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CALCULATIONS OF DRUG RELEASE RATES FROM CYLINDERS

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SUMMARY

Mathematical expressions have been derived to describe the rates of release of drugs from materials of cylindrical geometry. Included in the analysis is the possibility of a slow interfacial transfer step at the boundary of the controlled-release device. The use of micro-cylinders as controlled drug release devices is considered.

INTRODUCTION

The mathematics of diffusion from cylinders is important in the general understanding of implantable controlled-release devices (Baker and Lonsdale, 1974). In this paper we treat the problem in a similar manner to that of the geometry of the slab (Hadgraft, 1979) and show the general way of solving this type of diffusion expression. The theory is then extended to the case where slow interfacial kinetics may be important. We show how such a kinetic step influences release profiles and how it may be used to control overall release rates. We also indicate how some simple physicochemical properties of the device will influence the release profiles.

In order to produce relatively simple solutions we make several assumptions. Firstly that the release is only from the curved surface of the cylinder, i.e. there are no end effects. Secondly, the diffusion coefficients are concentration-independent..

DIFFUSION FROM A SIMPLE CYLINDER

Fick's second law of diffusion must be expressed in terms of cylindrical co-ordinates. The reduced form is given in Eqn. 1 (Carslaw and Jaeger, 1959).

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

where c is the concentration, t the time, r the radius of the cylinder and D the diffusion coefficient.

Solution of the equation is simplified by normalizing the variables as follows:

$$u = c/c_0 \tag{2}$$

$$\rho = r/r_0 \tag{3}$$

$$\tau = Dt/r_0^2 \tag{4}$$

where c_0 is the initial drug concentration in a cylinder of radius r_0. Eqn. 1 may then be rewritten in terms of the normalized variables:

$$\frac{\partial u}{\partial \tau} = \frac{\partial^2 u}{\partial \rho^2} + \frac{1}{\rho}\frac{\partial u}{\partial \rho} \tag{5}$$

This differential equation is solved by Laplace transformation and substitution of the appropriate boundary conditions. These are:

$$\tau = 0\,, \qquad u = 1 \tag{6}$$

$$\rho = 1\,, \qquad u = 0 \tag{7}$$

$$\rho = 0\,, \qquad \left(\frac{\partial u}{\partial \rho}\right)_0 = 0 \tag{8}$$

Condition 6 shows that initially there is a uniform drug concentration in the cylinder and and condition 7 that we are considering release occurring into sink conditions. Eqn. 8 shows that there is no reservoir of drug at the centre of the device. Using these limits, Laplace transformation of Eqn. 5 gives:

$$s\bar{u} - 1 = \frac{\partial^2 \bar{u}}{\partial \rho^2} + \frac{1}{\rho}\frac{\partial \bar{u}}{\partial \rho} \tag{9}$$

The general solution to differential equations of this type are given in terms of modified Bessel functions (I and K).

$$\bar{u} = AI_0(\sqrt{s}\rho) + BK_0(\sqrt{s}\rho) + \frac{1}{s} \tag{10}$$

The coefficients A and B in this equation may be eliminated by use of the boundary conditions discussed above. We can thus obtain the concentration gradient at the edge of the cylinder

$$\left(\frac{\partial \bar{u}}{\partial \rho}\right)_1 = -\frac{I_1(\sqrt{s})}{\sqrt{s}\, I_0(\sqrt{s})} \tag{11}$$

The amount of drug released, M_t, at time t is given by:

$$M_t = -Ac_0 r_0 \int_0^{\tau} \left(\frac{\partial u}{\partial \rho}\right)_1 d\tau \tag{12}$$

$$= Ac_0r_0 \mathcal{L}^{-1} \frac{I_1(\sqrt{s})}{s^{1.5} I_0(\sqrt{s})} \tag{13}$$

There is no simple inversion of this equation and we consider approximations that are valid for small and large values of τ.

Short-time approximation

For $\tau < 1$, $s > 1$ it is possible to approximate the modified Bessel functions (Abramowitz and Stegun, 1970) by an asymptotic expansion.

$$I_\nu(z) \simeq \frac{e^z}{\sqrt{2\pi z}} \left(1 - \frac{(\mu - 1)}{8z} + \ldots\right) \quad \text{where } \mu = 4\nu^2 \tag{14}$$

Thus,

$$M_t = Ac_0r_0 \mathcal{L}^{-1} \frac{1}{s^{1.5}} - \frac{3}{8s^2} \tag{15}$$

$$= Ac_0r_0 \left(\frac{2\tau^{1/2}}{\pi^{1/2}} - \frac{3\tau}{8}\right) \tag{16}$$

$$\frac{M_t}{M_\infty} = \frac{4\tau^{1/2}}{\pi^{1/2}} - \frac{3\tau}{4} \tag{17}$$

which is very similar to the expression given by Crank (1956). At very short times the second term in Eqn. 17 becomes very small and release follows the square-root of time as was found to be the case for the plane sheet (Hadgraft, 1979).

Long-time approximation

The appropriate conditions for long times is to approximate the modified Bessel functions by ascending power series (Abramowitz and Stegun, 1970). Using the appropriate approximations

$$\frac{M_t}{M_\infty} = 2 \mathcal{L}^{-1} \frac{\sqrt{s}}{2s^{1.5}\left(1 + \frac{s}{4}\right)} \tag{18}$$

and

$$\frac{M_t}{M_\infty} = 1 - \exp(-4\tau) \tag{19}$$

As would be expected, an exponential relationship is found which is similar to the release profile predicted by Crank (1956) on p. 66 of his text.

Release from a cylinder with an interfacial kinetic barrier

When a phase boundary exists at the surface of the cylinder it is possible that slow interfacial transfer is the rate-limiting step in the release process. This may be described in terms of a rate constant, k_I, where this defines the transfer of substrate from an

organic to an aqueous environment (Albery et al., 1974).

$$C_{org} \underset{k_{-I}}{\overset{k_I}{\rightleftharpoons}} C_{aq} \qquad K$$

It is more convenient to employ dimensionless variables in the solution of the differential equations and we define κ as follows

$$\kappa = \frac{k_I r_0}{D} \tag{20}$$

We consider the cylinder to be of an organic nature surrounded by an aqueous environment which provides sink conditions. Using the normalized variables, diffusion in the cylinder is given by Eqn. 5 with boundary conditions 6 and 8. Additionally the slow interfacial step gives rise to the condition:

$$\left(\frac{\partial u}{\partial \rho}\right)_1 = -\kappa u_1 \tag{21}$$

This condition is used to eliminate the coefficients A and B in the general solution given by Eqn. 10. As before B = 0 but a new value for A is obtained and

$$\left(\frac{\partial \bar{u}}{\partial \rho}\right)_1 = \frac{-\sqrt{s}\kappa I_1(\sqrt{s})}{s(\sqrt{s} I_1(\sqrt{s}) + \kappa I_0(\sqrt{s}))} \tag{22}$$

Thus

$$M_t = Ac_0 r_0 \mathcal{L}^{-1} \frac{\kappa I_1(\sqrt{s})}{s^{1.5}[s I_1(\sqrt{s}) + \kappa I_0(\sqrt{s})]} \tag{23}$$

This expression may be inverted by making short- and long-time approximations.
Short-time approximation:

for $\tau < 1$, $s > 1$; $I_0(\sqrt{s}) \sim I_1(\sqrt{s})$ and

$$M_t = Ac_0 r_0 \mathcal{L}^{-1} \frac{\kappa}{s^{1.5}(\sqrt{s} + \kappa)} \tag{24}$$

If interfacial transfer is rate-limiting, $\kappa < s$ and Eqn. 24 reduces to:

$$M_t = \mathcal{L}^{-1} \frac{Ac_0 r_0 \kappa}{s^2} \tag{25}$$

$$\frac{M_t}{M_\infty} = 2\kappa\tau \tag{26}$$

and at very early times the device will be releasing drug with zero-order as there will be little concentration depletion effect.

It is possible to invert Eqn. 24 to give an expression for the condition when $\kappa \simeq s$. This is achieved by separating Eqn. 24 by partial fractions and inverting the individual compo-

nents. If this procedure is adopted, a more complex expression is produced:

$$M_t = Ac_0 r_0 \left\{ \frac{2\sqrt{\tau}}{\sqrt{\pi}} + \frac{1}{\kappa}(\exp(\kappa^2\tau)\,\mathrm{erfc}(\kappa\sqrt{\tau}) - 1) \right\} \tag{27}$$

Long-time approximation:
for small s values corresponding to large τ, $I_0(\sqrt{s}) \simeq 1$ and $I_1(\sqrt{s}) \simeq \sqrt{s}/2$ (Abramowitz and Stegun, 1970). Substituting these values into Eqn. 23

$$M_t = Ac_0 r_0 \mathcal{L}^{-1} \frac{\kappa}{s(s + 2\kappa)} \tag{28}$$

Thus

$$\frac{M_t}{M_\infty} = (1 - \exp(-2\kappa\tau)) \tag{29}$$

DISCUSSION

The initial release pattern for the simple cylinder is shown in Fig. 1. Eqn. 17 gives the best representation of the release profile but it is clear that for $\tau < 0.01$ a simple $t^{1/2}$ relationship is adequate. Even up to $\tau \sim 0.05$ the simpler relationship is correct to within 10%. Fig. 2 shows the long-time release curve for a simple cylinder. It is a simple exponential relationship and it is apparent that most of the drug will be released by $\tau = 1$.

When interfacial kinetics are assumed to be at least partially rate-limiting a new set of equations give the release profiles plotted in Figs. 3 and 4. At short times (Fig. 3) a comparison is made for values of $\kappa = 1$ between the simple expression given by Eqn. 26 and

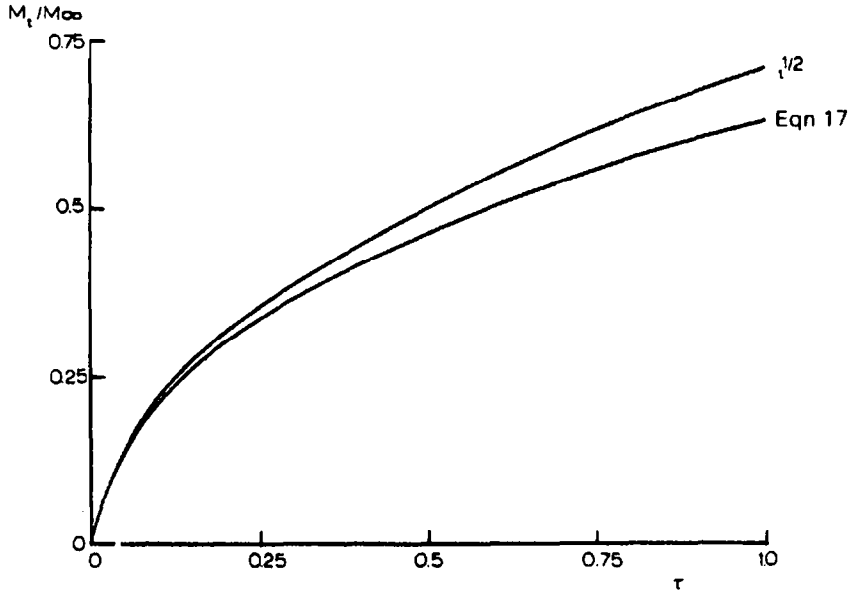

Fig. 1. Short-time release profile for the simple cylinder.

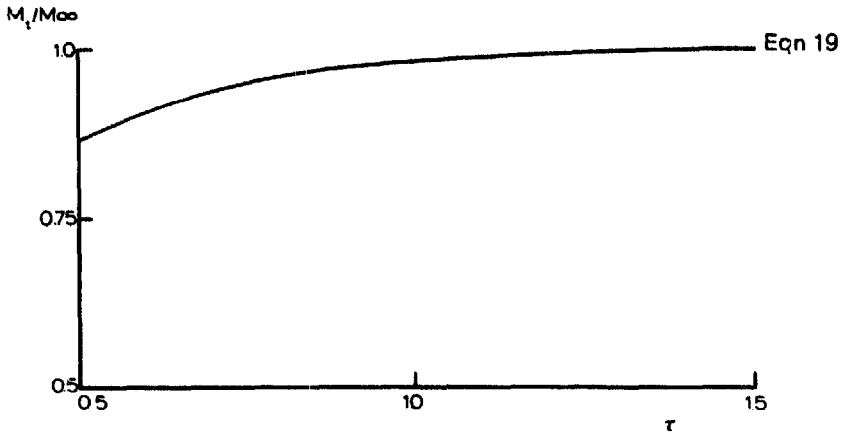

Fig. 2. Long-time release profile for the simple cylinder.

the more complex Eqn. 27. For values of $\tau < 0.05$ the difference between the expressions is less than 10%. Since the more complex expression has slight curvature, the difference increases with τ. For further comparison the curve is shown where $\kappa \to \infty$ and there is no interfacial barrier. Since Eqn. 26 is a linear function in κ and τ, any variation in κ will linearly affect the gradient of the release profile. As can be seen for $\kappa < 1$, the release profile is considerably modified.

Fig. 4 shows the effects of slow interfacial kinetics at long times. For $\kappa = 10$ the interfacial transport is sufficiently fast that it has negligible effect. Slight deviations occur for $\kappa = 1$ and for values of τ around 1. When κ becomes less than unity quite a pro-

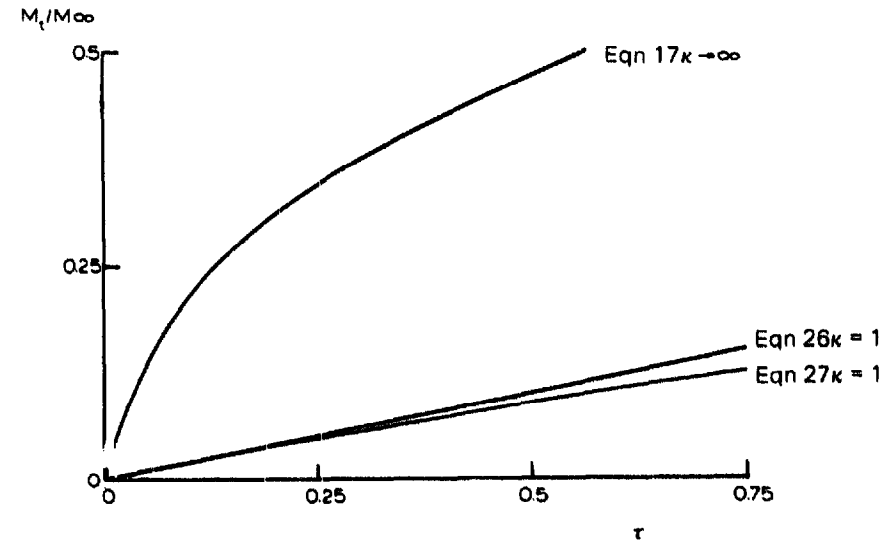

Fig. 3. Short-time release profile from a cylinder with slow interfacial kinetics. A comparison is shown between Eqns. 26 and 27 and the comparable situation when $\kappa \to \infty$.

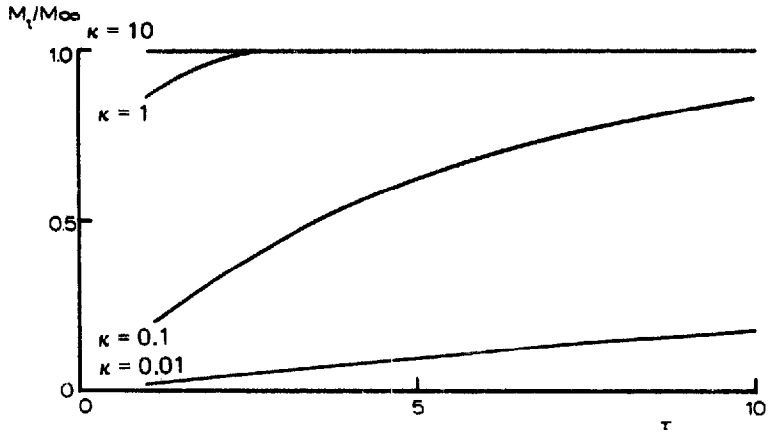

Fig. 4. Long-time release profile from a cylinder with slow interfacial kinetics. The effect of varying κ is shown.

nounced effect is observed and the interfacial barrier dominates the release characteristics.

In the development of polymeric devices which have cylindrical geometry it is possible that slow interfacial kinetics can be usefully employed to modify the overall release characteristics. The barrier should not be neglected and may be utilized to produce controlled drug release which has zero-order release properties.

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