Geometric Approach for Zero-Order Release of Drugs Dispersed in an Inert Matrix

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INTRODUCTION

Currently available controlled release drug delivery systems contain drugs to be released from polymeric material (1). The polymer may be either biodegradable or nonbiodegradable. One of the basic designs for nonbiodegradable polymers is a dispersion or solution of drug within a polymer matrix (2) where drug release is controlled by diffusion through the matrix.

We examined the release pattern from a device composed of a drug dispersed within a polymer matrix. These matrix devices are more easily prepared than other sustained release systems. Further, the use of a matrix device is essential to achieve release for certain applications, such as sustained release of macromolecules (3). A uniform drug suspension in a matrix is expected to provide a greater margin of safety than a drug core surrounded by a membrane, where any break in the device would lead to massive overdose and toxicity.

The major drawback to the use of dispersed matrix systems is that they do not display zero-order release kinetics. Many studies have used matrices in the form of a rectangular slab and it has been observed that the rate of release is proportional to the square root of time (4). This is because the release rate is inversely proportional to the distance the drug must travel within the matrix to the matrix surface. Since this diffusional distance increases with time, the release rate decreases with time in spite of the fact that the concentration difference across the depleted zone remains constant.

One possible means of altering release kinetics from a matrix system is to vary matrix geometry. It was predicted that a matrix in the shape of a sector of a circular cylinder would release drug at a zero-order rate (5,6). Zero-order release kinetics occurred from a hemisphere with all portions laminated with an impermeable coating except for a small cavity cut into the center of the flat surface (7,8). Recently a matrix design to achieve zero order release was introduced consisting of an inwardly tapered disk with a central releasing hole (9). However, limitations to these delivery systems include the need for effective production and that their particular shape may not be convenient in certain applications.

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The purpose of this study was to design a suitable geometry in a fashion that would compensate for the increasing diffusional distance across the drug-depleted zone to achieve a zero-order release.

THEORETICAL TREATMENT

A dispersed drug under matrix control will provide zero-order only if the ratio between the area from which the drug becomes available to the distance the drug has to travel to reach the surface (diffusional distance) remains constant. In this case the change in diffusional distance must be exactly compensated for by the increase in device surface area from which the drug is released. Defining the surface area from which the drug release as A, the change in the area with time as dAi, and X as the distance the drug has to travel to reach the surface of the device, $A+dAi/Xi$ must be constant to satisfy a zero-order release condition.

Representing a_o as the radius of the area A, a_1 as the radius of the new area $A+dA_1$ at distance X_1, a_2 as the radius of the area $A+dA_2$ at a distance X_2 and a_i as the radius of area element $(A+dA_i)$ at distance X_i, the ratio $(A+dA_i)/X_i$ must remain constant to achieve zero-order release. This is expressed as:

$$\frac{A+dA_i}{X_i} = \frac{\pi a_o^2+(\pi a_i^2-\pi a_o^2)}{X_i} = \text{constant} = k$$

where $\pi a_o^2+\pi a_i^2-\pi a_o^2 = k X_i \qquad i = 1,2,3, \ldots .$

then $$a_i^2 = \frac{k}{\pi} X_i = K X_i$$

A parabolic solid of revolution (Figure 1) satisfies this requisite condition in which the radius of any circular cross sectional area is proportional to the square root of distance (X) from the top.

Fick's law can be applied assuming the following conditions: a drug is released from a solid matrix device by diffusion, the diffusion coefficient "D_m" remains constant, steady state condition is existing, diffusion rather than dissolution is the rate determining step, and dissolution occurs in the matrix (not through pores).

If the drug is released only from the dotted surface (Figure 2), the ratio of the area $(A+dA_i)$ from which the drug is available to the distance that the drug has to travel within the matrix (X_i) remains constant (parabolic geometry), C_o is the total drug concentration or drug loading in the matrix and is initially much greater than the solubility of the drug in the matrix (C_s), Q is the amount of drug released, a_0 is the radius of the surface area through which drug may permeate, A is area of the diffusion face, C_I is drug concentration in matrix at solution/matrix interface, C_a is drug concentration in the solution media and C_m is drug concentration in the matrix, then

$$J = -D_m \frac{dC_m}{dX} = \frac{1}{A+dA_i}\frac{dQ}{dt} \quad \text{(Fick's first law)} \qquad (1)$$

and

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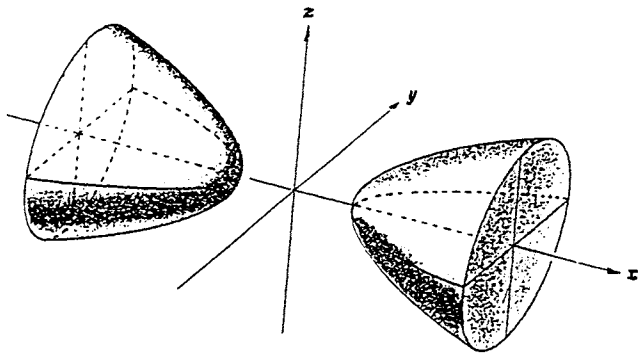

Figure 1. Parabolic solid of revolution.

$$\frac{dQ}{dt} = D_m (A + dA_i) \frac{dC_m}{dX} \quad \text{In accordance with the proposed geometry.} \quad (2)$$

$$\frac{dQ}{dt} = D_m (A + dA_i) \frac{(C_s - C_I)}{X_i}$$

for parabolic geometry, $\frac{A + dA_i}{X_i}$ = constant = K, or

$$\frac{dQ}{dt} = D_m K (C_s - C_I) = D_m K (C_s - Pc\ C_a) \quad (4)$$

where $PC = \frac{C_I}{C_a}$ = partition coefficient

Equation (4) is a zero order kinetic equation where D_m, K, C_s, Pc and C_a (under sink conditions) are constants. Integrating equation (4) from t = o to t = t leads to:

$$Q = D_m K (C_s - Pc\ C_a)\ t \quad (5)$$

which shows a linear relationship between Q and t indicative of zero-order release.

MATERIALS AND METHODS

To experimentally test the release kinetics for the proposed geometry, benzoic acid (Fisher Scientific Company, Fairlawn, N.J.) was dispersed in the fatty base Witepsol H15 (Nobel Dynamite, Witten Werke, F.R.G.). Release kinetics of benzoic acid from a slab (Cylindrical shape with identical cross sectional area throughout the matrix was considered as a slab in this study) were also studied for reference.

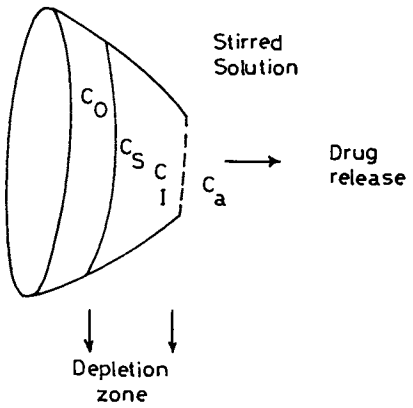

Figure 2. Hypothetical diagram for drug release under matrix control from matrix of parabolic geometry.

Matrices Preparation

Benzoic acid of particle size 180-250 μm was added to Witepsol H15 base that was melted at 40°C. The concentration of benzoic acid in the base was 20%. In order to ensure equal distribution of benzoic acid throughout the base, the mixture was poured while congealing into a steel mold with the desired dimensions and geometry. The molds were cooled to 5°C and solidified matrices of about 0.7 cm in length were then removed from the mold. The devices were then totally and tightly covered with impermeable flexible aluminum sheets. With the aid of a sharp blade and at a predetermined distance from the top of the parabolic geometry, of K values 0.6 and 1.0, a circular surface of radius 3 mm was exposed. With the exception of the exposed surface, the devices were impermeable to drug transport through all other sides. Procedures to fabricate slabs (cylindrical shape) followed methods similar to those described above. Drug release was attained only from one of the two circular surfaces of each slab. The exposed surfaces were also of radius 3 mm.

Dissolution Procedure

The amount of benzoic acid released from the matrices of slab and parabolic geometry of K values 0.6 and 1.0 was measured in distilled water at 25°C using the rotating paddle method (50.0 rpm). Each matrix was fixed by a metallic device in the dissolution apparatus, so that the uncovered surface was facing the stirring paddle. Since the relative position of the exposed surface of the matrix to the stirrer was constant (5 mm), the hydrodynamic conditions were exactly reproducible in all experiments.

The dissolution of benzoic acid was followed by withdrawing samples from the aqueous dissolution media as a function of time for analysis. The volume of the dissolution medium was kept constant by replacing the exact volume of sample withdrawn with fresh dissolution medium and ideal sink conditions were maintained throughout the runs. Benzoic acid samples were analyzed spectrophotometrically (Pye Unicam, Sp 6-550, England Spectrophotometer) at 270 nm and the amount of solute released was then calculated as a function of time. Parabolic and slab geometries of pure base containing no benzoic acid were prepared and were used as controls. Each dissolution point is the mean of four experiments. The aluminum sheet was re-tightened during the dissolution to ensure that drug release was limited to the exposed surface.

RESULTS AND DISCUSSION

The rate of benzoic acid release from fatty base matrices of parabolic and slab geometry are compared in Figure 3. The release of benzoic acid from two parabolic matrices of different K values are shown. Within 9 days, matrix geometries of K = 0.6 and 1.0 provided 24 and 35% drug release, respectively. The release kinetics from both parabolic geometries closely approximates zero-order. Control matrices of

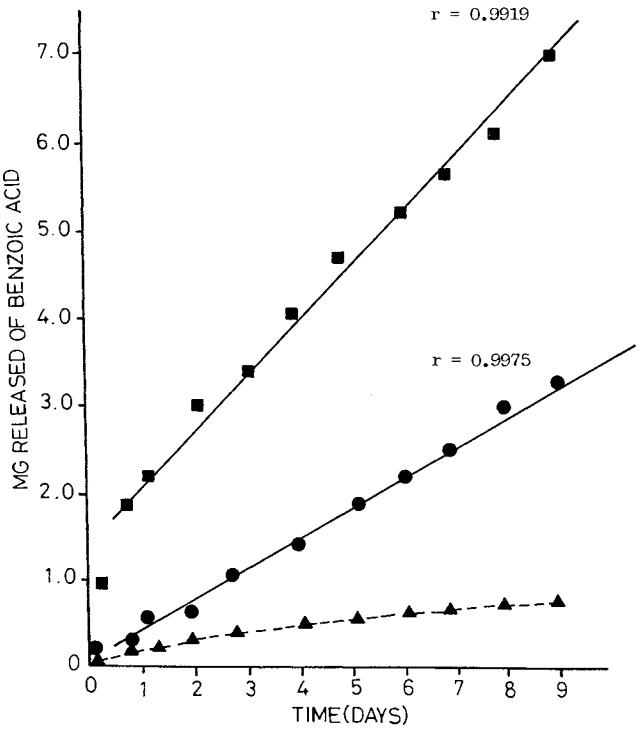

Figure 3. Cumulative amounts of benzoic acid released as a function of time from parabolic geometry and slab. Key: (■) parabolic geometry with K = 1, (●) parapolic geometry with K = 0.6, (▲) slab. Each point represents the mean of 4 samples. Standard error of the mean was within 5%.

pure base showed no material exhibiting spectrophotometric absorbance at 270 nm in aqueous media. The release kinetics from slab geometry was far from zero-order. The parabolic devices yield linear release profiles and the smaller K better approximated zero-order release and provided a higher regression coefficient, as compared to the higher K value (Fig. 3). The deviation for high K value may be explained by the fact that as K increases, nonlinear diffusion may occur toward the release surface. Although an initial burst effect was observed at the high K value, (which may be due to rapid change in matrix cross sectional area with diffusional distance) it was followed by a zero-order release at steady state. If the surface of release is mainly at the top of the parabolic shape, deviation from zero-order release can be minimized because drug molecules diffuse through the entire distance of the release device, and a constant ratio between diffusional distance and area is maintained.

The release profile for benzoic acid from the proposed geometry was shown to be reproducible as each experiment was repeated four times. Standard error of the mean did not exceed 4.8% for each dissolution point (C.V. did not exceed 9.6%). Reservoir systems in which a core of drug is surrounded by a polymeric shell can be utilized in zero-order release systems (10). In this case the drug will traverse the same diffusional distance through pure polymer coating rather than through polymer-drug matrix and the release rate will be constant. Benzoic acid sedimentation during fabrication was avoided to ensure that the zero order release from the proposed devices is not due to similar effect. Although the porosity and tortuosity of the matrix and the solubility and diffusion of drug from the device can affect release rates of drug, these factors were eliminated in this comparative study by controlling drug loading, particle size, and the method of fabrication of the parabolic and slabs devices.

The fatty base and coating material used in this study were chosen for ease of fabrication of the proposed geometry and the aim of this work was to characterize the release profile from an inert matrix. The geometry proposed in this work could be used in preparation of dosage forms such as tablets and suppositories as well as small devices for in-vivo implantations where careful choice of the matrix and coating materials is required. Techniques such as computer-aided design may be useful in preparing molds of such geometric design.

In summary, both theoretical and experimental analysis were utilized to demonstrate that a parabolic geometry can provide a zero-order release system for drug suspended in inert matrix for long periods of time with minimum deviation.

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