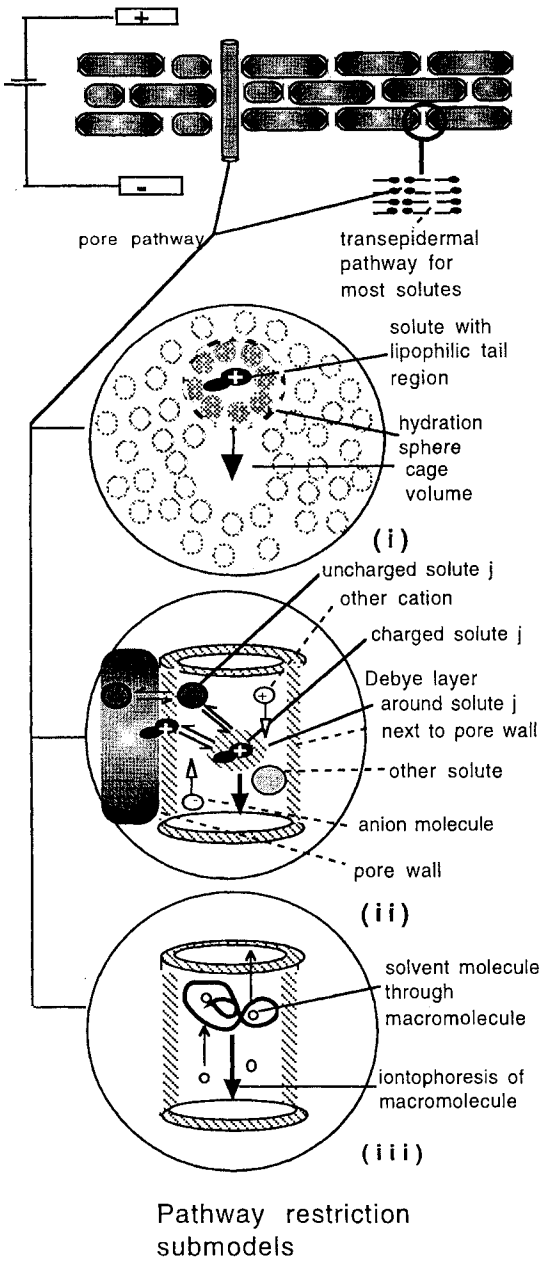


Fig. 1. Diagrammatic representation of pathway restriction terms used in the ionic mobility-pore model of epidermal iontophoretic transport: (i) free volume submodel, (ii) pore restriction submodel including Debye layer, unionized solute interaction with pore membrane, ionized solute interaction with pore membrane surface and convection, and (iii) macromolecule and pore-restriction submodel.

of 30 Å using a pore restriction approximation. The later and lower value of 8 Å reported by Yoshida & Roberts (10) is similar to the pore radius of 10 Å reported in the accompanying paper (13). Yoshida & Roberts (10) suggested that difficulties associated in applying this model to iontophoretic studies included nonspherical solute ions, when known heterogeneity exists in pore sizes, and potential interactions occur with the pore surface. Eq. 11 applies to rigid spherical molecules allowing the radius to be approximately determined from the molecular volume MV, assuming a sphere:

$$r = \sqrt[3]{\frac{3MV}{4\pi N_A}} \tag{12}$$

where N_A is Avogadro's number. In practice, the radius of the solute is increased by the Debye layer as discussed later in the section on additional effects of membrane and solute charge on transport. Eq. 11 is an approximation limited to $0 \leq \lambda_j < 0.4$ (14). A further expression for $0 \leq \lambda_j < 1$ is (14):

$$PRT_j^{PR} = \frac{6\pi(1-\lambda_j)^2}{3.18\pi^2(1-\lambda_j)^{-5/2}\left[1+\sum_{n=1}^{2} a_n(1-\lambda_j)^n\right] + \sum_{n=0}^{4} a_{n+3}(\lambda_j)^n} \tag{13}$$

where the coefficients are $a_1 = -1.22$, $a_2 = 1.53$, $a_3 = -22.51$, $a_4 = -5.61$, $a_5 = -0.34$, $a_6 = -1.22$ and $a_7 = 1.65$.

Three limitations associated with the above models are (i) the assumption of a spherical shape, (ii) the lack of recognition of solute and membrane charge effects, as discussed separately, later and (iii) macromolecules are porous bodies. In general, solutes with a nonspherical shape will have a lower Stokes-Einstein radius r_j than an equivalent sphere (14). When we define r_r as the radius of the major axis of rotation for an axisymmetric solute and γ as the ratio of r_r to the radius of rotation of the other axis r_o, we can estimate the Stokes-Einstein radius for various solutes r_j as sphere: $r_j = r_r = r_o$, ($\gamma = 1$); needle: $r_j \approx r_r/\ln(2\gamma)$, ($\gamma > 1$); disc: $r_j \approx 2r_r/\pi$, ($\gamma < 1$). Hence, nonspherical molecules have lower Stokes-Einstein radii than spheres. As macromolecules are porous bodies, their radius of gyration is larger than a sphere of equivalent Stokes-Einstein radius and water can flow through the molecule (16) (Fig. 1).

Convective Flow

Electroosmotic flow, defined as bulk fluid flow associated with a potential difference across a charged membrane is likely to be significant for macromolecules (17). The convective component of iontophoretic transport is also affected by pathway restriction, $(1 - \sigma)$ where the electroosmotic reflection coefficient σ for a membrane is defined by the fraction of solute "reflected" or rejected by the membrane relative to water (14). For the free volume model, the restriction term equals $exp(-MV/V_{av}^{\sigma})$. Yoshida & Roberts (10) found V_{av}^{σ} for nonelectrolytes (convective flow) was similar to that obtained for charged solutes V_{av}^{ι}. It is likely, however, that this V_{av}^{σ} would be shown to differ from that for iontophoresis V_{av}^{ι} if a wider range of solute sizes were chosen in discriminating between V_{av}^{ι} and V_{av}^{σ}. The electroosmotic transport equations corresponding to eq. 11 and 13 are (14):

$$1 - \sigma_j = (1-\lambda_j)^2(2-(1-\lambda_j)^2) \times (1 - 0.667\lambda_j^2 - 0.163\lambda_j^3) \tag{14}$$

for $0 \leq \lambda_j < 0.4$ and

$$1-\sigma_j=\frac{(1-\lambda_j)^2(2-(1-\lambda_j)^2)\left(3.18\pi^2(1-\lambda_j)^{-5/2}\times\left[1+\sum_{n=1}^{2}b_n(1-\lambda_j)^n\right]+\sum_{n=0}^{4}b_{n+3}\lambda_j^n\right)}{2\left(3.18\pi^2(1-\lambda_j)^{-5/2}\times\left[1+\sum_{n=1}^{2}a_n(1-\lambda_j)^n\right]+\sum_{n=0}^{4}a_{n+3}\lambda_j^n\right)} \quad (15)$$

for $0 \leq \lambda_j < 1$, where $b_1 = 0.12$, $b_2 = -0.04$, $b_3 = 4.02$, $b_4 = -3.97$, $b_5 = -1.92$, $b_6 = 4.39$, $b_7 = 5.01$.

Additional Effects of Membrane and Solute Charge on Transport

The pathway restriction term will be influenced by the charge of the solute itself, through electrostatic and dispersion forces. Munch et al. (18) modelled this influence by recognising the presence of a Debye layer l_D associated with charged surfaces on the effective radius of the moving charged solute and on the pore radius, yielding an effective solute radius ($r_j + l_D$) to effective pore radius ($r_p - l_D$) ratio λ_j^*:

$$\lambda_j^* = \frac{r_j + l_D}{r_p - l_D} \quad (16)$$

where l_D is defined by $\sqrt{\varepsilon kT/(8\pi z_s^2 e^2 N_A C_s)}$ (18) and ε is the solution dielectric constant, k is Boltzmann's constant, T is the absolute temperature, z_s is the charge of the supporting solute, e is the fundamental charge of a proton and C_s is the concentration of the supporting solute. A more complex model describing the effect of the Debye layer on pore transport has been reported by Deen (14).

It should also be noted that the pore proteins have an isoelectric point of 3–4 (1), favouring the entry of cations, but retarding the entry of anions at higher pH's. This effect of permselectivity in entry of solutes to pores have been recognised by including a term called the permselectivity factor. Based on the ratio of cation: anion transport of 0.6:0.4 (19), the permselectivity values Ω for cations, anions and uncharged solutes are $\Omega = 1.2$, $\Omega = 0.8$ and $\Omega = 1.0$, respectively. We therefore redefine PRT_j in eq. 9 as ΩPRT_j where $\Omega \neq 1.0$.

Pore Interaction for Partially Ionized Drugs

Solutes may interact with both the aqueous regions in pores and the lipid protein region surrounding the aqueous region of the pores. The present analysis recognises that (i) the unionized solute component of a partially ionized solute can partition into these lipid regions surrounding an "aqueous" pore, (ii) that such partitioning will lead to an effective mobility $\mu_{effective,j}$ which is less than the apparent mobility of the solute through the pore μ_j in the pore and (iii) ionized lipophilic cations interacting with the pore membrane may also reduce the effective mobility. The average velocity of the jth ion, $v_{av,j}$, in a pore is defined by the force applied F_j and the mobility of the solute in the medium μ_j where the force F in an electric field E is given by zeE, so that $v_{av,j} = F_j\mu_j = z_j eE\mu_j$.

We now recognise that a drag force $F_{d,j}$ is associated with solute mobility in the pore and is defined by the exchange rate of molecules $n_{ex,j}$ moles/time between the wall and the solution (i.e., partitioning into the pore wall). The rate is dependent on the rapidity of the exchange process and the number of binding sites present in the wall. Hence, if

$$F_{d,j} = \frac{n_{ex,j} MW_j v_{av,j} N_A}{C_j V_{pore}} \quad (17)$$

where V_{pore} is the volume of the pore, then $v_{av,j} = \mu_j(z_j eE - F_{d,j})$. Rearranging this expression with substitution of F_d from eq. 17 yields $v_{av,j} = \mu_{effective,j}\, z_j eE$, where

$$\mu_{effective,j} = \frac{\mu_{j,pore}}{1 + \dfrac{n_{ex,j} MW_j \mu_{j,pore} N_A}{C_j V_{pore}}} \quad (18)$$

When uptake into the "lipoidal" pore wall is restricted to unionized solute (concentration Cu_j), the number of exchanges onto the pore wall can be expressed in terms of an interfacial clearance for exchange CL_j (i.e., $n_{ex,j} = CL_j\, Cu_j$) and $\mu_{effective,j} = \mu_{j,pore}/(1 + fu_j\theta_{ju})$ where $\theta_{ju} = CL_{ju} MW_j \mu_{j,pore} N_A / V_{pore}$ and $fu_j = Cu_j/C_j$. It has been suggested that lipophilic cationic solutes may also interact with pores by two mechanisms (i) an interaction of the lipophilic component of the solute with the membrane and (ii) an electrostatic interaction of the cationic charge on the solute with the anionic charge at the pore surface (20). Accordingly, including this interaction term θ_{ji} for ionized solutes into $\mu_{effective,j}$ so that:

$$\mu_{effective,j} = \frac{\mu_{j,pore}}{1 + fu_j\theta_{ju} + (1 - fu_j)\theta_{ji}} \quad (19)$$

where $\theta_{ji} = CL_{ji} MW_j \mu_{j,pore} N_A / V_{pore}$. Hence, eq. 9 can be written as:

$$J_{j,iont,overall} = \left(\frac{2\mu_j fi_j F z_j I_T \Omega PRT_j}{(k_{s,a} + k_{s,c})[1 + fu_j\theta_{ju} + (1 - fu_j)\theta_{ji}]} \pm (1 - \sigma_j)v_m\right)C_j \quad (20)$$

Eq. 20 can also be expressed in terms of the overall iontophoretic permeability coefficient $PC_{j,iont,overall}$, the fraction of solute ionized fi_j and the iontophoretic permeability coefficient associated with iontophoresis alone, i.e. non-convective $PC_{j,iont}$:

$$J_{j,iont,overall} = PC_{j,iont,overall}\, C_j \quad (21)$$

and

$$PC_{j,iont,overall} = PC_{j,iont}\, fi_j \pm (1 - \sigma_j)v_m \quad (22)$$

where

$$PC_{j,iont} = \frac{2\mu_j F z_j I_T \Omega PRT_j}{(k_{s,a} + k_{s,c})[1 + fu_j\theta_{ju} + (1 - fu_j)\theta_{ji}]} \quad (23)$$

METHODS

Iontophoresis Data

Previously reported data on the pH dependence of the iontophoresis for a range of solutes and the corresponding passive diffusion data through human epidermal membranes from our group (4,21) was used in this study. The overall iontophoretic permeability coefficients were estimated from the

applied concentrations (eq. 5) after subtracting the observed passive diffusion flux from the total iontophoretic flux (eq. 1). Epidermal permeability and conductivity data from Yoshida & Roberts (7–8) were also used in the evaluation of eq. 22 in relation to conductivity and permselectivity effects.

Debye Layer Thickness

The Debye layer thickness l_D was calculated from eq. 16 assuming a supporting electrolyte of 147 mM NaCl (13).

Conductivity

The specific conductivity of 10 mM lidocaine HCl in deionized distilled water was measured using a conductivity meter (Radiometer, Copenhagen, model CDM80). Specific conductivity was measured by direct reading of the conductivity meter and given by $k = dG/a$, where d is the distance between the electrodes and a is the area of the electrodes, d/a corresponds to the cell constant and G is the conductance in reciprocal ohms. The units of specific conductivity is S (siemens) per cm. The specific conductivity of deionized distilled water was 0.50–0.75 μS/cm. The apparent mobility of the solute in solution μ_j is then estimated from k_{jw}, the solute concentration used in the determination of the conductivity, z_j (=1 for all ions in this study) and the Faraday number (9.648×10^4 C/mol).

Simulations

Eq. 10, 13, 15 were used to estimate PRT_j for apparent noncharged spherical solutes assuming $V^i_{av} = V^\sigma_{av} = 155$ cm^3/mol (10) and r_p of 10, 20 and 30 Å. The increase in radius of a charged solute and the decrease in radius of the pore was calculated using eq. 16 and the Debye layer thickness estimated for the supporting receptor solution used by Lai & Roberts (13). The program MINIM 3.0.8 (22) was used to generate the profiles of PRT_j against either r_j/r_p or MV_j/MV_p, where MV_p is the maximally sized sphere able to be transported down a pore. Macromolecule PRT_j versus r_j data for $\alpha = 10$ and a theta solvent estimated through a nonlinear least squares fit of a fifth order polynomial of data in Table I in Davidson & Deen (16), with a $1/y_{obs}$ weighting. The charged macromolecule was PRT_j versus r_j used in this polynomial with adjustment of r_j and r_p by the estimated Debye layer thickness.

Regressions

Eq. 23 was used to examine both the effect of solution conductivity and solute ionization on iontophoretic permeability coefficients. In the analysis of conductivity effects, the electroosmotic contribution to flux was assumed to be negligible. Inverting eq. 23 results in predicted linear relationship between the reciprocal of the iontophoretic permeability coefficient and either solution or donor conductivity, providing all other parameters remain constant, i.e., $1/PC_{j,iont} = (k_{s,a} + k_{s,c})$.constant, where constant = $[(1 + fu_j\theta_{ju}) + (1 - fu_j)\theta_{ji}]/(2\mu_j fi_j Fz_j I_T \Omega PRT_j)$. Nonlinear regression analysis of eq. 23 is more appropriate when the electroosmotic component becomes significant, as occurs when fi_j approaches 0. The nonlinear regression program MINIM 3.0.8 (22), eq. 22 and a weighting of $1/y_{obs}$ was employed to examine the relationship between $PC_{j,iont,overall}$ (i.e., corrected for passive diffusion), $fi_{j,s}$ and v_m.

RESULTS AND DISCUSSION

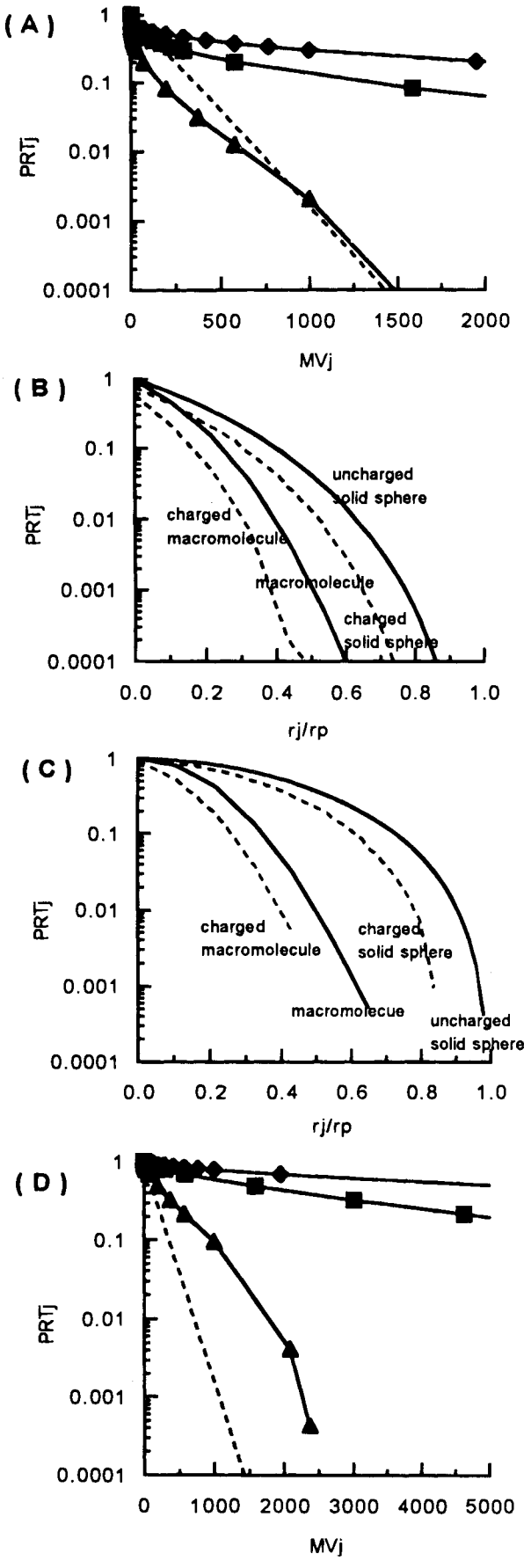
Our previous studies have recognised two independent models, using both the pathway restriction terms (9–10) and the role of solution conductivity in epidermal transport (7,10). The present analysis integrates the determinants of iontophoresis so that both terms appear in a single equation. Also included in the equation are terms for solute mobility, permselectivity of entry into pores, the separate conductivities in donor and receptor phases, the effect of partitioning into the pore wall, solute concentration and solute ionization. We now consider each of these determinants in more detail.

Molecular Size and Charge of Solutes

Figure 2 shows a diagrammatic representation of the size dependence of iontophoretic flux for a series of solutes using the different pathway restriction terms associated with the model developed in this work. Figure 2A shows PRT_j^{FV} based on an average "cage" volume of 155 MV (9) for the free volume term and PRT_j^{PR} for the pore restriction term using pore radii of 10 Å, 20 Å and 30 Å. Yoshida & Roberts (9) obtained a value of 30 Å on an analysis of literature data and in 1993 reported a pore radii of 8 Å based on their own data (10). In the accompanying paper, we estimated a pore radii of 10 Å, using iontophoretic transport of local anesthetics in which the effects of molecular size and ionic mobility for a series of local anesthetics on iontophoretic permeability coefficient are considered in detail (13). Dinh et al. (11) reported a radius of 25 Å, Ruddy & Hadzija (12) a radius of 18 Å for polyethylene glycols and Li et al. (23) reported a radius of 20 Å for calcein, salicylate and a series of polystyrene sulfonates. A comparison of the free volume and pore-restriction model predictions show that the free volume model predictions for PRT_j^{FV} are intermedi-

Table I. Ionic Mobility Calculated from Different Methods of Measurements

Solute	Ionic mobility ($\mu_j z_j e$)	pH	Method	Reference
Lidocaine HCl	1.5×10^{-4} cm^{2}V^{-1}s^{-1}	7.5	capillary isotachophoresis	27
	9.1×10^{-4} cm^{2}V^{-1}s^{-1}	not stated	conductivity	3
	5.2×10^{-4} cm^{2}V^{-1}s^{-1}	7.4	conductivity	this work
Salicylic Acid	3.2×10^{-4} cm^{2}V^{-1}s^{-1}	7.4	capillary electrophoresis	28
	3.5×10^{-4} cm^{2}V^{-1}s^{-1}	4.67	capillary electrophoresis	29
	2.1×10^{-4} cm^{2}V^{-1}s^{-1}	7.4	conductivity	8



ate between the pore restriction model predictions for PRT_j^{PR} using 10 Å and 30 Å pore radii for solutes of MV from 50 to 860. Whilst both the pore-restriction and free volume models for iontophoretic transport have been discussed previously in our earlier work (10), the work did not recognise the effects of solute charge, shape and conformation on iontophoretic transport.

Figure 2B shows the effect of shape and charge on PRT_j^{PR} versus r_j/r_p relationship when both the ion being iontophoresed and the pore wall is assumed to be associated with a Debye layer thickness of 2 Å as a result of charge, the iontophoretic flux is reduced relative when the Debye layer is ignored. Figure 2B also shows that macromolecules with a given Stokes-Einstein radius will be transported less efficiently than equivalent size solutes, existing as solid spheres. The slower transport reflects the larger radius of gyration associated with the coiling and hydration of the macromolecule as well as the flow of solvent through the coiled macromolecule (16). In practice, the flux of solutes may be faster than predicted for their r_r deduced assuming a spherical shape (eq. 12) as solutes are more likely to be ellipsoid in shape with the r_j for ellipsoids being less than that for spheres of equivalent r_r. The Stokes-Einstein radii (Fig. 2B) may therefore be more appropriate than molecular volume (Fig. 2A) in predicting iontophoretic transport as described in the theoretical section. Further, the estimation of Stokes-Einstein radii from solute diffusion in bulk solutions (23) may be more accurate than an estimation based on MV (eq. 12) as used in much of our work.

Figure 2C shows that the PRT_j^{PR} for convective transport in iontophoresis is more favoured (Fig. 2C) than the iontophoretic PRT_j^{PR} (Fig. 2A and B). The PRT_j for convective transport is more favoured than the iontophoretic PRT_j as the mechanism of transport through a pore comprises of both a drag force, due to interactions of the molecule with the walls of the pore, which increases with λ_j, and a "push" force, due to the electric field for iontophoretic transport and hydraulic force for convective transport. In iontophoresis, the "push" force is independent of λ_j, whereas for convective transport, the hydraulic force increases with λ_j to partially offset the increase in drag force with increasing λ_j. Pikal (17) has previously recognised the importance of convective flux in the iontophoresis of large solutes. Most previous studies have assumed the approximation shown in eq. 11 for PRT_j^{PR} (9,23) and eq. 14 $(1 - \sigma_j)$ (23). Whilst the full expressions (eq. 13 and 15) have been modelled in Fig. 2, it is not known the extent to which such a model is generalizable given that Pikal has previously suggested a distribution of pore sizes from 6.75 to

Fig. 2. (A) Simulation of PRT_j versus MV_j using the ionic mobility-pore model of iontophoretic transport: the free volume submodel (dotted line) (eq. 10), pore-restriction submodel (eq. 13) at pore sizes (r_p) of 10 Å (▲), 20 Å (■) and 30 Å (♦) (B) Simulation of the ionic mobility-pore model using eq. 13 for uncharged sphere, charged sphere, uncharged macromolecule and charged macromolecule for iontophoretic flux at r_j/r_p (C) Simulation of the ionic mobility-pore model using eq. 15 for uncharged sphere, charged sphere, uncharged macromolecule and charged macromolecule for convective flow at r_j/r_p (D) Simulation of convective flow of the free volume submodel (dotted line), pore-restriction submodel using eq. 10 and 15 at pore sizes (r_p) of 10 Å (▲), 20 Å (■) and 30 Å (♦).

27 Å in hairless rat skin (17) and larger solutes are likely to be macromolecules with a larger gyration radius and reduced drag force than a sphere with an equivalent Stokes-Einstein radius. Pikal (17) also assumed three pore types: positively charged, neutral and negatively charged. The present analysis suggests, that if the pore types are present, heterogeneity in transport arises from Debye layer effects (Fig. 2B and 2C), permselectivity effects and partitioning effects (eq. 21).

This analysis has highlighted the inclusion of the Debye layer which increases solute radius but decreases the effective pore radius. The equation for Debye layer (l_D) suggests that increasing ionic strength of the supporting electrolyte medium leads to a reduction in Debye layer. The importance of Debye layer as a determinant of iontophoretic transport has been recognised previously by Dinh et al. (11) and Ruddy and Hadzija (12). The present equations also recognise that the charge of the solute ion will also affect its entry into the negatively charged pore of the skin at pH's above the isoelectric point for human skin of between 3 and 4 (1). Permselectivity values Ω for cation, anion and uncharged solutes, based on the reported cation:anion transport ratio of 0.6:0.4 (19), are estimated to be 1.2, 0.8 and 1.0, respectively. The pore restriction modeling data for cations and anions (10) yields values for Ω of 1.08, 0.92 and 1.0, respectively.

The important difference in the free volume and the pore-restriction model is that the pore-restriction model predicts that very large solutes can penetrate through the skin by iontophoresis whereas the free volume does not. This effect is clearly illustrated in Fig. 2A for convective flow and less so in Fig. 2D. Consistent with the pore-restriction model and a pore radius of 20 to 30 Å (Fig. 2A), a number of large peptides and macromolecules with MW between 1000 and 12400 have been reported to be iontophoresed across the skin at fluxes ranging from 0.06 to 280 $\mu g/cm^2/hr$ (24). The effectiveness of iontophoretic transport for high MW solutes may then be less than hoped for as these are likely to be random coiled macromolecules with path restriction terms dependent on the macromolecule-solvent interaction (Fig. 2B and C) (16). The choice of a model is further complicated by the iontophoretic process affecting the conformation of the pore pathway (25) and $\Re_{pore}$ (eq. 7).

Conductivity in System

In our previous work, we obtained linear relationships between the iontophoretic flux of salicylic acid (SA) and the reciprocal of donor solution conductivity (8) but curvilinear relationships for the flux of phenylethylamine (PEA) against the reciprocal of donor solution conductivity (7). Eq. 20 suggests that both donor and receptor solution conductivity affect iontophoretic flux and that linear relationship between flux and donor solution conductivity will only be observed if the donor conductivity $k_{s,d}$ is much larger than receptor conductivity $k_{s,r}$ and the convective flux is negligible. Eq. 23 suggests that a more appropriate plot would be a reciprocal of iontophoretic permeability coefficient versus either donor or receptor conductivity. Figure 3 shows that linear relationships exist for both SA and PEA when plotted in this manner. Such a rearrangement must either correct for electroosmotic transport or assume it to be negligible relative to iontophoretic permeability coefficient. If this assumption cannot be made, a nonlinear regression analysis of eq. 22 is more appropriate.

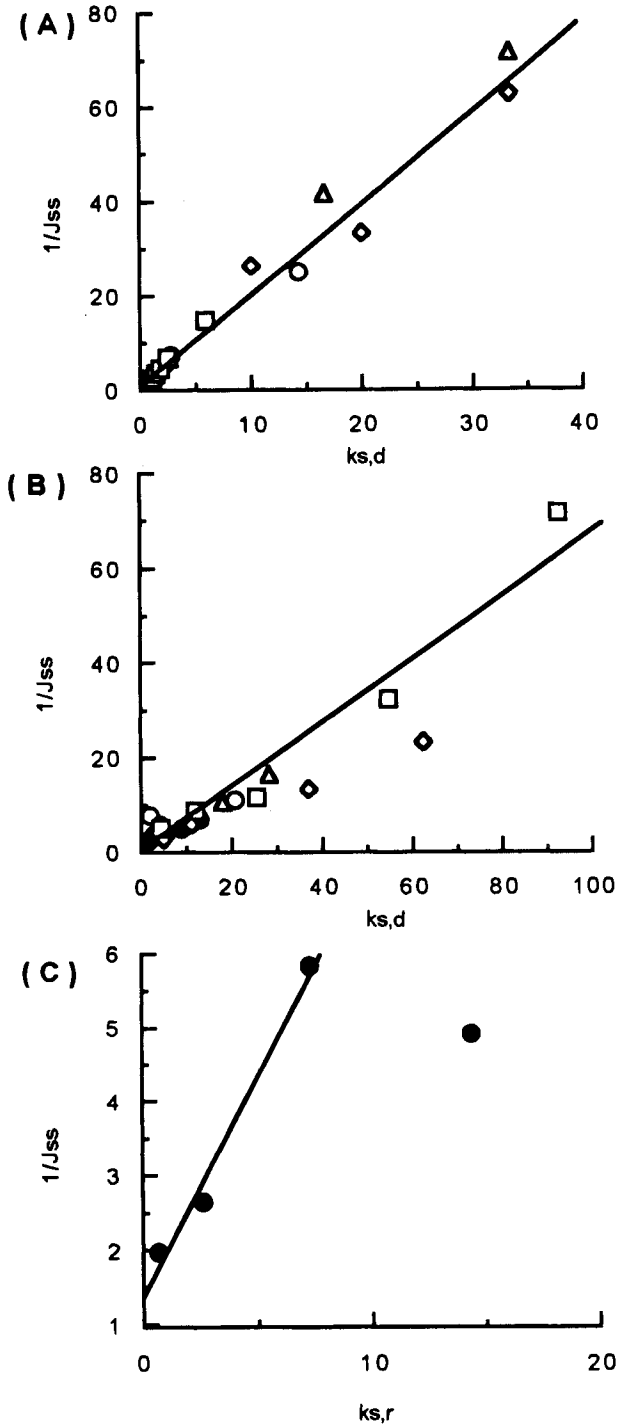


Fig. 3. Relationship of inverse flux ($1/J_{ss}$) and overall conductivity of (A) donor solution (k_{sd}) of salicylic acid (data from ref. 8), (B) donor solution ($k_{s,d}$) for PEA and (C) receptor solution ($k_{s,r}$) for PEA (data from ref. 7).

A failure to account for the contribution of receptor conductivity to the overall conductivity explains the curvilinear relationship reported for the flux of PEA against donor conductivity (7). Interestingly, we had demonstrated that receptor composition affected the iontophoresis of PEA (7). A replot of this data also as a reciprocal of permeability coefficient versus

receptor conductivity shows a linear relationship for low concentrations (Fig. 3C). The outlier observed at the high NaCl receptor concentration 150 mM may have been due to ion interactions.

Ionic Mobility of Solute

According to eq. 23, $PC_{j,iont}$ is directly related to the ionic mobility of the solute. Few studies have examined the importance of solute ionic mobility as a determinant of iontophoretic flux. An indirect determinant of ionic mobility, the solute conductivity has been recognised by Gangarosa et al. (3) and Yoshida and Roberts (8) as affecting iontophoretic flux. Kamath and Gangarosa (26) measured a range of ionic mobilities but did not relate experimentally iontophoretic fluxes to the mobilities obtained. In the accompanying work on iontophoretic transport of local anesthetics (13), we estimated ionic mobility from the conductivity in solution and showed it to be a key determinant of local anesthetic iontophoresis. The values of ionic mobility are obtained by different methods such as conductivity (8,13), isotachophoresis (27), paper electrophoresis (26) and capillary electrophoresis (28). Table I shows the values obtained by capillary electrophoresis and conductivity for lidocaine and salicylic acid.

Other Determinants

According to eq. 9, the overall iontophoretic flux is directly proportional to the total current I_T. Several studies have shown that the flux is linearly proportional with the applied current (1,2,4,5,9,19). The conductivity of skin also depends on the porosity of the skin and the dimensionless resistance parameter $\Re_{pore}$. A changing $\Re_{pore}$ is apparent with increasing E, as evident by the nonlinear I_T versus E profile (1). Scott et al. (15) have shown that iontophoresis can increase f_{pore}. A number of authors have shown that $\Re_{pore}$ reduces during iontophoresis due to a reorganization of lipid layers (25). Pikal (17) referred to iontophoresis affecting permeability in terms of a "damage" factor. Optimal flux is also directly related to drug concentration and fraction ionized (eq. 20).

Transport of Partially Ionized Solutes

In most previous studies on iontophoretic transport (4,7,8,10, 21), there has been assumed to be no uptake of solutes into the pore walls. If no uptake into the wall occurred, then according to eq. 22, $PC_{j,iont,overall}$ should be directly related to fraction ionized $fi_{j,s}$ with a slope defined by $PC_{j,iont}fi_{j,s}$ and an intercept of $\pm(1 - \sigma_j)v_m$. It should be emphasised that the contribution of passive flux (assumed to be uncharged solute transport through the intercellular lipids) at each pH was subtracted in order to define $PC_{j,iont,overall}$. The curvilinear relationships between $PC_{j,iont,overall}$ and $fi_{j,s}$ in Fig. 4 are in accordance with eq. 22 and suggests that significant uptake of solute to the walls reduces the overall iontophoretic flux. When only unionized solute is taken up by the pore membrane, eq. 22 suggests that as the fraction of solute unionized increases, there is an increasing amount of interaction of the solute with the lipophilic regions of the pore, leading to an observed decrease in the flux of the solute.

Eq. 19 suggests that interaction between the solute and the pore will affect ionic mobility. It is likely that CL_{ju} is greater

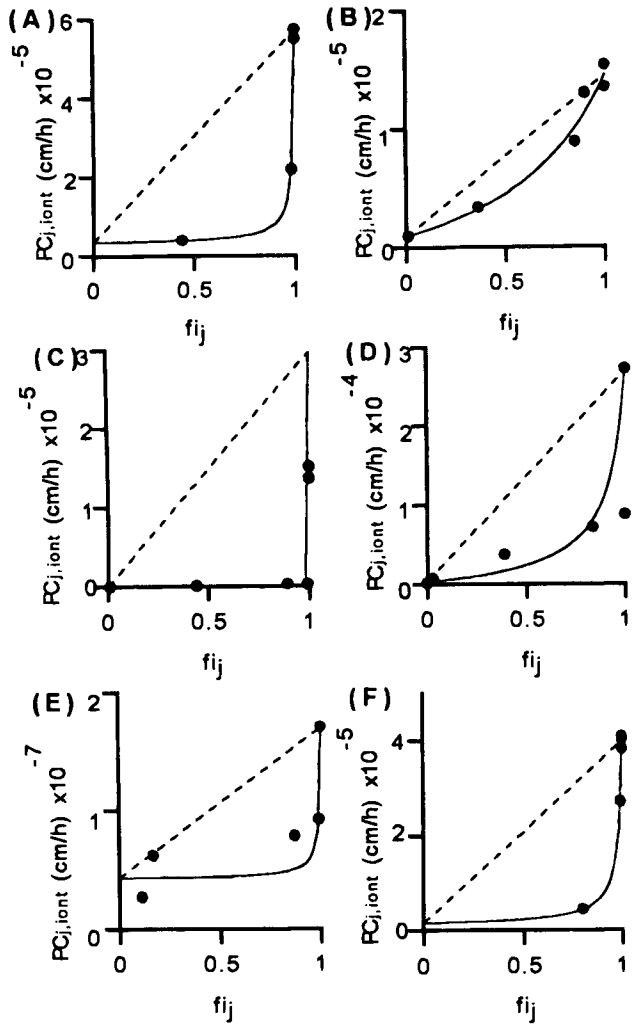


Fig. 4. Regression for ionic mobility-pore model using the pore-restriction submodel for (A) Aspirin, (B) Chlorpheniramine, (C) Chlorpromazine, (D) Lidocaine, (E) Methotrexate, (F) Salicylic acid (data from ref. 4, 21). The solid line represents the fit of the model, the dotted line is the fit of the model if the partitioning term ($fu_j\theta_{ju}$) is not taken into account.

than CL_{ji} because ionized solutes will be more strongly bound to membrane components through enthalpy related electrostatic mechanisms than unionized solutes whose partitioning into the membrane is probably entropy driven. Thus, for most values of fu_j, it is expected that the term $(1 - fu_j)\theta_{ji} << 1 + fu_j\theta_{ju}$ and the denominator $(k_{s,a} + k_{s,c})[1 + fu_j\theta_{ju} + (1 - fu_j)\theta_{ji}]$ in eq. 20 reduces to $(k_{s,a} + k_{s,c})(1 + fu_j\theta_{ju})$. In the particular case of $fu_j = 0$, due to the complete ionization of solutes under the conditions used, this becomes $(k_{s,a} + k_{s,c})(1 + \theta_{ji})$. This equation may be appropriate to describe the iontophoresis of lipophilic solutes ionized under the conditions applied. A significant θ_{ji} is consistent with proposals put by Hirvonen and Guy (20) that such solutes interact by both (i) "anchoring" the lipophilic part of the solute into the membrane by van der Waals forces and (ii) electrostatic interaction between the positive charge of the solute and negative charge of the skin.

Table II shows the values for θ_{ju}, PC_{iont} (at $fi_{j,s} = 1$) and $(1 - \sigma_j)v_m$ (at $fi_{j,s} = 0$) estimated from the regressions in

Table II. Properties of Solutes and Regression Results on Analysis of $PC_{j,iont,overall}$ Versus fi_j Using Data from Refs. 4 and 21

Compound	MW	log P[a]	pKa	R^2	$PC_{j,iont,overall}$ at $fi_j = 1$ (cm/h)	$\nu_m(1 - \sigma_j)$ at $fi_j = 0$ (cm/h)	θ_{ju}	Fraction due to iontophoresis alone
Aspirin	180	1.19	3.5	0.99	$5.43 \times 10^{-5} \pm 1.59 \times 10^{-6}$	$2.96 \times 10^{-6} \pm 1.42 \times 10^{-6}$	93.9	0.95
Chlorpheniramine	391	3.39	9.2	0.96	$2.15 \times 10^{-5} \pm 6.44 \times 10^{-6}$	$6.97 \times 10^{-6} \pm 6.76 \times 10^{-6}$	1.7	0.76
Chlorpromazine	355	5.19	9.3	0.99	$1.89 \times 10^{-3} \pm 1.11 \times 10^{-3}$	$1.12 \times 10^{-6} \pm 3.66 \times 10^{-6}$	122842	0.99
Lidocaine	234	2.26	7.4	0.94	$2.56 \times 10^{-4} \pm 3.91 \times 10^{-5}$	$2.88 \times 10^{-5} \pm 1.59 \times 10^{-5}$	1657.4	0.90
Methotrexate	454	−1.85	4.3, 5.5	0.89	$1.19 \times 10^{-7} \pm 2.92 \times 10^{-8}$	$5.29 \times 10^{-8} \pm 1.53 \times 10^{-8}$	161	0.69
Salicylic acid	138	2.26	3.0	0.99	$3.91 \times 10^{-5} \pm 1.87 \times 10^{-6}$	$8.56 \times 10^{-7} \pm 1.79 \times 10^{-7}$	48.8	0.98

[a] Data from ref. 30.

Fig. 3 together with the fraction of ionized iontophoretic flux estimated to be due to iontophoresis alone ($PC_{j,iont}/[PC_{j,iont} + (1 - \sigma_j)\nu_m]$), i.e., fraction not due to electroosmosis. The value of θ_{ju} depends both on partitioning (extent of binding), strength of binding, solute size and solute mobility in the pore (eq. 19). A simple linear relationship between θ_{ju} and partition coefficient is therefore unlikely although the data in Table II suggests a trend between θ_{ju} and partition coefficient.

Electroosmosis

Electroosmotic flow is the bulk flow of the solution which occurs when an electric field is applied across a charged membrane. As shown in Table II, the contribution of electroosmosis to the iontophoretic transport of the relatively small solutes studies is low. The convective force has been previously shown to be more effective for larger MW solutes than for small, charged solutes (17). Whilst electroosmotic transport is unlikely to be important for the small solutes studied in this and the accompanying paper (13), the presence of electroosmosis has been recognised in the derived equations and in the path restriction term dependence on solute size (Fig. 1).

CONCLUSIONS

This work has developed an ionic mobility-pore model to describe iontophoretic transport. The model incorporates the determinants of solute size (defined by MW), solute mobility (defined by solute conductivity), total current applied, presence of extraneous ions (defined by solvent conductivity), fraction of solute unionized (and hence interaction with the pore), solute concentration, interaction of the solute with the pore walls and epidermal permselectivity. The model also recognises the importance of electroosmotic flow. The conductivity of both the donor phase and the receptor phase, the solute and the extent of solute ionization must be considered in analysing iontophoretic transport. The fraction of ionization affects the extent to which the solute interacts with the pore wall.

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