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DISSOLUTION CHARACTERISTICS OF POLYCAPROLACTONE-POLYLACTIDE MICROSPHERES OF CHLORPROMAZINE

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ABSTRACT

Studies were conducted on the preparation of controlled release polycaprolactone-polylactide microcapsules of chlorpromazine and on release of the drug from the microcapsules in pH 7.0 buffer medium. A wide range of release rates of the drug was obtained by simple change in the polymer system. Chlorpromazine was released from the microspheres in a biphasic manner consisting of an initial fast release phase followed by a slow-release phase. Increasing the drug content increased the initial drug release rate but no significant drug loading effect on the second stage dissolution rate was noted. There was no significant effect of particle size on the drug release rate from the

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microspheres. The swelling property of the microspheres and the agglomerate nature of the sieve fractions may complicate the drug release kinetics and obscure the particle size effect on dissolution rate.

INTRODUCTION

Long-acting injectable anti-psychotic preparations are of value because patient compliance has always presented a major difficulty that challenges the medical profession in the management of psychotic disorders(1). An esterification approach has been reported and utilized to achieve longer duration of action for neuroleptic drugs(2,3,4). An encapsulated preparation of chlorpromazine has been reported in the literature(5).

Results of previous investigations demonstrated that using mixtures of two polymers to prepare microspheres may offer a means to regulate the drug release. In the present investigations, chlorpromazine base was chosen as a model neuroleptic to be encapsulated in a matrix using mixtures of polycaprolactone and polylactide as matrix materials.

The purpose of the present study was to develop a bio-degradable polymeric system for the sustained subdermal delivery of neuroleptics, to investigate the possibility of tailoring the drug dissolution from the polymeric system by use of mixtures of polycaprolacton and polylactide and to study factors such as particle size and drug-polymer ratio on the rate of chlorpromazine release.

EXPERIMENTAL

Materials

The materials used in this study were polycaprolactone (Scientific Polymer Products, Inc., Ontario, N.Y.), dilactide (Frinton Laboratories, Vineland, N.J.), chlorpromazine hydrochloride (Sigma Chemical Co., St. Louis, MO.), sodium Lauryl sulfate (Fisher Scientific Co., Fairlane, N.J.) methylene chloride (J. T. Baker Chemical Co., Phillipsburg, N.J.), benzene (J. T. Baker Chemical Co., Phillipsburg, N.J.), ethyl acetate (Fischer Scientific Co., Fairlawn, N.J.), Polyvinyl alcohol (Sigma Chemical Co., St. Louis, MO), tetraphenyl tin (Aldrich Chemical Co., Milwaukee, WI) and except for dilactide and chlorpromazine hydrochloride were used without further purification. Chlorpromazine hydrochloride was converted to its base by treatment with sodium hydroxide solution. The crude dilactide was recrystallized twice using ethyl acetate as solvent.

Methods

Polylactide was prepared from dilactide in an oven at 165°C for 6 hours using 0.02% tetraphenyl tin as a catalyst. The mean molecular weight of polylactide was determined viscometrically to be 7800 by using a Cannon-Fenske viscometer with benzene as a polymer solvent at 25°C.

Chlorpromazine microspheres were prepared by an emulsion-solvent evaporation process using polycaprolactone and polylactide as the matrix. Weighed amounts of polymer(s) and chlorpromazine 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 the 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.

Dissolution rate studies were carried out on sample of microspheres equivalent to 10 mg of chlorpromazine using a dissolution apparatus similar to one described in U.S.P. XX. 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. At each time interval 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 vessel.

RESULTS AND DISCUSSION

Preparation of Microspheres of polylactide-Polycaprolactone

When greater than 1:1 ratio of polylactide to polycaprolactone was used, sodium lauryl sulfate was not capable of main-

taining the integrity of the polymer droplets during the fabrication process and modification of the microencapsulation process was required. It was found that a macromolecular dispersing agent such as polyvinyl alcohol eliminated this problem. However, macromolecular dispersing agents tended to increase the time needed to solidify the polymers.

Since aliphatic polyesters degrade by hydrolysis, the microspheres should not be exposed to the aqueous dispersing medium for excessively long periods during the solvent evaporation step. However, no degradation was observed during the time required by solvent evaporation process used in this study. Table I shows the compositions, drug loading and percent drug loss for the microencapsulation formulations used in the present study.

Effect of Polycaprolactone and Polylactide Ratio on Dissolution Rate

Figure 1 and Figure 2 show the cumulative percent of drug release from microspheres prepared with different ratios of polycaprolactone and polylactide as a function of time. A wide range of release rates of the drug was obtained by simple change of the polymer ratio. An increase in polycaprolactone content of the microspheres brought about an increase in the release rate. Chlorpromazine was released from the microspheres in a biphasic manner consisting of an initial fast release phase followed by a slow-release phase. A linear relationship was noted between the amount of the initial fast release of chlorpromazine for each formulation and the polylactide/total polymer ratio. As the

TABLE I. Composition and Drug Loss of Polycaprolactone - Polylactide Microsphere Formulations Containing Chlorpromazine

Formulation	PCL[1] (g)	PL[2] (g)	CPZ[3] (g)	Theoretical loading % W/W	Assay loading % W/W	Yield %	Drug[4] Loss %
1	3.00	0.00	0.60	16.7	15.7	95.5	10.0
2	2.25	0.75	0.60	16.7	15.0	92.0	17.2
3	1.50	1.50	0.60	16.7	14.8	90.0	20.0
4[5]	0.75	2.25	0.60	16.7	14.2	91.0	22.4
5	0.00	3.00	0.60	16.7	13.0	88.3	25.9
6	0.75	2.25	0.10	3.2	3.0	91.0	15.4
7	0.75	2.25	0.30	9.0	7.0	92.0	29.2
8	0.75	2.25	1.20	28.6	25.0	89.2	21.9

1. Polycaprolactone
2. Polylactide
3. Chlorpromazine

4. $\%\ \text{Drug loss} = \left(1 - \frac{\text{Quantity of Chlorpromazine Incorporated}}{\text{Initial Quantity of Drug}}\right) \times 100$

5. Formulation 4 was employed to study particle size effect on dissolution rate

NOTE:

20 ml Methylene Chloride was used to dissolve the polymer(s).

60 ml distilled water containing 0.05% sodium lauryl sulfate plus 5% polyvinyl alcohol was used as a non-miscible dispersing media.

Stirring speed was 400 r.p.m.

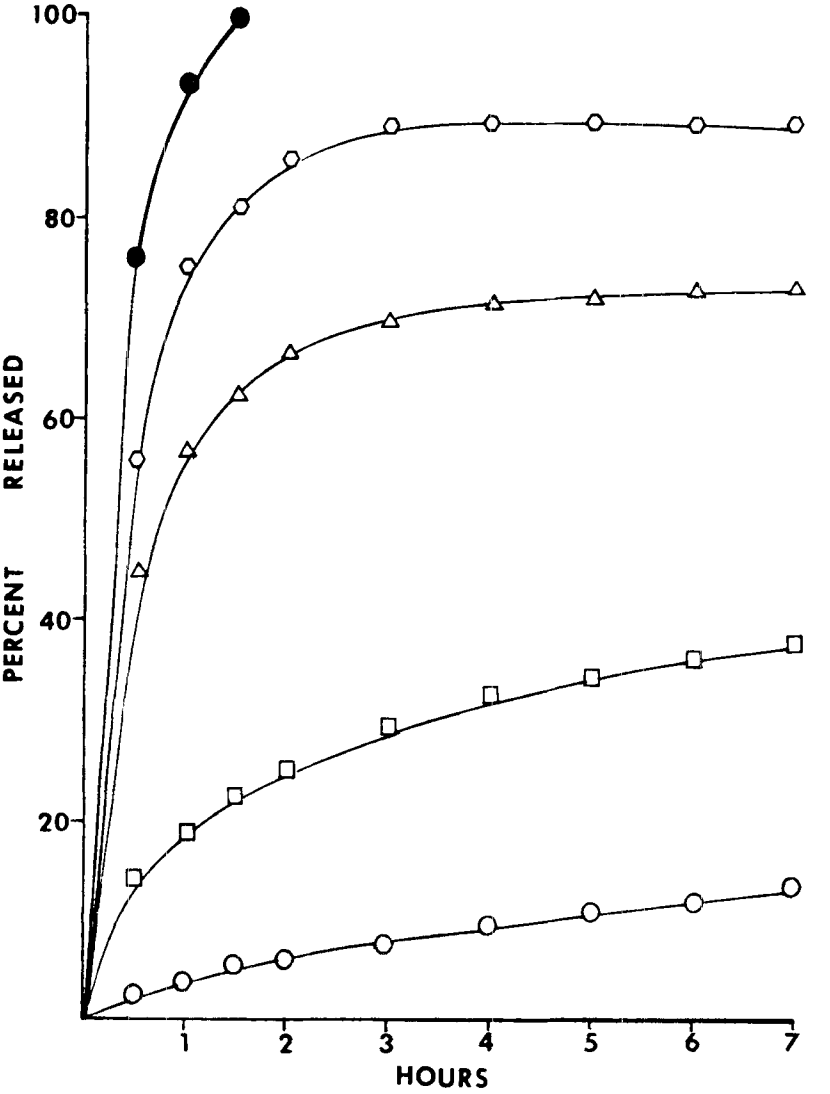

FIGURE 1
Effect of Polycaprolactone/Polylactide Ratio on Short Term (7 hours) Dissolution of Microspheres Containing Chlorpromazine
KEY: ● formulation 1, ⬡ formulation 2, △ formulation 3, □ formulation 4, o formulation 5

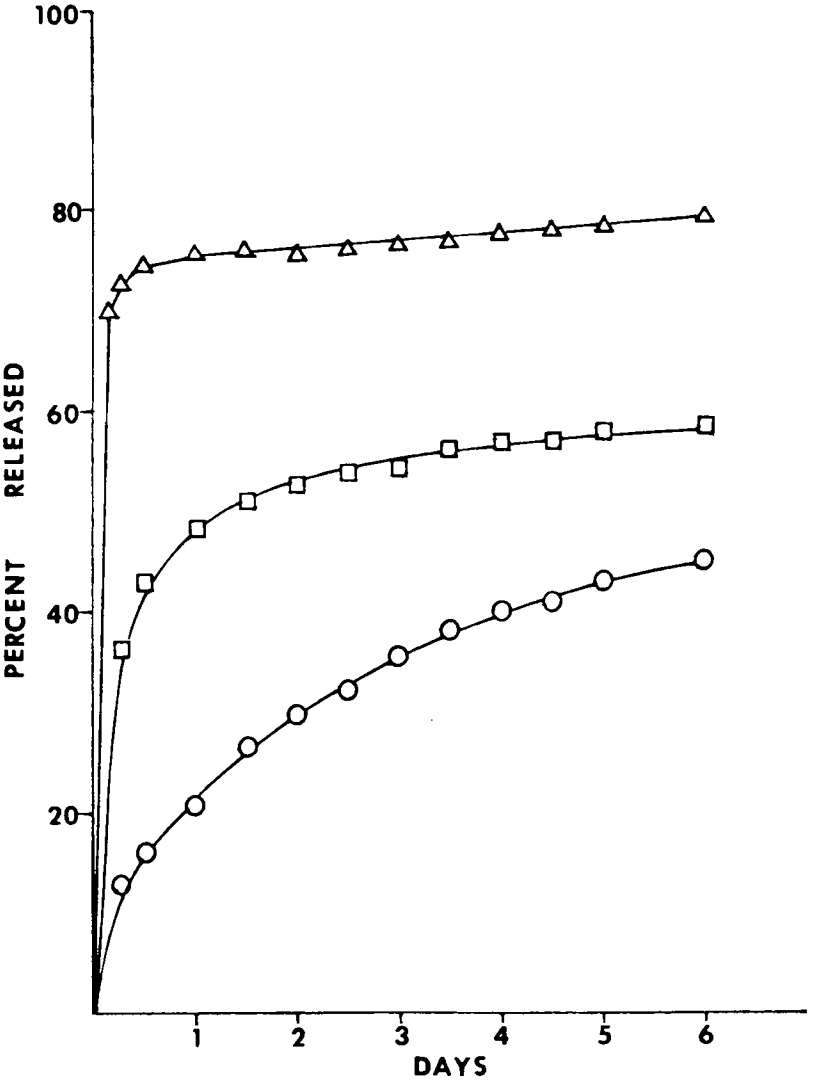

FIGURE 2
Effect of Polycaprolactone/Polylactide Ratio on Long Term (6 days) Dissolution of Microspheres Containing Chlorpromazine
KEY: △ formulation 3, □ formulation 4, ○ formulation 5

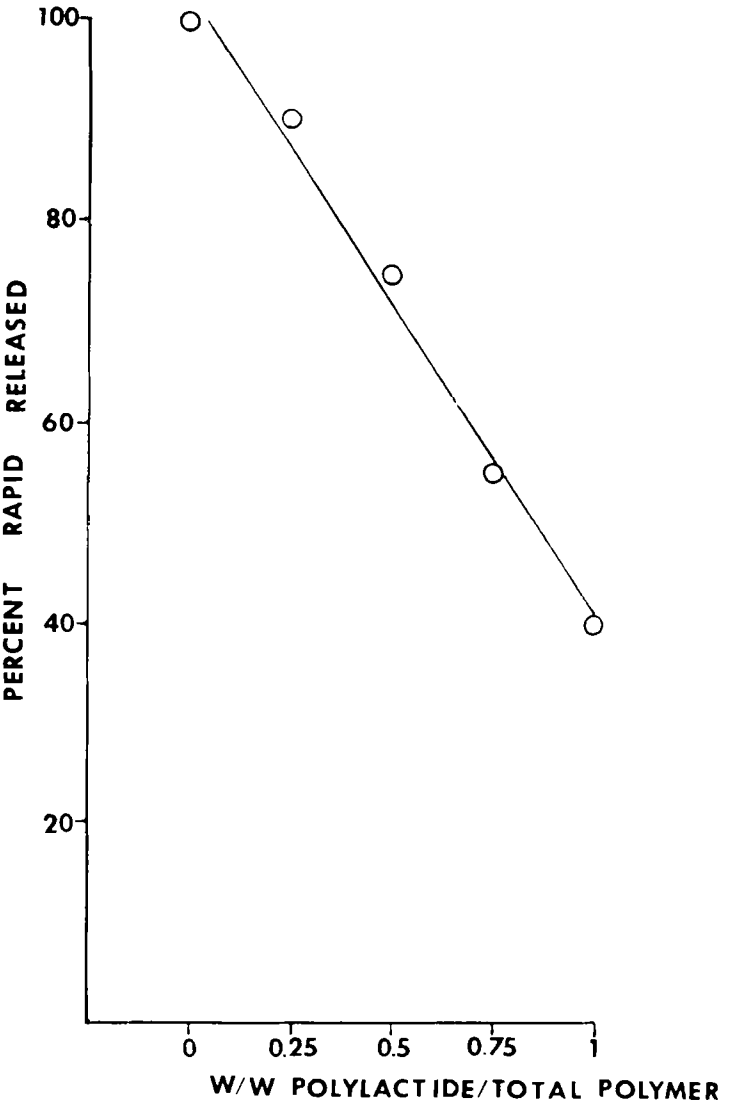

FIGURE 3
Relationship between the Amount of the Initial Release* and the Fraction of Polylactide
* Obtained from the point change to the approximately zero order release stage.

polylactide content of the polymer microsphere matrix increased, the amount of the initial chlorpromazine release decreased (Figure 3).

Effect of Drug Loading on Dissolution Rate

Figure 4 shows the effect of drug content on the release of chlorpromazine. As shown in Figure 4, a wide spectrum of release rates was achieved by altering the drug content. Increasing the drug content increases the initial drug release rate.

A linear relationship between the amount of initial fast chlorpromazine release and drug loading was noted (Figure 5). Drug loading had no significant effect on the second stage dissolution rate.

Regardless of the concentration of chlorpromazine initially incorporated into the polymer, the amount remaining after the fast release period was relatively constant, ranging from 0.89×10^{-4} to 2.18×10^{-4} mole/gram of microspheres and corresponding to molar ratios of drug to carboxyl end-group in polylactide of 0.96 to 2.64 (mean, 1.84 ± 0.68 S.D.). Rates of release were also relatively constant as noted from the slopes of the second phase dissolution lines. Drug remaining in the polymer matrix in a molar ratio of 2:1, is more strongly bound, and probably released only as the polymer is hydrolyzed. At least part of the initial drug release was due to drug located near the surface of the microspheres caused by migration during the solvent evaporation process. Dissolution from the polylactide microspheres was not typical of release from spherical matrix systems as de-

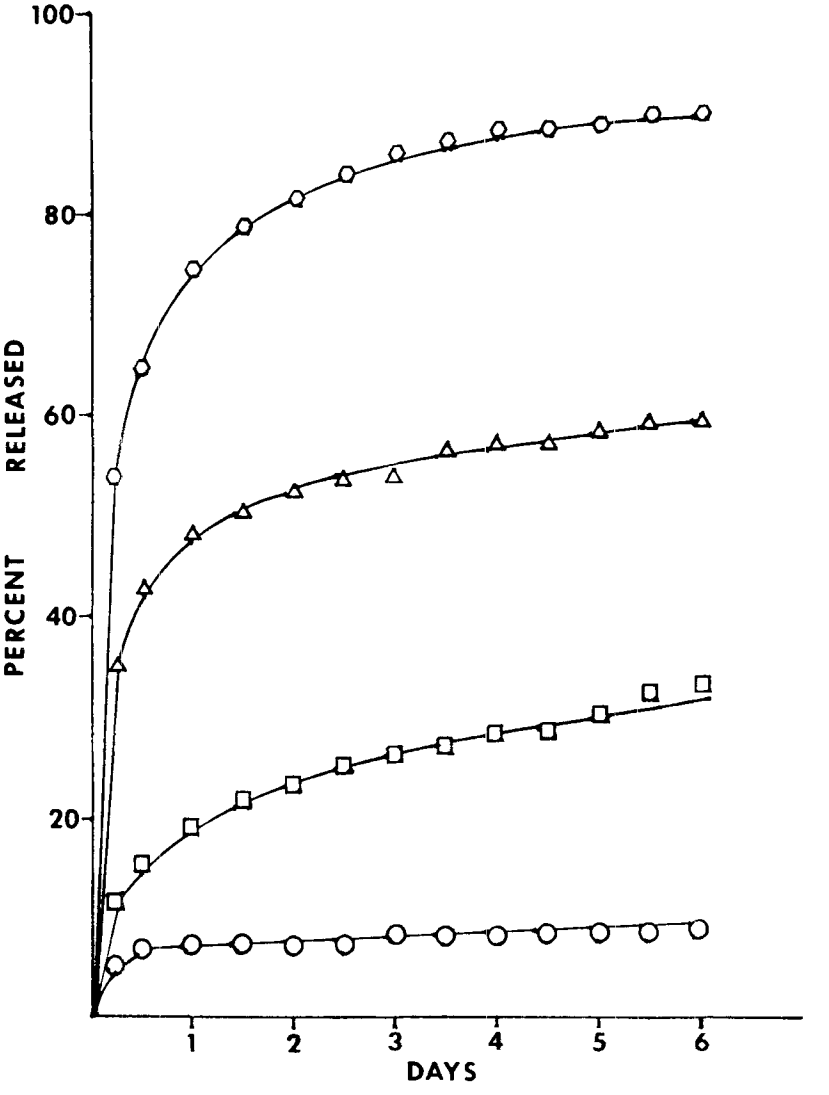

FIGURE 4
Effect of Drug Loading on Dissolution of Polylactide-Polycaprolactone Microspheres Containing Chlorpromazine
KEY: ○ drug content 3.0% w/w, □ drug content 7.0% w/w,
△ drug content 14.2% w/w, ⬡ drug content 25.0% w/w

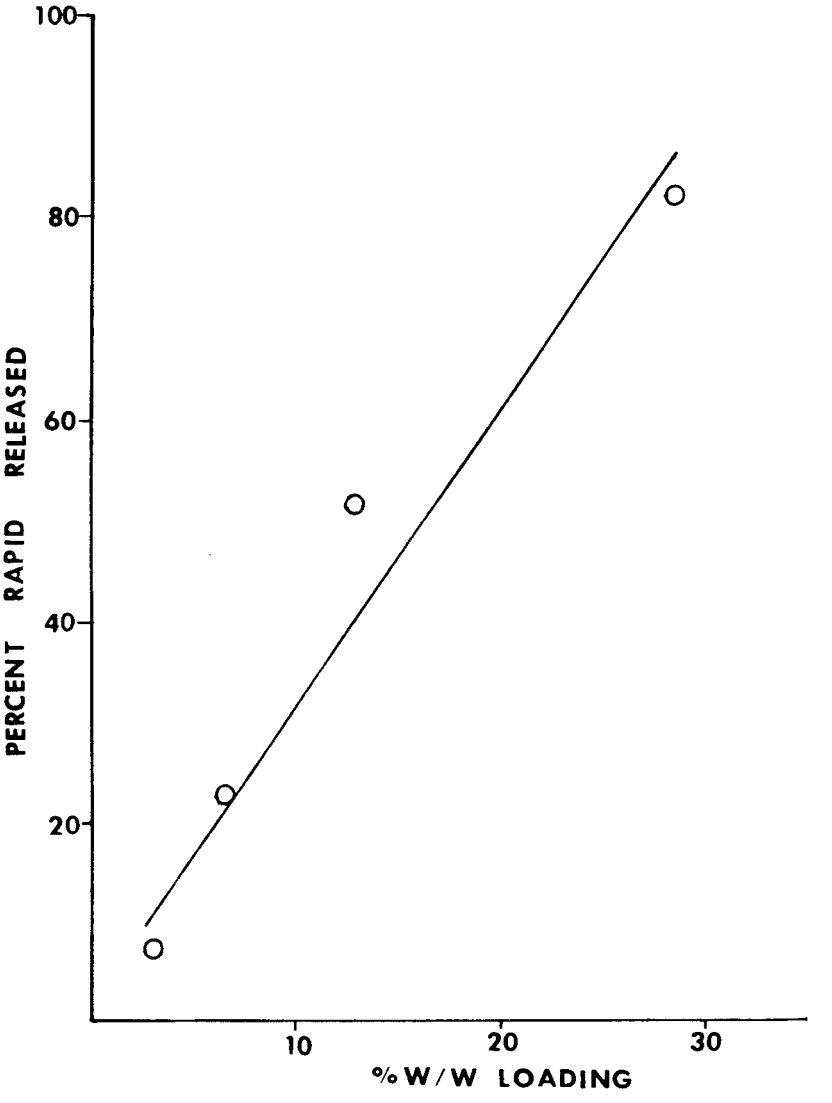

FIGURE 5
Relationship between the Amount of the Initial Release* and Drug Loading of Polylactide-Polycaprolactone Microspheres Containing Chloropromazine
* Obtained from the point change to the approximately zero order release stage.

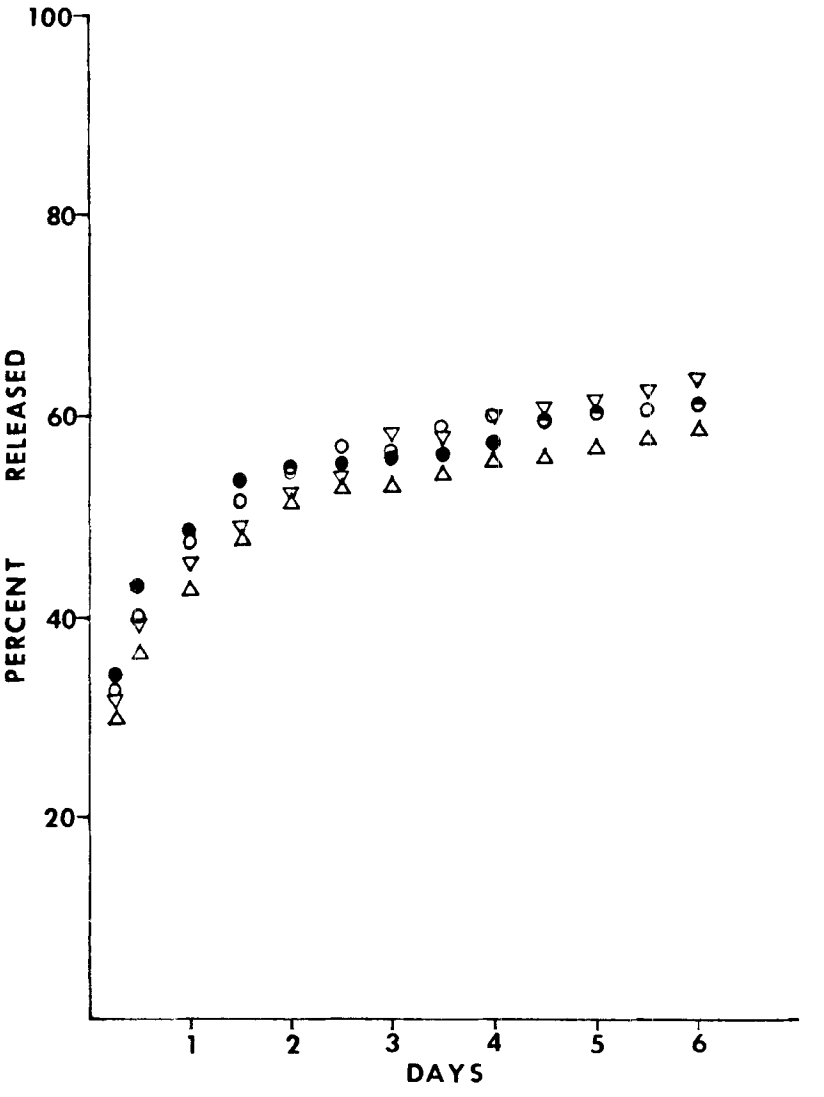

FIGURE 6
Effect of Particle Size on Dissolution of Polylactide-Polycaprolactone Microspheres Containing Chlorpromazine

KEY: ○ 44 microns, ▽ 107 microns, ● 157 microns, △ 214 microns

scribed by the Higuchi or Baker-Lonsdale models (6,7).

Effect of Particle Size on Dissolution Rate

Theoretically, the smaller the microspheres the more rapid the drug release due to the greater surface area. However, Figure 6 reveals that there was no significant effect of particle size on the drug release rate from the microspheres. The lack of particle size effect on dissolution may have been due to the agglomerate nature of the sieve fractions. Electron micrographs (Plates 1-3) revealed open-structered agglomerates of small particles. This structure would permit relatively free access of the dissolution fluid to the interior of the aggregate and all sieve fractions would have about the same dissolution characteristics. Another factor was that the polylactide prepared for this study was a low molecular weight polymer (approximately 7800) which tended to swell in the dissolution medium. The swelling of the microspheres complicates their drug release kinetics and may obscure the particle size effect on dissolution.

Morphology of Polylactide - Polycaprolactone Microspheres

Scanning electron micrographs (SEM) of polylactide microspheres containing chlorpromazine are shown in Plates 1-3. The pictures indicate aggregates of spherical microspheres with generally smooth surfaces. The appearance of polylactide - polycaprolactone (3:1) microspheres is similar to that of polylactide microspheres (plates 4 & 5). However, the appearance changed dramatically as the polycaprolactone content in the microsphere matrix increased. Plate 6 shows less spherical particles and

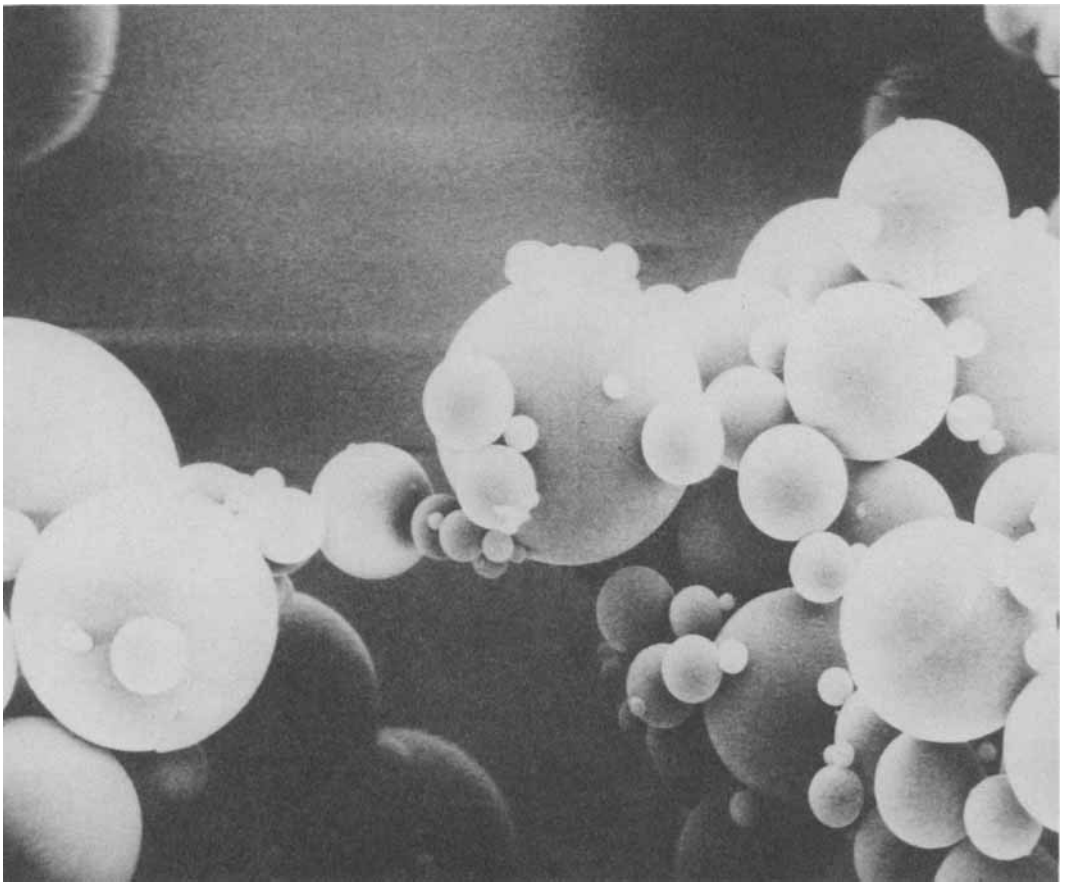

FIGURE 7
Scanning Electron Micrographs of Chlorpromazine Microspheres Prepared with Various Ratios of Polylactide and Polycaprolactone

KEY:
Plate 1, formulation 5 (x850)
Plate 2, formulation 5 (x3400)
Plate 3, formulation 5 (x8500)
Plate 4, formulation 4 (x3400)
Plate 5, formulation 4 (x8500)
Plate 6, formulation 3 (x850)
Plate 7, formulation 3 (x1700)
Plate 8, formulation 2 (x850)
Plate 9, formulation 2 (x3400)
Plate 10, formulation 1 (x1700)
Plate 11, formulation 1 (x17000)

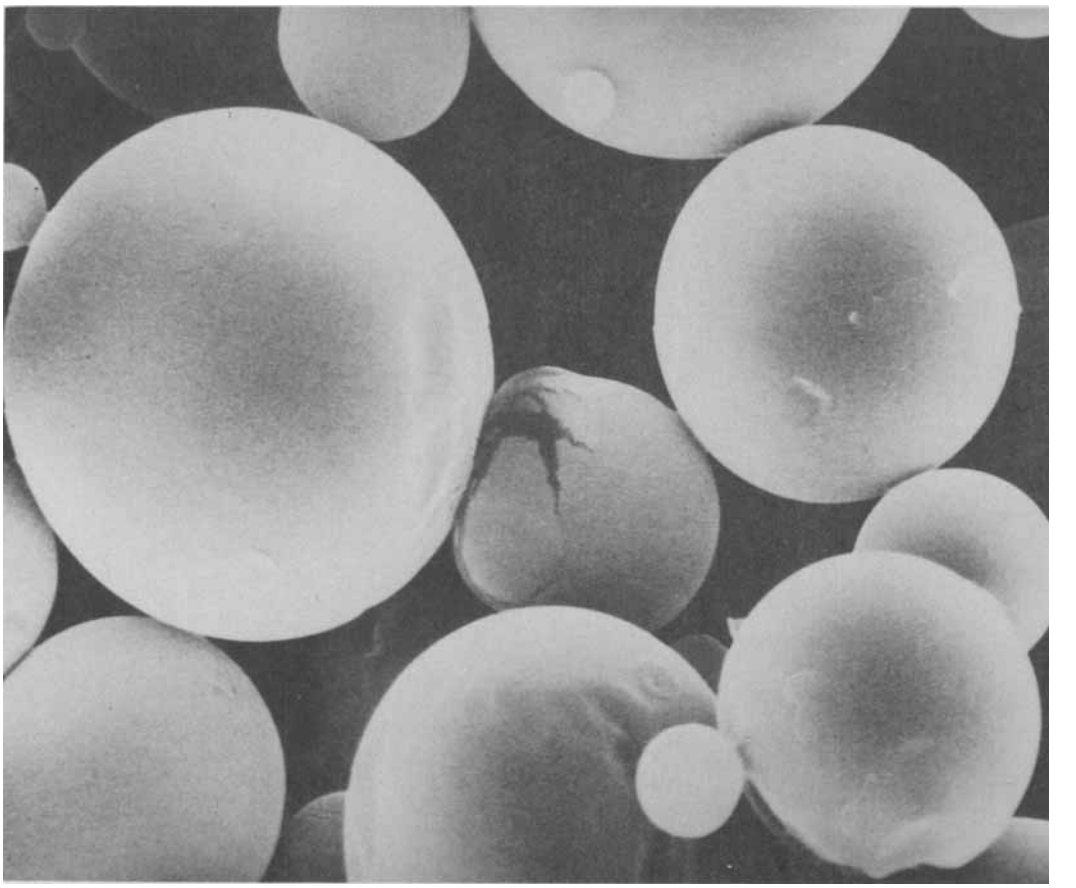

FIGURE 7, PLATE 2

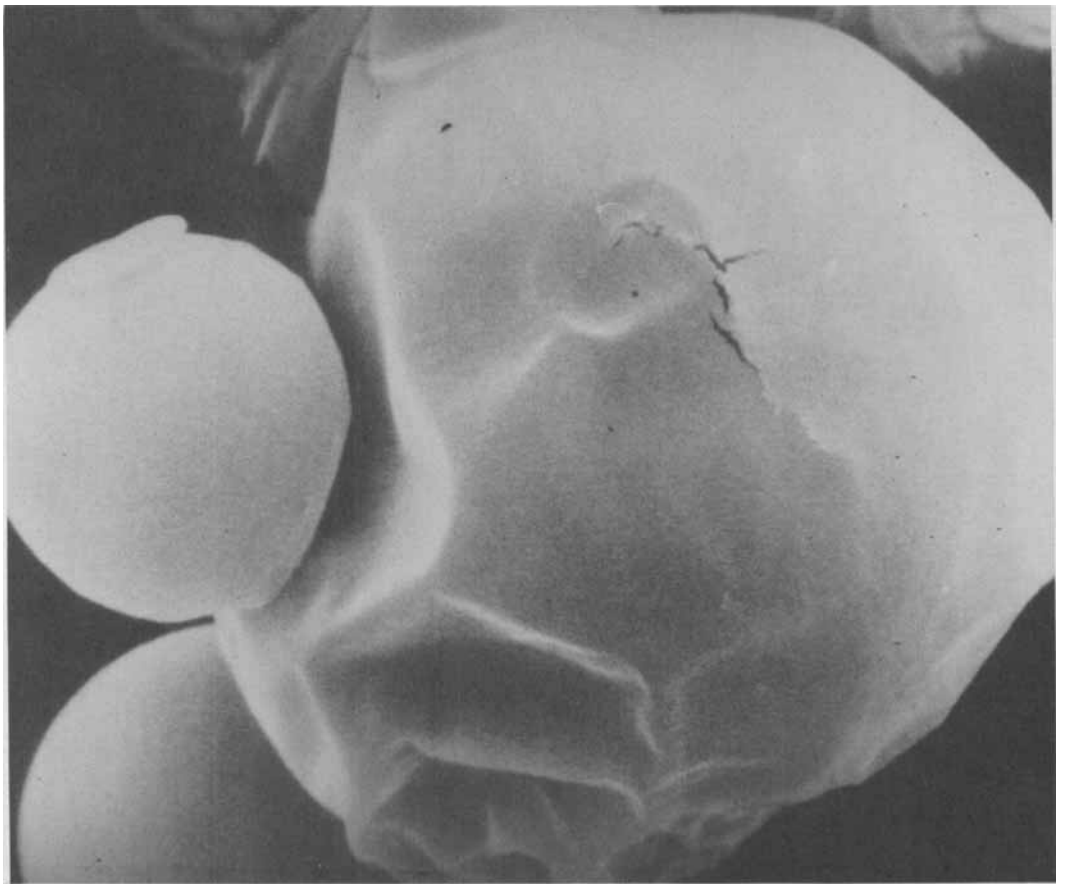

FIGURE 7, PLATE 3

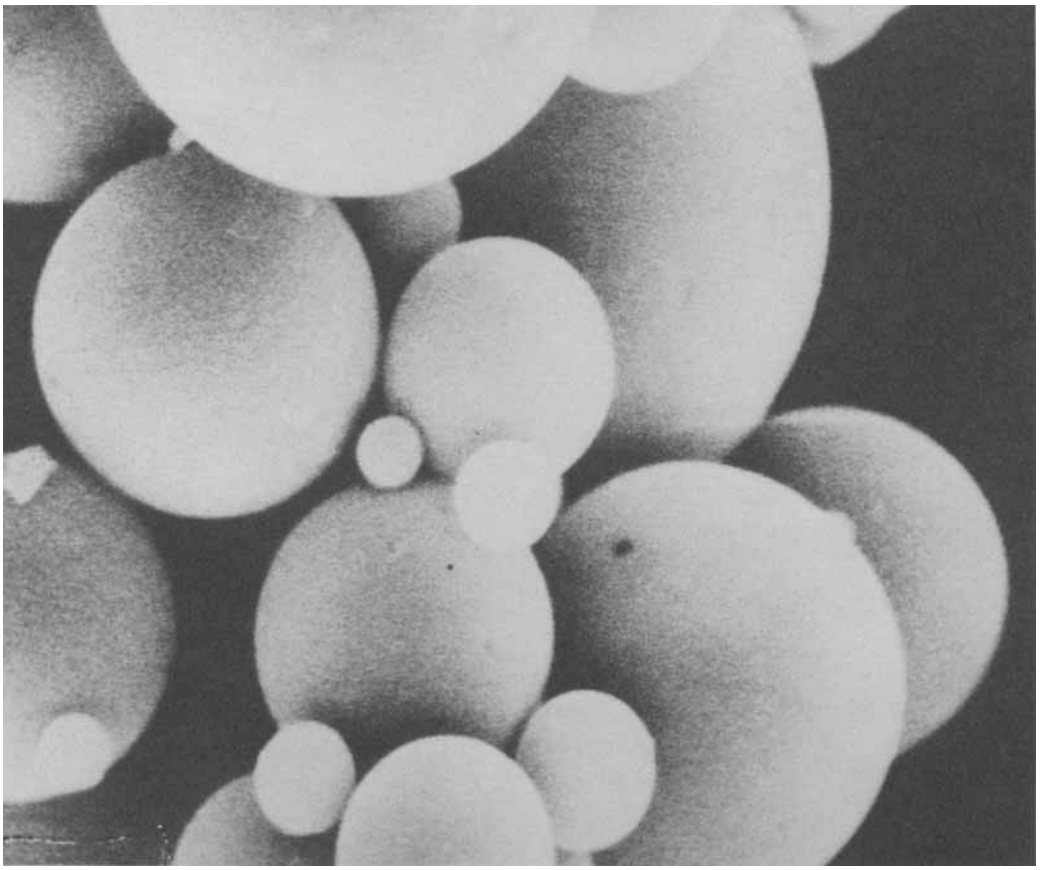

FIGURE 7, PLATE 4

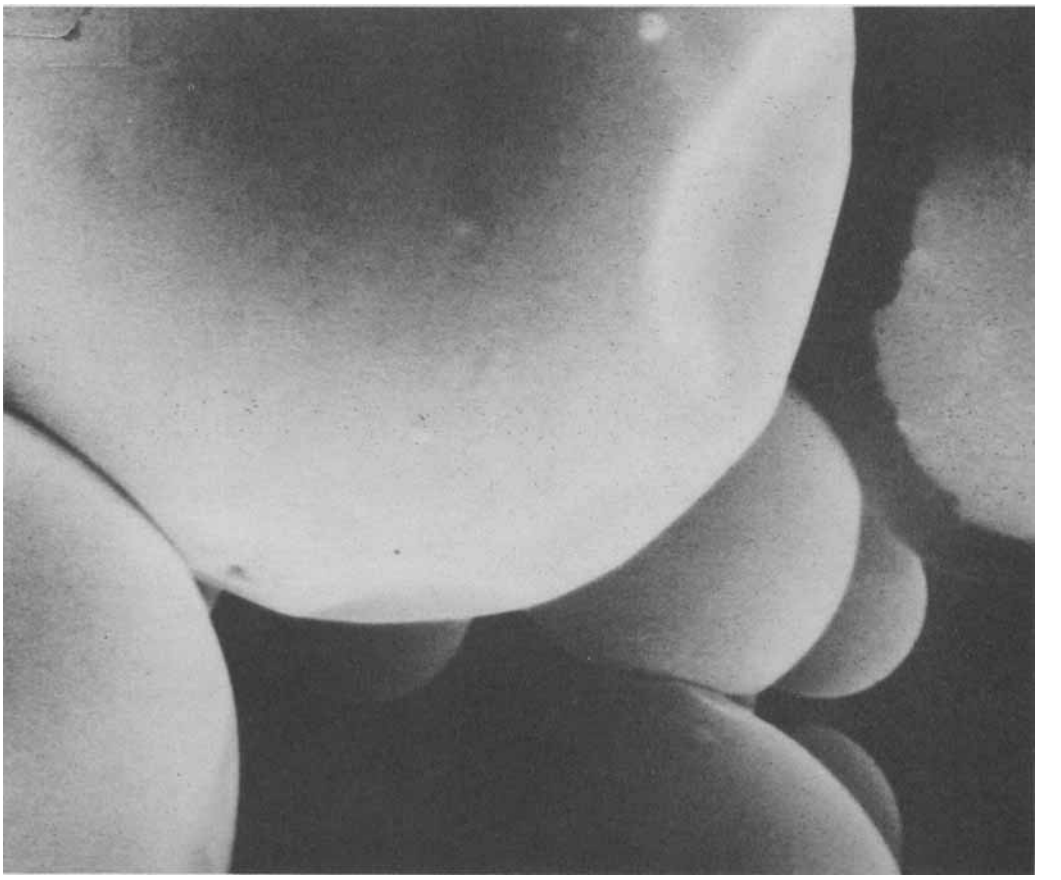

FIGURE 7, PLATE 5

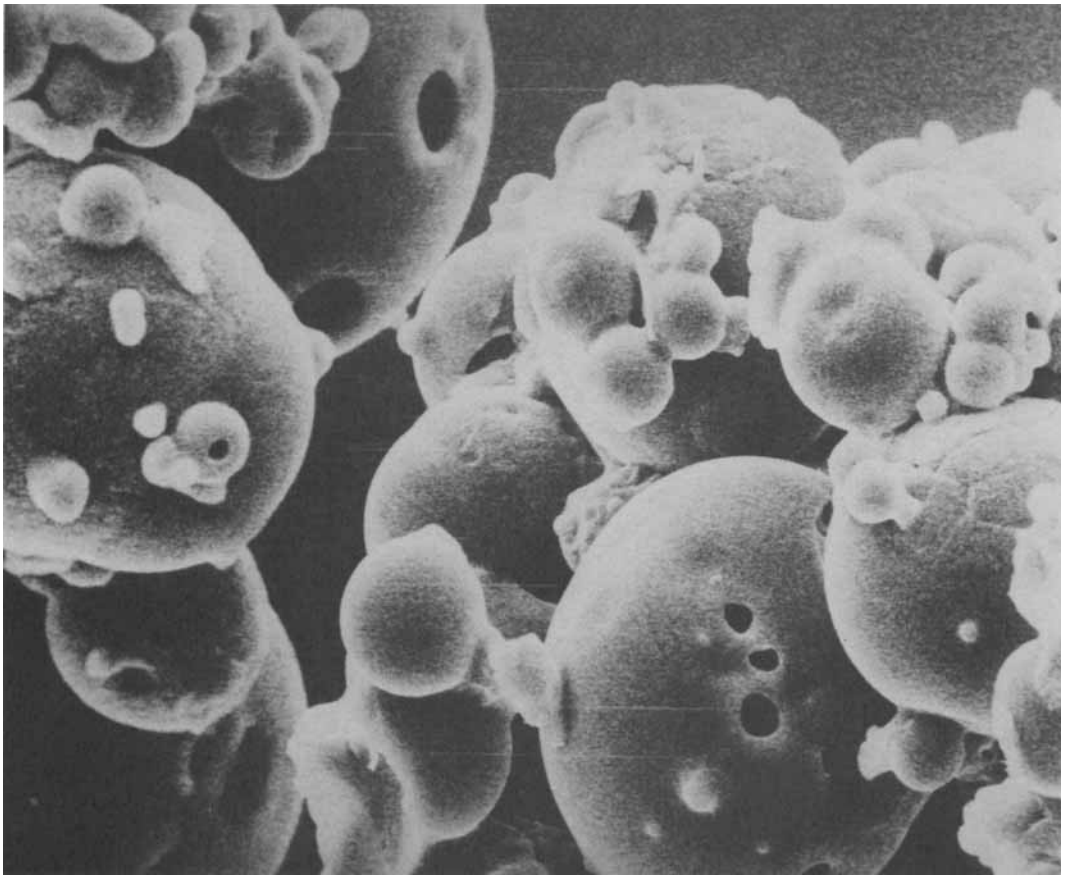

FIGURE 7, PLATE 6

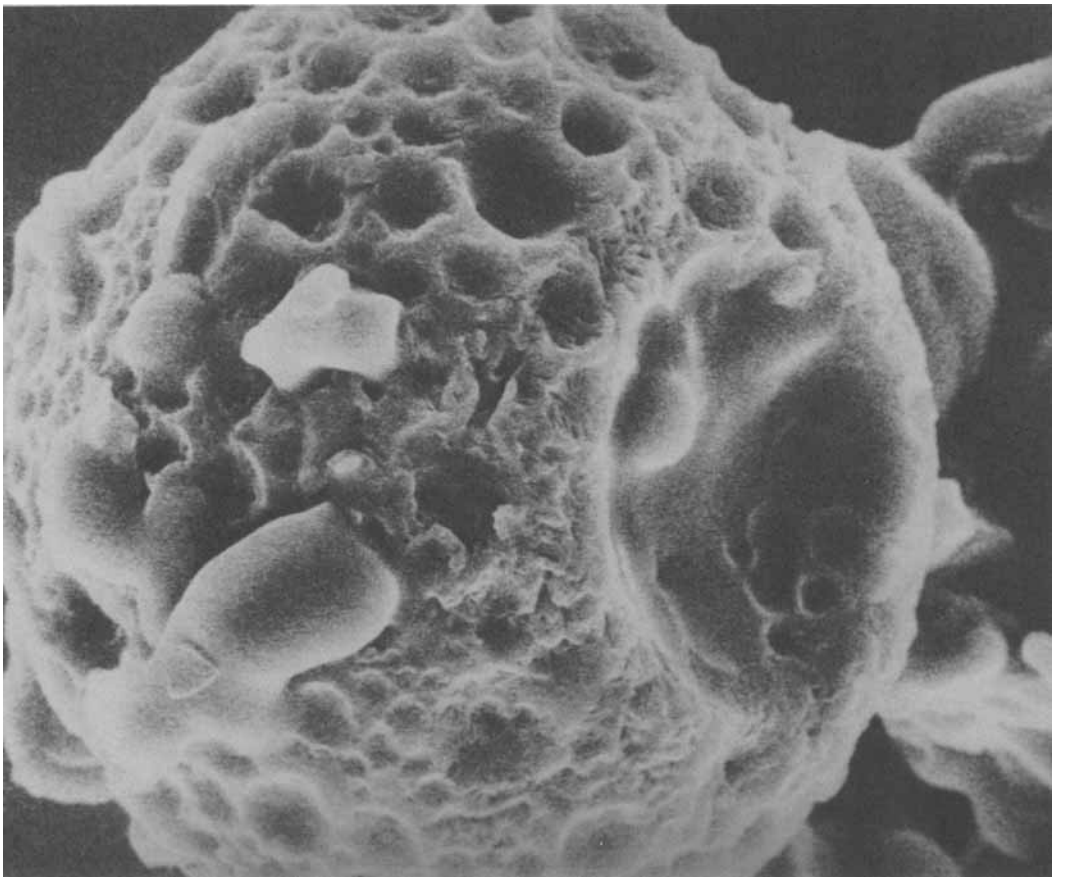

FIGURE 7, PLATE 7

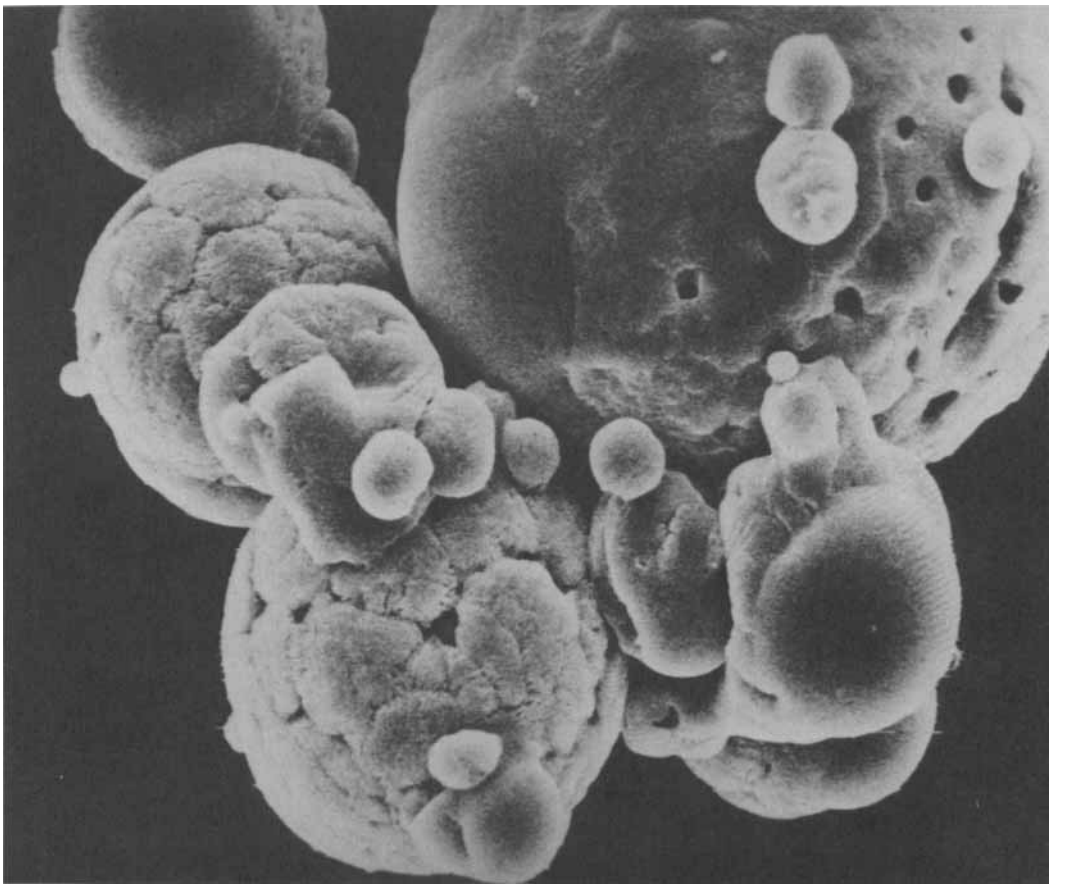

FIGURE 7, PLATE 8

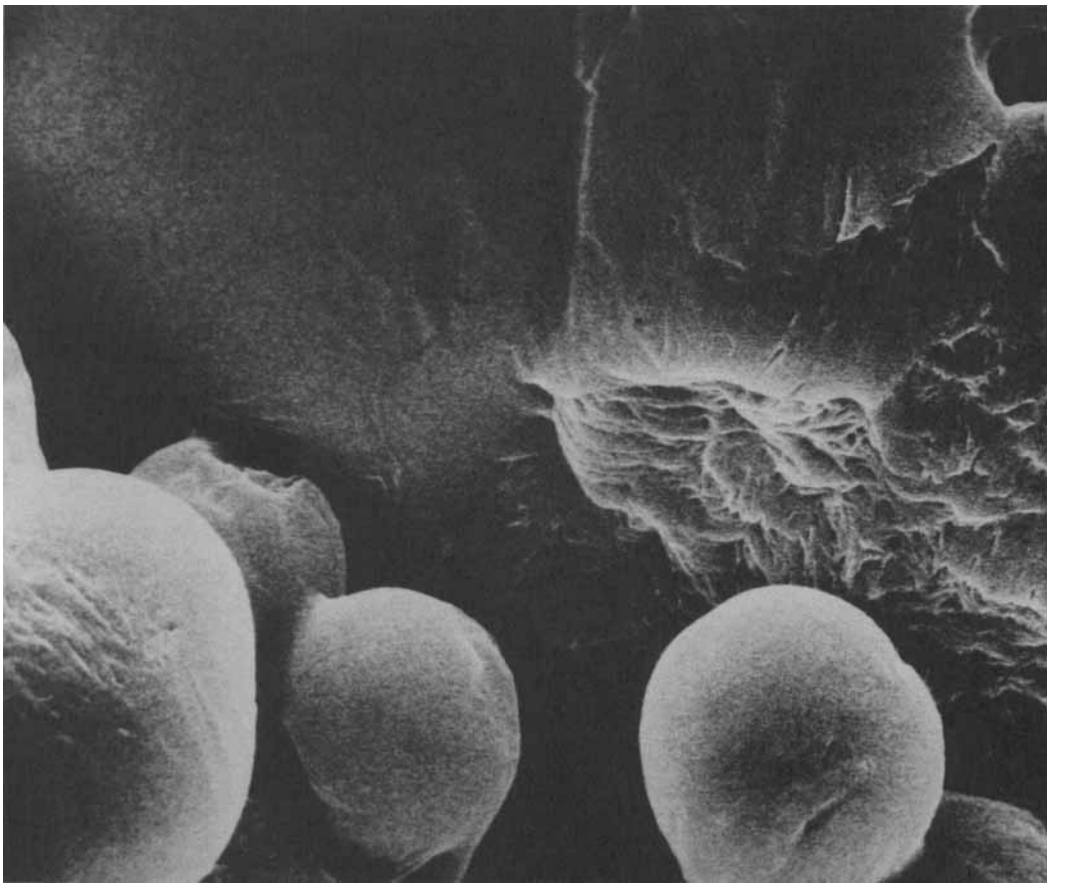

FIGURE 7, PLATE 9

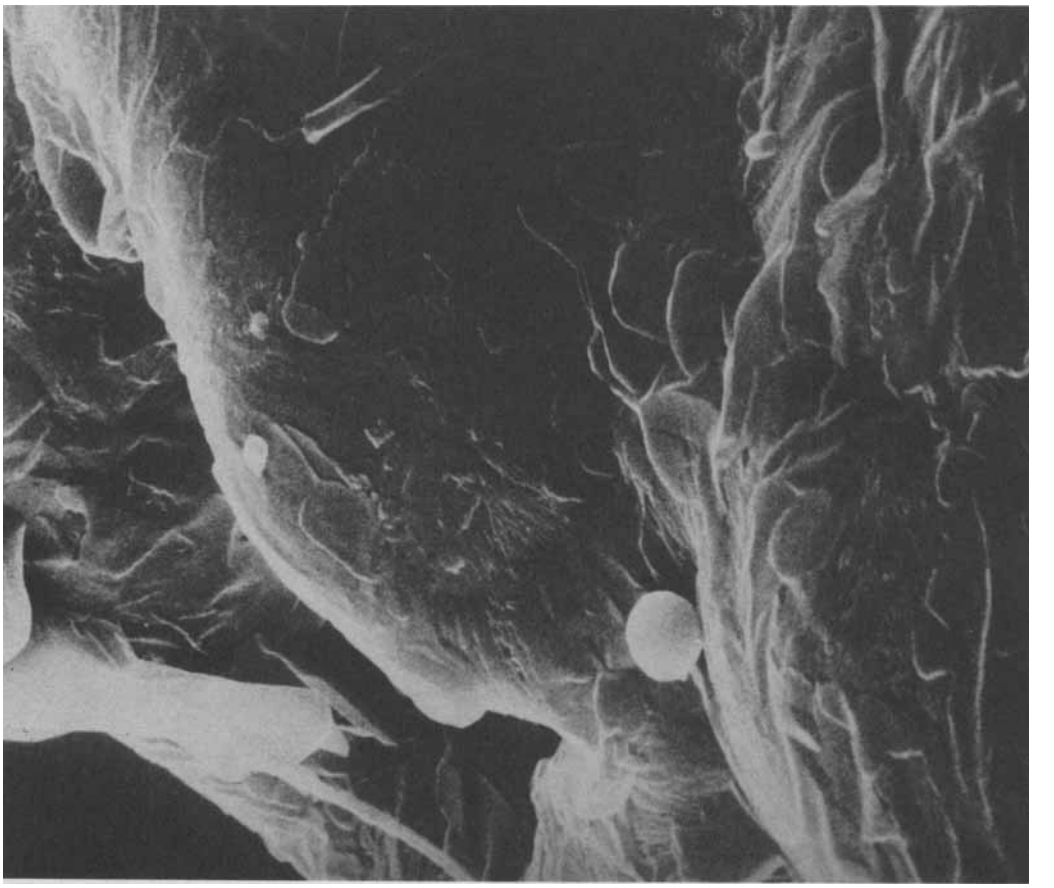

FIGURE 7, PLATE 10

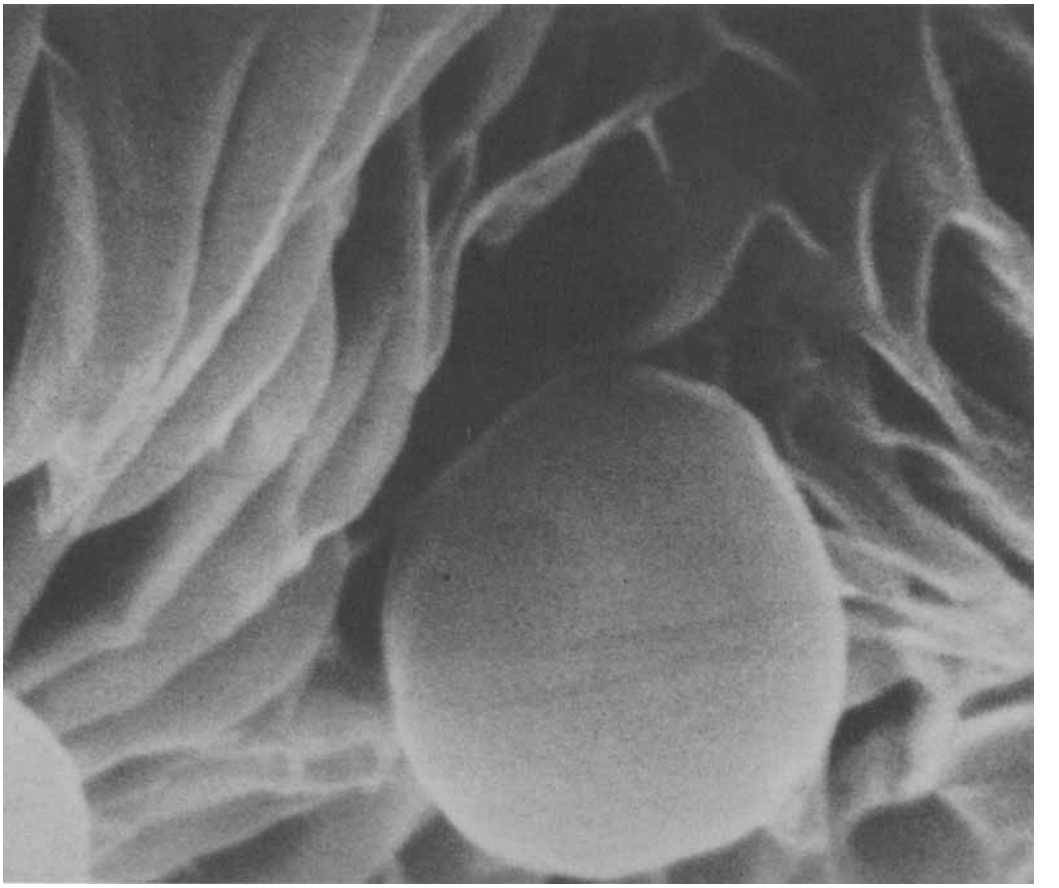

FIGURE 7, PLATE 11

large holes on the surface of polylactide - polycaprolactone (1:1) microspheres. Under higher magnification, surface depression can be seen in plate 7. The cavity structure still remained in polylactide - polycaprolactone (1:3) microspheres (Plate 8). However, no surface depressions were observed under higher magnification (Plate 9). Plates 10 and 11 show polycaprolactone microspheres containing drug. The surface of polycaprolactone microspheres is not smooth, and is comprised of valleys and ridges.

Microcapsules containing polycaprolactone showed greater apparent surface area than those prepared from pure polylactide. The increased surface area is the probable cause for the greater dissolution rates observed with microcapsules containing polycaprolactone.

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