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COMMUNICATION

EFFECT of MICROSPHERE SIZE and FORMULATION FACTORS on DRUG RELEASE from CONTROLLED-RELEASE FUROSEMIDE MICROSPHERES

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ABSTRACT

Controlled-release furosemide microspheres were prepared with various combinations of Eudragit L: Eudragit RS and Eudragit S: Eudragit RS and release of drug from microspheres containing these polymers in different ratios was studied. A wide range of release rates of drug can obtained by a simple change in the ratio of polymers. An increase in Eudragit RS content of polymer microsphere matrix brought about a decrease in the release rate.

On the other hand, the effect of particle size on the drug release rate from furosemide microspheres was also investigated. The effect of microsphere sizes on release rate depends on the type of Eudragit. The decrease in release rates of small microspheres may be due to agglomerate formation. Dissolution data indicated that the release followed Higuchi's matrix model kinetics.

INTRODUCTION

In previous paper, preparation and properties of controlled-release furosemide microspheres were performed by using spherical crystallization technique (1). However, the release of drugs which are associated with microspheres has been found to be dependent upon a large number of factors (2). On the other hand, mixtures of polymers can have properties significantly better than individual polymer for achieving controlled-release (3-5).

This paper concerns the use of acrylic polymer (Eudragit) mixtures to control the release characteristics of furosemide microspheres. Moreover the effect of microsphere size on drug dissolution was also studied.

EXPERIMENTAL

Materials

Furosemide (Hoechts A.G. Frankfurt, F.R.G.) Eudragit L100, Eudragit S100, Eudragit RL100 and Eudragit RS100 (Röhm Pharma GmbH, Darmstadt, F.R.G.), methylene chloride (E. Merck, Darmstadt, F.R.G.)

Methods

Preparation of Microspheres

Furosemide microspheres were prepared by the spherical crystallization technique of Kawashima et al. (6) using different Eudragit types as the matrix. Drug and polymer were dissolved in the mixture of methylene chloride-ethanol and dropped into O.IN hydrochloric acid solution with stirring. Microspheres were separated and washed. Experimental details were previously described (1).

Effect of Particle Size

By using single polymer (Eudragit RL or Eudragit RS), in (1:4) ratio, microspheres were prepared as mentioned above. The dried microspheres were sized through standard sieves to isolate fractions of desired diameters.

Effect of Formulation Factors

Different Eudragit L: Eudragit RS and Eudragit S: Eudragit RS ratios (1:4, 1:8 and 1:12) were employed to determine the effect of various combinations of polymers on drug release.

In each formulation, the ratio of furosemide to polymer (1:4), the total amount of polymer and solvent were held constant.

In Vitro Release Studies

A weighed amount of microspheres was suspended in a phosphate buffer (pH 7.4, 50 ml) contained in 100 ml glass bottle. The dissolution medium was stirred at 100 rpm in a horizontal laboratory shaker and maintained constant temperature (37° ± 0.1) in a water bath. Samples were periodically removed and analyzed spectrophotometrically (Varian Techtron Series 634 Spectrophotometer) at 275 nm. The mean of 6 determinations was given. Corrections were made for any absorption due to Eudragit.

Determination of Furosemide Content in Microspheres

A weighed amount of microspheres was dissolved in alcohol and drug content was spectrophotometrically assayed. Each determination was carried out in triplicate.

RESULTS and DISCUSSION

Effect of Polymer Combination Ratio

As seen in table 1 drug loading was not affected by polymer combination ratios when the drug: polymer ratio (1:4) was held constant. The similar results were reported by Pongpaibul et al. (3).

Figure 1 demonstrates the dissolution behavior of furosemide microspheres prepared with various combinations of Eudragit L: Eudragit RS. As seen in this figure, the total amount of drug released from microspheres decreased as the concentration of Eudragit RS increased. This may be due to polymeric properties of Eudragit L. It is an anionic polymer and insoluble in water but it becomes soluble in a neutral to weakly alkaline. Furthermore, the increase in release rate of furosemide caused by increasing Eudragit L concentration, probable makes available more channels for diffusion as reported earlier (3).

Similar results were obtained by using Eudragit S: Eudragit RS combinations. As shown in figure 2, the addition of Eudragit S to Eudragit RS would increase the release of furosemide from microspheres. The release pattern was easily changed by changing the ratios of these two polymers.

On the other hand, when the effect of two water-soluble polymers. Eudragit L and Eudragit S were

Table 1

Drug content of furosemide microspheres prepared in different polymer combinations.

Eudragit	Ratio of mixture	Theoretical Drug Content %	Assay Drug Content %	Incorporation Efficiency %
L:RS	1:4	20.00	16.50	82.50
	1:8	20.00	17.86	89.30
	1:12	20.00	17.24	86.20
S:RS	1:4	20.00	17.50	87.50
	1:8	20.00	17.70	88.50
	1:12	20.00	16.38	81.90

compared, a slight increase in drug release was observed by the addition of Eudragit S to polymer mixtures at high concentration. Indeed, less retardant effect of Eudragit S on furosemide release from microspheres was previously noted (1).

The release data were kinetically examined. An equation for the spherical matrix has been derived by Higuchi (7), Baker and Lonsdale (8) as:

$3/2 [1 - (1 - F)^{2/3}] - F = KT$ where F is the faction of drug released, K is a constant and T is time. Table 2 indicates correlation coefficients obtained by linear regression of $3/2 [1 - (1 - F)^{2/3}] - F$ versus time. A linear relationship between them

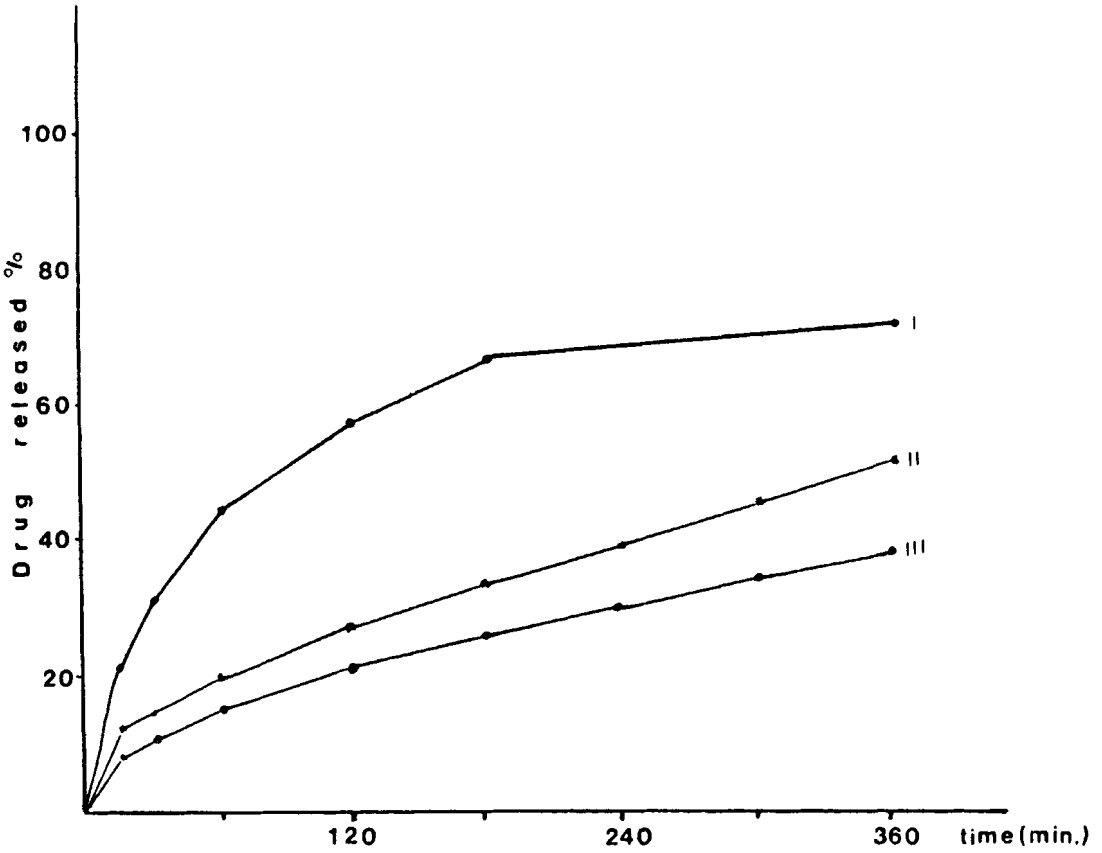

Figure 1

Effect of Eudragit L: Eudragit RS ratio on Dissolution Rate of Furosemide Microspheres

Key: Eudragit L: Eudragit RS (1:4) (I); (1:8) (II) and (1:12) (III).

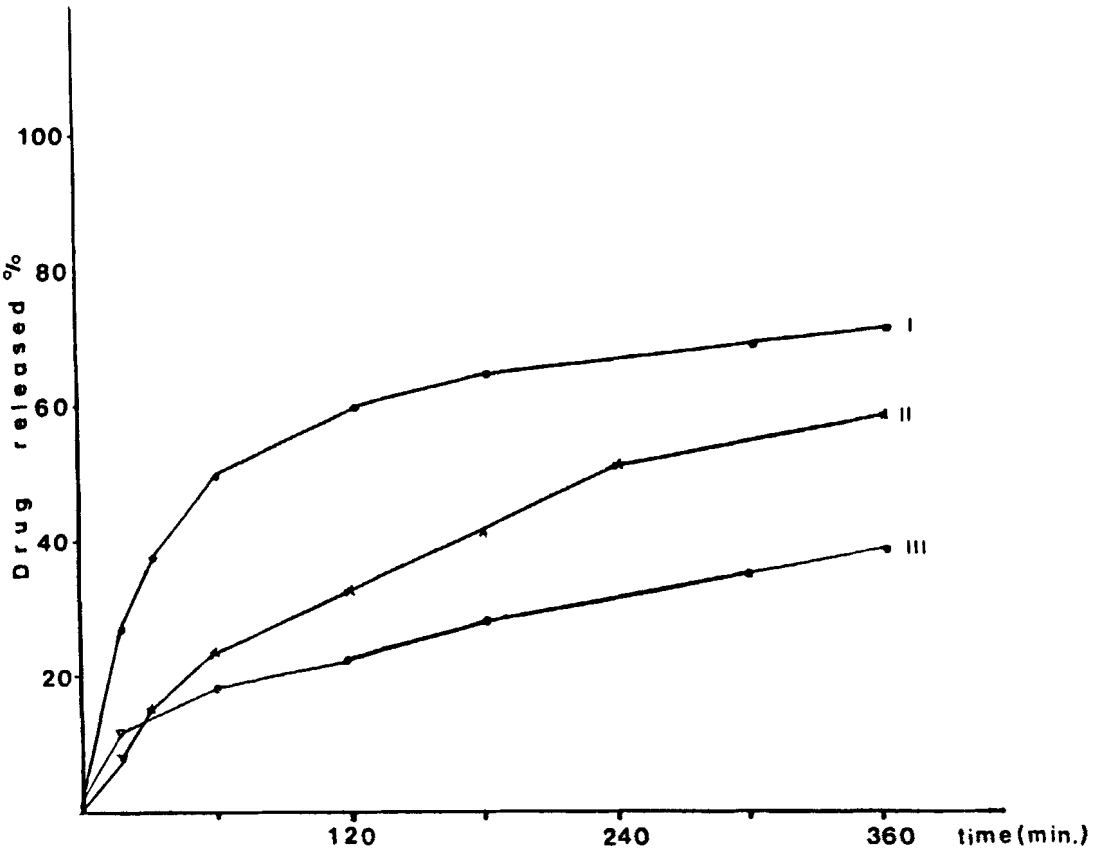

Figure 2

Effect of Eud ragit S: Eudragit RS ratio on Dissolution Rate of Furosemide Microspheres

Key: Eudragit S: Eudragit RS (1:4) (I); (1:8) (II) and (1:12) (III).

Table 2

Values of slopes and correlation coefficients from plots of $3/2\ [1 - (1 - F)^{2/3}] - F$ versus time

	Eudragit S: Eudragit RS			Eudragit L: Eudragit RS		
	1:4	1:8	1:12	1:4	1:8	1:12
Slope	6.79×10^{-3}	2.16×10^{-4}	8.28×10^{-5}	3.90×10^{-4}	1.43×10^{-4}	7.61×10^{-5}
r*	0.956	0.997	0.983	0.955	0.991	0.998

* correlation coefficient

which confirms the results of previous report (1), was obtained. This data showed that the results are in aggrement with Higuchi matrix model.

Effect of Particle Size on Release Rate

Figure 3 indicates the dissolution profiles of different particle sizes of microspheres prepared with Eudragit RS.

Generally, the smaller the microspheres the more rapid drug release due to the greater surface area (3,5). However, figure 3 reveals that there was no significant effect of particle sizes between 850 µm-75 µm on drug release rate from microspheres prepared with Eudragit RS except smaller than 75 µm. A reterdant effect was obtained with the smallest particle sizes of microspheres. This effect may be due to the agglomeration of particles. Results showed similarity with the findings of Pal and Pal (9) for Eudragit RS microcapsules. Furthermore, no particle size effect on drug dissolution from microspheres was also noted by Chang et al. (4).

On the other hand, a reverse pattern has been observed in case of Eudragit RL where the release rate increases with the decrease of particle size of microspheres except smaller than 75 µm. (figure 4). Agglomerate formation was observed during the release rate studies of small microspheres.

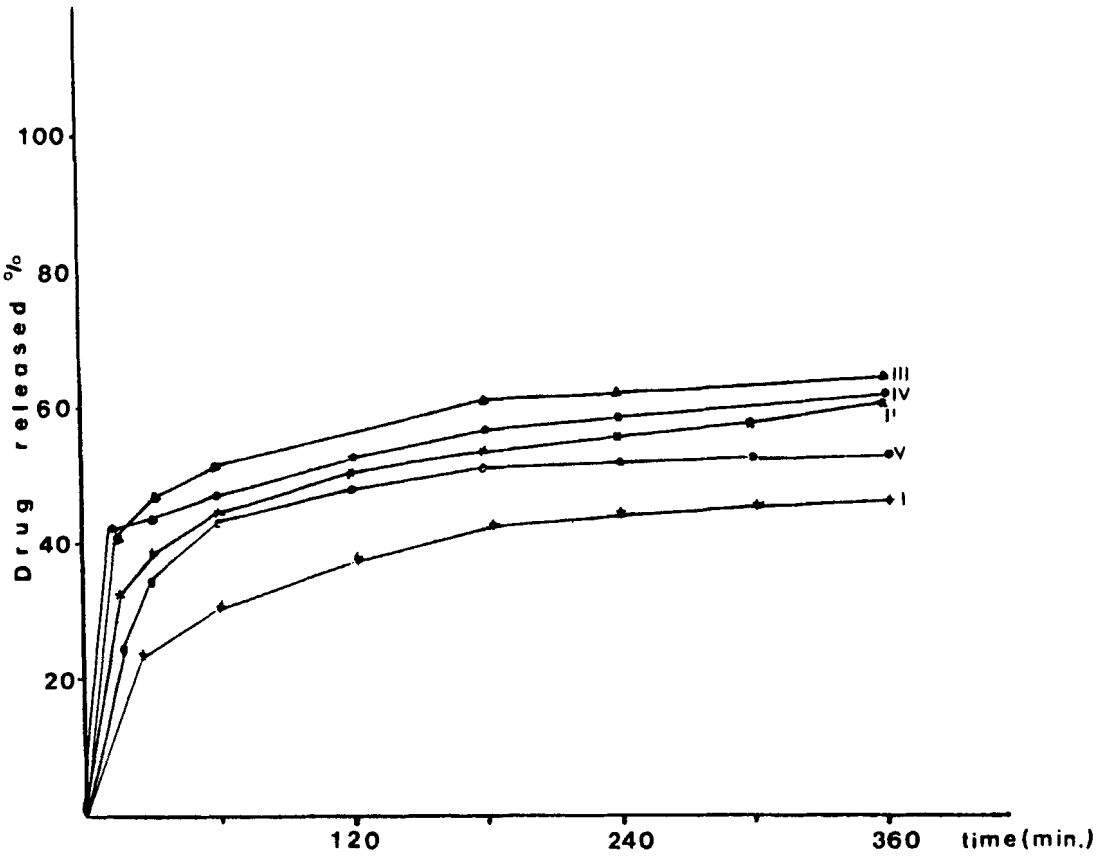

Figure 3

Effect of Particle Size on Dissolution Rate of Furosemide Microspheres prepared by Eudragit RS

Key: (I) > 850 µm; (II) 850-500 µm;
(III) 500-250 µm; (IV) 250-125 µm;
(V) < 75 µm.

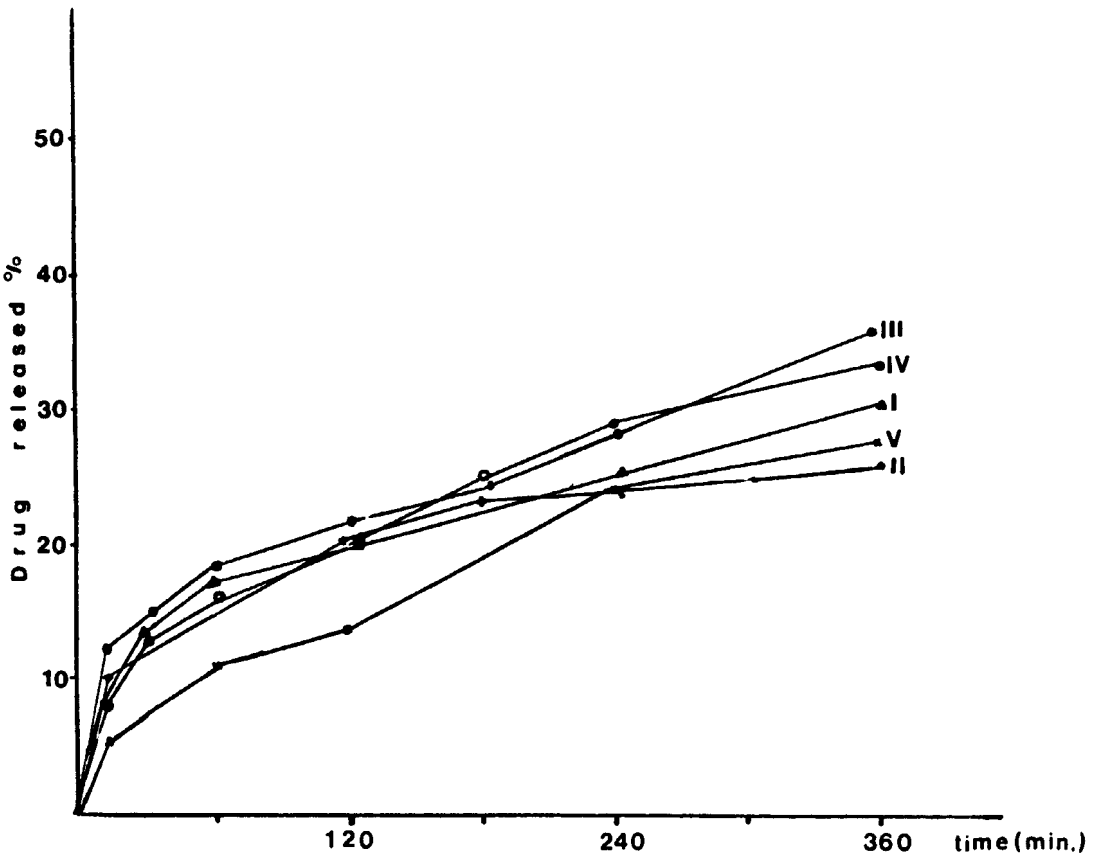

Figure 4

Effect of Particle Size on Dissolution Rate of Furosemide Microspheres prepared by Eudragit RL

Key: (I) > 850 µm; (II) 850-500 µm;
(III) 500-250 µm; (IV) 250-105 µm;
(V) < 75 µm.

Table 3

Values of slopes, intercepts and correlation coefficients from plots of $3/2\ [1 - (1 - F)^{2/3}] - F$ versus time

Types		Microsphere size (μm)				
		>850	850-500	500-250	250-125	<75
Eudragit RL	Slope	1.61×10^{-4}	1.75×10^{-4}	2.53×10^{-4}	2.54×10^{-4}	1.82×10^{-4}
	Intcp.	9.72×10^{-3}	2.97×10^{-2}	3.82×10^{-2}	1.84×10^{-2}	4.15×10^{-2}
	r*	0.999	0.966	0.964	0.951	0.914
Eudragit RS	Slope	4.66×10^{-5}	4.00×10^{-5}	5.86×10^{-5}	5.40×10^{-5}	4.56×10^{-5}
	Intcp.	1.56×10^{-3}	1.58×10^{-3}	2.79×10^{-3}	1.16×10^{-3}	5.66×10^{-4}
	r*	0.944	0.984	1.000	0.992	0.983

* correlation coefficient

Difference between two polymers, Eudragit RL and Eudragit RS can be explained from the view point of polymer characteristics. It has been described by Lehman (10) that Eudragit RS is weakly permeable to water and dissolved active ingredient whereas Eudragit RL is strongly permeable. Release data were examined kinetically and were found to follow diffusion-controlled model of Higuchi (7) and Baker and Lonsdale (8) as mentioned above. Table 3 illustrates the correlation coefficients obtained by

lineer regression of $3/2\ [1 - (1 - F)^{2/3}\ ] - F$ versus time for each size of microspheres.

As a conclusion, the combination of Eudragit RS (cationic resin) and Eudragit L or Eudragit S (anionic resin) as a matrix in furosemide microspheres was demonstrated to have good potential in controlled-release effect. The data revealed the fact that by decreasing the amount of Eudragit L or Eudragit S in the mixture, an evident decrease in the drug release from microspheres was obtained. Moreover the effect of microsphere size on drug release is dependent on the polymer type. The smaller particles, however, tend to form agglomerate and thus reduce the relase rate.

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