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COMMUNICATIONS

Drug Release from Spherical Particles Under Nonsink Conditions. I. Theoretical Evaluation

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ABSTRACT

Mathematical models have been developed to describe the release rate of drugs from spherical particles under nonsink conditions. Full and approximate analytical solutions have been derived for cases of solid-phase resistance only, for an additional interfacial resistance, and for membrane resistance only. These solutions provide a simple means for the determination of release characteristics of drugs from different types of formulations. It is shown that the perfect sink model is a special case of these nonsink models.

INTRODUCTION

The perfect sink boundary condition (1), in which the external concentration is almost constant at zero or some other value, has been frequently used as a basis for the design of certain drug delivery systems. In some instances, the designed system is either experimentally forced to follow this condition or is erroneously described by the above model. The perfect sink model becomes critical when very large dilutions are needed to prevent the sink from being saturated with the drug, or when there is a substantial decrease in the solution concentration or volume due to sampling (2). Practically, it is more useful and easier to follow the rate of release from the rate of change of concentration in a nonsink system (a constant and finite volume fluid).

THEORY

Release into a Fluid of Uniform Concentration

Consider a sphere of radius r_0 and volume V_s, invariant with time. Initially the solute is at a concentration C_0 uniformly distributed throughout the sphere, and subsequently diffuses out into a well-strirred solution of zero initial concentration and volume V_1. The concentration of the drug in the sphere is C, uniform at all times.

A mass balance on a spherical shell gives:

$$\frac{\partial C}{\partial t} = D\left[\frac{\partial^2 C}{\partial r^2} + \frac{2}{r}\frac{\partial C}{\partial r}\right] \tag{1}$$

subject to the following boundary conditions:

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$$\frac{\partial C}{\partial r} = 0, \quad r = 0, \quad t > 0 \tag{2}$$

$$C = C_0, \quad r < r_o, \quad t = 0 \tag{3}$$

$$\frac{V_1}{K}\frac{\partial C}{\partial t} = -4\pi r_0^2 D\left(\frac{\partial C}{\partial r}\right)_{r=r_0}, \quad r = r_0, t > 0 \tag{4}$$

$$C = 0, \quad r = r_0, \quad t = 0 \tag{5}$$

where D is the diffusion coefficient of the drug, independent of concentration; K is the distribution coefficient; t is the time; and r is the radial distance from the center of the sphere.

It is convenient to write the above equations in terms of the following dimensionless variables:

$$\theta = (C - C_\infty)/(C_0 - C_\infty) \tag{6}$$

$$R = r/r_0 \tag{7}$$

$$\tau = Dt/r_0^2 \tag{8}$$

where C_∞ is the concentration in the sphere at infinite time. The system of Eqs. (1) to (5) in terms of these variables becomes:

$$\frac{\partial \theta}{\partial \tau} = \frac{\partial^2 \theta}{\partial R^2} + \frac{2}{R}\frac{\partial \theta}{\partial R} \tag{9}$$

subject to

$$\frac{\partial \theta}{\partial R} = 0, \quad R = 0, \quad \tau > 0 \tag{10}$$

$$\theta = 1, \quad R < 1, \quad \tau = 0 \tag{11}$$

$$\frac{\partial \theta}{\partial \tau} = -3\alpha\frac{\partial \theta}{\partial R}, \quad R = 1, \quad \tau > 0 \tag{12}$$

$$\theta = -\alpha, \quad R = 1, \quad \tau = 0 \tag{13}$$

where

$$\alpha = \frac{V_s K}{V_1} = \frac{C_\infty}{C_0 - C_\infty} \tag{14}$$

Analytical Solutions

The Laplace transform of Eq. (9) is

$$\frac{d^2\bar{\theta}}{dR} + \frac{2}{R}\frac{d\bar{\theta}}{dR} - s\bar{\theta} + 1 = 0 \tag{15}$$

This has the general solution

$$\bar{\theta} = \frac{A}{R}\sinh\sqrt{s}R + \frac{B}{R}\cosh\sqrt{s}R + \frac{1}{s} \tag{16}$$

Eliminating A and B using Eqs. (10) and (12) gives

$$\bar{\theta} = \frac{(1+\alpha)}{R}\frac{\sinh\sqrt{s}R}{(3\alpha - s)\sinh\sqrt{s} - 3\alpha\sqrt{s}\cosh\sqrt{s}} + \frac{1}{s} \tag{17}$$

This equation may be inverted to the time domain by the method of residues (3). This gives:

$$\theta = \frac{-6\alpha(1+\alpha)}{R}\sum_{n=1}^{\infty}\frac{\sin\lambda_n R}{\sin\lambda_n}\frac{\exp(-\lambda_n^2\tau)}{9\alpha(1+\alpha) + \lambda_n^2} \tag{18}$$

where the λ_n are the nonzero positive roots of

$$\tan\lambda_n = \frac{3\alpha\lambda_n}{3\alpha + \lambda_n^2} \tag{19}$$

A mass balance on a spherical particle up to time t gives:

$$\frac{M_t}{M_\infty} = -3\int_0^\tau \frac{\partial\theta}{\partial R}\Big|_{R=1} d\tau \tag{20}$$

where M_t is the mass diffused up to time t and M_∞ is the corresponding amount after infinite time. Using Eqs. (12) and (20), it can be shown that:

$$\frac{M_t}{M_\infty} = 1 + \frac{\theta(1,\tau)}{\alpha} \tag{21}$$

or using Eq. (18)

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty}\frac{6(1+\alpha)}{9\alpha(1+\alpha) + \lambda_n^2}\exp(-\lambda_n^2\tau) \tag{22}$$

Equation (22) is valid at any time for any number of spherical particles and for the external solution as well. The infinite series given by Eq. (22) converges rapidly at long times but slowly for small times. Solutions suitable for these two extremes may be derived from Eq. (17) as follows:

a. Short Time Approximation

For small t (large s) $\sinh\sqrt{s} \approx \cosh\sqrt{s} \approx e^{\sqrt{s}}/2$. As a first approximation, 3α in the first term of the denomi-

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nator of Eq. (17) may be neglected compared to s, and Eq. (17) becomes:

$$\bar{\theta} = -\frac{(1+\alpha)}{R}\frac{e^{-\sqrt{s}(1-R)}}{\sqrt{s}(\sqrt{s}+3\alpha)} + \frac{1}{s} \tag{23}$$

Using tables of Laplace transforms (3):

$$\theta = 1 - \frac{(1+\alpha)}{R} e^{3\alpha(1-R)} e^{(3\alpha\sqrt{\tau})^2} \operatorname{erfc}\left(3\alpha\sqrt{\tau} + \frac{(1-R)}{2\sqrt{\tau}}\right) \tag{24}$$

$$\frac{M_t}{M_\infty} = \frac{(1+\alpha)}{\alpha}[1 - e^{9\alpha^2\tau}\operatorname{erfc}(3\alpha\sqrt{\tau})] \tag{25}$$

where erfc is the complementary error function. The exponential and erfc terms may be expanded for small and large values of α (4,5). Thus for very small α, Eq. (25) gives:

$$\frac{M_t}{M_\infty} = \frac{6(1+\alpha)}{\sqrt{\pi}}\sqrt{\tau} \tag{26}$$

while for large α

$$\frac{M_t}{M_\infty} = \frac{(1+\alpha)}{\alpha}\left[1 - \frac{1}{(3\alpha)\sqrt{\pi}\sqrt{\tau}} + \frac{1}{2(3\alpha)^3\sqrt{\pi}\tau^{3/2}} - \frac{3}{4(3\alpha)^5\sqrt{\pi}\tau^{5/2}} + \cdots\right] \tag{27}$$

A more general approximation may be obtained from Eq. (17) with 3α retained. This gives:

$$\theta = 1 - \frac{(1+\alpha)}{Rc}\left[be^{bh}e^{b^2\tau}\operatorname{erfc}\left(b\sqrt{\tau} + \frac{h}{2\sqrt{\tau}}\right) - de^{dh}e^{d^2\tau}\operatorname{erfc}\left(d\sqrt{\tau} + \frac{h}{2\sqrt{\tau}}\right)\right] \tag{28}$$

from which, for small α

$$\frac{M_t}{M_\infty} = \frac{6(1+\alpha)}{\sqrt{\pi}}\sqrt{\tau} - \alpha\left(\frac{89}{4}\alpha + 24\right)\tau \tag{29}$$

where $b = (3\alpha + c)/2$, $c = \sqrt{9\alpha^2 + 12\alpha}$, $d = (3\alpha - c)/2$, and $h = 1 - R$.

b. Long Time Approximation

As τ increases, Eq. (22) increases rapidly and may be represented by a single exponential term. Thus:

$$\frac{M_t}{M_\infty} = 1 - \frac{6(1+\alpha)}{9\alpha(1+\alpha) + \lambda_1^2}\exp(-\lambda_1^2\tau) \tag{30}$$

Numerical Solution

A large number of terms will be required to accurately represent the full-range solution of Eq. (22). However, as the number of terms increases, the corresponding values of the roots given by Eq. (19) also increase, and the infinite series solution given by Eq. (22) will no longer be adequate. Therefore numerical full-range solutions and approximate analytical solutions appropriate for short and long times have been developed.

The orthogonal collocation method (6) has been applied to many problems involving diffusion with chemical reaction with great success. It has been used here to solve the system of Eqs. (9) to (13). The roots of Eq. (19) have been calculated numerically using the subroutine ZSBOW from the IMSL library. The full-range solution is shown in Fig. 1 as the fraction of mass transfer against the square root of time for different values of α. Comparisons of this solution with the approximate solutions given by Eqs. (26), (29), and (30) are shown in Fig. 2 for $\alpha = 0.1$.

Diffusion Through a Sphere Across a Phase Boundary

In the case of an interfacial resistance, the mass flux evaluated at the fluid–solid interface due to diffusion through the solid is equated to mass transfer coefficient, k_m, and a linear driving force. It is assumed that large changes in the concentration of the fluid side occur only very near the boundary, and that the solution far from the boundary is well mixed.

The differential equation and the boundary conditions describing this situation, in terms of the dimensionless variables described previously, are as follows:

$$\frac{\partial\theta}{\partial\tau} = \frac{\partial^2\theta}{\partial R^2} + \frac{2}{R}\frac{\partial\theta}{\partial R} \tag{31}$$

$$\frac{\partial\theta}{\partial R} = 0, \quad R = 0, \quad \tau > 0 \tag{32}$$

$$\theta = 1, \quad R < 1, \quad \tau = 0 \tag{33}$$

$$\frac{\partial\theta}{\partial R} = -\beta\theta, \quad R = 0, \quad \tau > 0 \tag{34}$$

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where $\beta = k_m r_0/DK$.

The time-domain solution is

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=1}^{\infty} \frac{6\beta^2}{\lambda_n^2[\lambda_n^2 + \beta^2 - \beta]} \exp(-\lambda_n^2 \tau) \tag{35}$$

where the λ_n are the positive roots of:

$$\lambda_n \cot \lambda_n = 1 - \beta$$

a. Short Time Approximation

$$\frac{M_t}{M_\infty} = 3\beta\tau - \frac{4}{\sqrt{\tau}}\beta^2\tau^{3/2} - \frac{3\beta^2}{2}(1-\beta)\tau^2 \tag{36}$$

which is valid for any β. For small β, Eq. (36) becomes:

$$\frac{M_t}{M_\infty} = 3\beta\tau \tag{37}$$

b. Long Time Approximation

$$\frac{M_t}{M_\infty} = 1 - \exp\left[-3\beta\left(1 - \frac{\beta}{5}\tau\right)\right] \tag{38}$$

which is valid for small β.

Diffusion Through a Membrane With Controlling Resistance

The following derivation is suitable for membrane diffusion-controlled devices. It is assumed that the solute diffuses through a very thin membrane from a perfect source into a dilute, constant finite-volume solution, the concentration of which is changing with time and is initially equal to zero.

A mass balance on the external solution (of volume V) gives:

$$\frac{dC}{dt} = -\frac{AD}{Kl}(C_0 - C) \tag{39}$$

where A is the area of the membrane, D its diffusion coefficient, and l is its thickness; C is the concentration of the drug in the external solution, K is the partition coefficient, and C_0 is the concentration of the source. Integrating the above equation and expanding the arising logarithmic term for small C gives:

$$\frac{C}{C_0} = \frac{AD}{VlK}t \tag{40}$$

or

$$M_t = \frac{ADC_0}{Kl}t \tag{41}$$

DISCUSSION

The mathematical models developed can be used to predict release rates from pharmaceutical preparations such as emulsions, liposomes, hydrogels, and microcapsules. Equation (22) predicts the mass transfer rate, over the full range of time, from spherical particles into finite-volume fluids, with resistance being considered in the solid phase only; while the distribution of concentration in the sphere is given by Eq. (18). This is appropriate when the external solution is very well mixed. If an additional resistance exists in the external solution, the release rate may be adequately described by Eq. (35). These equations should be valid for dilute and constant-volume systems. Transport characteristics of controlled-release systems can be predicted using these theoretical profiles, e.g., the diffusion coefficient. If experimental values of M_t/M_∞, fitted to these profiles, are given against t, then τ can be read from the theoretical profile and D calculated from Eq. (8) knowing r_0.

Release profiles from spherical particles into a well-mixed finite-volume system, for different values of α, are shown in Fig. 1. These profiles have been calculated numerically. As the value of α increases, the deviation from the square root law increases. This relation cannot be valid for values of $M_t/M_\infty > 0.35$ at most. When the value of α approaches zero, the predicted profile coincides with that representing the perfect sink model. Thus the perfect sink model is only a special case of the more general uniform nonsink model. This can also be shown mathematically by noting that as $\alpha \to 0$, Eq. (19) predicts that $\lambda_n = n\pi$, and when this is substituted in Eq. (22), the perfect sink equation results. This is also true for the approximate solutions. Thus as $\alpha \to 0$, Eq. (26) reduces to:

$$\frac{M_t}{M_\infty} = \frac{6}{\sqrt{\pi}}\sqrt{\tau}$$

which predicts the release rate at short times, under perfect sink conditions, for any geometry.

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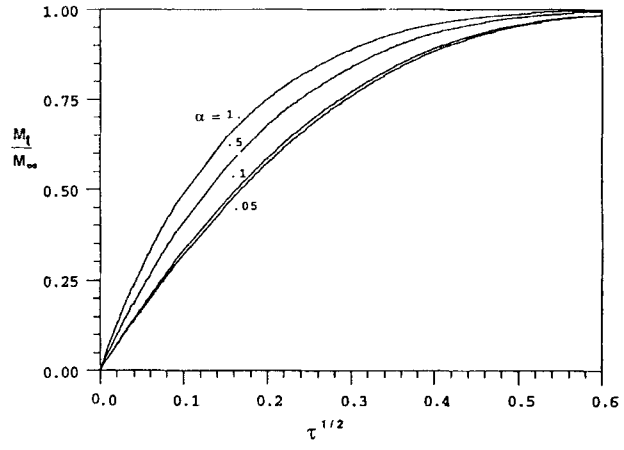

Figure 1. Profiles of release from spherical particles into a uniform nonsink for different values of α.

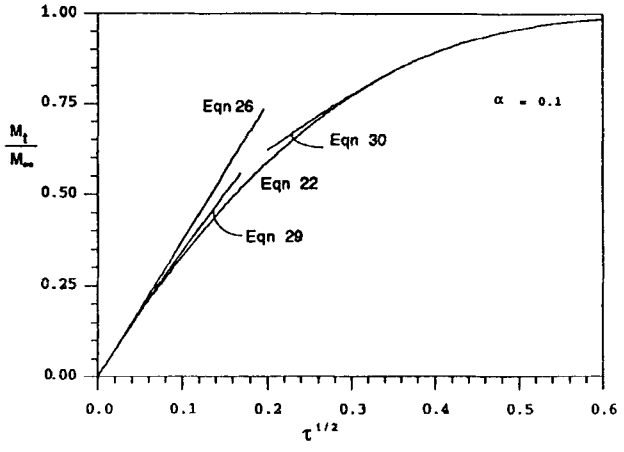

Figure 2. Profiles of release from spherical particles into a uniform nonsink showing full solution [Eq. (22)], short time [Eqs. (26) and (29)], and long time solutions [Eq. (30)] for α = 0.1.

Approximate analytical solutions appropriate for short and long times have been developed. Equation (26) is a special case suitable for small values of α and predicts a square root release rate which is the characteristic of systems without a rate-controlling membrane (7). Equation (37) predicts a zero-order release which might be important for relatively small spherical particles, where slow interfacial transfer is significant. Equation (41) may adequately describe the release rate of systems with rate-controlling membranes. It predicts a zero-order release, and applies for all geometries of the devices, because the flux inside the membrane is independent of the geometrical shape.

REFERENCES

1. R. H. Guy, J. Hadgraft, I. W. Kellaway, and M. J. Taylor, Int. J. Pharm., 11, 199 (1982).
2. C. Washington, Int. J. Pharm., 58, 1 (1990).
3. V. G. Jenson and G. V. Jeffreys, *Mathematical Methods in Chemical Engineering,* Academic Press, London, 1977, p. 138.
4. H. S. Carslaw and J. C. Jeager, *Conduction of Heat in Solids*, Clarendon Press, Oxford, 1959, p. 482.
5. J. Crank, *The Mathematics of Diffusion*, Oxford University Press, 1975, p. 37.
6. J. Villadsen and M. L. Michelsen, *Solution of Differential Equation Models by Polynomal Approximation*, Prentice-Hall, Princeton, NJ, 1978.
7. A. F. Kydonieus, *Controlled Release Technologies: Methods, Theory and Applications*, Vol.1, CRC Press, Boca Raton, FL, 1980, p. 13.

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