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Drug release from perforated matrices containing hydroxypropylcellulose

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Abstract

Perforated matrices were obtained using as excipient hydroxypropylcelluloses having different viscosity degrees. Furosemide release was affected by the polymer viscosity, while it was not related to the releasing surface area. In fact, the matrix having the highest hole diameter, and consequently the lowest releasing surface area, showed the highest release rate. The application of an impermeable coating on all the surfaces, except the hole surface, restricted the releasing surface area reducing the release rate. Furosemide release from the perforated coated matrices was the same regardless of the hole diameter (surface) as the data were related to the unitary releasing surface. The comparative analysis of the drug release mechanism showed the decrease of the erosion (polymer dissolution) component and the increase of the drug diffusion component of the process as the perforated matrices were coated. These results can be justified by the restriction of the matrix swelling produced by the impermeable coating.

Keywords: Perforated uncoated matrix; Perforated coated matrix; Hydroxypropylcellulose; Viscosity degree; Drug release; Drug diffusion; Matrix erosion

1. Introduction

Several cellulose ethers are commonly used in the pharmaceutical field as excipients for the preparation of matrix systems used in sustained release formulations. The drug release from these swellable and erodible matrices occurs by drug diffusion, polymer dissolution or by a combination of the two above processes (Huber et al., 1966; Alderman, 1984; Doelker, 1987; Mitchel et al., 1993; Skough et al., 1993; Pham and Lee, 1994; Gao et al., 1995; Sung et al., 1996). The drug release from these matrices can be modified by several factors, such as the type of polymer, the polymer concentration and viscosity, the drug particle size, and the presence of additives in the final formulation (Ford et al., 1985, 1987; Feely and Davis, 1988; Hogan, 1989).

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Table 1
Physical characteristics and drug content of the perforated uncoated and coated matrices of hydroxypropylcellulose

Hole diameter (mm)	Matrix weight (mg)	Drug content (mg)	Releasing surface area of the matrix (mm^2)	
			Uncoated	Coated
5	400 ± 2	40 ± 0.2	395.8	47.1
6	360 ± 2	36 ± 0.2	388.0	56.6
8	265 ± 2	27 ± 0.2	362.8	75.4

Changes in the matrix shape was one of the approaches proposed to modify the drug release. One of the suggestions consists in the modification of the cylindrical matrices boring a hole in the centre of the flat surfaces (Bechard and McMullen, 1988; Hansson et al., 1988; Sangalli et al., 1993; Vandelli and Cameroni, 1993; Vandelli et al., 1993; Benkorah and McMullen, 1994). The coating of appropriate surfaces of perforated matrices was previously suggested for the preparation of oral dosage forms for the concurrent administration of drugs, for their immediate and controlled release and for the colonic delivery (Vandelli et al., 1995a,b, 1996). In the literature, little attention was paid in order to evaluate both the release mechanism from perforated matrices of cellulose ethers and the modification produced by the application of an impermeable coating.

Therefore, this study aims to estimate the relative importance of drug diffusion and matrix erosion in the release process from perforated uncoated and coated matrices prepared with hydroxypropylcelluloses of different viscosity degree.

2. Experimental

2.1. Materials

Furosemide {5-(aminosulfonyl)-4-chloro-2-[(2-furanylmethyl)amino]benzoic acid} (FIS, Alte di Montecchio Maggiore, Italy) (MW 330.7; slightly soluble in water (< 1 mg/ml at 23°C), soluble in solution of alkali hydroxide) was used as the drug. Hydroxypropylcelluloses (HPCs) (Nippon, Tokyo, Japan) of four viscosity degrees (HPC-SL, HPC-L, HPC-M and HPC-H; viscosity of a 2% (w/w) water solutions at 20°C: 3.0–5.9; 6.0–10.0; 150–400; and 1000–4000 mPa.s, respectively) were utilised as the excipients. Ethylene: vinyl acetate copolymer (theoretical vinyl acetate content 40%, EVAc) (Aldrich, Milwaukee, WI) was the coating material. All the chemicals (pure grade, Carlo Erba, Milan, Italy) and materials were employed as received from the manufacturers.

2.2. Preparation of the perforated uncoated matrices

Cylindrical matrices (weight 450 ± 4 mg; diameter 13 ± 0.1 mm; thickness 3.0 ± 0.3 mm) were prepared by compression of homogeneous mixtures of furosemide and one of HPCs (1:10, w/w) using a hydraulic press (model M, Carver, Menomonee Falls, WI) (300 kg cm^{-1} for 1 min).

The perforated matrices were obtained boring a hole (8, 6 or 5 mm) in the centre of the flat surfaces through both sides of the cylindrical matrices. The weight and the drug content of the perforated matrices were modified by the hole diameter (Table 1), while the drug/polymer ratio (1:10, w/w) remains constant for the all the perforated matrices.

2.3. Preparation of the perforated coated matrices

The coated matrices were obtained applying by hand on all the surfaces, except the hole surface, five times a solution of EVAc dissolved in benzene (1:2, w/w), each time allowing the matrices to dry at 30°C for 30 min and then overnight at room temperature.

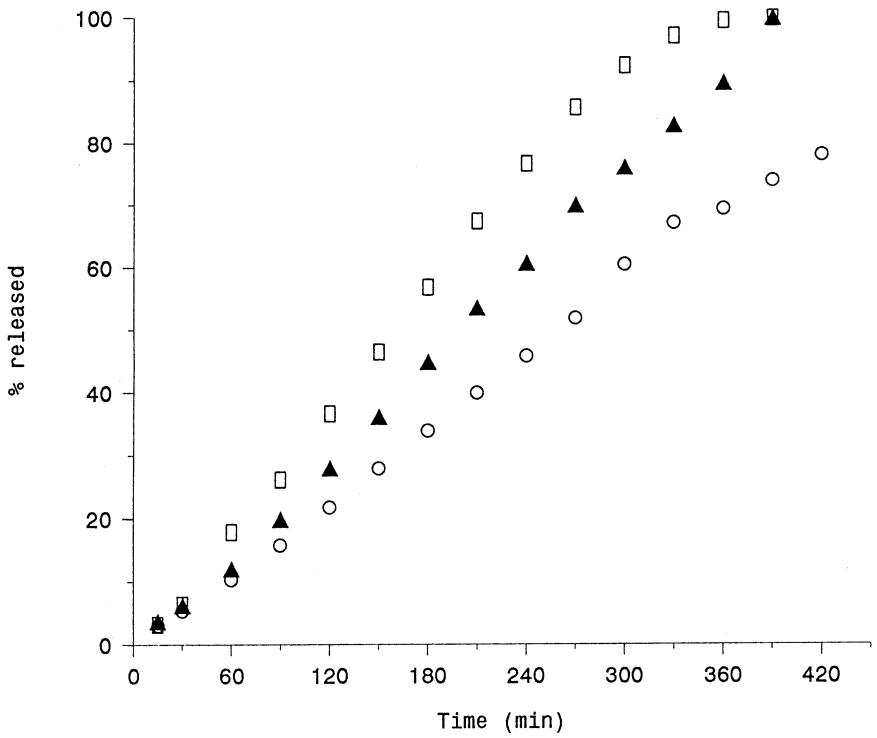

Fig. 1. Furosemide release from uncoated perforated matrices based on HPC-L. Hole diameter and releasing surface area: □ 8 mm–362.8 mm^2; ▲ 6 mm–388mm^2; ○ 5 mm–395.8 mm^2.

Obviously, this coating technique cannot be applied to prepare matrices to be administered owing to the safety problems related to the solvent. The aim of this work (the evaluation of the release process from perforated matrices and the modifications produced by the application of an impermeable coating) can justify the use of an unsafe solvent such as benzene.

2.4. Drug release studies

Drug release from the matrices was examined using a column-type apparatus (Dissotest CE-1, Sotax, Basel, Switzerland) according to the USP 23. The release tests (four replicates) were performed in 1000 ml of pH 5.8 phosphate buffer. All experiments were carried out at a temperature of 37 ± 0.2°C using a flow rate of 25 ml min^{-1}. The drug content in the solution was determined spectrophotometrically (Lambda 3A, Perkin-Elmer, Norwalk, CA) at appropriate wavelength (278 nm).

The coating was proved to be water-impermeable under the experimental conditions (Vandelli and Cameroni, 1993; Vandelli et al., 1993). To prove the impermeability of the EVAc coating, four tablets coated on all the surfaces were submitted to drug release experiments. No drug was determined in the solution under the above experimental conditions, proving the reproducibility of the technique to renders the matrices impermeable to water.

2.5. Analysis of the release data

The analysis of the drug release mechanism was done using the power law expression (Korsmeyer et al., 1983):

$$M_t/M_\infty = kt^n \quad (1)$$

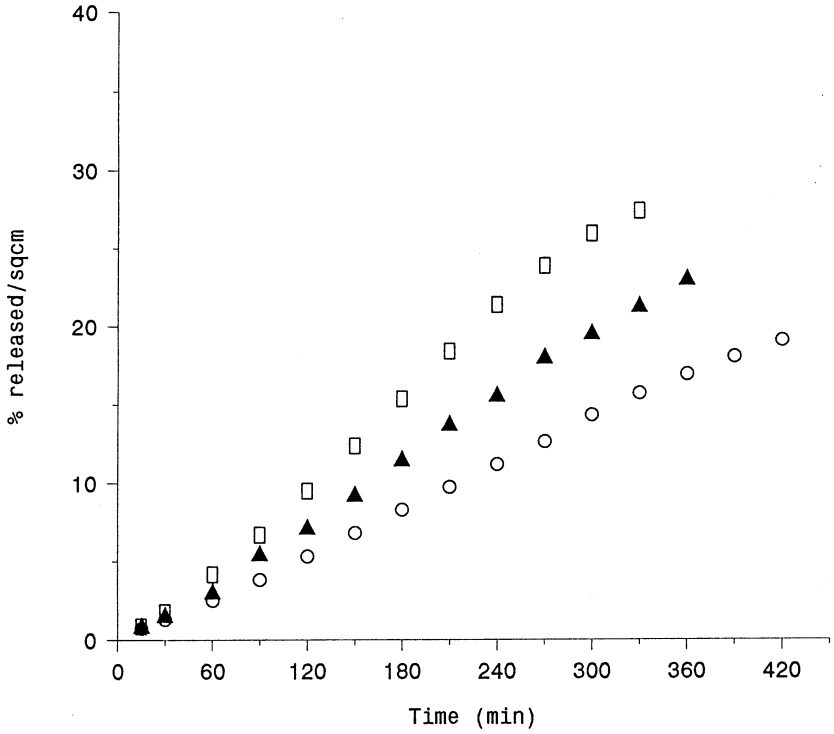

Fig. 2. Furosemide release from uncoated perforated matrices based on HPC-L according to the unitary releasing area. Hole diameter: □ 8 mm; ▲ 6 mm; ○ 5 mm.

where M_t/M_∞ denotes the drug fraction released at time t, k and n being the rate constant and the kinetic exponent of release, respectively.

The value of kinetic exponent n defines the mechanism of the release process (Sinclair and Peppas, 1984) according to the geometry of the systems (Ritger and Peppas, 1987a,b). However, the relationships between the release mechanism and the value of the kinetic exponent n are not defined for the perforated uncoated and coated matrices. Therefore, the n values are used in this work only to compare the relative importance of the matrix erosion and drug diffusion components of the release process.

3. Results and discussion

3.1. Perforated uncoated matrices

As the drug is released from a cylindrical matrix, the boundary where the drug is dissolved (dissolution surface) moves into the matrix from the surface from which the drug is released (releasing surface) increasing the diffusion pathlength. Therefore, the dissolution surface area remains constant as the drug release occurs from a planar surface and decreases as the drug release occurs from the lateral surface. As a consequence, the drug release from a cylindrical matrix produces the decrease of the dissolution surface area of the core within the matrix.

In the perforated uncoated matrices, the cylindrical shape is modified by the hole bored in the centre of the flat surface through both sides of the matrix. As the diffusion pathlength increases, the increase of the dissolution surface area has to be considered when the drug release occurs from the hole surface in addition to the decrease of the dissolution surface typical of a cylindrical matrix. Therefore a perforated uncoated matrix can be proposed to compensate for the influence of the cylindrical shape.

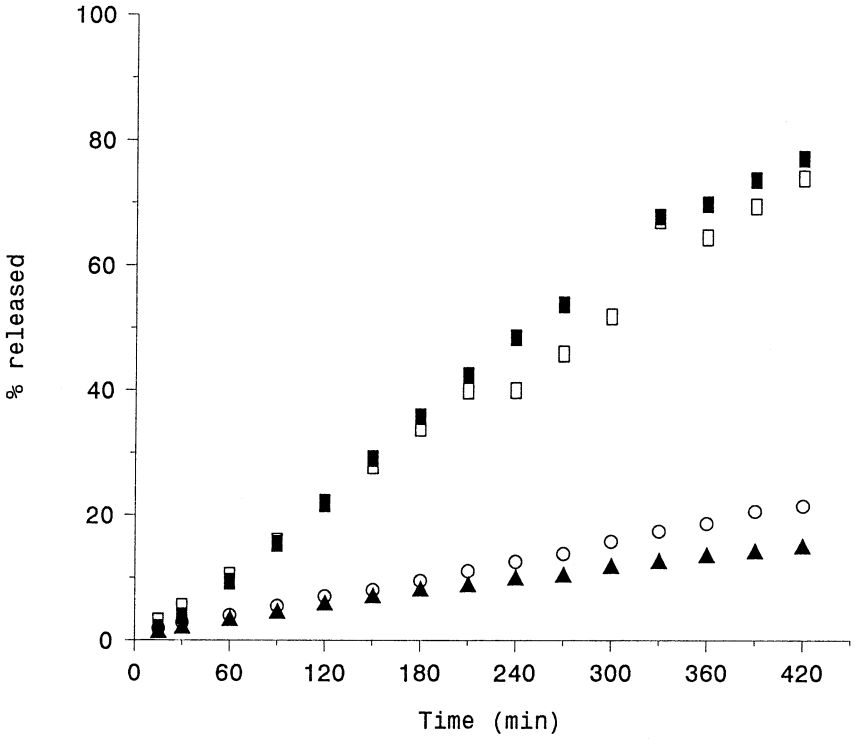

Fig. 3. Furosemide release from uncoated perforated matrices having a 5 mm hole diameter (surface area: 395.8 mm^2) according to the viscosity of the HPC used as excipient. ■ HPC-SL (3.0–5.9 mPa.s); □ HPC-L (6.0–10.0 mPa.s); ○ HPC-M (150–400 mPa.s); ▲ HPC-H (1000–4000 mPa.s).

The weight, the drug content and the surface area of the perforated uncoated matrices are reported in Table 1. The variation of the hole diameter changes the releasing surface area affecting the surface of the hole and the bases.

The surface of the bases is an annulus, i.e. the area enclosed by two concentric circles having the matrix diameter ($d_e = 13$ mm) and the hole diameter (d_i), respectively. The width $[(d_e - d_i)/2]$ and the surface area of the two annuli decrease as d_i increases. In fact, the matrices having a d_i value of 5, 6 and 8 mm hole diameter [$(d_e - d_i)/2$ of 4, 3.5 and 2.5 mm] had the surface area of the two annuli of 226, 209 and 165 mm^2, respectively. On the contrary, the surface area of the hole increases as d_i increases, being 47.1, 56.5 and 75.4 mm^2 for a d_i value of 5, 6 and 8 mm, respectively. Therefore, the improving effect on the releasing surface area determined by the hole is lower than the reduction its formation produces on the base surface. The lateral surface area of the matrix is the same regardless to the hole diameter (122.5 mm^2). Therefore, the whole releasing surface area of the perforated uncoated matrices decreases as the hole diameter increases (Table 1).

3.2. Effect of the hole diameter

The release of furosemide from the perforated uncoated matrices of HPC-L increased as the hole diameter increased from 5 to 8 mm (Fig. 1). As the releasing surface area of the perforated uncoated matrices decreased as the hole diameter increased (Table 1), the drug release cannot be related to the whole releasing surface in contrast to the theoretical expectations.

In fact, when the experimental release data are related to the unitary surface, the release is the highest from the matrix having the lowest surface area and the highest hole diameter (Fig. 2). There-

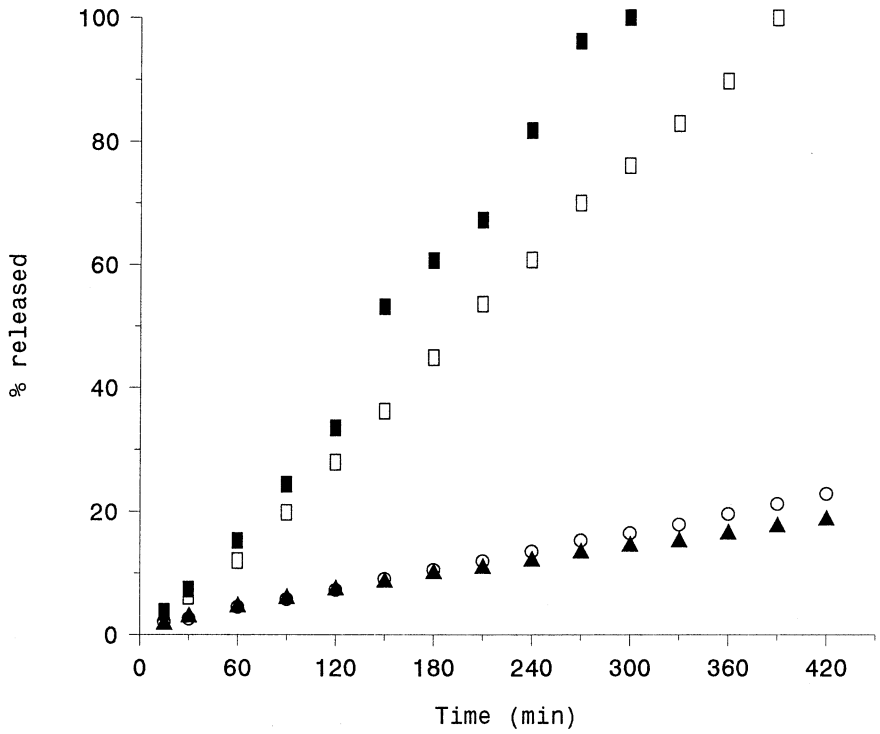

Fig. 4. Furosemide release from uncoated perforated matrices having a 6 mm hole diameter (releasing surface area 388 mm^2) according to the viscosity of the HPC used as excipient. ■ HPC-SL (3.0–5.9 mPa.s); □ HPC-L (6.0–10.0 mPa.s); ○ HPC-M (150–400 mPa.s); ▲ HPC-H (1000–4000 mPa.s).

fore, modifications of the hole diameter (surface) seems to have a greater importance than the increase of whole releasing surface. Hence, the increase of the hole surface improves the release notwithstanding the decrease of the base surface.

In our opinion, the experimental data allowed the conclusion to be drawn that the hole surface could release the drug with a faster rate than the basis and the lateral surface. To explain the reason of the faster drug release rate from the hole surface respect to the other matrix surfaces, a simple explanation can be proposed.

In fact, it should be borne in mind that the width $[(d_e - d_i)/2]$ of the two annuli decrease as d_i increases. In fact, matrices having a hole of 5, 6 and 8 mm in diameter had a $(d_e - d_i)/2$ value of 4, 3.5 and 2.5 mm, respectively. Therefore, the complete penetration of the dissolution medium in the matrices occurs in a time that is related to the width of the annulus, i.e. to the hole diameter. In fact, all the drug dispersed in the polymer is put into contact with the dissolution medium in a time depending to the width of the annulus. Therefore the drug release can occur with a rate related to the hole diameter, being the fastest as the hole diameter is the highest.

3.3. Effect of the polymer viscosity

The drug release from a hydrophilic matrix depends on the formation of a gel layer on the exposed surface. The release is affected both by the drug diffusion through the gel layer and the matrix erosion. In both cases, the polymer viscosity plays an important role affecting the relative importance of the two components of the release process.

Therefore, the drug release from perforated matrix based on HPCs having different viscosity degree (3.0–5.9, 6.0–10.0, 150–400 and 1000–

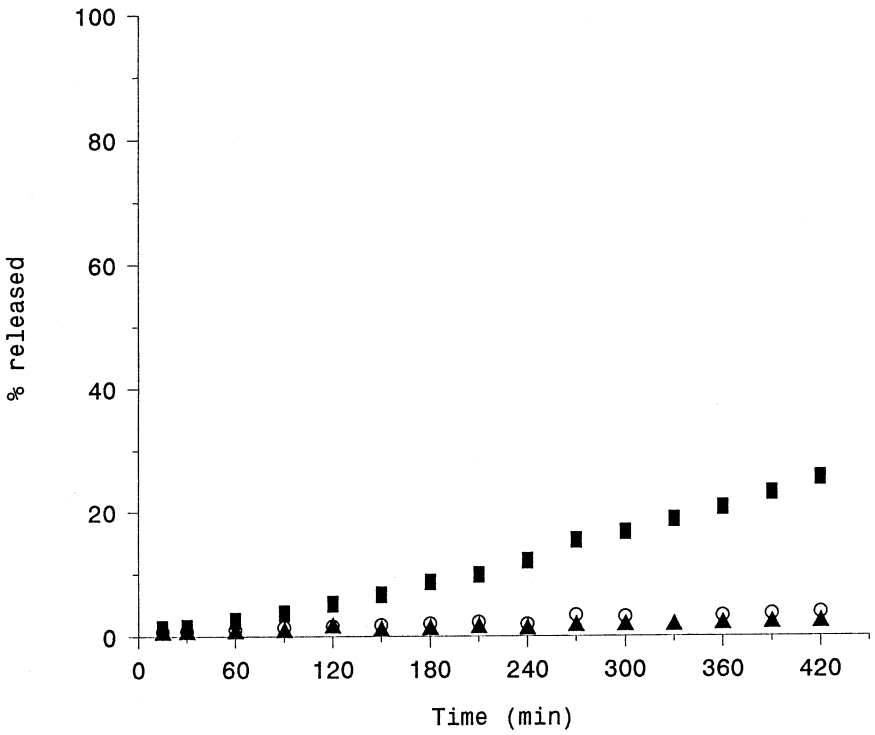

Fig. 5. Furosemide release from coated perforated matrices having a 6 mm hole diameter (releasing surface area 56.6 mm^2). ■ HPC-SL (3.0–5.9 mPa.s); ○ HPC-M (150–400 mPa.s); ▲ HPC-H (1000–4000 mPa.s).

4000 mPa.s) was examined (Figs. 3 and 4). According to the theoretical expectations, the highest was the viscosity degree of the polymer, the slowest was the release rate regardless to the hole diameter. On the bases of the visual inspection of the release profiles, the four polymers can be separated in two distinct groups: high viscosity (H and M) and low viscosity (SL and L) HPCs. The experimental results of the release from the matrices based on HPC-M (150–400 mPa.s) and HPC-H (1000–4000 mPa.s) are practically overimposed, although the high difference in the polymer viscosity (ten times about). Therefore, 150–400 mPa.s can be the limiting viscosity for HPC above which the release did not decreased as the viscosity increased. This value is lower than that reported by Sung et al. (1996) as limiting viscosity for hydroxypropylmethylcellulose (15000 mPa.s). An apparent difference can be observed in the drug release from matrices based on HPC-SL (3.0–5.9 mPa.s) and HPC-L (6.0–10.0 mPa.s) having a 6 mm hole (Fig. 4).

3.4. Perforated coated matrices

The coating of all the surfaces, except the hole surface, of the perforated uncoated matrix limits the releasing surface to the hole surface. Hence, both the matrix weight (excluding the coating) and the drug content are the same as in the uncoated matrices, while the releasing surface is reduced (Table 1), increasing as the hole diameter increased.

Therefore, the increase of the drug release according to the increase of the hole diameter is the obvious consequence of the increase of the releasing surface (Figs. 5 and 6). The hole diameter being the same, the release is related to the polymer viscosity, being the highest from the matrices based on the HPC having the lowest viscosity degree (HPC-SL and HPC-L).

The drug release from the coated perforated matrices is obviously lower than from the uncoated matrices as the releasing surface area is lower (Table 1).

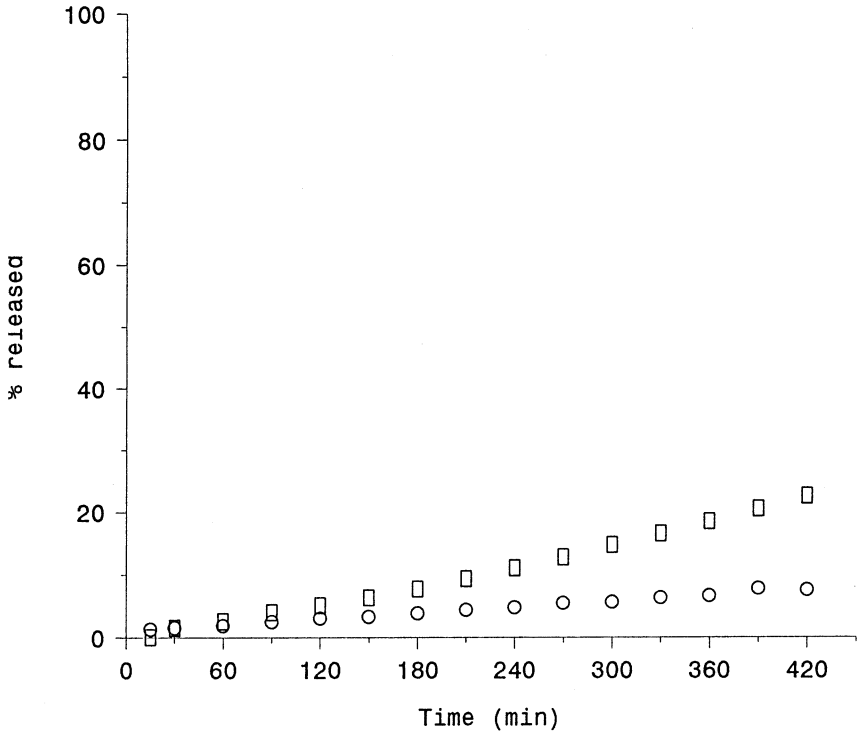

Fig. 6. Furosemide release from coated perforated matrices having a 8 mm hole diameter (releasing surface area 75.4 mm^2). □ HPC-L (6.0–10.0 mPa.s); ○ HPC-M (150–400 mPa.s).

In the perforated coated matrices, the percentage of drug released for unitary releasing surface area is practically unaffected by the hole diameter contrary to the results obtained for the uncoated matrices (Fig. 7).

As the dissolution medium penetrates in a coated matrix only from the hole surface, the lowest thickness of the matrix is related to highest releasing surface. Therefore, all the drug is put into contact with the dissolution medium in the shortest time in the matrix having the tinniest width of the matrix. As a consequence, the drug can be released with the fastest rate from the highest releasing surface area.

3.5. Analysis of drug release kinetics

According to previous works, drug release from matrices based on hydrophilic polymers can be attributed to matrix erosion (swelling and polymer dissolution), to drug diffusion through the gel layer or to a combination of these two mechanisms.

Notwithstanding the impossibility to determine the release mechanism of the drug from the perforated matrices by the values of the kinetics exponent, the different importance of the two components of the release process (matrix erosion and drug diffusion) can be hypothesised on the bases of the n value.

The value of the kinetics exponent n of the drug release from the perforated uncoated matrices based on low viscosity HPC (SL and L) is nearly 1, while it results about 0.7 for the matrices based on HPC-M and HPC-H (Table 2).

The results obtained for the drug release from perforated uncoated matrices are consistent with a release process where the Fickian release mechanism plays an important role along with matrix erosion, which is a considerable characteristics of

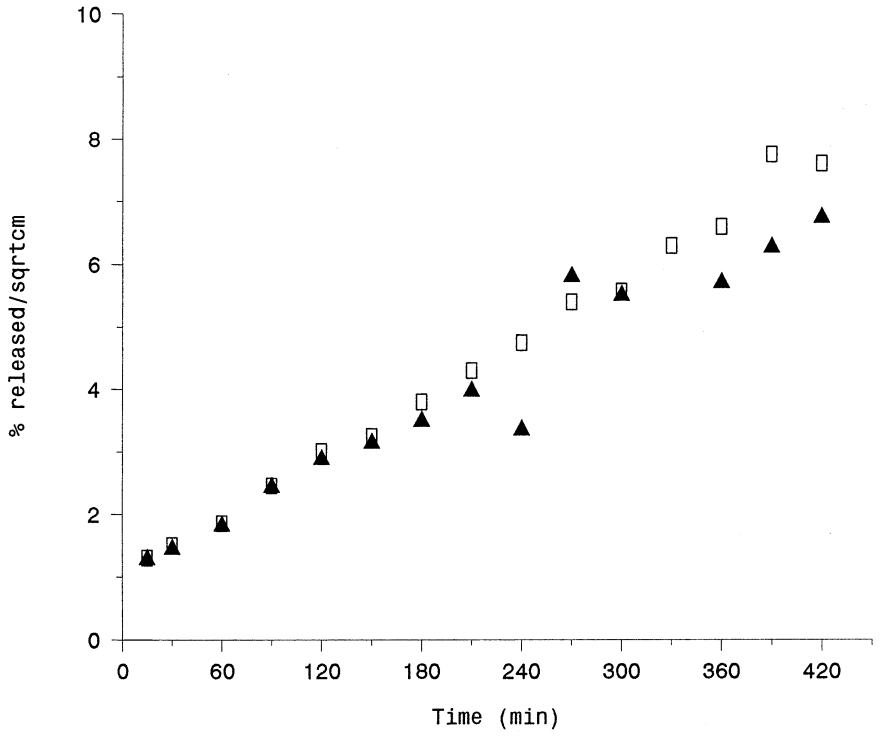

Fig. 7. Furosemide release from coated perforated matrices based on HPC-M (150–400 mPa.s) according to the unitary releasing area. Hole diameter: □ 8 mm; ▲ 6 mm.

systems based on hydrophilic polymers (Sung et al., 1996). The value of n increased from high viscosity (H and M) to low viscosity (SL and L) polymers. This finding indicates that the erosion of the matrix (swelling and polymer dissolution) increased its importance in the drug release mechanism as the polymer viscosity decreased.

In the case of the coated perforated matrices, the value of n shifts towards values indicating the decrease of the erosion component and the increase of the Fickian mechanism regardless to the polymer viscosity. The reduction of the erosion component could be produced by the effect of the coating on the HPC gelification owing to water penetration by the hole. As for the perforated uncoated matrices, the relative importance of the erosion component of drug release increased as the polymer viscosity decreased.

4. Conclusions

The release of furosemide from the perforated uncoated matrices increased as the hole diameter increased from 5 to 8 mm. Owing to the reduction of the releasing surface area with the increase of the hole diameter, the drug release is not related to the releasing surface contrary to the theoretical expectations. This finding can be justified by geometrical considerations. In an uncoated matrix, all the drug dispersed in the polymer is put into contact with the dissolution medium in a time depending to the width of the annulus. Therefore, the complete drug release occurs with the fastest rate from a matrix having the tinniest width of the annulus. Hence it can be justified a release rate related to the hole diameter and not to the whole releasing surface area of the matrix.

Table 2
Parameters of the release process from the perforated uncoated and coated matrices of hydroxypropylcellulose calculated according to Eq. (1)

Matrix polymer	Hole diameter (mm)	Uncoated matrices			Coated matrices		
		k	*n*	*r*	*k*	*n*	*r*
	5	0.077	1.18	0.9996	—	—	—
HPC-SL	6	0.189	1.08	0.9996	0.055	0.99	0.9994
	5	0.174	1.01	0.9990	—	—	—
HPC-L	6	0.184	1.05	0.9973	—	—	—
	8	0.125	1.17	0.9996	0.060	0.96	0.9925
	5	0.225	0.74	0.9912	—	—	—
HPC-M	6	0.223	0.75	0.9917	0.204	0.54	0.9897
	8	—	—	—	0.212	0.57	0.9971
	5	0.215	0.71	0.9986	—	—	—
HPC-H	6	0.324	0.67	0.9990	0.257	0.45	0.9974

Owing to the coating of all the surfaces, except the hole, the drug release is related to the releasing surface area which increases as the hole diameter increases.

As the comparison between the kinetics exponent of drug release of the uncoated and the coated perforated matrices showed, this behaviour can be justified by decrease of the erosion component when the drug release occurs only from the hole surface. In fact, modifying the position of the uncoated surface from which water can penetrate, the HPC particles are forced to swell towards preferential directions owing to the mechanical hindrance of the coating (Vandelli and Cameroni, 1993).

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