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Application of the Higuchi model for drug release from dispersed matrices to particles of general shape

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Summary

An equation has been derived which describes the short time behaviour of the release of a dispersed drug from a homogeneous matrix of general shape using the pseudo-steady-state approximation of Higuchi. The equation has been used successfully to describe the experimentally observed release in vitro of sulphamethizole from poly(hydroxybutyrate) or poly(hydroxybutyrate)/poly(hydroxyvalerate) microparticles of irregular shape for up to 5–8 h of dissolution time corresponding to between 40–70% drug release. The equation is only valid for systems where erosion or swelling of the matrix does not contribute to drug release during the short time period.

Introduction

The release of a drug from polymeric microparticles or matrices when placed in contact with a fluid is basically a mass transfer of drug molecules from a region of high concentration (dosage form) to a region of low concentration (surrounding fluid). For a rigid matrix of specified shape (slab, sphere or cylinder) containing drug dispersed within, a model originally proposed by Higuchi (1961) has been applied to date to describe the release of drugs from a number of delivery systems. In the present study it has been shown that the Higuchi model may also be applied to describe drug release from particles of general shape. Furthermore, the theoretical equation derived was used successfully to describe the in vitro experimental release of sulphamethizole from samples of polyester microparticles reported in a previous study (Brophy and Deasy, 1986).

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Theoretical

Introduction

Consider a matrix in which drug is dispersed at an initial loading C_0. Assume that the solubility of the drug in the matrix is given by C_s and that D is the diffusivity of the drug in the homogeneous matrix. If the drug-loaded matrix is placed into a perfect sink at $t = 0$, drug will start to release. Higuchi (1961) assumes that: (i) a region with depleted drug is penetrating into the matrix; and (ii) the rate of diffusion of drug per unit area (the

mass flux) throughout this depleted region is independent of the position on the surface.

For the slab geometry, the equation given by Higuchi (1961) may be used as follows to describe drug release:

$$M(t) = A\left[D \cdot C_s(2C_0 - C_s)t\right]^{1/2} \quad (1)$$

where $M(t)$ is the total mass released up to time t; A is the total area of a two-sided slab; C_0 is the initial drug loading; and t is the time.

In a subsequent paper, Higuchi (1963) considered drug release from spherical matrix systems. He found that (when $C_0 \gg C_s$):

$$\frac{3}{2}\left\{1 - \left(1 - \frac{M(t)}{M_\infty}\right)^{2/3}\right\} - \frac{M(t)}{M_\infty} = \frac{3D \cdot C_s}{r_0^2 \cdot C_0} t \quad (2)$$

where M_∞ is the total amount of drug in the sphere with radius r_0. If one looks at the behaviour of $M(t)$ for short times, one can use:

$$\left(1 - \frac{M(t)}{M_\infty}\right)^{2/3} \approx 1 - \frac{2}{3}\frac{M(t)}{M_\infty} - \frac{1}{9}\left(\frac{M(t)}{M_\infty}\right)^2 + \ldots \quad (3)$$

Substituting Eqn. 3 into Eqn. 2 then:

$$\frac{M(t)}{M_\infty} \approx \left(\frac{18D \cdot C_s \cdot t}{r_0^2 \cdot C_0}\right)^{1/2} \quad (4)$$

Since

$$M_\infty = \tfrac{4}{3}\pi \cdot C_0 \cdot r_0^3 \quad (5)$$

and the area of a sphere is

$$A = 4\pi \cdot r_0^2 \quad (6)$$

it is clear that (substituting Eqns. 5 and 6 into Eqn. 4),

$$M(t) \approx A(2D \cdot C_s \cdot C_0 \cdot t)^{1/2} \quad (7)$$

Thus under the assumption $C_0 \gg C_s$ for short times: (i) $M(t)$ is proportional to $t^{1/2}$, and (ii) $M(t)$ is proportional to the surface area of the matrix. Similarly, the amount of drug released from a homogeneous cylindrical matrix, as described by Roseman and Higuchi (1970), is also given by Eqn. 7. A in Eqn. 7 is then the area of a cylinder.

The present study shows that under the assumptions made by Higuchi (1961) any particle with a regular boundary will follow for a short time the release given by Eqn. 1 where A is the total area of the particle. Furthermore, the next order correction to the short time behaviour given by Eqn. 1 is computed. Before stating the main result let us define the area $A(x)$ of a surface parallel to the surface of the particle at a fixed distance x (see Fig. 1).

So, for example, a cube with volume L^3 will have:

$$A(x) = 6(L - 2x)^2 \quad (8)$$

and a sphere with volume $4/3\pi r^3$ will have

$$A(x) = 4\pi(r - x)^2 \quad (9)$$

A particle is said to have a regular surface if for small x there is a constant c, such that

$$A(x) = A - cx + \ldots \quad (10)$$

For instance, a cube has a regular surface because:

$$A = 6L^2 \quad (11)$$

so that Eqn. 10 is satisfied with constant $c = 24L$. For the sphere with radius r, $c = 8\pi r$.

The main result of this study is that for any particle with a regular surface and corresponding

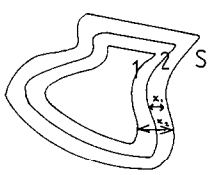

Fig. 1. Two surfaces (1, 2) parallel to the outer surface S at distances x_1 and x_2.

constant c for short time

$$M(t) = A\left[D \cdot C_s(2C_0 - C_s)t\right]^{1/2} - \tfrac{4}{9}cC_s\frac{3C_0 - 2C_s}{2C_0 - C_s}D \cdot t \qquad (12)$$

using the approximations of Higuchi. So each particle with a regular surface releases drug like a slab with corresponding area of exposure (short t). The second term in Eqn. 12 is a long time correction. This depends in more detail on the shape of the particle.

Derivation of Eqn. 12

In accordance with Higuchi's pseudo-steady-state approximation, it is assumed that the mass flux is independent of the position in the depleted region. Let $C(x)$ be the concentration of dissolved drug at the parallel surface (at distance x from the boundary of the matrix). Then Fick's first law is:

$$\phi = D \cdot A(x)\frac{\delta C(x)}{\delta x} \qquad (13)$$

where $\phi = \mathrm{d}M(t)/\mathrm{d}t$.

Since ϕ is not dependent upon x, Eqn. 13 may be integrated, assuming sink conditions at $x = 0$:

$$C(x) = \frac{\phi}{D}\int_0^x \frac{\mathrm{d}x}{A(x)} \qquad 0 < x < x' \qquad (14)$$

For short times t, x' (and x) should be small so

$$\frac{1}{A(x)} \approx \frac{1}{A - cx} \approx \frac{1}{A} + \frac{cx}{A^2} \qquad (15)$$

Substituting Eqn. 15 into Eqn. 14 one obtains

$$C(x) = \frac{\phi}{A \cdot D}\left(x + \frac{c \cdot x^2}{2A}\right) \qquad (16)$$

At the diffusion front,

$$C_s = C(x') \approx \frac{\phi}{A \cdot D}\left(x' + \frac{c \cdot x'^2}{2A}\right) \qquad (17)$$

Eliminating ϕ from Eqns. 16 and 17 gives

$$C(x) \approx C_s \cdot \frac{x + \dfrac{c \cdot x^2}{2A}}{x' + \dfrac{c \cdot x'^2}{2A}} \approx C_s \cdot \frac{x}{x'} \cdot \left(1 + \frac{c \cdot x}{2A} - \frac{c \cdot x'}{2A}\right) \qquad (18)$$

The total amount of dissolved drug remaining in the depleted region is therefore (using Eqn. 18):

$$\int_0^{x'} C(x)A(x)\,\mathrm{d}x \approx C_s\int_0^{x'} \frac{x}{x'} \cdot \left(1 + \frac{c \cdot x}{2A} - \frac{c \cdot x'}{2A}\right) \cdot (A - c \cdot x)\,\mathrm{d}x \approx C_s\left(\frac{Ax'}{2} - \tfrac{5}{12}c \cdot x'^2\right) \qquad (19)$$

The amount of dissolved drug remaining between two parallel surfaces at distances x' and $x' + \mathrm{d}x'$ from the boundary is then:

$$C_s\left(\frac{A}{2} - \tfrac{5}{6}c \cdot x'\right)\mathrm{d}x' \qquad (20)$$

The mass balance (for the region between the two parallel surfaces) becomes

$$\phi\,\mathrm{d}t \approx C_0 \cdot A(x')\,\mathrm{d}x' - \left(\frac{A}{2} - \tfrac{5}{6}c \cdot x'\right)C_s \cdot \mathrm{d}x' = \left(C_0 - \frac{C_s}{2}\right)A \cdot \mathrm{d}x' + \left(\tfrac{5}{6}c \cdot C_s - c \cdot C_0\right)x' \cdot \mathrm{d}x' \qquad (21)$$

ϕ can now be eliminated from Eqns. 17 and 20. This yields

$$D \cdot C_s \cdot A \cdot \mathrm{d}t = A\left(C_0 - \frac{C_s}{2}\right)x' \cdot \mathrm{d}x' - c\left(\frac{C_0}{2} - \tfrac{7}{12}C_s\right)x'^2 \cdot \mathrm{d}x' \qquad (22)$$

Integrating Eqn. 22 (using initial conditions $x' = 0$

at $t = 0$) gives:

$$D \cdot C_s \cdot A \cdot t = A\left(C_0 - \frac{C_s}{2}\right)\frac{x'^2}{2} - \frac{c}{6}\left(C_0 - \tfrac{7}{6}C_s\right)x'^3 \tag{23}$$

From Eqn. 17, ϕ as a function of x' is obtained as follows:

$$\phi = \frac{A \cdot D \cdot C_s}{x' + \dfrac{c \cdot x'^2}{2A}} \approx \frac{A \cdot D \cdot C_s}{x'} - \frac{c \cdot D \cdot C_s}{2} \tag{24}$$

From Eqn. 23 $1/x'$, as a function of t is obtained: Put $x' = 1/q$ into Eqn. 27 then:

$$\frac{2D \cdot C_s \cdot t \cdot q^3}{C_0 - \dfrac{C_s}{2}} = q - \frac{c}{3A} \cdot \frac{C_0 - \tfrac{7}{6}C_s}{C_0 - \dfrac{C_s}{2}} \tag{25}$$

Since one is only interested in approximate solution for short time the following equation:

$$q = \left(\frac{2D \cdot C_s \cdot t}{C_0 - \dfrac{C_s}{2}}\right)^{-1/2} + \delta \tag{26}$$

may be substituted into Eqn. 25 to give:

$$\delta = -\frac{c}{6A} \cdot \frac{C_0 - \tfrac{7}{6}C_s}{C_0 - \dfrac{C_s}{2}} \tag{27}$$

If Eqn. 27 is substituted into Eqn. 26, and Eqn. 26 is further substituted into Eqn. 24, one obtains:

$$\phi = A\left[D \cdot C_s\left(C_0 - \frac{C_s}{2}\right) \cdot \frac{1}{2t}\right]^{1/2} - \tfrac{4}{9}c \cdot D \cdot C_s \cdot \frac{3C_0 - 2C_s}{2C_0 - C_s} \tag{28}$$

Integrating Eqn. 28 between 0 and t gives Eqn. 12.

Validity of the results

In the case of a slab, Eqn. 1 can only hold for times such that:

$$M(t) \leqslant A \cdot C_0 \cdot d/2$$

Thus

$$t \leqslant T_1 = \frac{d^2 \cdot C_0^2}{4D \cdot C_s(2C_0 - C_s)} \tag{29}$$

The release mechanism will change when $2x' = d$. This happens at a time

$$T_2 = \frac{d^2}{16D \cdot C_s} \cdot (2C_0 - C_s) \tag{30}$$

Thus Eqn. 1 is only valid for times smaller than T_1 and T_2. For a more general matrix, one has the requirement $M(t) \leqslant V \cdot C_0$ where V is the volume of the matrix. Thus

$$T_1' = \left(\frac{V}{A}\right)^2 \cdot \frac{C_0^2}{4D \cdot C_s}(2C_0 - C_s). \tag{31}$$

So the thickness d in Eqn. 29 has been replaced by V/A in Eqn. 31. For general matrix systems, it is difficult to determine the time T_2', when diffusion fronts are going to coalesce. However, in view of Eqns. 29 and 31 it seems plausible that:

$$T_2' = \left(\frac{V}{A}\right)^2 \cdot \frac{2C_0 - C_s}{16D \cdot C_s} \tag{32}$$

Furthermore in the derivation of Eqn. 12, $cx'/2A \ll 1$ was used. This gives $t \leqslant T_3'$ where

$$T_3' = \frac{A^2}{c^2} \cdot \frac{2C_0 - C_s}{D \cdot C_s} \tag{33}$$

Experimental

Methods

Polyhydroxybutyrate (PHB) or copolymers of hydroxybutyrate/hydroxyvalerate (PHB/PHV) were used to prepare a drug-loaded matrix by a solvent evaporation process as described in a previous study (Brophy and Deasy, 1986). The matrix

containing sulphamethizole dispersed within was subsequently ground to give irregular-shaped microparticles of a desired size range. A number of the irregular microparticles were thus selected (see Table 1) for comparison of their in vitro experimental release with the theoretical equation for general shape (Eqn. 12) derived in this study.

Theoretical versus experimental

From Eqn. 12 it is evident that the fraction of drug released at time t is of the form

$$f(t) = B_1 t^{1/2} - B_2 t$$

Tables 2, 3, 4 and 5 and Figs. 2, 3, 4 and 5 show the theoretical release of a drug from matrices of general shape in comparison with the experimentally observed release of products A_I, A_{II}, B and C, respectively (Table 1). Agreement of the model with the in vitro release was good in all cases for up to 5–8 h release period when after such times the model is no longer applicable. This corresponded to approximately 50% drug release for three of the products tested and up to 70% drug release for the remaining product. In addition, the general model equation shows clearly that regardless of the shape of the particle, the mass released is proportional to $t^{1/2}$ and the area of the matrix for small values of t. Further, for large values of t the contribution of the term proportional to t becomes significant.

This general shape equation should be useful for a number of pharmaceutical systems where the matrix containing dispersed drug is irregular in shape. It is only strictly applicable to a rigid matrix and does not include any parameters for

TABLE 1

Characterization of polyester microparticles containing sulphamethizole dispersed within

Product	Polymer	Weight average molecular weight (M_w)	Drug loading (%)	Particle size range (μm)
A_I	PHB	1.4×10^5	50	425– 600
A_{II}	PHB	1.4×10^5	50	1180–2000
B	PHB	1×10^6	47	1180–2000
C	PHB/PHV	1.7×10^5	46	1180–2000

TABLE 2

Comparison of the theoretical release of a drug from a matrix of general shape (mean size 512.5 μm) using Eqn. 12 derived in this study and the experimental release of sulphamethizole from Product A_I (Table 1)

$f(t) = B_1 \cdot t^{1/2} - B_2 \cdot t$

$B_1 = 62.7\% \cdot \sqrt{h}^{-1}$; $B_2 = 13.3\% \cdot h^{-1}$

t (h)	$f(t)_{theor}$ (%)	$f(t)_{exp}$ (%)
0.08	17	21
0.25	28	28
0.5	38	40
1.0	49	49
1.5	57	57
2.0	62	61
3.0	69	68
4.0	72	72
5.0	74	77
6.0	75	89

TABLE 3

Comparison of the theoretical release of a drug from a matrix of general shape (mean size 1590 μm) using Eqn. 12 derived in this study and the experimental release of sulphamethizole from Product A_{II} (Table 1)

$f(t) = B_1 \cdot t^{1/2} - B_2 \cdot t$

$B_1 = 28.6\% \cdot \sqrt{h}^{-1}$; $B_2 = 3.5\% \cdot h^{-1}$

t (h)	$f(t)_{theor}$ (%)	$f(t)_{exp}$ (%)
0.083	7.98	10.55
0.1	11.1	13.15
0.25	13.43	15.25
0.33	15.34	16.85
0.5	18.47	19.7
0.67	21.0	21.0
0.83	23.20	23.35
1.0	25.10	24.1
1.5	29.78	30.2
2.0	33.44	33.25
3.0	39.04	39.5
4.0	43.2	41.2
5.0	46.45	45.75
6.0	49.06	49.5
7.0	51.17	51.45
8.0	52.96	53.6
10.0	55.44	59.5

TABLE 4

Comparison of the theoretical release of a drug from a matrix of general shape (mean size 1590 μm) using Eqn. 12 derived in this study and the experimental release of sulphamethizole from Product B (Table 1)

$f(t) = B_1 \cdot t^{1/2} - B_2 \cdot t$

$B_1 = 36.3\% \cdot \sqrt{h}^{-1}$; $B_2 = 5.3\% \cdot h^{-1}$

t(h)	$f(t)_{theor}$ (%)	$f(t)_{exp}$ (%)
0.08	10.1	12.6
0.25	16.8	18.0
0.5	23.0	23.3
1.0	31.0	30.5
1.5	36.5	35.4
2.0	40.7	39.9
3.0	46.9	45.1
4.0	51.4	49.3
5.0	54.7	55.5
6.0	57.1	57.8
7.0	58.9	61.9
8.0	60.3	65.0
10.0	61.8	69.9

the presence of moving boundaries such as swelling or erosion of the polymer. Such analysis requires complex mathematical treatment. In the

TABLE 5

Comparison of the theoretical release of a drug from a matrix of general shape (mean size 1590 μm) using Eqn. 12 derived in this study and the experimental release of sulphamethizole from Product C (Table 1)

$f(t) = B_1 \cdot t^{1/2} - B_2 \cdot t$

$B_1 = 26\% \cdot \sqrt{h}^{-1}$; $B_2 = 4\% \cdot \sqrt{h}^{-1}$

t (h)	$f(t)_{theor}$(%)	$f(t)_{exp}$ (%)
0.08	7.2	9.25
0.25	12.0	13.07
0.5	16.0	16.65
1.0	22.0	21.35
1.5	25.8	24.2
2.0	28.8	27.35
3.0	33.0	31.9
4.0	36.0	34.2
5.0	38.1	36.6
6.0	39.7	38.5
7.0	40.8	41.99
8.0	41.5	42.5
10.0	42.2	46.3
12.0	42.1	49.55

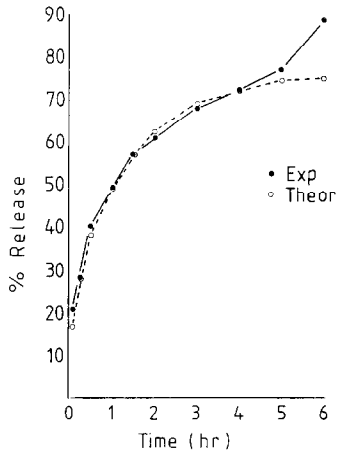

Fig. 2. Comparison of the theoretical versus experimental release of drug for particles, mean size 512.5 μm, using the general shape equation derived (Eqn. 12) and Product A_I (Table 1).

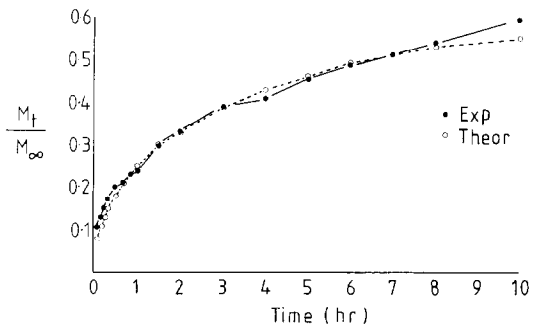

Fig. 3. Comparison of the theoretical versus experimental release of drug for particles, mean size 1590 μm, using the general shape equation derived (Eqn. 12) and Product A_{II} (Table 1).

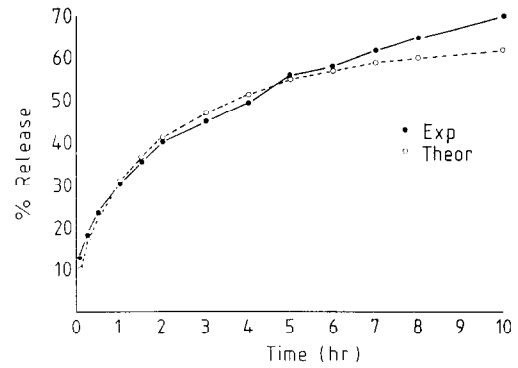

Fig. 4. Comparison of the theoretical versus experimental release of drug for particles, mean size 1590 μm, using the general shape equation derived (Eqn. 12) and Product B (Table 1).

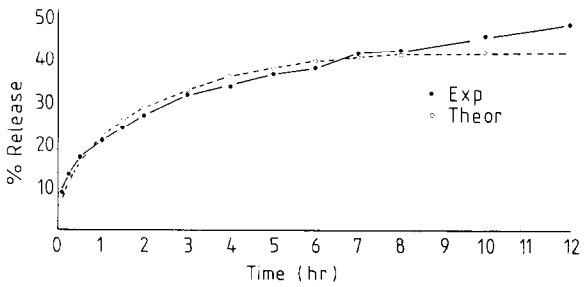

Fig. 5. Comparison of the theoretical versus experimental release of drug for particles, mean size 1590 μm, using the general shape equation derived (Eqn. 12) and Product C (Table 1).

case of PHB or its copolymers, PHB/PHV, the contribution of erosion of the polymer to the release of sulphamethizole was negligible over the time scale studied and thus the general shape equation derived was applicable. However, for longer release periods of several weeks to months, erosion of biodegradable polymers would probably contribute to the overall release characteristics of the drug and the general shape equation may then be unsuitable.

In conclusion, an equation has been derived, using the pseudo-steady-state approximations of Higuchi, which describes the release of a dispersed solute from a rigid matrix of general shape. The equation shows that for short time, drug release is proportional to $t^{1/2}$ and the area of the matrix regardless of the shape. In addition, for larger times the equation shows that the contribution of the term proportional to t is significant.

The equation derived, adequately described the in vitro experimental release of sulphamethizole from PHB microparticles of no specific shape. The equation should thus be useful to describe drug release from a variety of drug delivery systems where erosion or swelling of the matrix does not contribute to the release during the short time period.

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