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A SIMPLE MODEL BASED ON FIRST ORDER KINETICS TO EXPLAIN RELEASE OF HIGHLY WATER SOLUBLE DRUGS FROM POROUS DICALCIUM PHOSPHATE DIHYDRATE MATRICES

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ABSTRACT

A simple model was developed to explain release of highly water soluble drugs from inert, insoluble, non-swelling porous matrices. According to this model the release can be explained using a first order kinetic expression: $Q = Q_o e^{-Kt}$, where Q is amount released, Q_o is initial amount, and K is rate constant. The rate constant is related to the geometry of the matrix as: $K = K_d A/V$ where, K_d is a diffusion related proportionality constant, A is void area, and V is void volume. For cylindrical matrices, the rate constant can be expressed as $K = K_d 2(1/r + 1/h)$ where r is radius and h is height of the matrix.

Cylindrical as well as biconvex matrices were prepared on a single punch tablet machine with varying heights and radii, thus different specific surface areas. The rate constants were determined following dissolution testing. The experimental release profiles follow first order kinetics. Good correlation was found between the rate constant and specific surface area of the matrices studied.

INTRODUCTION

This work deals with development of a simple model to describe release of highly water soluble drugs from dicalcium phosphate dihydrate matrix at concentrations less than 5% w/w. This type of matrix can be classified as a granular or heterogeneous matrix where the concentration of drug in the matrix is far less than its solubility and the release occurs through porosity preexisting in the matrix.

The following equations/theories have been proposed to explain the release of drugs from various matrix delivery systems.

Higuchi equations[1,2]

$$Q = [D\varepsilon / \tau (2A - \varepsilon C_S) C_S t]^{1/2} \quad \text{Eqn. 1}$$

Where Q represents the amount of drug released per unit exposed area (g/cm^2) after time t(sec), D represents the diffusivity of the drug (cm^2/sec) in the permeating fluid, τ represents the tortuosity factor of the capillary system (approx. equals 3), A represents the total amount of drug present in the matrix per unit volume (g/cm^3) , C_S represents the solubility of the drug in the permeating fluid, and ε represents the porosity of the matrix.

Simonelli et al[2], have used equation 2 for a situation, where the drug is released from a porous matrix loaded with saturated drug solution, C_O is concentration of solution used. Other symbols have been previously described.

$$Q = [2C_O\varepsilon (Dt / \tau\pi)]^{1/2} \quad \text{Eqn. 2}$$

Baker et al[3] have proposed following equation for monolithic matrix systems or simple matrix systems.

$$dM_t/dt = A/2 (2D_W\varepsilon C_S C_O / \tau t)^{1/2} \quad \text{Eqn. 3}$$

where, D_W is diffusion coefficient of the drug in the medium that fills the pores of the matrix.

The matrices under consideration have continuous channels by virtue of the porosity thus it is above the percolation threshold and percolation theory may be applicable in this case[4]. The volume accessible for the dissolution medium through the connecting network is designated as ϕ. The diffusion coefficient through this network is designated as D_B or the bulk diffusion coefficient (cm^2/sec). d is the density of the drug. The release of the drug in terms of percolation parameters is given by equation 4.

$$Q = \{D_B C_S [2 \phi d - (\phi + \varepsilon) C_S] t\}^{1/2} \quad \text{Eqn. 4}$$

The above mentioned equations based on the Higuchi model[1] can be summarized by the following equation.

$$Q = K t^{1/2} \quad \text{Eqn. 5}$$

where K is a constant and is treated differently by different workers and theories. It has been previously shown that plotting cumulative release as a function of square root of time does not adequately describe the release.[5]

Noyes-Whitney[6] model and **Hixson-Crowell**[7] model have been used to describe release of drugs through non disintegrating isotropic devices. These theories may not be applicable to dicalcium phosphate dihydrate (DCPD) matrix system which is unisotropic system releasing drug through the porosity pre-existing in the matrix.

None of the theories described above in their current form can be applied to explain the release of drugs form DCPD matrices. However, good correlation was found when first order kinetics was applied to the same data. Thus, further investigation of the release kinetics based on first order kinetics was considered desirable. The following work further investigates the applicability of first order kinetics to explain release of drugs from dicalcium phosphate matrices. A simple model has been proposed and some of its implications have been tested.

THEORETICAL

The present model is based on a simple analogy to flow of liquid from a container with an opening on the side near the bottom. Flow of a liquid with low viscosity will not produce a gradient between the walls of the container provided the distance between them is sufficiently small. The rate and extent of liquid released with respect to time will be proportional to the height and therefore the volume of the liquid in the container. Thus, the flow would follow first order kinetics.

Assumptions involved

1. The matrix is insoluble, nonswellable, and inert towards the drug as well as the medium.
2. The drug is highly water soluble and the void volume of the matrix is sufficient for complete dissolution of the drug.
3. The penetration of dissolution medium into the matrix and dissolution of the drug occurs rapidly after contact with the dissolution medium.
4. After the initial change in porosity due to dissolution of the drug within the matrix the void volume or the porosity remains constant through out the release process. The time required for penetration of the medium into the matrix and subsequent dissolution of the drug is negligible compared to length of the test.
5. The matrix maintains its integrity throughout the release process and provides a constant area for diffusion of the drug.
6. The ratio of surface area to the volume of the tablet represents the ratio of void area to void volume.

The dissolution medium penetrates into the porosity of the matrix and dissolves the drug. The tablet surface represents the boundary between the drug inside the tablet and the drug released in the medium. The diffusion across this boundary can be explained using law of diffusion. The rate at which the drug will diffuse into the surrounding medium will be directly proportional to the concentration difference across it. If sink conditions are maintained the release rate across a constant area will be proportional to the drug concentration in the matrix, a situation well described by the statement of the Fick's first law.[8]

$$\text{flux} = dQ/(A^* dt) = K_d (C_i - C_o) \quad \text{Eqn. 6}$$

Where C_i is concentration inside the matrix and C_o is concentration outside the matrix. Q is the quantity of the drug and t is the time. Since there is no thickness involved, K_d the diffusion related proportionality constant, assumes the dimensions of velocity (cm/sec) same as those of permeability constant or mass transfer coefficient. A is the surface area.

Under sink conditions, ($C_i - C_o = C_i$), and will be denoted simply by C. We assume that the concentration at the surface represents the average concentration of drug within the matrix at all times; then we may write,

$$dQ/dt\ (\text{mg/sec}) = K_d\ (\text{cm/sec}) * C\ (\text{mg/cm}^3) * A\ (\text{cm}^2) \quad \text{Eqn. 7}$$

For a matrix with finite size one can write the following equation:

$$dQ/dt\ (mg/sec) = -K_d\ (cm/sec) * A\ (cm^2) * Q/V\ (mg/cm^3) \quad \text{Eqn. 8}$$

where V represents the void volume of the matrix and A represents void surface area. The negative sign indicates the amount of drug in the matrix rate is decreasing with respect to time. The void surface area and the void volume for a non disintegrating matrix are constant thus replacing these constants in the equation 8 by k_r one can write

$$k_r\ (1/sec) = K_d\ (cm/sec) * A/V\ (cm^2/cm^3) \quad \text{Eqn. 9}$$

Incorporating equation 9 into equation 8 and integrating for Q = Qo to Q and for t = 0 to t,

$$Q = Q_o e^{-krt} \quad \text{Eqn. 10}$$

This model has the following implications

1. The release of highly water soluble drugs from porous matrices follow first order kinetics as described by equation 10.
2. The first order rate constant is directly proportional to the specific surface area of the tablet, expressed in the units of length (area per unit volume), as described by equation 9. Thus, the rate constant is a linear function of the specific area expressed as area per unit volume. For cylindrical matrices, the rate constant will be a linear function of the reciprocal of the height when the radius of the matrix is held constant, and vice versa. For a sphere the rate constant will be inversely proportional to the radius.

For a right circular cylinder of radius r and height h one can write,

$$K_r = K_d\ 2\ (1/r + 1/h) \quad \text{Eqn. 11}$$

Surface area and volume of a convex tablet

The surface area and volume for this geometry is the addition of the respective quantities for the circular (convex) portion and the cylindrical portion. The equations for the area and volume for the circular portions was derived base on intersection of a sphere and a cylinder and given by equations 12 and 13. The total area and volume for the tablet are given by equations 14 and 15. Where 'H' is height of the cylinder, 'R' is the radius of the cylinder and 'a' is the radius of curvature for the convex part of the tablet.

$$\text{Area} = \int_0^{2\pi} \int_0^{R} a / (a^2 - r^2)^{1/2}\ r\, dr\, d\theta \quad \text{Eqn. 12}$$

$$\text{Vol} = 8 \int_0^{\pi/2} \int_0^{R} z\ r\, dr\, d\theta \quad \text{Eqn. 13}$$

$$\text{Area} = 2\pi RH + 4\pi a\,(a - (a^2 - R^2)^{1/2}) \quad \text{Eqn. 14}$$

$$\text{Vol} = \pi R^2[H - 2(a^2 - R^2)^{1/2}] + 4/3\pi\,[a^3 - (a^2 - R^2)^{3/2}] \quad \text{Eqn. 15}$$

The rate constant for biconvex tablets can be given by equation 20.

$$K_r = K_d\ \text{Eqn. 15} / \text{Eqn. 17} \quad \text{Eqn. 18}$$

MATERIALS AND METHODS

Chlorpheniramine maleate (CPM) was obtained from Napp chemicals Inc. Lodi, NJ. Unmilled dicalcium phosphate dihydrate (Emcompress®) was

supplied by Edward Mendell company, Inc., Carmel NY. Henceforth, dicalcium phosphate dihydrate will be referred to as DCPD. Magnesium stearate was purchased from Amend chemicals.

Tablets were manufactured by direct compression of mixtures of drug and excipient, using a single punch model F Tablet Press made by Stokes Machine Company, Philadelphia. Various sizes of punches, flat and concave, and dies, were made by the machine shop of Temple University, Philadelphia.

The drug was mixed with the diluent in a mortar using geometric dilution technique. This mixture was then lubricated with (1% w/w) magnesium stearate which was previously passed through #80 mesh sieve prior to compression. The tablets were compressed to a constant bulk density by monitoring the height of the tablets. The height was measured using a micrometer screw gauge with the least count of 10 microns. All the tablet, except when specified had CPM 4%, DCPD 95%, and magnesium stearate 1% w/w.

The release of drug from the tablets was studied using USP method II dissolution testing machine. Dissolution testing system Model 2000 made by Distek Inc., Somerset, NJ was used. The tests were carried out in purified water at 37°C and the peddle speed of 100 rpm.

The samples were withdrawn at various times and analyzed at 262 nm wavelength using a Hewlett Packard Diode Array UV spectrophotometer, model 8451A, Hewlett Packard Inc. San Fernando, CA.

RESULTS AND DISCUSSION

Kinetics of Release

A slightly different treatment of the release data from the one suggested by Schwartz et al.[9] was used in order to test the applicability of first order kinetics. A release profile following first order kinetics will have following properties (a) the release rate (dQ/dt) at any given time should be directly proportional to the drug concentration in the tablet; as given by equation 8. (b) The rate constant should be independent of the initial drug concentration. The rate constant, the release rate, and the drug concentration in the tablet were experimentally determined.

The rate constant can be calculated using the Log % retained versus time plot. The amount of drug present in the matrix can be determined since the amount released at certain time points is known. Thus, the release rate at any given time point can be calculated using equation 10.

Table 1 shows the rate constants obtained for tablets containing 1 to 5% w/w drug concentration. The rate constants obtained were fairly independent of concentration (R.S.D. 4.3%). Table 1 also shows the dissolution rates calculated at 4th hour and corresponding concentrations of drug in the matrix. Under sink conditions, the concentration of the drug in the matrix represents the concentration difference. Figure 1 depicts the plot of release rate as a function of concentration

TABLE 1
Effect of CPM Concentration in the Matrix on the Release Rate Constant.

Initial Drug content mg/tab	Rate Constant 'K_r' 1/hour	Release Rate at 4th hour $dc/dt = K_rC$ mg/hr	Concentration at 4th hour mg/mL*
4	0.178	0.318	11.168
8	0.190	0.617	23.977
12	0.175	0.876	35.302
16	0.178	1.172	47.515
20	0.169	1.473	56.619

Rate Constant Mean: 0.178 R.S.D.: 4.3%
Tablet Weight 400 mg, Radius: 3.44 mm, Height: 5.25 mm
* Volume of the tablet 0.198 mL

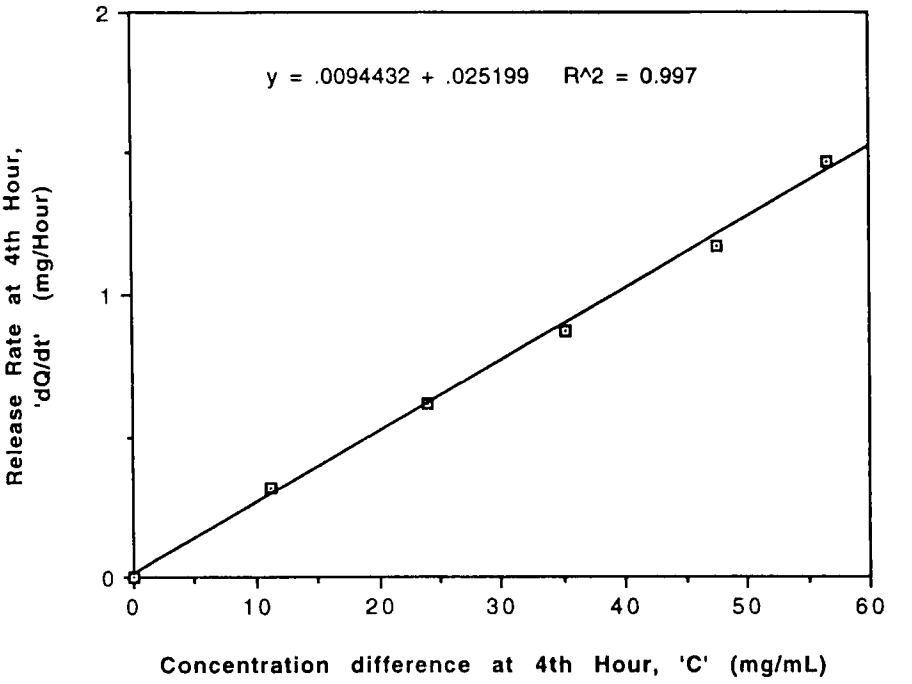

FIGURE 1
Release Rate as Function of Drug Concentration in the Tablet

of drug in the matrix showing excellent correlation and supporting the relationship described by equation 10. Thus it can be said that the drug release does fulfill the requirements of first order kinetic expressions.

Relationship between tablet geometry and the rate constant

Equation 9 implies a linear relationship between the rate constant and the surface area of the tablet under the assumption that the ratio of void surface area to the void volume represents the ratio of total surface to the total volume. Thus, the specific surface area of the tablet represents the area across which the release is taking place.

Using equation 11 the rate constant for cylindrical matrices can be described as a function of the reciprocal of either the radius or the height of the matrix. Equation 11 also provides two ways to calculate K_d, using the slope as well as the intercept.

Cylindrical matrices with increasing weights were prepared maintaining the bulk density (and therefore the porosity) of the tablet constant. In one case, the height of the tablet was increased keeping the radius constant (i.e. using same set of die and punches) and in the other case tablets with different radii were compressed to a constant height (i.e. different punch sizes). Figures 2 and 3 show the plots of release rate constants as a function of the reciprocals of the height and the radius, respectively. Linear regression analysis shows excellent correlation; 0.982 for both lines. Figure 4 shows the rate constant plotted as a function of the specific surface area as described by equation 9. Although all the plots are satisfactorily linear the intercepts do not correspond the expected values such as $2K_d/r$ in figure 2, $2K_d/h$ in figure 3, and zero in figure 4. This is probably due to lack of proper estimation for the void surface area. The value of K_d obtained using the slope was considered to be more reliable and was used for further predictions.

Rate constants for convex tablets

A very commonly used geometry / shape, biconvex was used for further testing the model. Tablets with constant drug concentration (4%), constant weight (900 mg), and constant bulk density were prepared using punches with varying radii of curvature. Thus, the tablets were expected to have consistent drug concentration, total and void volume except for the surface area.

Table 2 shows the experimentally determined rate constants as well as predicted rate constants for biconvex tablets. The rate constants for biconvex tablets were predicted by incorporating the value of K_d obtained for cylindrical tablets into equation 16. The predicted rate constants were significantly different from the ones observed experimentally as shown in table 2. This is probably due to error in estimation of K_d, which in turn may be due to limitations of the assumption regarding the void surface area. It should be noted that the specific surface area as calculated from the external dimensions of the tablet changed only

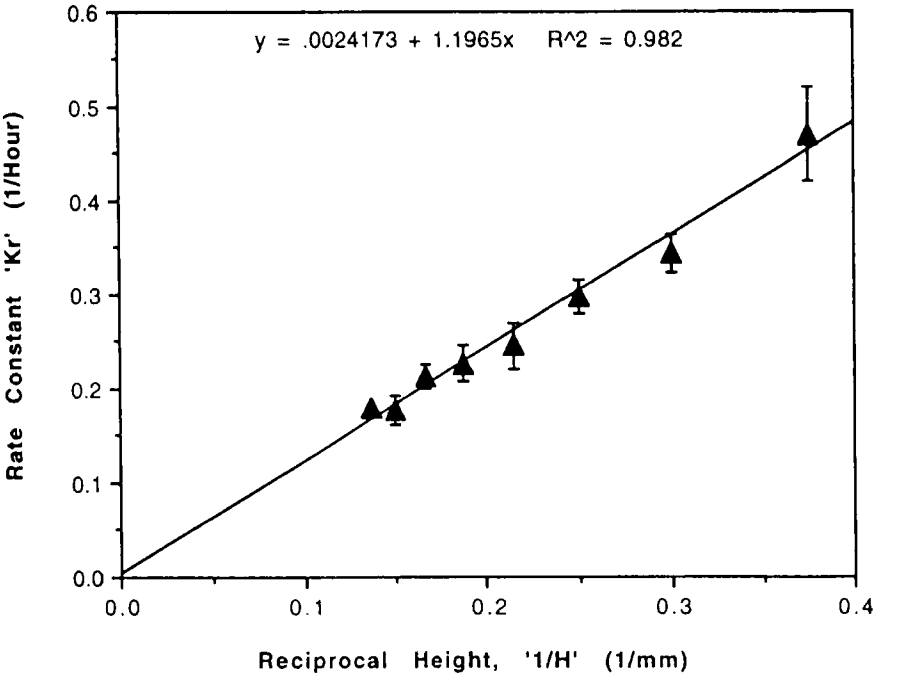

FIGURE 2

Rate Constant as Function of Reciprocal Height of Cylindrical Matrices

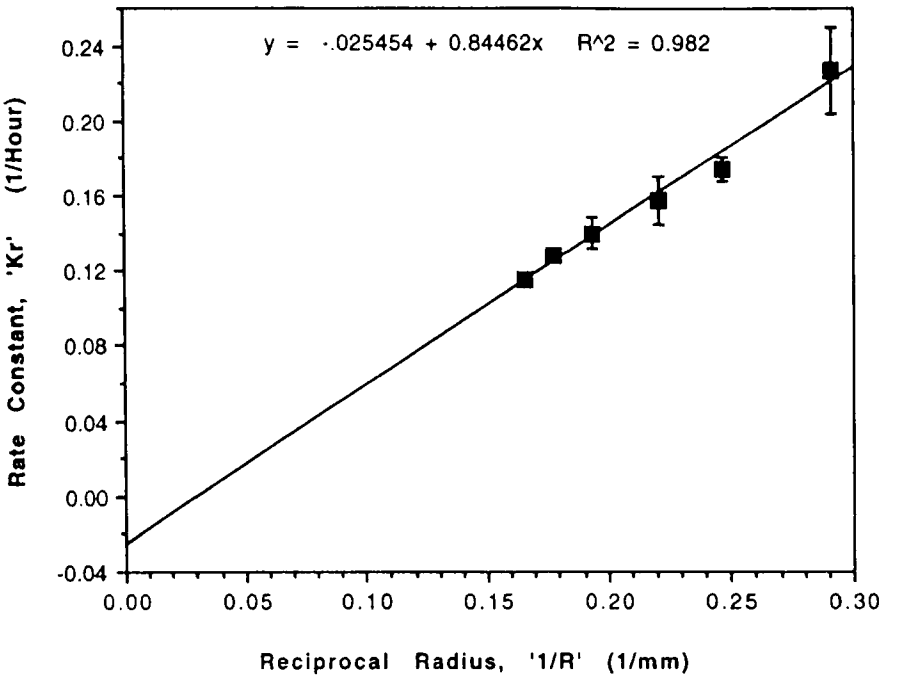

FIGURE 3

Rate Constant as Function of Reciprocal Radius of Cylindrical Matrices

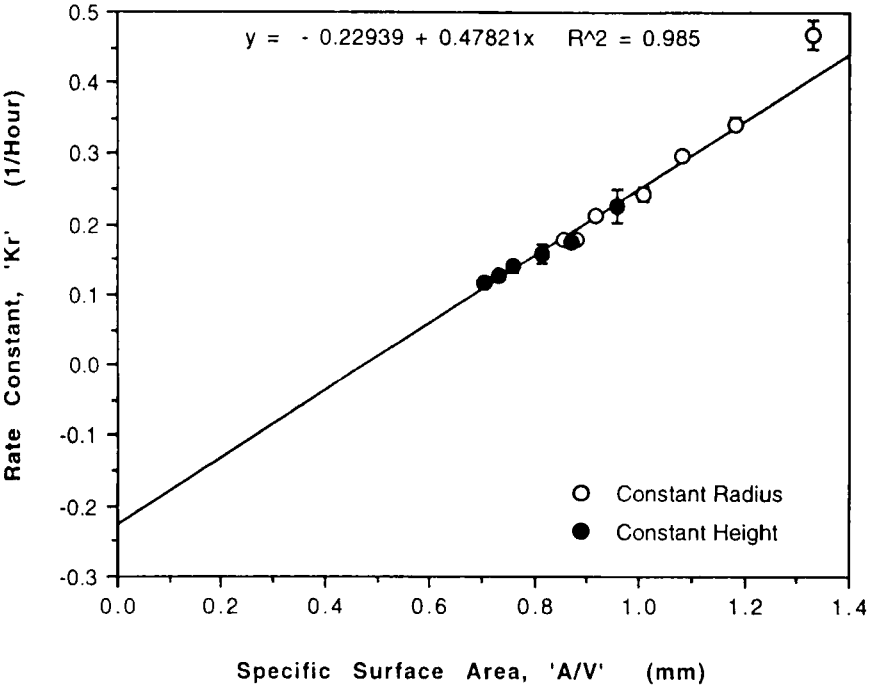

FIGURE 4

Rate Constant as Function of Specific Surface Area of Cylindrical Matrices

TABLE 2

Effect of Tablet face Geometry on the release Rate Constant: Convex Tablets

Radius of Curvature	Sp. Surface Area (mm)	Rate Constants (1/Hour) Expt. (Std Err)	Prediction I	Prediction II
5.537	0.6421	0.1363 (±5.86)0.777	0.1363	
6.35	0.6525	0.1402 (±7.35)0.826	0.1385	
7.925	0.6694	0.1307 (±3.80)0.907	0.1421	
9.925	0.6821	0.1451 (±3.60)0.968	0.1448	

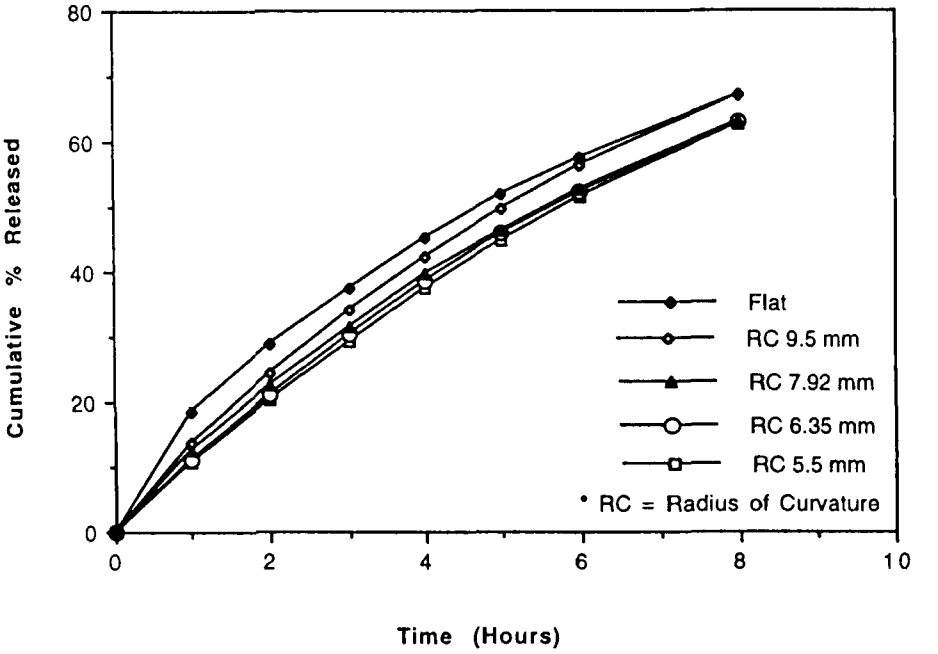

FIGURE 5

Release Profiles of Biconvex Tablets with Different Radii of Curvature

by 6% from the tablet with the least surface area (highest radius of curvature) to that with the greatest surface area. According to the model proposed it is to be expected that the rate constant would change proportionately to the extent of only 6%. The column designated as 'prediction II' shows the rate constants calculated relative to the observed rate constant for the first tablet and they are reasonably similar to those experimentally found.

Figure 5 shows the release profiles of the convex matrices. The tablets with lowest surface area (highest radius of curvature) showing slowest release. Due to small change in specific surface area the differences in the release profiles are also small. However, based on significant number of release profiles (3 x 6) the differences were found to be consistent and significant.

SUMMARY AND CONCLUSIONS

The release of highly water soluble drugs from dicalcium phosphate dihydrate matrices follows first order kinetics.

The rate constant is a linear function of the specific surface area of the tablet. For cylindrical matrices, good correlation was found between the rate constant and the reciprocals of radii and heights.

The constants obtained for the cylindrical matrices were used toward predicting the release rate constants geometry. The predicted values for the release rate constant for convex tablets did not match with those obtained experimentally. However, release and the rate constant decreased proportionally with decreasing surface area of the tablet. Mathematically precise prediction of rate constants based on the geometry of the matrix would need further investigation of precise determination of K_d.

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