Donnan Equilibrium of Ionic Drugs in pH-Dependent Fixed Charge Membranes: Theoretical Modeling

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We have studied theoretically the partition equilibrium of a cationic drug between an electrolyte solution and a membrane with pH-dependent fixed charges using an extended Donnan formalism. The aqueous solution within the fixed charge membrane is assumed to be in equilibrium with an external aqueous solution containing six ionic species: the cationic drug (DH+), the salt cations (Na+ and Ca2+), the salt anion (Cl−), and the hydrogen and hydroxide ions. In addition to these mobile species, the membrane solution may also contain four fixed species attached to the membrane chains: strongly acidic sulfonic groups (−SO3−), weakly acid carboxylic groups in dissociated (−COO−) and neutral (−COOH) forms, and positively charged groups (−COO−···Ca2+) resulting from Ca2+ binding to dissociated weakly acid groups. The ionization state of the weak electrolyte groups attached to the membrane chains is analyzed as a function of the local pH, salt concentration, and drug concentration in the membrane solution, and particular attention is paid to the effects of the Ca2+ binding to the negatively charged membrane fixed groups. The lipophilicity of the drug is simulated by the chemical partition coefficient between the membrane and external solutions giving the tendency of the drug to enter the membrane solution due to hydrophobic interactions. Comparison of the theoretical results with available experimental data allows us to explain qualitatively the effects that the pH, salt concentration, drug concentration, membrane fixed charge concentration, and Ca2+ binding exert on the ionic drug equilibrium. The role of the interface (Donnan) electric potential difference between the membrane and the external solutions on this ionic drug equilibrium is emphasized throughout the paper.

Key Words: ionic drug partition equilibrium; fixed charge membranes; pH effects; Donnan potential; theoretical modeling.

INTRODUCTION

Determining the partition equilibrium of an ionic drug between a membrane solution and an external electrolyte solution (1–15) constitutes a difficult problem not only because of the multi-ionic character of the system (the ionic drug, the salt ions, and the hydrogen and hydroxide ions) but also due to the great number of effects (the lipophilicity of the drug, the pH, salt, and drug concentrations of the external solution, the nature and concentration of the membrane fixed charge, the ion binding of certain divalent ions to the membrane fixed charges, etc.) that are present simultaneously. However, an understanding of the above effects is needed in most practical applications.

The partition equilibrium of a cationic drug in a membrane with pH-dependent fixed charges will be studied theoretically using the Donnan equilibrium formalism (16, 17). This formalism considers the aqueous solution in the fixed charge membrane to be in equilibrium with the external aqueous solution containing six ionic species: the cationic drug, the salt cations, the salt anion, and the hydrogen and hydroxide ions. The Donnan equilibrium leads to the constancy of the electrochemical potential through the membrane/solution interface for each ionic species (16, 17). In addition to the above mobile species, the membrane solution may also contain four fixed species attached to the membrane chains: strongly acidic sulfonic groups (−SO3−), weakly acid carboxylic groups in dissociated (−COO−) and neutral (−COOH) forms, and positively charged groups (−COO−···Ca2+) resulting from Ca2+ binding to dissociated weakly acid groups. The ionization state of the weak electrolyte groups attached to the membrane chains is analyzed as a function of the local pH, salt concentration, and drug concentration in the membrane solution. The lipophilicity of the drug is simulated by the chemical partition coefficient between the membrane and external solutions. This coefficient measures the tendency of the drug to enter the membrane solution due to specific (e.g., hydrophobic) interactions. Comparison of the theoretical results with available experimental data (1–3, 5–9) allows us to explain qualitatively the effects that the pH, salt, drug, and membrane fixed charge concentrations exert on the ionic drug equilibrium. In particular, we show that the Donnan potential difference between the membrane and the external solutions is crucial for the understanding of this equilibrium.

The results presented should be especially relevant to those experimental situations where the partition equilibrium of the ionic drug must be controlled by the external pH and salt concentration (e.g., drug delivery systems and separation processes...
The pH of the external solution is controlled by adding either HCl or NaOH. Therefore, in the most general case, the ionic mobile species present in the system are the cationic form of the drug (DH\(^7^+)\), the salt ions (Na\(^+\), Ca\(^{2+}\), Cl\(^-\)), and the hydrogen (H\(^+\)) and hydroxide (OH\(^-\)) ions. In the following, \(c_i\) stands for the concentrations of species \(i\) (i.e., DH\(^7^+\), Na\(^+\), Ca\(^{2+}\), H\(^+\), Cl\(^-\), and OH\(^-\)) and NaCl, CaCl\(_2\), and DHCl in the external solution phase. Overbars denote membrane solution concentrations. The external solution is assumed to be perfectly stirred, and the whole system is considered isothermal.

For a given value of \(pH\), the concentrations of the H\(^+\), OH\(^-\), DH\(^7^+\), and Ca\(^{2+}\) ions in the external solution are

\[
\begin{align*}
    c_{H^+} &= 10^{-pH}, \\
    c_{OH^-} &= K_w/c_{H^+}, \\
    c_{DH^7^+} &= c_{DHCl}, \\
    c_{Ca^{2+}} &= c_{CaCl_2},
\end{align*}
\]

where \(K_w = 10^{-14}\) M\(^2\).

The electroneutrality condition in the external solutions leads to

\[
c_{Na^+} + 2c_{Ca^{2+}} + c_{H^+} + c_{DH^7^+} = c_{Cl^-} + c_{OH^-}.
\]

In the case \(pH \leq 7\), HCl is added. The Na\(^+\) concentration remains constant,

\[
c_{Na^+} = c_{NaCl},
\]

and then Eqs. [4]–[6] give

\[
c_{Cl^-} = c_{NaCl} + c_{DHCl} + 2c_{CaCl_2} + c_{H^+} - c_{OH^-}.
\]

In the case \(pH > 7\), NaOH is added in order to fix the \(pH\) value of the external solution. The Cl\(^-\) concentration is then given by

\[
c_{Cl^-} = c_{NaCl} + 2c_{CaCl_2} + c_{DHCl},
\]

and Eqs. [4]–[6] yield

\[
c_{Na^+} = c_{NaCl} - c_{H^+} + c_{OH^-}.
\]

In addition to the six mobile species, the membrane may also contain four fixed species attached to the membrane matrix. These species are strongly sulfonic acid groups (\(-SO_3^-\)), weakly carboxylic acid groups in dissociated (\(-COO^-\)) and neutral (\(-COOH\)) forms, and positively charged groups (\(-COO^-\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\cdot\·
be in equilibrium with the H\(^+\) ions in the membrane solution according to

\[-\text{COOH} \xrightleftharpoons{K_N} \text{COO}^- + \text{H}^+, \tag{11}\]

where \(K_N\) is the equilibrium constant for the dissociation reaction.

The divalent ion Ca\(^{2+}\) is known to bind strongly to carboxylic groups, but not to sulfonic groups (3, 9). We assume that Ca\(^{2+}\) binds to \(-\text{COO}^-\) groups according to the scheme

\[-\text{COO}^- + \text{Ca}^{2+} \xrightleftharpoons{K_B} \text{COO} \cdots \text{Ca}^+, \tag{12}\]

where \(K_B\) is the equilibrium constant for the binding reaction. The resulting \(-\text{COO} \cdots \text{Ca}^+\) group acts as an anion-exchange group. Calcium binding to fixed charge groups is relevant not only in membranes (16) and ion-exchange fibers (9) but also in phospholipid monolayers (21) and biomacromolecules (22).

From Eqs. (11) and (12) we obtain

\[
10^{-pK_a} = K_N = \frac{X_C^N}{X_C^0}, \tag{13}\]

\[
k_B = \frac{X_C^P}{X_C^N X_C^{Ca^{2+}}}. \tag{14}\]

where \(X_C^N\), \(X_C^0\), and \(X_C^p\) are, respectively, the concentration of negative (\(-\text{COO}^-\)), neutral (\(-\text{COOH}\)), and positive \((-\text{COO} \cdots \text{Ca}^+\)) forms of the carboxylic groups. From Eqs (13) and (14) together with

\[
X_{\text{CT}} = X_C^P + X_C^N + X_C^0, \tag{15}\]

the membrane fixed charge concentration (with its sign) yields

\[-X_S + X_C^P - X_C^N = -X_S - \frac{1 - k_B \tilde{e}_{\text{Ca}^{2+}}}{1 + \tilde{e}_H^\text{H+} / k_N + k_B \tilde{e}_{\text{Ca}^{2+}}} X_{\text{CT}}. \tag{16}\]

Note that for pH \(\gg pK_a\), the membrane fixed charge concentration is \(-X_S - X_{\text{CT}}\) for \(k_B \tilde{e}_{\text{Ca}^{2+}} \ll 1\) and \(-X_S + X_{\text{CT}}\) for \(k_B \tilde{e}_{\text{Ca}^{2+}} \gg 1\). Binding constants for Ca\(^{2+}\) adsorption to fixed charge groups appear to be in the range 10–10\(^5\) M\(^{-1}\) (9, 21), though significantly higher values up to 10\(^6\) M\(^{-1}\) have been reported for trivalent (La\(^{3+}\)) cations (21).

The electroneutrality condition within the membrane solution leads to

\[
\tilde{e}_{\text{Na}^+} + \tilde{e}_H^\text{H+} + 2 \tilde{e}_{\text{Ca}^{2+}} + \tilde{e}_{\text{DH}^+} = \tilde{e}_{\text{CT}} + \tilde{e}_\text{OH}^- + X_S + \frac{1 - k_B \tilde{e}_{\text{Ca}^{2+}}}{1 + \tilde{e}_H^\text{H+} / k_N + k_B \tilde{e}_{\text{Ca}^{2+}}} X_{\text{CT}}. \tag{17}\]

The concentrations of the ionic species in the membrane (\(\tilde{c}_i\)) and the external (\(c_i\)) solutions are connected by the Donnan equilibrium equations

\[
\tilde{c}_i = k_i c_i \exp \left[ \frac{-z_i F (\tilde{\phi} - \phi)}{RT} \right], \tag{18}\]

\[
i = \text{Na}^+, \text{Ca}^{2+}, \text{H}^+, \text{DH}^+, \text{Cl}^-, \text{OH}^-, \tag{19}\]

where \(\tilde{\phi} - \phi\) is the Donnan potential difference between the membrane and the external solutions resulting from the ionic partition equilibrium, \(z_i\) is the charge number of species \(i\), constants \(F\), \(R\), and \(T\) have their usual meaning, and

\[
k_i = \exp \left[ -\frac{1}{RT} (\tilde{\mu}_i^0 - \mu_i^0) \right], \tag{20}\]

\[
i = \text{Na}^+, \text{Ca}^{2+}, \text{H}^+, \text{DH}^+, \text{Cl}^-, \text{OH}^- \tag{21}\]

is the chemical part of the partition coefficient of species \(i\) (note that \(k_i\) does not include the effect of the electric potential difference across the interface, as is clearly shown by Eq. (18)). In Eq. (19), \(\tilde{\mu}_i^0 - \mu_i^0\) is the standard chemical potential difference between the membrane and the external solutions of species \(i\). It is reasonable to assume that \(k_i = 1\) for all ionic species except for the cationic drug DH\(^+\), for which \(k_{\text{DH}^+}\) is a (chemical) partition coefficient that measures the tendency of the drug to enter the membrane solution due to specific (e.g., hydrophobic) interactions (9). Thus, the lipophilicity (\(\tilde{\mu}_{\text{DH}^+}^0 < \mu_{\text{DH}^+}^0\)) of the drug is simulated by a chemical partition coefficient \(k_{\text{DH}^+} > 1\) between membrane and external solutions. The more hydrophobic the drug, the larger the difference \(\mu_{\text{DH}^+}^0 - \tilde{\mu}_{\text{DH}^+}^0\), and the larger the value of \(k_{\text{DH}^+} = \exp[(\mu_{\text{DH}^+}^0 - \tilde{\mu}_{\text{DH}^+}^0)/RT]\). The coefficient \(k_{\text{DH}^+}\) is considered here a phenomenological parameter and no attempt will be made to evaluate it in terms of a microscopic model for the drug–membrane-specific interactions.

From Eqs. (18) and (19) we obtain

\[
\tilde{c}_{\text{DH}^+}/k_{\text{DH}^+} c_{\text{DH}^+} = \tilde{c}_{\text{Na}^+}/c_{\text{Na}^+} = \tilde{c}_{\text{H}^+}/c_{\text{H}^+} = \left(\frac{\tilde{e}_{\text{Ca}^{2+}}}{e_{\text{Ca}^{2+}}}\right)^{1/2} = \frac{\tilde{c}_{\text{CT}}}{c_{\text{CT}}} = \frac{c_{\text{OH}^-}}{\bar{c}_{\text{OH}^-}}. \tag{22}\]

Substitution of Eq. (20) in Eq. (17) yields

\[
2c_{\text{Ca}^{2+}} u^2 + (k_{\text{DH}^+} c_{\text{DH}^+} + c_{\text{Na}^+} + c_{\text{H}^+}) u - (c_{\text{CT}} + c_{\text{OH}^-}) \frac{1}{u} \quad \frac{-X_S - \frac{1 - k_B \tilde{e}_{\text{Ca}^{2+}}}{1 + \tilde{e}_H^\text{H+} / k_N + k_B \tilde{e}_{\text{Ca}^{2+}}}}{X_{\text{CT}} = 0, \tag{21}\]

where

\[
u \equiv \frac{\tilde{c}_{\text{DH}^+}}{k_{\text{DH}^+} c_{\text{DH}^+}}. \tag{22}\]

Equation (21) can be solved for \(u \neq 0\) using, e.g., a Newton-Raphson procedure. This procedure is very convenient even for low values of \(u\) provided that a reasonable initial guess for the
lower and higher solution bounds is made. Once \( n \) has been calculated, the Donnan potential difference between the membrane and external solutions is

\[
\bar{\phi} - \phi = \frac{RT}{F} \ln \left( \frac{k_{DH^+} c_{DH^+}}{c_{DH^+}} \right) = \frac{RT}{F} \left( \ln k_{DH^+} + \ln \left( \frac{c_{DH^+}}{c_{DH^+}} \right) \right).
\]

Equation [21] yields a very simple solution when \( c_{CaCl_2} = 0 \) and \( X_{CT} = 0 \) (no carboxylic acid groups)

\[
\frac{c_{DH^+}}{c_{DH^+}} = \sqrt{X_1^2 + 4(c_{Na^+} + c_{H^+} + c_{DH^+})(c_{Na^+} + c_{H^+} + k_{DH^+} c_{DH^+})} - X_S.
\]

RESULTS AND DISCUSSION

Figure 2 shows the ratio between the cationic drug concentration in the external and membrane solutions, \( c_{DH^+}/c_{DH^+} \), vs the external pH for \( X_S = 10^{-1} \) M (sulfonic groups, \(-SO_3\)) and \( c_{DHCl} = 10^{-2} \) M, with \( X_{CT} = 0 \) (carboxylic groups, \(-COO^-\)) and \( k_{DH^+} = 1 \left( \mu_0^{DH^+} = \mu_0^{H^+}, \right) \) no hydrophobic effects in the cationic drug equilibrium). The curves are parametric in the NaCl (continuous line) and CaCl_2 (discontinuous line) salt concentrations. pH values higher than 10 are not included because the drug could be in a neutral form in this case. On the other hand, the lower pH values in the figure are seldom employed experimentally. They are included only to show the limiting behavior of \( c_{DH^+}/c_{DH^+} \) when the hydrogen concentration \( c_{H^+} = 10^{-pH} > c_{DHCl} = 10^{-2} \) M. In this limit, the hydrogen substitutes for the cationic drug in the membrane solution, and then the negative fixed charge groups \(-SO_3^-\) are no longer compensated by \( DH^+ \) but by \( H^+ \). This ion-exchange process makes the drug concentration in the membrane and external solutions similar, and \( c_{DH^+}/c_{DH^+} \) tends to unity. Comparison of the theoretical curves for the salt cations \( Na^+ \) and \( Ca^{2+} \) shows that the incorporation in the external solution of the divalent cation \( Ca^{2+} \) instead of \( Na^+ \) significantly decreases the drug content in the membrane (for a fixed salt concentration, the ratio \( c_{DH^+}/c_{DH^+} \) is closer to one for CaCl_2 than for NaCl). This is in qualitative agreement with experimental results in ion-exchange fibers that show an increase in the drug release from the fiber as the salt concentration increases (9). Note finally that the above effect disappears when the salt concentration is made much higher than the fixed charge concentration \( X_S = 10^{-1} \) M since in this limit the effect of the membrane on the ionic equilibrium is negligible.

Figure 3 shows the ratio \( c_{DH^+}/c_{DH^+} \) vs the external solution concentrations \( c_{NaCl} \) (continuous line) and \( c_{CaCl_2} \) (discontinuous line) for \( X_S = 10^{-1} \) M (sulfonic groups, \(-SO_3^-\)) and \( c_{DHCl} = 10^{-2} \) M, with \( X_{CT} = 0 \) and \( k_{DH^+} = 1 \). The curves are parametric in the external pH. Figure 4 gives the Donnan potential difference between the membrane and external solutions, \( \Delta \phi = \bar{\phi} - \phi \), vs the external solution concentrations \( c_{NaCl} \) (continuous line) and \( c_{CaCl_2} \) (discontinuous line) for the same conditions as those of Fig. 3. For high pH values, increasing the NaCl concentration causes the drug concentration in the membrane to decrease (the ratio \( c_{DH^+}/c_{DH^+} \) increases) because of the gradual substitution of \( DH^+ \) in the membrane by \( Na^+ \) from the solution. As could be expected, this trend is even more apparent for the case of CaCl_2 because of the higher charge number of the salt cation. For low pH values, however, the above effects are not so marked because it is the hydrogen and not the

FIG. 2. The ratio between the cationic drug concentration in the external and membrane solutions, \( c_{DH^+}/c_{DH^+} \), vs the external pH for \( X_S = 10^{-1} \) M and \( c_{DHCl} = 10^{-2} \) M, with \( X_{CT} = 0 \) and \( k_{DH^+} = 1 \). The curves are parametric in the NaCl (continuous lines) and CaCl_2 (dashed lines) salt concentrations.

FIG. 3. The ratio \( c_{DH^+}/c_{DH^+} \) vs the external solution concentration \( c_{NaCl} \) (continuous lines) and \( c_{CaCl_2} \) (dashed lines) for \( X_S = 10^{-1} \) M and \( c_{DHCl} = 10^{-2} \) M, with \( X_{CT} = 0 \) and \( k_{DH^+} = 1 \). The curves are parametric in the external pH.
salt cation that compensates for the negative fixed charge in the membrane. Figure 4 shows that \( \Delta \phi \) closely follows the behavior of the ratio \( \frac{c_{DH^+}}{c_{DH^+}} \) in Fig. 3, as could be anticipated from Eq. [23]. Note finally that the results of Fig. 4 show clearly the effect of salt concentration on the cationic drug content in the membrane (see Fig. 3). Since the membrane fixed charge is negative, the Donnan potential is also negative (see Fig. 1) and tends to keep the cationic drug in the membrane solution in the case of low salt concentrations. However, the absolute value of the (negative) Donnan potential decreases with the external salt concentration and this lowers the cationic drug concentration in the membrane. The theoretical predictions of Figs. 3 and 4 are in good agreement with previously reported experimental results (2, 5–7, 9) showing the influence of salt concentration on ionic drug release, though other effects not included in our model (e.g., conformational changes in the membrane chains and membrane swelling) may also be important in some cases (2, 18). Therefore, the Donnan potential is a useful concept for the understanding of the ionic drug partition equilibrium, as it is observed with ion-exchange membranes (16, 23) and fixed charge conducting polymers in aqueous solution (24, 25).

Figure 5 shows the ratio \( \frac{c_{DH^+}}{c_{DH^+}} \) vs the external drug concentration \( c_{DHCl} \) for \( pH = 7 \) and \( c_{NaCl} = 0 = c_{CaCl_2} \), with \( X_{CT} = 0 \) and \( k_{DH^+} = 1 \). The curves are parametric in the fixed charge concentration \( X_S \). For a fixed value of \( X_S \), the incorporation of the divalent cation \( Ca^{2+} \) to the membrane solution significantly decreases the drug content in the membrane. This is essentially an ion-exchange process where the counterion \( DH^+ \) in the membrane solution is exchanged by the counterion \( Ca^{2+} \) from the external solution. As could be expected, this effect is more marked the higher the fixed charge concentration (2, 9).

Figure 6 shows the ratio \( \frac{c_{DH^+}}{c_{DH^+}} \) vs the external solution concentration \( c_{CaCl_2} \) for \( pH = 7 \) and \( c_{DHCl} = 10^{-2} \) M, with \( X_{CT} = 0 \), \( c_{NaCl} = 0 \), and \( k_{DH^+} = 1 \). The curves are parametric in the membrane fixed charge concentration \( X_S \). The theoretical predictions of Figs. 3 and 4 are in good agreement with previously reported experimental results (2, 5–7, 9) showing the influence of salt concentration on ionic drug release, though other effects not included in our model (e.g., conformational changes in the membrane chains and membrane swelling) may also be important in some cases (2, 18). Therefore, the Donnan potential is a useful concept for the understanding of the ionic drug partition equilibrium, as it is observed with ion-exchange membranes (16, 23) and fixed charge conducting polymers in aqueous solution (24, 25).

FIG. 4. The Donnan potential difference between the membrane and external solutions, \( \Delta \phi = \phi - \phi_e \), vs the external solution concentration \( c_{NaCl} \) (continuous lines) and \( c_{CaCl_2} \) (dashed lines) for \( X_S = 10^{-1} \) M and \( c_{DHCl} = 10^{-3} \) M, with \( X_{CT} = 0 \) and \( k_{DH^+} = 1 \). The curves are parametric in the external pH.

FIG. 5. The ratio \( \frac{c_{DH^+}}{c_{DH^+}} \) vs the external drug concentration \( c_{DHCl} \) for \( pH = 7 \) and \( c_{NaCl} = 0 = c_{CaCl_2} \), with \( X_{CT} = 0 \) and \( k_{DH^+} = 1 \). The curves are parametric in the fixed charge concentration \( X_S \).

FIG. 6. The ratio \( \frac{c_{DH^+}}{c_{DH^+}} \) vs the external solution concentration \( c_{CaCl_2} \) for \( pH = 7 \) and \( c_{DHCl} = 10^{-2} \) M, with \( X_{CT} = 0 \), \( c_{NaCl} = 0 \), and \( k_{DH^+} = 1 \). The curves are parametric in the membrane fixed charge concentration \( X_S \).
Figure 7 shows the ratio $c_{\text{DH}^+}/\tilde{c}_{\text{DH}^+}$ vs the external pH for $X_{\text{CT}} = 10^{-1}$ M (carboxylic groups, $p_{k_d} = 4$), $c_{\text{CaCl}_2} = 10^{-2}$ M, and $c_{\text{DHCl}} = 10^{-2}$ M, with $X_S = 0$, $c_{\text{NaCl}} = 0$, and $k_{\text{DH}^+} = 1$. The curves are parametric in the $\text{Ca}^{2+}$ ion binding constant $k_B$.

Figure 8 shows the ratio $c_{\text{DH}^+}/\tilde{c}_{\text{DH}^+}$ vs the external solution concentration $c_{\text{CaCl}_2}$ for $X_{\text{CT}} = 10^{-1}$ M ($p_{k_d} = 4$), pH = 7, and $c_{\text{DHCl}} = 10^{-2}$ M, with $X_S = 0$, $c_{\text{NaCl}} = 0$, and $k_{\text{DH}^+} = 1$. The curves are parametric in the $\text{Ca}^{2+}$ ion binding constant $k_B$.
be readily explained from Figs. 3 (see also Fig. 4) and 8. Figure 3 shows that when Ca$^{2+}$ binding can be ignored, substitution of the divalent cation Ca$^{2+}$ for Na$^+$ in the external solution significantly decreases the drug content in the membrane (the ratio $c_{DH^{+}}/\bar{c}_{DH^{+}}$ increases then with % CaCl$_2$ in Fig. 9), and Fig. 8 shows the effects of Ca$^{2+}$ binding on the $c_{DH^{+}}/\bar{c}_{DH^{+}}$ vs $c_{CaCl_2}$ curves. We emphasize finally that recent experimental data with ion-exchange fibers (9) have shown that the trend of increasing drug release (increasing $c_{DH^{+}}/\bar{c}_{DH^{+}}$ here) with increases in the fraction of CaCl$_2$ can be reversed for high enough values of % CaCl$_2$, confirming thus the theoretical predictions of Figs. 8 and 9.

Figure 10 shows the ratio $c_{DH^{+}}/\bar{c}_{DH^{+}}$ vs the external solution concentration $c_{NaCl}$ for $X_\text{S} = 10^{-1}$ M, pH = 7, and $c_{DHCl} = 10^{-2}$ M, with $X_\text{CT} = 0$ and $c_{CaCl_2} = 0$. The curves are parametric in the drug partition coefficient $k_{DH^{+}}$.

The ratio $c_{DH^{+}}/\bar{c}_{DH^{+}}$ vs the external solution concentration $c_{NaCl}$ for $X_\text{S} = 10^{-1}$ M, pH = 7, and $c_{DHCl} = 10^{-2}$ M, with $X_\text{CT} = 0$ and $c_{CaCl_2} = 0$. The curves are parametric in the drug partition coefficient $k_{DH^{+}}$.
observed for high enough binding constants leading to positive Donnan potentials in Figs. 8.) It has been reported (9) that high values of drug lipophilicity made a cation-exchange fiber behave as an anion exchanger, in agreement with the above theoretical results for the Donnan potential. As was the case in Figs. 3 and 4, the comparison of Figs. 10 and 11 shows that the Donnan results for the Donnan potential. As was the case in Figs. 3 and 4, the comparison of Figs. 10 and 11 shows that the Donnan potential is a useful magnitude in understanding the ionic drug partition equilibrium in fixed charge membranes (see also (9)).

Figure 12 shows finally the ratio $c_{\text{DH}^-}/c_{\text{DH}^+}$ vs the external solution concentration $c_{\text{CaCl}_2}$ for $X_{\text{CT}} = 10^{-1}$ M ($p_{K_B} = 4$), pH = 7, and $c_{\text{DCl}^-} = 10^{-2}$ M, with $X_S = 0$ and $c_{\text{NaCl}} = 0$. The curves are parametric in the Ca$^{2+}$ ion binding constant $k_B$ and the drug partition coefficient $k_{\text{DH}^+}$. Figure 12 points out that the drug partition equilibria in fixed charge membranes can show very rich behavior because many effects are present simultaneously. We emphasize finally that this behavior could be qualitatively explained on the basis of the results obtained in Figs. 3, 8, and 10 making use of relatively simple, fundamental concepts.

APPENDIX: LIST OF SYMBOLS

- $c_i$: concentration of species $i$ in the external solution phase (M)
- $\bar{c}_i$: concentration of species $i$ in the membrane solution phase (M)
- $\Delta \phi$: Donnan electric potential difference between the membrane and external solution (mV)
- $F$: Faraday constant (C/mol)
- $\phi$: electric potential in the external solution phase (mV)
- $\phi$: electric potential in the membrane solution phase (mV)
- $k_B$: equilibrium constant for the binding reaction of the carboxylic groups (M$^{-1}$)
- $k_i$: chemical partition coefficient of species $i$
- $K_W$: ionic product of water (M$^2$)
- $\mu_i$: standard chemical potential of species $i$ in the external solution phase (J/mol)
- $\bar{\mu}_i$: standard chemical potential of species $i$ in the membrane solution phase (J/mol)
- $p_{K_a}$: p$K_a$ value for the dissociation reaction of the carboxylic groups
- $R$: gas constant (J/mol K)
- $T$: absolute temperature (K)
- $X_C^N$: concentration of the carboxylic groups (neutral forms) within the membrane (M)
- $X_C^P$: concentration of the carboxylic groups (positive forms) within the membrane (M)
- $X_C^H$: concentration of the carboxylic groups (negative forms) within the membrane (M)
- $X_S$: concentration of sulfonic groups within the membrane (M)
- $z_i$: charge number of species $i$

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REFERENCES


