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Membrane permeation under continuous elution of the sink side of the membrane

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Abstract

Equations are presented which describe the kinetics of solute permeation through a membrane separating two compartments—donor and receiver—under the condition that the receiver compartment is continuously eluted. Their analytic solution reveals the following. Two processes are involved; permeation and elution. In the initial stage permeation through the membrane is dominant and in a later stage elution effects become dominant. Thus the solute concentration in the receiver as a function of time exhibits a maximum. Also, a time range is found over which the solute concentrations in the donor and the receiver vary almost linearly with time. The effect of elution can be considered equivalent to enlarging the receiver volume. A simple experimental system is proposed. The results are found to be well described with our model. Especially, agreement between theory and experiment is surprisingly good with respect to the location of the concentration maximum in the receiver when concentration is plotted as a function of time, in spite of the fact that our theory contains no adjustable parameter.

Keywords: Membrane permeation; Elution

1. Introduction

Membrane transport phenomena have been usually treated under the condition that permeation occurs due only to the concentration gradient of solutes between the donor and receiver phases [1–4]. However, in real transport processes, there is sometimes a flow in the receiver phase, as seen in a continuous-flow dialysis technique [5]. From this point of view, in transdermal drug delivery systems, for example, the drug release rate from the device should be considered to be affected not only by permeability of the drug through a matrix membrane but also by the flow rate of the outer phase of the device.

In the present paper, we derive a system of equations governing transport of solute across a membrane with continuous elution of the sink side of the membrane. We also present experimental data obtained from a system with a membrane separating two chambers, one of which is

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the donor phase and the other the receiver phase. The solution in the receiver chamber is continuously exchanged by a constant flow of distilled water. The measured solute concentrations in both chambers as a function of time are analyzed via our model.

2. Theory

Consider a transport of solute through a planar membrane separating two solutions 1 and 2 as shown in Fig. 1(a). Solution 1 is in the donor compartment and solution 2 in the receiver compartment which is continuously eluted with a constant flow. The volumes of both compartments are V_1 and V_2, respectively. Let the concentrations of the solute in solutions 1 and 2 at time t be $C_1(t)$ and $C_2(t)$, respectively. Under quasi-steady state conditions, the time course of the solute concentrations may be described as follows,

$$V_1\frac{dC_1(t)}{dt} = PA(C_2(t) - C_1(t)) \tag{1}$$

$$V_2\frac{dC_2(t)}{dt} = PA(C_1(t) - C_2(t)) - v(C_2(t) - C_2(0)) \tag{2}$$

where P is the permeability coefficient and A is the area of the membrane separating solutions 1 and 2. The second term on the right-hand side of eq. (2) expresses elution ($C_2(0) < C_1(0)$) with a constant flow rate v; $vC_2(0)$ is the solute amount (flux) entering the receiver compartment 2 per unit time and $vC_2(t)$ is that transfered out of the compartment.

The solution to eqs. (1) and (2) subject to the initial conditions

$$C_1(0) = C_{10} \tag{3}$$

$$C_2(0) = C_{20} \tag{4}$$

is expressed as

$$\frac{C_1(t)}{C_{10}} = \frac{C_{20}}{C_{10}} + \frac{(a-c)(a-d)}{a(a-b)}e^{-at} + \frac{(b-c)(d-b)}{b(a-b)}e^{-bt} \tag{5}$$

$$\frac{C_2(t)}{C_{20}} = 1 + \frac{(a-e)(a-f)}{a(a-b)}e^{-at} + \frac{(b-e)(f-b)}{b(a-b)}e^{-bt} \tag{6}$$

where

$$a = \frac{(\alpha+\beta) + \sqrt{(\alpha-\beta)^2 + 4\alpha\beta\phi}}{2} \tag{7}$$

$$b = \frac{(\alpha+\beta) - \sqrt{(\alpha-\beta)^2 + 4\alpha\beta\phi}}{2} \tag{8}$$

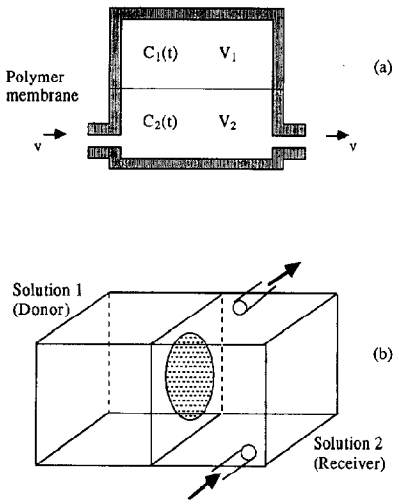

Fig. 1. (a) Schematic representation of solute permeation through a membrane separating donor and receiver compartments under the condition that the solution in sink side of the membrane is continuously eluted. (b) Experimental system. A membrane separates a donor solution and a receiver solution, the latter being continuously eluted with distilled water at a constant flow rate.

$$c = \frac{1}{2}\left[\left\{(\phi\alpha+\beta)+(1-\phi)\alpha\frac{C_{20}}{C_{10}}\right\}+\sqrt{\left\{(\phi\alpha+\beta)+(1-\phi)\alpha\frac{C_{20}}{C_{10}}\right\}^2-4\alpha\beta(1-\phi)\frac{C_{20}}{C_{10}}}\right] \quad (9)$$

$$d = \frac{1}{2}\left[\left\{(\phi\alpha+\beta)+(1-\phi)\alpha\frac{C_{20}}{C_{10}}\right\}-\sqrt{\left\{(\phi\alpha+\beta)+(1-\phi)\alpha\frac{C_{20}}{C_{10}}\right\}^2-4\alpha\beta(1-\phi)\frac{C_{20}}{C_{10}}}\right] \quad (10)$$

$$e = \frac{1}{2}\left[\left\{\beta+(1-\phi)\alpha+\phi\alpha\frac{C_{10}}{C_{20}}\right\}+\sqrt{\left\{\beta+(1-\phi)\alpha+\phi\alpha\frac{C_{10}}{C_{20}}\right\}^2-4\alpha\beta(1-\phi)}\right] \quad (11)$$

$$f = \frac{1}{2}\left[\left\{\beta+(1-\phi)\alpha+\phi\alpha\frac{C_{10}}{C_{20}}\right\}-\sqrt{\left\{\beta+(1-\phi)\alpha+\phi\alpha\frac{C_{10}}{C_{20}}\right\}^2-4\alpha\beta(1-\phi)}\right] \quad (12)$$

$$\alpha = PA\left(\frac{1}{V_1}+\frac{1}{V_2}\right) \quad (13)$$

$$\beta = v/V_2 \quad (14)$$

$$\phi = V_1/(V_1+V_2) \quad (15)$$

For $t < 0$, that is, before the time instant at which the permeation of solute from compartment 1 to 2 commences, solute in the solution 2 is subject only to a stationary liquid flow with a concentration of $C_2(0)$ and rate v so that the concentration of solution 2 is kept constant at $C_2(0)$ when $t < 0$. For $t > 0$, in addition to this stationary liquid flow membrane permeation occurs so that $C_2(t)$ deviates from $C_2(0)$. Finally $C_2(t)$ tends back to its initial value, $C_2(0)$. On the other hand, $C_1(t)$ changes following the difference between $C_1(t)$ and $C_2(t)$ tending also to $C_2(0)$.

Note that eqns. (5) and (6) satisfy the following conservation relation:

$$v\int_0^t [C_2(t)-C_{20}]\,dt = [C_{10}-C_1(t)]V_1 + [C_{20}-C_2(t)]V_2 \quad (16)$$

The left-hand side is the net amount of solutes transferred out of the receiver compartment between $t = 0$ and $t = t$. When $v = 0$, this quantity becomes zero so that eq. (16) reduces to the usual conservation law.

3. Experimental

3.1 Materials

Poly(sodium 4-styrenesulfonate) and Nuclepore (pore size 8.0 μm) were purchased from Aldrich Chemical Co. Inc., and Nuclepore Corporation.

3.2 Methods

The experimental system used is schematically shown in Fig. 1(b). A Nuclepore SN111114 membrane separates the donor and the receiver chambers. A poly(sodium 4-styrenesulfonate) solution and distilled water were placed in the donor and receiver chambers, respectively. The solution in each compartment was stirred sufficiently to establish a uniform concentration. The solution in the receiver chamber was eluted with distilled water at a constant flow rate. The solute concentration in each of the donor and the receiver phases was measured with a TOA conductivity meter (CM40S). The solution volume of the donor and receiver chambers was 62 ml each. Measurements were carried out at 30°C and the flow rates

of 0, 6.54×10^{-4}, 7.93×10^{-3}, and 1.99×10^{-2} ml/s. Experimental results will be given later in Figs. 7–10. in comparison with prediction from our model.

4. Results and discussion

We have derived a system of equations describing the time course of solute concentrations in solutions 1 and 2 under the condition that the receiver chamber is continuously eluted with a constant flow rate, v. Coupled equations (1), (2) and their numerical solutions have already been considered for the special case with the initial condition $C_2(0) = 0$ by Sparrow et al. [5]. We have derived analytic solutions to eqs. (1) and (2). The solution in the receiver chamber moves parallel to the membrane so that the permeation and elution processes can be considered to be independent of each other. In order to study the effects of v on the permeation kinetics of solute, we treat the special case of $C_{20} = 0$, in which eqs. (5) and (6) reduce to

$$C_1(t) = C_{10} \exp\left(-\frac{\alpha+\beta}{2}t\right) \times \left[\cosh\frac{\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}{2}t - \frac{\alpha(1-2\phi)-\beta}{\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}\sinh\frac{\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}{2}t\right] \quad (17)$$

$$C_2(t) = C_{10}\frac{2\phi\alpha}{\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}\exp\left(-\frac{\alpha+\beta}{2}t\right) \times \sinh\frac{\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}{2}t \quad (18)$$

and the conservation relation eq. (16) becomes

$$[C_{10} - C_1(t)]V_1 = C_2(t)V_2 + v\int_0^t C_2(t)\,\mathrm{d}t \quad (19)$$

Some of the results of calculation via eqs. (17) and (18) are shown in Figs. 2 and 3, which compare the results for $v = 0$ ($\beta = 0$) with those for

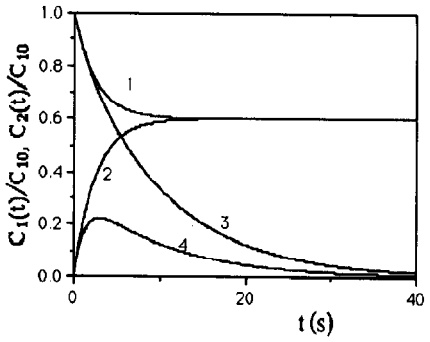

Fig. 2. Time course of $C_1(t)$ and $C_2(t)$ for several values β at $\alpha = 0.4$ (s^{-1}) and $\phi = 0.6$. Curves: 1, $C_1(t)/C_{10}$ for $\beta = 0$ (s^{-1}); 2, $C_2(t)/C_{10}$ for $\beta = 0$ (s^{-1}); 3, $C_1(t)/C_{10}$ for $\beta = 0.5$ (s^{-1}); and 4, $C_2(t)/C_{10}$ for $\beta = 0.5$ (s^{-1}).

$v \neq 0$ ($\beta \neq 0$). When $v = 0$, both $C_1(t)$ and $C_2(t)$ tend to the same nonzero equilibrium value, while when $v \neq 0$ both $C_1(t)$ and $C_2(t)$ become zero as a result of the continuous elution. It is of interest to note that $C_2(t)$ exhibits a maximum before it decays to zero. This can be explained as follows. The two factors are involved; permeation and elution. In the initial stage before the maximum appears, the outward permeation of solute from the donor compartment to receiver compartment is predominant. After the maximum appears, the elution process exceeds the permeation process. As β increases, the position of maximum shifts to smaller t and the maximum value decreases, as shown in Fig. 3(b). The time t_m at which $C_2(t)$ shows a maximum and $C_2(t_m)$ are calculated from the condition $\mathrm{d}C_2(t)/\mathrm{d}t = 0$ via eq. (18), viz.,

$$t_m = \frac{1}{\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}} \times \ln\left[\frac{\alpha+\beta+\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}{\alpha+\beta-\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}\right] \quad (20)$$

$$C_2(t_m) = C_{10}\frac{2\phi\alpha}{\sqrt{(\alpha+\beta)^2-(\alpha-\beta)^2-4\alpha\beta\phi}} \times \left[\frac{\alpha+\beta+\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}{\alpha+\beta-\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}\right]^{-(\alpha+\beta)/2\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}} \quad (21)$$

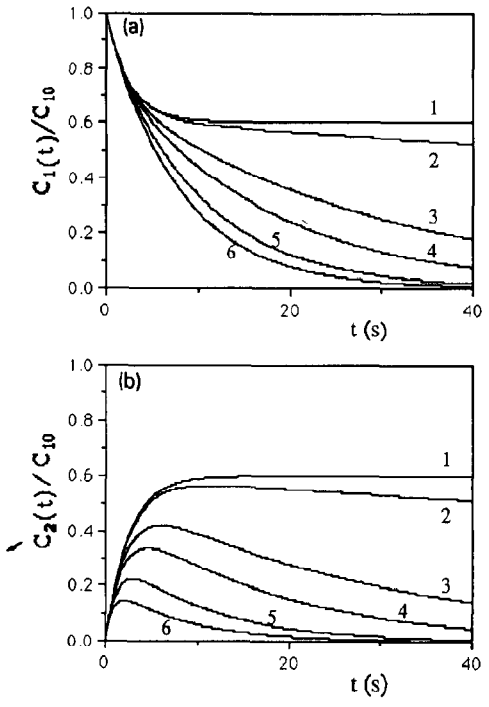

Fig. 3. (a) Effect of β on $C_1(t)/C_{10}$ at $\alpha = 0.4$ (s^{-1}) and $\phi = 0.6$. Curves: 1, $\beta = 0$ (s^{-1}); 2, $\beta = 0.01$ (s^{-1}); 3, $\beta = 0.1$ (s^{-1}); 4, $\beta = 0.2$ (s^{-1}); 5, $\beta = 0.5$ (s^{-1}); and 6, $\beta = 1$ (s^{-1}). (b) Effect of β on $C_2(t)/C_{10}$ at $\alpha = 0.4$ (s^{-1}) and $\phi = 0.6$. Curves: 1, $\beta = 0$ (s^{-1}); 2, $\beta = 0.01$ (s^{-1}); 3, $\beta = 0.1$ (s^{-1}); 4, $\beta = 0.2$ (s^{-1}); 5, $\beta = 0.5$ (s^{-1}); and 6, $\beta = 1$ (s^{-1}).

In Figs. 4(a) and (b) we plot αt_m and $C_2(t_m)/C_{10}$ as a function of β/α.

For small t, $C_2(t)$ is expressed as

$$C_2(t) \approx C_{10}\phi\alpha\left[t - \frac{(\alpha+\beta)}{2}t^2\right] \tag{22}$$

The initial slope of $C_2(t)$, before it reaches its maximum, does not depend on β. The influence of β is involved in terms of the order of t^2. For very large t, $C_1(t)$ and $C_2(t)$ are exponentially damped to zero in the form

$$\exp\left[-\frac{\alpha+\beta-\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}{2}t\right] \tag{23}$$

Note that this factor equals unity when $\beta = 0$, which means that in this case $C_1(t)$ and $C_2(t)$ do not tend to zero as $t \to \infty$. However, as is seen in Figs. 3(a) and (b), for small values (but not zero) of β there is a time region in which $C_1(t)$ and $C_2(t)$ vary almost linearly (not exponentially) with time, in other words, $dC_1(t)/dt$ and $dC_2(t)/dt$ are approximated by eqs. (24) and (25).

$$\frac{dC_1(t)}{dt} = -(1-\phi)C_{10}\left[\alpha\, e^{-\alpha t} + \phi\{1-(1+\alpha t)\, e^{-\alpha t}\}\beta + O(\beta^2)\right] \tag{24}$$

$$\frac{dC_2(t)}{dt} = \phi C_{10}\left[\beta\{(\phi-1)+(1-\phi-\phi\alpha t)\, e^{-\alpha t}\} + \alpha\, e^{-\alpha t} + O(\beta^2)\right] \tag{25}$$

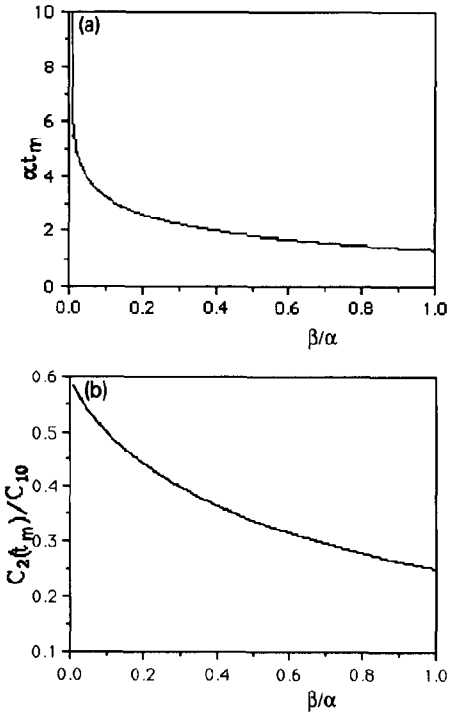

Fig. 4. (a) The scaled time instant αt_m at which $C_2(t)$ has a maximum as a function of β/α at $\phi = 0.6$. (b) The value of $C_2(t)/C_{10}$ at $t = t_m$ as a function of β/α at $\phi = 0.6$.

So it can be proved from eqs. (24) and (25), that if

$$\alpha \gg \beta \tag{26}$$

then in the range

$$1/\alpha \ll t \ll 1/\beta \tag{27}$$

$dC_1(t)/dt$ and $dC_2(t)/dt$ can be approximated by

$$\frac{dC_1(t)}{dt} \approx -\frac{dC_2(t)}{dt} \approx -C_{10}\phi(1-\phi)\beta \tag{28}$$

This means that in the time region (eq. 27), the release rate is nearly of the zeroth order. Physically, this behavior corresponds to the following situation: When α is large, permeation rate is very large so that $C_1(t)$ and $C_2(t)$ reach values which they would have at $t \to \infty$ and $\beta = 0$ (i.e., the difference between $C_1(t)$ and $C_2(t)$ becomes small), and then elution process becomes dominant over permeation.

We calculate the β-dependence of the half-life period, $t_{1/2}$, at which

$$C_1(t_{1/2}) = \tfrac{1}{2}C_{10} \tag{29}$$

It can be shown that the value of $t_{1/2}$ is given as the solution to the following transcendental equation:

$$\exp\left[\frac{\alpha+\beta+\sqrt{(\alpha-\beta)^2-4\alpha\beta\phi}}{2}t_{1/2}\right] = \exp\left(\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}\,t_{1/2}\right) \times\left(1-\frac{\alpha(1-2\phi)-\beta}{\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}}\right)+1 + \frac{\alpha(1-2\phi)-\beta}{\sqrt{(\alpha-\beta)^2+4\alpha\beta\phi}} \tag{30}$$

The results are given in Fig. 5, which shows $\alpha t_{1/2}$ as a function of β/α for several values of ϕ.

The effects of β on $C_2(t)$ can be interpreted by introducing the effective volume of the receiver phase, V_2^{eff}. In view of the fact that $\beta = 0$, eq. (19) reduces to

$$[C_{10} - C_1(t)]V_1 = C_2(t)V_2 \tag{31}$$

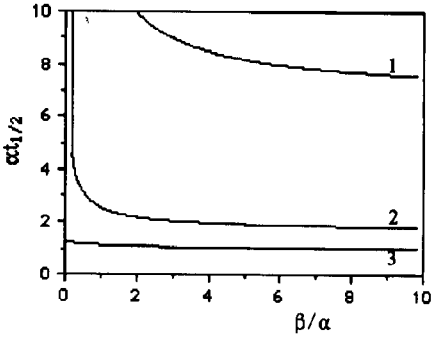

Fig. 5. The scaled half-life period $\alpha t_{1/2}$ for several values of ϕ as a function of β/α. Curves: 1, $\phi = 0.9$; 2, $\phi = 0.6$; and 3, $\phi = 0.3$.

We rewrite eq. (19) as

$$[C_{10} - C_1(t)]V_1 = C_2(t)V_2^{\text{eff}}(t) \tag{32}$$

where

$$V_2^{\text{eff}}(t) = V_2\left[1+\beta\frac{1}{C_2(t)}\int_0^t C_2(t)\,dt\right] \tag{33}$$

This is the definition of V_2^{eff}, which depends on t. Equation (32) can be rewritten as

$$\frac{V_2^{\text{eff}}(t)}{V_2} = \frac{C_{10}-C_1(t)}{C_2(t)}\frac{V_1}{V_2} \tag{34}$$

Note that $V_2^{\text{eff}}(t) > V_2$. This means that the elution process leads to an apparent increase of the volume of the receiver V_2.

In Fig. 6, we plot $(V_2^{\text{eff}}(t) - V_2)/V_2$ as a function of t for several values of β. It is seen that V_2^{eff} increases monotonously with time.

Experimental results are given in Figs. 7–10, which show the time course of the solute concentrations in the donor and receiver phases at the flow rates of 0, 6.54×10^{-4}, 7.93×10^{-3}, 1.99×10^{-2} ml/s α was estimated to be 3.51 10^{-5} (s^{-1}) via the experimental results at $v = 0$ ($\beta = 0$). It is seen that the experimental results are well described by our model in spite of the fact that our model involves no adjustable parameter. In particular, the time instant at which the solute concentration in the receiver phase shows a maximum agrees most completely with the value predicted from our model. The magnitude of the maximum value, however, differs by a factor of

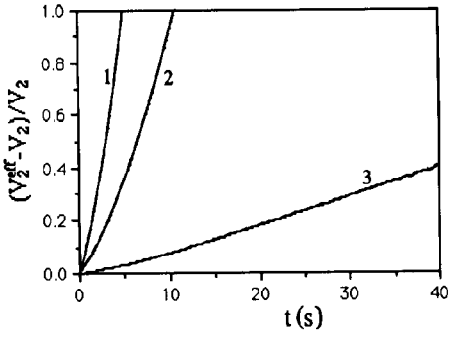

Fig. 6. The scaled effective volume $(V_2^{eff}(t)-V_2)/V_2$ of the receiver compartment as a function of t for several values of β at $\alpha = 0.4$ (s^{-1}) and $\phi = 0.6$. Curves: 1, $\beta = 0.25$ (s^{-1}); 2, $\beta = 0.1$ (s^{-1}); and 3, $\beta = 0.01$ (s^{-1}).

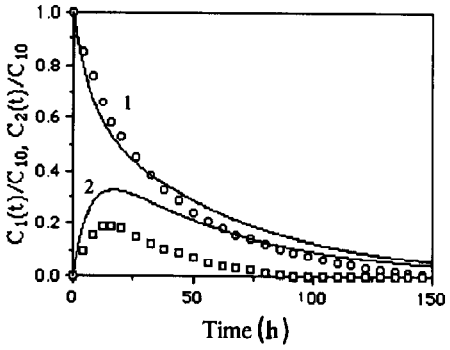

Fig. 8. Time course of $C_1(t)/C_{10}$ and $C_2(t)/C_{10}$ with a flow rate (v) of 6.54×10^{-4} (ml/s). Symbols are experimental results: (○) $C_1(t)/C_{10}$; and (□) $C_2(t)/C_{10}$ ($C_{10} = 3.45$ g/L). Curves are results calculated with $\alpha = 3.51\times10^{-5}$ (s^{-1}), $\beta = 1.05\times10^{-5}$ (s^{-1}) and $\phi = 0.5$. Curves: 1, $C_1(t)/C_{10}$; and 2, $C_2(t)/C_{10}$.

about 1.5. This discrepancy attributes partly to the fact that the elution flow, which is supposed to be in the direction parallel to the membrane surface, inevitably affects the permeation process to some extent. Another possible reason for the discrepancy is the effects of pressure difference between the two chambers, which in turn is caused by the concentration difference between them.

In conclusion we would like to stress that since the membrane transport process in real biological systems proceeds in a flow condition, they should

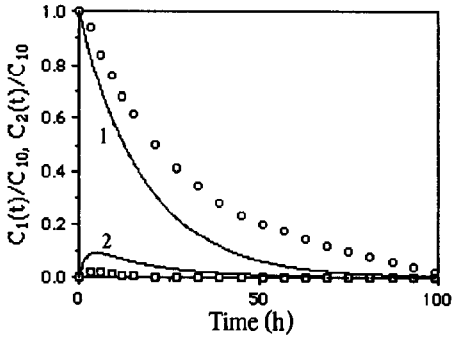

Fig. 9. Same as Fig. 8 except for $v = 7.93\times10^{-3}$ (ml/s) and $\beta = 1.28\times10^{-4}$ (s^{-1})

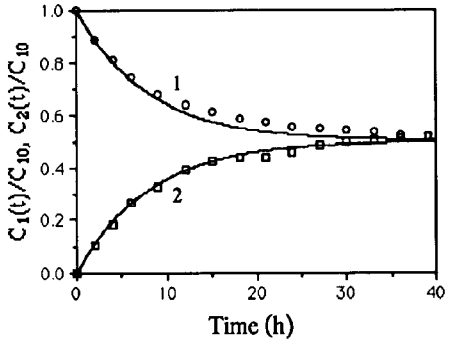

Fig. 7. Time course of $C_1(t)/C_{10}$ and $C_2(t)/C_{10}$ without flow. Symbols are experimental results: (○) $C_1(t)/C_{10}$; and (□) $C_1(t)/C_{10}$ ($C_{10} = 3.45$ g/L). Curves are results calculated with $\alpha = 3.51\times10^{-5}$ (s^{-1}), $\beta = 0$ (s^{-1}) and $\phi = 0.5$. Curves: 1, $C_1(t)/C_{10}$; and 2, $C_2(t)/C_{10}$.

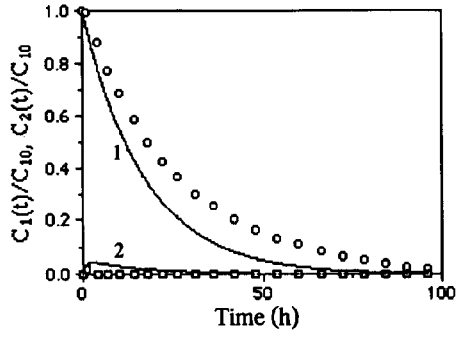

Fig. 10. Same as Fig. 8 except for $v = 1.99\times10^{-2}$ (ml/s) and $\beta = 3.21\times10^{-4}$ (s^{-1}).

be analyzed via transport equations taking into account of the elution effect. As we have shown in this paper, this effect may be taken into account by incorporating just one parameter β (eq. 14) into the conventional transport equations.

Acknowledgments

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References

1 W. Jost, Diffusion in solids, liquids, gases (Academic Press, New York, NY, 1960).
2 G.L. Flynn, S.H. Yalkowsky and T.J. Roseman, J. Pharm. Sci. 63 (1974) 479–510.
3 K. Makino, H. Ohshima and T. Kondo, Biophys. Chem. 35 (1990) 85–95.
4 K. Makino, H. Ohshima and T. Kondo, Biophys. Chem. 38 (1990) 231–239.
5 N.A. Sparrow, A.E. Russell and L. Glasser, Anal. Biochem. 123 (1982) 255–264.