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MATRIX TYPE TABLET FORMULATION FOR CONTROLLED RELEASE OF HIGHLY WATER SOLUBLE DRUGS

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ABSTRACT

Matrix type formulations with dicalcium phosphate dihydrate (DCPD) using a polymeric binder (Eudragit RSPM®) to obtain controlled release of highly water soluble drugs has been investigated.

The drug, DCPD and Eudragit RSPM® were granulated using isopropyl alcohol with and without a plasticizer (Diethyl phthalate, DEP). Addition of Eudragit did not appear to affect the release profile. However, addition of a plasticizer had a significant effect on the rate of release. The release appears to follow first order kinetics and the rate constant decreased linearly with increasing DEP concentration.

A directly compressible mixture was also formulated by coating DCPD particles with DEP with and without Eudragit RSPM®.

INTRODUCTION

Polymeric materials have been are considered almost essential for achieving sustained delivery of drugs. These materials have been used extensively for fabrication of controlled release matrices.[1,2] Several

methods have been used to incorporate a drug into a matrix. Methods such as solvent evaporation from polymer solutions with drug either dissolved[3] or dispersed[4] in it, heat molding the mixtures of the drug and the polymer,[5,6] may not be convenient for a large scale manufacture. Matrices have also been prepared using common tableting procedures such as direct compression[7,8] and wet granulation using polymer solutions,[9] polymer latex dispersions,[10] or addition of solvents to mixture of drug and polymers.[11] In many of the above mentioned case fairly high amounts of polymer were needed to control the release; Sometimes multiple granulations were used to provide sustained release of highly water soluble drug[10] which may make the process lengthy and expensive. Alternatively dicalcium phosphate may be used to make sustained release matrix type tablets[12]. However, Dicalcium phosphate dihydrate matrices did not maintain integrity at drug concentrations of higher that 5%. Thus, addition of a water insoluble polymer as a binder was considered. An acrylic polymer, Eudragit RSPM® was employed in this study. Acrylic polymers have been widely used for controlled release.[12,13] There are several reports in which Eudragits, namely Eudragit RSPM, Eudragit RLPM, Eudragit RS100, and Eudragit RL100, have been used for making matrices, employing direct compression[6,14,15] alone and with dicalcium phosphate. Wet granulation using solutions of these polymers[9] has also been reported.

Hydrophobic polymers with high glass transition temperatures tend to be brittle and lack adhesiveness. Plasticizers have been shown to improve the ability of the polymeric coat to retard drug release.[16,17] Addition of plasticizer along with the polymer may improve the latter's ability to interact with hydrophilic excipient and thus improving retardation of drug release.

The objective of this work was to investigate the effect of Eudragit RSPM® with and without plasticizer on the release of highly water soluble drugs from DCPD matrices.

MATERIALS

Chlorpheniramine maleate (CPM) was obtained from Napp chemicals Inc. Lodi, NJ 07644. Eudragit RSPM® was supplied by Rohm Tech Inc., Malden, MA 02148. 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. Dibutyl sebacate and diethyl phthalate were both purchased from Aldrich Chemical Company Inc., Milwaukee, WI 53233. All solvents used were of reagent grade and all the drugs and chemicals used were of pharmaceutical grade.

METHODS

Procedure for Wet Granulation:

The drug, DCPD, and the polymer were mixed in a wedgewood mortar using geometric dilution method. A predetermined amount of granulating solvent (typically 2 mL / 10 g of solids, isopropanol) was added in a continuous stream to the powder bed and mixed. The wet mass was passed through sieve number12 and dried at 50°C. The dried granules were sieved through sieve number 20. The resulting granules were lubricated using (1% w/w) Magnesium Stearate which was previously shifted through #80 mesh.

Manufacture of Tablets

Tablets were manufactured by compressing either granules prepared using the wet granulation procedure or direct compression of mixtures of drug and excipient, using a single punch Tablet Press. (Stokes Machine Company, Philadelphia, Model F, Lot No. B70366. Tablet weight was 200 mg and they were compressed to a hardness of 16 -20 kps.

In-Vitro Release Studies

The release of drug from the tablets was studied using USP apparatus II. (Distek Inc., Somerset, NJ).

The samples withdrawn at various times were analyzed using a Hewlett Packard Diode Array UV Spectrophotometer (model 8451A, Hewlett Packard Inc. San Fernando, CA) at 261 nm.

RESULTS AND DISCUSSION

It has been shown that DCPD is effective in controlling release of highly water soluble drugs[18]. However, if a higher loading of a drug (more than 50 mg) is desired, increase in tablet weight is needed to maintain the drug content below 5% of the tablet weight to ensure integrity of the matrix throughout the release process. Larger tablets may be inconvenient from point of view of the patient. Addition of an insoluble polymer may be useful in maintaining the integrity of the matrix as well as retarding the release of the active component even further. Eudragit RSPM® is a water insoluble polymer and widely used in controlled release formulations. It appears that these polymers would serve as a binder as well as it will coat the drug and excipient particles partially or completely to provide an additional barrier. This may render the matrix hydrophobic thus, decreasing the release rate even further.

Tablets were prepared containing different levels of polymer. Figure 1 shows the effect of Eudragit RSPM concentration (0 to 15%) on the release of CPM. Further increase in polymer content beyond 15%, seemed impractical because higher polymer content in the solid bed resulted in the formation of rubbery masses upon the addition of solvent and made granulation impossible. The release profiles do not show an orderly progression in cumulative release and values at any one time point are not significantly different from another; thus, the release seems to be insensitive to polymer content in the concentration range studied. It is

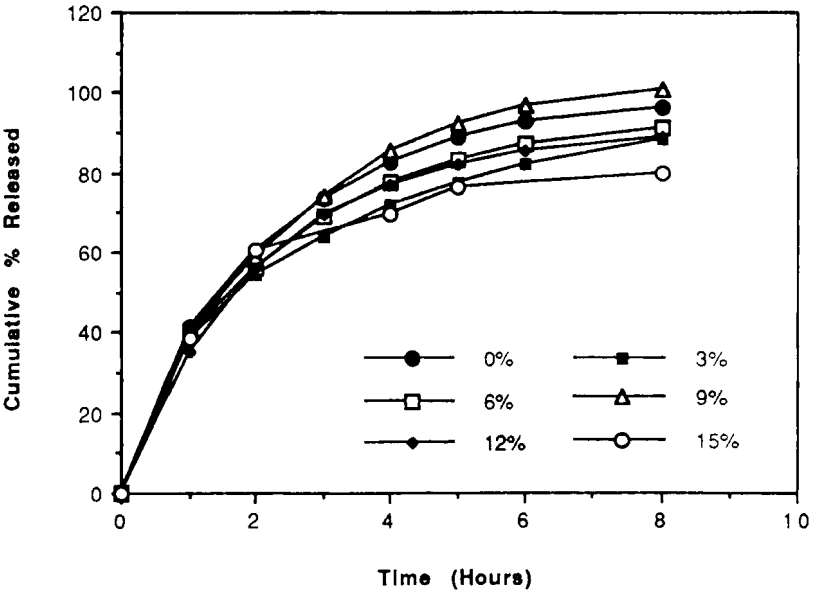

FIGURE 1
Effect of Polymer Concentration on the Release of CPM

possible to optimally use polymer content low enough to facilitate binding and high enough to provide ease in wet granulation procedures.

Hydrophobic polymers may not show good adhesion to water wettable substrate such as DCPD. Lack of adhesion between the matrix material and the polymer and the inherently elastic nature of polymers may produce tablets with higher porosities and may not efficiently retard release of the drug. Thus, addition of a suitable plasticizer was considered to remedy this problem. Plasticizers decrease the glass transition temperature of the polymers and render them more plastic. When added in sufficient quantities they can make the polymer tacky thus improving adhesion to the solid surface.

Dibutyl sebacate (DBS) and diethyl phthalate (DEP) are very widely used plasticizers and were selected for the study. Figure 2 shows release profiles of the formulations containing Eudragit RSPM (15%) granulated with isopropanol as well as 10% solutions of DBS and DEP in isopropanol

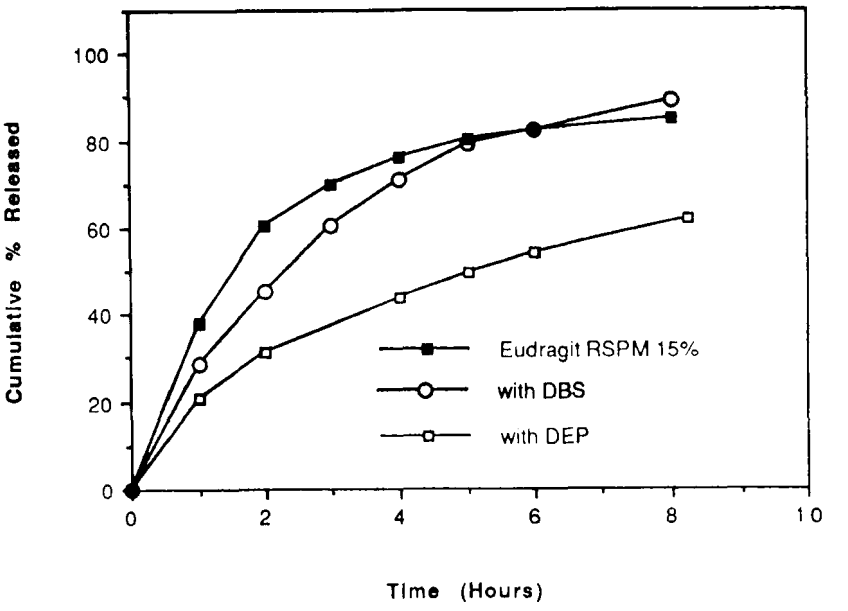

FIGURE 2
Effect of Plasticizer on the Release from DCPD-Eudragit™ Matrices

respectively. The Formulation containing diethyl phthalate showed remarkable retardation CPM release, but the formulation made with DBS did not differ significantly from tablets made without any plasticizer. This may be due to lack of interaction between Eudragit RSPM and DBS at room temperature. When suspended in the respective plasticizers, Eudragit RSPM is freely soluble in DEP but it did not show even slight swelling with DBS over a two week period.

To study the effect of plasticizer concentration on release profile a range of 0 to 25% (v/w of polymer) plasticizer content was used. Trial experiments showed that higher contents of plasticizer caused difficulty in drying and resulted in tacky granules which could not be tableted easily. Two Eudragit RSPM concentrations were tested, 6% and 15%. Figure 3 shows release profiles of the formulations containing 6% and 15% Eudragit RSPM respectively, with 25% (v/w of polymer) DEP. Increase in

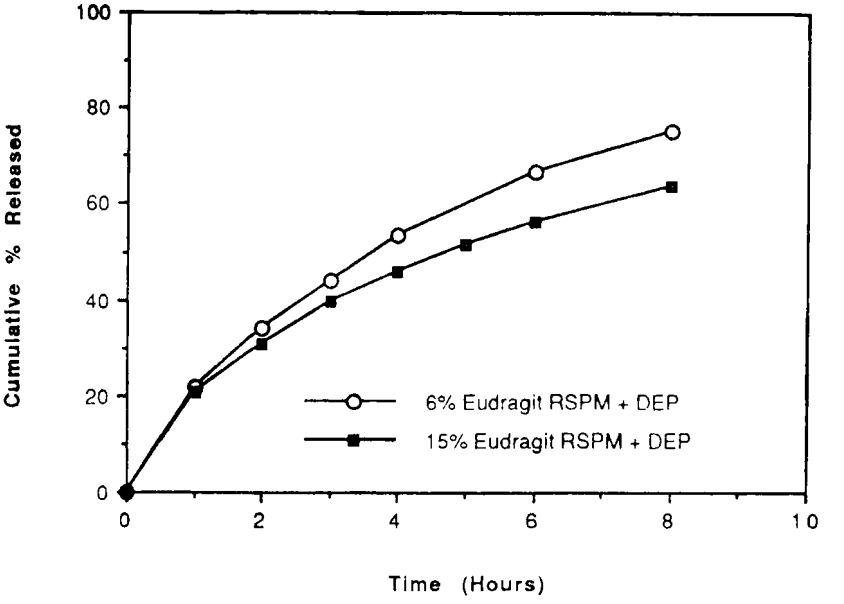

FIGURE 3
Release of CPM from Matrices with same Plasticizer Concentration

polymer content at constant relative concentration of plasticizer has little effect on the release.

Figures 4 depicts the release profiles of CPM from the DCPD - Eudragit RSPM matrices containing different amounts of plasticizer. The rate and extent of release generally decreased with increasing plasticizer concentration. The rate constants were calculated using slopes obtained from the regression analysis of log % retained versus time. Figure 5 shows increasing amounts of plasticizer cause an approximate linear decrease in rate constant.

In an attempt to improve the adhesion between DCPD and Eudragit RSPM, DCPD was coated with DEP. The solid was mixed with a solution of DEP in isopropyl alcohol and dried subsequently. Figure 6 shows release profile of CPM from a matrix made by direct compression of CPM with DCPD covered with DEP as well as with extragranular addition of

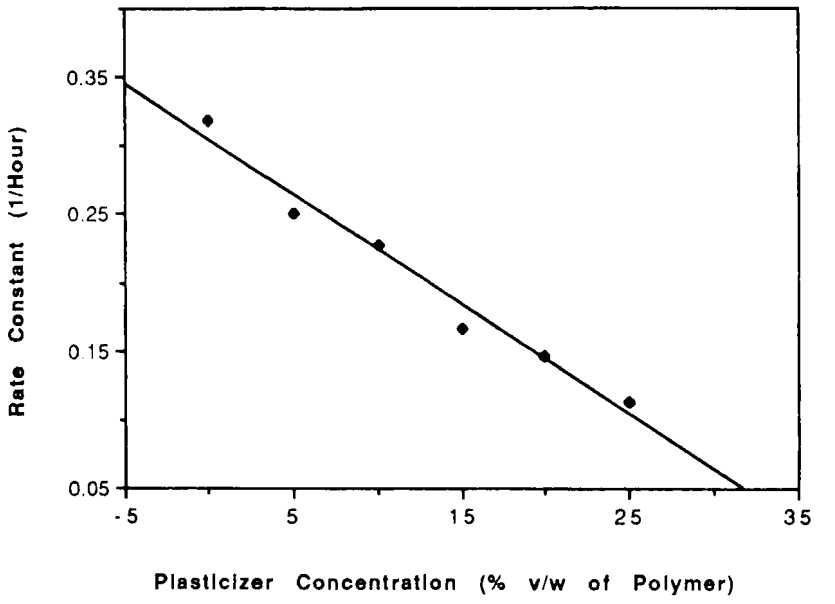

FIGURE 4
Rate Constant as Function of Plasticizer Concentration

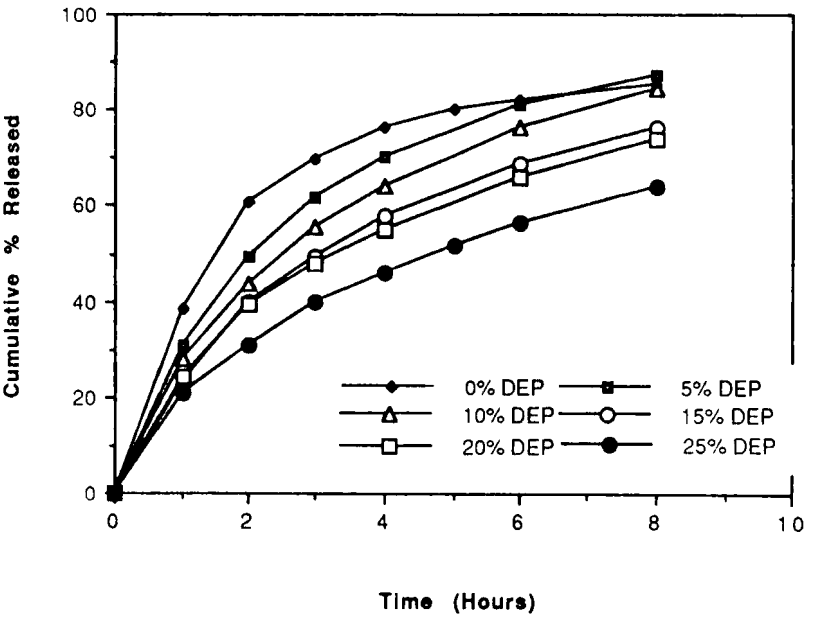

FIGURE 5
Effect of Plasticizer Concentration on Release of CPM from DCPD-Eudragit™ Matrices

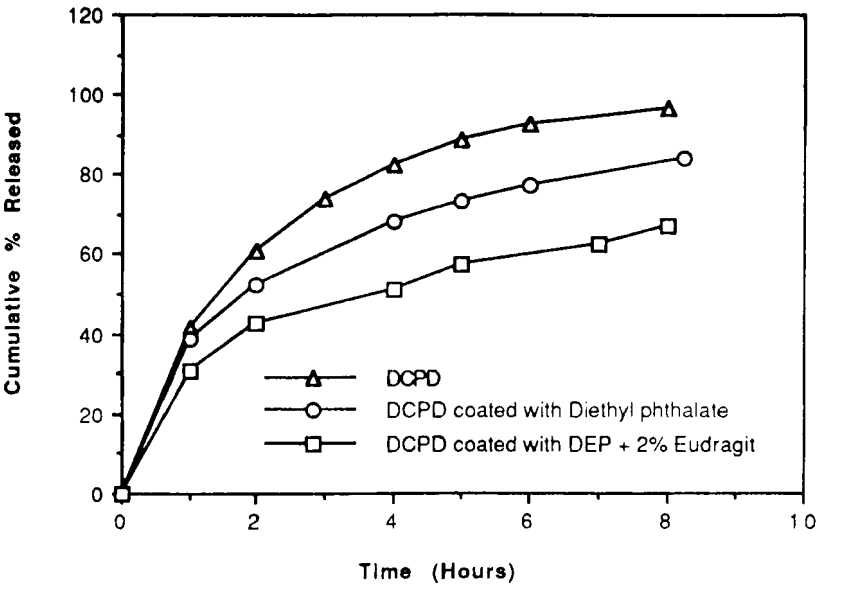

FIGURE 6
Release of CPM from three Directly Compressible Formulations

small amount (2%) of Eudragit. Addition of Eudragit RSPM resulted in a significant decrease in release rate. This supports the hypothesis that a hydrophobic polymer may have a difficulty binding or interacting with hydrophilic surfaces and therefore ineffective in reducing the rate release of drugs.

SUMMARY AND CONCLUSIONS

Addition of Eudragit RSPM to the formulation did not retard the release of CPM significantly beyond that obtained using DCPD alone. However addition of a compatible plasticizer (DEP) along with a polymer significantly affected the release of drugs from such matrices. It seems necessary that the plasticizer interacts with the polymer at room temperature to have an effect.

Polymers may not interact efficiently with water wettable excipient such as DCPD. However, DCPD can be coated with materials like DEP to improve its affinity toward the polymer. A directly compressible formulation can be made using DCPD coated with plasticizer and a polymer.

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