International Journal of Pharmaceutics, 76 (1991) 193–198

ADONIS 037851739100348E

IJP 02516

Research Papers

Furosemide-loaded ethyl cellulose microspheres prepared by spherical crystallization technique: Morphology and release characteristics

Julide Akbuğa

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Marmara, Nişantaşi, Istanbul (Turkey)

(Received 17 April 1991)
(Accepted 13 May 1991)

Key words: Ethyl cellulose; Controlled release; Microsphere; Spherical crystallization; Furosemide; Release rate; Higuchi model

Summary

Furosemide-loaded ethyl cellulose microspheres were prepared by a spherical crystallization technique. The average diameters were about 330–335 μm and the drug contents in the microspheres were 65–84%. The size and formation of microspheres can be controlled by the rate of agitation. Furthermore, as the concentration of ethyl cellulose increased, the release rate of furosemide decreased. The results are examined kinetically and the mechanism is discussed. Dissolution data indicated that the release followed the Higuchi matrix model. These results show that furosemide-loaded ethyl cellulose microspheres could be prepared providing a controlled release property.

Introduction

The spherical crystallization technique can provide characteristic advantages over conventional microsphere preparation methods (Kawashima et al., 1986; Akbuğa, 1989). On the other hand, ethyl cellulose has been used as carrier in microsphere preparation due to its safety, stability, inertness and because it is water permeable without being water soluble. It has been applied by solvent evaporation but the spherical crystallization technique has not been used for ethyl cellulose in the preparation of microspheres (Benita et al., 1988; Dubernet et al., 1988).

As previously reported, the spherical crystallization technique can be used successfully to prepare Eudragit microspheres containing furosemide (Akbuğa, 1989). In the present study, the same procedure was applied to prepare furosemide-loaded ethyl cellulose microspheres. Moreover, the effects of factors, such as drug/ethyl cellulose and solvent/polymer ratios and stirring rate, on drug release were studied.

Correspondence: J. Akbuğa, Dept of Pharmaceutical Technology, Faculty of Pharmacy, University of Marmara, Nişantaşi, Istanbul, Turkey.

Experimental

Materials

Furosemide (Hoechst AG, Frankfurt, Germany), ethyl cellulose (10 cps viscosity grade, Prodotti-fromi, Italy) and methylene chloride (E. Merck, Darmstadt, Germany) were used.

Methods

Preparation of microspheres All microspheres were prepared by the spherical crystallization technique (Akbuğa, 1989). Weighed amounts of furosemide and ethyl cellulose were dissolved in a mixture of methylene chloride and alcohol (1 : 1). The formed solution was poured into 500 ml of 0.1 N HCl solution stirred with a propeller type agitator (Ika-Werk, Janke & Kunkel, Germany). After 30 min stirring, the microspheres were separated by filtration, washed with water and then dried in vacuo. All batches were prepared at least three times.

Variation of formulation factors Different furosemide : ethyl cellulose ratios (1 : 1, 1 : 2, 1 : 3 and 1 : 4) were used in order to investigate the effect of drug : polymer ratio on release and the physical characterization of microspheres. Solvent-polymer ratios were varied by keeping polymer and drug ratio constant and the effect of the ratio was also studied.

Variation of process factors The effect of stirring rate (100 and 1000 rpm) on microsphere characteristics was investigated.

Physical characterization of microspheres Microscopy studies: scanning electron microscopy (SEM) (Jeol JVA 840 A) was used to evaluate the shape and surface characteristics of the microspheres. Size determination: size and size distributions were measured by sieve analysis.

In vitro release studies A weighed quantity of microspheres (332 μm) was suspended in 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 279 nm. The means of six determinations are given. Corrections were made for any absorption due to ethyl cellulose.

Determination of drug content in microspheres A weighed quantity of microspheres was dissolved in alcohol and drug content was spectrophotometrically assayed. The means of three assays are reported.

Results and Discussion

The surface topography and interval structure of the microspheres were investigated by scanning electron microscopy. As seen in Fig. 1, they were invariably spherical and exhibited porous surfaces with a large number of interstices.

As shown in Fig. 1A and B, no morphological differences were observed between the microspheres prepared with different furosemide : ethyl cellulose ratios.

The results of sieve analysis show that the average size of microspheres was about 332.0 μm (Table 1). However, it was found that the main factor determining the size of microspheres was the agitation speed of the system. As shown in Table 1, decreasing the stirring rate during the preparation of microspheres increases the mean diameter of microspheres. As previously reported (Kawashima et al., 1986), the increased mechanical shear force, produced by increasing the stirring rate, rapidly broke up the solution of polymer and drug into finer drops, leading to finer matrix spheres. However, microspheres were not formed well at low stirring rates. Microsphere formation is also dependent on the viscosity of ethyl cellulose used. With high-viscosity ethyl cellulose, microspheres containing furosemide could not be formed well enough.

Furthermore, with low polymer content, the particles agglomerated into crystals with the polymer.

The furosemide content of ethyl cellulose microspheres is summarized in Table 2. As listed in Table 2, the incorporation efficiency was high since it ranged from 70 to 80%. The recorded variations between the microsphere batches were considered to be due to the uncontrolled removal of the drug during the washing steps. The drug

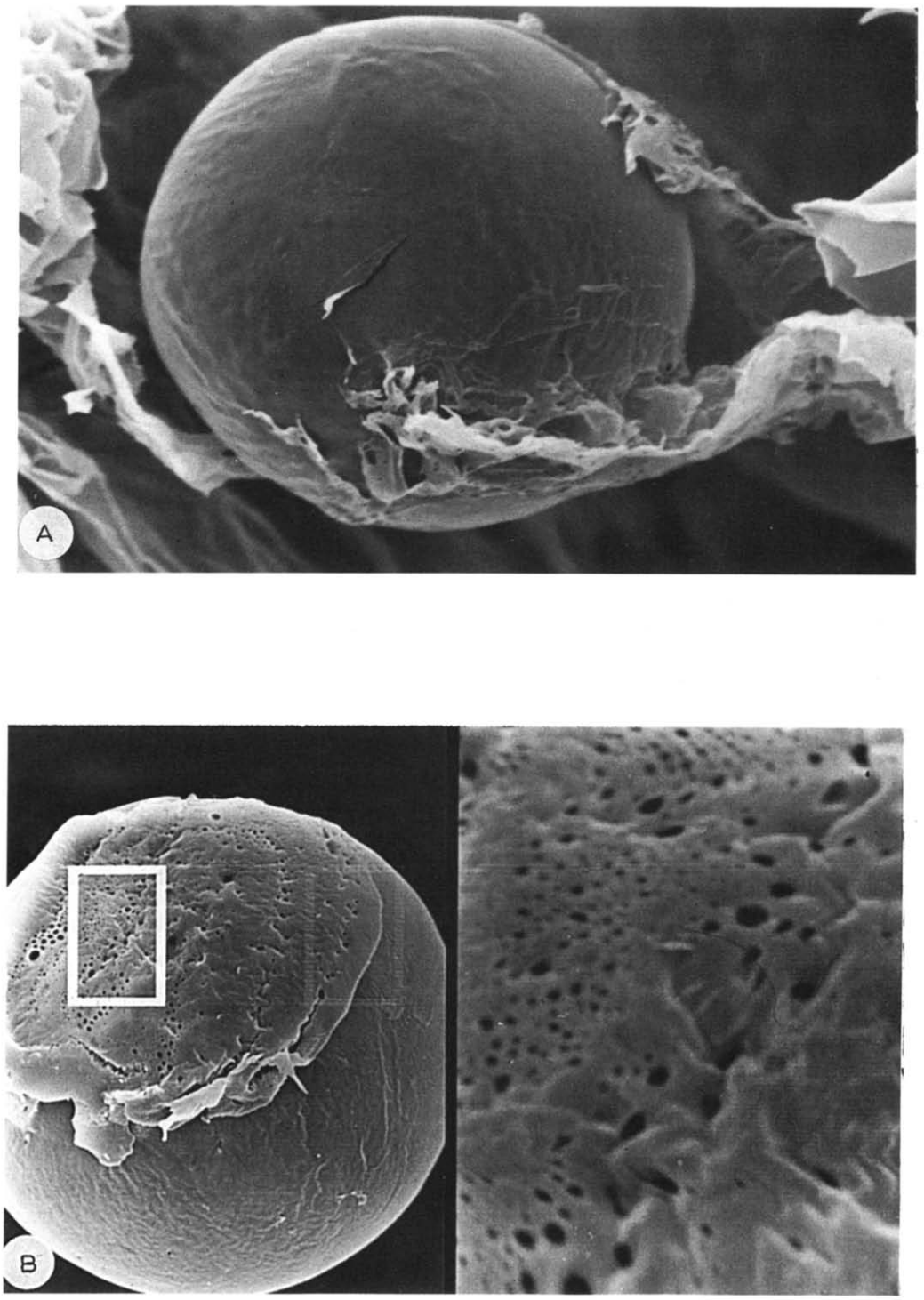

Fig. 1. Scanning electron micrographs of furosemide-loaded ethyl cellulose microspheres prepared with (1 : 1.5) drug : EC ratio (A), (1 : 4) drug : EC (B) ratios and surface of microspheres (6 × 1200).

TABLE 1

Particle sizes and drug content of furosemide microspheres prepared at different stirring rates

Stirring rate (rpm)	Theoretical drug content (%)	Assay drug content (%)	Mean particle size (μm ± SD)
100	33.33	34.12	441.31 (0.99)
1000	33.32	21.42	332.59 (8.37)

was uniformly encapsulated into the microspheres irrespective of the initial drug concentration. Moreover, Table 2 shows that drug loading was not affected by drug:ethyl cellulose ratio.

Release studies

The release profiles of furosemide from ethyl cellulose microspheres are illustrated in Fig. 2. It is evident that encapsulation of drug resulted in a marked decrease in drug release. The effect of retardation on the release rate depends on the drug : ethyl cellulose ratio. The effect of drug:polymer ratio on drug release profiles is also shown in Fig. 2; as the concentration of ethyl cellulose increased, the release rate of furosemide decreased.

During all experiments, microspheres formed from ethyl cellulose remained intact and no erosion was seen.

TABLE 2

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

Drug:EC ratio	Theoretical drug content (%)	Assay drug content (%)	Incorporation efficiency (%)
1:1	50.0	30.28	60.56
1:1.5	40.0	30.50	76.40
1:2	33.3	25.90	77.80
1:2.25	30.7	24.80	80.60
1:2.5	28.5	24.00	84.00
1:3	25.0	20.30	81.30
1:3.5	22.2	12.88	57.96
1:4	20.0	15.06	75.30

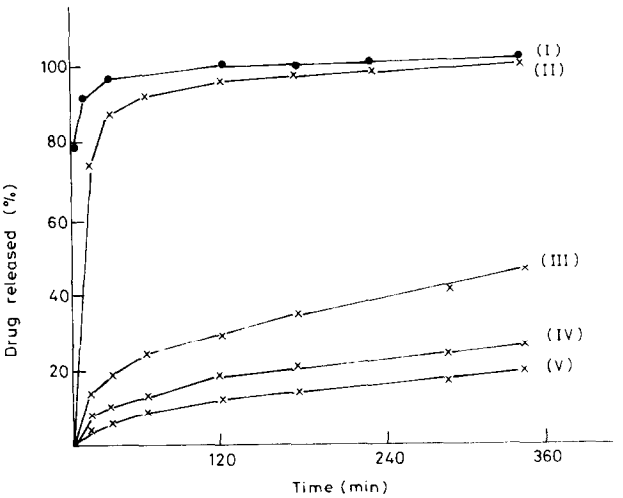

Fig. 2. Release profiles of furosemide-loaded ethyl cellulose microspheres prepared with different drug:polymer ratios. Furosemide powder (I), drug:ethyl cellulose (1:1) (II), (1:2) (III), (1:2.5) (IV), (1:4) (V).

Dissolution profiles of microspheres prepared with different solvent:polymer ratios are shown in Fig. 3. As can be seen, no noticeable change was observed in the release profiles of furosemide microspheres prepared with different solvent:polymer ratios. However, as reported above, the stirring rate during the preparation of microspheres had a strong effect on drug release. As

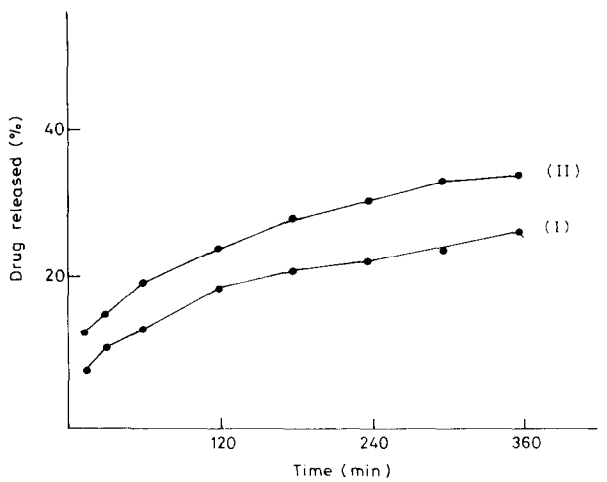

Fig. 3. Effect of solvent:polymer ratio on drug release from microspheres. Solvent:polymer ratios (10:2.5) (I), (25:2.5) (II).

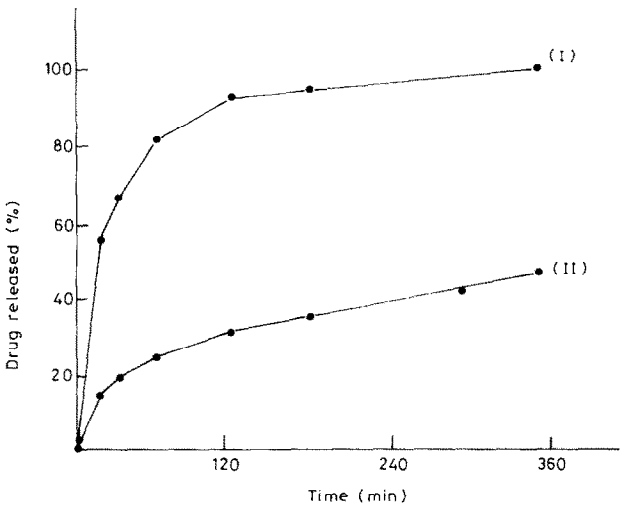

Fig. 4. Effect of stirring rate on drug release from microspheres: 100 rpm (I), 1000 rpm (II).

demonstrated in Fig. 4, furosemide release increased as the stirring rate decreased.

Release mechanism

As seen in Fig. 2, release from furosemide-loaded microspheres was not linear with time. In order to investigate the mechanism further, the release data were fitted to models representing zero-order, first-order, Higuchi's square-root of time, indicative of release mechanisms related solely to time, drug diffusion or its dissolution rate, respectively.

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).

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

$$3/2\left[1-(1-F)^{2/3}\right]-F=KT \qquad (1)$$

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

The linear regression analysis for each trial is summarized in Table 3. A survey of Table 3 shows that the coefficient of determination (r^2) was about 0.95–0.99 in each case, indicating that the data represent diffusion control.

This conforms with the contention that the mechanism of drug release from furosemide microspheres is mainly diffusion-controlled. However, a more stringent test was used to distinguish between the mechanisms of drug release. Release data were analyzed by the empirical equation (Higuchi, 1963; Cardinal, 1984):

$$Q(t)=at^n \qquad (2)$$

where $Q(t)$ is the fraction of drug released after time t and a is a coefficient.

TABLE 3

Kinetic data of furosemide-loaded microspheres

Kinetics		Drug:EC ratio							
		1:1	1:1.5	1:2	1:2.25	1:2.5	1:3	1:3.5	1:4
Zero-order	k	0.082	0.117	0.094	0.061	0.048	0.042	0.41	0.035
	r^2	0.636	0.856	0.765	0.925	0.958	0.935	0.950	0.910
First-order	k	9.41×10^{-4}	3.70×10^{-3}	3.00×10^{-3}	3.04×10^{-3}	3.05×10^{-3}	4.22×10^{-3}	3.24×10^{-3}	3.58×10^{-3}
	r^2	0.602	0.758	0.833	0.826	0.824	0.797	0.781	0.783
Higuchi	k	11.57	3.08	2.35	1.31	0.943	1.043	0.556	0.784
	r^2	0.884	0.996	0.954	0.986	0.974	0.977	0.968	0.990
Baker	k	9.97×10^{-4}	1.84×10^{-4}	1.10×10^{-4}	5.46×10^{-5}	3.16×10^{-5}	1.98×10^{-5}	2.05×10^{-5}	1.47×10^{-5}
Lonsdale	r^2	0.809	0.933	0.988	0.980	0.970	0.994	0.996	0.982

k, release rate constant; r^2, coefficient of determination.

TABLE 4

Coefficients and exponents of furosemide release functions according to $Q(t) = at^n$ for microspheres with various drug : ethyl cellulose ratios

	Drug : ethyl cellulose ratio							
	1 : 1	1 : 1.5	1 : 2	1 : 2.25	1 : 2.5	1 : 3	1 : 3.5	1 : 4
r^2	0.929	0.985	0.996	0.997	0.993	0.994	0.999	0.992
n	0.093	0.407	0.417	0.373	0.356	0.514	0.415	0.445
a	1.094	0.084	0.281	0.351	0.321	1.012	0.940	0.872

r^2, coefficient of determination; n, release exponent in Eqn 2; a, coefficient in Eqn 2.

Different values of n (release exponent) indicate different release mechanisms. It was shown that, for $n = 0.5$, the release is Fickian-diffusion controlled and follows a square root of time relationship (Peppas, 1985).

Values for the coefficient a and the exponent n are given in Table 4. The values of n were in the range 0.37–0.51, thus the release process is diffusion-controlled.

In conclusion, drug-loaded ethyl cellulose microspheres can be prepared by the spherical crystallization technique. The release rate can be varied by varying the concentration of ethyl cellulose. The release of furosemide from ethyl cellulose microspheres is dependent on the square root of time.

Acknowledgements

The author wishes to thank the Gebze Unit of TUBITAK and Z. Misirli for taking the scanning electron microphotographs.

References

Akbuğa, J., Preparation and evaluation of controlled release furosemide microspheres by spherical crystallization. *Int. J. Pharm.*, 53 (1989) 99–105.

Baker, R.W. and Lonsdale, H.K., In Tanquary, A.C. and Lacey, R.E. (Eds), *Controlled Release of Biologically Active Agents*, Plenum, New York, 1974, pp. 15–71.

Benita, S., Babay, D., Hoffman, A. and Donbrow, M., Relation between individual and ensemble release kinetics of indomethacin from microspheres. *Pharm. Res.*, 5 (1988), 178–182.

Cardinal, C.R., Drug release from matrix devices. In Anderson, J.M. and Kims, S.W. (Eds), *Recent Advances in Drug Delivery Systems*, Plenum, New York 1984, pp. 229–248.

Dubernet, C., Benoit, J.P. Peppas, N.A. and Puisieux, F., The Higuchi model as a tool to obtain information about the structure of ibuprofen-loaded ethyl cellulose microspheres. *Proceedings of 5th International Conference on Pharmaceutical Technology*, Paris, 1988, pp. 69–77.

Higuchi, T., Mechanism of sustained action medication. *J. Pharm. Sci.*, 52 (1963) 1145–1149.

Kawashima, Y., Handa, T., Takeuchi, H. and Niwa, T., Preparation of controlled release microspheres of ibuprofen with acrylic polymer (Eudragit) by the spherical crystallization technique. *Proceedings of 4th International Conference on Pharmaceutical Technology*, Paris, Vol. II, 1986, pp. 161–167.

Peppas, N., Analysis of Fickian and non-Fickian drug release from polymers, *Pharm. Acta Helv.*, 60 (1985) 110–111.