A simple equation for the description of solute release. III. Coupling of diffusion and relaxation

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Summary

The exponential expression of solute release from polymeric devices can be written in terms of the release mechanism's diffusional and relaxational contributions. The general form of this equation's exponent is related to the geometric shape of the releasing device through its aspect ratio. A methodology is presented for general analysis of the release behavior of controlled release systems using a coupled diffusion/relaxation model.

Introduction

In previous publications of this series (Ritger and Peppas, 1987a, b) we indicated that a simple exponential expression of the form of Eqn. 1 can be used to analyze the controlled release behavior of various pharmaceutical and other systems.

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

In this equation, M_t/M_∞ is the fraction of drug released, k is the kinetic constant (with units of T^{-n}), t is the release time and n is the diffusional exponent for drug release.

We have explained before that this equation can be used to analyze the first 60% of a release curve, regardless of geometric shape. We have also

shown that two competing release mechanisms, a Fickian diffusional release and a Case-II relaxational release, are the limits of this phenomenon (Sinclair and Peppas, 1984; Peppas, 1985).

Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case-II relaxational release is the drug transport mechanism associated with stresses and state-transition in hydrophilic glassy polymers which swell in water or biological fluids. Table 1 describes the limits of this analysis. Regardless of the geometric device used, the value of the exponent for Case-II transport mechanism is twice that of pure Fickian diffusional mechanism. This observation will be used below.

Development

Following a heuristic approach first developed by Alfrey et al. (1966) for the case of solvent transport in a polymer, the two phenomena con-

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TABLE 1

Diffusion exponent and solute release mechanism

Diffusion exponent (m)			Mechanism
Film	Cylinder	Sphere	
0.50	0.45	0.43	Fickian diffusion
0.50 < m < 1.00	0.45 < m < 0.89	0.43 < m < 0.85	Anomalous transport
1.00	0.89	0.85	Case-II transport

trolling the release can be considered as additive. Therefore, we may write

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \qquad (2)$$

where the first term of the right-hand side is the Fickian contribution, the second term being the Case-II relaxational contribution. The coefficient m is the purely Fickian diffusion exponent for a device of *any* geometrical shape which exhibits controlled release (see Table 1).

In a previous publication, this coefficient was given for any shape, including cylinders, tablets and films, by a diagram (Fig. 1) which can be easily fitted by a cubic spline. The curve of Fig. 1
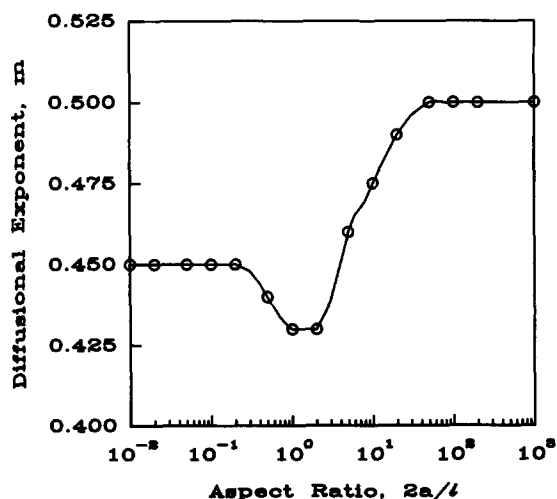

Fig. 1. Variation of the Fickian diffusional exponent, m, with the aspect ratio, $2a/l$, where $2a$ is the diameter and l is the thickness (height) of the device.

has two regions when the exponent is constant. For the aspect ratio, $2a/l$, varying from 10^{-1} to 10^2:

$$m = \begin{cases} 0.45 & \text{for} \quad 2a/l < 0.1 \\ 0.50 & \text{for} \quad 2a/l > 100 \end{cases} \qquad (3)$$

Eqn. 2 can be rewritten as

$$\frac{M_t}{M_\infty} = k_1 t^m \left[1 + \frac{k_2}{k_1} t^m \right] \qquad (4)$$

The percentage of drug release due to the Fickian mechanism, F, is clearly calculated as:

$$F = \frac{1}{1 + \dfrac{k_2}{k_1} t^m} \qquad (5)$$

which leads to the ratio of relaxational over Fickian contributions as:

$$\frac{R}{F} = \frac{k_2}{k_1} t^m \qquad (6)$$

Therefore, Eqns. 2 and 4 indicate that solute release from any device, irrespective of its geometric shape, can be written in terms of a Fickian and a relaxational contribution. If the Fickian contribution can be expressed as a function of t^m, then the relaxational contribution can be expressed as a function of t^{2m}. By comparison of Eqns. 1 and 2, it is concluded that $m = n$ when the relaxational mechanism is negligible.

Simulation and Discussion

To investigate the importance of the two mechanisms in the overall release behavior, we examined the release profiles for various values of k_1 and k_2. Fig. 2 indicates the fraction of drug released, M_t/M_∞, from a tablet with $m = 0.47$ for the case when $k_1 = 0.1$ min$^{-0.47}$ and $k_2 = 0.01$ min$^{-0.94}$, and the case of $k_1 = 0.01$ min$^{-0.47}$ and $k_2 = 0.1$ min$^{-0.94}$. The release profiles are significantly different, those corresponding to the sec-

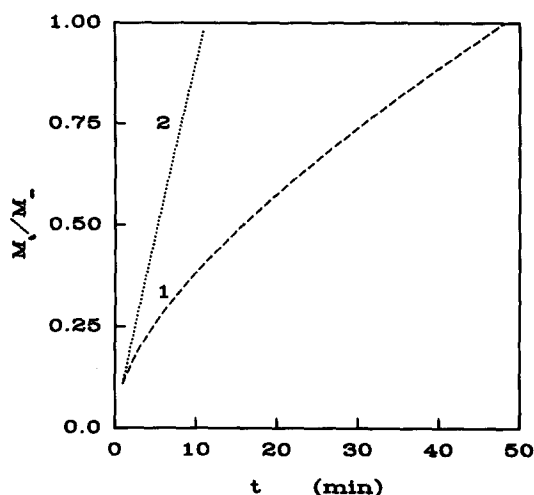Fig. 2. Fraction of drug released, M_t/M_∞ for a tablet with $m = 0.47$, as a function of release time, t. (Curve 1) $k_1 = 0.1$ $min^{-0.47}$, $k_2 = 0.01$ $min^{-0.94}$; (curve 2) $k_1 = 0.01$ $min^{-0.47}$, $k_2 = 0.1$ $min^{-0.94}$.

Fig. 4. Fickian release fraction, F, from a thin film with $m = 0.5$, as a function of release time, t, when $k_1 = 0.2$ $min^{-0.5}$. (Curve 1) $k_2 = 0.1$ min^{-1}; (curve 2) $k_2 = 0.01$ min^{-1}; (curve 3) $k_2 = 0.001$ min^{-1}.

ond set of k_1 and k_2 being more linear with time, indicating a relaxational mechanism that predominates. In Fig. 3 it is seen that as the magnitude of k_1 increases (while k_2 is kept constant), the diffusional mechanism predominates.

It is not possible to give an exact answer as to the importance of the Fickian or Case-II mecha-
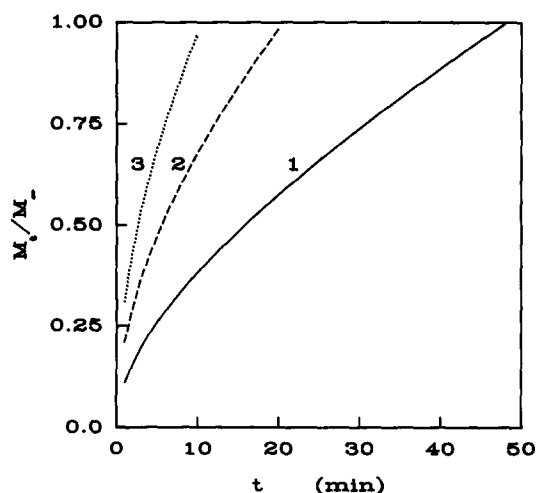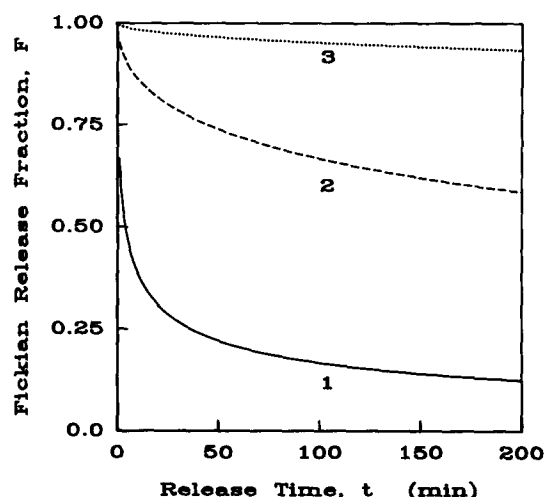
nism from measurement of k_1 and k_2. For these reasons, Eqn. 5 or 6 must be used. Fig. 4 indicates the Fickian release fraction, F, from thin films ($m = 0.5$) as a function of the relaxational constant k_2. Indeed, as k_2 decreases, the Fickian fraction of drug released becomes larger, ap-
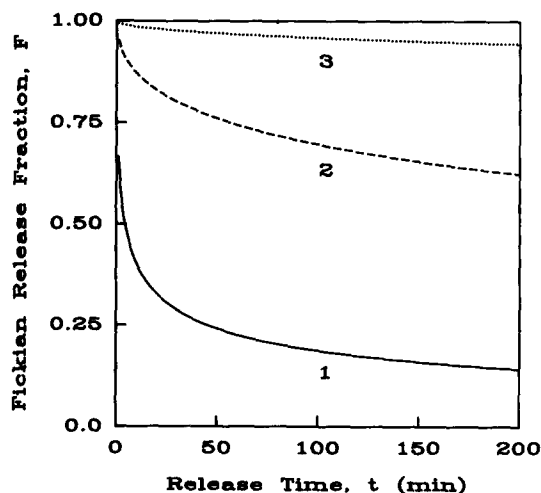

Fig. 3. Fraction of drug released, M_t/M_∞, from a tablet with $m = 0.47$, as a function of release time, t, when $k_2 = 0.01$ $min^{-0.94}$. (Curve 1) $k_1 = 0.1$ $min^{-0.47}$; (curve 2) $k_1 = 0.2$ $min^{-0.47}$; (curve 3) $k_1 = 0.3$ $min^{-0.47}$.

Fig. 5. Fickian release fraction, F, from a tablet with $m = 0.47$, as a function of release time, t, when $k_1 = 0.2$ $min^{-0.47}$. (Curve 1) $k_2 = 0.1$ $min^{-0.94}$; (curve 2) $k_2 = 0.01$ $min^{-0.94}$; (curve 3) $k_2 = 0.001$ $min^{-0.94}$.

proaching 100%. A similar behavior can be obtained for release from tablets (Fig. 5).

Based on this analysis, the following methodology is proposed for analysis of the release mechanism using a coupled diffusion/relaxation model:

(i) calculate the aspect ratio (diameter/thickness) of the device tested;
(ii) determine m from Eqn. 3 or from Fig. 1;
(iii) plot the experimental release data and fit the first 60% to Eqn. 2;
(iv) calculate k_1 and k_2; and
(v) use Eqn. 5 to determine the percentage of Fickian and relaxational drug release.

Conclusions

The previous analysis indicates that it is possible to calculate the *approximate* contributions of the diffusional and relaxational mechanisms in an anomalous solute release process by fitting the data to a heuristic model containing both phenomena.

References

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