Another Lag-Time Involved in Constant-Field Iontophoretic Mass Transport through a Homogeneous Membrane

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The time-dependent theoretical solution to ionic mass transport through a uniform membrane under the influence of a uniform electric field is derived, satisfying the initial condition of diffusional (non-iontophoretic) steady state. With increasing voltage magnitude, the lag times increase from zero, to attain the maximum and decrease to zero.

Keywords iontophoresis; diffusion; lag time; mass transport

Introduction

In the course of a study on iontophoretic drug transport through a uniform membrane, an *in-vitro* experiment using a two-chamber cell was designed. Under an infinite-sink condition and without electric field, diffusional behavior of a drug was studied for a sufficient period of time to attain diffusional steady state (stage 1). Then the experiment was continued under the influence of a uniform electric field (stage 2). A cumulative amount of the transported drug was determined at appropriate time intervals. (Fig. 1)

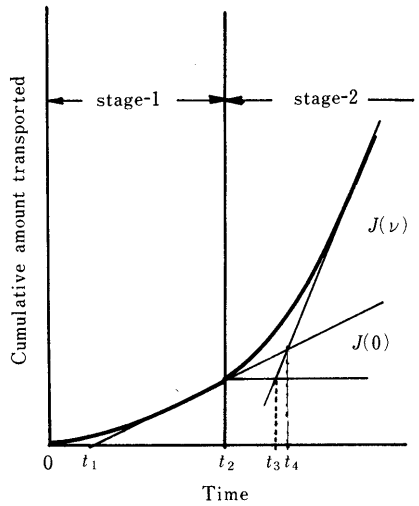

Fig. 1. Schematic Presentation of Transported Drug Amount

t_1, diffusional lag time, $t_L(0)$; t_2, beginning of stage 2; t_3-t_2, iontophoretic lag time, $t_L(v)$; t_4-t_2, intersection time, $t_{intersect}$; $J(0)$, diffusional transport rate; $J(v)$, iontophoretic transport rate.

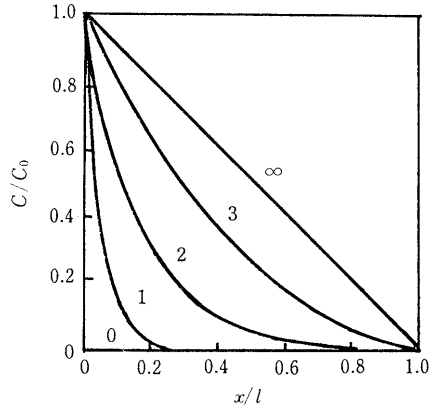

Fig. 2. Model of Passive Diffusion in a Membrane (Stage 1)

Steady-state transport rates of drug and lag times to establish the steady state were determined from the data of both stages. The obtained parameters were used for estimation of micro parameters such as diffusion constant, partition coefficient, membrane thickness *etc.* and for characterization of the iontophoretic drug transport.

Theoretical expressions for the steady-state transport rate of drug and the lag time, under the influence of a constant electric field, were derived by Keister *et al.*,[1] presuming that at time $t=0$, there is no drug in the membrane (initial condition). According to the above-mentioned experimental procedure, however, at the time when the iontophoresis is initiated, the drug has already accumulated in the membrane. Therefore, a slight revision of the theoretical expression is necessary. The aim of the present report is to supply a theoretical basis for the stage-2 experiment.

Theoretical Analysis

Stage 1 The model is shown in Fig. 2. The equation describing the drug flux J within the membrane is:

$$J=-D\frac{\partial C}{\partial x} \tag{1}$$

where D is the diffusion coefficient, C the drug concentration. Boundary conditions are as follows:

$$C(x=0)=C_0$$

$$C(x=l)=0$$

$$C(t=0)=0, \quad 0<x\leq l$$

If one takes the partial derivative of this equation with respect to x and uses the mass conservation equation, Fick's 2nd equation is obtained, as

$$\frac{\partial C}{\partial t}=D\frac{\partial^2 C}{\partial x^2} \tag{2}$$

The solution of Eq. 2 was reported by Barrer[2] as

$$C(x,t)=C_0\left(1-\frac{x}{l}\right)-\frac{2C_0}{\pi}\sum_{n=1}^{\infty}\frac{\sin\left(\frac{n\pi}{l}x\right)}{n}\exp\left(-\frac{n^2\pi^2Dt}{l^2}\right) \tag{3}$$

The amount of drug per unit area that has penetrated as a function of time at $x=l$, is given by Eq. 4.

$$Q(t)=\frac{DC_0}{l}\left(t-\frac{l^2}{6D}\right)+\frac{2C_0l}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^{n-1}}{n^2}\exp\left(-\frac{n^2\pi^2Dt}{l^2}\right) \tag{4}$$

The steady-state part of $Q(t)$ can be written as:

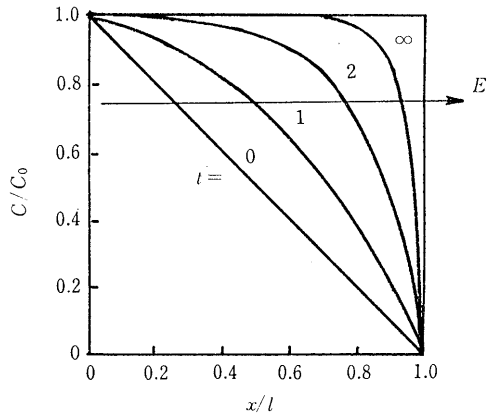

Fig. 3. Model of Iontophoresis Enhancement in a Membrane (Stage 2)

$$Q_{ss}(t)=\frac{DC_0}{l}\left(t-\frac{l^2}{6D}\right) \tag{5}$$

Stage 2 The problem considered is diffusion of an ionized drug through an uncharged homogeneous membrane under the influence of a constant electric field. The model is shown in Fig. 3. The equation describing the drug flux J within the membrane is:

$$J=-D\frac{\partial C}{\partial x}+D\frac{zFE}{RT}C \tag{6}$$

where D is the diffusion coefficient, C the drug concentration, as above, z the charge on the drug ion, F the Farady constant, E the electric field, R the gas constant, and T the absolute temperature. Boundary conditions are as follows:

$$C(x=0)=C_0$$

$$C(x=l)=0$$

$$C(t=0)=C_0(1-x/l),\quad 0\leq x\leq l$$

If one takes the partial derivative of this equation with respect to x and uses the mass conservation equation $dC/dt=-dJ/dx$, as above, Eq. 6 can be written as

$$\frac{\partial C}{\partial t}=D\frac{\partial^2 C}{\partial x^2}-\frac{Dv}{l}\frac{\partial C}{\partial x} \tag{7}$$

where $v=zFV/RT$. V is the voltage drop across the membrane and l is the membrane thickness, consequently $E=V/l$.

A major assumption is that the electric field is constant. According to Keister,[1] this is quite reasonable if the primary current-carrying ions are the smaller ions such as Na^+, Cl^-, *etc.*, and if we assume that these ions are distributed uniformly throughout the membrane.

Using separation of variables (*cf.* appendix A of reference[1]), the solution of Eq. 7 can be shown to be

$$C(x,t)=C_0\left[\frac{1-\exp\left\{-v\left(1-\frac{x}{l}\right)\right\}}{1-\exp(-v)}\right]$$

$$-2C_0v\exp\left(\frac{vx}{2l}\right)\sum_{n=1}^{\infty}\frac{(n\pi)\left\{1+(-1)^{n-1}\exp\left(-\frac{v}{2}\right)\right\}\sin\left(\frac{n\pi x}{l}\right)}{\left\{(n\pi)^2+\left(\frac{v}{2}\right)^2\right\}^2}$$

$$\times\exp\left[-\frac{\left\{(n\pi)^2+\left(\frac{v}{2}\right)^2\right\}Dt}{l^2}\right] \tag{8}$$

Equation 8 is definitely different from Eq. 4 of reference,[1] although seemingly similar.

Since the primary concern is the amount of drug per unit area that has penetrated as a function of time at $x=l$, one must integrate $J(x=l)$ over time.

$$Q(t)=\int_0^t J(x=l,\tau)d\tau=\int_0^t -D\frac{\partial C(x=l,\tau)}{\partial x}d\tau \tag{9}$$

Since $C(x=l)=0$, the second term of the expression from Eq. 6 for J must vanish. The final result for $Q(t)$ is:

$$Q(t)=\frac{DC_0}{l}\frac{v}{1-\exp(-v)}t-2C_0lv\sum_{n=1}^{\infty}\frac{(n\pi)^2\left\{1+(-1)^{n-1}\exp\left(\frac{v}{2}\right)\right\}}{\left\{(n\pi)^2+\left(\frac{v}{2}\right)^2\right\}^3}$$

$$\times\left[1-\exp\left[-\frac{\left\{(n\pi)^2+\left(\frac{v}{2}\right)^2\right\}Dt}{l^2}\right]\right] \tag{10}$$

The steady-state part of $Q(t)$ can be written as:

$$Q_{ss}(t)=\frac{DC_0}{l}\frac{vt}{1-\exp(-v)}-2C_0lv\sum_{n=1}^{\infty}\frac{(n\pi)^2\left\{1+(-1)^{n-1}\exp\left(\frac{v}{2}\right)\right\}}{\left\{(n\pi)^2+\left(\frac{v}{2}\right)^2\right\}^3} \tag{11}$$

Evaluating the infinite series in Eq. 11, the final expression Eq. 12 is obtained.

$$Q_{ss}(t)=\frac{DC_0}{l}\frac{v}{1-\exp(-v)}$$

$$\times\left[t-\frac{l^2}{Dv}\left\{\frac{1+\exp(-v)}{1-\exp(-v)}-\frac{1}{v}-\frac{1-\exp(-v)}{v^2}-\frac{1}{2}\right\}\right] \tag{12}$$

In order to confirm validity of Eq. 12, numerical evaluation of $Q(t)$ was attempted using the Laplace transform.

Laplace Transform of $Q(t)$ and Numerical Inversion The equations for the Laplace transform[3] $\bar{C}$ (stage 2) derived from Eq. 7 are:

$$\frac{d^2\bar{C}}{dx^2}-\frac{v}{l}\frac{d\bar{C}}{dx}-\frac{s}{D}\bar{C}=-\frac{C_0}{D}\left(1-\frac{x}{l}\right)\quad 0<x\leq l \tag{13}$$

with $\bar{C}=C_0/s \quad x=0$

$\bar{C}=0 \quad x=l$

Solution of these is:

$$\bar{C}=\frac{vDC_0}{s^2l^2}\left[1+\frac{\{\exp(p_2l)-1\}\exp(p_1x)-\{\exp(p_1l)-1\}\exp(p_2x)}{\exp(p_1l)-\exp(p_2l)}\right]$$

$$+\frac{C_0}{s}\left(1-\frac{x}{l}\right) \tag{14}$$

where

$$p_1=\frac{v}{2l}+\sqrt{\left(\frac{v}{2l}\right)^2+\frac{s}{D}}\quad\text{and}\quad p_2=\frac{v}{2l}-\sqrt{\left(\frac{v}{2l}\right)^2+\frac{s}{D}}$$

The Laplace transform of Eq. 9 is Eq. 15.

TABLE I. Steady-State Flux and Lag Time as a Function of v Evaluated by Eq. 16 Using FILT and by Eq. 12

v	$Q(t=9)$ (mg/cm^2)	$Q(t=10)$ (mg/cm^2)	Eq. 16 Slope (mg/cm^2·h)	Eq. 16 Lag time (h)	Eq. 12 Slope (mg/cm^2·h)	Eq. 12 Lag time (h)
2	0.183969	0.204784	0.020815	0.16171	0.020817	0.16145
4	0.323095	0.359761	0.036666	0.18816	0.036672	0.18830
6	0.477801	0.531927	0.054126	0.17243	0.054134	0.17255
8	0.637324	0.709338	0.072014	0.15000	0.072024	0.15002
10	0.798225	0.888221	0.089996	0.13044	0.090004	0.13003
20	1.606374	1.786353	0.179979	0.07466	0.180000	0.07458

$D=7.5\times10^{-8}$ cm^2/s, $l=0.030$ cm, $C_0=1.0$ mg/ml.

$$\bar{Q}=-\frac{D}{s}\left(\frac{d\bar{C}}{dx}\right)_{x=l} \tag{15}$$

The final result for Q is:

$$\bar{Q}=\frac{DC_0}{ls^2}-\frac{D^2C_0v}{s^3l^2}\left[\frac{p_1\{\exp(p_2l)-1\}\exp(p_1l)-p_2\{\exp(p_1l)-1\}\exp(p_2l)}{\exp(p_1l)-\exp(p_2l)}\right] \tag{16}$$

For arbitrarily chosen parameter values of $D=7.5\times10^{-8}$ cm^2/s, $l=0.030$ cm and $C_0=1.0$ mg/ml, numerical inversion of Eq. 16 was performed using a fast inversion of Laplace transform (FILT) algorithm proposed by Hosono.[4] Q values for $t=9$(h) and 10(h) as a function of v are shown in Table I. The slope and the t-axis intercept of the line connecting two sets of (t, Q) values, as well as the slope and the lag time calculated by Eq. 12 are also included in Table I.

The fact that the values obtained by quite a different approach agreed 4 to 5 places below the decimal point, confirms the validity of Eq. 12 and usability of FILT algorithm.

Discussion

The two most important aspects between Eq. 5 and Eq. 12, which are observed experimentally in stages 1 and 2, are the transport enhancement effects of the applied voltage and the effective lag time. The expression for the enhancement ratio, *i.e.*, the ratio of steady-state flux with applied voltage divided by steady-state passive flux, $J(v)/J(0)$ is given in Eq. 17.

$$\frac{J(v)}{J(0)}=\frac{v}{1-\exp(-v)} \tag{17}$$

In the reference,[1] an identical equation has been presented and some features of the enhancement ratio are discussed.

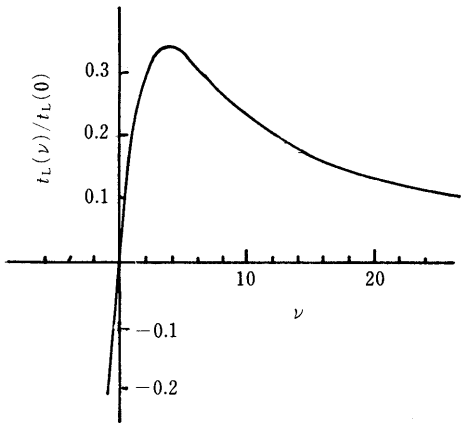

Fig. 4. Lag Time Factor ($t_L(v)/t_L(0)$) *versus* v

The ratio of the voltage-enhanced lag time to the passive lag time, $t_L(v)/t_L(0)$ is given in Eq. 18.

$$\frac{t_L(v)}{t_L(0)}=\frac{6}{v}\left\{\frac{1+\exp(-v)}{1-\exp(-v)}-\frac{1}{v}-\frac{1-\exp(-v)}{v^2}-\frac{1}{2}\right\} \tag{18}$$

Figure 4 shows the variation of $t_L(v)/t_L(0)$ *versus* v.

The ratio $t_L(v)/t_L(0)$ has some interesting features. The effective lag time is first increased by the application of a voltage, then is decreased passing the maximum value. Maximum lag time ratio of 0.3393 occurs at $v=3.80$. A reversal of voltage will tend to shut down the drug flow. Steady-state flux is less than the initial flux of stage 2. A negative effective lag time results.

Experimentally, it is easier to determine the intersection time, $t_{\text{intersect}}$ (t_4 in Fig. 1). One simply extends each linear portion of the transported-amount–time curve for stage 1 and stage 2, and reads the time scale of the intersection. Theoretically, the ratio of iontophoretic lag time and intersection time is given by Eq. 19.

$$\frac{t_L(v)}{t_{\text{intersect}}}=\frac{t_3-t_2}{t_4-t_2}=1-\frac{1-\exp(-v)}{v} \tag{19}$$

Although FILT algorithm presented by Hosono[4] has made it easy to evaluate numerically complex expressions for drug transport through a membrane, the importance of analytical representation should not be underestimated. Mathematical expressions for lag time, steady-state flux *etc.* are obtained by analytical procedures.

References

1) J. C. Keister, *J. Membrane Sci.*, **29**, 155 (1986).
2) R. M. Barrer, "Diffusion in and through Solids," Cambridge University Press, Cambridge, 1951, p. 15.
3) J. Crank, "The Mathematics of Diffusion," Oxford University Press, Oxford, 1975, pp. 19—27.
4) T. Hosono, *Radio Sci.*, **16**, 1015 (1981).