ELSEVIER International Journal of Pharmaceutics 115 (1995) 17–27

international journal of pharmaceutics

A contribution to a mathematical theory for polymer-based controlled release devices

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Received 14 March 1994; accepted 6 July 1994

Abstract

This paper presents a tentative mathematical theory based on Fick's second law to describe the performance of most polymer-based controlled release devices. These devices have two simultaneous counter-current fluxes. The first flux is the rate at which the diffusing material is released at an interface by relaxation of the glassy polymer. The second flux is the rate at which the material diffuses away from the interface. When the two rates or fluxes are equal, a critical point occurs. The length of the diffusional path from the surface to this point is defined as the 'critical length' and the time at which it is reached is defined as the 'critical time'. The parameters governing the release of the dissolved material are: the rate at which the interface moves, the diffusivity of the dissolved material in the rubbery polymer, and the total length of the diffusional path. The rates at which material was released from eleven different controlled release devices are compared here with rates predicted by mathematical derivation.

Keywords: Controlled release; Mathematical theory; Critical length; Critical time; Fick's law; Polymeric material

1. Introduction

Higuchi (1963) presented the first conceptual mathematical model for controlled release devices, dealing with a medicament suspended in a homogeneous matrix insoluble in the solvent (body fluids). He recognized that leaching diffusible material from the matrix would result in two sections divided by a sharp interface. In the section between the interface and the solvent, part of the diffusible material was leached out, however, nothing was leached in the section behind the front and the concentration of diffusible material there would be at its original value, c_i.

Higuchi also recognized that the concentration downstream of the interface was usually less than the concentration upstream of the interface, and that the concentration gradient downstream was determined by the rate the material diffused away from the interface into a perfect sink. He made the approximation that the concentration gradient downstream of the interface was linear and in 'pseudo steady-state'.

The physical system studied by Higuchi (1963) is similar, but not identical, to the system considered here, in which a solvent permeates a polymeric material according to Case II transport. In

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SSDI 0378-5173(94)00227-4

such systems the rate of permeation of the solvent into the polymer is constant with time. Alfrey et al. (1966) wrote an excellent review on the theory of Case II transport.

Both this system and that of Higuchi have in common a diffusional flux of dissolved material diffusing outwards from a moving interface. This flux is governed by Fick's law, and the rate of extraction decreases as the diffusional path grows longer.

2. Theoretical outline

Developing a theoretical understanding of how such systems work is the objective of this research. Mathematical functions for the amount of diffusible substance extracted over the course of time have been derived on the basis of Fick's second law. Data from the literature have been correlated with these mathematically derived extraction curves.

Fig. 1 is a schematic diagram of the model system. A rod, or sheet, made of the polymeric matrix containing the diffusible material, is placed in contact with a solvent. The polymer originally holds c_i grams of the diffusible substance in each cubic centimeter. The concentration in the polymer at the end in contact with the fresh solvent is c_o g/cm^3. As the solvent advances, diffusible material released at the interface diffuses out into the solvent. A sharp boundary is formed at the interface where diffusible material is being released. The interface moves at the rate of R cm/s.

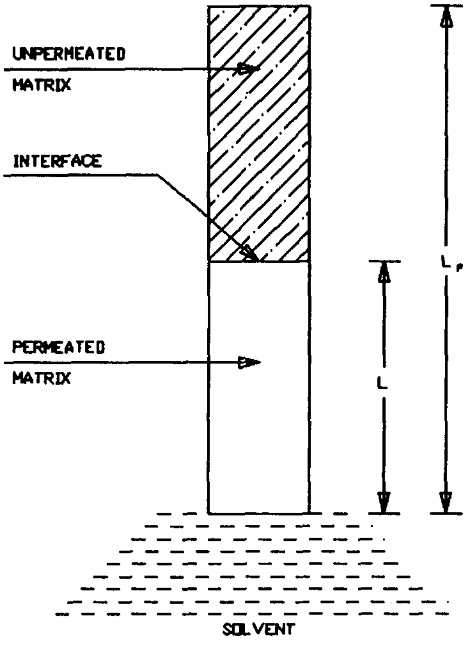

Fig. 1. Physical model.

Two limiting cases are: (1) When solvent penetrates the polymer instantaneously, the material is in solution and ready to diffuse out immediately, in conformity with Fick's law. The mathematical solution for this case can be expressed as an infinite trigonometric series. (2) When the solvent permeates the rod extremely slowly, but dissolved material diffuses out rapidly. Here, the rate of extraction from the rod is the same as the rate of release at the interface. At this limit, the rate of the solvent's permeation of the polymer determines the rate of extraction for the material. Cases of interest in pharmaceutical and other applications fall between these two limits.

When a rod is initially placed in contact with solvent, the diffusion path's length is zero. As time progresses, the interface moves further and further away from the surface, the diffusion path gets longer, and the concentration of the diffusing substance in the rubbery polymer on the downstream side of the interface increases.

In initial stages, the concentration downstream of the interface in the rubbery polymer is less than concentration upstream in the glassy polymer. A sharp break in the concentration profile occurs at the interface. Eventually, the concentration on the downstream side becomes equal to the concentration on the upstream of the interface.

Since Higuchi (1963) first proposed the use of a pseudo-steady state a number of other authors have attempted to improve that assumption (Paul and McSpadden, 1976; Lee, 1980; Korsmeyer et al., 1985; Singh and Fan, 1986; Cohen and Erneux, 1988a,b).

Cooke (1991) recently reviewed this work and presented a model, based on Fick's second law, which leads to an exact expression for the concentration gradient.

When the concentration of the diffusing material downstream of the interface becomes equal to the concentration upstream, then, at that instant, the concentration change across the interface is zero. The distance from the surface to that point is defined as the 'critical length', and the length of time from the start of the process is defined as the 'critical time'.

Fick's law for one-dimensional diffusion is given by Eq. 1:

$$\partial Z/\partial t = D(\partial^2 Z/\partial x^2) \qquad (1)$$

The variable Z in Eq. 1 is the dimensionless concentration:

$$Z = (c - c_o)/(c_i - c_o) \qquad (2)$$

When $c = c_o$ $Z = 0$, and when $c = c_i$ $Z = 1$.

The following 'base case assumptions' are used:
(a) Diffusivity is constant, or it may vary with concentration. If it varies with concentration, D in Eq. 1 is an 'apparent diffusivity', an average value of the diffusivity. This matter is discussed further in the section dealing with Lee's data.
(b) The interfacial boundary is distinct and infinitesimally thin and has no concentration gradient through it.
(c) The interfacial boundary moves into the matrix at a constant rate, i.e., by Case II transport.
(d) The concentration of the diffusible material upstream of the interface always remains at its original constant value.
(e) The concentration of the diffusing material in contact with fresh solvent is kept constant in both polymer and solvent.

If the physical conditions conform to the above, then the mathematical solution conforms to the observed extraction curve. Conversely, if the observed extraction curve conforms to the mathematically derived curve, then the physical conditions are as stated in the base case assumptions.

In principle, systems of this type could be influenced by effects other than those postulated by the base case assumptions. For example, the rate at which the solvent permeates the polymer might accelerate with the passage of time. This is known as Super Case II Transport. Jacques et al. (1974) have reviewed this subject.

Anomalous cases should be detected by a poor fit of the data points to the theoretical curves. The ultimate aim is to find the sets of assumptions necessary to predict extraction curves agreeing with all cases.

The moving interface's position is measured from the end of the matrix, which is in contact with the fresh solvent.

2.1. Phases of the process

Four distinct phases govern the extraction of the diffusible material from the system. The initial phases, A and B, occur just after the process starts, when the position of the interface is less than, or equal to, the critical length.

In phase A, the final length of the diffusional path, L_f, the length of the rod, is less than the critical length. In phase B, the reverse is true. Phase B ends when the moving interface reaches the critical length.

Phase C follows phase A. When the interface reaches the end of the rod and stops moving, the material still in the system continues to diffuse out. The instant the end of the rod is reached, the concentration profile is known from the surface up to the end of the rod or sheet from the solution obtained for phase A. In phase C, the problem is the classic one of 'diffusion in a rod with known initial and boundary conditions'. The solution can be expressed as a Fourier series.

Phase D follows phase B. Here the moving interface moves beyond the critical length. Before the critical length is reached, material can diffuse away from the moving interface faster than it is supplied at the interface. Afterwards the reverse is true; the interface is moving faster than the diffusion front. The instant the critical length is reached, the concentration profile is known from the surface up to the critical length from the solution obtained for phase B.

At distances greater than the critical length, the material, has not yet been affected by the diffusion front, and the concentration profile is constant from the critical length to the final length. The phase D problem is similar to that of phase C, but it has different initial and boundary conditions. It also has a Fourier series solution.

3. Mathematical solution

Mathematical equations used in the interpretation and correlation of data are summarized here. A full account of the derivation is given in a paper by Cooke (1991).

Solutions to Eq. 1 can be sought in the form:

$$Z = e^{-\lambda^2 Dt}(K \sin \lambda x + K' \cos \lambda x) \quad (3)$$

The position of the interface, L, and the time, t, during phase A and phase B are related by the equation:

$$t = L/R \quad (4)$$

The separation constant, λ, can be defined as another constant, W, divided by the critical length, L_c.

$$\lambda = W/L_c \quad (5)$$

To simplify the notation define the dimensionless group:

$$U = RL_c/D \quad (6)$$

Eq. 3 can be written as:

$$Z = Ke^{-(W^2/U)(t/t_c)}[\sin(Wx/L_c)] \quad (7)$$

A material balance of the diffusible material at the moving interface between the glassy and rubbery polymer, shows that:

$$\mathrm{d}Z/\mathrm{d}x = (R/D)(1 - Z) \quad (8)$$

Eq. 4 can be used in Eq. 7 to eliminate t and give an equation relating Z to L for all times up to the point when L equals L_c. Changes in concentration across the surfaces $x = L = 0$ and $x = L = L_c$ are the same for both variables x and L.

Differentiating Eq. 7 when $x = L$:

$$\frac{\mathrm{d}Z}{\mathrm{d}L} = \frac{KW}{L_c} e^{-(W^2/U)(L/L_c)}\left[\cos\frac{WL}{L_c} - \frac{W}{U}\sin\frac{WL}{L_c}\right] \quad (9)$$

Mathematical notation

Symbol	Meaning
B_n	constants
D	diffusivity
D'	apparent diffusivity
F	dimensionless variable
G	dimensionless variable
K	a constant = 1.96434808
L	length to interface
L_c	critical length
L_f	final length
M	mass
M_f	total diffusible mass in the system
N	goodness of fit parameter
R	rate of interface movement
U	a constant = 2.1606150
W	a characteristic value 1.09991455
Y	dimensionless yield
Z	dimensionless concentration
c	concentration
c_i	original concentration
c_o	concentration at surface
e	a constant = 2.7182818
f	dimensionless variable
g	dimensionless variable
n	an integer, a counter
t	time
t_c	critical time
t_f	time at final length
x	distance
π	a constant = 3.14159265
Ψ	$(2n - 1)\pi/2$

When $L = L_c$ and $Z = 1$, according to Eq. 8, $\mathrm{d}Z/\mathrm{d}L = 0$. Therefore:

$$W \tan W = U \quad (10)$$

When $L = 0$, and $Z = 0$:

$$\mathrm{d}Z/\mathrm{d}L = R/D \quad (11)$$

This leads to the eigenequation:

$$e^{W/\tan W} = \tan W \sin W \quad (12)$$

This equation has an infinite number of roots but, only the first characteristic value of 1.099915 has physical meaning.

Eq. 7 satisfies all the boundary conditions when $W = 1.099915$ and is a valid solution of Eq. 1 for times less than the critical time.

After the critical length is reached, the solution to Eq. 1 for the remainder of the process is readily found by Fourier series solution (see Crank (1975)).

Define the dimensionless ratios as:

$$f = L/L_c = t/t_c \tag{13}$$

$$F = Wf = WL/L_c = Wt/t_c \tag{14}$$

From Eq. 9, 11 and 14 it follows that:

$$(W^2/U)(t/t_c) = F/K \tag{15}$$

Eq. 7 can then be written as:

$$Z = Ke^{-F/K}\sin(Wx/L_c) \tag{16}$$

Eq. 16 gives values of the dimensionless concentration through the rubbery polymer for any position of the interface during phase A or phase B. Define the dimensionless ratios:

$$g = L_f/L_c \tag{17}$$

and

$$G = Wg = WL_f/L_c \tag{18}$$

By integration of Eq. 16, the fractional yield, Y, is:

$$Y = (F/G) - (K/G)e^{-F/K}(1 - \cos F) \tag{19}$$

In phase A, when f equals g, the interface has reached the final length and phase A ends. A curve marking the end of phase A can be derived and is shown on the graphs as a solid line. In phase B the final length is longer than the critical length. Phase B ends when the moving interface reaches the critical length. This boundary is also shown on the graphs as a solid line.

Phase C follows phase A. When the interface stops at the end of the rod, the equation for the concentration profile is known. The phase C problem is the classic diffusion in a rod with known initial and boundary conditions, it is solved by a Fourier series solution. The solution is:

$$Y = 1 - \sum_n \frac{B_n}{\Psi_n} e^{\frac{\Psi_n^2}{KG^2}(G-F)} \tag{20}$$

where

$$B_n = \frac{2Ke^{-G/K}(-1(-1)^n)G\cos G}{\left[(2n-1)\frac{\pi}{2}\right]^2 - G^2} \tag{21}$$

and

$$\Psi_n = \frac{(2n-1)\pi}{2} \tag{22}$$

Phase D follows phase B. When the moving interface moves beyond the critical length, it is then moving faster than the diffusion front. At the instant the critical length is reached, the concentration profile is known. The material, at distances greater than the critical length, has not yet been affected by the diffusion front, and the concentration profile is constant beyond the critical length up to the final length. The problem in phase D is similar to that of phase C, but initial and boundary conditions are different. It is solved by a Fourier series solution. The solution is:

$$Y = 1 - \sum_n \frac{B_n}{\Psi_n} e^{\frac{\Psi_n^2}{KG^2}(W-F)} \tag{23}$$

where

$$B_n = \frac{2\left[\frac{G}{K}\sin\frac{\Psi_n}{g} - \Psi_n\cos\frac{\Psi_n}{g}\right]}{\Psi_n^2 - G^2} + \frac{2\cos\frac{\Psi_n}{g}}{\Psi_n} \tag{24}$$

3.1. The external physical parameters

This system has three external physical parameters; D, the diffusivity; R, the rate of permeation of the solvent; and L_f, the final length of the diffusional path. Two independent variables are: t, the time; and x, the distance from the surface. A third variable L, the position of the interface from the surface, is linked by Eq. 4 to the time. The dependent variable, Y, is the fractional amount of material extracted.

In addition there is an eigenvalue, $W = 1.099915$, and two other constants, $K = 1.964348$ and $U = 2.160617$, related to it.

Several other variables were used in deriving Eq. 19; in particular, F and G. These two dimensionless groups can be expressed in terms of external physical variables;

$$F = R^2t/KD \tag{25}$$

$$G = RL_f/KD \tag{26}$$

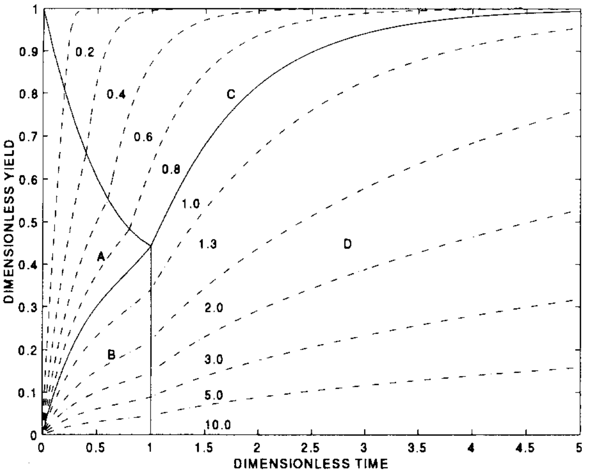

Fig. 2. Graph showing the variation of the dimensionless yield vs the dimensionless time for various values of the parameter g.

and therefore Eq. 19 can be written as:

$$Y=\frac{Rt}{L_{\mathrm{f}}}-\frac{K^{2}D}{RL_{\mathrm{f}}}e^{-R^{2}t/K^{2}D}\left(1-\cos\frac{R^{2}t}{KD}\right) \qquad (27)$$

This expresses the fractional amount extracted as a function of time before the critical point is reached, subject to values of the external physical parameters. Eq. 20 and 23, governing extraction after the critical point has been reached, can be expressed similarly. If external physical parameters have been determined, then the dimensionless groups in Eq. 27 can be calculated and the amount extracted as a function of time is known.

3.2. Dimensionless plot of extraction curves

Fig. 2 shows how Y (the dimensionless yield) varies with f (the dimensionless time), for different values of the parameter g (the ratio of the final length to the critical length). The four different phases, A–D are marked on Fig. 2.

3.3. Plot of rate of extraction vs the amount extracted

The rate of extraction vs the amount extracted can be shown by differentiating Eq. 19, 20 and 23 and plotting the slope, $\mathrm{d}Y/\mathrm{d}f$ vs Y, for various values of g. The value of $\mathrm{d}Y/\mathrm{d}f$, when f equals zero, is $1/g$. To plot all the curves on the same coordinates, the differential is multiplied by g, giving all curves a value of unity when f equals zero. The resulting slope is the 'normalized slope', shown in a graph in Fig. 3. The graph indicates how the release rate varies with different values of g.

4. Comparison of the model with experimental data

The theory is tested by comparing mathematical predictions with experimental data. Several sets of extraction data in the literature can be used, however, none of these include a complete set of the external parameters.

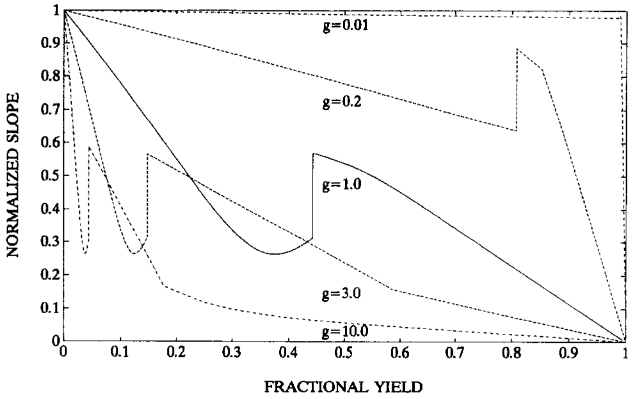

Fig. 3. Graph showing the variation of the rate of extraction vs the amount extracted.

Table 1
Parameters found by least-squares curve fitting for all data

Data file	g	t	M_f	N
Chien and Lambert	4.32	2.40 days	20.32	99.7
Yolles1	0.907	22.23 days	89.89	99.9
Yolles2	1.10	22.21 days	112.1	99.2
YollesA	1.58	5.23 days	0.816	97.9
YollesB	3.31	1.16 days	0.774	99.8
YollesC	3.34	1.05 days	0.704	99.6
Lee1	1.71	0.295 hrs	1.00	99.5
Lee2	1.34	0.507 hrs	1.00	99.5
Lee3	1.32	1.109 hrs	1.00	99.3
Hopfenberg1	0.026	8.12 days	1.98	99.7
Hopfenberg2	0.035	8.13 days	6.2	99.8

Ideally, these values should be given: D, the diffusivity of the active substance through the relaxed polymer; R, the rate at which the solvent permeates the polymer; and L_f, the thickness of the diffusional path. Data reported usually consist only of the amount extracted at various times. These data can be fitted to the theoretical model to find the critical time, t_c, and the ratio of the final length to the critical length, g. If the final length, the half thickness of the sheet, L_f, is known, then D and R can be determined.

4.1. Method of correlation of data

The values of the parameters $g = L_f/L_c$, the fractional length, t_c, the critical time, and M_f, the ultimate extract, were found by a least-squares fit of the literature data, using a computer-based search program. The measure of the goodness of fit of the model to the experimental points, N, is called the 'percentage of the fit represented by the model' (see Chatfield (1970)). The values of these parameters are listed in Table 1.

4.2. Data of Chien and Lambert (1974)

Chien and Lambert studied release of ethynodiol diacetate from a silicone device using a 62.5% polyethylene glycol 400 solution. Data are from Fig. 6, page 519, of their article. They observed that the initial rate of release was approximately proportional to elapsed time, but the rate of release later became proportional to the square root of the time. They considered the initial phase to be 'partition-controlled' and the latter phase to be 'matrix-controlled'. The phase they termed partition-controlled corresponds to phase B in this paper and matrix-controlled corresponds to phase D.

Fig. 4 plots these data as dimensionless yield vs the square root of dimensionless time, as was done in their paper. The data correlate very well with the mathematical theory.

4.3. Data of Lee (1988)

Lee investigated the fractional release of thiamine HCl from initially dry poly(2-hydroxyethyl methacrylate) (PHEMA) sheets at 37.5°C. Data are from Fig. 6, page 75, of the article cited. Each of three sheets had different initial concentrations of thiamine HCl. The thickness of the sheets was 0.0516 ± 0.005 cm (personal communication from Professor Lee in 1992), making the half thickness 0.0258 cm. Using this value, the critical length, L_c, can be calculated from the value found for g. R, the rate of advance of the interface, is the ratio L_c/t_c.

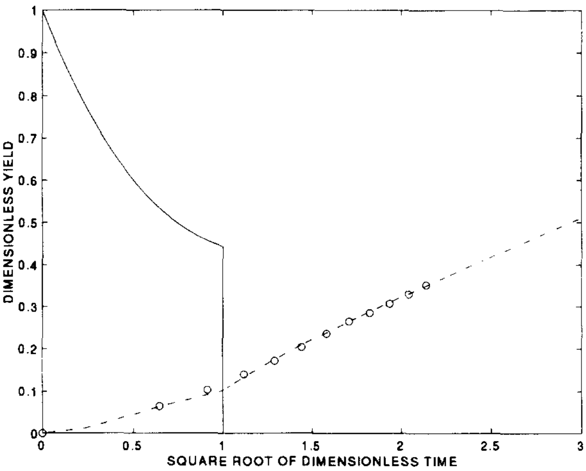

Fig. 4. Data of Chien and Lambert plotted as dimensionless yield vs the square root of dimensionless time.

Table 2
Parameters calculated for Lee's data

	Parameter			
	c_i (%)	L_c (m) ($\times 10^4$)	R (m/s) ($\times 10^7$)	D (m^2/s) ($\times 10^{12}$)
Lee1	26.06	1.509	1.426	9.944
Lee2	17.91	1.925	1.057	9.417
Lee3	9.21	1.955	0.489	4.417

In these sets of data, diffusivity varies with concentration. Tsang (1961) and Tsang and Hammarstrom (1987) have shown that when the diffusivity varies with concentration, the solution of the differential equation can still be represented as series expansion of orthogonal functions, as was done here. Diffusivities determined for these three sets of data are 'apparent diffusivities,' which are average diffusivity values over the course of the extraction.

The apparent diffusivity, D', is equal to $L_c R/2.1606$. Table 2 tabulates these values and the data are plotted in Fig. 5. Both R and D' increased as initial concentrations increased.

4.4. Data of Yolles et al. (1974)

Yolles et al. studied the release of cyclazocine (2-cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan) from a polyethylene sheet implanted in rats. The body fluids permeated and relaxed the polymer. Some cyclazocine was tritiated and the excretion could be followed radiometrically. Data referred to as Yolles1 came from their Fig. 4, page 182. Data referred to as Yolles2 came from their Fig. 3, page 181. The same chemical system was used.

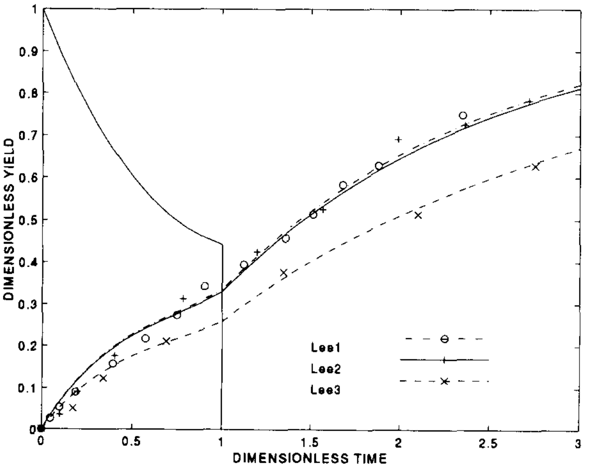

Fig. 5. Data of Lee plotted as dimensionless yield vs dimensionless time.

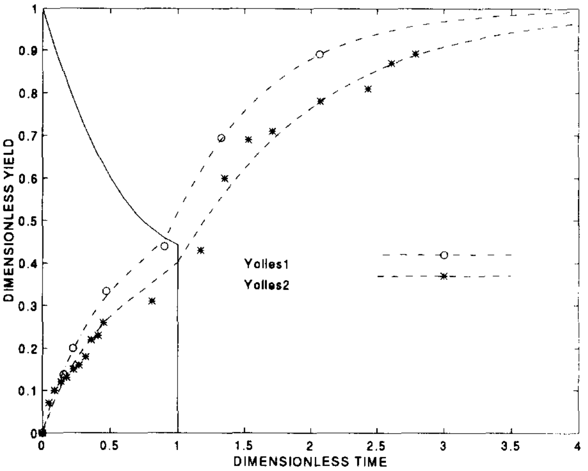

Fig. 6. Data of Yolles 1 and 2 plotted as dimensionless yield vs dimensionless time.

The value for the critical time, t_c, was found to be almost the same in the two samples, as would be expected. The two values for $g = L_f/L_c$ differed slightly, presumably because the sheets were not exactly the same thickness. In these data g is close to unity, and the 'sigmoidal wiggle' is the most pronounced.

Three sets of data, referred to as YollesA, YollesB, and YollesC, are obtained from Fig. 5, page 183, of their article studying controlled release of cyclazocine from polylactic acid (PLA) with molecular weights varying from 45 000 to 70 000. PLA is metabolized by body fluids and disintegrates over a period of time. If cyclazocine were released as a result of the metabolism of the surface of the sheet, the device would be classed as an erodible type. An erodible sheet device would be expected to erode at a constant rate and release the cyclazocine at a constant rate. This is not the case here, however. Initially the

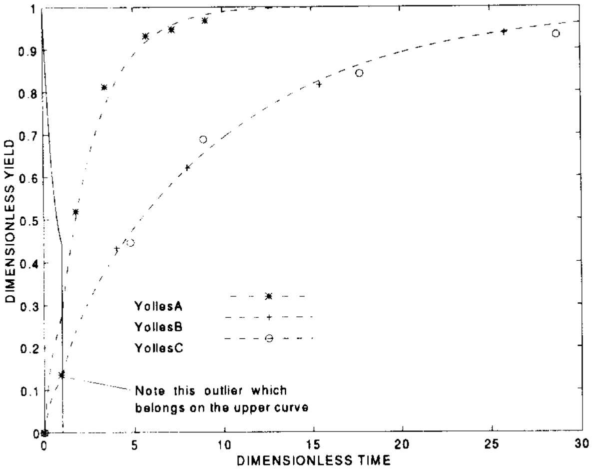

Fig. 7. Graph of the data of YollesA, YollesB, and YollesC plotted as the dimensionless yield vs the dimensionless time.

cyclazocine is released slowly, then the release rate increases rapidly to a maximum, at about 6 days, and then decays slowly. Fig. 6, page 184, of their article shows this.

The data for YollesB and YollesC with molecular weights of 60 000 and 45 000 have values of g which are almost identical: 3.31 and 3.34, respectively. The curves for these two sets of data overlap each other on Fig. 7. The values of t_c are also close at 1.16 and 1.05 days. The increase of molecular weight from 45 000 to 60 000 has made an insignificant change in the parameters of the model.

An excellent fit results with these two data sets. Our interpretation is that the release of cyclazocine is governed by the mechanism described here, at least initially. The disintegration of the matrix by metabolism is much slower, and affects the release rate in a minor way, if at all.

However, the third set, YollesA, with a molecular weight of 70 000, is very different with $g = 1.58$, and $t_c = 5.23$ days. The increase of molecular weight to 70 000 has changed both g and t_c markedly. The increase of the molecular weight to 70 000 obviously changed the ratio of the diffusivity to the permeation rate.

The experimental data in this case do not fit the mathematical predictions as well as that of any other case examined. The percentage fit of this set of data is only 97.86% as compared to over 99% for all the other data sets. The cause of the poor fit is the outlying data point, indicated on Fig. 7, at dimensionless time = 0.959 and dimensionless yield = 0.136. This data point is almost at the 'critical point' and therefore its position is indicative that this data set may be 'anomalous'. It is unlikely that this point is an experimental error, since the authors state that it is the mean value for three or four experiments. Clearly, the release mechanism for this system, using PLA with a molecular weight of 70 000, is different from that for the other systems.

However, if this is an anomalous case, indicating that the physical system was different from that postulated by the base case assumptions, it would be pure speculation to suggest which of the base case assumptions does not apply. More data are required to resolve the issue.

4.5. Data of Hopfenberg (1981)

The data of Hopfenberg are included here, although the system is not one used in pharmacy, because it shows that, if the system has a very small value of g, then the release rate is almost linear with time. Hopfenberg extracted Sudan Red IV from polystyrene films using hexane. The data selected were for the first two experiments shown in Fig. 1, page 40, in the article cited.

These two sets of data permit an independent check on the validity of the model. Sheet no. 1 was 3.30×10^{-3} cm thick and contained 1% of the diffusible material dissolved in it. Sheet no. 2 was 4.38×10^{-3} cm thick and contained 2.2% of the diffusible material.

The solvent, the polymer, and the diffusible substance were the same in both cases. According

Table 3
Parameters calculated for Hopfenberg's data

	Parameter				
	c_i (%)	L_f (m) ($\times 10^5$)	L_c (m) ($\times 10^5$)	R (m/s) ($\times 10^{10}$)	D (m^2/s) ($\times 10^{13}$)
Hopfenberg1	1.1	3.30	62.7	8.93	2.60
Hopfenberg2	2.2	4.36	62.6	8.92	2.58
% difference	–	–	0.136	0.159	0.290

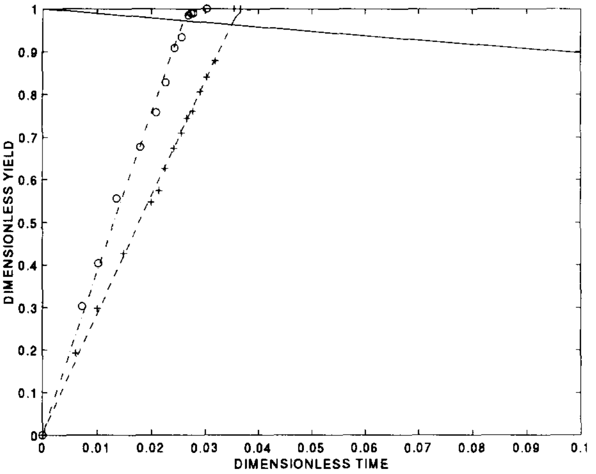

Fig. 8. Data of Hopfenberg plotted as dimensionless yield vs dimensionless time.

to the model, R, D, L_c and t_c should be the same. The values recorded in Tables 1 and 3 show that this is the case. These two sets of data are plotted on Fig. 8. As can be seen, the extraction rate is nearly linear with time.

5. Discussion

The partial differential equation governing the release of material in these types of devices is Fick's equation for unsteady state diffusion. No modification of the differential equation is necessary. The key to the problem's solution lies in incorporating the rate at which the interfacial boundary moves into the boundary conditions. This solution leads to the concept of a critical length and a critical time. The parameters which determine these values are D, the diffusivity of the solute, and R, the rate at which the interfacial boundary moves. The shape of the extraction curve is determined by g, the ratio of the final length, to the critical length.

The validity of the theory is demonstrated in the following ways:

(a) Ten sets of experimental data coming from four independent research groups are all fitted by the theory. The percentage of the fit is 99.2% or better in these cases.

(b) The theory predicts that the critical time and the critical length are the same for similar chemical systems, i.e., a system in which D and R are the same. The two sets of data from Hopfenberg (1981) and two sets of data from Yolles et al. (1974) confirm this point with the difference of the critical times being about 0.1% in both cases.

(c) The theory predicts that if g is quite small, say less than 0.05, then the extraction curve will be almost linear with time over its entire length. The data of Hopfenberg (1981) conform to this prediction.

(d) The theory predicts a sigmoidal 'wiggle' in the curve when g is near unity. The data of Yolles1 and Yolles2 conform to this prediction.

(e) The theory predicts that if g is greater than unity, there will be an induction period in the extraction curve, followed by a longer period in which the amount of extraction varies with the square root of time. The data of Chien and Lambert (1974) and the data of Lee (1988) conform to this prediction.

It should be noted that the concentration of the dissolved material had a marked effect on both R, the rate of solvent permeation, and D, the diffusivity, in experiments carried out by Lee (1988); but in the experiments of Hopfenberg (1981), both R and D were unaffected by a change in concentration.

One set of experimental data, namely, that of YollesA for cyclazocine being extracted from polylactic acid having a molecular weight of 70000, is not fitted as well as the other data. While experimental error cannot be ruled out, this poorer fit may indicate that some factor other than, or in addition to, the base case assumptions is influencing the release rate in this particular system.

The theory presented here should be a valuable tool for effectively designing polymeric controlled release devices by selection and combination of the three external physical parameters; D, R, and L_f.

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