DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(6), 1119-1135 (1987)

CONTROL OF DRUG RELEASE RATE BY USE OF MIXTURES OF POLYCAPROLACTONE AND CELLULOSE ACETATE BUTYRATE POLYMERS

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ABSTRACT

Chlorpromazine microspheres were prepared by an emulsion solvent evaporation technique using polycaprolactone and cellulose acetate butyrate as the matrix. The fluidity of the polymer solution was easily adjusted by use of mixtures of two polymers and thus provided a practical means to control the microsphere size. The In Vitro release pattern was easily changed by changing the ratios of these two polymers. An increase in polycaprolactone content of the polymer microsphere matrix brought about an increase in the release rate. Drug loading had no predictable effect on the dissolution rate, but smaller microspheres gave more rapid drug release due to the greater surface area.

INTRODUCTION

Mixtures of polymers can have properties significantly better than an individual polymer for achieving sustained release. This investigation demonstrates the feasibility of using mixtures of polycaprolactone and cellulose acetate butyrate to control the release characteristics and size of microspheres containing chlorpromazine. Several other factors affecting the release rate of chlorpromazine from this system were also studied.

EXPERIMENTAL

Materials

The materials were used as received from the supplier and they were polycaprolactone and cellulose acetate butyrate (Scientific Polymer Products, Inc., Ontario, NY), sodium lauryl sulfate (Fisher Scientific Co., Fairlane, NJ), methylene chloride (J.T. Baker Chemical Co., Phillipsburg, NJ). Chlorpromazine hydrochloride (Sigma Chemical Co., St. Louis, MO) was converted to its base by treatment with sodium hydroxide solution.

Methods

Chlorpromazine microspheres were prepared by an emulsion-solvent evaporation technique using polycaprolactone and cellulose acetate butyrate as the matrix. The technique involved the dispersion of drug in a methylene chloride solution of the polymers, followed by emulsification of the polymer solution in water using sodium lauryl sulfate as the emulsifier. After continuous stirring for one hour at room temperature, the solvent evaporated and a rigid polymer microspheres were formed. The microspheres were separated by filtration through filter paper, washed copiously with water and then dried in vacuo at room temperature for at least 24 hours. The dried microspheres were subjected to sieve sizing to obtain the desired microsphere sizes for the dissolution tests.

Content analysis was performed by dissolving an accurately weighed quantity of 10 mg to 15 mg microspheres in 50 ml of methylene chloride. The concentration of chlorpromazine was determined spectrophotometrically at 314 nm. Each determination was performed in triplicate.

The dissolution rate studies were carried out on samples of microspheres equivalent to 10 mg of chlorpromazine using a dissolution apparatus similar to one in U.S.P. The dissolution medium consisted of 1000 ml pH 7.0 phosphate buffer solution maintained at 37°C. Constant stirring at 100 r.p.m. was performed by a mechanical propeller stirrer to ensure the non-aggregation of the microspheres and to attain hydrodynamic equilibrium in the dissolution fluid. At each time interval an aliquot was withdrawn, filtered through 0.45 micron pore size Millipore filter and assayed spectrophotometrically at 255 nm for its chlorpromazine content. After analysis, the aliquot was returned to the dissolution tank.

RESULTS AND DISCUSSION

Preparation of Microspheres of Cellulose Acetate Butyrate and Polycaprolactone

Several polymers in addition to cellulose acetate butyrate were tried as binary polymeric matrix systems with polycaprolactone. When polymethylmethacrylate or polycarbonate was used, a sticky mass formed which prevented recovery of the microspheres. However, microspheres were easily prepared from mixtures of polycaprolactone with cellulose derivatives including ethyl cellulose, cellulose acetate butyrate, and cellulose propionate. Because of its high permeability to chlorpromazine, ethyl cellulose was not suitable to mix with polycaprolactone to regulate the drug release. Therefore, cellulose acetate butyrate was selected in this study. Table I shows the composition of microsphere formulations used in this study.

TABLE I. Composition of Drug Loss of Polycaprolactone - Cellulose Acetate Butyrate Microsphere Formulations

Formulation	PCL[1] (g)	CAB[2] (g)	CPZ[3] (g)	Theoretical Drug Content % W/W	Assay of Drug Content % W/W	Yield %	Drug[4] Loss %
1	0.00	3.00	0.60	16.7	16.3	89.0	13.0
2	0.40	2.60	0.60	16.7	16.0	89.4	14.2
3	0.75	2.25	0.60	16.7	15.9	91.5	12.7
4[5]	1.50	1.50	0.60	16.7	15.6	92.0	13.9
5	2.25	0.75	0.60	16.7	15.4	91.0	15.9
6	3.00	0.00	0.60	16.7	14.6	91.5	19.8
7	1.50	1.50	0.30	9.1	8.1	88.0	21.6
8	1.50	1.50	0.90	23.1	21.3	90.8	16.2
9	1.50	1.50	1.20	28.6	26.8	91.2	14.5

1. Polycaprolactone
2. Cellulose Acetate Butyrate 3. Chlorpromazine
4. % Drug Loss = $(1 - \frac{\text{Quantity of Chlorpromazine Incorporated}}{\text{Initial Quantity of Drug}}) \times 100$
5. Formulation 4 was employed to study particle size effect on dissolution rate

NOTE: 20 ml methylene chloride was used to dissolve the polymers.
60 ml distilled water containing 0.3% sodium lauryl sulfate was used as a non miscible dispersing media
Stirring speed was 1200 r.p.m.

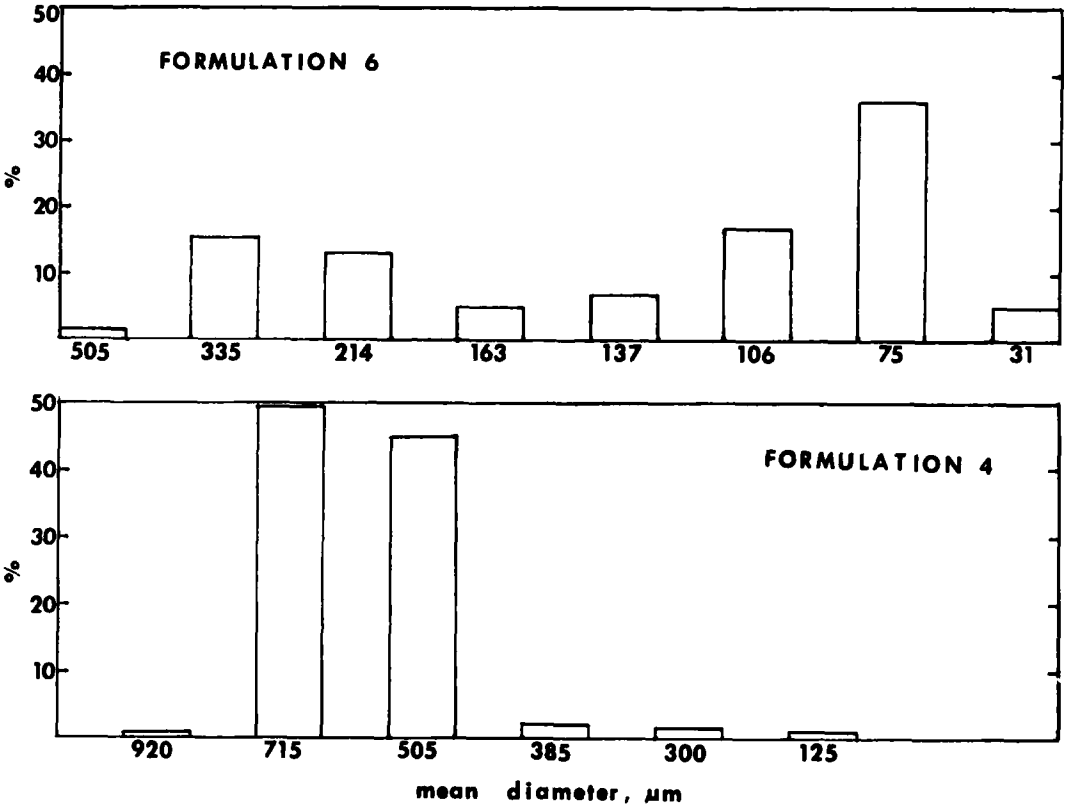

FIGURE 1
Typical Particle Size Distribution for Formulation 4 and Formulation 6

Effect of Mixture of Polycaprolactone and Cellulose Acetate Butyrate on Particle Size

Figure 1 shows the typical size distribution for formulation 4 and formulation 6. Polycaprolactone microspheres behaved as a moderately coarse powder and passed through a 40 mesh standard sieve. Because of the emulsion system used to prepare the microspheres, a wide range particle size distribution was expected. Instead a narrow particle size distribution with 95% of microspheres between No. 20(850 um) and No.40(425 um) sieves was obtained for the polycaptrolactone-cellulose acetate butyrate

microspheres. This result indicates that the use of mixtures of two polymers to control microsphere size is feasible.

Microsphere size can be largely controlled by rate of agitation, but is also dependent on the viscosity, interfacial tension, and density of the microsphere materials. Because of mechanical limitations and emulsion instability, utilization of different rates of agitation to control the capsule size is not feasible in some situations. The fluidity of the polymer solution can be easily adjusted by use of mixtures of two polymers and thus provides a practical means to control the capsule size.

Effect of Polycaprolactone and Cellulose Acetate Butyrate Ratio on Dissolution Rate

Figure 2 shows the cumulative percent release of drug from microspheres prepared with different ratios of polycaprolactone and cellulose acetate butyrate. The release pattern was easily changed by changing the ratios of these two polymers. It was surprising that cellulose acetate butyrate was almost impermeable to chlorpromazine and gave only 3.3% drug release at end of a 7 hour dissolution test. An increase in polycaprolactone content of the polymer microsphere matrix brought about an increase in the release rate, but a 3:1 ratio of polycaprolactone to cellulose acetate butyrate enhanced dissolution only slightly over that obtained for a 1:1 ratio. This ratio seems to approach the fast dissolution extreme for the polycaprolactone-cellulose acetate butyrate system. Because the desired particle size for polycaprolactone microspheres was not obtained, no dissolution test was conducted for formulation 6.

An equation for the spherical matrix has been derived by Higuchi (1) and Baker, et al. (2) as: $3/2(1-(1-F)^{2/3})-F = KT$, where F is the fraction of drug released, K is a constant and T is time. Table II shows the calculated $3/2(1-(1-F)^{2/3})-F$ values at each sampling time and correlation coefficients obtained by linear regression of $3/2(1-(1-F)^{2/3})-F$ versus time for each formulation.

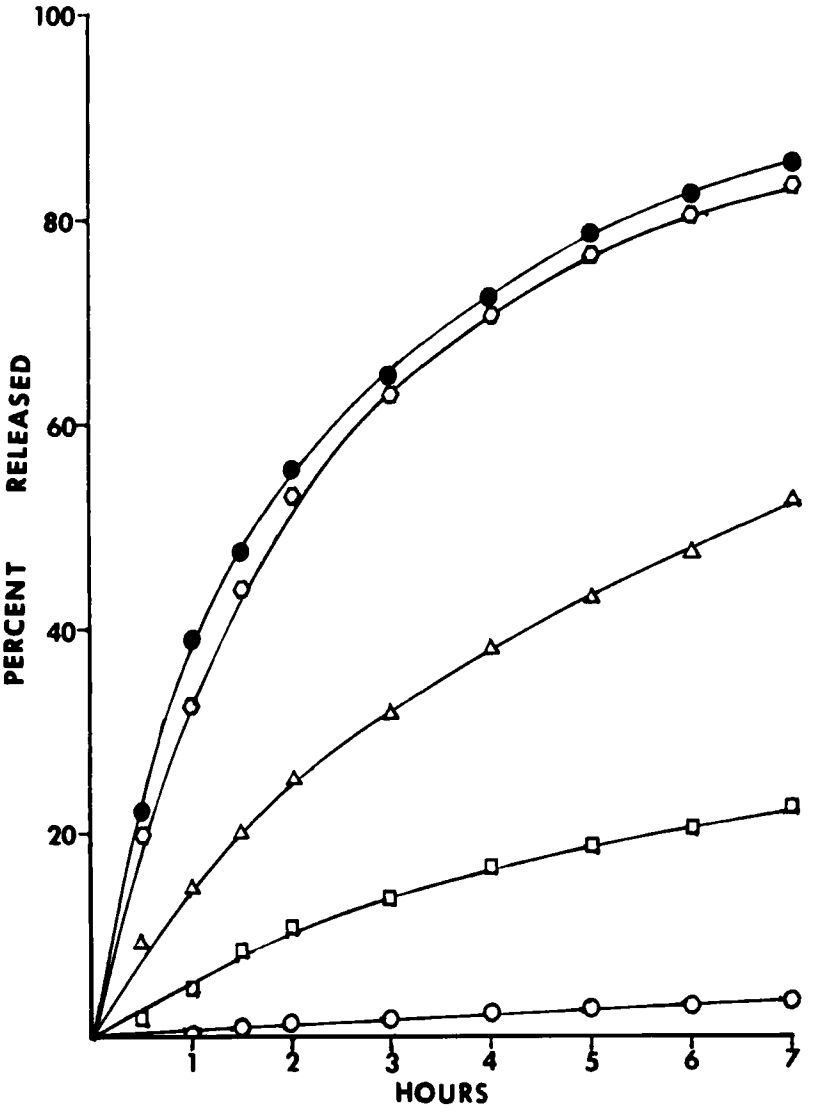

FIGURE 2
Effect of Polycaprolactone/Cellulose Acetate Butyrate Ratio on Dissolution Rate of Microspheres Containing Chlorpromazine
KEY: ○ formulation 1, □ formulation 2, △ formulation 3, ⬡ formulation 4, ● formulation 5

TABLE II. Calculated $3/2(1-(1-F)^{2/3})$ - F Values for Each Sampling Time of Formulations 2 - 5

	Formulation			
	2	3	4	5
	0.40/2.60*	0.75/2.25	1.50/1.50	2.25/0.75
Time (hours)	Calculated $3/2(1-(1-F)^{2/3})$ - F Values			
0.5	0.0000	0.0014	0.0077	0.0117
1.0	0.0004	0.0036	0.0205	0.0309
1.5	0.0012	0.0072	0.0407	0.0483
2.0	0.0018	0.1020	0.0632	0.0710
3.0	0.0031	0.0195	0.0957	0.1025
4.0	0.0046	0.0293	0.1318	0.1407
5.0	0.0062	0.0388	0.1638	0.1780
6.0	0.0074	0.0483	0.1928	0.2065
7.0	0.0093	0.0624	0.2154	0.2337
Corr.	0.9984	0.9955	0.9976	0.9986
Slope	0.0014	0.0093	0.0330	0.0347
Intcp.	-0.0010	-0.0062	-0.0066	-0.0020

*. Polycaprolactone/Cellulose Acetate Butyrate, 3 grams total Polymer

Figure 3 shows a linear relationship between calculated $3/2(1-(1-F)^{2/3})-F$ values and time which confirm the results of a previous report by Lai (3).

Effect of Drug Loading on Dissolution Rate

Lower drug loading results in a greater proportion of encapsulating material and relatively longer diffusion path length. Balancing this factor, more microspheres are required for a given dose, therefore a larger surface area is available for contact with the dissolution media. The dissolution rate is influenced by these two contradictory factors.

Figure 4 reveals that drug loading did not have predictable effect on the dissolution rate when a constant drug dose was employed for dissolution.

Effect of Particle Size on Dissolution Rate

Because of the narrow particle size distribution obtained, the effect of particle size on dissolution rate was examined by using only three particle sizes. As shown in Figure 5, the smaller the microspheres the more rapid the drug release due to the greater surface area.

The drug release from microspheres with different particle size or drug loading can be described by Higuchi or Baker and Lonsdale's model for dissolution from spherical matrices.

Morphology of Cellulose Acetate Butyrate - Polycaprolactone Microspheres

Scanning electron micrographs of cellulose acetate butyrate-polycaprolactone microspheres containing chloropromazine are shown in Plates 1 - 7. Cellulose acetate butyrate microspheres had large holes on the surface possibly caused by rapid vaporization of the solvent and subsequent formation of bubbles during the fabrication process (Plate 1). The same surface at the higher magnification in Plate 2 is shown to be very porous. Cellulose acetate butyrate-poly- caprolactone microspheres bear a resemblance to the surface of the cellulose acetate butyrate micro-

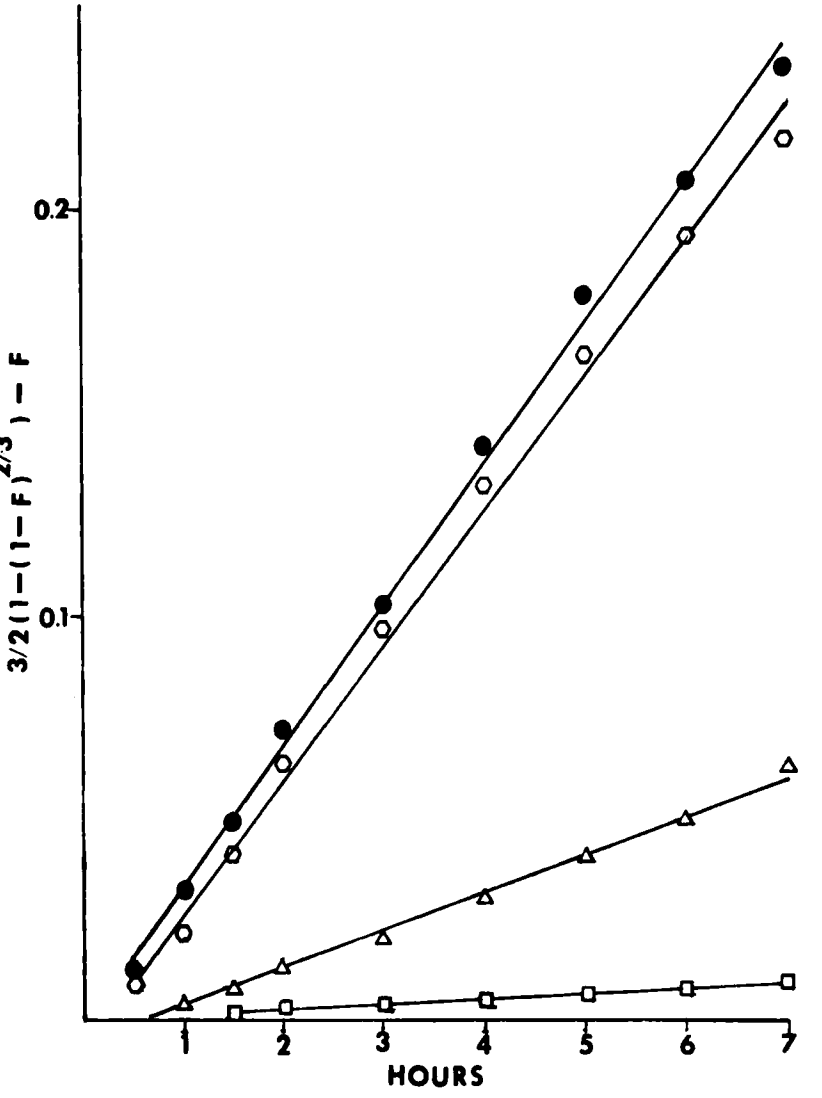

FIGURE 3
Relationship between Calculated Value of $3/2(1-(1-F)^{3/2}) - F$ and Time for Cellulose Acetate Butyrate - Polycaprolactone Microspheres Containing Chlorpromazine
KEY: □ formulation 2, △ formulation 3, ⬡ formulation 4, ● formulation 5

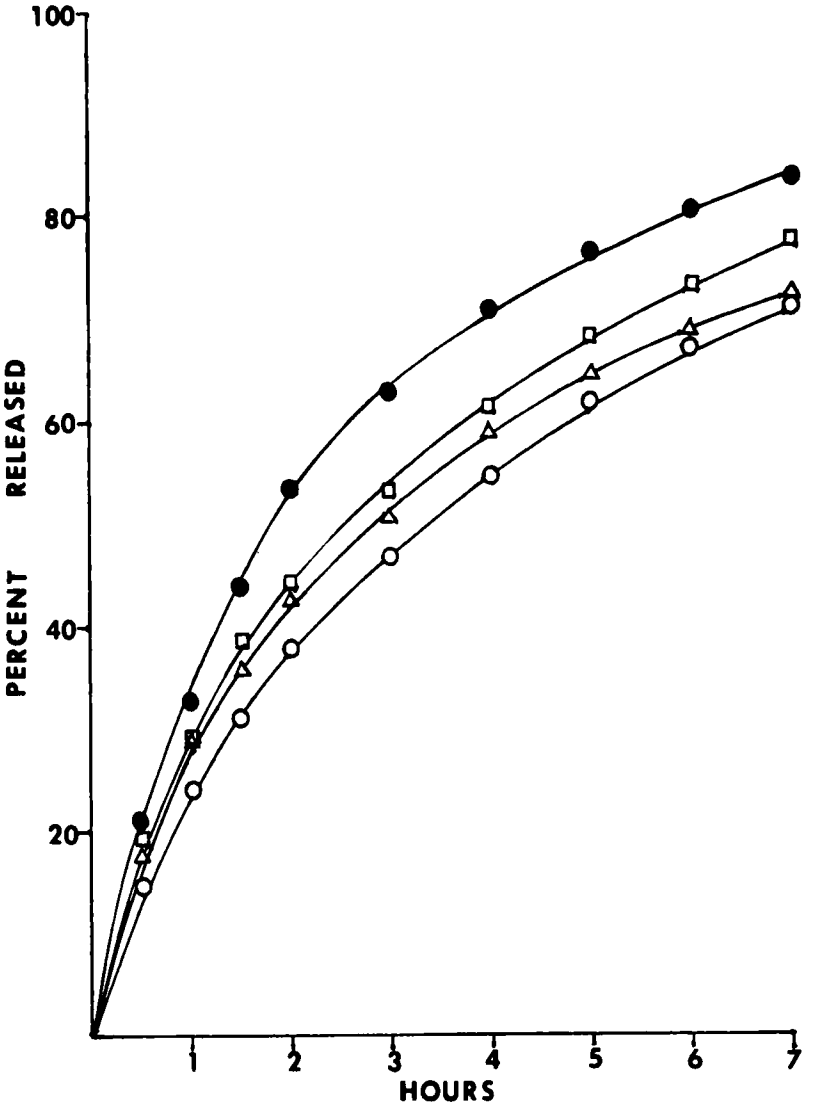

FIGURE 4
Effect of Drug Loading on Dissolution Rate of Cellulose Acetate Butyrate - Polycaprolactone Microspheres Containing Chlorpromazine
KEY: △ drug content 8.1% W/W ● drug content 15.6% W/W
□ drug content 21.3% W/W ○ drug content 26.8% W/W

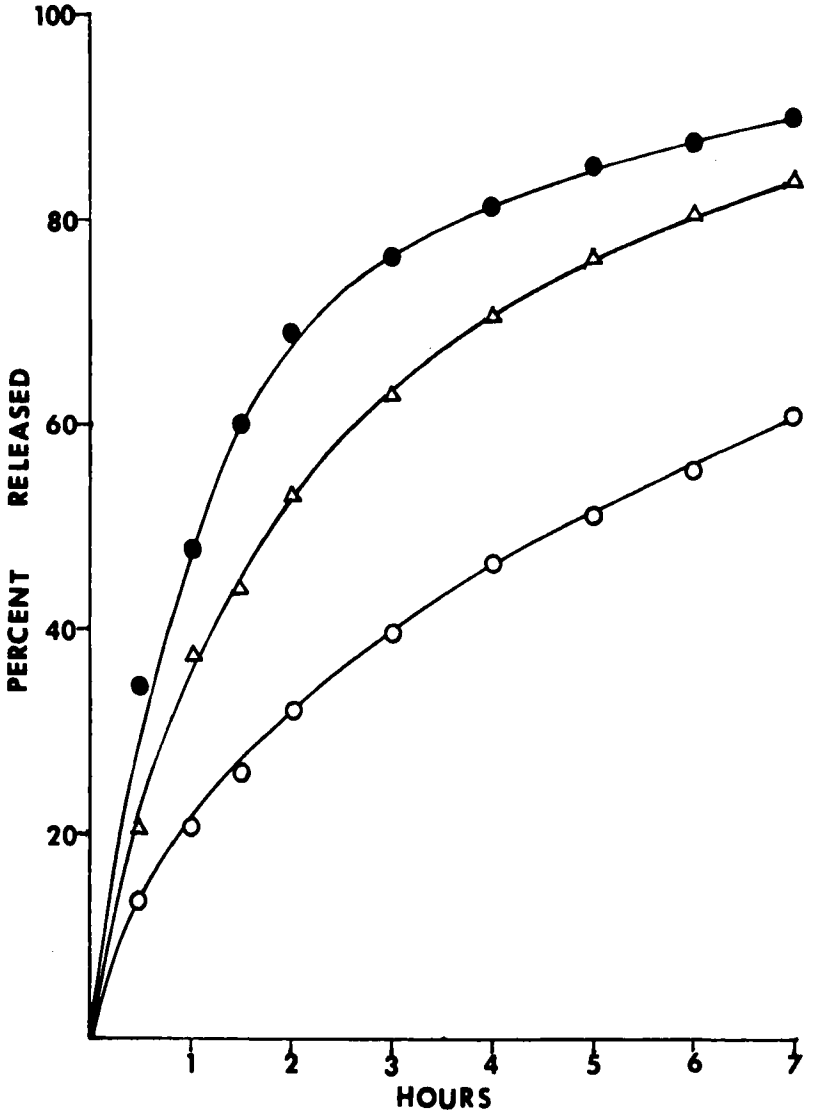

FIGURE 5
Effect of Particle Size on Dissolution Rate of Cellulose Acetate Butyrate - Polycaprolactone Microspheres Containing Chlorpromazine
KEY: ● 210 microns, △ 505 microns, ○ 715 microns

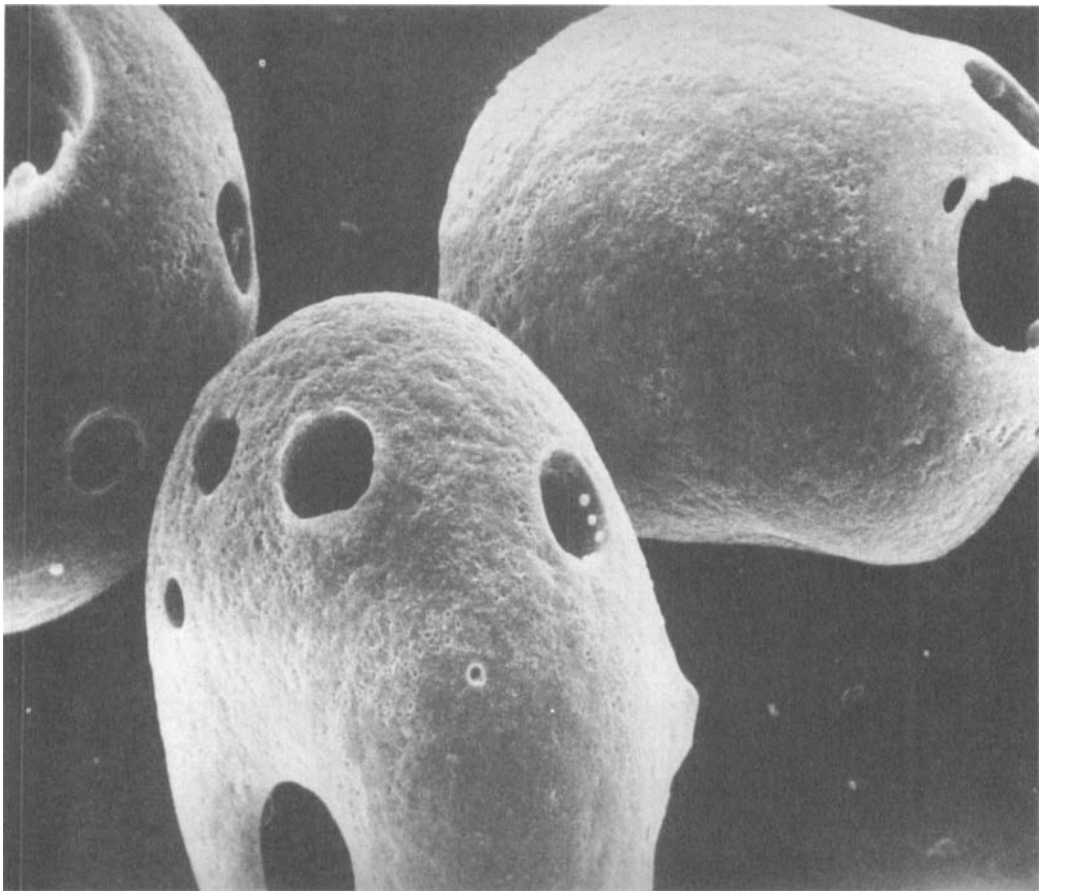

FIGURE 6
Scanning Electron Micrographs of Chlorpromazine Microspheres Prepared with Various Ratios of Polycaprolactone and Cellulose Acetate Butyrate
KEY: Plate 1, formulation 1 (x 170)
Plate 2, formulation 1 (x 1700)
Plate 3, formulation 2 (x 170)
Plate 4, formulation 2 (x 170)
Plate 5, formulation 3 (x 170)
Plate 6, formulation 4 (x 170)
Plate 7, formulation 5 (x 170)

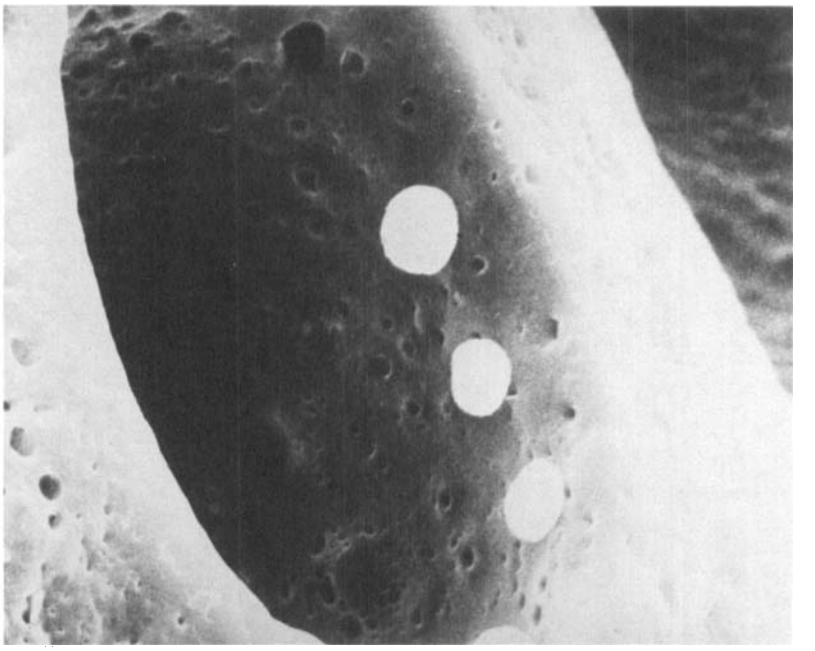

FIGURE 6 CONTINUED: PLATE 2, formulation 1 (x1700)

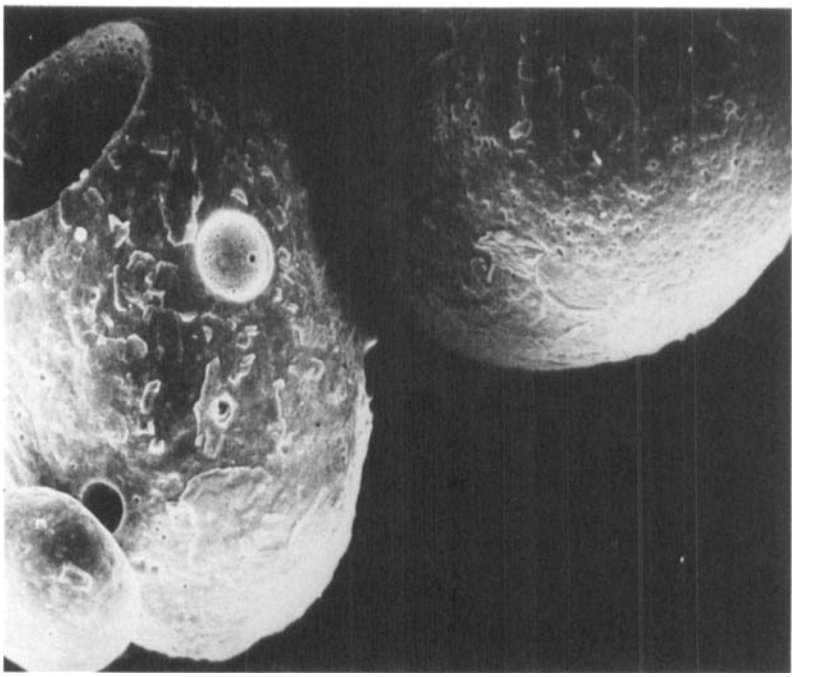

FIGURE 6 CONTINUED: PLATE 3, formulation 2 (x170)

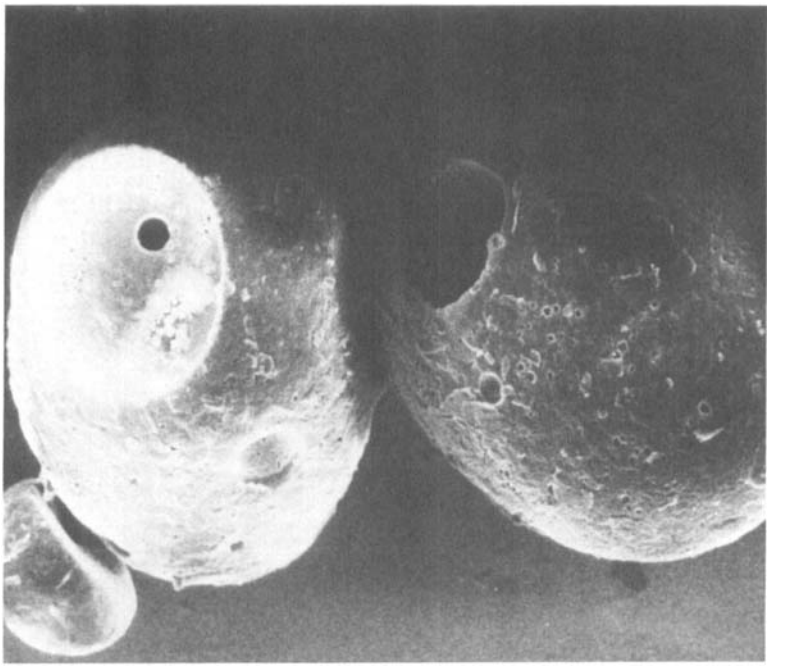

FIGURE 6 CONTINUED: PLATE 4, formulation 2 (x170)

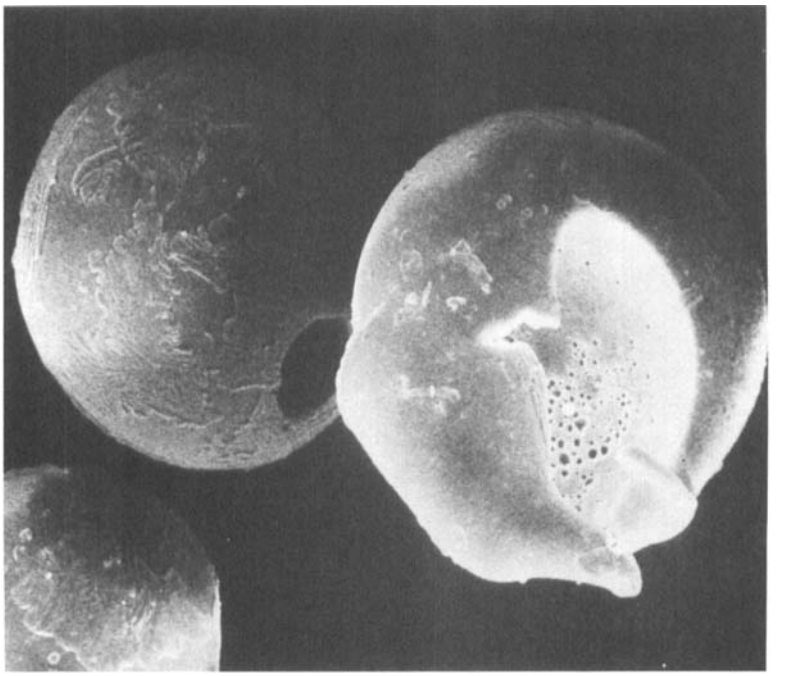

FIGURE 6 CONTINUED: PLATE 5, formulation 3 (x170)

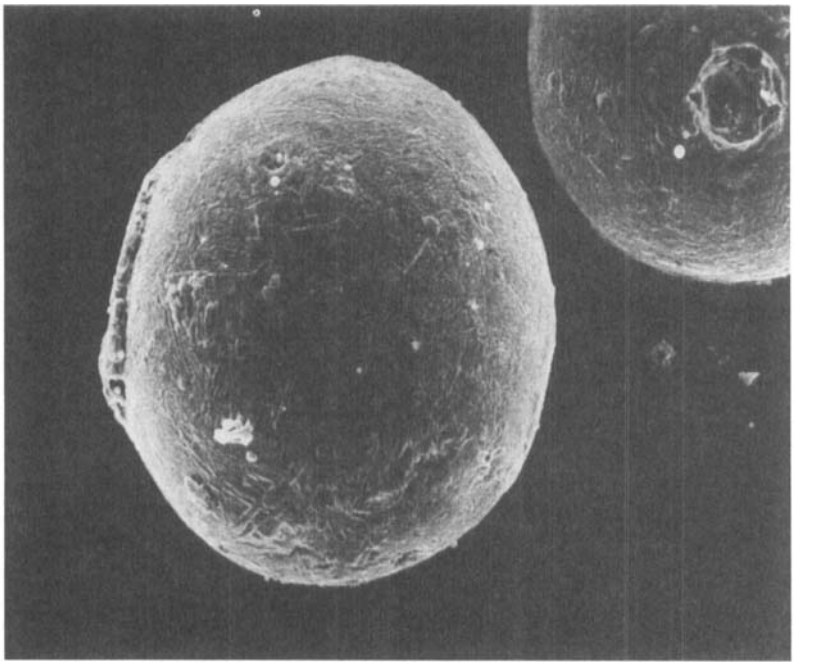

FIGURE 6 CONTINUED: PLATE 6, formulation 4 (x170)

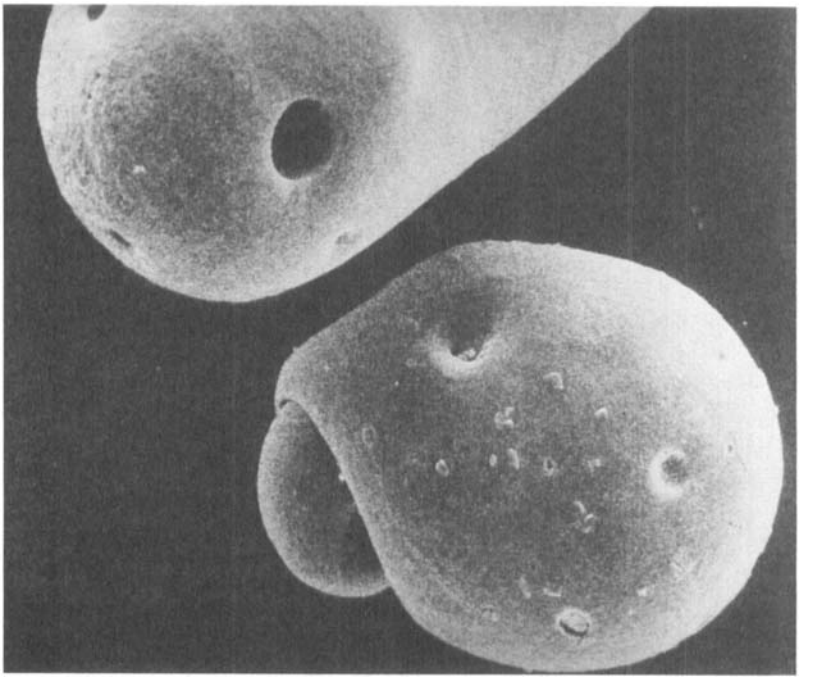

FIGURE 6 CONTINUED: PLATE 7, formulation 5 (x170)

spheres. However, there is no deposition of polymer segments or pieces on the surface of cellu- lose acetate butyrate micro-spheres shown in Plate 1, as there are in Plates 3-7. This result suggests that deposition of polymer segments or pieces is due to the polycaprolactone.

REFERENCES

1. T. Higuchi, J. Pharm. Sci., 52, 1145, 1963.
2. R.W. Baker and H.K. Lonsdale, In "Controlled Release of Biologically Active Agents", A.C. Tanguary and R.E. Lacey, Eds., Plenum Press, New York, 1974, p.p. 15-71.
3. J.W. Lai, M.S. Thesis, University of Georgia, Athens, Georgia 1982