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Preparation and evaluation of controlled release furosemide microspheres by spherical crystallization

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Summary

Furosemide (Frusemide) microspheres were prepared and evaluated by a spherical crystallization technique using different acrylic polymer (Eudragit) types as the matrix. For preparation of microspheres, different types of acrylic polymers such as Eudragit L 100, Eudragit S 100, Eudragit RL 100 and Eudragit RS 100 were used. The microspheres were spherical. The average diameters were about 250–280 μm and the drug contents in the microspheres were 75–80%. Microsphere size can be largely controlled by rate of agitation. The release pattern of furosemide was easily changed by modifying the type of Eudragit. The most retardant effect was obtained by using Eudragit RS. On the other hand, as the concentration of Eudragit increased, the release rate of furosemide decreased. Release data were examined kinetically and the mechanism was also discussed. Dissolution data showed that the release followed Higuchi matrix model kinetics. These results indicated that furosemide microspheres could be prepared providing a sustained release property.

Introduction

Furosemide (Frusemide) is a potent and widely used diuretic. However, diuretic ineffectiveness of some of the furosemide products is known. Although some studies have been reported on controlled release forms of furosemide (Zhu et al. 1985; Verhoeven et al. 1986; El-Shattawy et al. 1987), no reports relating to preparation of controlled release microspheres of furosemide have appeared.

On the other hand, methacrylate copolymers (Eudragit) have recently received increased attention for preparing modified dosage forms because of their inertness, solubility in relatively non-toxic solvents and availability of resins with different properties (Pongpaibul et al., 1984; Benita et al., 1985; Cameron and McGinity, 1987). Furthermore, the spherical crystallization technique of Kawashima et al. (1986), which was used in this study, is a simple process that is also inexpensive enough for scaling up to a commercial level.

The purpose of the present study was to prepare furosemide microspheres by using a spherical crystallization technique, to investigate the possibility of tailoring the drug dissolution from this form by the use of different types of Eudragit and

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to study the effective factors such as drug–polymer, solvent–polymer ratios and stirring rate on microsphere properties and drug release. The release mechanism of furosemide from microspheres was also discussed.

Materials and Methods

Materials

Furosemide (Hoechst AG, Frankfurt, F.R.G.), Eudragit L 100, Eudragit S 100, Eudragit RL 100 and Eudragit RS 100 (Röhm Pharma GmbH, Darmstadt, F.R.G.), methylene chloride (E. Merck, Darmstadt, F.R.G.).

Methods

Preparation of microspheres. All microspheres were prepared by the spherical crystallization technique of Kawashima et al. (1986). Weighed amounts of furosemide and acrylic polymer were dissolved in a mixture of methylene chloride-alcohol (1 : 1). The formed solution was poured into 500 ml of 0.1 N hydrochloric acid solution stirred with a propeller type agitator (Ika-Werk, Janke & Kunkel, F.R.G.). After 30 min of stirring, the microspheres were separated by filtration, washed with water and then dried in vacuo. All batches were prepared at least 3 times.

Variation of formulation factors. Four different types of acrylic polymer [Eudragit L100, Eudragit S100, Eudragit RL100 and Eudragit RS100] were employed to determine the effect of Eudragit type on microsphere properties.

Different furosemide : polymer ratios (1 : 1, 1 : 2, 1 : 3 and 1 : 4) were used in order to investigate the effect of drug : polymer ratio on drug release and the physical characterization of microspheres. Solvent–polymer ratios were varied while keeping polymer and drug ratios constant and the effects of this ratio was also studied.

Variation of process factor. The effect of stirring rate (100, 500 and 1500 rpm) on microsphere characteristics was investigated.

Physical characterization of microspheres. Scanning electron microscopy (SEM) (Joel JVA 840A) was used to evaluate the shape and surface characteristics of the microspheres. Size and size distributions were measured by sieve analysis (Retsch, Haan, F.R.G.).

In vitro release studies. A weighed quantity of microspheres (250–280 μm) was suspended in a phosphate buffer (pH 7.4 USP, 37 °C, 50 ml) contained in a 100 ml glass bottle. The dissolution medium was stirred at 100 rpm in a horizontal laboratory shaker and maintained at constant temperature (37 °C $\pm$ 0.1) in a water bath. Samples were periodically removed and analyzed spectrophotometrically (Varian Techtron Series 634 Spectrophotometer) at 275 nm. The means of six determinations were given. Corrections were made for any absorption due to Eudragit.

Determination of drug content in microspheres. A weighed quantity of microspheres was dissolved in alcohol. Drug content was assayed spectrophotometrically. The means of 3 assays were reported.

Results and Discussion

Characterization of furosemide microspheres

By using this technique spherical microspheres were obtained. Fig. 1 shows the scanning electron micrographs of furosemide microspheres. They were invariably spherical and exhibited porous surfaces with a large number of interstices. Micropores (diameter > 1 μm) were seen on the surface of microspheres and also a honeycomb-like matrix of the polymer was formed inside the sphere in which drug seemed to be embedded. Some of the microspheres were lightly aggregated.

Aritmethric mean diameters of the microspheres are shown in Table 1. Particle size analysis of microspheres prepared by using different types of acrylic polymer (Eudragit) did not reveal any significant variation in the particle sizes of microspheres. The type of Eudragit had no effect on the particle sizes of microspheres; this finding was in contrast to the earlier report by Kawashima et al. (1986). On the other hand, stirring rate during the preparation of microspheres has influence on the particle sizes of microspheres. As shown in Table 2, increasing the stirring rate decreases the mean diameter of microspheres and reduces the range of the size distributions. The increased mechanical shear force, produced by increasing the stirring

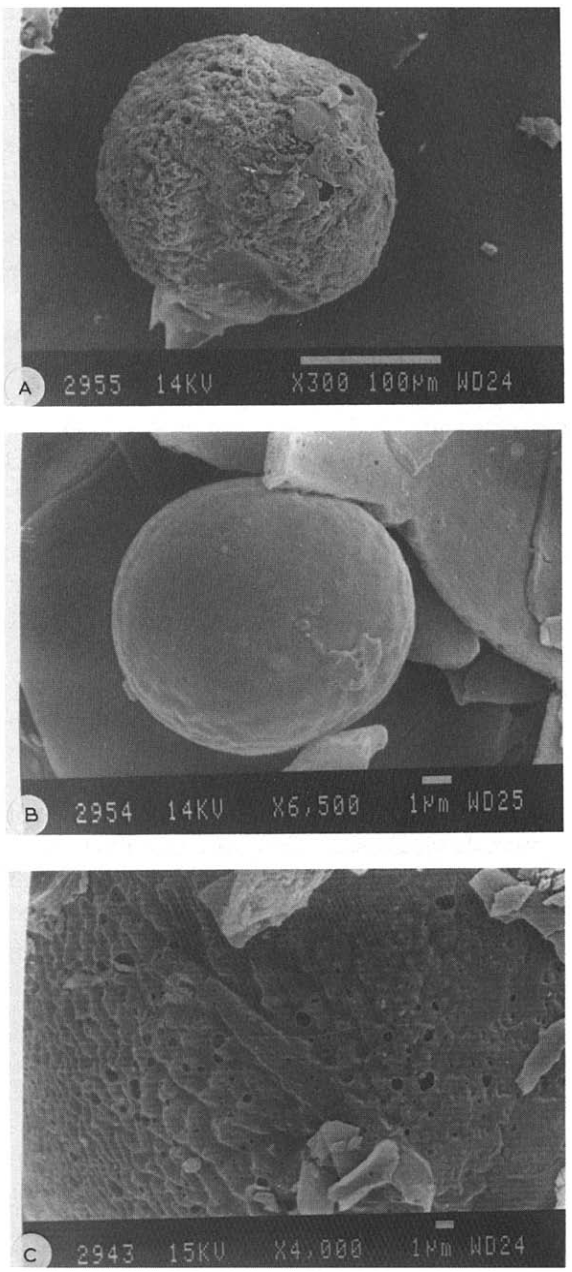

Fig. 1. Scanning electron micrographs of furosemide microspheres prepared with Eudragit RS (A) and Eudragit S (B) and surface of microsphere (C).

rate, divided rapidly the solution of polymer and drug into finer drops, leading to finer matrix spheres as previously reported (Kawashima et al., 1986).

TABLE 1

Particle sizes of furosemide microspheres prepared by different ratios of drug : polymer

Drug : polymer ratio	Eudragit			
	L	S	RL	RS
1 : 1	270.6 (1.94)	222.1 (1.87)	316.9 (1.83)	322.6 (1.79)
1 : 2	258.8 (5.21)	332.7 (1.68)	287.6 (1.99)	200.0 (6.77)
1 : 3	243.0 (1.89)	226.6 (1.78)	306.9 (1.83)	271.9 (4.88)
1 : 4	223.9 (5.87)	265.7 (4.84)	350.0 (1.53)	251.2 (2.75)

Values are arithmetic mean particle size (µm); geometric S.D.s are given in parentheses.

On the other hand, it is evident that the stirring rate had no detectable influence on the drug content of microspheres (Table 2).

Table 3 indicates the furosemide content of microspheres and also drug loss. As seen in this table highly drug-loaded microspheres were obtained. Incorporation efficiency was high since it ranged from 70 to 75%. The recorded variations between the microsphere batches were believed to be due to the uncontrolled removal of furosemide during the washing steps. Furthermore, incorporation efficiency almost remained unchanged. The drug was uniformly encapsulated into the microspheres irrespective of initial drug concentrations. As seen in this table drug loading was not also affected by drug : polymer ratio.

TABLE 2

Effect of stirring rate on microsphere content and size

Stirring rate (rpm)	Theoretical drug content (%)	Assay drug content (%)	Mean particle size (µm)
100	20.0	15.0	1155.0 (2.26)
500	20.0	15.9	287.6 (1.99)
1500	20.0	14.7	282.9 (1.60)

Arithmetic mean size and geometric S.D.s are given for particle size.

TABLE 3

Drug content of furosemide microspheres prepared in different drug:polymer ratios

Eudragit	Drug: polymer ratio	Theoretical drug content (%)	Assay drug content (%)	Incorporation efficiency (%)
L	1:1	50.0	31.2	78.1
	1:2	33.3	25.0	75.3
	1:3	25.0	17.9	71.0
	1:4	20.0	15.9	79.4
S	1:1	50.0	34.8	69.6
	1:2	33.3	23.0	69.0
	1:3	25.0	21.0	84.0
	1:4	20.0	17.6	88.1
RL	1:1	50.0	39.7	79.5
	1:2	33.3	24.5	73.5
	1:3	25.0	17.5	70.0
	1:4	20.0	14.1	70.6
RS	1:1	50.0	34.9	69.8
	1:2	33.3	24.2	72.4
	1:3	25.0	14.8	59.2
	1;4	20.0	15.5	77.5

Release studies

The release profiles of furosemide from different Eudragit microspheres are illustrated in Fig. 2. It is evident that encapsulation of drug resulted in a marked decrease in dissolution rate. The effect of retardation on the dissolution rate depends on the type of Eudragit. Different types of polymers showed different retardation effects on drug release. The effect of polymer type on the retardation of drug release rate was in the following order: Eudragit RS > Eudragit RL > Eudragit L > Eudragit S. Eudragit RS was the most potent to reduce the drug dissolution. Similar findings were reported for ibuprofen microspheres by Kawashima et al. (1986).

By using water soluble polymers, such as Eudragit L and Eudragit S, water penetrates into the microspheres, hydrating and dissolving the polymers and also dissolving the drug. In contrast, with water swellable polymers, Eudragit RL and Eudragit RS, the swollen polymer may have behaved as a rate-limiting membrane for the dissolution of drug in the interior of microspheres. However, due to the content of the quaternary ammonium groups, the Eudragit RS is only slightly permeable, hence drug release is relatively retarded whereas the Eudragit RL is freely permeable, so that release is less retarded. The effect of drug–polymer ratio on drug release profiles is shown in Fig. 3; as the concentration of the polymer in the system increased, the release rate of furosemide decreased. The most retardant effect was obtained by using 1 : 4 ratio of drug-Eudragit RS 100. A significant difference was not obtained as the drug-polymer ratio was varied from 1 : 4 to

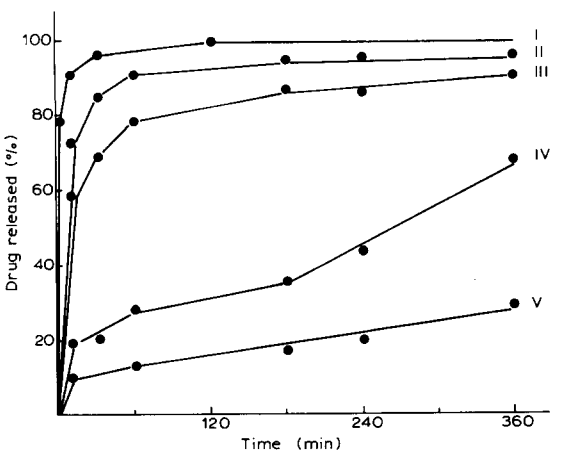

Fig. 2. Release profiles of furosemide microspheres prepared with Eudragit: Eudragit L (II), Eudragit S (III), Eudragit RL (IV), Eudragit RS (V), and furosemide powder (I).

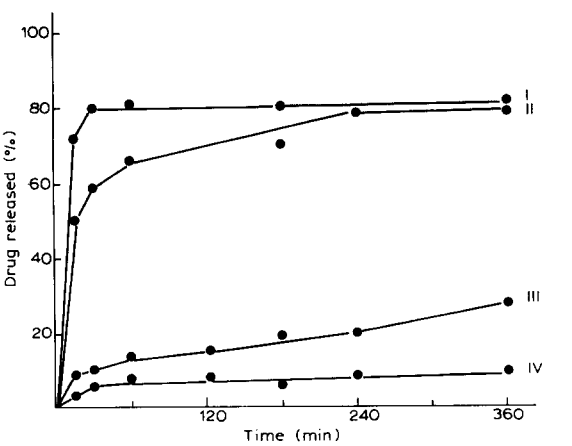

Fig. 3. Effect of different drug:polymer ratios on release profiles of furosemide microspheres. Furosemide: Eudragit RS 1:1 (I), 1:2 (II), 1:4 (III) and 1:5 (IV).

TABLE 4

Effect of solvent:polymer ratio on drug release from furosemide microspheres

Solvent:polymer ratio	Eudragit RL		Eudragit RS	
	k	r	k	r
10/1	1.16	0.92	1.22	0.99
20/1	1.42	0.97	3.27	0.94
50/1	1.75	0.98	1.12	0.85

Drug release (k) in μmol/min$^{1/2}$; r, correlation coefficients.

1:5. On the other hand, this retardant effect was not clear for Eudragit S 100 and Eudragit L 100 in 1:1 and 1:2 drug to polymer ratios because of the hydrophilic characterization of these types.

During all the experiments, microspheres formed from Eudragit RL and Eudragit RS remained intact, no erosion was observed.

Dissolution parameters of microspheres prepared with different solvent–polymer ratios are shown in Table 4. As shown in this table the release of furosemide increased as the solvent–polymer ratio increased; a similar effect was noted by Pongpaibul et al. (1984).

Drug release mechanism

The release rates were determined by least-squares linear regression analysis.

The main models which have been suggested to describe drug release kinetics from microspheres are zero-order model, the first-order model and matrix model. These models have been discussed and the zero-order model was found to be inapplicable since release was non-linear (Fig. 3).

Fig. 4 illustrates the release profiles of furosemide when plotted as the logarithm of the percent of remaining drug as a function of time. A linear relationship indicating a first-order release was obtained up to the end of 30 min. However, except for low levels of Eudragit S (drug:polymer = 1:1 or 1:2), a discontinuous linearity was obtained thereafter. This indicates that another mechanism may be effective. It is known that the rate of release from a planar matrix is usually proportional to the square root of time (Higuchi, 1963) while the release from spherical matrices has been described by Baker and Lonsdale (1974).

Findings according to Higuchi's equation are given in Table 5 and Fig. 5.

An equation derived by Higuchi (1963) and Baker and Lonsdale (1974) was used:

$$3/2\left[1-(1-F)^{2/3}\right]-F=K\cdot T,$$

where F is the fraction of drug released, K is a constant and T is time. Table 5 shows the correlation coefficient values obtained by linear regression of $3/2[1-(1-F)^{2/3}]-F$ vs time for each formulation.

This confirms that the mechanism of drug release from furosemide microspheres is mainly diffusion-controlled. However, a more stringent test

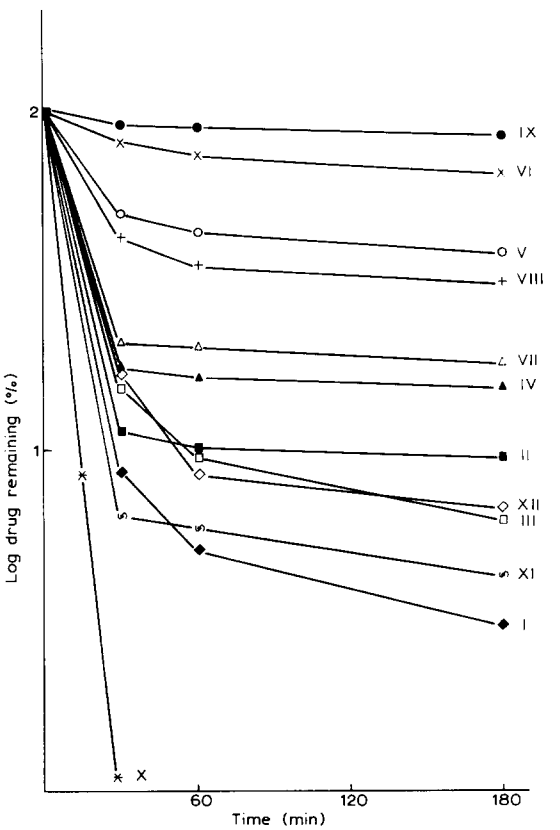

Fig. 4. First-order furosemide release profiles from microspheres prepared using different drug-polymer ratios. Furosemide-Eudragit L 1:1 (I), 1:2 (II), 1:4 (III); Furosemide-Eudragit RL 1:1 (IV), 1:2 (V), 1:4 (VI); Furosemide-Eudragit RS 1:1 (VII), 1:2 (VIII), 1:4 (IX); Furosemide-Eudragit S 1:1 (X), 1:2 (XI) and 1:4 (XII).

TABLE 5

Kinetic data of furosemide microspheres

Drug: polymer ratio		First order kinetics		Higuchi kinetics		Baker and Lonsdale kinetics	
		k	r	k	r	k	r
Eudragit L	1:1	0.289	0.840	0.886	0.913	0.073	0.880
	1:2	0.271	0.501	0.859	0.767	0.035	0.910
	1:3	0.370	0.750	3.09	0.967	0.039	0.980
	1:4	0.209	0.574	1.87	0.862	0.061	0.570
Eudragit S	1:1	0.536	1.000	1.99	0.820	1.16	1.000
	1:2	0.360	0.760	1.72	0.728	0.072	0.770
	1:3	0.314	0.582	1.69	0.821	0.046	0.760
	1:4	0.151	0.825	1.96	0.925	0.051	0.940
Eudragit RL	1:1	0.181	0.852	2.24	0.895	1.2×10^{-3}	0.860
	1:2	0.086	0.876	1.16	0.920	1.0×10^{-4}	0.895
	1:3	0.036	0.877	0.580	0.946	7.42×10^{-5}	0.918
	1:4	0.130	0.980	0.870	0.947	1.4×10^{-5}	0.980
Eudragit RS	1:1	0.040	0.680	0.883	0.760	2.0×10^{-4}	0.691
	1:2	0.100	0.920	1.09	0.956	4.0×10^{-4}	0.930
	1:3	0.054	0.987	1.06	0.988	3.33×10^{-5}	0.967
	1:4	0.050	0.990	1.22	0.999	3.6×10^{-5}	0.960

k, release rate constant; r, correlation coefficient.

was used in order to distinguish between the two mechanisms of drug release: first-order and diffusion-controlled. As proposed by Schwartz et al.

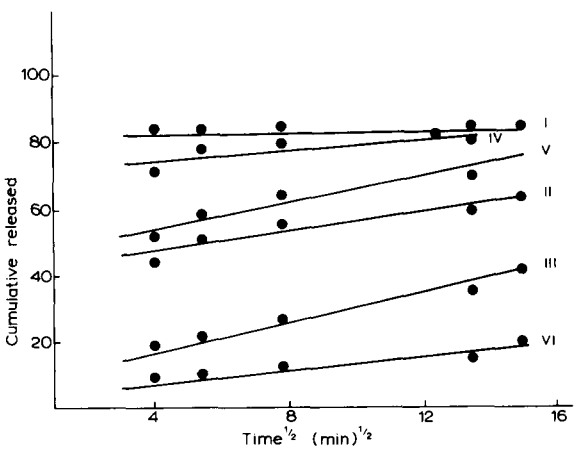

Fig. 5. Release profiles of furosemide microspheres prepared using different drug-polymer ratios, when plotted according to the diffusion model. Furosemide-Eudragit RL 1:1 (I), 1:2 (II), 1:4 (III). Furosemide-Eudragit RS 1:1 (IV), 1:2 (V) and 1:4 (VI).

TABLE 6

Comparison of linearization parameters (correlation coefficients) for plots of release rate against drug release

Drug: Eudragit ratio	Eudragit RS		Eudragit L	
	I	II	I	II
1:1	0.911	0.920	0.831	0.861
1:4	0.941	1.000	0.926	0.941

For I, rate is plotted versus Q'; For II, rate is plotted versus $1/Q'$.

(1968) by using rate equations, two mechanisms can be differentiated. For the matrix mechanism, according to this equation;

$$\frac{dQ'}{dt} = \text{rate} = \frac{K^2S^2}{2Q'}$$

where Q' = total amount of drug released, S = surface area, K = release constant; the rate is inversely proportional to Q'. The rate predicted by the first order kinetics is given by the following equation:

$$\frac{dQ'}{dt} = k_1W_0 - k_1Q'$$

(where W_0 = initial amount of drug) which indicates that the rate is proportional to Q'.

As seen in Table 6, rate is inversely proportional to Q'. Kinetics representing the mechanism of furosemide release follows diffusion controlled kinetics.

In conclusion, controlled-release microspheres of furosemide can be prepared by using the spherical crystallization technique. This process is very simple, economical and also convenient to scale up to a commercial level.

The release profiles of these microspheres can be modified by controlling Eudragit concentration, and by changing solvent–polymer ratio. In vitro dissolution findings showed that particularly Eudragit RL and Eudragit RS gave prolonged release of furosamide and drug release appeared to fit the Higuchi matrix model.

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