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# ENHANCEMENT OF DISSOLUTION RATE BY INCORPORATION INTO A WATER INSOLUBLE POLYMER, POLYCAPROLACTONE

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## ABSTRACT

This report concerns the use of water insoluble polymer, polycaprolactone, as a carrier to enhance the dissolution rate of two drugs, chlorpromazine and progesterone. Polycaprolactone microspheres containing these drugs were prepared by an emulsion-solvent evaporation technique and dissolution characteristics were compared to pure drug.

Dissolution studies revealed that both chlorpromazine-polycaprolactone and progesterone - polycaprolactone microspheres exhibited a faster dissolution rate than the pure drugs. Molecular or colloidal dispersion of drugs in the polycaprolactone microshere matrix and the high permeability of polycaprolactone to the drugs and water are possible reasons for the rapid release properties observed.

## INTRODUCTION

The preparation of drug-carrier dispersions by fusion and solvent techniques has successfully increased dissolution properties and bioavailability of poorly water-soluble drugs. Many water soluble carriers including urea, solid polyethylene glycols, citric acid, succinic acid, pentaerythritol, pentaerythrityl tetraacetate, mannitol, dextros, and other sugars have been employed as solid dispersion systems and new water soluble agents continue to be tested (1,2).

There are no reports on the use of water insoluble carriers to enhance dissolution rate. This report concerns the use of a water insoluble polymer, polycaprolactone, as a carrier to enhance the dissolution rate of two drugs, chlorpromazine and progesterone. Solid dispersion microspheres of these drugs in polycaprolactone were prepared by an emulsion-solvent evaporation technique and dissolution characteristics were compared to pure drug.

## EXPERIMENTAL

### Materials

The materials used in this study were polycaprolactone (Scientific Polymer Products, Inc., Ontario, N.Y.), chlorpromazine hydrochloride, progesterone, and polyvinyl alcohol (Sigma Chemical Co., Fairlane, N.J.). Chlorpromazine hydrochloride was converted to its base by treatment with sodium hydroxide solution.

### Methods

Chlorpromazine and progesterone microspheres were prepared by an emulsion-solvent evaporation technique using polycaprolactone as the matrix. Weighed amounts of polymer and the drug were dissolved in methylene chloride. The solution was emulsified by stirring in distilled water containing 5% polyvinyl alcohol and 0.05% sodium lauryl sulfate. After twelve hours of stirring, the microspheres were separated by filtration through filter paper, washed with water and then dried at room temperature under vacuum for at least 24 hours. The dried microspheres were sized through standard sieves to isolate fractions of the desired diameter.

Drug loading of microspheres was determined by dissolving an accurately weighed quantity of 10 mg to 15 mg microspheres in 50 ml of methylene chloride and then measuring the U.V. absorbance at 314 nm for chlorpromazine and at 238 nm for progesterone.

Dissolution rate studies were carried out on samples of microspheres equivalent to 10 mg of chlorpromazine or 15 mg of progesterone using a dissolution apparatus similar to one in U.S. P. XX. For chlorpromazine, the dissolution medium consisted of 1000 ml pH 7.0 phosphate buffer solution. In order to eliminate the low solubility problem of progesterone, 0.5 part of propylene glycol and 9.5 parts of pH 7.0 phosphate buffer solution was used as the dissolution medium. Constant stirring at 100 r.p.m. was performed by a mechanical propeller stirrer. At each time interval an aliquot was withdrawn, filtered through 0.45 micron pore size filter and assayed spectrophotometrically. Chlorpromazine was assayed at 255 nm and progesterone at 248 nm. After analysis, the aliquot was returned to the dissolution vessel.

Thermograms of progesterone powder and its microsphere system were obtained using a Perkin-Elmer differential scanning calorimeter; heating rate was 20°C/min. The differential thermograms were obtained in the presence of static air.

## RESULTS AND DISCUSSIONS

Fast releasing copecipitates are commonly prepared by a solvent method. The emulsion-solvent evaporation technique can be regarded as a modified solvent method which involves dissolving the drug and the inert carrier in a common solvent, emulsification of the solution in an immiscible liquid, followed by evaporation of the solvent in the emulsified state. This modified technique produces a fine powder consisting of spherical par-

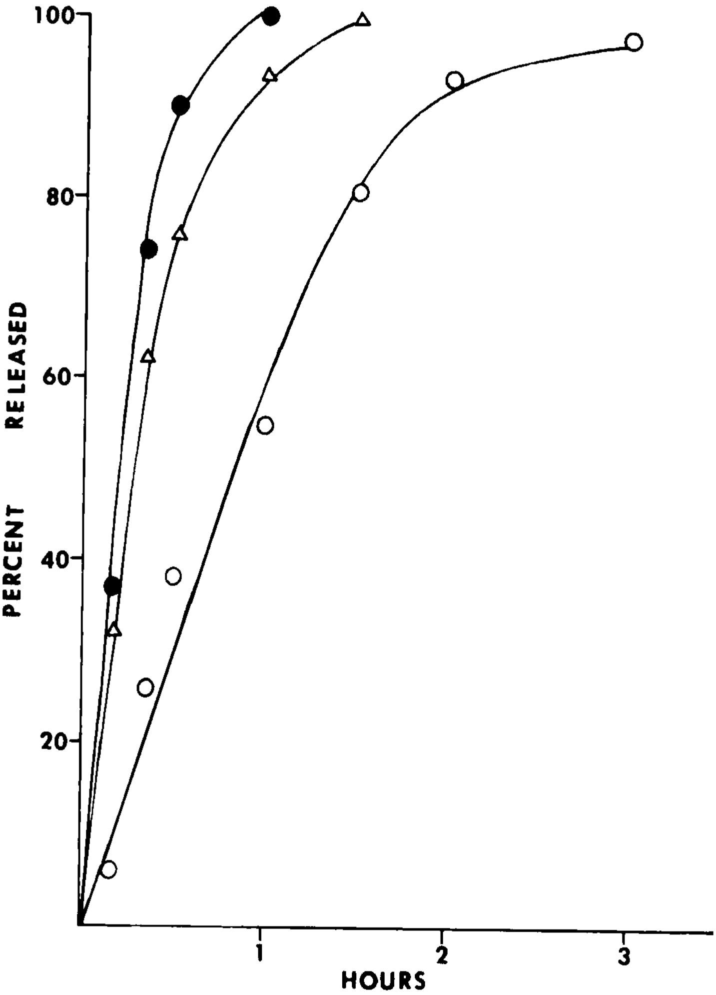

FIGURE 1

Dissolution Profiles of Chlorpromazine from powder and from Polycaprolactone microspheres

KEY:
- ○ Chlorpromazine powder (average particle size, 21 microns).
- △ Microsphere (using polyvinyl alcohol as a dispersing agent, average particle size, 45 microns).
- ● Microsphere (without using polyvinyl alcohol in preparation, average particle size, 30.5 microns).

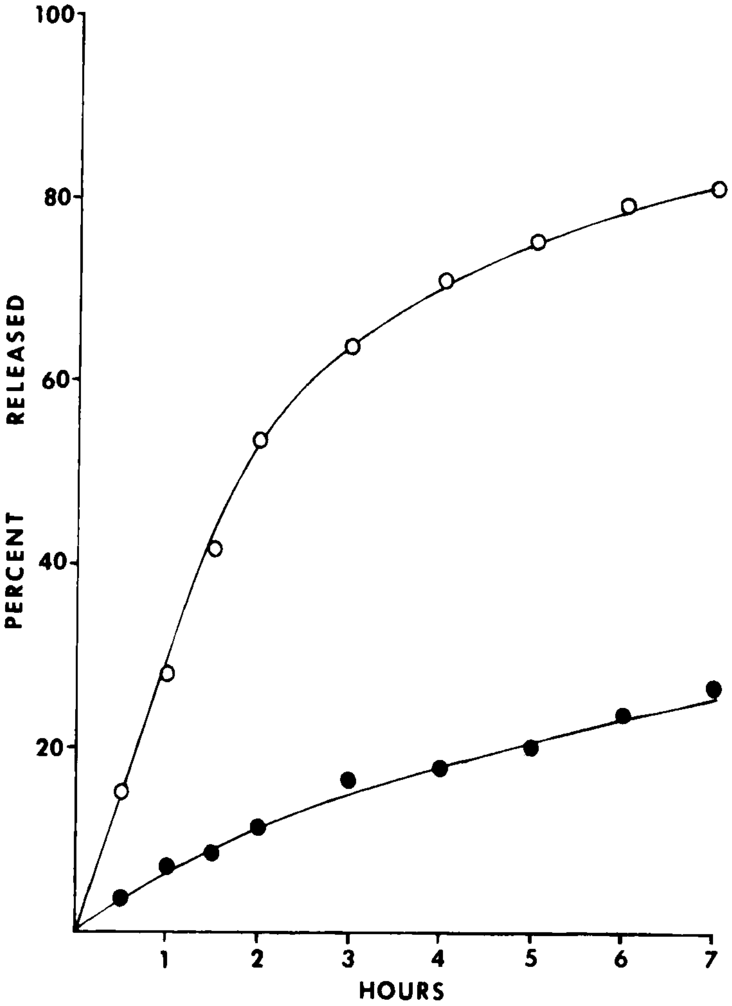

FIGURE 2

Dissolution Profiles of Progesterone from powder and from Polycaprolactone microspheres

KEY: ● Progesterone powder (average particle size, 44 microns).

○ Microsphere (average particle size, 34 microns).

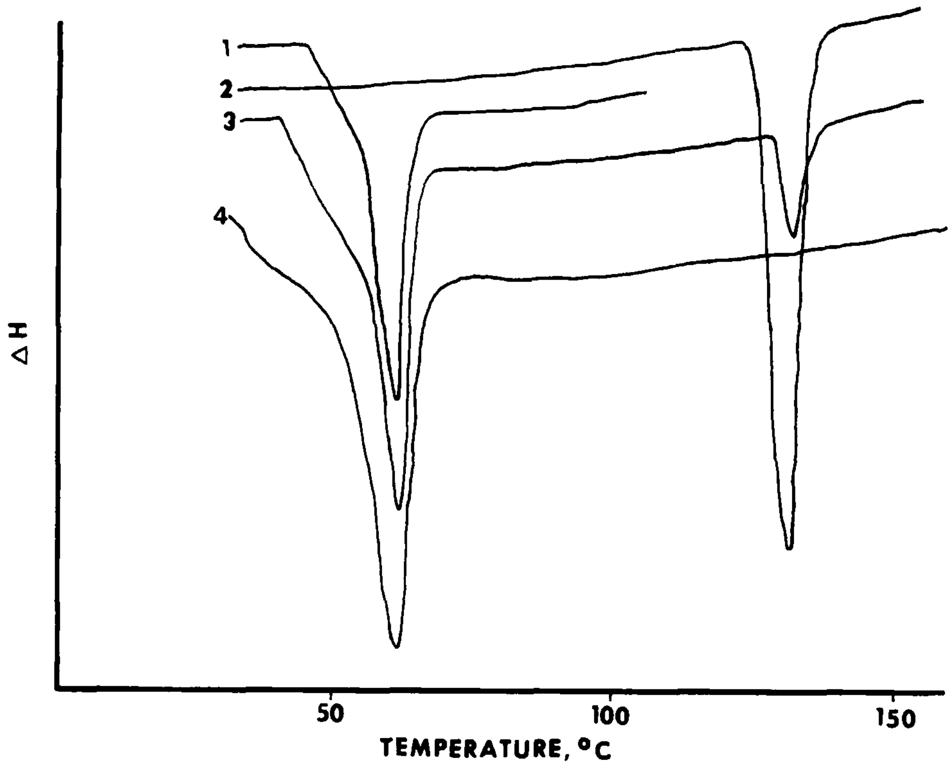

FIGURE 3

Thermograms of Progesterone, Polycaprolactone, physical mixture and microsphere

KEY:
1 Polycaprolactone
2 Progesterone
3 Physical mixture of Polycaprolactone and Progesterone
4 microspheres

ticles and eliminates the pulverization process which is needed for traditional solvent methods. Although the present study utilize a water insoluble polymer as a matrix, microspheres of matrix, microspheres of water soluble carriers also can be prepared by the emulsion-solvent evaporation technique.

## Chlorpromazine-polycaprolactone System

The release data of chlorpromazine from both polycaprolactone microspheres with and without polyvinyl alcohol as a dispersing agent and from chlorpromazine powder are shown in Figure 1. The release rate of chlorpromazine from microspheres prepared without using polyvinyl alcohol was slightly faster than that from microspheres using polyvinyl alcohol in preparation. This result may be due to more rapid vaporization of methylene chloride which caused the formation of holes on the surface. It is surprising that the release rate of chlorpromazine powder was slower than that from polycaprolactone microspheres. Because the melting points of both chlorpromazine and polycaprolactone are around 60°C, it was not possible to use thermal analysis to evaluate the chlorpromazine-polycaprolactone system. Polycaprolactone microspheres containing 16% chlorpromazine were translucent under the microscope. This observation indicates that the drug was molecularly or colloidally dispered in the matrix.

### Progesterone-polycaprolactone System

The dissolution data of the pure progesterone and progesterone-polymer microspheres are shown in Figure 2. It is clearly evident that the 15.6% progesterone-polycaprolactone microspheres exhibited a faster dissolution rate than the plain progesterone. Since polycaprolactone is a water-insoluble polymer, factors such as increased wettability and solubilization of the drug by the carrier at the diffusion layer do not explain the enhancement of dissolution rate of progesterone dispersed in polycaprolactone microspheres. Figure 3 shows the thermograms of the drug, polymer, physical mixture and microspheres. 15.6% progesterone-polycaprolactone microspheres exhibited the characteristic melting endotherm of the polymer but not that of progesterone. This thermal evidence tends to rule out the formation of progesterone polymorphic forms, the interaction between the drug and polycaprolactone during the preparation of microspheres, and eutectic formation. Molecular or colloidal dispersion of progesterone in the polycaprolactone microsphere matrix and polycaprolactone's high permeability to progesterone and water are possible alternative reasons for the rapid release properties observed.

## REFERENCES

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2. J.W. McGinity, Pharm. Tech., 3, 50, 1978