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An Examination of Assumptions Underlying the First-Order Kinetic Model for Release of Water-Soluble Drugs from Dicalcium Phosphate Dihydrate Matrices

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ABSTRACT

It has been shown that the release of highly water-soluble drugs from compressed dicalcium phosphate dihydrate matrices follows first-order kinetics (1). Good correlation between the rate constant and tablet geometry (2) was also reported. However, the rate constants for different geometry could not be predicted accurately by using the constants obtained for cylindrical tablets. In this work the assumptions regarding the surface area, porosity, and inertness of the drug toward the matrix have been tested using simple experimental designs and techniques such as porosimetry, electron microscopy, and differential scanning calorimetry. No interactions between the drug and the matrix were observed. The assumptions regarding porosity/void volume seemed to hold. Using water as a penetrant gave better estimate of porosities than those obtained using mercury. The assumption regarding surface area needs correction; however, a better alternative has not been proposed.

INTRODUCTION

Previous work explains a model (2) which describes release as a first-order process and the rate constant K_r as a function of the specific surface area of the tablet, Eqs. (1)-(3).

$$Q = Q_0 e^{-kt} \quad (1)$$

$$K_r = K_d A/V \quad (2)$$

For a right circular cylinder of radius R and height H:

$$K_r = K_d\, 2(1/R + 1/H) \quad (3)$$

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The model is based on following assumptions:

1. The matrix is insoluble, nonswellable, and inert toward 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 throughout 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.

According to Eq. (2) the rate constant is a linear function of the void specific surface area of the tablet expressed as area per unit volume. To allow prediction, the void area needs to be known. Since the void area could not be measured directly, it was assumed to be equal to the specific surface area of the tablet. Although the rate constant varied linearly with change in the specific surface area, a precise prediction of the rate constant was not possible for a differently shaped tablet.

According to the model the linear plot of rate constant versus specific surface area of tablet should not yield an intercept on either axis. Previous work shows that a nonzero intercept was obtained for such a plot. The specific surface area of a cylinder can be represented as a function of the height and the radius, and therefore the rate constant, Eq. (3). This equation offers two ways to calculate K_d; using the slope ($2K_d$) and the intercept (either $2K_d$/radius or $2K_d$/height). Data presented in previous work (2) show rate constants plotted as functions of reciprocal of the height and the radius. The slopes are similar but the intercepts do not provide reasonable estimates for K_d. However, this apparent limitation of the assumption does not invalidate of the entire model but only the precise calculation of K_d. This work is intended to take a closer look at the model and the assumption involved.

MATERIALS

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 is referred to as DCPD. Magnesium stearate was purchased from Amend Chemicals.

METHODS

Tablets were manufactured by direct compression of mixtures of drug and excipient, using a single-punch model F Tablet Press may be Stokes Machine Company (Philadelphia). Various sizes of punches, flat and concave, and dies, were made by the Machine Shop, Temple University (Philadelphia, PA). All the formulations contained the following ingredients: CPM 4%, DCPD 95%, magnesium stearate 1%.

The release of drug from the tablets was studied using a USP II dissolution testing machine. Dissolution testing system Model 2000 made by Distek Inc. (Somerset, NJ) was used. The tests were carried out in distilled water at 37°C and the peddles rotated at 100 rpm. The samples withdrawn at various times were analyzed using a Hewlett-Packard Diode Array UV spectrophotometer, model 8451 A (Hewlett Packard Inc. San Fernando, CA).

Differential scanning calorimetric (DSC) and thermal gravimetric analysis (TGA) were carried out using a Perkin-Elmer Delta Series 7 DSC-TGA (Exton, PA). The machine was equipped with a temperature controller (-70° to 550°C) and was computer controlled.

The tablets were coated with carbon using Biorad E6100 vacuum coater (Polaron Equipment Ltd., Watford, Hertfordshire) prior to observation under a scanning electron microscope (Model JSM 840 scanning microscope, Jeol USA Inc., Peabody, MA).

Porosity Measurement Using Mercury Intrusion Porosimetry

Preweighed tablets were placed in a glass tube equipped with an electrode at one end and an opening at the other end. The tablets were evacuated by subjecting them to vacuum. Mercury was then allowed to fill the glass tube containing tablets. The tube was weighed and then placed in the high-pressure chamber. The porosity was calculated based on the volume of mercury that

penetrated into the tablets subjected to 33,000 psi pressure. The mercury intrusion porosimeter (model Autoscan 33 porosimeter made by Quantachrom Corp., Syosset, NY used for these porosity measurements was equipped with a computer for data collection and analysis.

Porosity Measurement Using Water Penetration: Before Drug Release

Preweighed tablets were placed in a plastic petri dish, and distilled water was slowly poured into these dishes until the water level was as high as the top surface of the tablets. The tablets were allowed to stand without agitation in water for 30 min. The tablets were then removed from the petri dishes and reweighed, followed by drying at room temperature to a constant weight. The water remaining in the petri dishes was dried to constant weight; the amount of drug leached was found to be negligible. The time required for the water front to reach the center of the tablet was also recorded and was termed as the *penetration time*.

Porosity Measurement After Drug Release

Tablets were placed in the dissolution testing equipment with 100 rpm agitation and allowed to release the drug for 30 hr. The tablets were removed from the dissolution medium (water). Excess water was removed by draining and blotting from edge of the tablet. The tablets were then weighed and dried to constant weight at room temperature.

RESULTS AND DISCUSSION

Figures 1 and 2 show electron micrographs of the surface of tablets after contact with the dissolution medium and after release has taken place. Figures 3 and 4 show porosities at higher magnification present on the cylindrical and flat sides of a cylindrical tablet. The porosities are quite apparent. The electron micrographs also show that the surface is uneven and has no definite size or shape, making it difficult to assess the area. This difficulty led to the assumption that the ratio of void area to void volume equals the ratio of total area to total volume, in order to facilitate some prediction.

If this assumption is valid, the tablets with equal surface area but different void volumes (or different bulk densities) should have the same release profile as well as the rate constant. Figure 5 shows the release profiles of the matrices and Fig. 6 shows rate constant plotted as a function of tablet density. Both the figures show that the release and the rate constant change significantly with change in the bulk density of the tablet beyond 1.9 g/cm^3. This may suggest that it may not be realistic to use the specific surface area of the tablet as a true rep-

Figure 1. Scanning electron micrograph: tablet immediately after contact with medium.

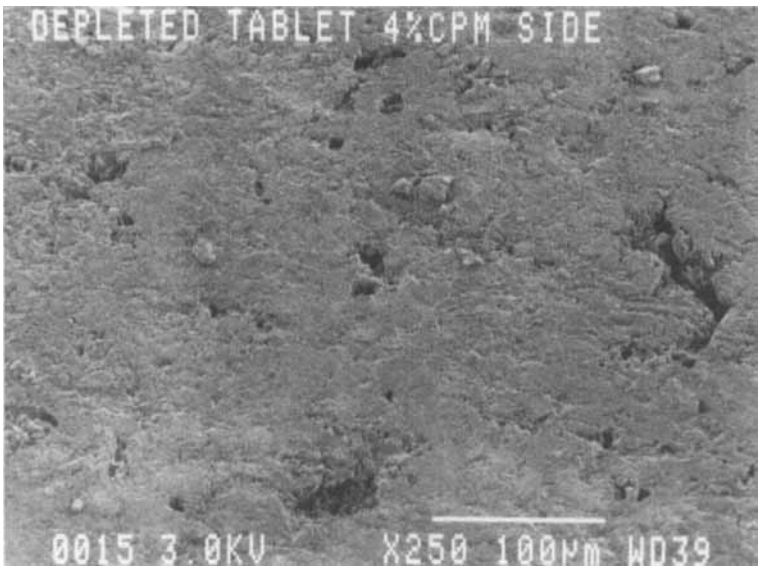

Figure 2. Scanning electron micrograph: tablet after release.

resentative of the area across which the release is taking place. The following explanations may be offered.

Visual examination revealed that tablets with higher bulk density had smoother surfaces. Differences in surface roughness may contribute toward errors in estimation of surface area and therefore change in rate constants.

Change in density of the tablet or the size may change the structure of the porous network. Although the void volume decreased linearly with increasing den-

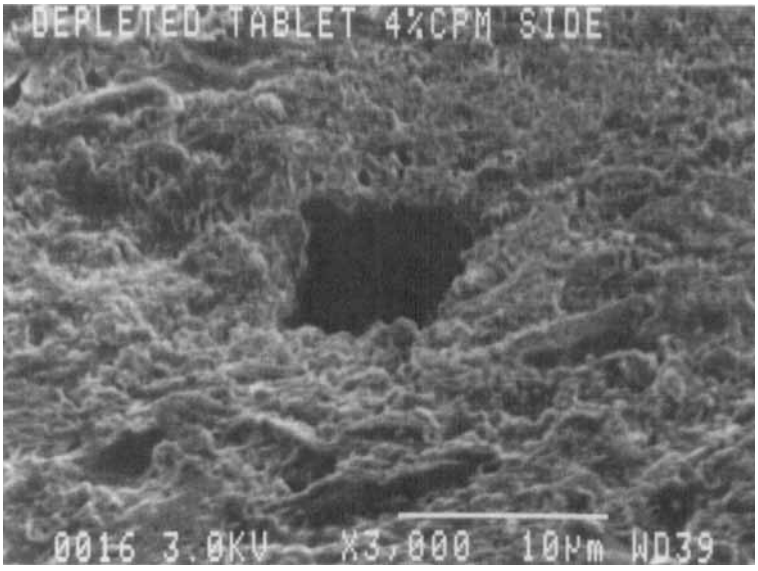

Figure 3. Scanning electron micrograph: cylindrical side at higher magnification.

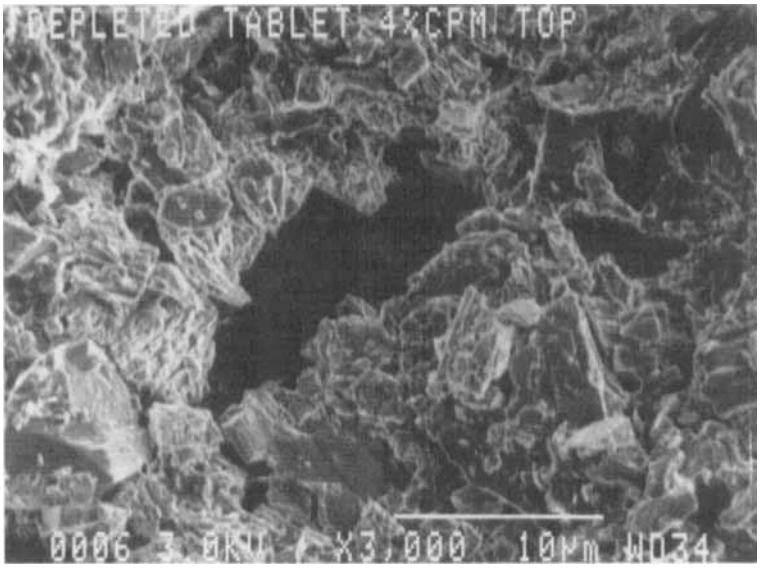

Figure 4. Scanning electron micrograph: flat side at higher magnification.

sity, the time required to penetrate to the center of the matrix increased exponentially, as shown in Fig. 7. One may reason that the radius of the pores in matrices decreased with increasing density and thereby provided added resistance to the influx of water into the matrix. The tortuosity may also be a contributing factor toward the discrepancies in predicted rate constant. This may suggest that addition of a correction factor may be necessary to account for the pore size or the penetration time.

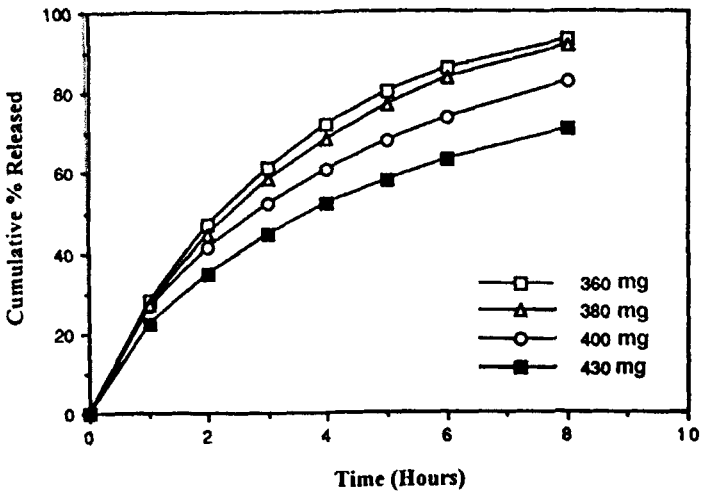

Figure 5. Release profiles as function of tablet bulk density.

The porosity of the tablets was examined using two different techniques. The obvious choice was to use mercury intrusion porosimetry. Table 1 shows the results from mercury intrusion porosimetry for tablets with different sizes. The bulk density of the tablets was kept essentially constant. Interestingly, volume penetrated by mercury consistently increased with the size of the tablet; the average pore radius also increased consistently. A possible explanation could be that mercury has a very high contact angle on most materials (approximately 147° for most noninteracting surfaces) and is unable to penetrate the ultrafine pores even under 33,000 psi pressure. However, this does tell us that the tablets with same bulk density but different sizes have different porous structure.

DCPD, although water insoluble, has near zero the contact angle with water. The drug release was studied using water as the medium. It was thought that water may be a good choice for a penetrant to measure porosity of the matrix. Figure 8 shows the void volume plotted as a function of bulk density of the tablet. There is a linear decrease in the void volume with increase in bulk density. The intercept on the x axis should correspond to the true density of DCPD, and the y intercept should correspond to the volume of the tablet. Values

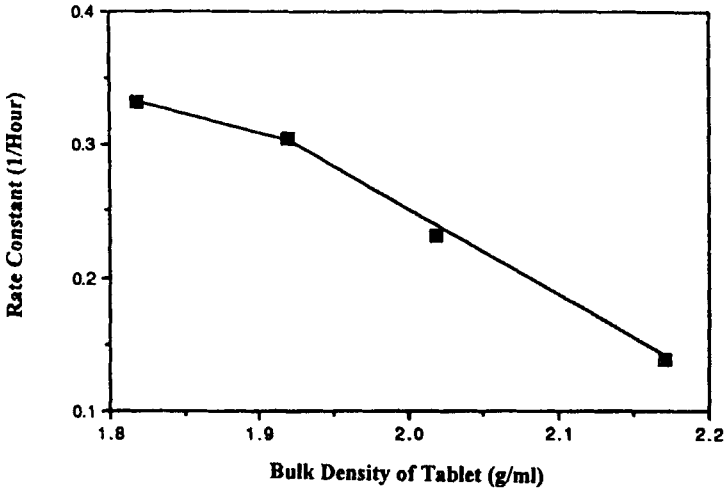

Figure 6. Rate constant as function of tablet bulk density.

obtained for both the intercepts are close to the expected values (reported density of DCPD 2.31 g/ml, x intercept 2.34 g/ml, volume of the tablet 200 μl, y intercept 224 μl). This supports the validity of using water as a penetrant for measuring porosity.

Table 2 shows the porosities measured for tablets with same bulk density but different total volume before and after the release. Both the plots are satisfactorily linear and support the hypothesis that water may be a better penetrant than mercury. The data indicates that

Table 1

Porosity Measurements Using Mercury Intrusion

Tablet Weight (mg)	Tablet Height (mm)	Volume Intruded (μl/g)	Bulk Density (g/ml)	Mean Radius (Å)	Pore Area (m^2/g)
200	2.58	20.2	2.138	246.0	1.28
300	3.87	31.5	2.104	311.9	2.20
400	5.16	36.9	2.074	395.1	1.93
500	6.40	44.0	2.070	474.6	2.38

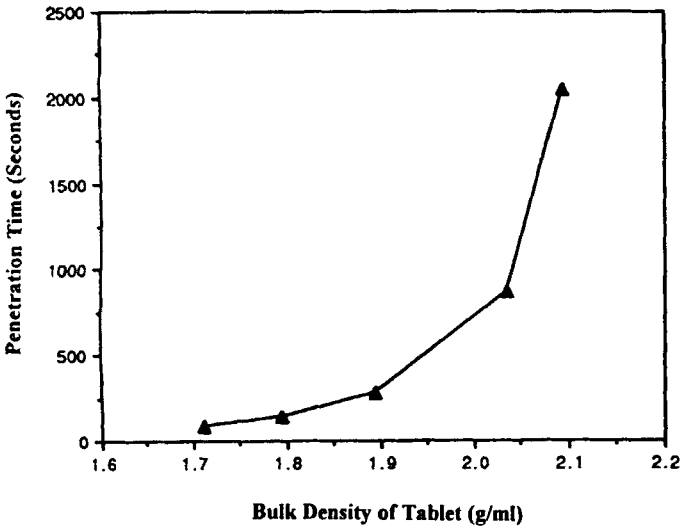

Figure 7. Penetration time as function of bulk density.

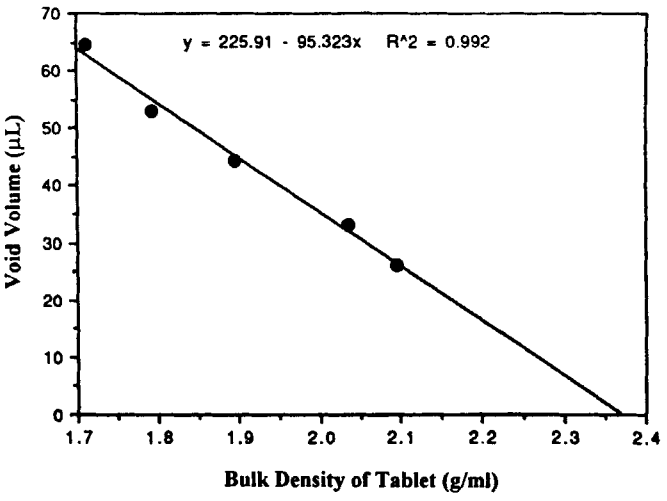

Figure 8. Void volume as function of bulk density.

Table 2

Porosity Measurements Using Water Penetration

Tablet Weight (mg)	Void Volume (μl/g) Before Release	Void Volume (μl/g) After Release
200	61.9	86.3
250	71.9	94.2
300	73.6	103.2
350	68.4	100.6
400	67.4	96.5
450	71.0	100.7
500	72.3	99.9
550	79.0	117.3
Mean	70.7 (± 6.6%)	99.8 (± 8.3%)

Note. Tablet radius: 3.44 mm; tablet density: 2.0194 g/ml.

Table 3

Differential Scanning Calorimetric Studies on Physical Mixtures of CPM and Dicalcium Phosphate

Concentration of CPM, % w/w	Heat of Fusion,[a] ΔH_f, J/g	Melting Point, °C
20	24.24 (121.20)	134.6
40	52.81 (132.03)	134.9
60	78.23 (130.38)	132.4
80	101.16 (126.45)	133.1
100	177.18	133.6

[a]The values in parentheses represent calculated heat of fusion for pure CPM.

the void volume per unit tablet weight remains essentially constant if the bulk density is constant in contrast to the results obtained by mercury intrusion porosimetry. The difference in slopes gives an estimate of the increase in porosity due to drug dissolution. The matrix initially contained 40 mg/g of CPM. Table 2 shows initially the porosity is 70 μl, which increases by 29 μl upon the release of drug. It may be reasoned that increase in porosity is entirely due to dissolution of CPM. CPM is highly water soluble and the matrix provides enough void volume; thus, the drug is expected to dissolve quickly as the medium penetrates the matrix. It can also be said that the porosity of the matrix remains constant throughout entire but the most initial portions of the release interval.

The interaction of DCPD and anhydrous DCP and CPM was studied using differential scanning calorimetry. The tablets contained only 4% drug. Consequently the DSC scans obtained for the powdered tablets could not give reliable data for the heat of fusion of CPM. Mixtures of CPM and DCP were prepared containing 20%, 40%, 60%, and 80% CPM with DCP; and the shift in melting point and the change in the heat of fusion was observed. The data are presented in Table 3.

SUMMARY AND CONCLUSIONS

The rate constant for the release is a function of the void surface area per unit volume of the tablet. Since the void area could not be determined, the ratio of void area to void volume is assumed to be equal to the ratio of total area to total volume of the tablet. This assumption was found to be an approximation. Matrices with the same surface area and volume but different void volumes showed different release rate constants. The rate constant seems to vary linearly with bulk density of the matrix. This may be attributed to the increased surface roughness of the matrix with decreasing bulk density, leading to increased rate of release.

The time required for the medium to penetrate the matrix increased exponentially with increasing bulk density of the tablet. This implies increased resistance to the flow. Tortuosity factors may also be responsible for the apparent density dependance of the rate constant.

The porosity of the matrix was measured using mercury intrusion as well as water penetration. The porosity measurements using water penetration were found to be more reliable.

There was no noticeable increase in porosity beyond the porosities created by dissolution of the drug. CPM is a highly water-soluble drug. The tablet has enough void volume for complete dissolution of CPM. It is expected that the drug dissolves completely in relatively short time; hence, the assumption about the constancy of the porosity is considered valid.

The thermal analysis showed that there was no physical interaction between the drug and the matrix.

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