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Research Article

Design and Manufacture of a Zero-Order Sustained-Release Pellet Dosage Form Through Nonuniform Drug Distribution in a Diffusional Matrix

Douglas C. Scott[1] and R. Gary Hollenbeck[1,2]

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A theoretical basis is presented for the design of dosage forms containing a drug which is initially distributed throughout a noneroding diffusional matrix in a nonuniform manner, for the purpose of achieving zero-order release. Modeling of these dosage forms is based on Higuchi's square root of time diffusional model. Derivations of theoretical drug release profiles for both flat slab and spherical geometry are included. Pellets were prepared utilizing this nonuniform distribution concept using fluid bed suspension layering technology. A gradient pumping system used in conjunction with a specially fabricated miniature fluid bed apparatus was utilized to prepare pellets containing drug nonuniformly dispersed. Actual drug release profiles were obtained for pellets containing drug distributed in the traditional uniform manner and the nonuniform manner described above. Nonuniform distribution of drug in a noneroding diffusional matrix, in theory and practice, is shown to linearize dissolution profiles.

KEY WORDS: nonuniform distribution; diffusional matrix; fluid bed coating; sustained release.

INTRODUCTION

Constant-rate release dosage forms are of much interest, but their optimization remains a challenge. Most sustained-release dosage forms can be placed in one of three general categories: (i) membrane reservoir, (ii) erodible matrix, or (iii) noneroding diffusional matrix. In this work, a noneroding diffusional matrix has been chosen over the other types because of disadvantages they possess. Membrane reservoir systems should yield zero-order release but, in reality, often do not. Since the cores commonly used are manufactured by extrusion and spheronization, or suspension or powder layering, a complex diffusional process may be involved where the drug must diffuse through the core prior to diffusion through the membrane. Erodible systems release drug through attrition and dissolution of the matrix and erosion may vary depending on the mixing and stirring conditions of the surrounding environment, *in vitro* or *in vivo*. Erodible systems also possess nonlinear release due to the constantly diminishing surface from which drug release takes place.

In contrast, matrix systems are relatively insensitive to changes in mixing and stirring conditions because diffusion from the noneroding matrix is the rate controlling factor. Changes in the static diffusion layer surrounding the dosage form as a consequence of variable agitation will occur but generally do not have a major effect on the overall release of drug. Conventional diffusional matrix systems, such as erodible matrices, suffer from nonlinear release; however, this fact is due to the longer distance that drug in deeper layers of the matrix must travel to exit the delivery system. This concept is best represented by Higuchi's flat slab diffusional model (Fig. 1) (1,2). The classical theoretical release profile from a system of this type is seen in Fig. 2. During the drug dissolution and diffusional processes the boundary layer moves back into the matrix while its surface area is maintained. For other shapes, such as spheres and cylinders, a constantly diminishing boundary layer surface contributes to an even greater deviation from linear drug release.

The concept of nonuniform drug distribution, in which drug is more concentrated in deeper layers of a matrix, has been investigated by only a few researchers. Zoglio and Carstensen derived models for erodible devices containing drug nonuniformly dispersed (3). To test their theory, a triple-layer tablet was prepared by compressing two coats around a core. The core and coats were homogeneous, but each contained different amounts of drug to create a nonuniform distribution. This approach demonstrated the nonuniform distribution concept but lacked the ability to achieve a continuous nonuniform distribution.

P. I. Lee also investigated this concept using hydrogel beads (4–6). Beads containing drug uniformly dispersed were first created. The beads were then subjected to a leaching solvent to partially extract drug, resulting in a nonuniform residual distribution of drug. This approach suffers from the

[1] Pharmaceutics Department, University of Maryland at Baltimore, Baltimore, Maryland 21201.

[2] To whom correspondence should be addressed at University of Maryland, School of Pharmacy, Pharmaceutics Department, 20 North Pine Street, Baltimore, Maryland 21201.

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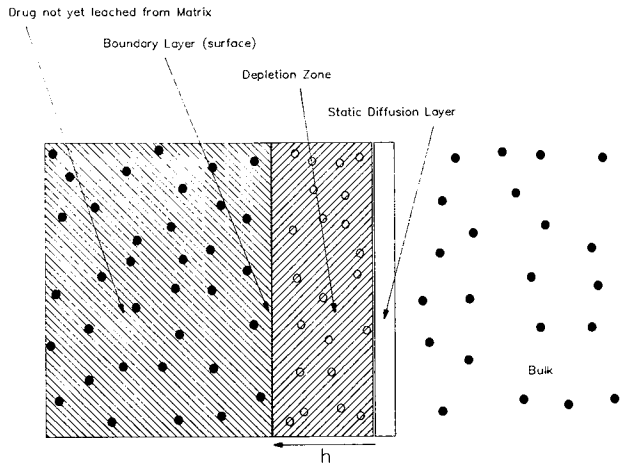

Fig. 1. A model of a noneroding flat slab matrix undergoing dissolution adapted from Higuchi (h = distance of boundary layer from slab surface) (1).

difficulties of mass manufacture but does result in a continuous nonuniform distribution of drug.

For noneroding matrix systems of any geometry, it is logical to assume that loading drug in higher concentrations in deeper matrix layers should mitigate the decreasing release rate traditionally seen with these systems. The keys to utilization are identification of the correct nonuniform distribution to achieve zero-order release and manufacture of the delivery system in a feasible manner.

THEORETICAL

The following derivations consider noneroding porous matrix devices in which the drug is not soluble. After dissolution of the drug at the boundary layer, diffusion takes place through pores filled with dissolution medium created as drug is leached from the matrix. In the interest of simplicity, the systems described below have no initial porosity; however, derivations can be performed in a similar manner for systems which do have an initial porosity. Excess drug loading is assumed to maintain a saturated solution of drug at the boundary layer and drug making up the concentration gradient is assumed to be negligible.

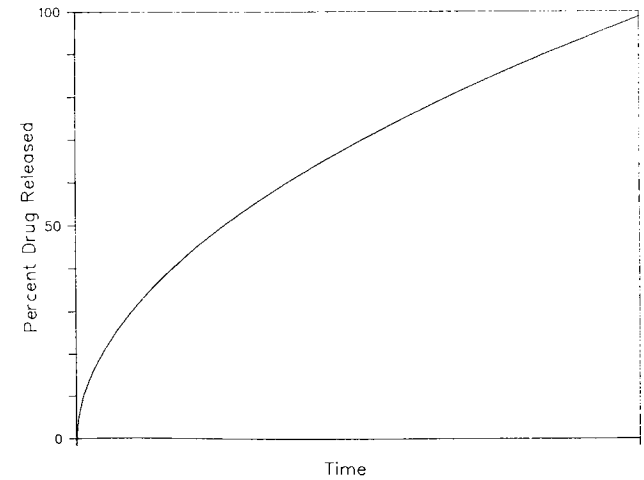

Fig. 2. Theoretical drug release profile from a flat slab as in Fig. 1 (1).

Flat Slab Geometry

Consider a flat slab partitioned into hypothetical layers. Since the longer diffusional distance that the drug in each successive layer must travel to exit the device is responsible for the traditional nonlinear release, the initial drug concentration at some position in the matrix, $C_m(h)$, may be assumed to be linearly related to the distance (h) a drug molecule must travel from its position in the matrix to the bulk dissolution medium,

$$C_m(h) = \alpha \cdot h \tag{1}$$

where α = a proportionality constant (Fig. 3). A further consideration is that the total porosity of the depleted zone, $\epsilon(h)$, will increase with time as the boundary moves back into the matrix, because a void is left behind as drug is leached from the matrix. Since deeper layers contain more drug, the depletion zone porosity increases as dissolution takes place.

Let

M = mass of drug leached,
δ = density of drug,
V_d = volume of depleted zone, and
A_b = surface area of boundary layer,

where M and V_d can be described as functions of distance (h). Porosity as a result of drug depletion can be expressed as a fraction of the total volume of the depletion zone, so

$$\epsilon(h) = M(h)/[\delta \cdot V_d(h)] \tag{2}$$

Since

$$dV_d = A_b \cdot dh \tag{3}$$

It follows from Eq. (1) that

$$dM = C_m(h) \cdot dV_d = \alpha \cdot h \cdot A_b \cdot dh \tag{4}$$

Since M and V_d, are zero at $h = 0$,

$$V_d(h) = A_b \cdot h \tag{5}$$
$$M(h) = \alpha \cdot A_b \cdot h^2/2 \tag{6}$$

Substitution of Eqs. (5) and (6) into Eq. (2) yields

$$\epsilon(h) = \alpha \cdot h/(2 \cdot \delta) \tag{7}$$

An equation for drug release based on Higuchi's flat slab model can now be derived. Equation (6) describes the cumulative amount of drug that is leached from the matrix at a given boundary layer position. As in Higuchi's model, Fickian diffusion [Eq. (8)] is assumed to describe mass transfer of the drug through the depleted zone and into the bulk medium:

$$dM = \frac{D \cdot C_s \cdot \epsilon \cdot A_b}{T \cdot h} dt \tag{8}$$

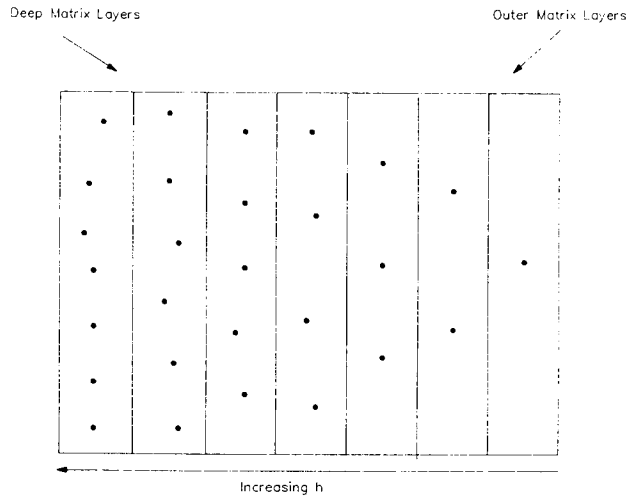

Fig. 3. Initial nonuniform drug distribution in a flat slab to achieve zero-order release [graphical presentation of Eq. (1)].

where

C_s = concentration of drug in solution at boundary layer (saturated solution),
D = diffusion coefficient,
T = tortuosity, and
t = time.

Considering Eqs. (4), (7), and (8), the following is obtained:

$$h\,dh = \frac{D \cdot C_s}{2 \cdot \delta \cdot T}\,dt \tag{9}$$

Recognizing that at $t = 0$, $h = 0$, integration of both sides of the equation yields

$$h^2/2 = \frac{D \cdot C_s}{2 \cdot \delta \cdot T}\,t \tag{10}$$

Rearranging and substituting Eq. (6) into Eq. (10) result in the following final equation:

$$M = \frac{D \cdot C_s \cdot \alpha \cdot A_b}{2 \cdot \delta \cdot T}\,t \tag{11}$$

The result of nonuniform drug distribution is clearly demonstrated in Eq. (11) since cumulative mass released is linearly related to time.

Spherical Geometry

The same principles can be applied to a spherically shaped delivery system. Drug in deeper matrix layers still has a longer diffusional path through the depleted zone, but in addition, the surface area of the boundary layer is constantly decreasing as it moves back into the matrix during drug release. Therefore, there is a need for compensation of both factors contributing to the traditional nonlinear release.

As in the flat slab case, initial drug concentration in the matrix may be assumed to be directly proportional to h. To compensate for the waning surface area of the boundary layer, a similar approach can be taken to that of Zoglio and Carstensen for compensation of the waning surface of erosion (3). Concentration is assumed to be inversely proportional to r^2, where r is the radius of the spherical boundary layer surface (Fig. 4):

$$C_m(h) = \alpha \cdot h/r^2 \tag{12}$$

The porosity of the depleted zone again will be constantly increasing. Equation (2) is a general expression for the depletion zone porosity and can be used here along with the general differential expressions for the depletion zone volume and cumulative mass of drug leached [Eqs. (3) and (4), respectively]. Therefore, for a spherical geometry,

$$dV_d = A_b \cdot dh = 4 \cdot \pi \cdot r^2 \cdot dh \tag{13}$$
$$dM = C(h) \cdot dV_d = \alpha \cdot h \cdot 4 \cdot \pi\,dh \tag{14}$$

Also,

$$r = R - h \tag{15}$$

where R is the radius of the spherical dosage form. By substitution of Eq. (15) into Eq. (13) and recognizing that V_d and M are zero at $h = 0$, the following equations are obtained:

$$V_d(h) = 4/3 \cdot \pi \cdot [R^3 - (R - h)^3] \tag{16}$$
$$M(h) = \alpha \cdot 2 \cdot \pi \cdot h^2 \tag{17}$$

Again, as in the flat slab case, an equation for porosity is constructed:

$$\epsilon(h) = \frac{3 \cdot \alpha \cdot h^2}{2 \cdot \delta \cdot [R^3 - (R - h)^3]} \tag{18}$$

As in the previous derivation, the relationship between cumulative mass of drug leached and boundary layer position has been developed [Eq. (17)]. Fickian diffusion is again assumed to describe the movement of a drug molecule through the depleted zone. A modified form of Fick's first law is used which describes diffusion through a spherical geometry (7):

$$dM = \frac{D \cdot C_s \cdot \epsilon \cdot 4 \cdot \pi \cdot R \cdot r}{T \cdot (R - r)}\,dt \tag{19}$$

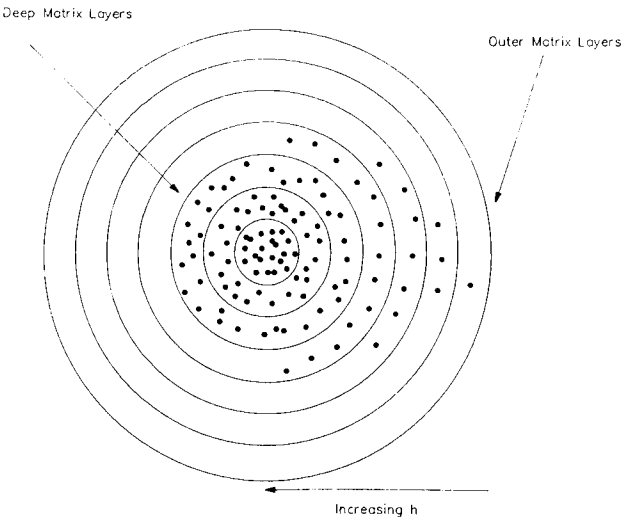

Fig. 4. Initial nonuniform drug distribution in a sphere to achieve zero-order release. [graphical presentation of Eq. (12)].

Equations (14) and (18) are substituted into Eq. (19), simplified and integrated recognizing that $h = 0$ at $t = 0$.

$$R^3 \cdot \ln(R) - R^3 \cdot \ln(R - h) + (R - h)^3/3 - R^3/3 = \frac{3 \cdot D \cdot C_s \cdot R}{2 \cdot \delta \cdot T} t \quad (20)$$

This equation cannot be solved explicitly for h and substituted into Eq. (17) to get a direct relation between cumulative mass released and time as in the flat slab case above. However, if values of h are chosen, corresponding values for cumulative mass released (M) and time (t) can be determined using Eqs. (17) and (20). A theoretical dissolution profile can be generated in this manner.

The derivation for a sphere containing drug homogeneously dispersed is not included here but is analogous to the spherical case presented where C and ϵ are constants. This spherical model does not behave as simply as flat slab models as the boundary layer approaches the deepest layers because the surface area approaches zero as r approaches zero. However, this model does behave as desired up to the point where the radius of the boundary surface is approximately one-third of the total radius of the pellet.

Figure 5 shows the theoretical dissolution profiles for a flat slab and sphere containing drug uniformly and nonuniformly dispersed. For the spherical case, the release profiles represent pellets in which only the outer two-thirds of the radius of the pellet contains drug. This volume corresponds to more than 90% of the total volume of the pellet. The release profile for the flat slab matrix containing drug nonuniformly dispersed is linear, and in the case of the sphere it acceptably approximates linearity. Nonuniform distribution also results in longer release times due to the lower porosities of the depletion zone during the dissolution event.

The semiempirical derivation presented above demonstrates the effect of compensation for physical factors responsible for nonlinear release. In the flat slab case the equation presented is the exact function needed to achieve zero-order release. In the spherical case near-linear release is achieved, even though compensation for both factors contributing to nonlinear release has been considered. An alternative approach can be taken to obtain exact concentration functions ($C_m(h)$) to achieve zero-order release. Here the release rate in Fick's first law (dM/dt) is set to a constant. This approach and practical applications will be presented in future papers.

Proportionality Constant, α

One parameter that must be determined prior to a theoretical or practical application of nonuniform drug distribution is the proportionality constant α. This parameter must be known to construct an actual initial concentration function [$C_m(h)$] and represents the magnitude of drug loading in the matrix. The greater the magnitude of α, the greater the concentration of drug at any position in the matrix which results in a greater total amount of drug in the device.

Flat Slab Geometry

The total amount of drug loaded into the matrix can be represented by Eq. (6) when h reaches is maximum value. If

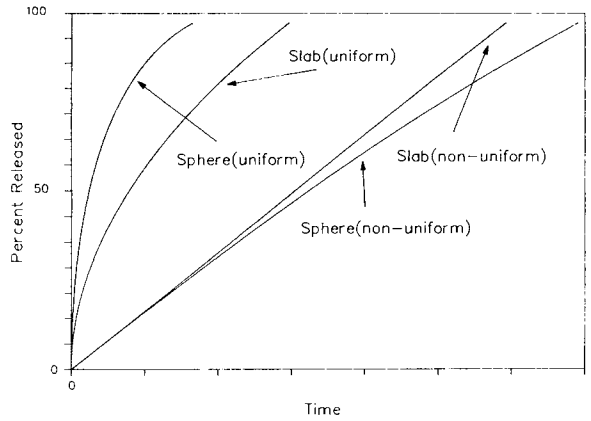

Fig. 5. Theoretical release profiles for a flat slab and a sphere containing drug uniformly and nonuniformly dispersed. These profiles represent devices of equivalent volume and thickness (slab thickness = 2/3 sphere radius).

h_{max} is defined as the slab thickness and m is the total mass of drug loaded into the matrix, then from Eq. (6),

$$\alpha = 2 \cdot m/(A_b \cdot h_{max}^2) \quad (21)$$

Spherical Geometry

In the spherical case, the total amount of drug loaded into the matrix is represented by Eq. (17). If h_{max} is defined as the thickness of the spherical layer containing drug and m is defined as above, then from Eq. (17),

$$\alpha = m/(2 \cdot \pi \cdot h_{max}^2) \quad (22)$$

To determine α, only a knowledge of desired drug loading and device geometry is needed.

PRACTICAL APPLICATION OF THE NONUNIFORM DISTRIBUTION CONCEPT

One way in which a drug can be layered appropriately in a solid matrix diffusional system is to build the dosage form from the inside out. Once the appropriate drug concentration vs pellet radius function has been defined, it is possible to apply a polymeric-based matrix formulation by a spraying technique using fluid bed technology. The release-controlling formulation in solution or suspension and the drug in a separate solution or suspension can be combined in the correct proportion during the coating operation using two separately controlled pumps. By spraying the resultant drug-containing matrix solution or suspension onto a core in a predetermined manner, the desired nonuniform drug distribution can be achieved. High-solid content suspensions (40–50%, w/w) containing matrix materials can be rapidly sprayed onto this core and result in the building up of a relatively thick layer in a reasonable period of time. In this report, pellet preparations consisting of equal-thickness, discrete layers, containing appropriate amounts of drug layered onto nonpareil seeds, were examined.

MATERIALS AND METHODS

The applied matrix includes a water-insoluble polymer

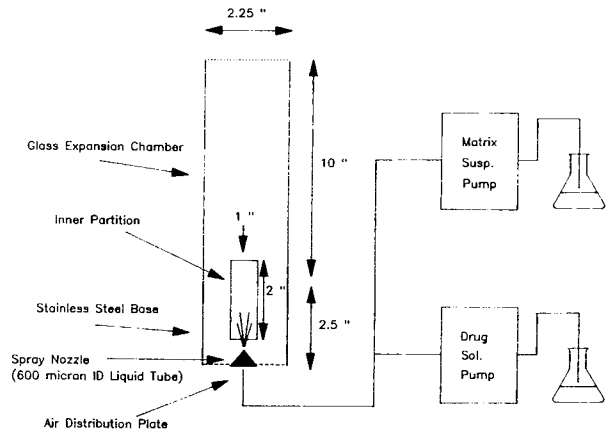

Fig. 6. Schematic of the miniature fluid bed system and gradient pumping system.

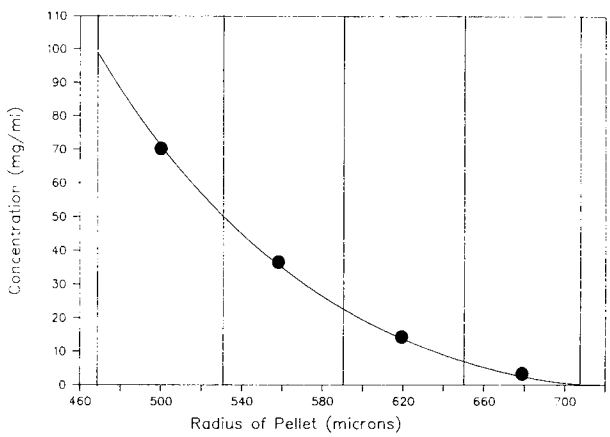

Fig. 7. Initial nonuniform drug concentration distribution as a function of position in the solid matrix. (Seed core contains no drug.)

(Eudragit RS 30D), a plasticizer (Triacetin No. T5376, Sigma), and an antiadherent agent (Talc, Ruger).

Chlorpheniramine maleate USP (Hexagon Labs) was chosen as the model drug because it is very water soluble and represents a rigorous test of the sustained-release character of the system. A specially fabricated miniature Wurster column was used in conjunction with a gradient pumping system to apply the matrix suspension and drug solution. The gradient pumping system consists of two peristaltic pumps (Rainin Rabbit Plus); one unit pumps the matrix suspension and the other pumps a drug solution. The effluent from each pump is joined at a tee and the mixture is then sprayed into the fluid bed unit. A schematic of this sytem is presented in Fig. 6.

Sugar spheres NF (Nu-Pareil PG, Ingredient Technology) were used as a core substrate to which the matrix was applied. The formulas for the matrix suspension and drug solution are presented in Table I. The total applied layer thickness was approximately 256 μm. Figure 7 is a graphical representation of the needed nonuniform distribution for the case described below using Eq. (12). Drug loading into the applied matrix was approximately 2% by weight, which corresponds to an α value of 7.98. The total applied layer was partitioned into four discrete layers to approximate a continuous nonuniform distribution of drug. Midpoint layer drug concentrations were used as the concentration of drug for each of four discrete applied layers that correspond to the four discrete drug pumping rates seen in Table II. The midpoint layer drug concentrations from the innermost layer to the outermost layer are, respectively, 70.93, 39.85, 19.30, and 5.30 mg/ml (mass of drug per volume of applied matrix). The matrix suspension was sprayed at a constant rate throughout the entire coating run.

Pellets in which the drug was uniformly dispersed in the applied layer (constant matrix and drug pumping rates) were also prepared as controls using the same formula as above under the same conditions. The only difference between the control and the sample is that the control has drug uniformly dispersed and the sample has the drug layered nonuniformly based on theoretical equations intended to produce zero-order release. Processing parameters can be found in Table II.

After coating, the pellets were cured for 24 hr at 60°C. The USP method No. 1 (basket) dissolution test was performed on two 400-mg samples of pellets with 500 ml of distilled water as the dissolution medium. The basket was rotated at a speed of 75 rpm. Ultraviolet detection in conjunction with a flow-through cuvette was used to assess drug concentration in the dissolution medium.

Table I. Formulas for the Matrix Suspension and Drug Solution

Matrix suspension formula	
Eudragit RS 30D	80 g
Talc	70 g
Triacetin	6 g
Ethanol USP	75 g
Dist. H_2O	19 g
Total	250 g = 100 g solids applied
Drug solution formula	
Chlorpheniramine maleate	2.81 g
1/3 water, 2/3 ethanol mixture by weight	QS 25 ml
(only 16.5 ml applied which contains 1.86 g drug)	

Table II. Processing Parameters Used for the Preparation of Pellets Containing Drug Uniformly and Nonuniformly Dispersed

Inlet temp.	53 ± 2°C
Bed temp.	47 ± 1.5°C
Spray pressure	25 psi
Nu-Pareil charge	35 g
Spraying time	155 min

	Pump rate	
Time (min)	Matrix suspension (g/min)	Drug solution (ml/min)
0 to 27	1.6	0.270
27 to 61	1.6	0.151
61 to 103	1.6	0.0733
103 to 155	1.6	0.0201

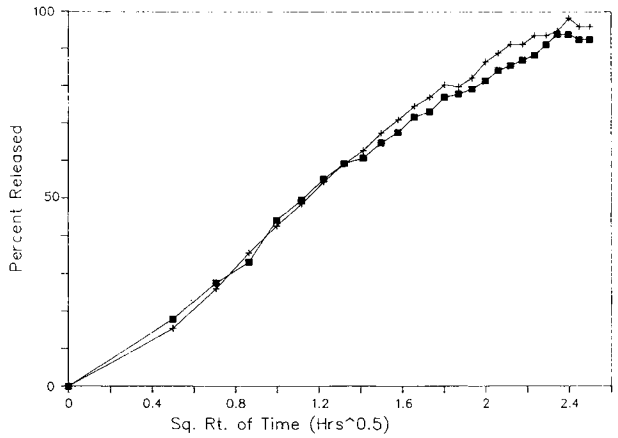

Fig. 8. Actual square root of time release profiles for duplicate samples of pellets containing drug homogeneously dispersed.

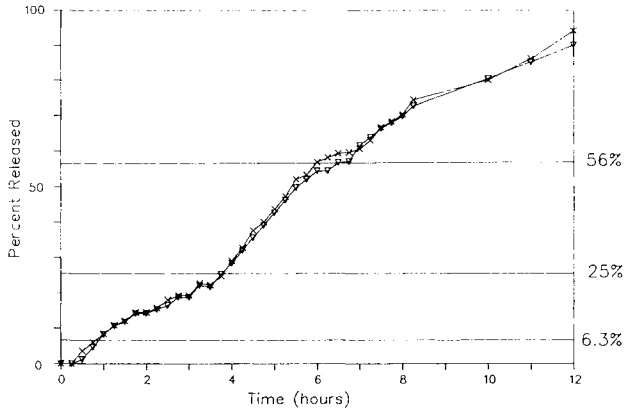

Fig. 10. Actual dissolution profiles for duplicate samples of pellets containing drug nonuniformly dispersed showing expected sites of discontinuity.

RESULTS AND DISCUSSION

Figure 8 shows the cumulative percentage released as a function of the square root of time for two samples of pellets containing drug uniformly dispersed. While plotting the results in this fashion is normally not appropriate for spheres, in this example a thick layer is applied to a core and this layer can be viewed as a flat slab stretched over the face of a sphere. The boundary layer surface area does decrease during release but not to the same extent as if the whole pellet contained drug. It is evident that the drug release process taking place here conforms reasonably well to the equations derived by Higuchi.

In Fig. 9 the sample and control pellets are compared with a linear time axis. It is evident from the release data that nonuniform drug distribution in a noneroding diffusional matrix is of benefit. When a comparison is made between the pellets in which drug is uniformly distributed and the pellets in which the drug is nonuniformly distributed, the effective time of drug release (0–90%) is doubled and the resulting curve approximates linearity. These longer release times for pellets containing drug nonuniformly dispersed were predicted. Discontinuities do exist, however, due to the fact that four discrete layers were used to approximate a continuous gradient.

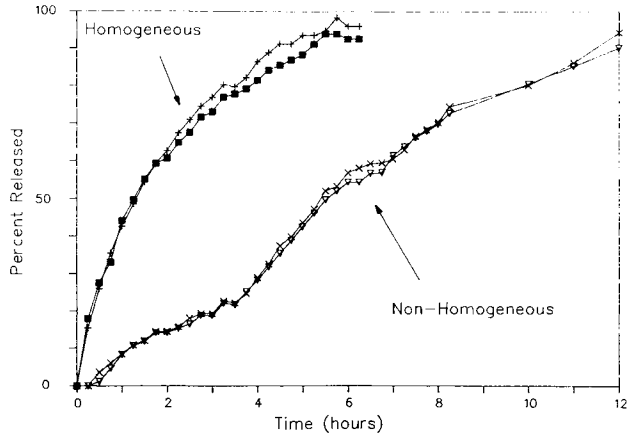

Fig. 9. Actual release profiles for duplicate samples of pellets containing drug uniformly and nonuniformly dispersed.

The theoretical amount of drug in each layer is known and these discontinuities occur when each successive layer of drug starts to appear in the bulk dissolution medium. In Fig. 10, horizontal lines have been placed over the release profile of the nonuniform distribution pellets where the change in the rate of release should occur. The values associated with these lines are the cumulative amount contained in the preceding layers. If a continuous gradient were created, a smoother profile would result. The pumps used in this system can be driven by a computer so that process automation and the creation of a continuous gradient are possible. This work, which is presently being pursued, will allow further study of systems that take advantage of the nonuniform drug distribution concept.

ACKNOWLEDGMENTS

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