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Analysis of Case II drug transport with radial and axial release from cylinders

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Abstract

Analysis is presented for Case II drug transport with axial and radial release from cylinders. The previously reported [J. Control Release 5 (1987) 37] relationships for radial release from films and slabs are special cases of the general solution derived in this study. The widely used exponential relation $M_t/M_\infty = kt^n$ describes nicely the first 60% of the fractional release curve when Case II drug transport with axial and radial release from cylinders is operating.

Keywords: Drug release; Case II transport; Cylinder; Controlled release

1. Introduction

Controlled release polymeric systems have been used extensively to deliver drugs and other bioactive agents. The extent and the rate with which drug molecules appear in the medium bathing the controlled release device are usually considered as a combination of diffusion and Case II transport of drug molecules through the polymer chains (Ritger and Peppas, 1987). In such cases, diffusion is governed by Fick's law while Case II transport (Enscore et al., 1977) reflects the influence of polymer relaxation on molecules' movement in the matrix. A plethora of studies dealing with Case II drug transport have been reported in the literature (Colombo et al., 1995, 1999; Conte et al., 1994; Ferrefo et al., 2000; Juárez et al., 2001; Peppas and Sahlin, 1989; Siepmann and Peppas, 2001; Skoug et al., 1991).

The semiempirical Eq. (1) is widely used to describe the release of solute when the prevailing mechanism is a combination of drug's diffusion and Case II transport (Ritger and Peppas, 1987):

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

where M_t is the drug released at time t, M_∞ the quantity of drug released at infinite time, k the kinetic constant and n is an exponent. The value of n is related to the geometrical shape of the formulation and determines the release mechanism; thus, n is equal to 0.5/0.45/0.43 and 1.0/0.89/0.85 (thin films/cylinders/spheres), when pure diffusion or pure Case II transport is operating, respectively. Eq. (1) avoids exact analysis of the data, describes all three cases of geometries and applies to the first 60% of the fractional release curves. In reality, Eq. (1) is an approximate expression of the exact solution of Case II drug transport from cylinder and sphere, when one-dimensional radial release is considered.

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Although the cylinder is the most common geometrical shape of the devices used in pharmaceutics, only the analysis of one-dimensional radial release from cylinder according to Case II transport has been reported (Enscore et al., 1977; Ritger and Peppas, 1987). Hence, the use of semiempirical Eq. (1) is restricted to slabs whereas only radial release can be considered. In this study, we analyze Case II drug transport with axial and radial release from cylinder. We find that the one-dimensional radial release is a special case of the general solution involving both axial and radial mass transport. We also study the applicability of Eq. (1) to the analysis of transport when both axial and radial release from a cylinder are taking place simultaneously.

2. Analysis of drug release

The analysis of Case II drug transport with axial and radial release from the cylinder depicted in Fig. 1 is based on two assumptions: (i) a boundary is formed between glassy and rubbery phase of the polymer, and (ii) the movement of this boundary takes place under constant velocity. In order to study the release from a cylinder we firstly determine the release surface. A cylinder of height $2L$ that is allowed to release from all sides can be treated as a cylinder of height L that can release from the round side and the top only, Fig. 1. This second case is easier to analyze

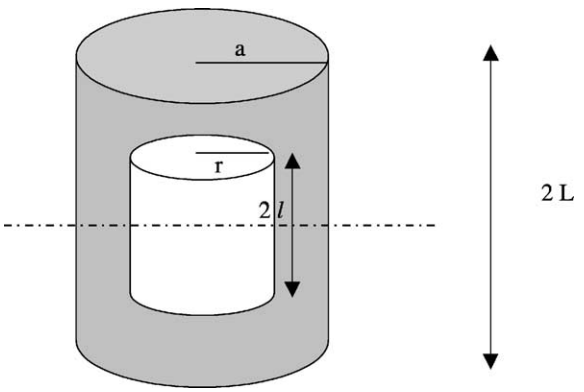

Fig. 1. Case II drug transport with axial and radial release from a cylinder of height $2L$ and radius a at $t = 0$. Drug release takes place from all sides of the big cylinder. The drug mass is contained in the grey region. After time t the height of the cylinder is reduced to $2l$ and its radius to r (small cylinder).

and is also implied in Ritger and Peppas (1987) for the release of drug from a thin film of thickness $l/2$ (see Appendix A). Notice that if the big cylinder of Fig. 1 is cut in half across the horizontal line, two equal cylinders, each of height L, will be formed. If drug release from the two newly formed areas (top or bottom) of the two small cylinders is not considered, the two cylinders of height l exhibit the same release behavior as the big cylinder, i.e. $M_{t(2L)} = 2M_{t(L)}$ and $M_{\infty(2L)} = 2M_{\infty(L)}$; consequently,

$$\frac{M_{t(2L)}}{M_{\infty(2L)}} = \frac{M_{t(L)}}{M_{\infty(L)}}$$

We will use this fact and we should note that our results will describe both the following cases: either a cylinder of height L that releases from the round and top surface or a cylinder of height $2L$ that releases from all sides, Fig. 1.

At zero time, the height and radius of the cylinder is L and radius a, respectively, Fig. 1. After time t the height of the cylinder decreases to l and its radius to r assuming Case II drug transport for both axial and radial release, Fig. 1. For the decrease rate of radius r and height l of the cylinder we can write:

$$\frac{dr}{dt} = \frac{dl}{dt} = -\frac{k_0}{C_0} \tag{2}$$

where k_0 is the Case II relaxation constant and C_0 is the drug concentration considered uniform (Enscore et al., 1977). The assumption for the k_0/C_0 value of the penetration layer speed is implied by the analysis of the cases studied in Enscore et al. (1977) and Ritger and Peppas (1987), which are simpler than our present case. Boundary conditions for the above equations are simply $r(0) = a$ and $l(0) = L$.

After integration of Eq. (2), we derive Eqs. (3) and (4) as well as the time for which each one is operating,

$$r = a - \frac{k_0}{C_0}t, \quad t \le \frac{C_0}{k_0}a \tag{3}$$

$$l = L - \frac{k_0}{C_0}t, \quad t \le \frac{C_0}{k_0}L \tag{4}$$

This means that the smaller dimension of the cylinder (a or L) determines the duration of the phenomenon.

The amount of drug released at any time t, is given by the following mass balance equation:

$$M_t = C_0\pi(a^2L - r^2l) \tag{5}$$

Substituting Eqs. (3) and (4) in Eq. (5), we obtain the following expression for mass M_t as a function of time:

$$M_t = C_0\pi\left[a^2L - \left(a - \frac{k_0}{C_0}t\right)^2\left(L - \frac{k_0}{C_0}t\right)\right] \quad (6)$$

For the mass released at infinite time, we can write:

$$M_\infty = C_0\pi a^2 L \quad (7)$$

From Eqs. (6) and (7), we derive for the fraction released $f = \frac{M_t}{M_\infty}$ as a function of time t:

$$f = \frac{M_t}{M_\infty} = \left(\frac{2k_0}{aC_0} + \frac{k_o}{C_0L}\right)t + \left(-\frac{k_0^2}{a^2C_0^2} - \frac{2k_0^2}{aC_0^2L}\right)t^2 + \frac{k_0^3}{a^2C_0^3L}t^3 \quad (8)$$

Eq. (8) describes the entire fractional release curve for Case II drug transport with axial and radial release from a cylinder. Again, Eq. (8) indicates that the smaller dimension of the cylinder (a or L) determines the total duration of the phenomenon. When $a \gg L$, Eq. (8) can be approximated by Eq. (9):

$$\frac{M_t}{M_\infty} = \frac{k_0}{C_0L}t \quad (9)$$

which is identical to the solution proposed by Ritger and Peppas (1987) for a thin film or slab with the difference of a factor of 2 due to the fact that our cylinder height is $2L$ (see Appendix A). When $a \ll L$, Eq. (8) can be approximated by Eq. (10):

$$\frac{M_t}{M_\infty} = \frac{2k_0}{C_0a}t - \left[\frac{k_0}{C_0a}t\right]^2 \quad (10)$$

which is also the solution proposed by Ritger and Peppas (1987) for one-dimensional radial release under Case II transport from a cylindrical swellable polymer of radius a.

These results demonstrate that the previously derived Eqs. (9) and (10) are special cases of the general solution, Eq. (8).

3. Applicability of Eq. (1) for the analysis of drug release data obeying Eq. (8)

The exact solution for the fraction of drug released from a cylinder with axial and radial release and Case II transport Eq. (8) was compared with the approach proposed by Ritger and Peppas (1987). In this case, pure Case II drug transport and release is approximated by the following equation:

$$\frac{M_t}{M_\infty} \approx kt^{0.89} \quad (11)$$

We calculated the sum of the squared differences of the two functions normalized by the time of the operation of the two functions, $\langle x^2\rangle$, as a measure of the difference between the two expressions, Eqs. (8) and (11). Since Eq. (11) is used to describe the first 60% of the release data, the cutoff time point was set at $t = 0.6(C_0/k_0)a$. This time limit corresponds to the Case II when $a \ll L$ and is based on the duration of the 60% of the release process, Eq. (3). Therefore, $\langle x^2\rangle$ can be expressed by the following equation:

$$\langle x^2\rangle = \frac{1}{0.6(C_0/k_0)a}\int_0^{0.6(C_0/k_0)a}(f - kt^{0.89})^2\,\mathrm{d}t \quad (12)$$

The calculation of the polynomial integral in Eq. (12) is trivial. However, there should be a value of k which minimizes the integral of Eq. (12). This value of k was found by equating the partial derivative of the $\langle x^2\rangle$ in respect to k with 0:

$$\frac{\partial\langle x^2\rangle}{\partial k} = 0 \quad (13)$$

Eq. (13) was solved analytically; the calculated value of k was substituted in Eq. (12) to derive the value of $\langle x^2\rangle$ that characterizes the minimum deviation that can be achieved between the two functions, Eqs. (8) and (11). It turns out that

$$\langle x^2\rangle = 0.000459 + 0.0017\frac{a}{L} + 0.0019\left(\frac{a}{L}\right)^2 \quad (14)$$

Note that this result is independent of the ratio C_0/k_0 and, therefore, the value of $\langle x^2\rangle$ is exclusively dependent on the ratio a/L.

A plot of $\langle x^2\rangle$ versus the ratio a/L is presented in Fig. 2. The value of $\langle x^2\rangle$ increases nonlinearly with (a/L) and reaches a maximum value $\approx$0.04 when $a/L = 1$. This suggests that the approximation used is quite acceptable. This means that Eq. (11) can be used for the description of the first 60% of fractional release curve when Case II drug transport with axial

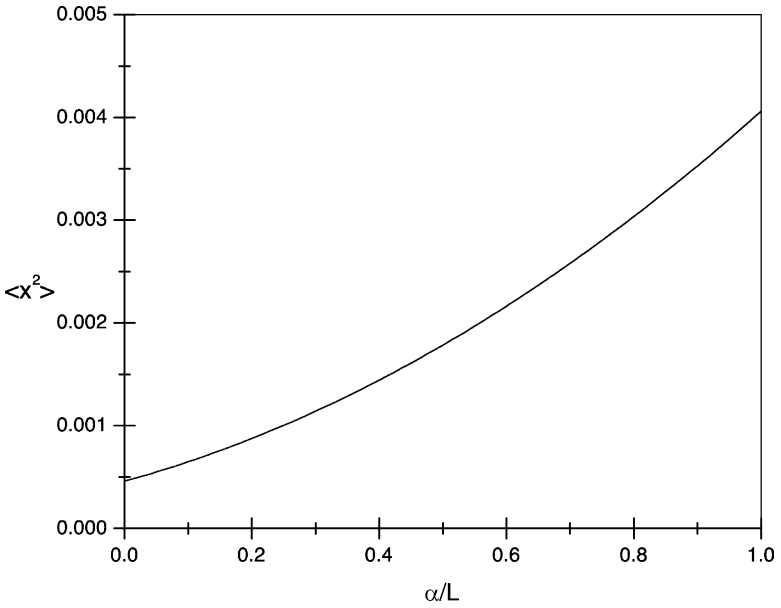

Fig. 2. Plot of the sum of the squared differences of the two functions, Eqs. (8) and (11), normalized by the time of the operation of the two functions, $\langle x^2 \rangle$, as a function of the ratio a/L (Eq. (14)).

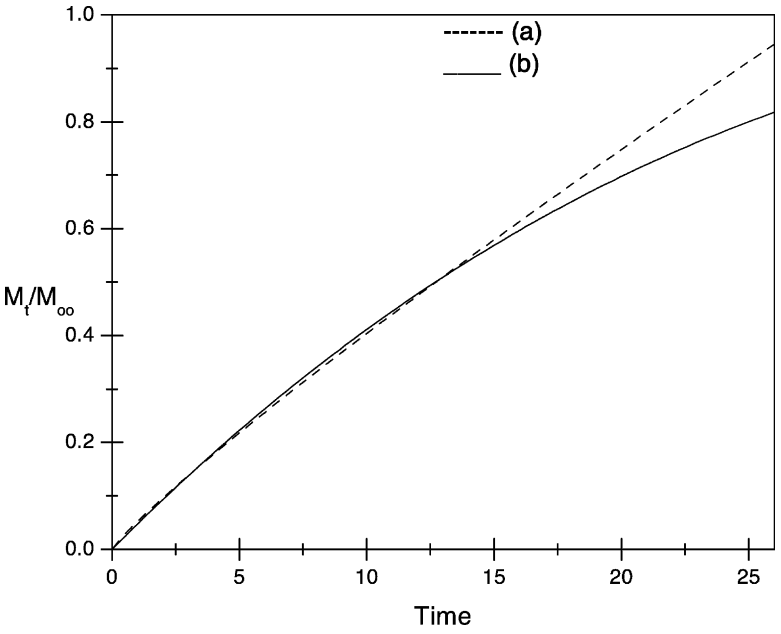

Fig. 3. Fractional drug release, M_t/M_{∞}, vs. time for Case II transport with axial and radial release from a cylinder. Comparison of the solutions presented by Eq. (8) (curve (a), with $k_0 = 0.01$, $C_0 = 0.5$, $a = 1$ and $L = 2.5$) and Eq. (11) (curve (b), with $k = 0.052$).

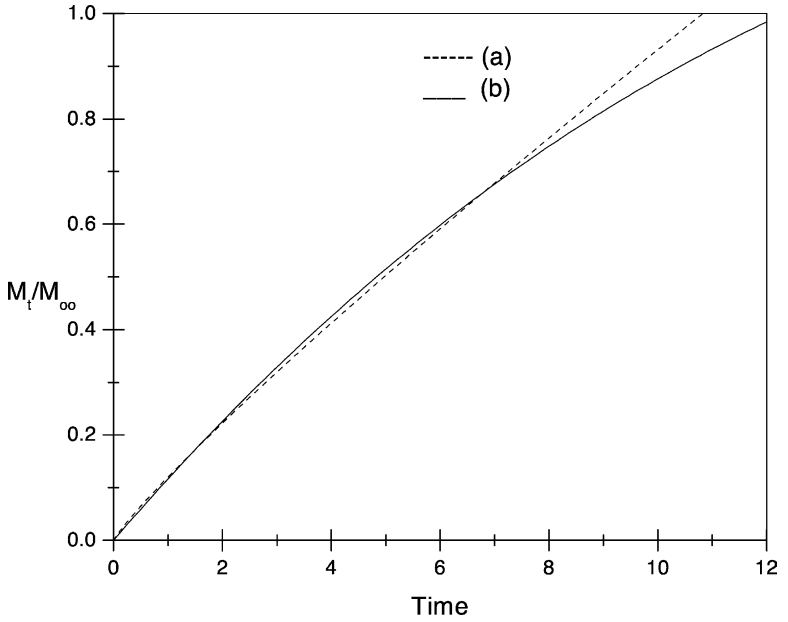

Fig. 4. Fractional drug release, M_t/M_∞, vs. time for Case II transport from a cylinder. Comparison of the solutions presented by Eq. (8) (curve (a), with $k_0 = 0.1$, $C_0 = 0.5$, $a = 10$ and $L = 2.5$) and Eq. (11) (curve (b), with $k = 0.12$).

and radial release from cylinders is examined. A typical example of comparison between Eqs. (8) and (11) when $a < L$ is shown in Fig. 3.

In case $a > L$, the release process is completed at time $t = (C_0/k_0)L$, Eq. (4). The analysis follows the same pattern as above by adjusting the time limit at $0.6(C_0/k_0)L$. A typical example of comparison between Eqs. (8) and (11) when $a > L$ is shown in Fig. 4.

In conclusion, the kinetics of Case II drug transport with axial and radial release from a cylinder is defined by Eq. (8). Our analysis did not prove that the release exponent $n = 0.89$ in Eq. (1) is the best choice for the analysis of data obeying Eq. (8). However, we have demonstrated that this choice, which is widely used in literature, can indeed be considered as a good choice when Case II drug transport with axial and radial release from cylinders is examined.

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Appendix A

Ritger and Peppas (1987) intend to study release from both sides of a thin film of thickness l. To do so, they use the fact that the ratio M_t/M_∞ of such a film is the same as the M_t/M_∞ of a thin film of thickness $l/2$ which can "leak" only from one of the two sides. The latter case is easier to study as there is only one moving front that has to be considered.

If we consider the case of one-dimensional release from the thin film, the amount of drug release at time t is

$$M_t = k_0 A t \tag{A.1}$$

and not as Eq. (A.2), as it is included in Ritger and Peppas (1987):

$$M_t = \frac{4k_0 A}{x} t \tag{A.2}$$

where x is thickness and A is the surface of the film. Also, $M_\infty = C_0 A l/2$ (i.e. the mass when swelling is completed) and not $2C_0 A/l$ which is mentioned in Ritger and Peppas (1987) and which of course does not have dimensions of mass.

Ritger and Peppas (1987) arrive at the equation

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

which correctly describes the release from both sides of a film of thickness l. This is the same as our limiting Eq. (9) since we have treated a cylinder of height $2L$. Replacing $l = 2L$ in the last equation, one takes our Eq. (9).

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