Drug Release Mechanism from a Microcrystalline Cellulose Pellet System

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A common form of modified release is the encapsulation of specially formulated or coated pellets. An important first step in the development of a multiparticulate coated dosage form is to characterize the uncoated pellet. In earlier work, an uncoated pellet system developed in these laboratories and prepared from microcrystalline cellulose (MCC) was investigated and found to exhibit both the physical characteristics of an inert matrix and varying degrees of *in vitro* modified release. The use and characterization of MCC as a spheronization matrix material forms the basis for this formulation study. The drug release mechanism has been verified by varying selected formulation factors and evaluating the resulting pellets according to the relationship developed by T. Higuchi for granular inert matrices. In all cases, this MCC pellet system adhered to the theoretical relationships and the drug release mechanism can, therefore, be classified as an inert matrix.

KEY WORDS: drug release mechanism; inert matrix; microcrystalline cellulose; pellet(s); spheronization.

INTRODUCTION

Interest in modified release has continued for over three decades in pharmaceutical research. The methods of achieving modified release have been the subject of several review articles (1–3) and a textbook edited by Robinson (4). A common form of modified release is the encapsulation of specially formulated or coated pellet systems. An important first step in the development of a multiparticulate coated dosage form is the characterization of the uncoated pellet to ascertain the contribution, if any, the pellet may have in the overall drug release behavior of the final pellet system.

In earlier work (5,6), uncoated pellet systems developed in these laboratories were investigated and found to exhibit varying degrees of modified release during *in vitro* dissolution testing. In this work, the matrix material is microcrystalline cellulose, NF (MCC), which is more specifically a purified, depolymerized alpha cellulose derived from plant sources (7). The pharmaceutical uses of MCC have been reported to include diluent, binder, wicking agent, disintegrant, and flow aid. The novel use of MCC as a modified release matrix material forms the basis for this report.

The modified release potential of this MCC matrix had been previously established (5,6); however, more study of this matrix system is needed to verify the drug release mechanism. In this work, these MCC pellet systems were tested according to the square root of time relationship developed by T. Higuchi (8) for drug release from granular inert matrices in which diffusion of the drug substance occurs through the intragranular spaces or pores. The square root of time relationship has been established as an accepted method for evaluating inert matrices and its application to plastic matrices (9), wax matrices (10), methyl acrylate–methyl methacrylate copolymer matrices (11), and ethylcellulose/stearic acid matrices (12) is well documented in the literature.

In this study, selected formulation factors affecting parameters in the square root of time relationship were varied in a series of formulations for this MCC pellet system. These experimental pellet systems have been subjected to *in vitro* dissolution testing to evaluate adherence of the data to the theoretical relationships which have been proven to describe an inert matrix.

THEORETICAL

As previously described, the theoretical considerations for this work are attributed to a relationship reported by T. Higuchi (8) in 1963. The square root of time relationship predicts a linear dependence between the amount of drug release per unit area and the square root of time. The equation which has been reported to describe this relationship is as follows:

$$Q = \sqrt{\frac{D\epsilon}{\tau}(2A - \epsilon C_s)\, C_s t} \tag{1}$$

or, more simply,

$$Q = kt^{1/2} \tag{2}$$

where Q is the amount of drug release per unit surface area of the matrix (mg/cm^2), D is the diffusion coefficient (cm^2/min), ϵ is the porosity factor, τ is the tortuosity factor, A is the concentration of drug in the matrix (mg/cm^3), C_s is the concentration of a saturated solution of drug or solubility (mg/cm^3), t is time (min), and k is the proportionality constant or slope.

One of the assumptions involved in the derivation of Eq. (1) requires that $2A \gg \epsilon C_s$ based on the physical model which describes diffusion from a liquid–solid boundary. Using this assumption, a simplified form of square root of time relationship, which isolates both porosity and drug solubility as single terms, has also been reported as follows:

$$Q = \sqrt{\frac{2D\epsilon AC_s t}{\tau}} \tag{3}$$

The total porosity factor refers to the effective volume in the void or drugless portion of the matrix. This value differs from the initial porosity by the volume previously occupied by the soluble components in the matrix (8). In equation form, this can be expressed as

$$\epsilon = \epsilon_a + \epsilon_d + \epsilon_o = \epsilon_a + \sum_{i=1}^{n} K_i A_i \tag{4}$$

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where ϵ is the total porosity, ϵ_a the initial porosity, ϵ_d the porosity due to drug, ϵ_o the porosity due to other soluble components in the matrix, K the specific volume of each soluble component (cm^3/mg), and A the concentration of that component in the matrix (mg/cm^3).

For specific cases where the drug is the only soluble component in the matrix and the volume fraction of the drug is large relative to the initial porosity, Eq. (1) can be reduced, by appropriate substitution and rearrangement, to

$$\frac{Q}{A} = \sqrt{\frac{DK}{\tau}(2 - KC_s)\, C_s t} \tag{5}$$

which predicts for these specific systems that the fraction of drug released is independent of the amount of drug in the matrix (8).

To simplify data handling and plotting, Q can be modified to isolate the surface area term, by using the following relationship:

$$Q' = Q\,(S) \tag{6}$$

where Q' is the amount of drug released (mg) and S is the surface area available for drug release (cm^2). A constant surface area term can be incorporated into the proportionality constant in Eq. (2) as follows:

$$Q' = kSt^{1/2} = k't^{1/2} \tag{7}$$

where k and k' are the slopes of the square root of time relationships with respect to Q and Q', respectively. In this work, Q' is substituted for Q in all plots and discussion. The square root of time relationship as described in Eq. (7) can be further manipulated by a log–log transformation to yield the following equation (10):

$$\log Q' = \tfrac{1}{2} \log t + \log k' \tag{8}$$

which has been documented to be the definitive test to differentiate between square root of time release and first-order drug release. This equation predicts that the slope of a plot of $\log Q'$ *versus* $\log t$ should equal one-half for inert matrix systems. This form of the equation has been used solely to discriminate between a first-order drug release mechanism and a square root of time or inert matrix release mechanism.

MATERIALS AND METHODS

Materials

The matrix material selected for this study was microcrystalline cellulose, NF (Avicel PH-101, FMC Corp.). Lactose hydrous, USP (Sheffield Products), was used as a soluble diluent.

The active ingredients used in this work included chlorpheniramine maleate, USP (VitaAmerican Corp.), hydrochlorothiazide, USP (supplied by Squibb Institute for Medical Research), quinidine sulfate, USP (supplied by FMC Corp.), and anhydrous theophylline, USP (Knoll Fine Chemicals). Anhydrous theophylline, USP, was also obtained in specific particle size distributions (supplied by Rorer Central Research), including regular, micronized, and 325-mesh material.

Methods

Pellet Manufacturing

A 1-kg batch of dry powders, formulated on a weight percentage basis, were initially blended for 5 min in a planetary mixer (Model A-200T, Hobart Corp.). The loss on drying (LOD) was determined for the blended powders using a moisture balance (Cenco, Cenco Scientific, Chicago, IL) to establish an equilibrium moisture content for the final drying unit operation. Purified Water, USP, was added to the mixing powders to achieve the proper consistency for extrusion. The amount of purified water required for processing was dependent on the concentrations of both the matrix material (MCC) and the nonmatrix ingredients and is shown in Table I for each formulation; no adjustment was made for changes in model compound. The wetted mass was passed through the extruder (Model EXDS-60, Elanco Products) fitted with 1.5-mm screens. The extrudate was then processed in the spheronizer (Marumerizer, Model Q-230, Elanco Products) immediately following extrusion using a 2.0-mm friction plate. Product was collected after a 2-min residence time and dried on paper-lined trays in a hot-air oven (Stokes, Model 38C, Pennwalt Corp.) at 40°C until the LOD was equal to the equilibrium moisture content of the blended dry powders.

Dissolution Testing

Dissolution testing was performed in triplicate on a 1-g sample of 16/20-mesh pellets. A specific mesh cut of pellets was used to standardize the surface area available for drug release, which simplifies data manipulation and plotting. The dissolution procedure employed the USP Apparatus II at a paddle rotational speed of 100 rpm over a 2-hr time period. The dissolution medium was 900 mL of distilled water maintained at 37°C. All samples were analyzed by UV spectroscopy at a maximum wavelength determined by an absorbance *versus* wavelength scan (Table II).

Previous studies evaluated the effect of dissolution test methodology on drug release from these microcrystalline cellulose pellet systems (13). Results of those studies, as expected for an inert matrix, indicate that sample size, apparatus type, rotational speed, and medium type had a negligible effect on *in vitro* drug release. In addition, the reproducibility of these MCC pellet systems was previously supported by statistical comparison of mean dissolution profiles for duplicate testing and USP S_2 level testing ($n = 12$).

Table I. Amount of Purified Water Used in Preparing Pellets Based on Pellet Formulation

Concentration of matrix ingredients (% w/w)			
Model compound	Lactose	Microcrystalline cellulose	Amount of water (mL)
5	0	95	1150
10	0	90	1100
20	0	80	995
30	0	70	900
5	5	90	1050
5	15	80	900
5	25	70	775

Table II. Physicochemical Data for Selected Model Compounds

Model compound	Solubility (mg/mL)	λ_{max} (nm)
Chlorpheniramine maleate	160	262
Quinidine sulfate	11	234
Theophylline	8	272
Hydrochlorothiazide	1	270

Porosimetry Testing

Porosimetry testing was conducted by a mercury intrusion technique on samples of pellets before and after dissolution testing in an attempt to compare calculated porosity values to measured porosities. The measured total porosity values were determined from the penetration volume at 34.5-MPa pressure, which corresponds to the first plateau value for these systems and should be sufficient to penetrate the intragranular pores.

RESULTS AND DISCUSSION

The study of drug release from inert matrices is not a new concept in the pharmaceutical sciences; however, the drug release mechanism for this novel microcrystalline cellulose matrix system has not been verified according to accepted theoretical considerations. The physical properties of pellets prepared with this matrix material (5,6) appear to behave as expected for an inert matrix. Specifically, the pellets did not visibly change their geometry when in contact with the dissolution medium, nor did any detectable disintegration occur during prolonged exposure. These statements are supported by examination of the pellets recovered after dissolution testing; these pellets were visibly unchanged, even after drying.

The experimental plan was designed to exploit the parameters detailed in Equation (1), namely A, ϵ, and C_s. In particular, drug concentration (A) was evaluated at a 5, 10, 20, and 30%, by weight, theophylline concentration. From Eq. (4) it is apparent that an increase in drug concentration will also result in an increase in porosity (ϵ). To separate the effect of porosity from that of drug concentration, various concentrations of lactose were added to the matrix at a constant drug concentration. To study the effect of aqueous solubility, several model compounds were selected to represent a range of aqueous solubility and were then incorporated into the matrix at a 10% concentration. In addition to the parameters in the square root of time relationship, the effect of varying the particle size of theophylline was evaluated by using samples characterized into three particle size distributions.

The tortuosity of the matrix may be affected throughout the experimental series outlined in the previous paragraph; however, tortuosity cannot be directly measured, nor can tortuosity changes be inferred from the formulation of the pellet. The effect of tortuosity must be kept in mind during data interpretation.

Drug Concentration

The results of *in vitro* dissolution testing for pellets containing various concentrations of theophylline are shown in Fig. 1. Consistent with Eq. (1), an increase in the concentration of drug in the matrix results in an increase in the amount of drug dissolved at any time, t. In addition, the slopes of the linear approximations (dashed) have been calculated by linear regression and increase stepwise from 4.76 to 26.5 mg/min$^{1/2}$ for the 5 to 30% theophylline concentrations, respectively. Once again, it must be noted that a change in the concentration of drug in the matrix (A) will affect the porosity (ϵ) and may possibly affect the tortuosity (τ) of the matrix.

In this case, the drug is the only soluble component in the matrix and these same data can be replotted according to Eq. (5) as the fraction or percentage drug dissolved [$100(Q')/A$] *versus* the square root of time, as shown in Fig. 2. The percentage drug dissolved has been calculated based on the theoretical total amount of drug in the matrix and is supported by the plateau or infinity value found during dissolution testing. The similarity of the 10, 20, and 30% theophylline concentration data illustrates the independence of drug release relative to drug concentration. In accordance with the basic assumption necessary to derive Eq. (5), the volume fraction occupied by the drug must be sufficiently large relative to the initial porosity at or above the 10% theophylline concentration. On the other hand, the initial porosity must still have an appreciable contribution to the total porosity at the 5% theophylline concentration, which is a possible explanation for the slight increase in the percentage drug dissolved at any time, t, for this formulation.

The results of mercury porosimetry testing on the intact pellets and the drug depleted pellets are listed in Table III. The porosity values measured for the intact pellets correspond to the initial porosity (ϵ_a) or porosity due to air, while those measured for the depleted pellets correspond to the total porosity ($\epsilon = \epsilon_a + \epsilon_d$) as described in Eq. (4). The calculated porosities and those measured by mercury porosimetry are comparable, with the possible exception of those for pellets containing 30% theophylline. In an earlier study (6), the nondisintegrating nature of these MCC pellets was found to be dependent on the concentration of the matrix

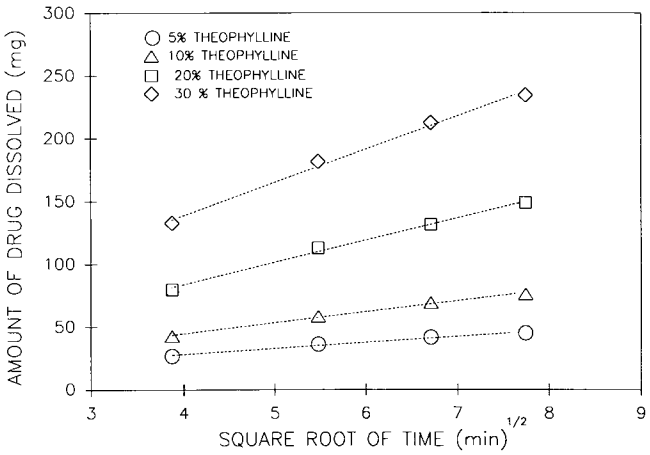

Fig. 1. Dissolution data for pellets containing various concentrations of theophylline in a microcrystalline cellulose matrix plotted as the amount of drug dissolved in milligrams (Q') *versus* the square root of time in (minutes)$^{1/2}$.

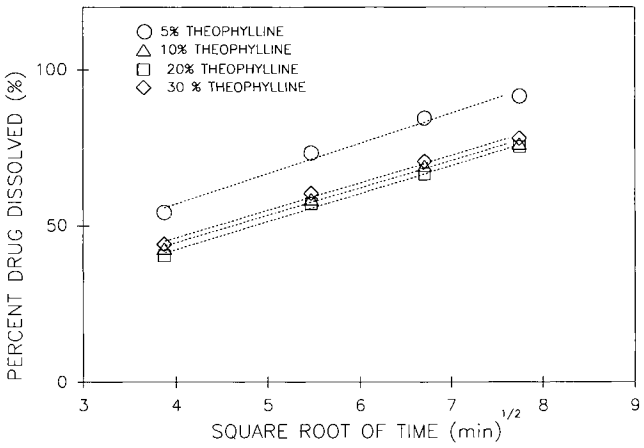

Fig. 2. Dissolution data for pellets containing various concentrations of theophylline in a microcrystalline cellulose matrix plotted as the percentage drug dissolved *versus* the square root of time in $(\text{minutes})^{1/2}$.

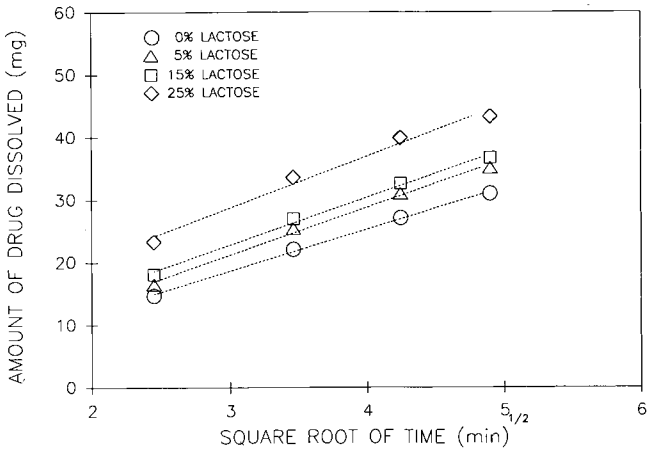

Fig. 3. Dissolution data for pellets containing 5% theophylline and various concentrations of lactose in a microcrystalline cellulose matrix plotted as the amount of drug dissolved in milligrams (Q') *versus* the square root of time in $(\text{minutes})^{1/2}$.

material and it has been documented that the drug-depleted pellets become weaker at higher drug concentrations. Therefore, it is possible that at the higher concentrations of drug, a small portion of the matrix may have become dislodged from the drug-depleted pellet during subsequent handling of the pellets prior to porosimetry testing. This could account for the higher measured porosity value for the pellets containing 30% theophylline.

Porosity

The results of *in vitro* dissolution testing for pellets containing various concentrations of lactose at constant drug concentration are shown in Fig. 3. As predicted by Eq. (4), an increase in lactose concentration will contribute to the total porosity (ϵ) of the matrix in the ϵ_o term for other soluble components in the matrix. Once again, it should be noted that the tortuosity value could vary in this experiment. Although the increment from batch to batch is quite small, a stepwise increase in the amount of drug released (Q') is observed at any time, t, as the lactose concentration increases in rank order. On a qualitative basis, this behavior is consistent with Eq. (3) and supports an inert matrix drug release mechanism. Quantitatively, the slopes, as calculated previously, increase from 6.7 to 8.3 $\text{mg/min}^{1/2}$ for the pellets containing 0 and 25% lactose by weight, respectively. The slopes calculated for both 5 and 15% lactose concentrations are between these limits; however, the regression values were found to be similar at 7.6 $\text{mg/min}^{1/2}$.

This series of pellets was also subjected to mercury porosimetry testing. The porosity values calculated for the drug/lactose mixtures are not well reflected in the measured porosity values reported in Table IV. A possible explanation of this inconsistency can be based on the work of Desai *et al.* (14), which describes the effect of micropores, and Schwartz *et al.* (15), which describes the effect of ink bottle pores on drug release from inert matrices. In either case, the extremely small pore openings may not allow complete penetration of mercury at the pressure selected for porosimetry testing, which could result in a lower measured value. In addition, this may also provide a possible explanation for the extremely small increments in the amount of drug released at any time, t. It should also be noted that the measured porosity values have a corresponding effect on the slopes of the linear approximations described above.

Table III. Measured and Calculated Porosity Values for Pellets Containing Various Concentrations of Theophylline in a Microcrystalline Cellulose Matrix Before (Intact) and After (Drug-Depleted) Dissolution Testing

Theophylline concentration (%, w/w)	Intact pellet porosity (ϵ_a)[a]	Drug-depleted pellet porosity ($\epsilon_a + \epsilon_d$)[a]	Total porosity[b]
5	0.01	0.05	0.04
10	0.01	0.08	0.09
20	0.01	0.22	0.19
30	0.01	0.40	0.29

[a] Porosity values measured by mercury porosimetry.
[b] Total porosity values calculated from average pellet volume and the theoretical true volume of microcrystaline cellulose remaining in the drug-depleted pellets, as follows: $\epsilon = (V_{pellet} - V_{MCC})/V_{pellet}$.

Table IV. Measured and Calculated Porosity Values for Pellets Containing 5% (w/w) Theophylline and Various Concentrations of Lactose in a Microcrystalline Cellulose Matrix Before (Intact) and After (Drug-Depleted) Dissolution Testing

Lactose concentration (%, w/w)	Intact pellet porosity (ϵ_a)[a]	Drug-depleted pellet porosity ($\epsilon_a + \epsilon_d$)[a]	Total porosity[b]
0	0.01	0.05	0.04
5	0.01	0.07	0.09
15	0.02	0.08	0.19
25	0.02	0.16	0.29

[a] Porosity values measured by mercury porosimetry.
[b] Total porosity values calculated from average pellet volume and the theoretical true volume of microcrystalline cellulose remaining in the drug-depleted pellets, as follows: $\epsilon = (V_{pellet} - V_{MCC})/V_{pellet}$.

Aqueous Solubility

The results of dissolution testing for pellets containing various active ingredients are plotted in Fig. 4. As described previously, these active ingredients were chosen to provide a wide range of aqueous solubility or C_s (Table II). An increase in aqueous solubility was found to correspond to an increase in the amount of drug dissolved at any time, t. Since the aqueous solubilities of theophylline and quinidine sulfate are similar, it is not surprising that the drug release profiles are essentially superimposable. The calculated slopes for two of the linear approximations are 3.3 and 10.9 mg/min$^{1/2}$ for the pellets containing a 10% concentration, by weight, of hydrochlorothiazide and either theophylline or quinidine sulfate, respectively. These data are qualitatively consistent with Eq. (3) for this pellet system. In addition to those formulations adhering to the basic assumption used in deriving Eq. (3), the drug release data for chlorpheniramine maleate, also at a 10% concentration, are in Fig. 4 to illustrate the effect of high aqueous solubility. This behavior is predicted by and consistent with Eq. (1), although the C_s term is not isolated as a single term.

Particle Size

A basic assumption in the derivation of the square root of time relationship is that drug release is diffusion controlled and not dependent on the intrinsic dissolution rate of the drug substance. The results of dissolution testing for pellets containing 5% theophylline which has been previously classified into various particle size distributions are shown in Fig. 5. As required by the basic assumption, the curves for this series of pellets are essentially superimposable for these selected particle size distributions. These data support the assumption of a diffusion-controlled drug release mechanism and provide additional support for an inert matrix drug release mechanism for this pellet system.

Log–Log Transformation

An example of a log–log transformation, described by Eq. (8), is shown in Fig. 6 for pellets containing 5% theophylline. The log–log plot for this representative pellet formulation can be adequately described as a straight line having a slope calculated by linear regression of 0.495. Similar analysis on all formulations yielded individual slopes in the range of 0.4 to 0.6. The linear nature of these plots and magnitudes of the slopes provide the final supporting data indicating an inert matrix drug release mechanism.

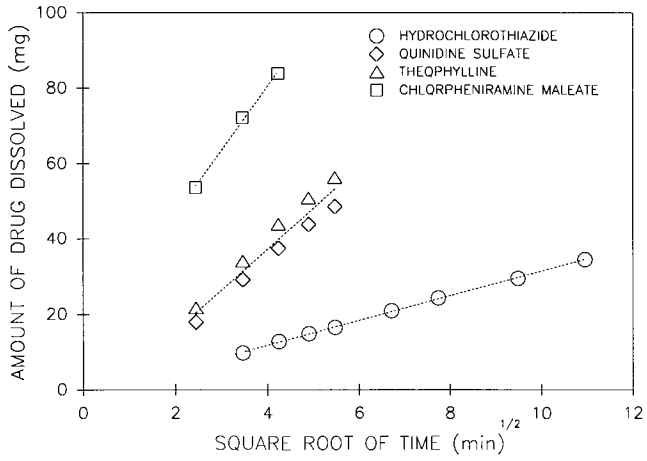

Fig. 4. Dissolution data for pellets containing a 10% concentration of various active ingredients in a microcrystalline cellulose matrix plotted as the amount of drug dissolved in milligrams (Q') *versus* the square root of time in (minutes)$^{1/2}$.

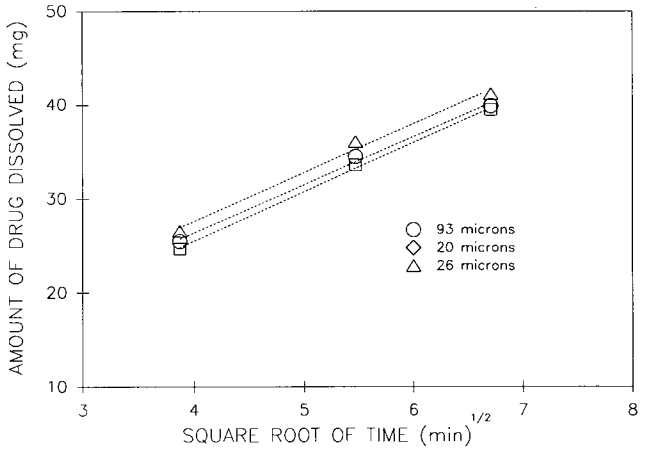

Fig. 5. Dissolution data for pellets prepared from various particle sizes of theophylline at a 5% concentration in a microcrystalline cellulose matrix plotted as the amount of drug dissolved in milligrams (Q') *versus* the square root of time in (minutes)$^{1/2}$.

CONCLUSIONS

The objective of this study was to establish the drug release mechanism for this microcrystalline cellulose matrix system. This objective has been accomplished using a formulation study for this pelleted matrix system by establishing adherence to the theoretical relationship developed by T. Higuchi for inert granular matrices. In all cases, this pellet system adhered to these theoretical considerations and the drug release mechanism can, therefore, be classified as an inert matrix.

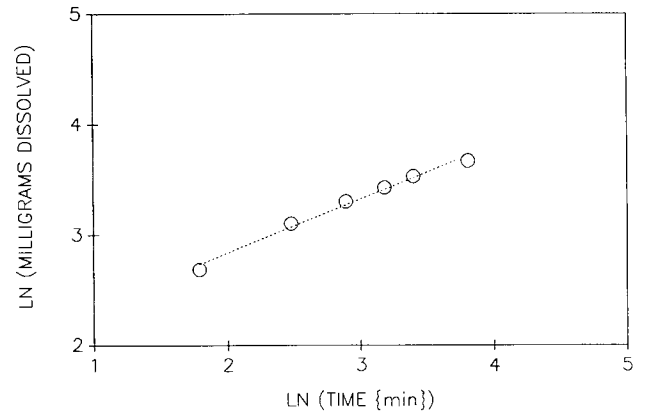

Fig. 6. Dissolution data for pellets containing 5% theophylline in a microcrystalline cellulose matrix plotted as the natural log of the amount of drug dissolved in milligrams *versus* the natural log of time in minutes.

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