

Estimation of the Moments of the Residence Time and First Passage Time from Experimentally Measurable Permeation Parameters via a New Formulation of the Transmission Matrix

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Siegel's analysis on membrane transport in the Laplace domain [J. Phys. Chem. **95** (1991) 2556] in terms of transmission matrix, $T(s)$, has been extended to a more useful formulation. This is achieved by combining uses of the matrix transport equations appropriate for void initial condition, or for saturated equilibrium, or of Dirac delta functional type and the theorem $\det[T(s)] = 1$. This formulation enables us to expand $T(s)$ in power series of the Laplace variable, s , with the expansion coefficients as the algebraic functions of the experimentally measurable transport parameters. Utility of the formulation is illustrated in the estimation of the experimentally inaccessible time moments for the first passage or residence times. It was also applied to the percutaneous drug delivery to obtain from the experimental data. The higher moments of the time lag or time lead using a graphic method.

Keywords: Transmission matrix; Membrane transport; Percutaneous drug delivery.

INTRODUCTION

Permeation transport across membranes is of great importance in science and technology, and has played a crucial role in such diverse fields as chemical sensors,^{1,2} controlled release,^{3,4} separation processes,⁵ protection against pollution,⁶ electro dialysis,⁷ to name just a few. In practical applications, three modes of membrane transport are employed:⁸ (a) absorptive permeation, where the initial activity within the membrane is zero and the activities at the upstream and downstream faces are at a constant level a_0 and zero, respectively; (b) desorptive permeation, where the initial condition is of saturated equilibrium with activity a_0 throughout the whole membrane. If the activity is a_0 at the upstream face, zero at the downstream face, then we have forward desorptive permeation; and if, on the other hand, the boundary conditions at two faces are exchanged, then we have backward desorptive permeation; (c) desorption, where the initial activity a_0 prevails throughout the whole membrane and the boundary conditions at both faces are kept at zero activity. For heterogeneous membranes, where the diffusivity $D(x)$ and partition coefficient $K(x)$ depending on position, the permeation can be mathematically described by the Smoluchowski equation,⁹⁻¹¹ $\frac{\partial}{\partial t}\rho(x,t)$

$= \frac{\partial}{\partial x} D(x) K(x) \frac{\partial}{\partial x} \frac{\rho(x,t)}{K(x)}$. The complete knowledge about

the membrane permeation entails the full time-dependent solution to the diffusion equation subject to appropriate boundary and initial conditions. Unfortunately full, analytical solution is seldom obtained except for some simple, trivial cases. Thus one is usually satisfied with obtaining a few diffusion parameters characteristic of the permeation such as permeation (P), time lag (t_L) for absorptive and time lead (t_+) for desorptive permeation and their higher moments.^{12,13} All these permeation parameters can be obtained directly from the suitably designed experiments. For details, see section 4 below. Theoretically, they can also be formulated via the Taylor expansion of the transmission matrix, $T(s)$, in power series of s with the expansion coefficients expressed in terms of the repeated integrals of $[K(x)D(x)]^{-1}$ and $K(x)$ ¹⁴ or by the method of repeated integration of the diffusion equation.^{9,15} However, these formulations are useful only in the cases where the functions $K(x)$ and $D(x)$ are known beforehand.

Another concern about diffusion transport is the moments of the first passage time^{10,11,16} and residence time.^{17,18} As a rule, neither is obtainable directly from the experiments. Mathematically the former can be obtained by solving the adjoint (or backward) diffusion equation^{10,11} and the latter by the Green's function of the diffusion equation.^{17,18} Again these tasks are feasible only when $K(x)$ and $D(x)$ are known ahead of time.

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In this communication we will contrive a device which makes it possible to estimate the moments of the residence time and first passage time from permeation parameters obtained directly from suitably designed permeation experiments. Using the measurable permeation parameters of component laminae, it is also useful for the estimation of various time moments of a composite laminate. This device is the Taylor expansion of the transmission matrix, $T(s)$, in power series of s with the expansion coefficients expressed in terms of the measurable parameters: permeability, time lag and time lead and their higher moments. With this device, evaluation of most of the diffusion time moment amounts merely to a task of algebraic manipulation. The rest of this article will be organized as follows: Section 2 presents the matrix transport equations for void and saturated equilibrium initial conditions. In conjunction with the theorem $\det[T(s)] = 1$, we are able to correlate the fluxes of various modes with the matrix elements to express the expansion coefficients of $T(s)$ in terms of various permeation time moments. Section 3 illustrates the application of this device to the time moments of the first passage time, residence time, and percutaneous drug delivery. Section 4 suggests a graphical method for the treatment of the experimental data to obtain the time moments for absorptive and desorptive permeation and finally the last section gives a concluding remark.

TAYLOR EXPANSION OF $T(s)$ IN TERMS OF PERMEATION PARAMETERS

We start with the matrix transport equation for void initial concentration within the whole membrane^{14,19-21}

$$\begin{bmatrix} \hat{a}_d(s) \\ \hat{J}_d(s) \end{bmatrix} = T(s) \begin{bmatrix} \hat{a}_u(s) \\ \hat{J}_u(s) \end{bmatrix} = \begin{bmatrix} T_{11}(s) & T_{12}(s) \\ T_{21}(s) & T_{22}(s) \end{bmatrix} \begin{bmatrix} \hat{a}_u(s) \\ \hat{J}_u(s) \end{bmatrix} \quad (1)$$

This equation relates the pair (activity, $\hat{a}_u(s)$, and flux, $\hat{J}_u(s)$) in the Laplace domain at the upstream face to the counterpart, $\hat{a}_d(s)$ and $\hat{J}_d(s)$, at the downstream face. For membrane absorptive permeation, $\hat{a}_u(s) = \frac{a_0}{s}$ and $\hat{a}_d(s) = 0$ are the boundary conditions. The permeation flux at the downstream face is calculated to be

$$\hat{J}_d^{(a)}(s) = -\frac{1}{T_{12}(s)} \frac{a_0}{s} \quad (2)$$

where the superscript (a) is indicative of ‘‘absorptive’’. In terms of $\hat{J}_d^{(a)}(s)$, the diffusion parameters steady-state per-

meability (P), time lag (t_L) and its second and third moments ($t_L^{(2)}, t_L^{(3)}$) for absorptive permeation can be defined as shown in Eqs. (3)–(6). A subsequent use of Eq. (2) leads to

$$P \equiv \frac{J_{d,ss}^{(a)}}{a_0} = \lim_{s \rightarrow 0} \frac{s \hat{J}_d^{(a)}(s)}{a_0} = -\lim_{s \rightarrow 0} \frac{1}{T_{12}(s)} \quad (3)$$

$$t_L \equiv \lim_{s \rightarrow 0} \frac{-\frac{d}{ds} s \hat{J}_d^{(a)}(s)}{J_{d,ss}^{(a)}} = \lim_{s \rightarrow 0} \frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \quad (4)$$

$$\begin{aligned} t_L^{(2)} &\equiv \lim_{s \rightarrow 0} \frac{\frac{d^2}{ds^2} s \hat{J}_d^{(a)}(s)}{J_{d,ss}^{(a)}} = \lim_{s \rightarrow 0} \left\{ 2 \left(\frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \right)^2 - \frac{\frac{d^2}{ds^2} T_{12}(s)}{T_{12}(s)} \right\} \\ &= 2 t_L^2 - \lim_{s \rightarrow 0} \frac{\frac{d^2}{ds^2} T_{12}(s)}{T_{12}(s)} \quad (5) \end{aligned}$$

$$\begin{aligned} t_L^{(3)} &\equiv \lim_{s \rightarrow 0} \frac{-\frac{d^3}{ds^3} s \hat{J}_d^{(a)}(s)}{J_{d,ss}^{(a)}} \\ &= \lim_{s \rightarrow 0} \left\{ 6 \left(\frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \right)^3 + \frac{\frac{d^3}{ds^3} T_{12}(s)}{T_{12}(s)} - 6 \frac{\frac{d^2}{ds^2} T_{12}(s)}{T_{12}(s)} \frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \right\} \\ &= 6 t_L t_L^{(2)} - 6 t_L^3 + \lim_{s \rightarrow 0} \frac{\frac{d^3}{ds^3} T_{12}(s)}{T_{12}(s)} \quad (6) \end{aligned}$$

where $J_{d,ss}^{(a)}$ is the steady-state flux for absorptive permeation. Equations (4)–(6) are equivalent to the statement that $t_L, t_L^{(2)}$ and $t_L^{(3)}$ are the first, second and third time moments based on the distribution $(\frac{d}{dt} J_d^{(a)}(t))/J_{d,ss}^{(a)}$, respectively. On rearranging Eqs. (3)–(6), the Taylor expansion of $T_{12}(s)$ can be represented in terms of the diffusion parameters of the absorptive permeation by

$$\begin{aligned} T_{12}(s) &= -\frac{1}{P} - \frac{t_L}{P} s - \frac{2 t_L^2 - t_L^{(2)}}{2 P} s^2 - \frac{6 t_L^3 - 6 t_L t_L^{(2)} + t_L^{(3)}}{6 P} s^3 - \dots \\ &= -\beta_0 - \beta_1 s - \beta_2 s^2 - \beta_3 s^3 - \dots \quad (7) \end{aligned}$$

where the definition of β_i ($i = 0, 1, 2, 3$) is self-explanatory in Eq. (7).

To find a similar series for $T_{22}(s)$ the forward desorp-

tive permeation mode is employed, which in turn requires the transport equation for initial saturated equilibrium^{14,21}

$$\begin{bmatrix} \hat{a}_d(s) - \frac{a_0}{s} \\ \hat{J}_d(s) \end{bmatrix} = \begin{bmatrix} T_{11}(s) & T_{12}(s) \\ T_{21}(s) & T_{22}(s) \end{bmatrix} \begin{bmatrix} \hat{a}_u(s) - \frac{a_0}{s} \\ \hat{J}_u(s) \end{bmatrix} \quad (8)$$

with $\hat{a}_d(s) = 0$, $\hat{a}_u(s) = \frac{a_0}{s}$, appropriate for this mode of permeation, the permeation flux at downstream face is given by

$$\hat{J}_d^{(d)}(s) = -\frac{T_{22}(s)}{T_{12}(s)} \frac{a_0}{s} \quad (9)$$

where the superscript (d) is indicative of “desorptive”. Again we can define the forward time lead t_+ , and its higher moments in terms of $\hat{J}_d^{(d)}(s)$ and use Eq. (9) to obtain

$$t_+ = \lim_{s \rightarrow 0} \frac{-\frac{d}{ds} s \hat{J}_d^{(d)}(s)}{J_{d,ss}^{(d)}} = \lim_{s \rightarrow 0} \left(\frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} - \frac{\frac{d}{ds} T_{22}(s)}{T_{22}(s)} \right) \quad (10)$$

$$t_+^{(2)} = \lim_{s \rightarrow 0} \frac{\frac{d^2}{ds^2} s \hat{J}_d^{(d)}(s)}{J_{d,ss}^{(d)}}$$

$$= \lim_{s \rightarrow 0} \left\{ \frac{\frac{d^2}{ds^2} T_{22}(s)}{T_{22}(s)} - \frac{\frac{d^2}{ds^2} T_{12}(s)}{T_{12}(s)} - 2 \frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \frac{\frac{d}{ds} T_{22}(s)}{T_{22}(s)} + 2 \left(\frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \right)^2 \right\} \quad (11)$$

$$t_+^{(3)} = \lim_{s \rightarrow 0} \frac{-\frac{d^3}{ds^3} s \hat{J}_d^{(d)}(s)}{J_{d,ss}^{(d)}}$$

$$= \lim_{s \rightarrow 0} \left\{ 3 \frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \frac{\frac{d^2}{ds^2} T_{22}(s)}{T_{22}(s)} - 6 \frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \frac{\frac{d^2}{ds^2} T_{12}(s)}{T_{12}(s)} - 6 \frac{\frac{d}{ds} T_{22}(s)}{T_{22}(s)} \left(\frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \right) \right\}$$

$$+ 3 \frac{\frac{d}{ds} T_{22}(s)}{T_{22}(s)} \frac{\frac{d^2}{ds^2} T_{12}(s)}{T_{12}(s)} - \frac{\frac{d^3}{ds^3} T_{22}(s)}{T_{22}(s)} + \frac{\frac{d^3}{ds^3} T_{12}(s)}{T_{12}(s)} + 6 \left(\frac{\frac{d}{ds} T_{12}(s)}{T_{12}(s)} \right)^3 \quad (12)$$

The subscript, +, in t_+ , $t_+^{(2)}$ and $t_+^{(3)}$ is used to specify the permeation in the forward direction. With the fact that steady-state permeabilities for absorptive and desorptive permeation are identical, and after inserting Eq. (9) into Eqs. (10)–(12), the Taylor expansion of $T_{22}(s)$ can be repre-

sented after rearrangement by

$$T_{22}(s) = 1 + \bar{t}_+ s + \frac{2t_L \bar{t}_+ - \bar{t}_+^{(2)}}{2} s^2 + \frac{\bar{t}_+^{(3)} + 6\bar{t}_+ t_L^2 - 3t_L \bar{t}_+^{(2)} - 3t_L^2 \bar{t}_+}{6} s^3 + \dots$$

$$= \delta_0 + \delta_1 s + \delta_2 s^2 + \delta_3 s^3 + \dots \quad (13)$$

where $\bar{t}_+ = t_L - t_+$, $\bar{t}_+^{(2)} = t_L^{(2)} - t_+^{(2)}$ and $\bar{t}_+^{(3)} = t_L^{(3)} - t_+^{(3)}$, and the definition of δ_i for $i = 0, 1, 2, 3$ is self-explanatory.

To find the Taylor expansion of $T_{11}(s)$, we use the backward desorptive permeation flux, $\hat{J}_u^d(s)$, which is calculated using Eq. (8) with $\hat{a}_d(s) = \frac{a_0}{s}$ and $\hat{a}_u(s) = 0$ to obtain

$$\hat{J}_u^d(s) = \frac{T_{11}(s)}{T_{12}(s)} \frac{a_0}{s} \quad (14)$$

In a fashion similar to that used to obtain $T_{22}(s)$ in Eq. (13), we find

$$T_{11}(s) = 1 + \bar{t}_- s + \frac{2t_L \bar{t}_- - \bar{t}_-^{(2)}}{2} s^2 + \frac{\bar{t}_-^{(3)} + 6\bar{t}_- t_L^2 - 3t_L \bar{t}_-^{(2)} - 3t_L^2 \bar{t}_-}{6} s^3 + \dots$$

$$= \alpha_0 + \alpha_1 s + \alpha_2 s^2 + \alpha_3 s^3 + \dots \quad (15)$$

where $\bar{t}_- = t_L - t_-$, $\bar{t}_-^{(2)} = t_L^{(2)} - t_-^{(2)}$ and $\bar{t}_-^{(3)} = t_L^{(3)} - t_-^{(3)}$, with t_- being the time lead for backward desorptive permeation and $t_-^{(2)}$ and $t_-^{(3)}$ its second and third moments, respectively.

For $n = 0, 1, 2, 3$ the α_i are defined in Eq. (15).

A further application of the theorem²¹

$$\det[T(s)] = T_{11}(s)T_{22}(s) - T_{12}(s)T_{21}(s) = 1 \quad (16)$$

allows us to obtain for $T_{21}(s)$ the Taylor series expansion

$$T_{21}(s) = -P[\bar{t}_+ + \bar{t}_-]s - \frac{P}{2}[2\bar{t}_+ \bar{t}_- - \bar{t}_+^{(2)} - \bar{t}_-^{(2)}]s^2$$

$$- \frac{P}{6}[\bar{t}_+^{(3)} + \bar{t}_-^{(3)} - 3\bar{t}_+ \bar{t}_- - 3\bar{t}_+ \bar{t}_-^{(2)} + 6t_L \bar{t}_+ \bar{t}_-]s^3 + \dots$$

$$= \gamma_1 s + \gamma_2 s^2 + \gamma_3 s^3 + \dots \quad (17)$$

Again, the definition of γ_i ($i = 1, 2, 3$) is self-explanatory.

Results collected from Eqs. (7), (13), (15) and (17) represent the Taylor expansion of $T(s)$ in power series of s with the coefficients expressed in terms of permeation time moments which are measurable from the experiments. They can be looked upon as a supplement to the Taylor expansion of $T_{ij}(s)$ in power series of s with coefficients expressed in terms of repeated integrals of $K(x)$ and $[k(x)D(x)]^{-1}$ as revealed in reference.¹⁴ These representa-

tions are the central result of the article and will be applied to the estimation of the time moments of the following problems.

APPLICATIONS

As the first example, we consider the first passage time for a particle initially located at x_0 between a reflecting face x_u and an absorbing face x_d , $x_u < x_0 < x_d$.^{11,16} Solving this problem requires the matrix transport equation for an initial condition of δ -function type^{14,19}

$$\begin{bmatrix} \hat{a}_d(s) \\ \hat{J}_d(s) \end{bmatrix} = T(s) \begin{bmatrix} \hat{a}_u(s) \\ \hat{J}_u(s) \end{bmatrix} + T^*(s) \begin{bmatrix} 0 \\ 1 \end{bmatrix} \tag{18}$$

where $T^*(s)$ is the transmission matrix for the subdomain from x_0 to x_d . After substitution of $\hat{J}_u(s) = 0$ and $\hat{a}_d(s) = 0$ into Eq. (18), the flux escaping from the face x_d is calculated to be

$$\hat{J}_d(s) = \frac{T_{11}(s)T_{22}^*(s) - T_{21}(s)T_{12}^*(s)}{T_{11}(s)} \tag{19}$$

The mean first passage time can be represented by

$$\mu_1 = \frac{\int_0^\infty t J_d(t) dt}{\int_0^\infty J_d(t) dt} = - \lim_{s \rightarrow 0} \frac{d}{ds} \hat{J}_d(s) \tag{20}$$

where the denominator represents the initial total amount which is equal to unity. Putting Eq. (19) into Eq. (20) followed by expanding the transition matrix elements in terms of Eqs. (7), (13), (15) and (17), we obtain

$$\mu_1 = [\bar{t}_+ + \bar{t}_-] \frac{P}{P^*} - \bar{t}_+^* \tag{21}$$

Here the quantity associated with the superscript * denotes the fact that this quantity is to be specified to the sub-domain, $x_0 < x < x_d$. The second moment of first passage time is also easily calculated by

$$\begin{aligned} \mu_2 &= \frac{\int_0^\infty t^2 J_d(t) dt}{\int_0^\infty J_d(t) dt} = \lim_{s \rightarrow 0} \frac{d^2}{ds^2} \hat{J}_d(s) \\ &= 2 t_L^* \bar{t}_+^* - \bar{t}_+^{(2)*} + \frac{P}{P^*} [\bar{t}_+^{(2)} + \bar{t}_-^{(2)} + 2 \bar{t}_-^2 - 2 t_L^* (\bar{t}_+ + \bar{t}_-)] \end{aligned} \tag{22}$$

where $\bar{t}_+^* = t_L^* - t_+^*$ and $\bar{t}_+^{(2)*} = t_L^{(2)*} - t_+^{(2)*}$. Thus with each quantity on the right-hand sides of Eqs. (21) and (22) being experimentally accessible, μ_1 and μ_2 can be estimated.

The second example goes to the estimation of the moments of the residence time for the first example.^{17,18} These residence time moments are not measurable directly from experiments. The residence time is related to the Green's function $\hat{G}(x, s | x_0)$ associated with the diffusion equation.^{14,18} Such a Green's function can be constructed by the following strategy. The diffusion domain is partitioned into three sub-domains labeled by A, B, C. A is from x_u to x , B from x to x_0 and C from x_0 to x_d . The matrix transport equation between the x_u and x_d , where the initial location x_0 is confined, reads¹⁹

$$\begin{bmatrix} \hat{a}_d(s) \\ \hat{J}_d(s) \end{bmatrix} = T^{(ABC)}(s) \begin{bmatrix} \hat{a}_u(s) \\ \hat{J}_u(s) \end{bmatrix} + T^{(C)}(s) \begin{bmatrix} 0 \\ 1 \end{bmatrix} \tag{23}$$

The transport equation for the sub-domain between x_u and x , where the particle is not initially located, reads

$$\begin{bmatrix} \hat{a}_x(s) \\ \hat{J}_x(s) \end{bmatrix} = T^{(A)}(s) \begin{bmatrix} \hat{a}_u(s) \\ \hat{J}_u(s) \end{bmatrix} \tag{24}$$

The superscript capitals A, B, C signify the regions with which the transmission matrices associate and the subscript x denotes "at the interface x". Substituting the boundary conditions $\hat{a}_d(s) = 0$ and $\hat{J}_u(s) = 0$, $\hat{a}_x(s)$ is found from Eqs. (23) and (24) to be

$$\hat{a}_x(s) = \hat{a}(x, s) = - \frac{T_{12}^{(C)}(s)T_{11}^{(A)}(s)}{T_{11}^{(ABC)}(s)} \tag{25}$$

Upon using Eqs. (7) and (15), we obtain

$$\begin{aligned} \hat{a}_x(s) = \hat{a}(x, s) &= \frac{1}{P^{(C)}} + \frac{t_L^{(C)} + \bar{t}_-^{(A)} - \bar{t}_-^{(ABC)}}{P^{(C)}} s + \left\{ \beta_2^{(C)} + \beta_0^{(C)} \alpha_1^{(ABC)} (\alpha_1^{(ABC)} - \alpha_1^{(A)}) \right. \\ &\quad \left. - \beta_0^{(C)} (\alpha_2^{(ABC)} - \alpha_2^{(A)}) - \beta_1^{(C)} (\alpha_1^{(ABC)} - \alpha_1^{(A)}) \right\} s^2 + \dots \end{aligned} \tag{26}$$

But it should be noted that it is the concentration Green's function which gives residence time not the activity. With the relation^{14,19,20} $\hat{a}(x, s) = \frac{\hat{p}(x, s)}{K(x)}$ we find the mean residence time at x for infinitely long observation time to be

$$\tau(x) = K(x) \frac{\bar{t}_-^{(ABC)} - t_L^{(C)} - \bar{t}_-^{(A)}}{P^{(C)}} \tag{27}$$

and its second moment to be

$$\tau^{(2)}(x) = 2K(x)[\beta_2^{(C)} + \beta_0^{(C)}\alpha_1^{(ABC)}(\alpha_1^{(ABC)} - \alpha_1^{(A)}) - \beta_0^{(C)}(\alpha_2^{(ABC)} - \alpha_2^{(A)}) - \beta_1^{(C)}(\alpha_1^{(ABC)} - \alpha_1^{(A)})] \quad (28)$$

The value of $K(x)$ may be obtained from the experimentally measurable permeability $\frac{D(x)K(x)}{\Delta x}$ and time lag $\frac{(\Delta x)^2}{6D(x)}$ for a slice of material between x and $x + \Delta x$, with Δx thin enough to be considered homogeneous. In the case of $x > x_0$, a similar calculation yields

$$\tau(x) = K(x) \left\{ \frac{\bar{t}_-^{(A'B'C')} - t_L^{(B'C')} - \bar{t}_-^{(A'B')}}{P^{(B'C')}} + \frac{t_L^{(B')}}{P^{(B')}} \right\} \quad (29)$$

$$\tau^{(2)}(x) = 2K(x)[\beta_2^{(B'C')} - \beta_2^{(B)} + \beta_0^{(B'C')} \alpha_1^{(A'B'C')} (\alpha_1^{(A'B'C')} - \alpha_1^{(A'B')}) - 2K(x)[\beta_0^{(B'C')} (\alpha_2^{(A'B'C')} - \alpha_2^{(A'B')}) + \beta_1^{(B'C')} (\alpha_1^{(A'B'C')} - \alpha_1^{(A'B')})] \quad (30)$$

where the sub-domain A' is from x_u to x_0 , B' from x_0 to x , C' from x to x_d . Thus we have demonstrated that experimentally inaccessible residence time moments can be estimated from the experimentally measurable quantities.

As a third example, consider a membrane initially in a state of saturated equilibrium at a constant activity, a_0 , that undergoes desorption leakage from either ends. The traditional desorption experiment measures the total release from both sides, hence, is unable to give the release time moments for a particular side. This difficulty, however, can be overcome by our method. The Laplace transform of the escaping flux at the downstream face is found to be

$$\hat{J}_d(s) = \frac{1 - T_{22}(s)}{T_{12}(s)} \frac{a_0}{s} \quad (31)$$

by substituting $\hat{a}_u(s) = \hat{a}_d(s) = 0$ into Eq. (8) as required for desorption experiment. If Eqs. (7) and (13) are used, $\hat{J}_d(s)$ can be expanded as a power series in s to be

$$\hat{J}_d(s) = \left[\frac{\delta_1}{\beta_0} + \frac{\beta_0 \delta_2 - \beta_1 \delta_1}{\beta_0^2} s + \frac{\beta_0^2 \delta_3 - \beta_0 \beta_2 \delta_1 - \beta_0 \beta_1 \delta_2 + \beta_1^2 \delta_1}{\beta_0^3} s^2 + \dots \right] a_0 \quad (32)$$

It immediately follows upon using Eqs. (7) and (17) that the first time moment, t_d , for release from the downstream face is

$$t_d = \lim_{s \rightarrow 0} \frac{-\frac{d}{ds} \hat{J}_d(s)}{\hat{J}_d(s)} = \frac{\beta_1}{\beta_0} - \frac{\delta_2}{\delta_1} = \frac{\bar{t}_+^{(2)}}{2\bar{t}_+} \quad (33)$$

upon using Eqs. (7) and (17). The second moment $t_d^{(2)}$ for release from the downstream face is found to be

$$t_d^{(2)} = \lim_{s \rightarrow 0} \frac{\frac{d^2}{ds^2} \hat{J}_d(s)}{\hat{J}_d(s)} = 2 \left[\frac{\delta_3}{\delta_1} - \frac{\beta_2}{\beta_0} - \frac{\delta_2}{\delta_1} \frac{\beta_1}{\beta_0} + \frac{\beta_1^2}{\beta_0^2} \right] = \frac{\bar{t}_+^{(3)}}{3\bar{t}_+} \quad (34)$$

Similar calculation on the first (t_u) and second ($t_u^{(2)}$) moments of the release time from the upstream face gives

$$t_u = \frac{\bar{t}_-^{(2)}}{2\bar{t}_-} \quad (35)$$

$$t_u^{(2)} = \frac{\bar{t}_-^{(3)}}{3\bar{t}_-} \quad (36)$$

Again, the time moments for escaping from a particular boundary, which is experimentally inaccessible, can be estimated from the experimentally accessible permeation parameters.

As the last example, we consider a percutaneous drug delivery from a patch matrix attached to the skin. The matrix is homogeneously saturated with the drug. During administration, the drug molecules diffuse through the matrix and skin (specifically, stratum cornea) into the tissue. The configuration of the permeation system is sketched in Fig. 1, indicating that the upstream face is reflecting, i.e., impermeable, and the downstream face is absorbing. The matrix transport equations for this drug delivery system are as adapted from Eqs. (1) and (8).

$$\begin{bmatrix} \hat{a}_{x_0}(s) - \frac{a_0}{s} \\ \hat{J}_{x_0}(s) \end{bmatrix} = T(s) \begin{bmatrix} \hat{a}_u(s) - \frac{a_0}{s} \\ \hat{J}_u(s) \end{bmatrix} \quad (37)$$

$$\begin{bmatrix} \hat{a}_d(s) \\ \hat{J}_d(s) \end{bmatrix} = T^*(s) \begin{bmatrix} \hat{a}_{x_0}(s) \\ \hat{J}_{x_0}(s) \end{bmatrix} \quad (38)$$

The quantity with the subscript u (0, d) is that at the face x_u

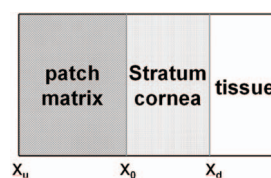


Fig. 1. Lay out of the percutaneous drug delivery, x_u , is an impermeable boundary, x_0 is the interface between the matrix and stratum cornea, x_d is the interface between stratum cornea and tissue, and is assumed to be absorbing.

(x_0, x_d). The superscript * is used to specify the quantity in the stratum cornea. The quantity without * as its superscript is the one which be specified in the patch matrix. Solve $\hat{J}_d(s)$ from Eqs. (37) and (38) after substituting $\hat{a}_d(s) = 0$, $\hat{J}_u(s)$, results in

$$\hat{J}_d(s) = \frac{-T_{12}(s)}{T_{21}(s)T_{12}^*(s) + T_{11}(s)T_{11}^*(s)} \frac{a_0}{s} \quad (39)$$

The Taylor expansion of $\hat{J}_d(s)$ in power series of s can be obtained upon using Eqs. (7), (13), (15) and (21) and is found to be

$$\hat{J}_d(s) = (P + Qs + Rs^2 + \dots) a_0 \quad (40)$$

with

$$P = \gamma_1 \quad (41)$$

$$Q = \gamma_2 - \gamma_1(\alpha_1 + \alpha_1^* + \beta_0^* \gamma_1) \quad (42)$$

$$R = \gamma_3 - \gamma_1(\alpha_2 + \alpha_1 \alpha_1^* + \alpha_2^* + \beta_0^* \gamma_2 + \beta_1^* \gamma_1) - \gamma_2(\alpha_1 + \alpha_1^* + \beta_0^* \gamma_1) + \gamma_1(\alpha_1 + \alpha_1^* + \beta_0^* \gamma_1)^2 \quad (43)$$

The first moment for the drug delivery is then

$$\begin{aligned} \langle t \rangle &= \lim_{s \rightarrow 0} \frac{-\frac{d}{ds} \hat{J}_d(s)}{\hat{J}_d(s)} = \alpha_1 + \alpha_1^* + \gamma_1 \beta_0^* - \frac{\gamma_2}{\gamma_1} \\ &= \bar{t}_-^* + \bar{t}_- + \frac{P}{P^*} (\bar{t}_+ + \bar{t}_-) - \frac{2\bar{t}_+ \bar{t}_- - \bar{t}_+^{(2)} - \bar{t}_-^{(2)}}{2(\bar{t}_+ + \bar{t}_-)} \quad (44) \end{aligned}$$

and the second moment is

$$\begin{aligned} \langle t^{(2)} \rangle &= \lim_{s \rightarrow 0} \frac{\frac{d^2}{ds^2} \hat{J}_d(s)}{\hat{J}_d(s)} \\ &= 2 \left[\frac{\gamma_3}{\gamma_1} - \alpha_2 - \alpha_1 \alpha_1^* - \alpha_2^* - \beta_0^* \gamma_2 - \beta_1^* \gamma_1 + (\alpha_1 + \alpha_1^* + \beta_0^* \gamma_1 - \frac{\gamma_2}{\gamma_1})(\alpha_1 + \alpha_1^* + \beta_0^* \gamma_1) \right] \quad (45) \end{aligned}$$

where the Greek letters can be found specified in Eqs. (7), (13), (15) and (17).

DATA TREATMENT

The feasibility of this new methodology gears to the permeation parameters: permeability, time lag for absorptive permeation and time leads for forward and backward

descriptive permeations and their higher moments. The permeability, time lag and time lead are usually obtained from the slope and the intercept with the time axis of the linear asymptote for a plot of total release, $Q(t) = \int_0^t J(\tau) d\tau$,

against time, t (see Fig. 2).²² This graphic method can be also extended to the determination of higher moments. From the definition of the n -th moment of the time lag in the Laplace domain, Eqs (4)–(6), which can be transformed into the time domain. After integration by parts, we have

$$t_L^{(n)} = \lim_{t \rightarrow \infty} \frac{\int_0^t \tau^n \frac{dJ_d(\tau)}{d\tau} d\tau}{J_{d,ss}} = \lim_{t \rightarrow \infty} \left[t^n - \frac{n}{J_{d,ss}} \int_0^t \tau^{n-1} J_d(\tau) d\tau \right] \quad (46)$$

After arrangement, Eq. (46) becomes

$$\lim_{t \rightarrow \infty} \int_0^t \tau^{n-1} J_d(\tau) d\tau = \frac{J_{d,ss}}{n} (t^n - t_L^{(n)}) \quad (47)$$

Thus a plot of $y = \int_0^t \tau^{n-1} J_d(\tau) d\tau$ against $x = t^n$ will exhibit a linear asymptote with a slope $\frac{J_{d,ss}}{n}$ and an intercept (with

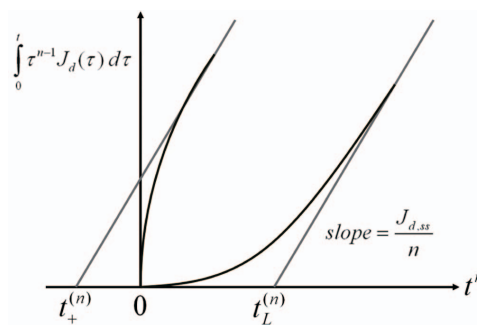


Fig. 2. Plot of $\int_0^t \tau^{n-1} J_d(\tau) d\tau$ against t^n to obtain the n -th

moment of the time lag for absorptive permeation from the intercept on t^n axis by the right-hand side linear asymptote, and the n -th moment of the time lead for forward desorptive permeation from the intercept on t^n axis by the left-hand side linear asymptote. The two linear asymptotes has the same slope $\frac{J_{d,ss}}{n}$. The plot

for the n -th moment of the time lead of the backward desorptive permeation is not shown but is similar to that for forward desorptive permeation.

the x-axis) $t_L^{(n)}$ (see Fig. 2). Proceeding as in the derivation of Eq. (47), an equation for the time lead can be found

$$\lim_{t \rightarrow \infty} \int_0^t \tau^{n-1} J_u(\tau) d\tau = \frac{J_{d,ss}}{n} (t^n - t_+^{(n)}) \quad (48)$$

Again, a plot of $y = \int_0^t \tau^{n-1} J_d(\tau) d\tau$ against $x = t^n$ give a linear asymptote whose slope is $\frac{J_{d,ss}}{n}$ and intercept with the x-axis is $t_+^{(n)}$.

The arguments for the foregoing data treatment are based on a model that diffusivities and partition coefficients depend on position only. Thus the cases of position-dependent and/or concentration-dependent diffusivities and partition coefficients are excluded in this data treatment. Moreover, as to be consistent with the prescribed absorbing boundary condition, it is also required that an infinite volume of the downstream receiver, which is impractical experimentally. The measurements of permeation time lag, time leads and their higher moments, as a rule, are subject to systematic error²³ and random error.²⁴ The former is due to the finite volume of the downstream receiver and incomplete attainment of the steady state. Therefore, care must be exercised to balance between the maximum precision in the measurements and minimum derivation of the experimental line from the linear asymptote.²⁵ The influence of systematic and random errors on, and the optimized design of the experiments toward the accuracy of the measurements of diffusivity, partition coefficient, time lag and time leads had been discussed in detail by Petropoulos and Myrat.^{25,26}

CONCLUSION

As indicated in Eqs. (7), (13), (15) and (17), the Taylor expansion of the transmission matrix, $T(s)$, has been contrived in the form of a power series in s , with expansion coefficients as the functions of the experimentally measurable diffusion parameters permeability, time lag, time lead and their higher moments. This is accomplished by combining the matrix transport equation for the void initial concentration (Eq. (1)) with that for the initial condition of saturated equilibrium (Eq. (8)) and the definitions of the above mentioned parameters. The results are expressed by Taylor expansions for $T_{12}(s)$, $T_{22}(s)$ and $T_{11}(s)$ (Eqs. (7), (13) and (15)). A further use of $\det[T(s)] = 1$ gives the corresponding expansion for $T_{21}(s)$ (Eq. (17)). With such a

Taylor expansion of transmission matrix as a tool and in co-operation with appropriate matrix transport equations, the problems of time moments for first passage time, residence time and the percutaneous drug delivery can be solved algebraically. As a result, various time moments can be expressed by the algebraic function of the above-mentioned measurable parameters. Thus, some experimentally inaccessible time moments can be estimated from permeation parameters measurable in appropriate permeation experiments. This methodology for the estimation of the time moments would provide a useful vehicle for the treatment of the membrane permeation and other problems in diffusive transports.

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