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A SIMPLE EQUATION FOR DESCRIPTION OF SOLUTE RELEASE II. FICKIAN AND ANOMALOUS RELEASE FROM SWELLABLE DEVICES

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The previously (Ritger and Peppas, 1987) introduced exponential relation $M_t/M_\infty = kt^n$ *may be used to describe the Fickian and non-Fickian release behavior of swelling-controlled release systems which swell to a moderate equilibrium degree of swelling and are prepared by incorporation of a drug in a hydrophilic, initially glassy polymer. Again the diffusional exponent,* n, *is an important indicator of the mechanism of transport of a drug through the polymer. Analysis is presented for solute release from sheets, cylinders, spheres and polydisperse samples.*

INTRODUCTION

In the previous publicaton of this series [1] we presented an empirical equation which can be used to analyze data of Fickian and non-Fickian diffusional release from non-swellable polymeric delivery systems and to avoid the sometimes cumbersome exact analysis of the data:

$$\frac{M_t}{M_\infty} = kt^n \tag{1}$$

In swelling-controlled (and in general swellable) controlled release systems the dissolution medium (penetrant) surrounding the controlled release device may enter the polymer at a rate that controls the drug release. As has been discussed previously, under certain experimental conditions zero-order release can be achieved [2]. The prevailing molecular mechanism is a coupling of diffusion and macromolecular relaxation as a result of which the drug diffuses outward with a kinetic behavior that is dependent on the relative ratio of diffusion and relaxation [3,4].

Modeling of release from swellable polymeric systems belongs to a category of diffusion problems known as moving-boundary or Stefan–Neumann problems [5,6]. Crank [7] has pointed out that the required equations for fitting of data in this case are significantly different and more complicated than those presented for non-swellable systems in Ref. [1]. In fact, since the constitutive equation for drug transport in the presence of both diffusional and relaxational phenomena is highly non-linear, exact analytical solutions are not available. Instead, numerical solutions must be used.

The exponential dependence of the amount of drug released, M_t/M_∞, on time, t, as described by eqn. (1) can be still used for the analysis of swelling-controlled release systems (e.g., systems based on hydroxypropyl methyl cellulose, poly(vinyl alcohol), poly(2-hydroxyethyl methacrylate), etc.) as long as these systems swell only moderately in the penetrant (water, biological fluid). A first estimate of applicabil-

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ity of this equation in swellable systems is that the system does not swell more than 25% of its original volume. Here, we will show how the diffusional exponent, n, can be used to obtain important information about the diffusional release mechanism of a drug from a polymeric device.

ANALYSIS OF DRUG RELEASE

Models to describe drug release from a plane sheet

Case-I (Fickian diffusion) and Case-II solute release behavior in swelling-controlled release systems are unique in that each can be described in terms of a single parameter. Case-I transport is described by a *diffusion coefficient*, while Case-II transport is described by a *characteristic relaxation constant*. Non-Fickian behavior, by comparison, requires two or more parameters to describe the coupling of diffusion and relaxation phenomena.

Fickian diffusional release from a thin polymer film

As in our previous work [1], the same equations can be used to analyze Fickian release from moderately swelling slabs. The short-time approximation of the fractional drug released can be given again by eqn. (2)

$$\frac{M_t}{M_\infty}=4\left(\frac{Dt}{\pi l^2}\right)^{1/2} \tag{2}$$

Here, M_t/M_∞ is the fraction of drug released, D is the drug diffusion coefficient, l is the initial film thickness and t is the release time.

Case-II release from a thin polymer film

The mathematical analysis of Case-II drug transport from a thin polymer film is presented here by analogy to the analysis presented by Enscore et al. [8] for Case-II penetrant transport in a spherical polymer particle. Consider a thin polymer film of cross-sectional area A and thickness l undergoing drug release under Case-II transport. In the swollen region defined by $X \leqslant x \leqslant l/2$, where X is the position of the advancing front, there is a linear change of drug concentration. In the glassy region defined by $0 \leqslant x \leqslant X$, there is essentially no drug diffusion. The release kinetics is assumed to be controlled by a rate-limiting relaxation phenomenon positioned at the advancing front. If k_0 is defined as the Case-II relaxation constant, then the simple first-order kinetic expression describing release from this thin section may be given by

$$\frac{dM_t}{dt}=k_0 A \tag{3}$$

The amount of drug, M_t, released from the swollen region of volume V, where V is equal to $A(l/2-X)$, at any time t is given by the following mass balance

$$M_t=C_0 A\left[\frac{l}{2}-X\right] \tag{4}$$

Substituting for M_t from the above mass balance into the kinetic expression one finds upon simplification

$$\frac{dX}{dt}=-\frac{k_0}{C_0} \tag{5}$$

Solving for X and substituting this expression into the mass balance, one obtains the following expression for M_t as a function of time

$$M_t=\frac{4k_0 A}{l}t \tag{6}$$

Equation (6) may also be written as follows

$$M_t=\left[\frac{2C_0 A}{l}\right]\left[\frac{2k_0}{C_0 l}t\right] \tag{7}$$

The term $2C_0A/l$ is the release at long times, M_∞. Equation (7) applies only up to values of time $t=C_0l/2k_0$; at this time an abrupt change to M_∞ is observed (see Fig. 1). Thus, eqn. (7) can be written as

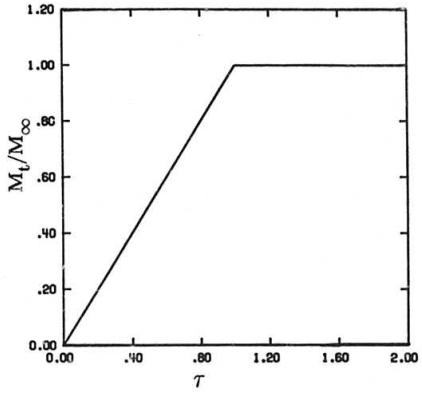

Fig. 1. Fractional drug release, M_t/M_∞, versus τ for Case-II transport from a plane sheet.

$$\frac{M_t}{M_\infty}=\frac{2k_0}{C_0 l}t \tag{8}$$

As indicated by eqn. (8), Case-II drug release from a thin polymer film is characterized by a linear time dependence of the drug release (approximately until the two diffusing penetrant fronts of the penetrant meet at the center of the slab). A graphical representation of the Case-II solution for slab geometry, plotted as normalized release, M_t/M_∞, versus dimensionless time, τ, which is defined for Case-II kinetics as $2k_0t/C_0l$, is shown in Fig. 1.

The model presented above has been generalized [8] for alternative geometries of interest and is given by equation [9]

$$\frac{M_t}{M_\infty}=1-\left[1-\frac{k_0}{C_0 a'}t\right]^N \tag{9}$$

Here a' is the diffusional length of the sample, which is equal to the radius, a, for cylindrical and spherical samples or to the film half-thickness, l, for planar samples. The exponent N is determined by sample geometry and has values of 1 for films, 2 for cylinders, and 3 for spheres.

Semi-empirical equation for drug release from thin polymer slabs

The simple semi-empirical equation (1) can be now used to express drug release from swellable polymers. For Fickian release from a thin film, eqn. (2) indicates that the first 60% of the fractional release at any time can be characterized by some constant multiplied by the square root of time. For the second limiting case, Case-II transport, eqn. (8) indicates that until the two penetration fronts meet the fractional release at any time is linearly related to that time. Many release processes from swellable polymers fall between these two limiting cases: as such, they can be represented by a coupling of the Fickian and Case-II transport mechanisms. A simple expression of this observation can be heuristically written by adding the diffusion-controlled and relaxation-controlled release terms according to eqn. (10):

$$\frac{M_t}{M_\infty}=k_1\sqrt{t}+k_2 t \tag{10}$$

The generalized expression of the previous equation is eqn. (1). The constant k incorporates characteristics of the macromolecular network system and the drug, whereas the *diffusional exponent*, n, is indicative of the transport mechanism. In eqn. (1), Fickian and Case-II release are defined by n equal to 0.50 and 1.00, respectively. For these two limiting cases the constant k has physical significance, i.e., $k=4(D/\pi l^2)^{1/2}$ for Fickian diffusion, and $k=2k_0/C_0l$ for Case-II transport. Anomalous release behavior is intermediate between Fickian and Case-II; this is reflected by the fact that anomalous behavior is defined by values of n between 0.50 and 1.

Release behavior in cylinders and spheres

Release from cylinders

For one-dimensional radial release from a cylindrical swellable polymer of radius a, under perfect sink initial and boundary conditions, with a constant drug diffusion coefficient, D,

and under moderate swelling, eqn. (1) may still be used as discussed before [1]. The limiting diffusional exponent of eqn. (1) for Fickian release from cylinders is again $n=0.451\pm0.004$. For a cylinder of radius a, under perfect sink conditions, Case-II release is defined by eqn. (9) with $N=2$ to give

$$\frac{M_t}{M_\infty}=1-\left[1-\frac{k_0}{C_0 a}t\right]^2=\frac{2k_0}{C_0 a}t-\left[\frac{k_0}{C_0 a}t\right]^2 \quad (11)$$

Release from spheres

For one-dimensional radial release from a sphere of radius a, under perfect sink initial and boundary conditions, with a constant drug diffusion coefficient, D, the exponential expression of eqn. (1) applies with $n=0.432\pm0.007$ for Fickian release. For a sphere of radius a, under perfect sink conditions, Case-II release is expressed by eqn. (9) with $N=3$. This yields

$$\frac{M_t}{M_\infty}=1-\left[1-\frac{k_0}{C_0 a}t\right]^3 =\frac{3k_0}{C_0 a}t-3\left[\frac{k_0}{C_0 a}t\right]^2+\left[\frac{k_0}{C_0 a}t\right]^3 \quad (12)$$

Dependence of the diffusional exponent on geometry

Fickian release is defined by an initial $t^{1/2}$ time dependence of the fractional release for slabs, cylinders, and spheres. Analogously, Case-II transport is defined by an initial linear time dependence of the fractional release for all geometries.

In order to evaluate the dependence of the value of n on geometry, eqn. (1) was applied to the first 60% of the fractional release curves for Fickian and Case-II release from a cylinder. Fickian diffusion and Case-II transport from a cylinder are defined by $n=0.451\pm0.004$ and $n=0.89\pm0.02$, respectively (see Fig. 2). (Throughout this work, the confidence limits presented for any parameter are the 95% confidence limits.) For Fickian diffusion and Case-II transport from a swellable sphere the exponent takes the values $n=0.432\pm0.007$ and $n=0.85\pm0.02$, respectively (see Fig. 3). Table 1 summarizes the range of values of the diffusional exponent n, and the related transport mechanism for each geometry. A value of $n=1$, however, means that the drug release is independent of time, regardless of the geometry. Thus, zero-order release can exist for any geometry; only for slabs does this release coincide with Case-II transport.

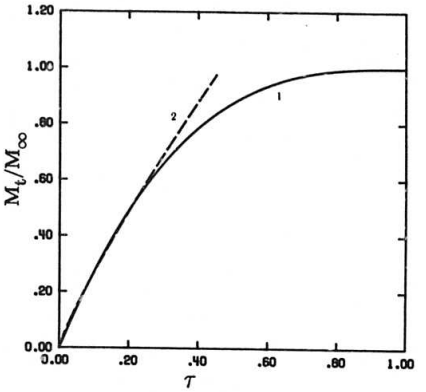

Fig. 2. Fractional drug release, M_t/M_∞, versus τ for Case-II transport from a cylinder. Comparison of the solutions presented by eqn. (11) (curve 1) and eqn. (1) with $n=0.89$ (curve 2).

Effect of particle size distributions on release behavior

As discussed before [1], the polydispersity of a microparticulate controlled release sample leads to changes in the observed release kinetics. The distribution of the particle sizes affects the diffusion time.

Mathematical model for release from polydisperse systems

For Fickian diffusional release, the equation describing the fractional release for moderately swelling systems is the same as before (eqn. (25) of Ref. [1]).

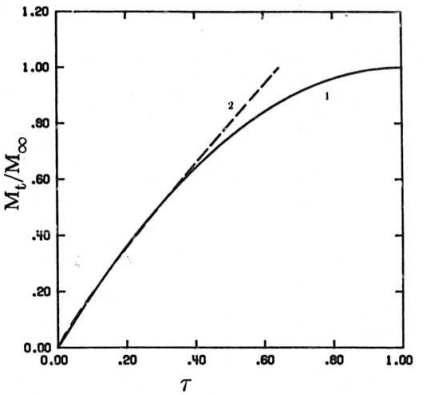

Fig. 3. Fractional drug release, M_t/M_∞, versus τ for Case-II transport from a sphere. Comparison of the solutions presented by eqn. (12) (curve 1) and eqn. (1) with $n=0.85$ (curve 2).

For release from a monodisperse microparticulate systems which obeys Case-II transport, the release kinetics was defined by eqn. (12). For release from a hetero-dispersed sample of the same system the following model can be proposed:

$$\frac{M_t}{M_\infty}=1-\sum_i \omega(a_i)\left[1-\frac{k_0}{C_0 a_i}t\right]^3 \quad (13)$$

In eqn. (13) the weight fraction, $\omega(a_i)$, represents the portion of the total sample population having precisely a radius a_i, i.e., the weight fraction is defined at discrete values of the particle size distribution. The number of discrete values of a_i used in eqn. (13) must reflect the fact that the real particle size distribution is a continuous function.

Effects of a particle size distribution on the drug release kinetics

Comparison was made of the release behavior for Fickian diffusion and Case-II transport from a monodisperse sample of 100 μm particles and a hypothetical mixture of 20% 20 μm, 60% 100 μm, and 20% 500 μm particles. The empirical equation (1) was used to characterize the first 60% of the release behavior obtained from the hypothetical distribution. For the Fickian diffusion process n was 0.30 ± 0.01 and for the Case-II transport process n was 0.45 ± 0.02. These values are considerably different than values of n obtained from a monodispersed sample, i.e., $n=0.43$ and $n=0.85$, respectively. In fact, for the above hypothetical distribution, the Case-II transport mechanism very nearly approximated a normal Fickian diffusional process.

It should be emphasised that the characteristic effect of a particle size distribution on solute release is to accelerate the release process at short times and decelerate the transport at long times. For a monodisperse system which exhibits Case-II transport, an appropriate distribution can be defined so as to approximate Fickian diffusion. A particle size distribution cannot slow down the release process at early

TABLE 1

Diffusional exponent and mechanism of diffusional release from various swellable controlled release systems

Diffusional exponent, n			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.5	0.45	0.43	Fickian diffusion
$0.5<n<1.0$	$0.45<n<0.89$	$0.43<n<0.85$	Anomalous (non-Fickian) transport
1.0	0.89	0.85	Case-II transport

times. Thus, for a monodisperse system which exhibits Fickian diffusion no particle distribution can be defined for which solute release can be approximated by Case-II drug transport.

CONCLUSIONS

The previously developed empirical expression relating the fractional drug released as a function of time can be used to analyze swelling-controlled release systems as long as the equilibrium swelling ratio is not higher than 1.33 (25% water content by volume).

The diffusional exponent of eqn. (1) is an indication of the mechanism of drug release and takes various values depending on the geometry of the release device.

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