DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(7), 1121-1145 (1994)

PREPARATION OF A CONTROLLED RELEASE DRUG DELIVERY SYSTEM OF INDOMETHACIN

Shun Por Li[1,2], Kenneth M. Feld[1] and Chana R. Kowarski[2]

[1]Pharmaceutical Research and Development Division,
Rorer Central Research, Rorer Pharmaceutical Corp.,
Fort Washington, PA 19034

[2]Department of Pharmacy, School of Pharmacy,
Temple University, Philadelphia, PA 19140

ABSTRACT

The preparation of a sustained release dosage form for indomethacin was studied. Pellets (I) containing indomethacin were prepared by spraying a slurry of indomethacin, Eudragit® S-100, dibutyl sebacate and alcohol onto non-pareil seeds via Wurster column processing. The resultant pellets were further coated with various combinations of Eudragit® RS (poorly water permeable) and Eudragit® RL polymers (readily water permeable) also using the Wurster column. In-vitro dissolution tests were conducted in a USP dissolution apparatus containing 900 ml of phosphate buffer at either pH 6.5 or 7.2. The in-vitro release studies of pellets (I) at pH 6.5 phosphate buffer exhibited a $\sqrt{T}$ dependence indicating a diffusion controlled process from a matrix formulation. At pH 7.2 phosphate buffer, pellets coated with Eudragit® RS showed the most retardation in the release rate of drug. As expected, the total amount of drug released

from the coated pellets increased as the concentration of Eudragit® RL increased in the barrier coating. Pellets coated with Eudragit® RL alone showed the fastest release rate of drug.

INTRODUCTION

Indomethacin has been used in the treatment of rheumatoid arthritis for more than a decade. Owing to its relatively short plasma half-life, the usual dosage schedule is to give the dose three times a day.[1,2] Patients taking the conventional capsule often complained of gastrointestinal and central nervous system side effects. The severity of the centrally-medicated side effects is related to the plasma concentration occurring after administration of the dosage form.[3,4] Indomethacin delivered by a sustained release dosage form would be an ideal means of reducing the unwanted side effects by reducing and/or delaying the peak plasma concentration without affecting the extent of indomethacin bioavailability.

In reviewing the pharmaceutical literature, a few methods have been investigated for the preparation of sustained release indomethacin. Sustained release indomethacin microspheres, prepared by different types of microencapsulation techniques, have been studied extensively.[5,6,7,8] There are several references dealing with the manufacture of sustained release indomethacin tablets.[9,10,11] Among all the mechanical methods

dealing with the preparation of sustained release indomethacin formulations, the most interesting and practical method was reported by Dempski et al.[12] They prepared sustained release indomethacin pellets via an extrusion/spheronization process.

It is interesting to note that there are no reports in the literature relating to the use of a layering process via a Wurster column to produce sustained release indomethacin pellets. Hsiao successfully prepared sustained release theophylline pellets utilizing the Wurster column process.[13]

This report concerns the use of Eudragit® resins to prepare sustained release indomethacin pellets via a Wurster column process. In addition, the in-vitro release rate profiles of these indomethacin sustained release pellets are compared to Indocin® SR (commercially available indomethacin sustained release capsule) to assess the value of this particular manufacturing process.

EXPERIMENTAL

Materials

Indomethacin[a] and polyethylene glycol 8000[b] were NF grade. Talc[c], non-pareil seeds[d] (18/20 mesh) and alcohol were USP grade. Dibutyl sebacate[e] was used as received. Eudragit® S-100[f], RS[f], and RL[f] were gifts from Rohm Pharma. All reagents were analytical grade or better. Indocin®

25 mg capsules[g] and Indocin® SR 75 mg capsules[g] were used as received.

Preparation Methods for Indomethacin Sustained Release Pellets

Preparation of Indomethacin/Eudragit® S-100/Alcohol Slurry

To a two-liter stainless steel container holding 500 g of alcohol equipped with a lightning mixer, 6.8 g of dibutyl sebacate was added and mixed. Sixty-eight grams of Eudragit® S-100 were added gradually into the container and mixed until all the Eudragit® S-100 powders were dispersed. Three hundred grams of indomethacin was then introduced and mixed until all powders were dispersed. The resultant slurry was then passed through a Colloid mill[h]. The slurry was then filled to 1080 g total weight with additional alcohol. The solids content of the slurry was 34.6% w/w.

Preparation of Indomethacin-Eudragit® S-100 Pellets (IS Pellets)

Pellets containing indomethacin were prepared by spraying the indomethacin/Eudragit® S-100/alcohol slurry onto 500 grams of the 18/20 mesh fractions of nonpareil seeds via the Wurster column (Aeromatic Strea-1 Coater[i]). The coating parameters for this process are given in Table I. The resultant pellets were dried at 50°C for 32 hours to remove the residual solvent from the pellets.

Coating Operation of Indomethacin Sustained Release Pellets

Seven hundred grams of indomethacin Eudragit® S-100 pellets were coated in an Aeromatic S-1 coater using either Eudragit® RS

TABLE I

GENERAL OPERATING PARAMETERS OF THE AEROMATIC S-1 COATER AND THE SETTINGS DURING THE MANUFACTURING OF INDOMETHACIN EUDRAGIT® S-100 PELLETS

Operating Parameters	Setting
Atomizing air pressure	2 Bars
Fluidizing air velocity	30 - 60 M^3/H
Partition Height	2 cm
Pump/Drive	Masterflex 16 Pump Head[j]
Nozzle	1.2 mm Schnick nozzle[k]
Inlet Temperature	52 - 56°C
Outlet Temperature	34 - 36°C
Flow Rate of coating solution	10 - 20 g/min

or RL polymers or a combination of RS and RL polymers. The composition for the dispersions are presented in Table 2. Different amounts of the Eudragit® RS or RL coatings were applied to IS pellets by spraying predetermined amounts of the coating dispersion onto the pellets. Five different ratios of Eudragit® RS to Eudragit® RL (100:0, 75:25, 50:50, 25:75, 0:100) were prepared to determine the effects on indomethacin dissolution rates. In all, a total of 20 samples were collected for testing and evaluation.

Testing

Sieve Analysis

The size distribution of the IS pellets was evaluated by a sieve-analysis technique using a set of US standard sieves, namely #12, #14, #16, #18, #20, #25 and base pan. The sieving load was 10 g. The sieve nest was shaken using an ATM Sonic

TABLE 2

COMPOSITION OF EUDRAGIT® RS AND/OR RL DISPERSION

	Wt. (g)
Eudragit® RS or RL	6.0*
Talc, USP	1.8
Polyethylene Glycol 8000, NF	0.6
Alcohol, USP	86.6
Distilled Water	5.0

*$|X_i + Y_i| = 6$ where X_i is equal to the amount of Eudragit® RS, and Y_i equal to the amount of Eudragit® RL.

Sifter[1] for five minutes. The net weight that was retained on each sieve was then determined and recorded. Duplicate samples were run for each batch of IS pellets. The average values were used for the calculation of particle size distribution. The arithmetic mean diameter of IS pellets was determined from the sieve analysis as discussed by Parrott[14].

True Density

The true density of each sample of IS pellets was determined by using a solvent displacement method.

Assay Procedures

Total drug content of the IS pellets was determined by dissolving accurately weighed portions of each batch in 100 ml methanol and observing the spectrophotometric absorbance at 318 nanometers (λmax for indomethacin). Duplicate samples were

assayed and the mean values reported. Absorbance followed Beer's Law over the range of concentrations encountered. The same procedures were followed to determine indomethacin content in the RS and/or RL coated pellets.

In-Vitro Dissolution Studies

The dissolution tests were conducted using apparatus II, USP XXI/NF XVI with paddles. An agitation speed of 100 rpm was used in this study. An amount of indomethacin sustained release pellets containing 75 mg of indomethacin were used with 900 ml of dissolution medium at 37°C. The dissolution medium consisted of either pH 6.5 or 7.2 phosphate buffers. Samples were removed at suitable time intervals. The collected samples were assayed spectrophotometrically using a Beckman DU®-6 Spectrophotometer™ at 318 nm for indomethacin content. Each determination was carried out in triplicate.

RESULTS AND DISCUSSION

Physical Properties of Indomethacin Eudragit® S-100 Pellets (IS Pellets)

Table 3 shows that the Wurster column coating process is a reproducible means of preparing indomethacin sustained release pellets. The true density values, assay values of Indomethacin content in the finished pellets, and the yield of pellets for five batches of IS pellets were similar. Furthermore, the

TABLE 3

Physical Properties and Physical Testing Data for Five Batches of IS Pellets

Batch No.	Yield of the Process(%)	Assay Drug Content (%)	$\frac{\text{Actual Assay}}{\text{Theoretical Assay}} \times 100(\%)$	True Density (g/ml)	Particle Size Distribution 14/16 mesh	16/18 mesh	18/20 mesh	Mean Particle Diameter (Microns)
1	89.9	27.3	79.5	1.22	74.9	24.5	0.6	1239
2	89.3	27.1	79.0	1.18	73.7	25.1	1.2	1235
3	88.8	27.2	79.4	1.19	80.5	19.0	0.5	1250
4	89.1	27.4	79.8	1.21	80.8	18.3	0.9	1250
5	89.3	26.7	77.9	1.20	78.1	21.0	0.9	1240

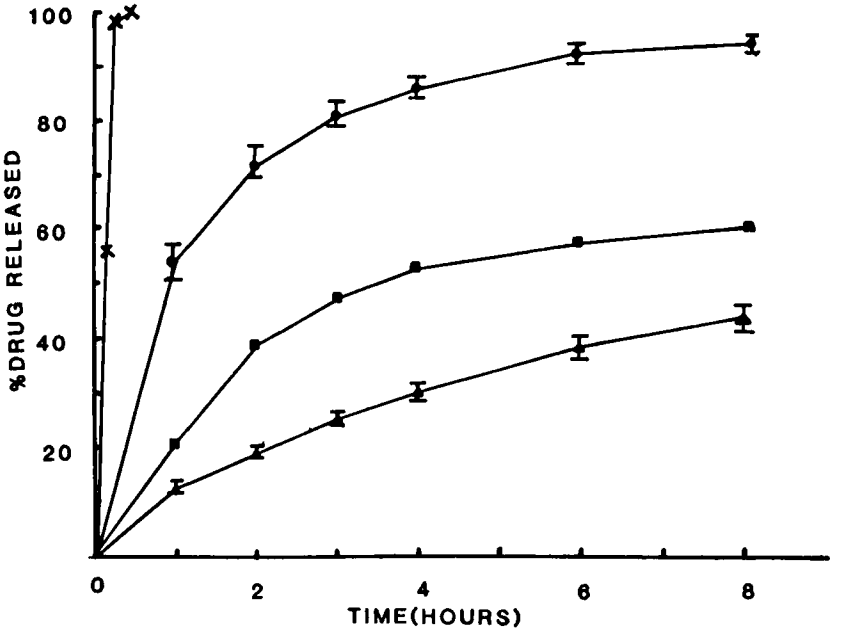

FIGURE I

Cumulative Amount (%) of Indomethacin released from two sustained release formulations in pH 6.5 Phosphate Buffer.

Key :
- X Indocin® 25 mg capsule
- • Indocin® SR 75 mg capsule
- ■ Sustained Release portion of Indocin® SR 75 mg capsule
- ▲ Indomethacin Eudragit® S-100 Pellets (Each point represents mean ± SD of five batches of IS pellets valves)

particle size distribution for these five replicate batches of IS pellets also demonstrated that the process is reproducible. Ninety-nine percent of the finished pellets were found on a 14/18 mesh cut. The average pellet diameters ranged from 1235 to 1250 microns. These data indicate that the process is very reproducible for preparing the IS pellet.

In-Vitro Release Rates from Indomethacin Eudragit® S-100 Pellets (IS Pellets)

Figure 1 shows a plot of cumulative percent indomethacin released from the five replicate batches of IS pellets and from commerically available indomethacin products in pH 6.5 phosphate buffer. The standard deviations for the release rate data for the five batches of IS pellets were very small indicating that the coating process was very reproducible.

The release rate profile of the IS pellets was much slower than the commercial indomethacin capsules. This indicated that the IS pellets exhibited sustained release characteristics. As can be seen from Figure 1, 44% of the total drug content was released at the end of 8 hours.

These in-vitro release rate data were examined according to Higuchi's model[15]. As can be seen from Figure 2, all five replicate batches of IS pellet exhibited a $\sqrt{T}$ dependence illustrating release from a typical matrix formulation. The correlation coefficient for the release of indomethacin on the basis of the Higuchi matrix model was $r^2 = 0.9997$.

Studies conducted at pH 7.2 phosphate buffer, showed a much faster release of indomethacin from the IS pellets. For instance, 96% of the drug content was released at the 45 minute interval (refer to Figure 3). The reason for the difference in release rate profiles of the IS pellets in two different pH

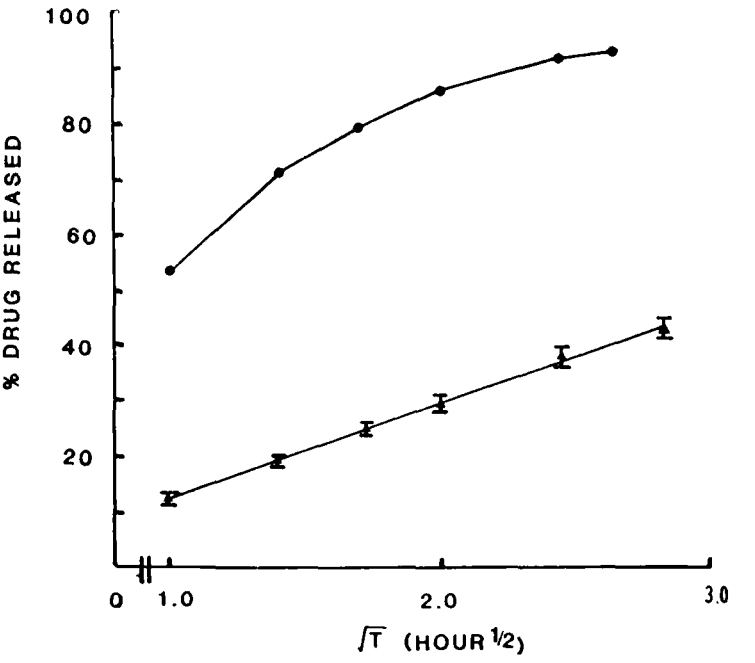

FIGURE 2

Release rate profiles of Indomethacin from IS pellets and Indocin® SR plotted assuming Higuchi matrix equation.

Key: ● Indocin® SR 75 mg capsule
▲ IS Pellets (each point represents mean ± SD of five batches of IS pellets valves)

phosphate buffers can be explained as follows. At pH 6.5, Eudragit® S-100 remained intact. Therefore, the release of indomethacin from these pellets remained a diffusion controlled process. However, in pH 7.2 media, the Eudragit® S-100 started to dissolve. This destroys the Eudragit® S-100 matrix and allows for more rapid release of the indomethacin.

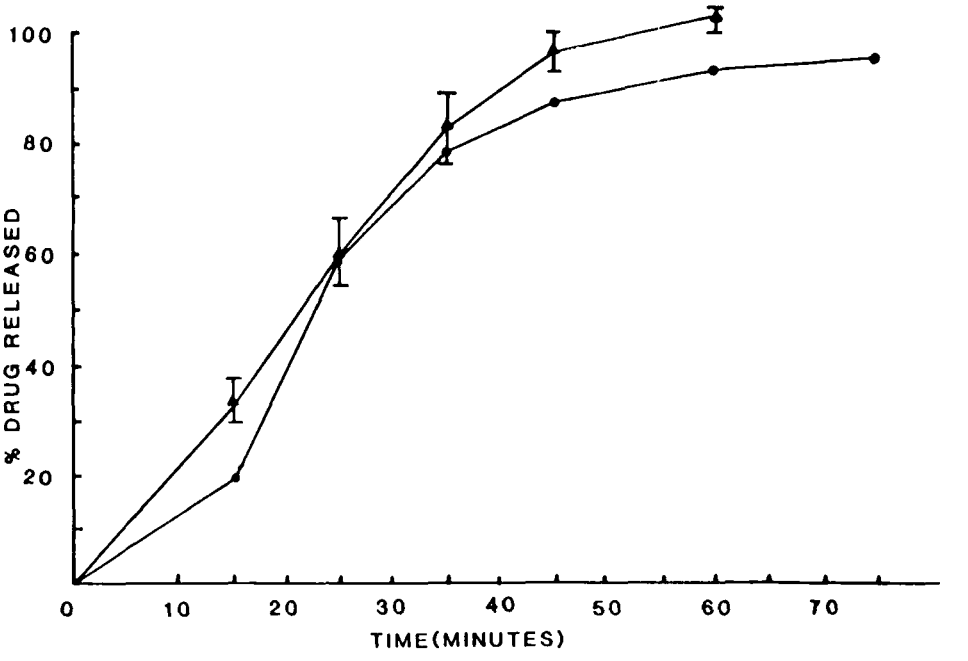

FIGURE 3

Cummulative amount (%) of Indomethacin released from two sustained release formulations in pH 7.2 Phosphate Buffer.

Key: ▲ IS pellets (each point represents mean ± SD of two batches of IS pellets valves)
● Indocin® SR 75 mg capsule

Comparison of In-Vitro Release Rate Profile between Indomethacin Eudragit® S-100 Pellets and Indocin® S.R. Capsule

In order to evaluate whether the formulations presented in this paper can produce satisfactory sustained release indomethacin pellets, the in-vitro release rate profile of the commercially available sustained release indomethacin formulation (Indocin® S.R. 75 mg capsule) was determined. The results were compared with the in-vitro release rate profile of IS pellets.

As Figure 1 shows, the release rate of indomethacin from Indocin S.R. was much faster than from IS pellets in pH 6.5 phosphate buffer. For instance, only 12% of the drug was released from IS pellets at the first hour, while 53% of the total indomethacin was released from the Indocin® SR. The reason for this phenomenon may be attributed to the fact that Indocin® SR contains 33.3% of the total drug dose as a loading dose[1,16]. Consequently, a very high initial concentration of indomethacin was observed in the first hour. If 33.3% of the total indomethacin released was substracted from the original release rate data of Indocin® SR capsules, the release rate profile for the sustained release portion of Indocin®SR was found to be much closer to the release rate profile of the IS pellets (Figure 1).

The in-vitro release rate of Indocin® SR was examined according to Higuchi's model. The release rate profile of this formulation did not exactly follow Higuchi's matrix release model (Figure 2). The correlation coefficient of this formulation was $r^2 = 0.9500$. As mentioned above, IS pellets showed a matrix release rate profile.

Dissolution studies conducted at pH 7.2 phosphate buffer, illustrated that the release rate profile of Indocin® SR was similar to IS pellets (Figure 3). This observation can be explained as follows. In pH 7.2 media, polyvinylacetate, which was used as the slowly dissolving polymer to coat indomethacin pellets[12], started to dissolve. This destroys the

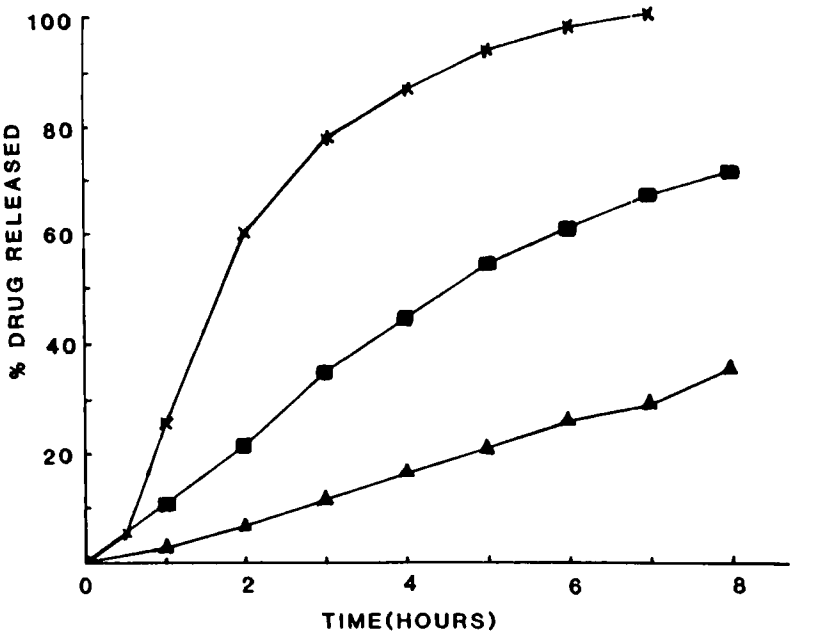

FIGURE 4

The dissolution profiles of IS pellets coated with three levels of Eudragit® RS in pH 7.2 phosphate buffer

Key: X 1.0% Coating
■ 1.5% Coating
▲ 2.0% Coating

polyvinylacetate coating and allows for more rapid release of the indomethacin from Indocin® SR pellets.

The in-vitro release rate profiles of IS pellets were not exactly similar to Indocin® SR. However, only a bioavailability study can really demonstrate how these differences in in-vitro release rates can effect the in-vivo performance of these two sustained release indomethacin formulations.

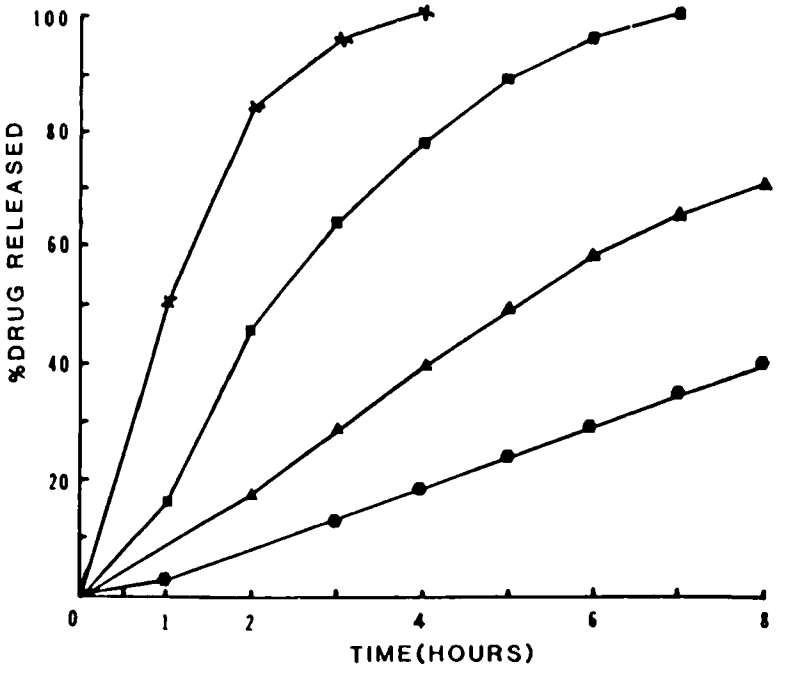

FIGURE 5

The dissolution profiles of IS pellets coated with four levels of Eudragit® RL in pH 7.2 phosphate buffer

Key:
X 1.0% Coating
■ 1.5% Coating
▲ 2.0% Coating
● 3.0% Coating

Effect of Polymer Type and Concentration on the Release Rate of the Eudragit® RS/RL Coated IS Pellets

As can be seen from Figures 4 to 8, the release rates of indomethacin from coated pellets in pH 7.2 phosphate buffer decreased as the concentration of the polymers increased, regardless of the type or ratio of Eudragit® RL or RS used in the

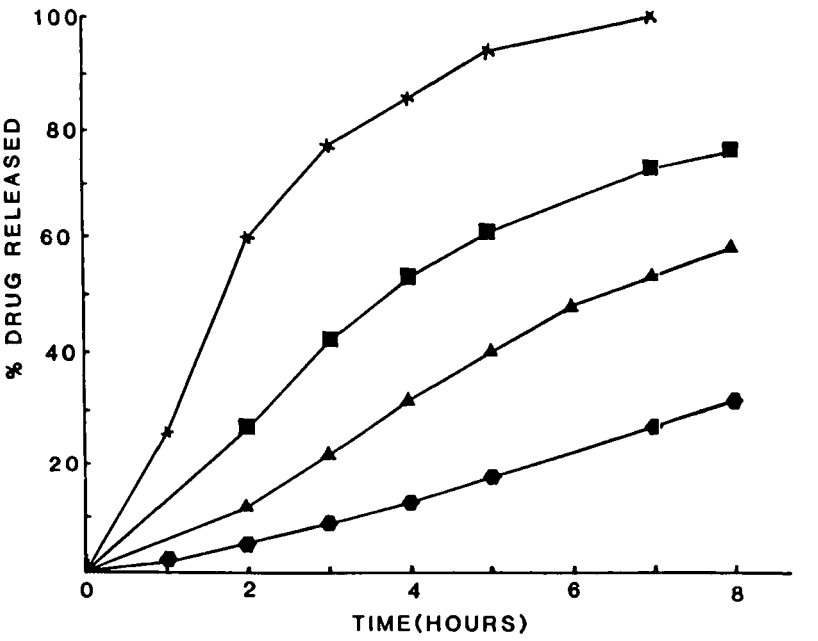

FIGURE 6

The dissolution profiles of IS pellets coated with four levels of Eudragit® RS/RL (50/50) in pH 7.2 phosphate buffer.

Key:
X 1.0% Coating
■ 1.5% Coating
▲ 2.0% Coating
● 3.0% Coating

coating. These release rate data (0 - 8 hours) were then examined according to zero order release kinetics as well as first order release kinetics. Correlation coefficients were determined and were tabulated.

As Table 4 shows, the release kinetics for pellets coated with 1.0 to 1.5% of polymer loads fit more closely first order kinetics regardless of the ratio or the amount of Eudragit® RS or

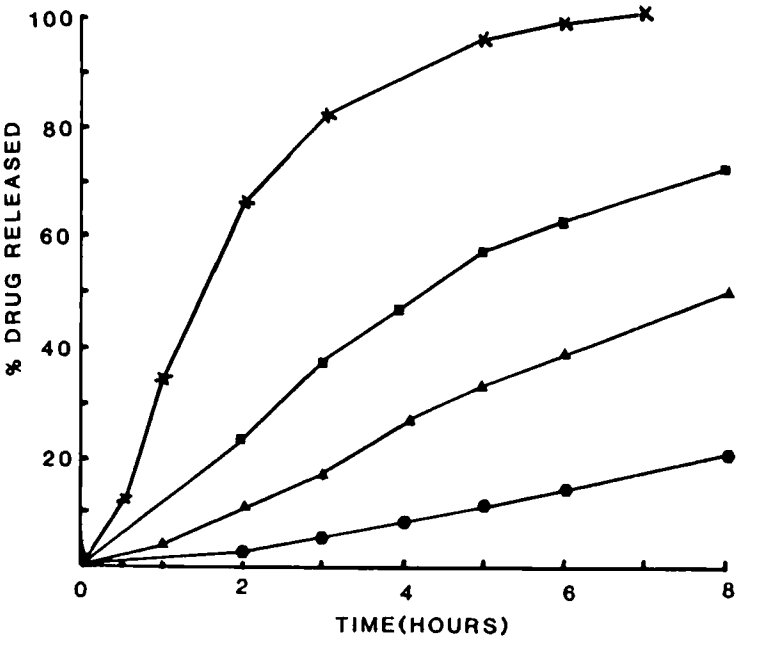

FIGURE 7

The dissolution profiles of IS pellets coated with four levels of Eudragit® RS/RL (75/25) in pH 7.2 phosphate buffer.

Key: X 1.0% Coating
■ 1.5% Coating
▲ 2.0% Coating
● 3.0% Coating

RL in the coating. However, considering all data points for the pellets coated with 2.0 to 3.0% loads, the best correlation coefficients were obtained with a zero-order release model.

These observations can be explained as follows. At low levels of RS and/or RL coatings, the IS pellets tend to be only partially covered with the Eudragit polymers. Consequently, the release of indomethacin tends to be less restricted. As coating

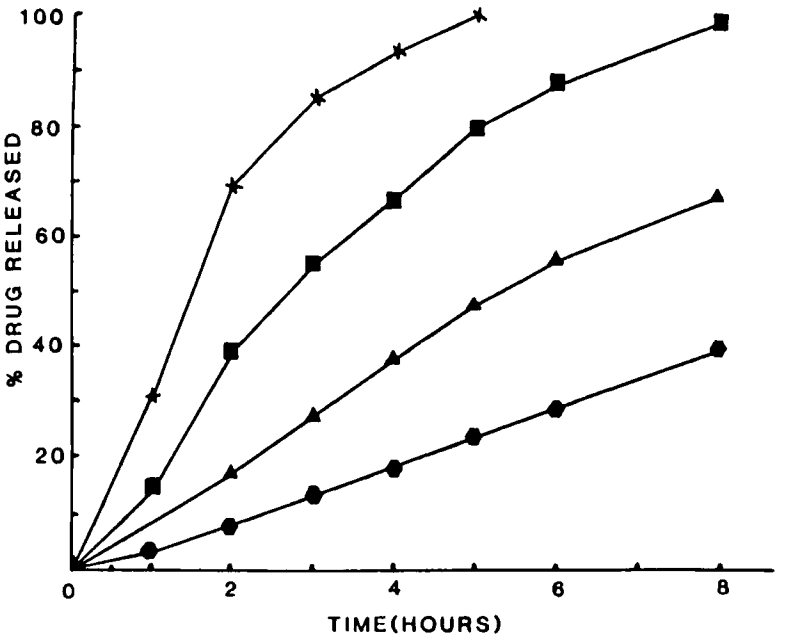

FIGURE 8

The dissolution profiles of IS pellets coated with four levels of Eudragit® RS/RL (25/75) in pH 7.2 phosphate buffer.

Key:
X 1.0% Coating
■ 1.5% Coating
▲ 2.0% Coating
● 3.0% Coating

levels are increased (2% to 3% RS and/or RL levels), the coverage of the IS pellets is more uniform and continuous.

The release rate of indomethacin tends to become zero order indicating that the Eudragit® coating acts as a membrane to regulate the drug release. The rate limiting step for the release of indomethacin from the coated pellets was primarily controlled by the thickness of the membrane.

TABLE 4

Correlation Coefficient for the Release of Indomethacin (0 - 8 Hours) at pH 7.2 Phosphate Buffer on the Basis of First-Order Kinetics and Zero Order Kinetics

Formulation Coating Level(%)	Eudragit RS:RL; 100:0		Eudragit RS:RL; 75:25		Eudragit RS:RL; 50:50		Eudragit RS:RL; 25:75		Eudragit RS:RL; 0:100	
	First-Order	Zero-Order	First-Order	Zero-Order	First-Order	Zero-Order	First-Order	Zero-Order	First-Order	Zero-Order
1.0	0.9964	0.9363	0.9971	0.9216	0.9970	0.9339	0.9954	0.9432	0.9977	0.9578
1.5	0.9995	0.9847	0.9996	0.9765	0.9992	0.9729	0.9899	0.9692	0.9929	0.9591
2.0	0.9564	0.9985	0.9724	0.9963	0.9962	0.9923	0.9951	0.9932	0.9947	0.9933
3.0	-	-	0.9250	0.9949	0.9429	0.9982	0.9619	0.9990	0.9590	0.9997

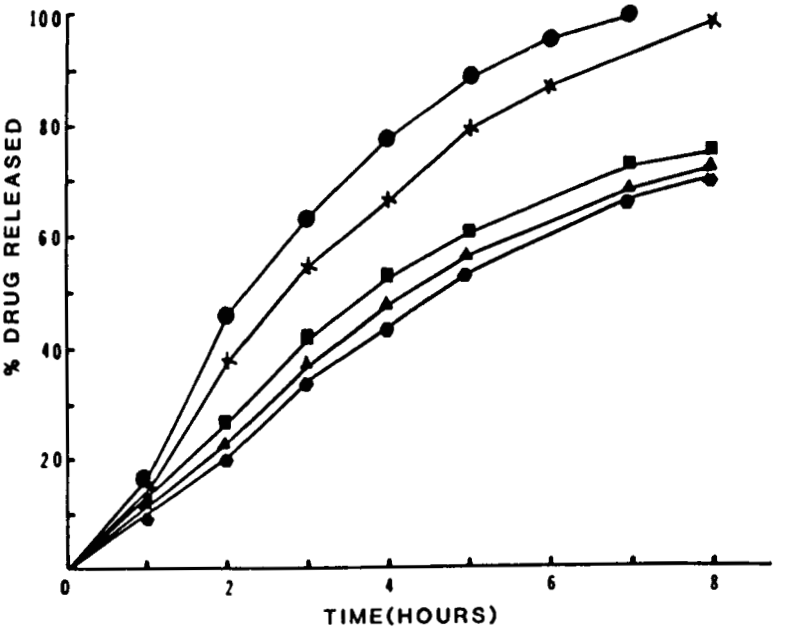

FIGURE 9

Effect of different polymer ratios on dissolution profiles of indomethacin pellets coated with 1.5% coating.

Key:
- ● Eudragit RS to Eudragit RL, 0:100
- X Eudragit RS to Eudragit RL, 25:75
- ■ Eudragit RS to Eudragit RL, 50:50
- ▲ Eudragit RS to Eudragit RL, 75:25
- ⬢ Eudragit RS to Eudragit RL, 100:0

Figures 9 to 11 show plots of % indomethacin released versus time for five batches of IS pellets coated with the same levels of Eudragit® RS, RL or combinations of RS/RL. With the same levels of coating, the release rate of indomethacin from the coated pellets is directly related to the type of Eudragit® used. As expected, pellets coated with the poorly water

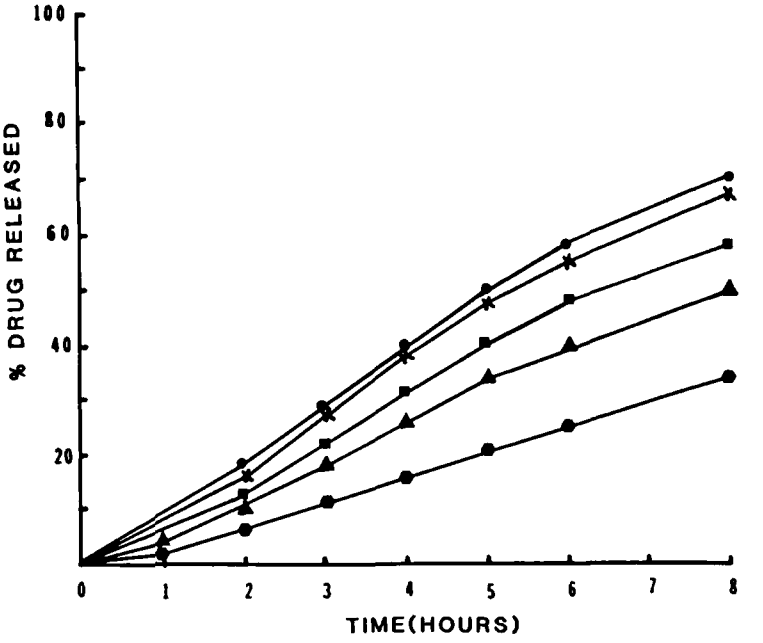

FIGURE 10

Effect of different polymer ratios on dissolution profiles of Indomethacin pellets coated with 2.0% coating.

Key:
- ● Eudragit RS to Eudragit RL, 0:100
- X Eudragit RS to Eudragit RL, 25:75
- ■ Eudragit RS to Eudragit RL, 50:50
- ▲ Eudragit RS to Eudragit RL, 75:25
- ● Eudragit RS to Eudragit RL, 100:0

permeable Eudragit® RS, showed the most retardation in release rate of drug. The total amount of drug released from the coated pellets increased as the concentration of Eudragit® RL increased in the barrier coating. Pellets coated with the readily water permeable Eudragit® RL alone showed the fastest release rate of drug as compared to other batches of coated pellets within a given coating level.

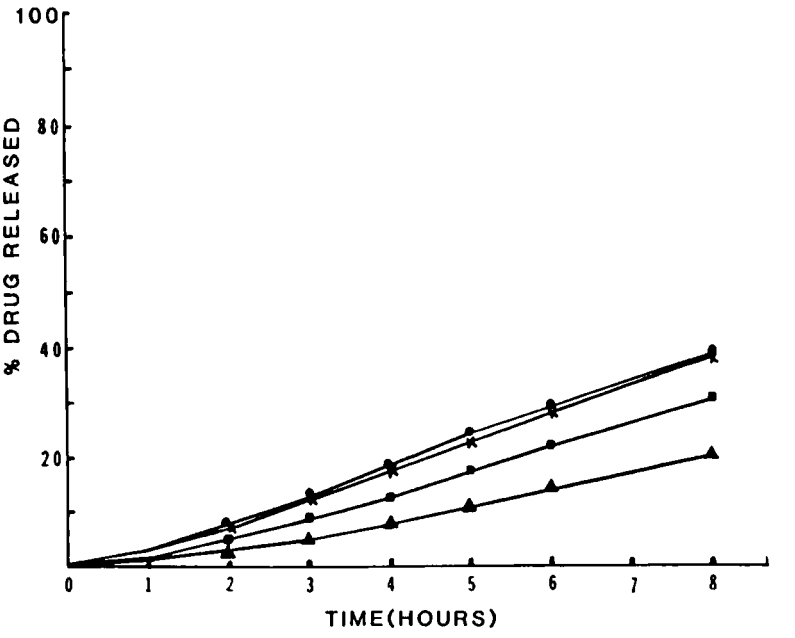

FIGURE 11

Effect of different polymer ratios on dissolution profiles of Indomethacin pellets coated with 3.0% coating.

Key:
- ● Eudragit RS to Eudragit RL, 0:100
- X Eudragit RS to Eudragit RL, 25:75
- ■ Eudragit RS to Eudragit RL, 50:50
- ▲ Eudragit RS to Eudragit RL, 75:25

SUMMARY

Based on the data and discussion presented in this article, several conclusions can be drawn regarding this work. (1) The manufacture of an indomethacin sustained release pellet product using a column process is extremely convenient. (2) The processing technique is relatively simple and reproducible. (3)

Retardation in the release rate of indomethacin can be achieved via the coating of different types and ratios of Eudragit® polymers. (4) The amount of the polymers applied was the determining factor in controlling the release rate.

In-vivo performance of these sustained release indomethacin formulations will be evaluated using a dog model in future studies.

ACKNOWLEDGMENTS

The authors wish to thank Ms. Mary Pellak for typing this manuscript, Dr. Deepak Phadke for his technical advice and Dr. Robert Felt for his helpful suggestions in the preparation of the manuscript.

FOOTNOTES

a. Industrie Chimiche Parmaceutiche Italiane.

b. Carbowax®-8000 Flake, Union Carbide Corp.

c. Charles B. Chrystal Company, Inc., New York, NY.

d. Ingredient Technology Corporation, Pennsauken, NJ.

e. Union Camp, Chemical Division, OH.

f. Rohm Tech., Inc., Malden, MA.

g. Merck, Sharp and Dohme Research Laboratories, West Point, PA.

h. Gifford-Wood, Model W200V, Greerco Corp. Hudson, NH.

i. Aeromatic Ltd., Towaco, NJ.

j. Cole-Parmer Instrument Co., Chicago, IL.

k. Model 970/0-S3, Gustav Schlick Coburg, West Germany.

l. ATM Corporation, Milwaukee, WI.

m. Smith Kline Beckman Inc., Philadelphia, PA.

REFERENCES

1. "Physicians' Desk Reference", 41th Ed., Medical Economics Company, Oradell, NJ, p. 1307 (1987)

2. E.S. Waller, Pharmacotherapy., 3, 324 (1983).

3. D.M. Woodbury, E. Fingl, in "The Pharmacological Basis of Therapeutics, 5th ed., L.S. Goodman, A. Gilman, eds., Macmillan, New York, NY 1975, p. 341.

4. H. Bechgaard, R. R. Brodie, L. F. Chasse and, P. Houmoller, J. O. Hunter, P. Siklos and T. Taylor, Eur J. Clin. Pharmacol, 21, 511 (1982).

5. J.S. Rowe and J.E. Carless, J. Pharm. Pharmacol, 33, 561 (1981).

6. H. Suryakusuma and H. W. Jun, J. Pharm. Pharmacol, 36, 493 (1984).

7. T. Umeda, A. Matsuzawa, T. Yokoyama, K.Kuroda and T. Kuroda, Chem. Pharm. Bull. 31 (8), 2793 (1983).

8. Y. Pongpaibul, J. C. Price and C. W. Whiteworth, Drug Development and Industrial Pharmacy, 10 (10), 1597 (1984).

9. R. Laakso, E. Kristoffersson and M. Marvola, International Journal of Pharmaceutics, 19, 35 (1984).

10. R. Laakso and K. Paulamski, Act. Pharm. Fenn, 93, 193 (1984).

11. P. Bonsen, P.S. Wong, F. Theeuwes, U.S. Pat. 4265874 (1981).

12. R.E. Dempski, G.N. Mehta and J.C. Saboe, U.S. Pat. 4173626 (1979).

13. C.H. Hsiao, U.S. Patent 4587118 (1986).

14. E.L. Parrott, in "The Theory and Practice of Industrial Pharmacy", L. Lachman, H.A. Lieberman and J.L. Kanig, eds., 2nd ed., Lea & Febiger, Philadelphia, 1976, p. 466.

15. T. Higuchi, J. Pharm. Sci. 52, 1145 (1963).

16. K.C. Yeh, Seminars in Arthritis and Rheumatism 12 (2) (Suppl. 1), 136 (1982).