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A SIMPLE EQUATION FOR DESCRIPTION OF SOLUTE RELEASE I. FICKIAN AND NON-FICKIAN RELEASE FROM NON-SWELLABLE DEVICES IN THE FORM OF SLABS, SPHERES, CYLINDERS OR DISCS

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The simple exponential relation $M_t/M_\infty = kt^n$ *is introduced to describe the general solute release behavior of controlled release polymeric devices, where* M_t/M_∞ *is the fractional solute release,* t *is the release time,* k *is a constant, and* n *is the diffusional exponent characteristic of the release mechanism. It is shown that this equation can adequately describe the release of drugs or other solutes from slabs, spheres, cylinders and discs (tablets), regardless of the release mechanism. It is shown that in cases of pure Fickian release the exponent* n *has the limiting values of 0.50, 0.45 and 0.43 for release from slabs, cylinders and spheres, respectively. For tablets, and depending on the aspect ratio, i.e., the ratio of diameter to thickness, the Fickian diffusion mechanism is described by* $0.43 < n < 0.50$. *For drug release from spherical polymer particles of a wide distribution, the value of the exponent* n *for Fickian diffusion depends on the width of the distribution.*

INTRODUCTION

Modelling of controlled release of drugs from polymeric devices has been the subject of considerable research over the past fifteen years. Several reviews [1–4] have been written which address the principles of modelling of diffusional release from polymers.

Most of the models that have been developed are based on solutions of the Fickian diffusion equation published in the classic book of Crank [5]. In the pharmaceutical field, several other equations have found acceptability for the analysis of drug release from tablets, etc., such as the Higuchi model [6], its more exact counterpart developed by Paul and McSpadden [7], the models of Roseman and Higuchi [8,9] and the recently developed diffusion/dissolution models [10].

Unfortunately, over the years the solutions [1–5] of the Fickian diffusion equation have been often misinterpreted or misunderstood by those working in the pharmaceutical and controlled release fields. One finds a plethora of publications where these equations have been erroneously applied.

To simplify somewhat the analysis of controlled release data from polymeric devices of varying geometry we proposed in 1984 [11,12] a new empirical, exponential expression which relates the fractional release of drug, M_t/M_∞, to the release time, t. The purpose of this contribution is to investigate the importance of the diffusional exponent, n, of this equation and to establish simple methods of analysis of controlled release data from various classical geo-

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metric shapes for the case of non-swellable polymeric delivery systems.

ANALYSIS OF DRUG RELEASE

Models to describe drug release from a plane sheet

Fickian diffusional release from a thin polymer film

Consider one-dimensional, isothermal solute release from a thin polymer slab of thickness l where the system is initially maintained at a constant uniform drug concentration, C_1, and its surfaces are kept at a constant drug concentration, C_0. This situation corresponds to typical experimental conditions for a release experiment and is referred to as the *perfect sink condition*. For an assumed constant drug diffusion coefficient, D, with one-dimensional diffusion in the x direction, Fick's second law, along with the appropriate initial and boundary conditions, may be written as

$$\frac{\partial C}{\partial t}=D\frac{\partial^2 C}{\partial x^2} \tag{1}$$

where

$$\begin{array}{lll} t=0 & -l/2<x<l/2 & C=C_1 \\ t>0 & x=\pm l/2 & C=C_0 \end{array}$$

The solution to Fick's law in the form of a trigonometric series under the above-specified conditions is

$$\frac{M_t}{M_\infty}=1-\sum_{n=0}^{\infty}\frac{8}{(2n+1)^2\pi^2}\exp\left[\frac{-D(2n+1)^2\pi^2}{l^2}t\right] \tag{2}$$

where M_t is defined as the mass of drug released at time t, and M_∞ is the mass of drug released as time approaches infinity. An alternate solution to eqn. (1) that is useful for interpretation of short-time behavior is given in the form of an error function series.

$$\frac{M_t}{M_\infty}=4\left[\frac{Dt}{l^2}\right]^{1/2}\left[\frac{1}{\pi^{1/2}}+2\sum_{n=1}^{\infty}(-1)^n\,\mathrm{ierfc}\,\frac{nl}{2\sqrt{Dt}}\right] \tag{3}$$

where ierfc x represents the integrated complementary error function of x. For "small times", i.e., small values of the dimensionless time τ, defined as $4Dt/l^2$, eqn. (3) can be approximated by

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

As indicated by eqn. (4), Fickian diffusional release from a thin film is characterized by an initial $t^{1/2}$ time dependence of the drug released. The short-time approximation is valid for the first 60% of the total released drug ($M_t/M_\infty \leqslant 0.60$).

Semi-empirical equation for drug release from thin polymer slabs

A simple semi-empirical equation is introduced to express general drug release behavior from polymers. For Fickian diffusion in a thin film, eqn. (4) 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. A second limiting case is one where the drug release rate is independent of time, i.e., the kinetics is of zero-order. Such a situation is described by a general equation of the form

$$\frac{M_t}{M_\infty}=k't \tag{5}$$

Many situations of release processes fall between these limiting cases, i.e., they can be represented by coupling of a Fickian and a non-Fickian mechanism. Then, a simple expression of this observation can be heuristically written by adding the two expressions of eqns. (4) and (5):

$$\frac{M_t}{M_\infty}=k_1\sqrt{t}+k_2 t \tag{6}$$

A generalized expression of the previous equation can be written as

$$\frac{M_t}{M_\infty}=kt^n \tag{7}$$

where k is a constant incorporating characteristics of the macromolecular network system and the drug, and n is the *diffusional exponent*, which is indicative of the transport mechanism. Equation (7) is valid again for the first 60% of the fractional release. Fickian diffusion is defined by n equal to 0.50 and non-Fickian by n greater than 0.50.

Utility of the empirical equation

The empirical transport equation (7) represents an extension of the short time solutions for Fickian and non-Fickian diffusional release from a thin film. In theory, this equation should only be applicable to the first 60% of fractional release from thin slabs, for which the assumption of one-dimensional diffusion under perfect sink conditions is valid. In practice, however, the equation has been applied to systems of different geometries, to systems where one-dimensional diffusion cannot be assumed, and to systems where perfect sink boundary conditions are not maintained.

For example, several investigators have utilized this expression to analyze the first 60% of the release process from spherical particles. While the general form of eqn. (7) should be valid for non-planar geometries, it is not correct to assume that the values of the diffusional exponent n which define the limiting transport mechanisms of Fickian diffusion and zero-order release are independent of geometry. In the application of eqn. (7) to non-planar geometries, it has generally been assumed that the geometric considerations are taken into account by the constant k; no geometric dependency has been assumed for the diffusional exponent n. Unfortunately, these assumptions are not correct.

Deviations from one-dimensional diffusion behavior and changes in the boundary conditions should also affect the interpretation of the constant k and the diffusional exponent n.

Release behavior from cylinders and spheres

Release from cylinders

For one-dimensional radial release from a cylinder of radius a, under perfect sink initial and boundary conditions, with a constant drug diffusion coefficient D, Fick's second law may be written as

$$\frac{\partial C}{\partial t}=D\left[\frac{\partial^2 C}{\partial r^2}+\frac{1}{r}\frac{\partial C}{\partial r}\right] \tag{8}$$

where

$$\begin{array}{lll} t=0 & 0<r<a & C=C_1 \\ t=0 & r=a & C=C_0 \end{array}$$

The solution to Fick's law under the above-specified conditions is [5]:

$$\frac{M_t}{M_\infty}=1-\sum_{n=1}^{\infty}\frac{4}{a^2\alpha_n^2}\exp[-D\alpha_n^2 t] \tag{9}$$

where the terms α_n are the positive roots of

$$J_0(a\alpha_n)=0$$

J_0 is the Bessel function of the first kind of zero order, and $a\alpha_n$ are the zeros of that function. An alternate solution [1,3] useful for interpretation of short-time behavior is given as

$$\frac{M_t}{M_\infty}=4\left[\frac{Dt}{\pi a^2}\right]^{1/2}-\pi\left[\frac{Dt}{\pi a^2}\right]-\frac{\pi}{3}\left[\frac{Dt}{\pi a^2}\right]^{3/2}+\ldots \tag{10}$$

A graphical comparison of eqns. (7) and (10) shows that the semi-empirical equation (7) with $n=0.50$ and $k=4(D/\pi a^2)^{1/2}$ is valid only for the first 15 to 20% of the total release process, i.e., it is incorrect to analyze solute release

data from cylindrical devices using the $t^{1/2}$ dependence of the quantity of solute released.

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, Fick's second law may be written as

$$\frac{\partial C}{\partial t}=D\left[\frac{\partial^2 C}{\partial r^2}+\frac{2}{r}\frac{\partial C}{\partial r}\right] \tag{11}$$

where

$$\begin{array}{lll} t=0 & 0<r<a & C=C_1 \\ t>0 & r=a & C=C_0 \end{array}$$

The solution to Fick's law under the above specified conditions is [5]:

$$\frac{M_t}{M_\infty}=1-\frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left[\frac{-Dn^2\pi^2 t}{a^2}\right] \tag{12}$$

An alternate solution [1,3] useful for interpretation of short-time behavior is given as

$$\frac{M_t}{M_\infty}=6\left[\frac{D\,t}{a^2}\right]^{1/2}\left[\frac{1}{\pi^{1/2}}+2\sum_{n=1}^{\infty}\text{ierfc}\frac{n\,a}{\sqrt{D\,t}}\right]$$
$$-3\frac{D\,t}{a^2}=6\left[\frac{D\,t}{\pi a^2}\right]^{1/2}-3\frac{D\,t}{a^2} \tag{13}$$

A graphical comparison of eqns. (7) and (13) shows that the empirical equation (7) defined by $n=0.50$ and $k=6(D/\pi a^2)^{1/2}$ gives a $t^{1/2}$ dependence which is valid only for the first 10 to 15% of the total drug released. Again, a $t^{1/2}$ dependence cannot be used when analyzing data of solute release from spherical devices.

Dependence of the diffusional exponent on geometry

From a theoretical standpoint, Fickian diffusion may be defined by an initial $t^{1/2}$ time dependence of the fractional release for slabs, cylinders, and spheres. From an experimental standpoint, however, the characteristic time dependence of Fickian diffusion is of little utility in analyzing release data obtained from spherical or cylindrical systems; this time dependence only predicts the first 15% of the total fractional release by these two mechanisms. Thus, application of the empirical equation (7) to the first 60% of the release process in either cylindrical or spherical systems cannot be correctly interpreted with reference to the diffusional limits of n as were defined from planar geometry.

The empirical equation (7) can be modified for application to non-planar geometries in one of two ways: (i) one can restrict analysis of the data to the initial 15% of the fractional release, a ridiculous idea indeed; or (ii) one can define new diffusional limits of n for each geometry based on the first 60% of the fractional release. Only the latter represents a useful modification. Limiting the analysis of experimental data to the first 15% of the release process could render any value of n obtained statistically insignificant.

In order to evaluate the dependence of the value of n on geometry, eqn. (7) was applied to the first 60% of the fractional release curves for Fickian diffusion from a cylinder. The results of this analysis are presented in Fig. 1. Fickian diffusion from a cylinder is defined by eqn. (7) with $n=0.451\pm0.004$ (throughout this work the confidence limits presented for any parameter are the 95% confidence limits). Similar analysis was performed on the first 60% of the release process for Fickian diffusion from a sphere. Figure 2 represents the results of this analysis. For a sphere, Fickian diffusion is defined by eqn. (7) with $n=0.432\pm0.007$. It should be noted that this analysis predicts values of $n<0.5$; this corrects an earlier statement that n may take values only equal or greater than 0.5 [12].

The relationship between the diffusional exponent n and the corresponding release mechanism is clearly dependent upon the geometry employed as shown in Table 1. 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.

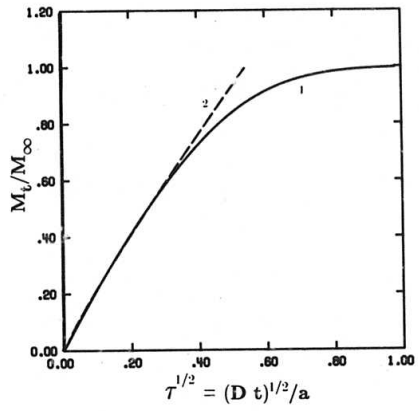

Fig. 1. Fractional drug release, M_t/M_∞, versus square root of dimensionless time, $\sqrt{\tau}$, for Fickian diffusional release from a cylinder. Comparison of the solutions presented by eqn. (9) (curve 1) and eqn. (7) with $n=0.45$ (curve 2).

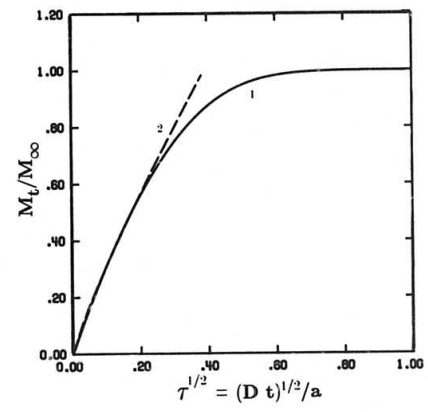

Fig. 2. Fractional drug release, M_t/M_∞, versus square root of dimensionless time, $\sqrt{\tau}$, for Fickian diffusional release from a sphere. Comparison of the solutions presented by eqn. (12) (curve 1) and eqn. (7) with $n=0.43$ (curve 2).

Three-dimensional release behavior

For analysis of three-dimensional release from a polymer disk a model first developed by Fu et al. [13] was used. Cylindrical coordinates were utilized in the solution of Fick's second law and diffusion in both the radial direction, r, and the axial direction, z (diffusion in the third direction θ is symmetric), was considered. This model is applicable to systems that range in shape from a flat disk or tablet (where the radius is much larger than the sample thickness) to that of a cylindrical rod (where the length of the sample is much larger than the radius).

Description of the mathematical model

Consider release from a disk which can be characterized by a thickness l and a diameter $2a$; this system is defined by an aspect ratio of $2a/l$. Initially the system is maintained at a constant uniform drug concentration, C_1, and the surfaces are kept at a constant drug concentration, C_0. For an assumed constant drug diffusion coefficient D with diffusion in both the r and z directions, Fick's second law, along with the appropriate initial and boundary conditions, may be written as

$$\frac{\partial C}{\partial t}=D\left[\frac{\partial^2 C}{\partial r^2}+\frac{1}{r}\frac{\partial C}{\partial r}+\frac{\partial^2 C}{\partial z^2}\right] \tag{14}$$

where

$$\begin{array}{lll} t=0 & \begin{array}{l}-l/2<z<l/2\\ 0<r<a\end{array} & C=C_1 \\ t>0 & \begin{array}{l}z=\pm l/2\\ r=a\end{array} & C=C_0 \end{array}$$

The concentration profile defined by the above diffusion equation was obtained by Carlsaw and Jaeger [14]. From this drug concentration profile Fu et al. [13] calculated the total

TABLE 1

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

Diffusional exponent, n			Drug release mechanism
Thin film	Cylindrical sample	Spherical sample	
0.50	0.45	0.43	Fickian diffusion
$0.50<n<1.00$	$0.45<n<1.00$	$0.43<n<1.00$	Anomalous (non-Fickian) transport
1.0	1.0	1.0	Zero-order release

drug transferred across the lateral surface and the two end surfaces of the disk. (The reader should note that Fu et al. used $2l$ as the thickness of this disk whereas the equations presented here have been adjusted by defining the thickness by l.) In terms of normalized drug released, M_t/M_∞, the solution can be written as follows

$$\frac{M_t}{M_\infty}=1-\sum_{n=1}^{\infty}\frac{4}{a^2\alpha_n^2}\exp[-D\alpha_n^2 t]\times\sum_{m=0}^{\infty}\frac{8}{l^2\beta_m^2}\exp[-D\beta_m^2 t] \quad (15)$$

where the terms β_m are defined as

$$\beta_m=\frac{(2m+1)\pi}{l}$$

and the terms α_n are the positive roots of

$$J_0(a\alpha_n)=0$$

Here J_0 is the zero-order Bessel function of the first kind and $a\alpha_n$ are the zeros of that function.

This model reduces to the equations governing one-dimensional diffusional release from a slab or from a long cylinder for $a\to\infty$ and $l\to\infty$, respectively. For the slab case, as $a\to\infty$ each exponential term $\exp(-D\alpha_n^2 t)$ of the summation goes to 1, since $\alpha_n\to 0$. Thus one finds

$$\lim_{a\to\infty}\sum_{n=1}^{\infty}\frac{1}{a^2\alpha_n^2}\exp[-D\alpha_n^2 t]=\sum_{n=1}^{\infty}\frac{1}{a^2\alpha_n^2}=\frac{1}{4} \quad (16)$$

Substituting this result into eqn. (15) one obtains eqn. (2) which defines one-dimensional release from a thin slab. For the long cylinder case, as $l\to\infty$, $\beta_m\to 0$ so that each exponential term $\exp(-D\beta_m^2 t)$ of the summation goes to 1. Thus, one finds

$$\lim_{l\to\infty}\sum_{m=0}^{\infty}\frac{1}{l^2\beta_m^2}\exp[-D\beta_m^2 t]=\sum_{m=0}^{\infty}\frac{1}{l^2\beta_m^2}=\frac{1}{8} \quad (17)$$

For this case, eqn. (15) reduces to eqn. (9), which defines one-dimensional release from a cylinder.

Development of a short-time approximation

An approximate solution valid for describing short-time behavior can be obtained from consideration of the short-time behavior for one-dimensional release from slabs and cylinders. From eqns. (2), (3), (15) and (16) one finds that the fractional release of drug for one-dimensional diffusion from a slab can be written as

$$\frac{M_t}{M_\infty}=1-\sum_{m=0}^{\infty}\frac{8}{l^2\beta_m^2}\exp[-D\beta_m^2 t]=4\left[\frac{Dt}{l^2}\right]^{1/2}\left[\frac{1}{\pi^{1/2}}+2\sum_{n=1}^{\infty}(-1)^n\,\mathrm{ierfc}\,\frac{nl}{2\sqrt{Dt}}\right] \quad (18)$$

For short times each term in the function ierfc $(nl/2\sqrt{Dt})$ approaches zero. Thus, eqn. (18) can be written as

$$\sum_{m=0}^{\infty}\frac{8}{l^2\beta_m^2}\exp[-D\beta_m^2 t]=1-4\left[\frac{Dt}{\pi l^2}\right]^{1/2} \quad (19)$$

Similarly for one-dimensional release from a cylinder, eqns. (9) and (10) can be equated for short times. From this analysis one finds that

$$\sum_{n=1}^{\infty}\frac{4}{a^2\alpha_n^2}\exp[-D\alpha_n^2 t]=1-4\left[\frac{Dt}{\pi a^2}\right]^{1/2}+\pi\left[\frac{Dt}{\pi a^2}\right]+\frac{\pi}{3}\left[\frac{Dt}{\pi a^2}\right]^{3/2} \quad (20)$$

Substituting eqns. (19) and (20) into eqn. (15) one finds that for short times the fractional release from a disk can be written as

$$\frac{M_t}{M_\infty}=4\left[\frac{Dt}{\pi a^2}\right]^{1/2}-\pi\left[\frac{Dt}{\pi a^2}\right]-\frac{\pi}{3}\left[\frac{Dt}{\pi a^2}\right]^{3/2}+4\left[\frac{Dt}{\pi l^2}\right]^{1/2}-\frac{2a}{l}\left[8\left(\frac{Dt}{\pi a^2}\right)-2\pi\left(\frac{Dt}{\pi a^2}\right)^{3/2}-\frac{2\pi}{3}\left(\frac{Dt}{\pi a^2}\right)^2\right] \quad (21)$$

This solution simply represents the sums of the short-time solutions for one-dimensional diffusional release from the cylinder and the thin slab with the addition of a "coupling term" which scales according to the aspect ratio, $2a/l$.

Figures 3, 4, and 5 represent a comparison of the short-time solution given by eqn. (21) and the exact solution given by eqn. (15). They are presented as fractional drug release versus square root of dimensionless time, $\sqrt{\tau}$, for aspect ratios of 100 (thin film), 1 (thick disk), and 0.01 (long cylinder), respectively. The dimensionless time τ for all these comparisons is defined as Dt/a^2. For aspect ratios $2a/l\gg 1$ and $2a/l\ll 1$ the short time solution is valid for

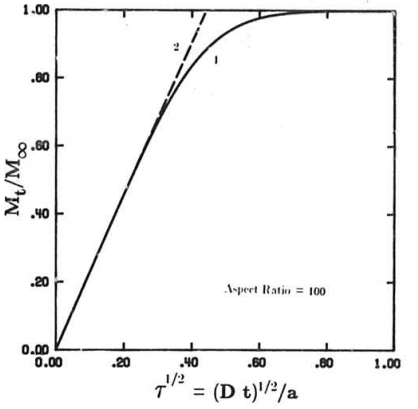

Fig. 3. Fractional drug release, M_t/M_∞, versus square root of dimensionless time, $\sqrt{\tau}$, for Fickian diffusional release from a tablet with an aspect ratio of 100 (thin disc). Comparison of the solutions presented by eqn. (15) (curve 1) and eqn. (21) (curve 2).

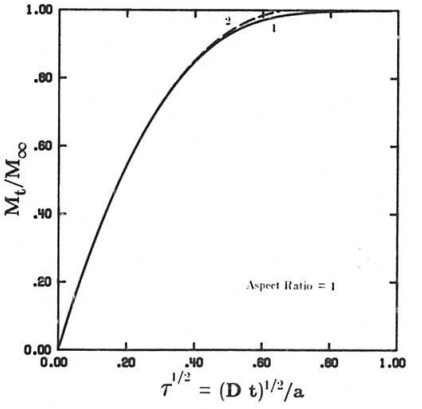

Fig. 4. Fractional drug release, M_t/M_∞, versus square root of dimensionless time, $\sqrt{\tau}$, for Fickian diffusional release from a tablet with an aspect ratio of 1 (disc). Comparison of the solutions presented by eqn. (15) (curve 1) and eqn. (21) (curve 2).

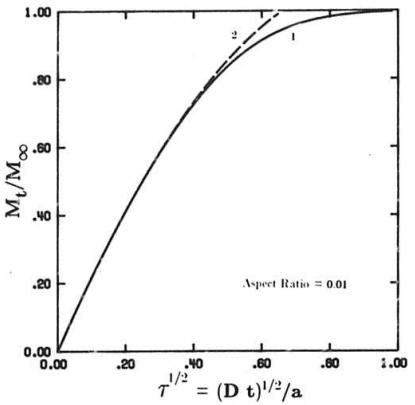

Fig. 5. Fractional drug release, M_t/M_∞, versus square root of dimensionless time, $\sqrt{\tau}$, for Fickian diffusional release from a tablet with an aspect ratio of 0.01 (long cylinder). Comparison of the solutions presented by eqn. (15) (curve 1) and eqn. (21) (curve 2).

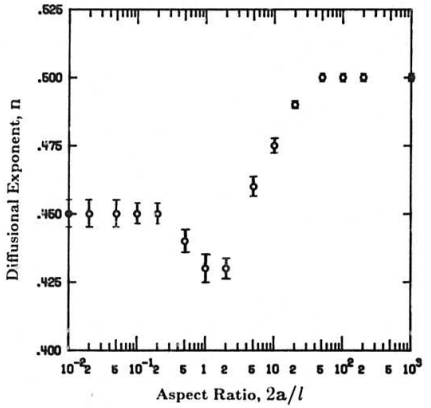

Fig. 6. Diffusional exponent, n, of eqn. (7) for Fickian diffusional drug release from tablets, as a function of their aspect ratio, $2a/l$.

the first 65 to 70% of the total release; this is consistent with the predictive ability of the short-time solutions for one-dimensional diffusional release from slabs and cylinders. For aspect ratios of the order 1 the predictive capability of the short-time solution increases to include the first 85 to 90% of the total drug released.

Effect of aspect ratio on diffusional exponent n

A convenient method of defining the regions of one-dimensional and three-dimensional diffusional processes is in terms of the aspect ratio. Equation (21) explicitly incorporates the aspect ratio in describing the fractional release for systems exhibiting Fickian diffusion; this fact will be exploited in determining the minimum aspect ratio for which the assumption of one-dimensional diffusion is valid. The first 60% of the fractional release defined by eqn. (15) can be approximated by eqn. (21) for any aspect ratio. The first 60% of this diffusional process can also be described by the empirical equation (7). Thus, one can define the diffusional exponent n for Fickian diffusion as a function of the aspect ratio. The results of such an analysis are presented graphically in Fig. 6. The confidence limits shown in the Figure represent the 95% confidence limits on the value of n obtained at each aspect ratio.

From Fig. 6 it is obvious that for slabs which are defined by an aspect ratio greater than 50 the diffusional exponent n is equal to 0.5. Thus an aspect ratio of 50 defines the minimum aspect ratio for which one-dimensional diffusion in a slab can be assumed. Similarly, for cylinders which are defined by an aspect ratio smaller than 0.2, the diffusional exponent n is equal to 0.45. Hence, an aspect ratio of 0.2 defines the maximum aspect ratio for which the assumption of one-dimensional diffusion in a cylinder is valid. The transition from one-dimensional diffusion in a slab to one-dimensional diffusion in a cylinder is not represented by a linear function. The diffusional exponent n passes through a minimum value of 0.43 at an aspect ratio of 1.

This non-monotonic behavior is a direct result of the three-dimensional nature of systems defined by aspect ratios between 0.2 and 50. A simple measure of the three-dimensional nature of the system can be obtained from considering the ratio of the total surface area across which diffusion occurs, A_t, to the surface area of the "secondary" surface, A_s, for the system. If one considers a cylinder of length l and diameter $2a$, the area of the lateral surface is equal to $2\pi al$ and the area of the two end surfaces is equal to $2\pi a^2$.

For a thin disk with an aspect ratio of 10 ($l=0.2a$), the area of the secondary surface, A_s, i.e., the lateral surface, is equal to $0.4\pi a^2$ and the area of the primary surface, A_p, is equal to $2\pi a^2$. Thus the ratio of the total surface area to the secondary surface area, A_t/A_s, is equal to 6/1. The secondary surface represents almost 17% of the total surface area for release. For a thick disk with an aspect ratio of 1 ($l=2a$), the lateral surface area is equal to $4\pi a^2$ and the two end surfaces have area equal to $2\pi a^2$. For this case the secondary surface represents 33% of the total surface area for drug release. Finally, for a cylinder with an aspect ratio of 0.1 ($l=20a$), the area of the secondary surface, A_s, i.e., the two end surfaces, is equal to $2\pi a^2$ and the area of the primary surface, A_p, is equal to $40\pi a^2$. The secondary surface area for this case represents less than 5% of the total surface area. Thus, the transition from a thin slab to a long cylinder occurs in a region of maximum secondary surface area contribution. This corresponds to the region of minimum diffusional exponent n observed in Fig. 6.

Effect of particle size distributions on release behaviour

The diffusional analysis presented before related changes in the geometry of a system, i.e., sample half-thickness for slabs and sample radius for cylinders and spheres, to changes in the observed release kinetics. For a distribution of particle sizes, a distribution of diffusion times should be expected. The effect that such a distribution has on the observed drug release behavior can be conveniently interpreted in terms of variations of the diffusional exponent n from the value of n for monodisperse systems.

Rosin and Rammler [15] developed a unimodal distribution law to describe the size distributions found in powdered samples. The Rosin–Rammler (R–R) distribution law is given as

$$W(x) = \exp[-bx^m] \tag{22}$$

Here $W(x)$ is the weight of the sample batch which consists of particles whose diameter is greater than or equal to x, the distribution constant, m, defines the breadth of the distribution, and the size constant, b, defines the mean sample size for the distribution. The larger the value of m the narrower the distribution, i.e., when m approaches infinity, then eqn. (22) describes a monodisperse system.

In this section, the effects of a particle size distribution which is described by the R–R distribution law on both Fickian and non-Fickian diffusional release will be considered. The discussion will be restricted to size distributions in spherical particles. The analysis, however, can be easily extended to include distributions in slab and cylindrical geometries.

Description of the particle size distribution

The particle size distribution function based on the Rosin–Rammler weight distribution law is given by eqn. (23):

$$\psi(x) = -\frac{dW(x)}{dx} = bmx^{m-1}\exp[-bx^m] \tag{23}$$

The mean particle size, $\bar{x}$, can be defined by eqn. (24):

$$\bar{x} = \frac{\Gamma[1+1/m]}{b^{1/m}} \tag{24}$$

where $\Gamma[1+1/m]$ is the gamma function.

Mathematical model for release from polydisperse spheres

The release model presented here is a modification of a model developed by Berens and Huvard [16] from heuristic arguments to describe the sorption kinetics in heterodisperse PVC powders. For polydispersed polymer samples the release kinetics can be modeled using a modified form of eqn. (12), as given by eqn. (25), where $\omega(a_i)$ is the weight fraction of particles having a radius of a_i:

$$\frac{M_t}{M_\infty}=1-\frac{6}{\pi^2}\sum_i \omega(a_i)\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left[\frac{-Dn^2\pi^2 t}{a_i^2}\right] \tag{25}$$

This equation simply states that the total drug released at any time t from a polydispersed sample is equal to the sum of the individual contributions of the mixture components.

Effects of a particle size distribution on the release kinetics

A comparison of the Fickian release behavior from a monodisperse sample of 100 μm particles and a hypothetical mixture of 20% 20 μm, 60% 100 μm, and 20% 500 μm particles is shown in Fig. 7. In comparison to the release behavior from a monodisperse sample, the presence of a particle size distribution causes a substantial acceleration of the transport at early times and a marked retardation of the transport for longer times. For any heterodisperse sample one can define a mean sample size. This corresponds to a mean diffusion time for the system. The acceleration of the early portion of the release curve is the result of release from particles smaller than the mean size. Particles that are larger than the average size cause the retardation of the transport at long times.

The empirical equation (7) was used to characterize the first 60% of the release behavior obtained from this hypothetical distribution. For the Fickian diffusion process it was found

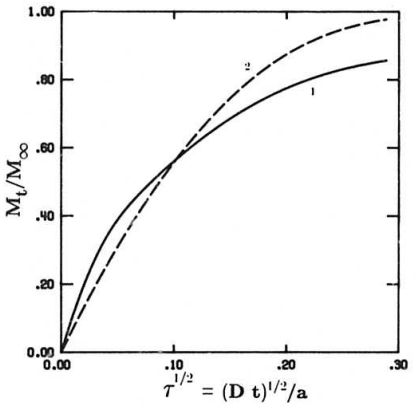

Fig. 7. Fractional drug release, M_t/M_∞, versus $\sqrt{\tau}$ for Fickian diffusional release. Comparison of drug release from a sample with a particle size distribution of 20% 20 μm, 60% 100 μm and 20% 500 μm particles (curve 1) and from a monodisperse sample of 100 μm particles (curve 2).

that the data of curve 1 of Fig. 7 could be predicted by eqn. (7) with $n=0.30\pm0.01$, which is considerably different from the value of n obtained for release from a monodispersed sample, i.e., $n=0.43$.

In the analysis of the effects of different geometries and different aspect ratios on the diffusional exponent, we were able to define characteristic limiting values of n for Fickian and non-Fickian transport. The effect that a particle size distribution has on the value of n varies with the breadth of the distribution and the general shape of that distribution. Thus, no such "limits" can be set on the value of n obtained for release from samples with particle size distributions.

Comparison of release from particle size distributions described by Rosin–Rammler and step function distribution laws

The effects of two distinctly different particle distribution functions on the observed release kinetic behavior were also considered by

comparing a R–R distribution law with $m=3.0$ and $b=5.7$ (narrow distribution) to the flat profile. Careful examination of the R–R distribution law defined by eqn. (22) reveals that as m approaches zero the distribution of particle sizes broadens. In fact, for $m=0$, the distribution function is equal to a constant and the size distribution is infinitely broad. This case is analogous to the flat distribution function. Thus, the effects of a narrow particle size distribution on the drug release behavior can be compared to the effects of an infinitely broad particle size distribution for the same range of particle sizes.

Example I: Wide range of particle sizes: Consider a R–R particle size distribution between 150 μm and 850 μm. The particle distribution between the two particle size limits can be approximated by 20 discrete particle sizes and the characteristic diffusion time for one-dimensional release from a sphere can be calculated using eqn. (26), where the characteristic diffusion length is the radius of the sphere, a

$$\theta \cong \frac{a^2}{D} \tag{26}$$

The drug diffusion coefficient, D, is constant for a given macromolecule/drug pair. Thus, the distribution of diffusion times will be proportional to the square of the distribution of the particle sizes. In this example, the longest diffusion time, which corresponds to the 850 μm particles, is approximately 30 times as large as the shortest diffusion time, which corresponds to the 150 μm particles.

The observed release kinetics for Fickian diffusion using the narrow and the flat distribution profiles is shown in Fig. 8. For both transport mechanisms the flat distribution profile results in a larger acceleration of the drug release at short times and a greater retardation of the release at long times by comparison to the narrow distribution. This is a result of the fact that greater "weight" is given to the particles on either side of the mean sample size in

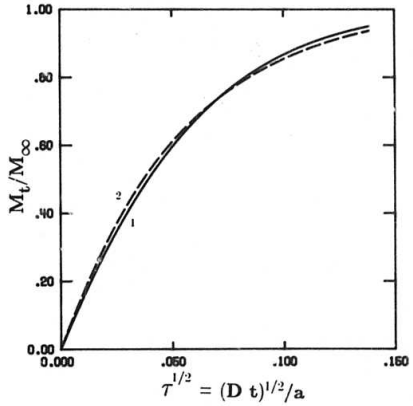

Fig. 8. Fractional drug release, M_t/M_∞, versus $\sqrt{\tau}$ for Fickian diffusional release from spherical particles with Rosin–Rammler distribution (curve 1) and a flat distribution profile (curve 2) according to Example I in text.

the flat profile. For Fickian diffusion, the diffusional exponents obtained through analysis using the empirical equation (7) were $n=0.42\pm0.01$ for the narrow distribution and $n=0.40\pm0.01$ for the flat distribution. By comparison with the release behavior from a monodisperse 500 μm system, the narrow distribution profile has no effect on the release curve, whereas the infinitely broad distribution has a statistically noticeable effect.

Example II: Narrow range of particle sizes: Consider the experimental situation where the polymer sample described in Example I was sieved into two fractions: (i) 150 μm to 500 μm; and (ii) 500 μm to 850 μm. The particle size distribution of the first fraction may be approximated using 10 discrete particles. The particle size distribution for this fraction consists of only particles smaller than 500 μm, which was the mean particle size in the original distribution described by the R–R distribution function. The corresponding flat distribution is characterized by a mean particle size of 325 μm with equal

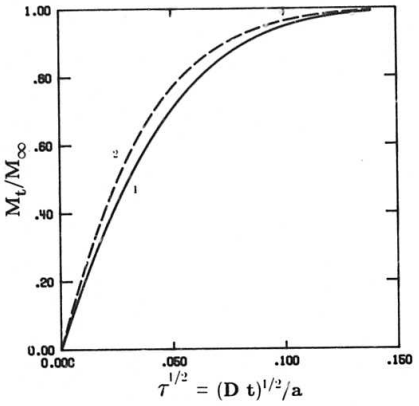

Fig. 9. Fractional drug release, M_t/M_∞, versus $\sqrt{\tau}$ for Fickian diffusional release from spherical particles with Rosin-Rammler distribution (curve 1) and a flat distribution profile (curve 2) according to Example II in text.

weight given to all the discrete particle sizes. In this example the longest diffusion time is approximately 10 times as large as the shortest diffusion time.

The Fickian release kinetic profiles from the narrow particle size distribution and the broad size distribution in this fraction are shown in Fig. 9. The flat distribution shows a marked acceleration in the drug release at short times by comparison to the narrow distribution. This effect, however, is not real. It is simply a consequence of the smaller average particle size for the flat distribution, i.e., the flat distribution has a smaller mean characteristic diffusion time. Comparison of the diffusional exponents which characterize the release behavior obtained from the narrow and the flat distribution profiles indicates no significant deviations from monodisperse release behavior. For Fickian release, the diffusional exponents obtained by analysis using the empirical equation (7) are $n=0.41\pm0.02$ for the flat distribution profile and $n=0.42\pm0.01$ for the narrow distribution.

Effect of variable boundary conditions on release behavior

The mathematical analysis presented here was developed with the assumption of perfect sink initial and boundary conditions. This implies that the surface concentration is kept at a constant solute concentration, C_0, during the experiment. In reality, the surface drug concentration may change and *increase up to* the constant value C_0. We will consider the effect that a variable boundary condition has on the observed solute release behavior. The analysis presented here is parallel to that developed in Crank [5].

For a system where the drug concentration in the dissolution medium is initially zero but during the release experiment it approaches an equilibrium concentration exponentially, Fick's law (eqn. 1) can be solved with the following initial and boundary conditions

$$t=0 \quad -l/2<x<l/2 \quad C=0$$
$$t>0 \quad x=\pm l/2 \quad C=C_0[1-\exp(-\beta t)]$$

This model can be used to represent the conditions encountered in a dynamic release experiment where the drug diffuses into a liquid reservoir. The solution to Fick's law for the above conditions is given as

$$\frac{M_t}{M_\infty}=1-\exp(-\beta t)\left[\frac{4D}{\beta l^2}\right]^{1/2}\tan\left[\frac{\beta l^2}{4D}\right]^{1/2} -\frac{8}{\pi^2}\sum_{n=0}^{\infty}\frac{\exp\left[\frac{-D(2n+1)^2\pi^2}{l^2}t\right]}{(2n+1)^2\left[1-(2n+1)^2\pi^2\left[\frac{D}{\beta l^2}\right]\right]} \quad (27)$$

When $\beta=\infty$, the drug concentration in the dissolution medium rises instantaneously to C_0; for this case eqn. (27) reduces to eqn. (2). The release curves for finite values of $\beta l^2/4D$ are shown in Fig. 10 plotted as normalized drug

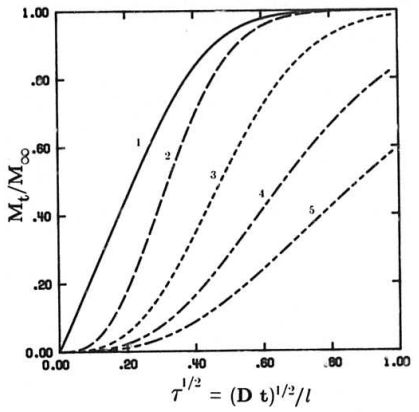

Fig. 10. Fractional drug release, M_t/M_∞, versus $\sqrt{\tau}$ for Fickian diffusional release under variable boundary conditions defined by $\beta l^2/4D$ of 500 (curve 1), 5.0 (curve 2), 1.0 (curve 3), 0.5 (curve 4) and 0.25 (curve 5).

release versus square root of dimensionless time, $\sqrt{\tau}$. It is quite obvious that the empirical equation (7) cannot be used to correctly describe this release behavior. Only for one case, that corresponding to $\beta l^2/4D=5.0$, the diffusional exponent of eqn. (7) could be obtained as $n=1.08\pm0.03$.

CONCLUSIONS

The empirical equation (7) can be used to relate the amount of drug released as an exponential function of the release time. The diffusional exponent, n, specifies the mechanism of release.

This equation can be used to analyze drug release from sheets, cylinders, spheres, discs (tablets) and polydisperse microspheres under perfect sink conditions. Characteristic diffusional exponents for Fickian diffusional release have been defined in each case, for fitting of the first 60% of the release curve.

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REFERENCES

1 R.W. Baker and H.K. Lonsdale, Controlled release: Mechanisms and rates, in: A.C. Tanquarry and R.E. Lacey (Eds.), Controlled Release of Biologically Active Agents, Plenum Press, New York, NY, 1974, p. 15.
2 T.J. Roseman and N.F. Cardarelli, Monolithic polymer devices, in: A.F. Kydonieus (Ed.), Controlled Release Technologies, Vol. 1, CRC Press, Boca Raton, FL, 1980, p. 21.
3 N.A. Peppas, Mathematical modelling of diffusion processes in drug delivery polymeric systems, in: V.F. Smolen and L.A. Ball (Eds.), Controlled Drug Bioavailability, Vol. 1. Drug Product Design and Performance, Wiley, New York, NY, 1984, p. 203.
4 N.A. Peppas, Mathematical models for controlled release kinetics, in: R.S. Langer and D. Wise (Eds.), Medical Applications of Controlled Release Technology, Vol. 2, CRC Press, Boca Raton, FL, 1984, p. 169.
5 J. Crank, The Mathematics of Diffusion, Clarendon Press, Oxford, 1975.
6 T. Higuchi, Rate of release of medicaments from ointment bases containing drugs in suspension, J. Pharm. Sci., 50 (1961) 874.
7 D.R. Paul and S.K. McSpadden, Diffusional release of a solute from a polymer matrix, J. Membrane Sci., 1 (1976) 33.
8 T.J. Roseman and W.I. Higuchi, Release of medroxy progesterone acetate from a silicone polymer, J. Pharm. Sci., 59 (1970) 353.
9 T.J. Roseman, Release of steroids from a silicone polymer, J. Pharm. Sci., 61 (1972) 46.
10 N.A. Peppas, A model of dissolution-controlled solute release from porous drug-delivery polymeric systems, J. Biomed. Mater. Res., 17 (1983) 1079.
11 G.W. Sinclair and N.A. Peppas, Analysis of non-Fickian transport in polymers using simplified exponential expression, J. Membrane Sci., 17 (1984) 329.
12 N.A. Peppas, Analysis of Fickian and non-Fickian drug release from polymers, Pharm. Acta Helv., 60 (1985) 110.
13 J.C. Fu, C. Hagemeier and D.L. Moyer, A unified mathematical model for diffusion from drug-polymer composite tablets, J. Biomed. Mater. Res., 10 (1976) 743.

14 H.S. Carlsaw and J.C. Jaeger, Conduction of Heat in Solids, Clarendon Press, Oxford, 1959.
15 P. Rosin and E. Rammler, Laws governing the fineness of powders, J. Inst. Fuel, 7 (1933) 29.
16 A.R. Berens and G.S. Huvard, Particle size distribution of polymer powders by analysis of sorption kinetics, J. Disp. Sci. Technol., 2 (1981) 359.