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RESEARCH PAPERS

USE OF DICALCIUM PHOSPHATE DIHYDRATE FOR SUSTAINED RELEASE OF HIGHLY WATER SOLUBLE DRUGS

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ABSTRACT

The utilituy of Dicalcium phosphate dihydrate (DCPD), a commonly used water insoluble pharmaceutical excipient, has been investigated for its use in formulating a controlled release matrix type tablet for highly water soluble drugs. Various drugs were formulated into a tablet by direcly compressing mixture of the drug, dicalcium phosphate dihydrate, and magnecium stearate on a single punch tablet machine. Effects of drug concentation and tablet weight on the release profiles were studied using USP II dissolution machine.

The release from these matrices followed first order kinetics rather than square root time rule. The release profile and the first order rate constant seemed to be dependent upon the the size of the tablet. Incorporation of drug in a quantity excess of 5% w/w of the tablet resulted in disintegration of the tablet and subsequent rapid release of the drug.

Dicalcium phosphate may be a simpler, cheaper, and a viable way to formulating directly compressible sustained release formulations.

INTRODUCTION

Oral ingestion has been the most convenient and commonly employed route of drug delivery. Because of flexibiliity in dosage form design and their testing, oral sustained release systems have received a great deal of attention[1].

The cost of formulation development, raw materials and manufacturing are significant factors in choosing formulation techniques and materials. Thus, it is not surprizing to see that formulating drugs into matrix type devices have been well researched and is one of the most widely used methods for drug delivery.[2,3] The matrix system also appears to be a very attractive approach from process development and scale-up points of view.[4]

Various materials like waxes,[4,5] hydrophilic polymers and gums,[6,7] have been employed in the formulation of matrix type tablets. Dimensional instability and heat sensitivity are major disadvantages of formulations involving waxes and pose a danger of dose dumping. The rate of release through hydrogel matrices is governed by the rate and extent of swelling of the polymer; consequently ionic strength and pH value of surrounding medium affect the release rates from such matrices[8]. Hydrophobic polymers may not have these drawbacks and have been used extensively for fabrication of controlled release matrices.[9,10] Exclusive use of polymers to provide a controlled release matrix may have certain disadvantages: (a) polymers can be toxic, (b) they may not possess physical stability toward heat, good compression and flow properties, and (c) high cost could also be a factor.

Verma et al. have successfully utilized calcium salts to provide slow release for water insoluble herbicides.[11-14] However, the potential of calcium phosphates for pharmaceutical use in controlling the release of drugs has not been explored. The following research deals with evaluation of the ability of dicalcium phosphate dihydrate to provide controlled release of water soluble drugs.

THEORETICAL CONSIDERATIONS

Higuchi[15] has proposed the following equations to explain the release of drugs from various matrix delivery systems.

$$Q = [\, D\varepsilon / \tau \; (2A - \varepsilon C_s)\, C_s\, t \,]^{1/2} \qquad \text{Eqn. 1}$$

Where Q (g/cm^2) is the amount of drug released per unit exposed area after time t(sec), D (cm^2/sec) is the diffusivity of the drug in the permeating fluid, τ is the tortuosity factor of the capillary system, A (g/cm^3) is the total amount of

drug present in the matrix per unit volume, C_S is the solubility of the drug in the permeating fluid, and ε is the porosity of the matrix.

The equations would be essentially valid for systems in which 'A', the amount of drug per unit volume, is greater than C_S or εC_S by a factor of three or four. In the case of the matrix described, if $A < C_S$ there equation 2 applies. This equation used by Simonelli et al,[16] describes a situation where the drug is released from a porous matrix loaded with saturated drug solution.

$$Q = [\, 2C_0\tau\, (Dt / \tau\pi)\,]^{1/2} \qquad \text{Eqn. 2}$$

Irrespective of which equation is used if the theory is applicable, the plot of percent released versus square root of time would be linear.

Wagner[17,18] observed that the in-vitro dissolution profiles of disintegrating dosage forms follow an apparent first order kinetics.

$$Q = Q_0 e^{-kt} \qquad \text{Eqn. 3}$$

where Q is quantity of the drug release at time t; Qo is quantity of the drug present initially in the dosage form; and k is a constant. Although Wagner et al. described disintegrating dosage forms, the mathematics may be applicable in this case.

MATERIALS

Chlorpheniramine maleate (CPM) and brompheniramine maleate were obtained from Napp chemicals Inc. Lodi, NJ 07644. Theophylline and niacinamide were purchased from Aldrich Chemical Company Inc., Milwaukee. Dextromethorphan hydrobromide, procaine hydrochloride, and diphenhydramine hydrochloride were purchased from Ammend chemicals. Ephedrine hydrochloride was purchased from J. T. Baker chemical company, Philipsberg, NJ 08865. Unmilled dicalcium phosphate dihydrate (Emcompress™) was supplied by Edward Mendell company, Inc., Carmel NY. Henceforth, dicalcium phosphate dihydrate will be referred to as DCPD. Eudragit RSPM™ was supplied by Rohm Tech Inc., Malden, MA 02148. Magnesium stearate was purchased from Amend chemicals.

METHODS

Tablets were manufactured by direct compression of mixtures of drug and excipient, using a single punch Tablet Press made by Stokes Machine Company, Philadelphia, Model F, Lot No. B70366. Various sizes of punches, flat and concave, and dies, were made by the Machine shop, Temple University Medical School, N. Broad St. Philadelphia, PA.

The drug was mixed with the excipient 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 manufactured for formulation studies were compressed at constant hardness (16-18kp).

The release of drug from the tablets was studied using 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^{o}C and the paddle speed was 100 rpm.

The samples withdrawn at various times were analyzed using a Hewlett Packard Diode Array UV spectrophotometer, model 8451A, Hewlett Packard Inc. San Fernando, CA. Absorption maxima and the slopes of the absorbance versus concentration plots are given in Table 1; linearity of the plots was tested by regression analysis.

All the formulation contained following ingredients, Drug 4%, Diluent 95%, Magnesium stearate 1%.

RESULTS AND DISCUSSION

Chlorpheniramine maleate (CPM), a commonly used antihistaminic drug was used for studying the release from DCPD matrices because of its high water solubility and ease of analysis

Figure 1 shows release of CPM from tablets formulated using DCPD and Eudragit RSPM™ at a constant tablet weight of 200 mg. Eudragit matrix released the drug over a period of 4 hours and DCPD matrix controlled the release up to 6 hours. Eudragit RSPM™, due to its lower density compared to DCPD as well as its significantly higher elasticity, produced tablets which were twice as large and much more porous compared to those of DCPD. Although

TABLE 1

Analytical Parameters for Ultraviolet Analysis and Solubilities of the Drugs

Name	Absorption Maximum (nm)	Slope[a] (x 10^2)	Solubility[b] (mL)
Chlorpheniramine Maleate	262	1.408	4.0
Brompheniramine Maleate	262	1.301	5.0
Theophylline	272	5.596	120.0
Niacinamide	264	2.361	1.5
Dextromethorphan HBr	282	0.490	65.0
Procaine HCl	290	6.041	1.0
Diphenhydramine HCl	220	3.647	1.0

a Slope of the linear plot of Absorbance versus Concentration.

b mL of water required to dissolve 1 gram of drug at 25°C

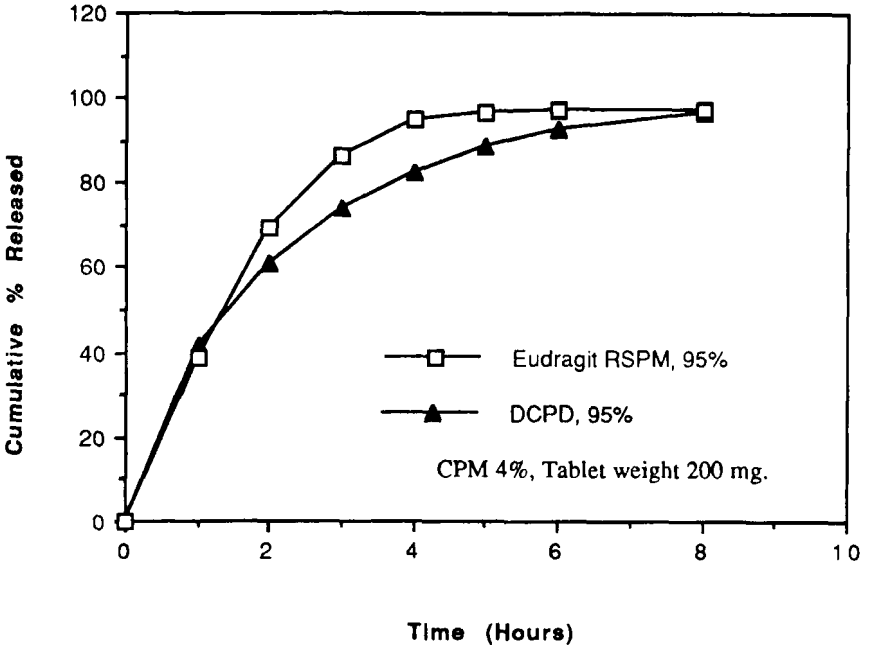

FIGURE 1

Release of CPM from DCPD and Eudragit RSPM™ Matrices

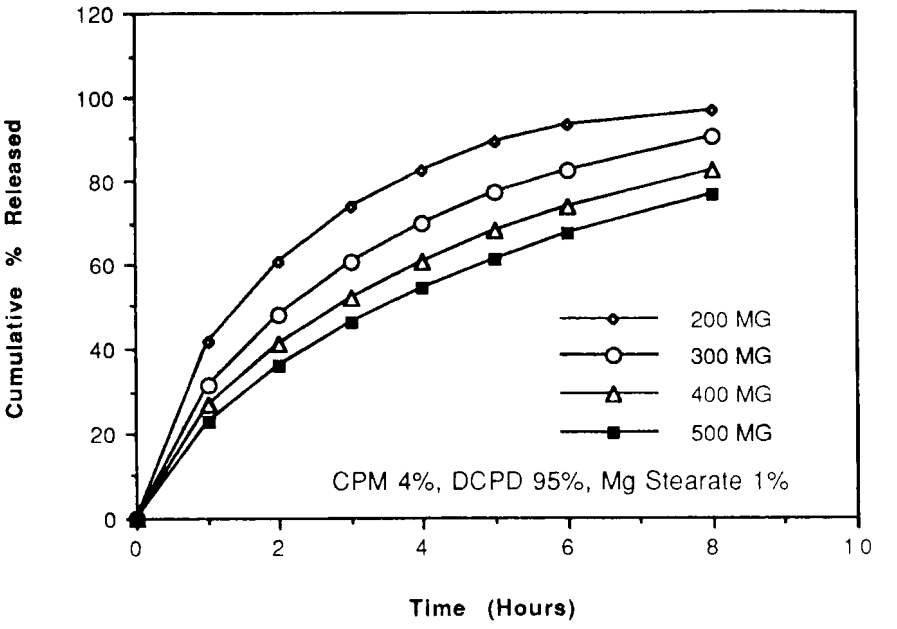

FIGURE 2

Effect of Tablet Weight on the Release of CPM from DCPD Matrices

these tablets had acceptable hardness (7 kp), they appeared considerably more porous compared to DCPD matrix resulting in a relatively rapid release of CPM. Further increase in the weight of Eudragit RSPM™ may make the tablet unacceptably large. Most polymers show poor compression properties due to their inherent elastic nature. Also, their heat sensitivity and poor flow properties may make them unsuitable for high speed manufacture. By contrast, DCPD is heat stable and has good flow properties. DCPD, therefore, may be an inexpensive and attractive alternative to provide an insoluble matrix to control the release of highly water soluble drugs.

Tablets with different target weights were prepared using flat as well as concave punches. Figure 2 illustrates the effect of increase in the tablet weight on the release profiles. Thus, the release of CPM can be further retarded by merely increasing the size of the tablet.

Figure 3 shows the release profiles plotted according to equation 1 and figure 4 shows the according to first order kinetics along with the linear

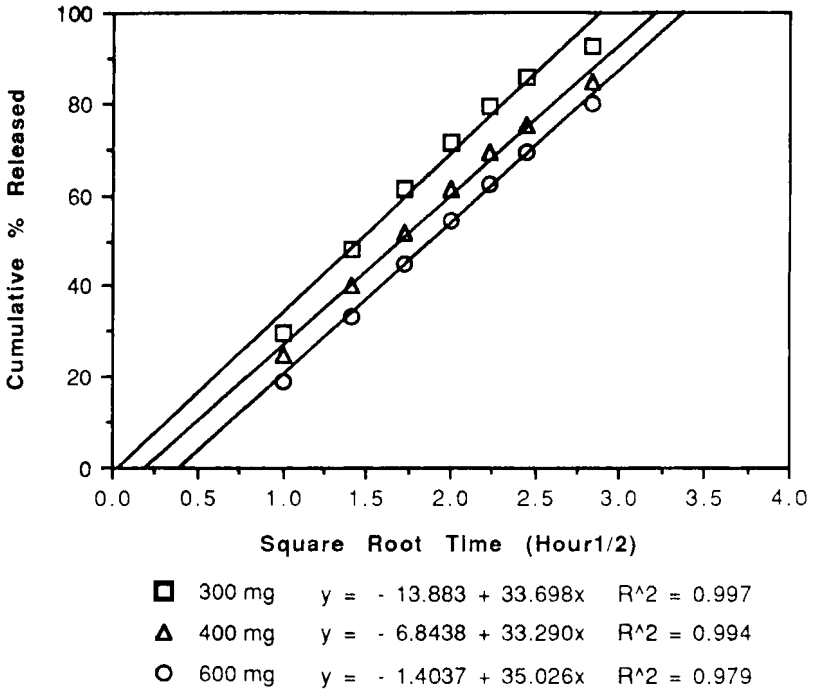

FIGURE 3

Release of CPM as function of Square Root of Time

equations using regression analysis. The curves in figure 3 are approximately linear but the correlation coefficients are lower compared to those shown in figure 4. The plot of release versus square root of time, according to the theory, should show intercept on neither axis and the slopes of these lines should be proportional to the surface area of the tablet provided the drug concentration is constant. The intercepts obtained are significantly different from zero as well as the slopes obtained are not significantly different from each other. Thus it may be concluded that the Higuchi theory may not be applicable in this case.

Figure 4 shows release of CPM from DCPD matrices plotted as log % retained versus time. The linearity of the plots and an intercept on 'Y' axis corresponding to approximately 2, (log 100%) imply that the release could be described by first order kinetics.

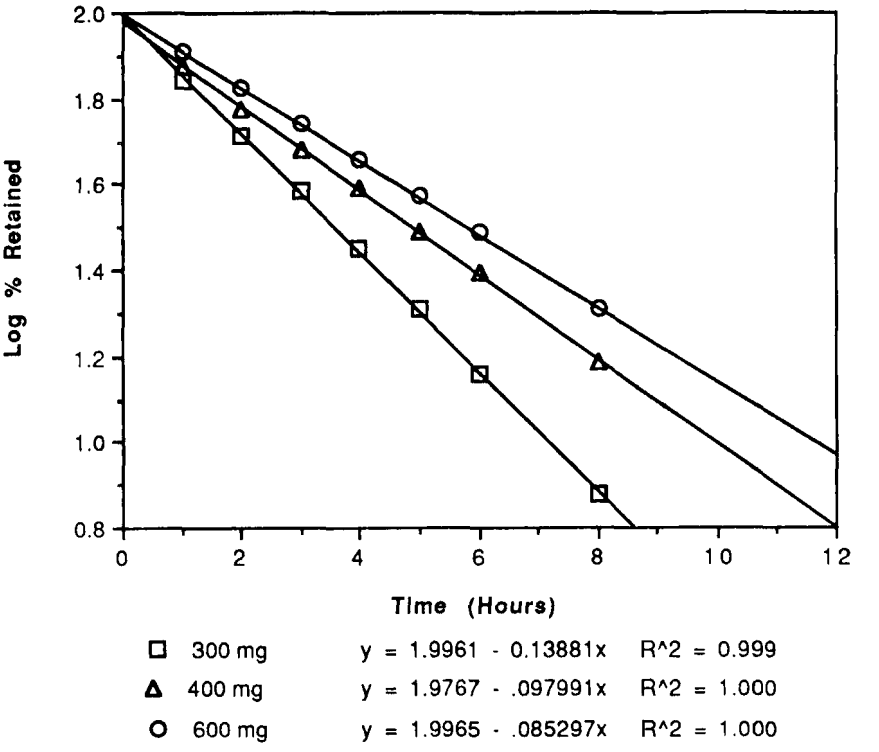

FIGURE 4

Relase of CPM Plotted acoording to First Order Kinetics

One of the disadvantages of formulating drugs in an insoluble matrix is that the release rate continuously diminishes with time. in accord with first order kinetics; equation 3. If the matrix is infinitely large the rate constant will approach zero, thus yielding a pseudo zero order release.

It may be predicted that a geometry which has smaller specific surface area will also decrease the rate constant. Figure 5 compares release profiles of two matrices significantly different in size as well as shape. The smaller tablet was cylindrical weighing of 200 mg (radius 3.44 mm) and the larger tablet was an approximately spherical weighing 900 mg (radius 5.13 mm). Thus, DCPD can be used as an insoluble matrix to retard the release of highly water soluble drugs.

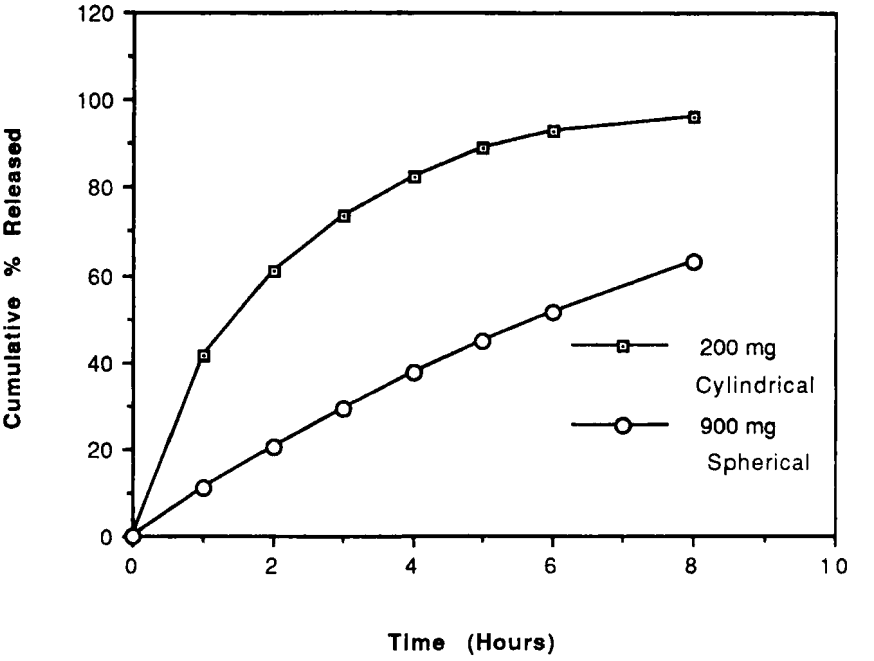

FIGURE 5

Effect of Size and Shape of the Matrix on the Release of CPM

Several highly soluble drugs when formulated with DCPD using direct compression showed a sustained release; the release profiles are depicted in figure 6. Drugs with higher water solubilities such as Diphenhydramine and Procaine hydrochloride showed faster release compared to less soluble drugs like Dextromethorphan hydrobromide and Theophylline.

To achieve controlled release it is necessary that the tablet maintains its integrity throughout the release profile. In order to find out the maximum concentration of the drug that can be used tablets containing increasing amounts of drug were compressed and the disintegration behavior was observed. Table 2 shows the disintegration behavior of DCPD matrices containing different amounts of drug. It seems the drug concentration must be kept below 5% of the tablet weight to maintain tablet integrity .

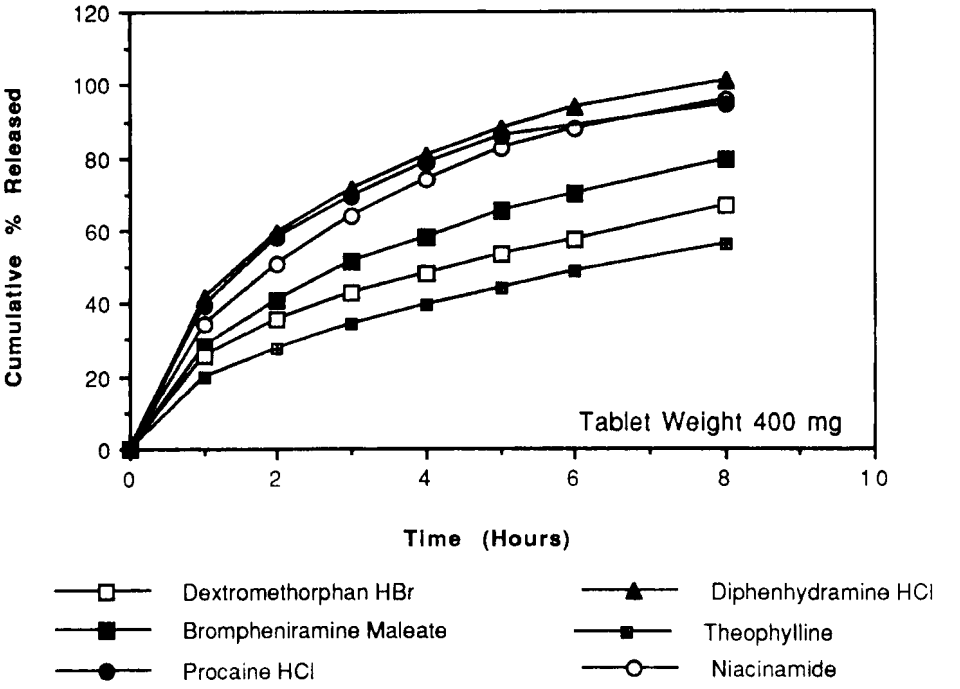

FIGURE 6

Release of some Water Soluble Drugs From DCPD Matrices

TABLE 2

Disintegration Time as a Function of Concentration of CPM in the Tablet

CPM Concentration % w/w	Disintegration Time Sec
5	indeterminant*
10	indeterminant**
20	600
30	180
40	10
50	5

* The tablets did not disintegrate even after 72 hours.

* The tablets developed cracks around the periphery in about 3 hours.

Tablet weight 400 mg, Hardness 18 - 20 kps.

SUMMARY AND CONCLUSIONS

Release of CPM and some water soluble drugs can be controlled using DCPD alone. The release rate continually diminishes with time, but by using large size and proper geometry for the tablet, release profile which approximates linearity can be obtained.

The release of highly water soluble drugs from porous, insoluble and nonswellable matrices can be explained using first order kinetics as predicted by equation 3. The Higuchi equation does not seem to be applicable in describing release from such matrices.

To prevent dose dumping the drug concentration has to be maintained at or below 5% of the tablet weight.

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