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PREPARATION AND EVALUATION OF CONTROLLED RELEASE INDOMETHACIN MICROSPHERES

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ABSTRACT

Microspheres containing indomethacin were prepared with various combinations of polymers Eudragit RS and Eudragit L. The effects of different ratios of polymers, solvent-polymer ratio, polymer-drug ratio and evaporation temperature on the physical characteristics of the microspheres as well as the in vitro release rate of the drug were investigated. All the factors studied had an influence on the physical characteristics of the microspheres. In vitro dissolution results showed that all formulations gave prolonged release of indomethacin and the release followed apparent zero order kinetics until 80% of drug had been released.

INTRODUCTION

Indomethacin is a non-steroid anti-inflammatory drug for arthritis(1) that is usually administered orally in a conventional capsule form.

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However, this dosage form results in gastrointestinal and central nervous system side effects in some patients. The severity of these side effects seems to be related to the high initial plasma concentration that occurs after ingestion(2). It is probable that a sustained release dosage form would reduce the severity of these effects.

Commercial pharmaceutical forms of acrylic resins are good candidates for the preparation of modified dosage forms because of their inertness, solubility in relatively non-toxic solvents (alcohol), and availability of resins with widely different properties. Although the resins have been used for conventional tablet and particle coating for various reasons, there are no reports in the literature relating to their use to prepare controlled release microspheres of indomethacin.

This report concerns the use of two of these resins, Eudragit RS[1] and Eudragit L[1] to prepare controlled release microspheres with dissolution properties which can be varied by simply changing the ratio of the two polymers. Indomethacin was used as a model drug.

EXPERIMENTAL

Preparation of Microspheres

All microspheres were prepared by an emulsion-solvent evaporation method using an external phase consisting of 270 ml light mineral oil[2] and 30 ml silicone fluid (DC 556)[3]. Sorbitan Trioleate (Span 85)[4] 1% was added to facilitate emulsification. The internal phase consisted of anhydrous alcohol[5], polymer and indomethacin[6]. Polymer, drug and internal phase solvent quantity were varied to obtain microspheres with different properties.

After emulsification, the mixture was cooled in an ice bath and continuously stirred over 6 hours while the temperature gradually

increased to 21°C. Stirring was continued for another 6 hours to evaporate the alcohol solvent.

Four hundred milliliters n-hexane was then added and the mixture filtered to separate the microspheres. The product was washed with two more 400 ml portions of hexane to remove oil from the surface of the microspheres. The microspheres were then dried at room temperature, weighed and separated into size fractions using standard sieves. At least two batches of each formulation were prepared.

Variation of Formulation and Processing Factors

1) Four different ratios of Eudragit RS to Eudragit L (1:1, 1:1.25, 1:1.5 and 1:1.67) were employed to determine the effects on physical characteristics and dissolution properties. In each formulation, the total amount of polymer was 6 g, the amount of drug was 3.5 g and the internal phase was 200 ml.

2) Polymer content was varied (4, 6, 8 and 10 g) while drug content was held constant at 3.5 g and internal phase solvent was 200 ml.

3) Four polymer:drug ratios (1.3:1, 1.7:1, 2.4:1, 3.0:1) were prepared by keeping polymer constant at 6.0 g and varying drug content. Internal phase solvent was constant at 200 ml.

4) Solvent-polymer ratios were varied by keeping polymer constant (6 g) and changing the amount of solvent. Drug content was unchanged at 3.5 g.

Density and Porosity Determination

Densities of the polymers and the drug were determined with the aid of an air comparison pycnometer (Beckman Model 930). Each determination was carried out in triplicate and densities were calculated from the mean of the three determinations.

Theoretical densities and volumes of the microspheres were calculated from the relative proportions of the ingredients (as determined by assay) and their respective densities.

Actual densities of the microspheres including enclosed void spaces were calculated from the weight of the microspheres and the volume as determined by mercury displacement.

Porosity (%) was calculated from

$$\% \text{ Porosity} = \frac{Vg - Vp}{Vg} \times 100$$

where Vg = measured particle volume (mercury displacement)

Vp = theoretical volume = $\frac{M_1}{D_1} + \frac{M_2}{D_2} + \frac{M_3}{D_3}$

M_1, M_2, M_3 are weights of the polymers and drug and D_1, D_2, D_3 are densities of the polymers and drug

Assay Procedures

Total drug content of the microspheres was determined by dissolving accurately weighed portions of each batch in 100 ml methanol and observing the spectrophotometric absorbance at 316 nanometers. It was established that Beer's Law was followed and that the polymers did not interfere with the assay. Triplicate samples were assayed and the mean values reported.

Dissolution aliquots (pH 6.5 phosphate buffer) were analyzed spectrophotometrically at 318 nm after filtration. Absorbance followed Beer's Law over the range of concentrations encountered.

In Vitro Dissolution Studies

Dissolution tests were carried out in standard U.S.P. dissolution beakers containing 900 ml phosphate buffer at pH 6.5 and $37^{\circ} \pm 1^{\circ}C$. Polysorbate 80[4] (.02%) was added to the dissolution fluid to overcome the poor wettability of indomethacin powder and the microspheres. The

solution was stirred at 100 RPM. Accurately weighed samples of microcapsules were used which were calculated to contain 50 mg indomethacin. Five ml aliquots were withdrawn at 10, 20, 30, 60, 90, 120 then hourly intervals up to seven hours. These were spectrophotometrically assayed directly after filtration and returned to the beakers. Each determination was carried out in triplicate.

RESULTS AND DISCUSSION

Effect of Formulation and Processing Variables on Physical Properties

Effect of Polymer Ratio--When the total amount of polymer was held constant but the ratio of Eudragit RS to Eudragit L was varied there was little change in density, porosity or drug loading that could be correlated to the change in polymer ratio (see Table 1). Drug loading was not affected by polymer ratio, but was consistently slightly lower than theoretical loading.

Effect of Polymer Content--Variation of total polymer while solvent and drug were held constant resulted in a noticeable change in particle size of the microspheres. Table 2 shows that as total polymer increased, particle size also increased. This can be attributed to the greater viscosity of the solutions with higher polymer content. Assayed drug content averaged about 3% less than theoretical and did not appear to be affected by polymer content in the range tested.

Changing the polymer content while maintaining the solvent constant resulted in a change in solvent:polymer ratio which ranged from 10:1 to 50:1 in this series of experiments. As noted in Table 2, porosity increased as the solvent polymer ratio increased. When the solvent polymer ratio was further increased (by increasing the amount of solvent) this trend continued. At 83:1 very friable microspheres were produced

Table 1

EFFECT OF POLYMER RATIO ON DENSITY, POROSITY AND DRUG LOADING

Polymer Ratio[a] RS : L	Density g/cm^3		Porosity %	Theoretical Drug Content[b] %	Assay Drug Content % ± S.D.
	Theoretical	Actual			
1.00 : 1	1.203	0.737	35.6	36.8	34.4 ± 0.3
1.25 : 1	1.203	0.863	25.0	36.8	34.6 ± 0.0
1.50 : 1	1.203	0.759	35.5	36.8	34.4 ± 0.2
1.67 : 1	1.203	0.712	40.5	36.8	34.4 ± 0.3

[a] Total polymer constant at 6.0 grams, solvent volume constant at 200 ml (Solvent/Polymer Ratio = 33.3/1)

[b] Indomethacin starting quantity 3.5 grams

Table 2

EFFECT OF POLYMER CONTENT ON MICROSPHERE CHARACTERISTICS

Polymer Content[a] grams	Solvent/Polymer Ratio	Porosity %	Particle Diameter[b] µm ± S.D.	Theoretical Drug Content %	Assayed Drug Content %
4.0	50/1	42.7	140 ± 21	46.7	43.2
6.0	33.3/1	35.6	207 ± 41	36.8	34.4
8.0	25.0/1	40.2	242 ± 67	30.4	26.8
10.0	20.0/1	31.0	295 ± 70	25.9	24.1

[a] Solvent volume and drug quantity were held constant to 200 ml and 3.5 grams respectively while total polymer was varied. The ratio of Eudragit RS to L was constant at 1:1.

[b] Determined microscopically, at least 250 particles counted.

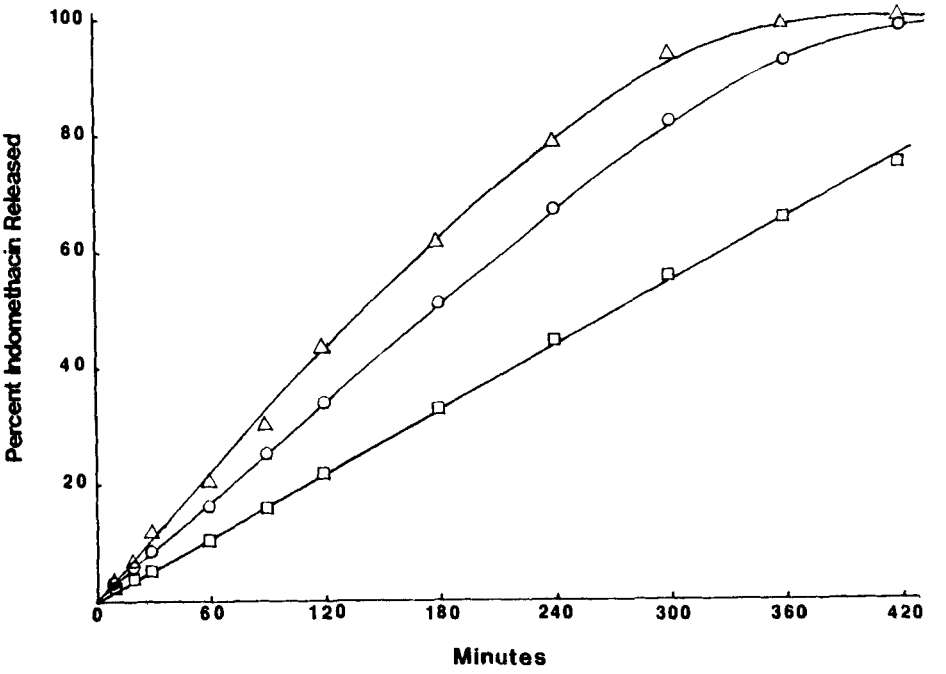

FIGURE 1

Effect of Particle Size on Dissolution Rate Profiles of Indomethacin Microspheres[a].

Key: □ 505 microns

○ 359 microns

△ 273 microns

[a] Eudragit RS to Eudragit L, 1 : 1.5 (6 gm total)

but not tested; at 100:1 it was not practical to produce microspheres.

Effect of Formulation and Other Variables on Dissolution

Particle Size--Figure 1 shows dissolution curves of three sizes of microspheres, 273, 359 and 505 μm. The dissolution rates are inversely related to the particle size as would be expected from surface area relationships. A plot of particle size versus time 50% release (T_{50}) in

Figure 2 indicates a nearly linear relationship between T_{50} and particle size over the range tested.

Effect of Variation of Polymer Ratio--Drug release from plastic matrices can be increased by the addition of water soluble inert substances (3). Therefore, it would be reasonable to expect that the addition of Eudragit L (which is soluble in buffer pH 6 and higher) to Eudragit RS (which is a water insoluble plastic material) would increase the release of drug from the microspheres. Figure 3 is a plot of cumulative percent of indomethacin released as a function of time. All indomethacin microspheres released the drug more slowly than the indomethacin powder.

The in vitro dissolution of the drug was zero order until about 80% of the drug was released. The dissolution half life ranged from 2.5 hours for the 1:1.67 ratio of Eudragit RS to Eudragit L to 7.5 hours for a polymer ratio of Eudragit RS to Eudragit L of 1:1. The total amount of drug released from the microspheres increased as the concentration of Eudragit L increased. The total amount of drug released from polymer ratio of 1:1.67 Eudragit RS to Eudragit L microspheres during the first three hours was approximately three times greater than that from the 1:1 polymer ratio in the matrix. The increase in release rate of the drug caused by increasing the Eudragit L concentration probably makes available more channels for diffusion, and in this way increases the effective porosity in the polymer matrix. The zero order release rates were 10.32, 8.31, 4.14 and 2.94 mg per hour for the microspheres prepared from Eudragit RS to Eudragit L ratios of 1:1.67, 1:1.50, 1:1.25 and 1:1, respectively.

Effect of solvent-polymer ratio

The dissolution profiles of microspheres prepared with different

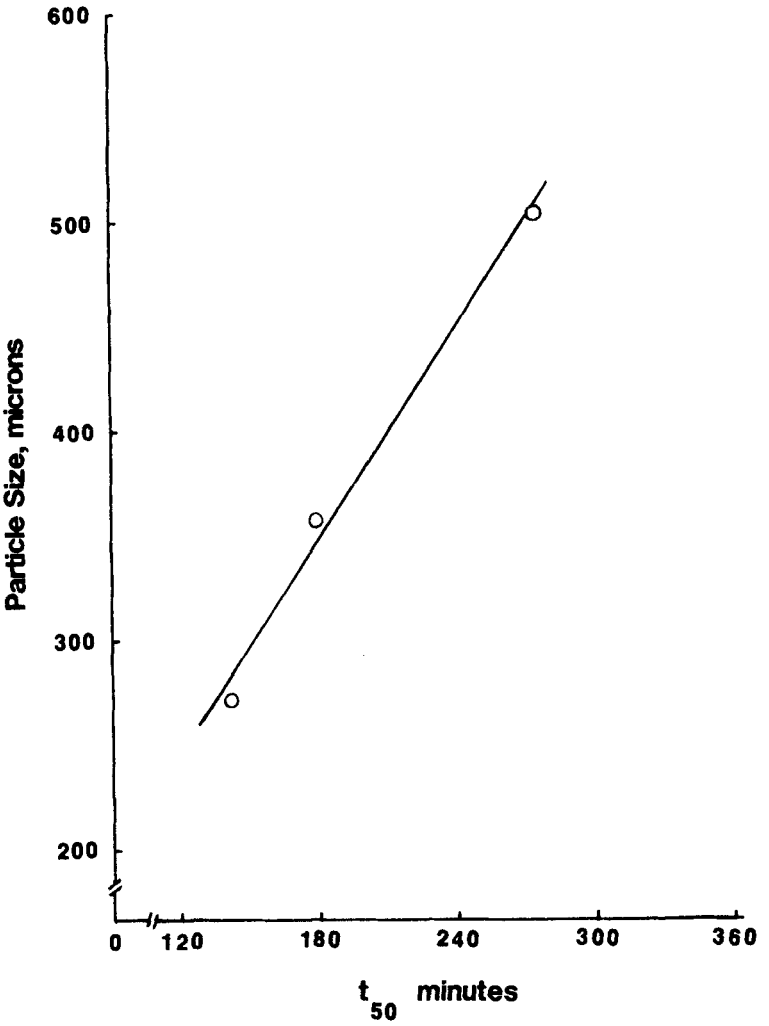

FIGURE 2

Effect of Particle Size on the In Vitro t_{50} of Indomethacin Microspheres[a].

[a] Eudragit RS to Eudragit L, 1 : 1.56 (6 gm total)

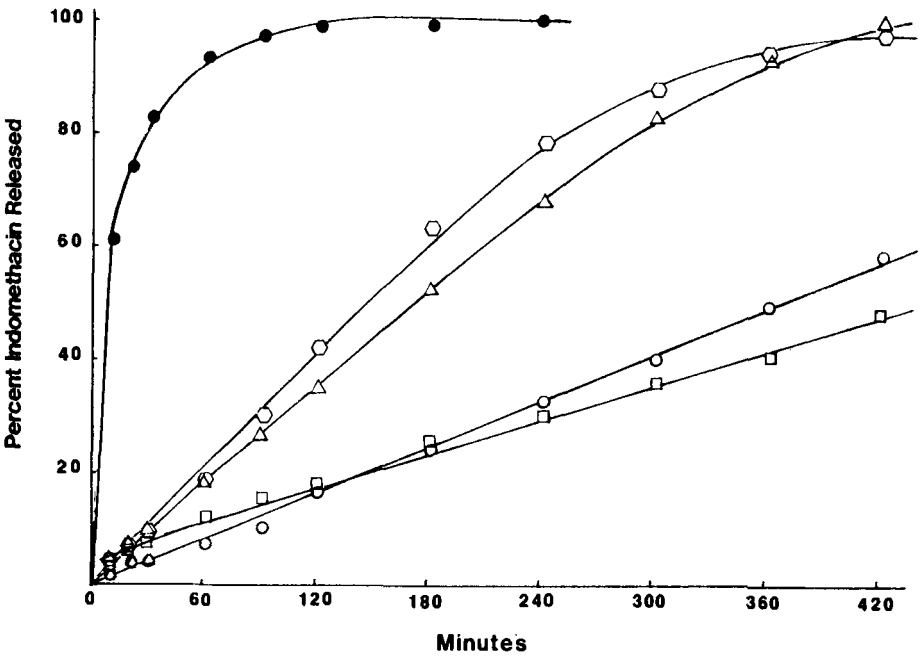

FIGURE 3

Effect of Different Polymer Ratios on Dissolution Rate Profiles of Indomethacin Microspheres[a].

Key: ● Indomethacin powder

⬡ Eudragit RS to Eudragit L, 1 : 1.67

△ Eudragit RS to Eudragit L, 1 : 1.50

○ Eudragit RS to Eudragit L, 1 : 1.25

□ Eudragit RS to Eudragit L, 1 : 1.00

[a] Constant quantity of polymer of 6 gm

solvent-polymer ratios are shown in Figure 4. With the exception of the 25.0:1 ratio, the release rate of indomethacin increased as the solvent-polymer ratio increased. These results were due to the increase in porosity resulting from the increase in solvent-polymer ratio as shown in Table 2.

The *in vitro* t_{50} is the time for 50% of the indomethacin to dissolve and has been suggested to be the best *in vitro* variable for correlation to *in vitro* activity (4). Table 3 shows the t_{50} for various batches of microspheres and Figure 5 is a plot of t_{50} as a function of porosity. A nearly linear relationship is shown.

Effect of polymer-drug ratio on dissolution rate

The effect of polymer-drug ratio on the release rate profiles is shown in Figure 6. All formulations gave nearly zero-order release rates during the first 5 hours of the dissolution period. The rate of

Table 3

A Comparison of the *In Vitro* t_{50} for Various Batches of Microspheres

Solvent-polymer ml/gm	t_{50} min	Porosity %
Drug powder	10.2	-
50.0/1	52.8	61.7
33.3/1	145.2	40.5
25.0/1	210.0	31.5
20.0/1	177.0	37.2

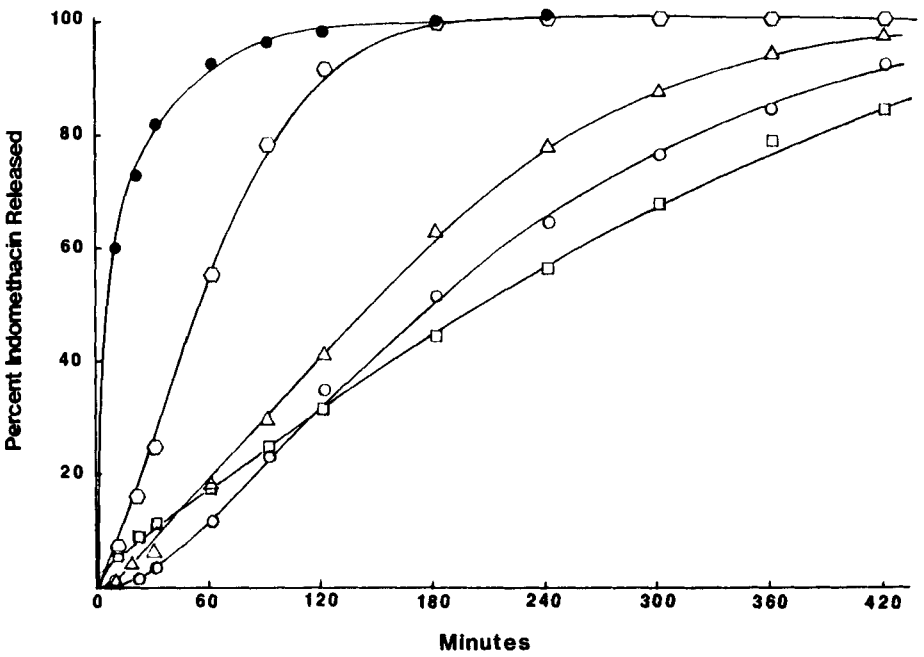

FIGURE 4

Effect of Solvent-Polymer Ratio on Dissolution Rate Profiles of Indomethacin Microspheres[a].

Key: ● Indomethacin powder

⬡ Solvent-polymer ratio, 50.0 : 1

△ Solvent-polymer ratio, 33.3 : 1

□ Solvent-polymer ratio, 25.0 : 1

○ Solvent-polymer ratio, 20.0 : 1

[a] Eudragit RS to Eudragit L, 1 : 1 (6 gm total)

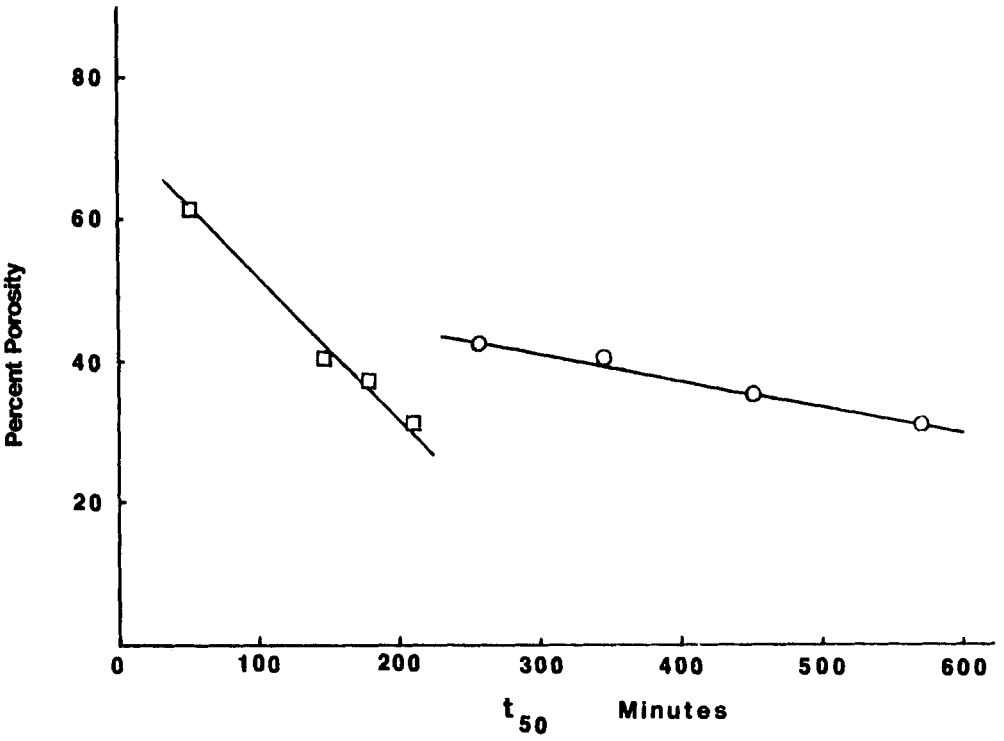

FIGURE 5

In Vitro t_{50} as a Function of Granule Porosity of Indomethacin Microspheres Prepared with Constant Polymer Ratio.

Key: □ Eudragit RS to Eudragit L, 1 : 1.67

○ Eudragit RS to Eudragit L, 1 : 1.00

release was in the range of 7.60 to 8.80 mg per hour. These results indicated that the effect of polymer-drug ratio on release rate is not significant.

Matrix systems generally do not display zero-order release kinetics. The rate of release from a planar matrix is usually proportional to the square root of time (5) while the release from spherical matrixes has

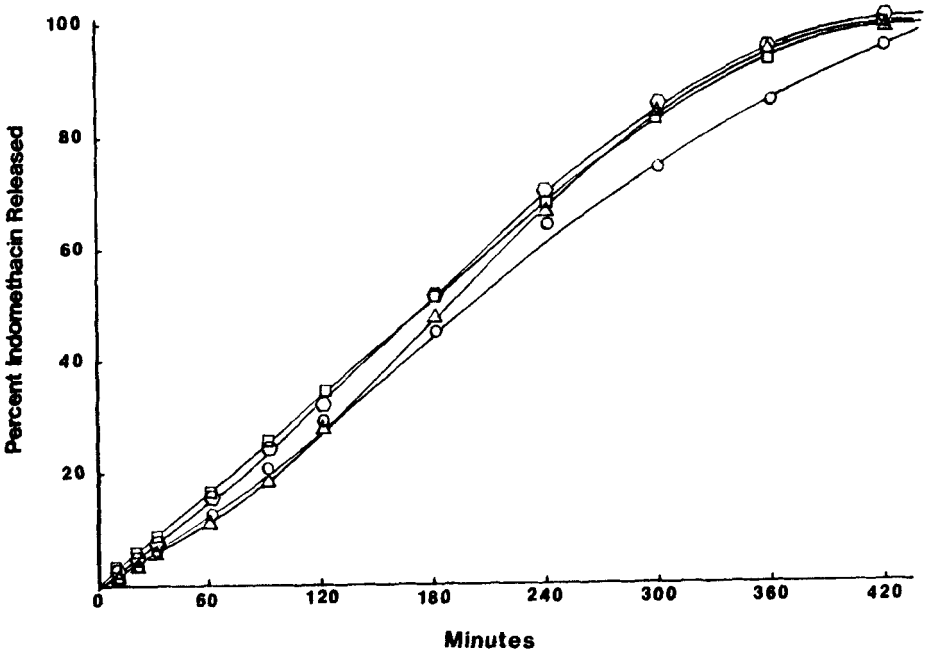

FIGURE 6

Effect of Polymer-Drug Ratio on Dissolution Rate Profiles on Indomethacin Microspheres[a].

Key: ○ Polymer-drug ratio, 3.0 : 1

⬡ Polymer-drug ratio, 2.4 : 1

□ Polymer-drug ratio, 1.7 : 1

△ Polymer-drug ratio, 1.3 : 1

[a] Eudragit RS to Eudragit L, 1 : 1.5 (6 gm total)

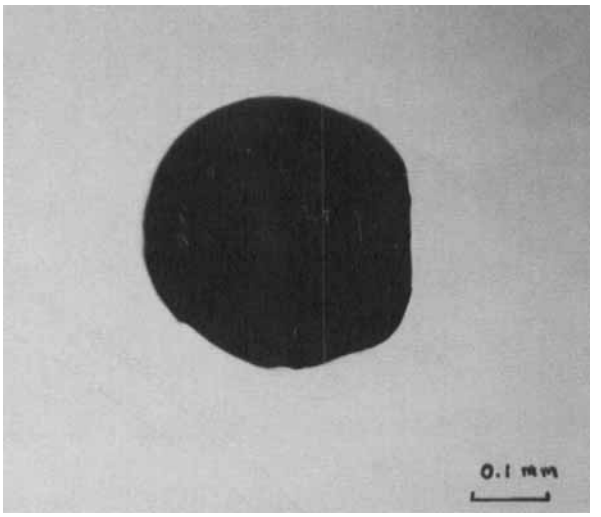

FIGURE 7

Photomicrograph of Microsphere Containing Indomethacin Before Being Placed in Dissolution Medium

been described by Baker & Lonsdale (6). Non-zero order release in matrix systems can be attributed to the changing distance the drug must travel from within the matrix to the matrix surface. Since this diffusional distance increases with time, the release rate decreases. However, release of the drug from the matrix system reported here was zero-order until about 80% of the drug dissolved. In this case, the matrix system consisted of the swellable polymer, Eudragit RS and the water soluble polymer, Eudragit L. Water penetrates into the microsphere, hydrating and dissolving the polymers and also dissolving the drug, which then diffuses out through the hydrated matrix. The swelling of polymers in the dissolution medium resulted in increasing the porosity, thus compensating for what would normally be seen as a decreased release rate with time.

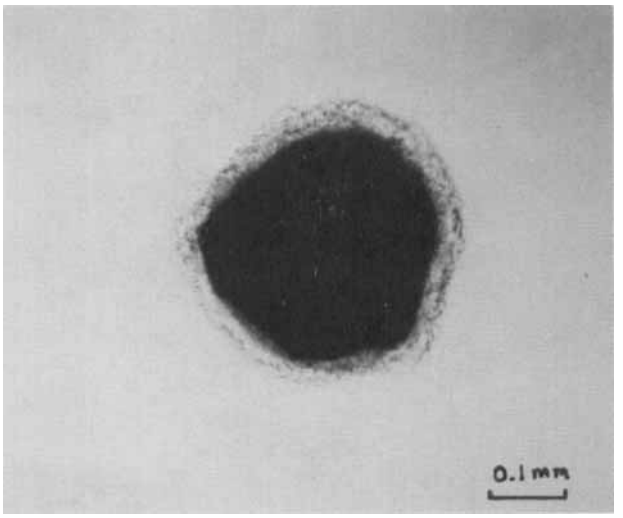

FIGURE 8

Photomicrograph of Microsphere Containing Indomethacin One Hour After Being Placed in Dissolution Medium

Alternatively, the swollen polymer may have behaved as a rate limiting membrane for the dissolution of the drug in the interior of the microcapsule.

The swelling of the matrix system can be seen in the series of photographs (Figures 7-10) which were taken with an optical microscope during dissolution studies. Figure 7 displays the microsphere before being placed in to the dissolution medium. Figure 8 shows the microsphere after being in the dissolution medium for 1 hour. As the drug dissolved and diffused from the matrix, a clear annular zone appeared. Figure 9 was made after microsphere had been in the dissolution medium for 5 hours. The clear annular zone increased as more drug was released from the matrix. Figure 10 shows the spherical matrix remaining after the drug had diffused out. The spherical matrix remained intact but

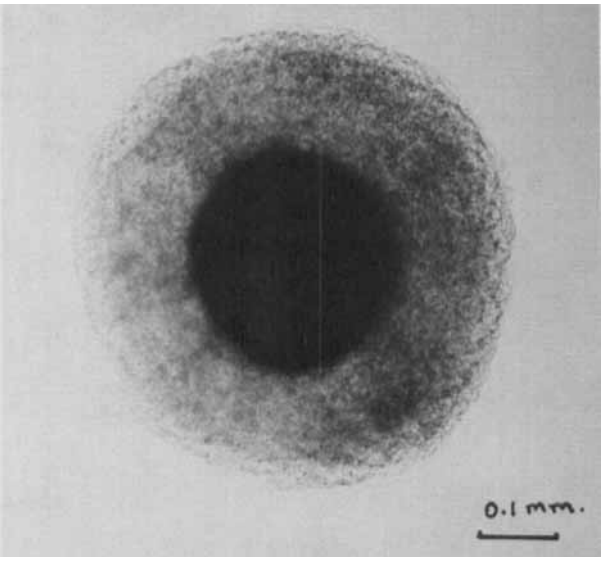

FIGURE 9

Photomicrograph of Microsphere Containing Indomethacin Five Hours After Being Placed in Dissolution Medium

swelled to approximately two times its original diameter during the course of the dissolution experiments.

In summary, it was determined that particle size of the microspheres and also changes in the ratio of the two polymers and the solvent-polymer ratio influenced on drug release from the microspheres. Variations in the polymer-drug ratio had no significant effect on indomethacin dissolution. For a given polymer combination, the differences in dissolution results from different formulations were related mainly to changes in porosity.

FOOTNOTES

1. Rohm Pharma - GMBH

2, Fisher Scientific Company - Fairlawn, N.J.

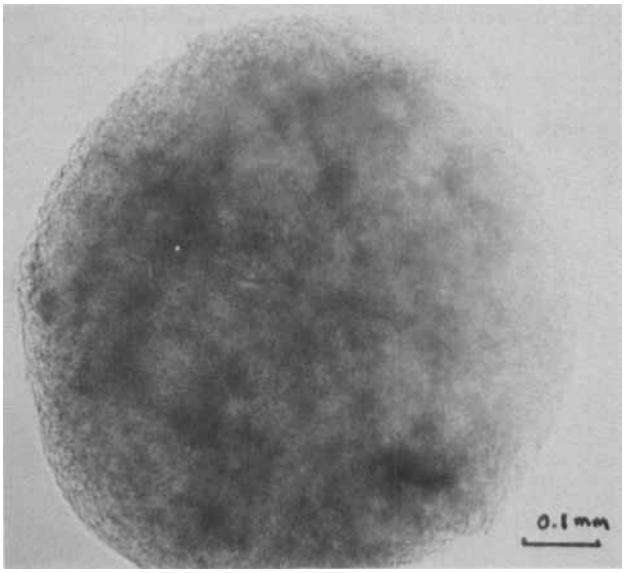

FIGURE 10

Photomicrograph of Microsphere Containing Indomethacin Seven Hours After

3. Ruger Chemical - Irvington, N.J.
4. ICI United States, Inc. - Wilmington, DE
5. U.S. Industrial Chem. - New York, N.Y.
6. Merck, Sharpe and Dohme - West Point, PA

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