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Calculations of drug release rates from spherical particles

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Summary

Mathematical expressions have been derived to describe the rates of release of drugs from spherical entities. The profiles thus predict probable release characteristics from formulations such as emulsions, microcapsules and liposomes. Multiphase systems have been considered and the effects of slow interfacial transfer are discussed.

Introduction

The mathematics of diffusion from spheres is of importance in a range of pharmaceutical preparations. Formulations such as emulsions, creams, ointments and microcapsules all contain spherical species and the rates at which these preparations release their active ingredient may depend on the release rates from the individual spheres. Recent work (e.g. Ryman and Tyrrell, 1979) has demonstrated the potential of liposomes as drug delivery agents and, due to their spherical geometry, the release patterns will be similar to those of an emulsion. It is thus pertinent to calculate how some simple physicochemical parameters affect overall release profiles from spherical objects.

This paper is a continuation of earlier publications (Hadgraft, 1979; Guy and Hadgraft, 1981) in which diffusion from plane sheets and cylinders was considered. The diffusion equations will be extended to provide solutions to the differential

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equations describing release from spheres and the effect of interfacial transport on the kinetic process. In the first part of the paper simple diffusion equations will be derived for the cases in which no phase boundaries occur and this section will illustrate the mathematics involved in this type of calculation. The complexity of the systems will then be extended to encompass multiphase configurations which have relevance to pharmaceutical formulations.

In order to maintain fairly simple solutions to the differential equations the sphere size will be assumed to be invariant with time and the diffusion coefficients will be considered to be concentration independent.

Theory

(1) Diffusion from a simple sphere (no phase boundaries)

Since we are considering diffusion from spheres it is necessary to express Fick's second law of diffusion in terms of spherical co-ordinates (Carslaw and Jaeger, 1959). The reduced form which is applicable both to heat flow and diffusion is given in Eqn. 1.

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

where c is the drug concentration in the sphere, t is the time and r is the radial distance from the centre of the sphere. D is the integral diffusion coefficient of the substrate.

This differential equation may be simplified by using the substitution.

$$u = rc \tag{2}$$

in which case Eqn. 1 may be rewritten as:

$$\frac{\partial u}{\partial t} = D\frac{\partial^2 u}{\partial r^2} \tag{3}$$

This expression then has the same form as Fick's second law expressed for a linear co-ordinate system. Solution of this differential equation is further simplified by the use of normalized parameters (Hadgraft, 1979). The following normalized parameters are defined:

$$\eta = cr/c_0 r_0 \tag{4}$$

$$\rho = r/r_0 \tag{5}$$

$$\tau = Dt/r_0^2 \tag{6}$$

where c_0 is the initial concentration of the drug in a sphere of radius r_0. Eqn. 3 can then be expressed in terms of the normalized variables

$$\frac{\partial \eta}{\partial \tau} = \frac{\partial^2 \eta}{\partial \rho^2} \tag{7}$$

The solution of this differential equation will depend on the boundary conditions imposed by the experiment. In the case of a simple sphere with no effective interfacial terms and where the concentration at the surface of the sphere is maintained at zero, the following conditions exist:

$$\tau = 0, c = c_0, \eta = \rho \tag{8}$$

$$\rho = 1, \eta = 0 \tag{9}$$

$$\rho = 0, \eta = 0 \tag{10}$$

Solution of the differential equation is then achieved by using Laplace transforms. Transforming Eqn. 7 gives:

$$s\bar{\eta} - \rho = \frac{\partial^2 \bar{\eta}}{\partial \rho^2} \tag{11}$$

where s is the Laplace time variable. This equation has a general solution:

$$\bar{\eta} = A \cosh s^{1/2}\rho + B \sinh s^{1/2}\rho + \rho/s \tag{12}$$

The coefficients A and B may be eliminated by using boundary conditions 9 and 10 to give:

$$\bar{\eta} = \frac{\rho}{s} - \frac{\sinh s^{1/2}\rho}{s \sinh s^{1/2}} \tag{13}$$

The amount of drug which diffuses out of the sphere in time t, M_t, is given by

$$M_t = -DA\int_0^t \left(\frac{\partial c}{\partial r}\right)_{r=r_0} dt \tag{14}$$

which may be expressed in terms of the normalized parameters

$$M_t = -Ac_0 r_0 \int_0^\tau \left(\frac{\partial \eta}{\partial \rho}\right)_1 d\tau \tag{15}$$

where A is the surface area of the sphere. However, $\frac{1}{3}Ac_0r_0$ is the total amount of drug contained within the sphere at time zero and is thus the amount that would be

released after infinite time, M_∞. Hence

$$\frac{M_t}{M_\infty} = 3\int_0^\tau \left(\frac{\partial \eta}{\partial \rho}\right)_1 d\tau \tag{16}$$

The integral in Eqn. 16 may be evaluated by differentiation of Eqn. 13, division by the Laplace time variable, s, and subsequent inversion

$$\frac{M_t}{M_\infty} = 3\mathcal{L}^{-1}\left(\frac{\coth s^{1/2}}{s^{1.5}} - \frac{1}{s^2}\right) \tag{17}$$

Inverting this equation (Spiegel, 1965):

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp(-n^2\pi^2\tau) \tag{18}$$

This is the full solution to the differential equation and shows the way in which drug is released over the complete time range of diffusion.

As described in a previous publication (Hadgraft, 1979) simplifications may be made by using approximations which are valid for the initial and final periods of release, i.e. at short and long times.

(a) Short-time approximation

The hyperbolic terms in Eqn. 17 may be approximated since $\tau < 1$, $s > 1$ and therefore $\coth s^{1/2} \simeq 1$. By inverting the approximate equation,

$$\frac{M_t}{M_\infty} = 3\left[\frac{2\tau^{1/2}}{\pi^{1/2}} - \tau\right] \tag{19}$$

At very short times, $\tau \ll 1$, $\tau^{1/2} > \tau$ and

$$M_t = 6M_\infty \tau^{1/2}\pi^{-1/2} \tag{20}$$

or

$$M_t = 2Ac_0 r\tau^{1/2}\pi^{-1/2} \tag{21}$$

which is the same form of equation as that for a plane sheet. Thus at very short times a sphere will release material as though it did not possess a curved surface.

(b) Long-time approximations.

If the hyperbolic term is approximated as a series expansion (Abramowitz and Stegun, p85) and the first two terms in the expression taken

$$\frac{M_t}{M_\infty} = 3\mathcal{L}^{-1}\frac{1}{3s} \tag{22}$$

Therefore $M_t = M_\infty$ and all the material contained within the sphere is released.

A further approximation is to simplify Eqn. 18; as τ increases the series converges so rapidly that only the first term need be taken. Thus

$$\frac{M_t}{M_\infty} = 1 - \frac{6}{\pi^2} \exp(-\pi^2 \tau) \tag{23}$$

Comparison of full and approximate solutions.

Fig. 1 shows the theoretical release curves obtained from Eqns. 18, 19, 21 and 23. Considering firstly the short-time approximations, the simpler expression, Eqn. 20, is valid for only a very short time period and deviations from the full solution occur at values of $\tau > 10^{-2}$ and when the sphere has released approximately 30% of its contents. The more complete short-time approximation given by Eqn. 19 is accurate for a greater time period. Significant deviations do not occur until $\tau > 0.25$ and over 90% of the material contained within the sphere has been released.

Secondly, the long-time approximation given by Eqn. 23 is shown to be accurate for $\tau > 0.1$. There are thus two expressions which accurately describe the release from a simple sphere over the complete time range. The expressions are Eqns. 19 and 23 and these overlap in the range $0.1 < \tau < 0.25$.

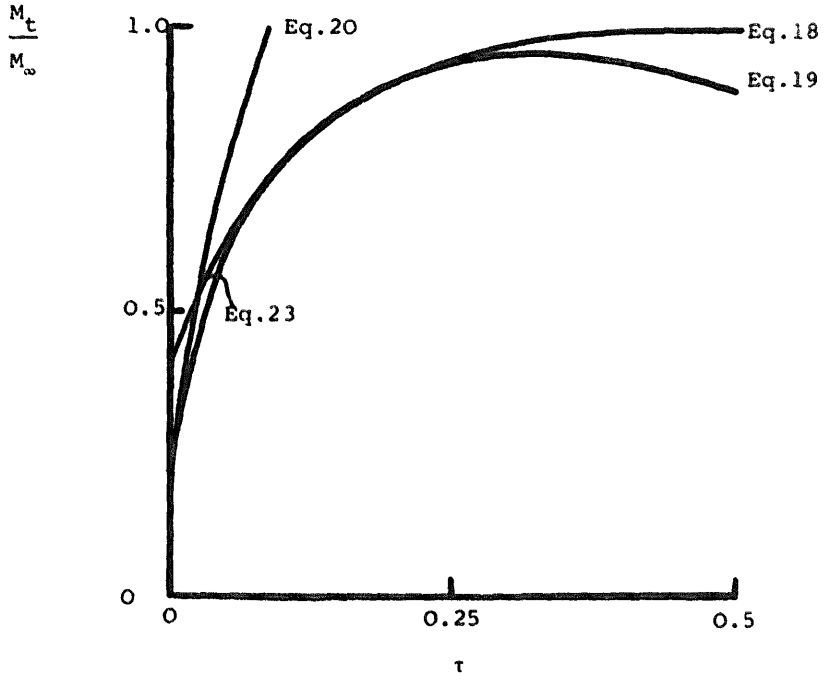

Fig. 1. Release profile for a simple sphere showing the full solution (Eqn. 18) and approximations at short times (Eqns. 19 and 20) and long times (Eqn. 23).

(2) Diffusion from a sphere with a phase boundary

When a phase boundary exists at the surface of the sphere it is possible that slow interfacial transfer is the rate-limiting process for drug release. This may be described in terms of a kinetic rate constant k_1 where this is the process of transfer of substrate from the organic to the aqueous environment (Albery et al., 1974).

$$C_{organic} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_{aqueous} \qquad K$$

As in the previous section, it is more convenient to use dimensionless variables in the solution of the differential equations. The same notation will be used but an additional term is included, κ, which describes the interfacial transfer process:

$$\kappa = k_1 l / D$$

We consider the sphere to be composed of an organic phase which is surrounded by an aqueous environment that will act as a perfect sink. At zero time the drug will be distributed such that there is zero concentration in the aqueous phase.

Using the normalized variables previously described, diffusion in the sphere is given by

$$\frac{\partial \eta}{\partial \tau} = \frac{\partial^2 \eta}{\partial \rho^2} \tag{24}$$

and the following boundary conditions must be fulfilled.

$$\rho = 0, \eta = 0 \tag{25}$$

At the interface, $\rho = 1$

$$\left(\frac{\partial u}{\partial \rho}\right)_1 = -\kappa u_1 \tag{26}$$

but

$$\frac{\partial u}{\partial \rho} = \frac{1}{\rho}\left(\frac{\partial \eta}{\partial \rho}\right) - \frac{u}{\rho} \tag{27}$$

The Laplace transform of Eqn. 24 gives

$$s\bar{\eta} - \rho = \frac{\partial^2 \bar{\eta}}{\partial \rho^2} \tag{28}$$

which has the general solution

$$\bar{\eta} = A \cosh s^{1/2}\rho + B \sinh s^{1/2}\rho + \rho/s \tag{29}$$

Using the boundary conditions 25 and 26 the coefficients A and B are eliminated to give

$$\left(\frac{\partial \bar{\eta}}{\partial \rho}\right)_1 = \frac{\tanh s^{1/2} - s^{1/2}}{s \tanh s^{1/2}\left(1 + \dfrac{s^{1/2}}{\kappa \tanh s^{1/2}} - \dfrac{1}{\kappa}\right)} \tag{30}$$

There is no simple inversion of this transform to substitute into Eqn. 15 and approximations have to be considered.

(i) Fast interfacial kinetics

If there is fast transport at the interface $\kappa > 1$ and the two terms involving κ disappear. Thus

$$M_t = Ac_0 r\mathcal{L}^{-1}\frac{s^{1/2} - \tanh s^{1/2}}{s^2 \tanh s^{1/2}} \tag{31}$$

$$= Ac_0 r\mathcal{L}^{-1}\frac{1}{s^{1.5}\tanh s^{1/2}} - \frac{1}{s^2} \tag{32}$$

which is identical to Eqn. 17.

(ii) Slow interfacial kinetics

In this class we must consider both long- and short-time approximations.

(a) Short time. At short periods of time we require solutions for $s > 1$ and $\kappa < 1$. The hyperbolic terms in Eqn. 30 may be simplified by appropriate approximations and

$$M_t = Ac_0 r\mathcal{L}^{-1}\frac{\kappa}{s^2} \tag{33}$$

$$M_t = Ac_0 r\kappa\tau \tag{34}$$

Release over short periods of time will be effectively zero-order since the concentration c_0 will not be depleted significantly.

(b) Long times. For the long-time approximation $\tau > 1$, $s < 1$ and after simplification of the hyperbolic terms Eqn. 30 reduces to

$$M_t = Ac_0 r\mathcal{L}^{-1}\frac{\kappa}{s(s + 3\kappa)} \tag{35}$$

and

$$M_t = \tfrac{1}{3}Ac_0 r(1 - e^{-3\kappa\tau}) \tag{36}$$

Discussion

Eqn. 32 where $\kappa \to \infty$, gives a solution which is identical to the situation in which we have considered there to be no interfacial kinetic processes (Eqn. 17). This shows that the equations derived for the two-phase case have the correct form. More complex multiphase configurations may also be derived using the normalization procedures outlined above and the appropriate boundary conditions as explained in a previous publication (Hadgraft, 1979).

The approximation derived for the case where interfacial transfer becomes rate-limiting are given in Eqns. 34 and 36. Eqn. 34 expresses the short-time approximation and shows that the amount of drug released is proportional both to the bulk concentration (the thermodynamic driving force) and to the interfacial rate constant. This finding is identical to release from devices of other geometries (Hadgraft, 1979; Guy and Hadgraft, 1981). It may be contrasted with the case where no interfacial kinetics are present and release is proportional to the square-root of time.

At long periods of time, $\tau > 1$, the release pattern is exponential (Eqn. 36) and the variation with κ is given in Fig. 2. The effect of slow interfacial transfer becomes particularly significant for $\kappa < 1$. For values of $\kappa > 1$ the contribution from any interfacial kinetics may be ignored but for κ values less than unity it is important to consider their general effect on release characteristics.

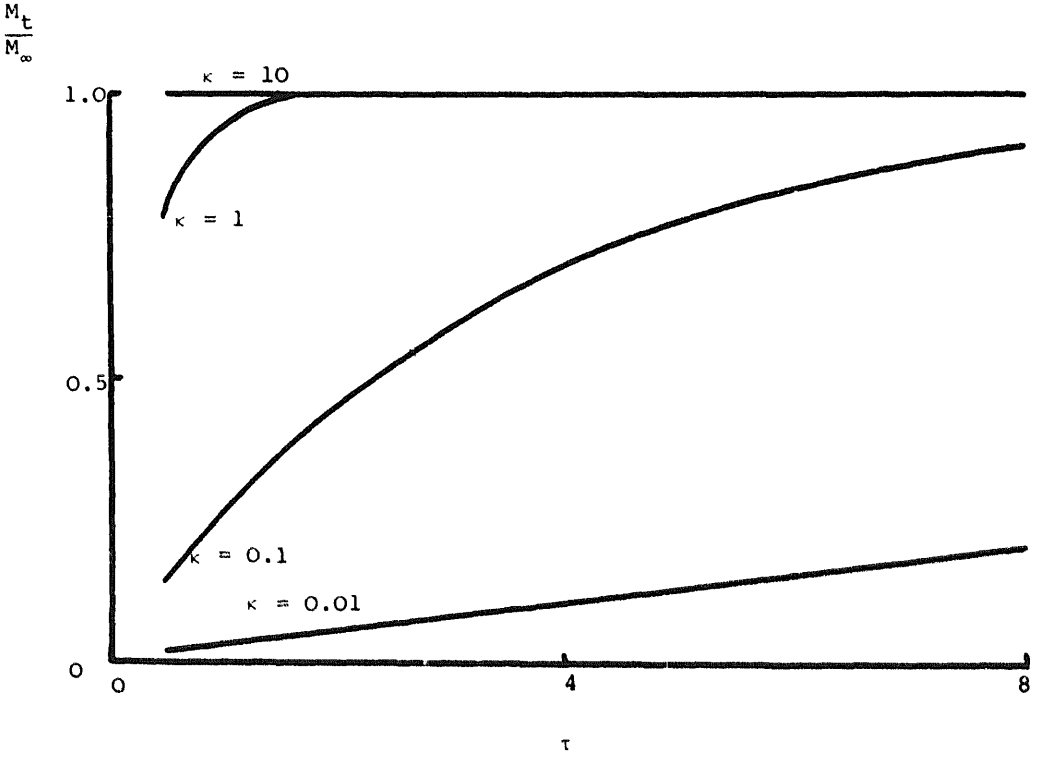

Fig. 2. Long-time release profile for a sphere showing the effect of an interfacial kinetic barrier (Eqn. 36).

Interfacial rate constants have been measured (Albery et al., 1976) and have a magnitude $\sim 10^{-6}$ ms^{-1}. Diffusion coefficients in an organic phase will be $\sim 10^{-9}$ m^2s^{-1}. Under these circumstances interfacial transfer kinetics will become at least partially rate-limiting for spheres having a radius of less than 1 mm. Most emulsions and pharmaceutically important systems will have lipid spheres very much smaller than this and slow interfacial transfer will become the dominant step.

In emulsion formulation and other instances where small spherical species are present it is pertinent to take into account effects caused by interfacial transfer kinetics. It may be possible to modify these or utilize their existence to produce systems in which the release of drugs is well controlled by this kinetic process.

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