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International Journal of Pharmaceutics 111 (1994) 251–259

international journal of pharmaceutics

Release of propranolol hydrochloride from matrix tablets containing hydroxypropylmethylcellulose K4M and carbopol 974

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Received 21 January 1994; modified version received 8 April 1994; accepted 28 April 1994

Abstract

The release of propranolol hydrochloride from matrices containing hydroxypropylmethylcellulose and carbopol has been examined at different ratios of the polymers. Similar dissolution rates were found from the data corresponding to 5–35% of total drug release from matrices containing the same weight of polymer, but a burst release occurred from formulations containing 1: > 3 HPMC/carbopol once 35% of the drug had dissolved. In order to explain these results, studies on cloud points, water distribution, hydration and viscosity were carried out. Mixtures of both polymers resulted in a decrease in the values of the cloud points. Increased quantities of free water in the gels were apparent, producing a reduction in viscosity. Hydration studies, determined by DSC, on carbopol gels and matrices indicated that two different types of water were present in the scans of melting process. Additionally, the amount of water imbibed for this polymer was lower than that by HPMC or 1:1 mixture of the polymers. The burst release, during dissolution, may be explained by the formation of a complex between propranolol and carbopol.

Keywords: Hydroxypropylmethylcellulose; Carbopol; Propranolol hydrochloride; Matrix tablet; Dissolution; Cloud point; DSC; Viscosity

1. Introduction

In recent years, hydrophilic matrices have attracted considerable attention as sustained drug release devices (Vazquez et al., 1992). Various types of polymers can be used in hydrophilic matrices and the hydration of these polymers results in the formation of an outer gel layer that controls the release of drugs (Ford et al., 1991).

In oral controlled drug delivery, zero-order drug release from the dosage forms is desired (Guinchedi et al., 1992). Recently, combinations of non-ionic and ionic cellulose ethers have been extensively explored as means of obtaining constant release of some, especially basic, active

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SSDI 0378-5173(94)00152-U

principles (Ranga Rao et al., 1990; Bonferoni et al., 1992).

Hydroxypropylmethylcellulose (HPMC) – a non-ionic cellulose ether – is commonly used in the formulation of hydrophilic matrix systems. The release of drugs from its matrices has been extensively studied regarding both the mechanisms and technological factors involved in drug release (Daly, 1984; Ford et al., 1985, 1987). On the other hand, carbopol, an acrylic acid derivative, has also attracted interest for its use in controlled release (Capan et al., 1989; Perez-Marcos et al., 1991a,b). HPMC provides release which is dependent on the pK_a of the drug (Mitchell et al., 1990) whereas carbopol gels at above pH 7.3 and therefore provides a pH dependent release. This paper examines the potential of combining these polymers to extend the dissolution of a model drug, propranolol hydrochloride and seeks to rationalise the role played by the polymers in controlling drug release.

2. Materials and methods

Hydroxypropylmethylcellulose K4M (Methocel K4M, Dow Chemicals, U.S.A.), carbopol 974 (B.F. Goodrich, U.S.A.), propranolol hydrochloride B.P. (particle size < 125 μm) and magnesium stearate (BDH, Poole, Dorset) were used.

2.1. Matrix preparation and dissolution testing

Tablets, 12.7 mm flat-faced, were directly compressed at 197 MN m^{-2} using a Manesty F3 tableting machine. Tablets contained 160 mg of propranolol hydrochloride, 40, 90 or 140 mg polymer and 0.75% magnesium stearate as lubricant. The ratios of polymer used were 0:1, 1:3, 1:1, 3:1 or 1:0 HPMC/carbopol 974. Dissolution was studied using the USP 1 basket method, rotating at 100 rpm in 1000 ml distilled water maintained at 37°C (Pharmatest GmbH, Germany). Propranolol was determined spectrophotometrically at 288 nm using a Hewlett Packard HP8452A Diode array spectrophotometer. The mean of six tablets was used to characterise each batch.

2.2. Cloud points

Gels were prepared containing HPMC/carbopol at ratios (% w/v) 0.5:0, 0.4:0.1, 0.3:0.2, 0.2:0.3, 0.1:0.4 or 0:0.5 by adding the required amounts of polymers to the total amount of distilled water and dispersing them by vigorous stirring. Once prepared, the gels were stored overnight in a refrigerator. Cloud points were determined by the method of Mitchell et al. (1990) as the temperature at which the gels showed a 50% transmission.

2.3. Viscosity measurements

Dilute gels were prepared to contain 0.1, 0.2, 0.3, 0.4 or 0.5% w/v HPMC or carbopol and HPMC/carbopol at ratios (% w/v) 0.1:0.4, 0.2:0.3, 0.3:0.2 or 0.4:0.1 as described under section 2.2. Tests were performed at 37°C, in U-tube viscometers, grade B or C (British Standard 188, 1957). Gels were maintained at a temperature of 37°C throughout the study. The times taken were the means of three successive measurements for each gel, which were within 0.5% of each other.

2.4. DSC

Gels containing 10, 20, 30 or 40% w/v HPMC, carbopol or their 1:1 mixtures were prepared as described under cloud points above. DSC was employed to measure the water contents of gels. A Perkin Elmer (Beaconsfield, U.K.) differential scanning calorimeter (model DSC 7) with automatic cooling facilities was used. This equipment was controlled by a Perkin Elmer TAC 7. The equipment was calibrated using indium and zinc.

The samples, approx. 5 mg accurately weighed, were placed in sealed sample pans (Perkin Elmer, 40 μl), cooled from ambient temperature to -30°C at a controlled rate of -5°C/min using liquid nitrogen, and then scanned at 5°C/min to 30°C in order to measure the enthalpy of melting of the 'free' water at approx. 0°C. Empty sample pans were used as reference. Melting enthalpies were determined in at least triplicate for each gel concentration. The determined standard deviations were within ± 3.3% of the mean value.

2.5. Hydration

The methods of Mitchell et al. (1993a) were used. Approx. 10 mg samples of HPMC, carbopol or their 1:1 mixture, were manually compressed into thin wafers, 6.35 mm diameter. The wafers were accurately weighed and placed in aluminium samples pans into which had been accurately weighed approx. 10 mg quantities of distilled water. A closely fitting aluminium lid (6.35 mm diameter) was then placed on top to prevent water loss by evaporation, the pan being left unsealed. Samples were held at room temperature for 1, 5, 10, 15, 30 and 60 min prior to analysis. After storage for the prescribed times, the pans were placed into the sample compartment of the Perkin Elmer DSC 7 differential scanning calorimeter which was at −30°C to promote instant freezing of any unbound water. Each sample was heated at 10°C/min to 20°C and the enthalpy of fusion of ice determined. This was used to determine the quantity of water which had not been bound into the polymers. Each experiment was duplicated. The quantity of bound water was then calculated from the differences between the water weighed into the pan and the amount of unbound water equivalent to the enthalpy of fusion. The standard deviations were within ±5% of the mean value.

3. Results and discussion

Fig. 1 shows the release profiles of propranolol hydrochloride from matrices containing 90 mg of total polymer and is typical of the data obtained in this study. Generally, the standard deviations for the dissolution data were within ±3% of the mean, although where burst release occurred, this value rose to ±15%. Dissolution rates (Table 1) were quantified by treating the data as a function of the square root of time. Although this corresponded to 5–60% release for most matrices tested, those containing 40 or 90 mg polymer (0:1 or 1:3 HPMC/carbopol) and 140 mg polymer (0:1 HPMC/carbopol) were examined in the range 5–35% since a more rapid release of drug then occurred.

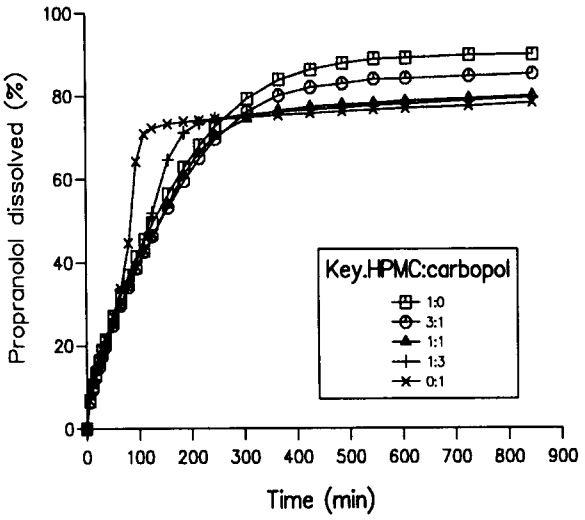

Fig. 1. Release of propranolol hydrochloride from tablets containing 90 mg of polymer.

For each HPMC/carbopol ratio, the dissolution rate of propranolol decreased as the content of total polymer increased. However, the dissolution rates in the range 5–35% were generally independent of the polymer ratio.

To analyse the mechanism of release of drug from these tablets, the dissolution data obtained were fitted, using a computer program (Ford et al., 1991) to Eq. 1:

$$Q = k(t - l)^n \quad (1)$$

where Q is the percentage of drug released, K represents a kinetic constant, t is the release time, l denotes the lag time prior to dissolution and n is the exponent release indicative of mechanism of release. Values of n near 0.6 indicate

Table 1
Dissolution rates (% $min^{-1/2}$) of propranolol hydrochloride from matrices containing HPMC K4M, carbopol 974, or their mixtures

Ratio HPMC/carbopol	Polymer content (mg)		
	40	90	140
1:0	7.33	5.02	4.06
3:1	6.51	4.34	3.81
1:1	6.86	4.75	3.74
1:3	6.94	4.10	3.46
0:1	6.65	4.73	3.93

Table 2
Values of exponent n calculated in the ranges 5–35% and 5–60% release, from matrices containing HPMC K4M, carbopol 974 or their mixtures

Ratio HPMC/carbopol	Range 5–35% polymer content (mg)			Range 5–60% polymer content (mg)		
	40	90	140	40	90	140
1:0	0.757	0.690	0.633	0.698	0.646	0.608
3:1	0.562	0.700	0.625	0.602	0.676	0.623
1:1	0.627	0.704	0.612	0.709	0.739	0.613
1:3	0.834	0.842	0.558	0.837	1.170	0.594
0:1	0.740	0.717	0.702	0.896	1.160	1.060

diffusion control and of 1 correspond to zero-order release (Ford et al., 1991).

Table 2 lists the calculated values of n in the ranges 5–35 and 5–60% drug release. Those values, calculated from the 5–35% range, were around 0.6 for each formulation which indicates that the main mechanism of release for propranolol hydrochloride was by diffusion. Similar values of n of 0.63 (Ranga Rao et al., 1990) and 0.64 (Ford et al., 1987) were found for propranolol hydrochloride release from HPMC K4M and HPMC K15M matrices, respectively. Other values of n obtained for soluble drugs include 0.71 for centperazine release (Baveja and Ranga Rao, 1986) and 0.59 for alprenolol release (Ranga Rao et al. 1990) from matrices containing sodium carboxymethylcellulose and HPMC, indicating diffusional-controlled release.

Furthermore, for each group of formulations (40, 90 or 140 mg of total polymer), the ability of a matrix to release its total dose of propranolol was reduced as the carbopol content increased

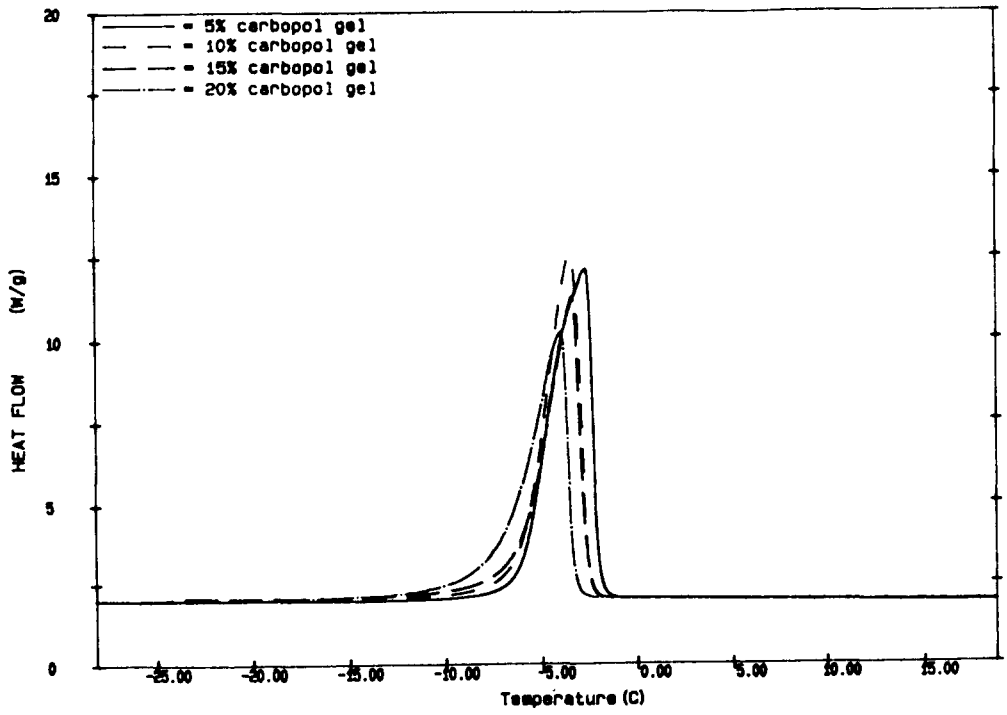

Fig. 2. DSC scans of gels containing 10, 20, 30 or 40% carbopol 974.

(Fig. 1). It is well known that cationic drugs form complexes with either anionic polymers (Feely and Davis, 1988a; Padmalatha Devi et al., 1989) or anionic surfactants (Daly et al., 1984; Feely and Davis, 1988b) and that the complexes influence the release of the drug from the matrix. When propranolol hydrochloride was added to gels containing carbopol, an insoluble precipitate, presumably of a propranolol/carbopol complex, formed. This interaction is possibly the reason for the observed reduction in the total release of the drug, as the percentages of the dose released after 14 h were 85, 78 and 71% in matrices containing solely 40, 90 and 140 mg of carbopol, respectively.

Once 35% of the propranolol hydrochloride had dissolved, a burst release was found from matrices containing 40 or 90 mg polymer (0:1 or 1:3 HPMC/carbopol) or 140 mg polymer (0:1 HPMC/carbopol). Since drug release from HPMC matrices is controlled by factors including the hydration process, water distribution into polymers, the extent of swelling, the cloud point and viscosity, it was considered necessary to study these parameters for HPMC, carbopol and their mixtures.

The values of the cloud points of the polymers and their mixtures were > 75, 50, 44, 44, 57 and > 75°C for gels containing % ratios of 0.5:0, 0.4:0.1, 0.3:0.2, 0.2:0.3, 0.1:0.4 and 0:0.5 HPMC/carbopol, respectively. The cloud points of gels containing solely HPMC or carbopol were higher than those of any of their mixtures. This means that the polymers mutually reduced the solubility of each other and indicates a potential for control of dissolution from their matrices by erosion.

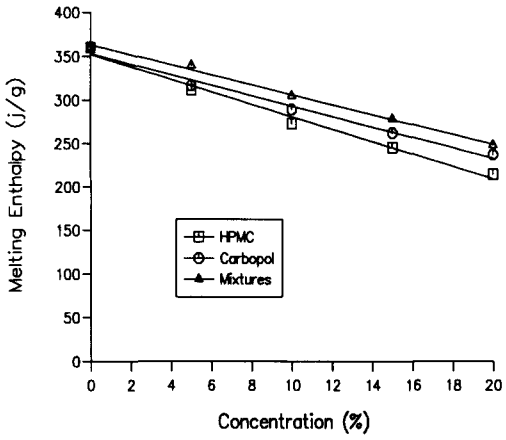

Fig. 3. Effect of concentration of polymer on the melting enthalpy of gels containing HPMC K4M, carbopol 974 or their 1:1 mixture.

DSC was used to determine the amount of bound and free water in the gels, because the interaction between polymer and water, i.e., the formation of the gel, is ultimately the mechanism by which the polymers act as the basis for sustained release matrices.

Fig. 2 shows the DSC scans of gels containing 10, 20, 30 and 40% carbopol and is also representative of gels containing HPMC or their 1:1 mixture. In each case, the value of the melting enthalpy decreased as the concentration of polymer in the gel increased. There were linear relationships, for each polymer or their mixture, between the free water detected and the concentration of polymer (Fig. 3), as shown previously for HPMC gels (Mitchell et al., 1989). The total amount of free water in the gels was higher for the mixtures than for each individual polymer. Extrapolation of the linear portions to zero enthalpy indicated that the compositions of the fully hydrated gels were 49.4:50.6, 58.9:41.1 and 63.6:36.4 polymer/water for gels containing HPMC, carbopol or their 1:1 mixture, confirming that more free water was present in the mixture of polymers. These results are comparable to those of the cloud points. The gels containing 1:1 polymers had lower cloud points indicating that they were more easily dehydrated than the gels containing solely one polymer but of equal total concentration of polymer.

In order to determine the speed of water uptake, the method of Mitchell et al. (1993a) was used. Fig. 4 and 5 show the DSC scans obtained for the water uptake of discs containing carbopol and the 1:1 mixture, respectively. The data describing the water uptake into HPMC discs have already been described (Mitchell et al., 1993a). Over the period of 60 min, the amount of water taken up by each type of disc increased. The scans of discs of carbopol showed, besides the main endotherm, another peak at approx. −15°C

which indicates that two different types of water were present in the melting process. The mean values calculated for the bound water for samples containing HPMC, carbopol and their 1:1 mixture are shown in Table 3 as a function of time. These results show that the water uptake into HPMC and 1:1 HPMC/carbopol discs was similar over the period of study. However, carbopol showed the lowest amount of water imbibed for up to 1 h and this polymer imbibed most of its water in the initial 5 min of contact. Thereafter, its uptake of water was very slow. This uptake could be further impeded by the interaction betweeen carbopol and propranolol hydrochloride and could result in a failure of the hydrating matrices to maintain their structure.

Table 4 shows the viscosities of HPMC, carbopol or their mixtures at different concentrations. Gels containing carbopol had higher viscosities than the corresponding HPMC gels at the equivalent concentration and those differences were more apparent with increase in polymer concentration. On the other hand, the viscosities of the mixtures were lower than predicted from the viscosities of either polymer at equivalent concentrations. When a non-ionic polymer (such as HPMC) was blended with NaCMC (a hydrophilic anionic swellable polymer) a synergistic effect occurred whereby the resultant viscosity was considerably higher than anticipated (Walker and Wells, 1982). This was attributed to the strong hydrogen bonding between the carboxyl groups on NaCMC and the hydroxyl groups on the HPMC, leading to strong cross-linking between the two gums. Such synergy was not found between HPMC and carbopol. DSC of the gels showed that the amount of free water in the mixture was greater than in each polymer of equivalent concentration and hence a reduction in their viscosities would be caused by a reduced hydration of the polymers in their 1:1 blends. Gel viscosity is not a primary factor in controlling the release of drugs from matrices (Ford et al., 1985; Feely and Davis, 1988b). The reduction of

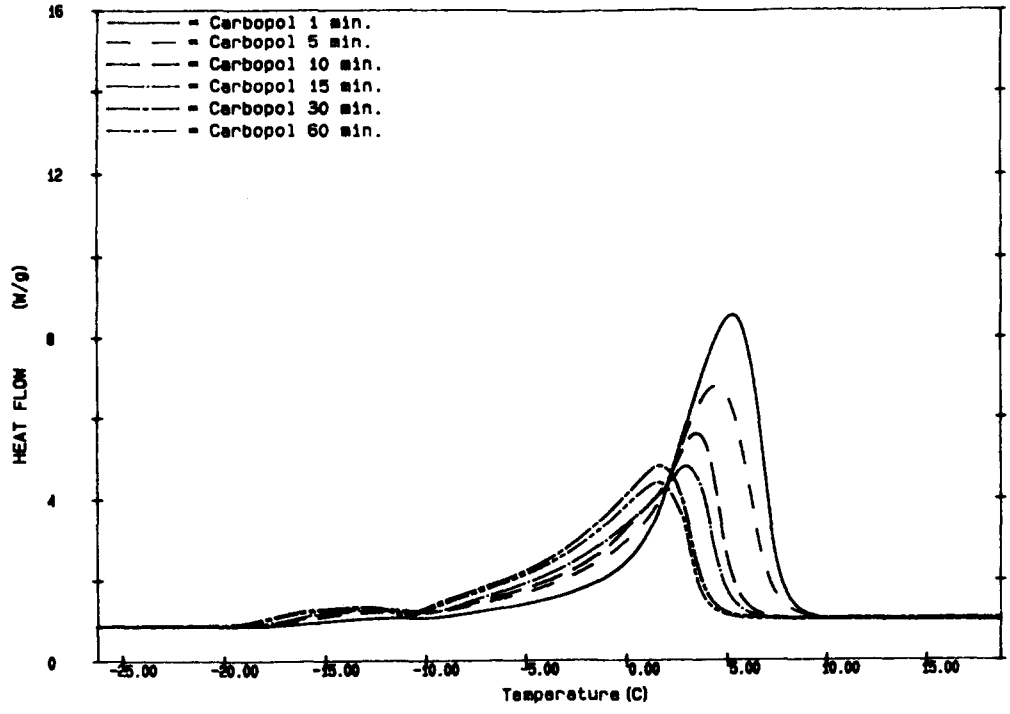

Fig. 4. DSC scans showing the melting endotherms of free water in contact with carbopol 974 discs (10 mg) stored in contact with 10 mg water at room temperature.

Table 3
Effect of time on the amount of water (mg) bound by 10 mg discs containing HPMC K4M, carbopol or 1:1 HPMC: carbopol 974 over a period of 60 min at room temperature (standard deviation in parentheses)

Time (min)	HPMC	Carbopol	1:1 mixture
1	2.44	2.13	2.51
	(0.07)	(0.13)	(0.61)
5	3.30	3.13	4.27
	(0.47)	(0.34)	(0.52)
10	4.85	4.44	4.43
	(0.14)	(0.33)	(0.72)
15	5.23	4.52	5.95
	(0.07)	(0.52)	(0.21)
30	6.09	4.42	5.95
	(0.24)	(0.32)	(1.28)
60	6.99	5.14	6.57
	(0.02)	(0.54)	(0.13)

Table 4
Values of viscosity from gels containing HPMC K4M, carbopol 974 or their mixtures

HPMC					
Concentration (w/v)	0.1	0.2	0.3	0.4	0.5
Viscosity (cS)	1.31	2.41	4.57	6.45	10.05
carbopol					
Concentration (w/v)	0.4	0.3	0.2	0.1	0.5
Viscosity (cS)	17.86	6.50	3.12	1.40	66.85
Mixtures					
0.5% Polymer HPMC/carbopol (w/v)	0.1:0.4	0.2:0.3	0.3:0.2	0.4:0.1	
Viscosity (cS)	10.01	3.48	2.40	3.54	

the viscosity found in the mixtures did not give a faster release of propranolol hydrochloride.

The results indicate that the factors controlling the release of propranolol from these matrices are complicated. Thus, propranolol forms a complex with carbopol and, moreover, is known to increase the hydration of HPMC (Mitchell et al., 1993b). On the other hand, the mixture of HPMC

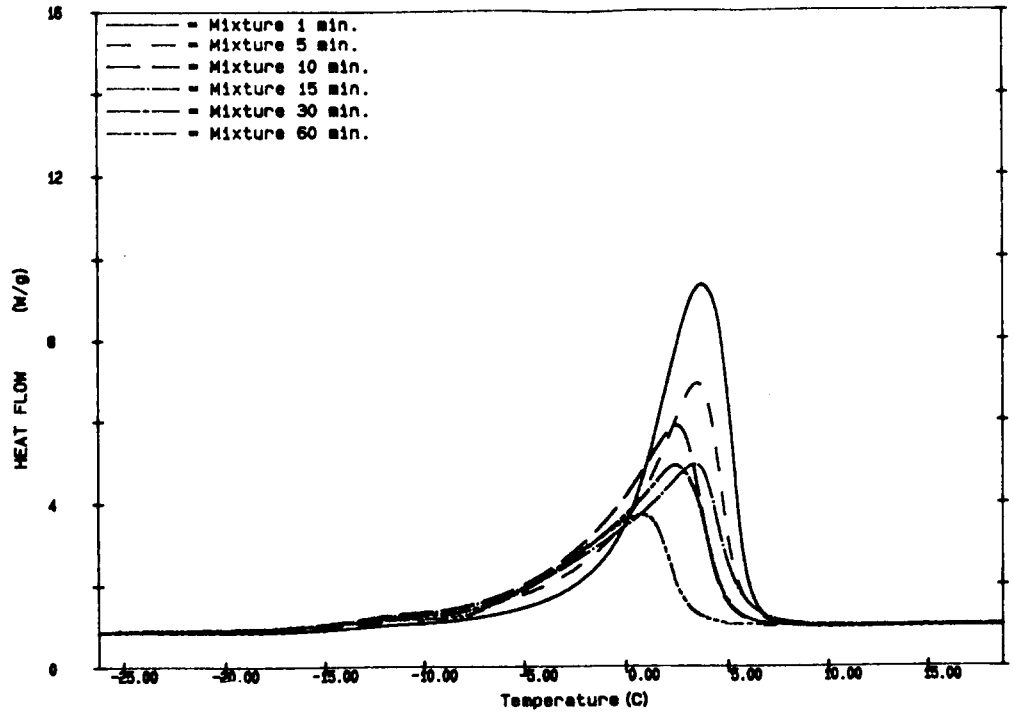

Fig. 5. DSC scans showing the melting endotherms of free water in contact with 1:1 HPMC K4M:carbopol 974 discs (10 mg) stored in contact with 10 mg water at room temperature.

and carbopol showed reduced polymer solubility and hence less water would be absorbed into the matrices containing both HPMC and carbopol. The explanation of burst release of propranolol, found in formulations containing 1: > 3 HPMC/carbopol, is probably connected to the propranolol/carbopol complex. This may have precipitated within the gel during the hydration process giving imperfect matrices and making them more easily erodible. The complexed carbopol could not contribute to the integrity of the gel. In addition, the lower solubility of the polymers in the mixture would also result in a decreased role played by the carbopol in maintaining the integrity. Due to this more rapid erosion of the gel, the diffusional path length for the drug would be smaller and would reduce the role that diffusion plays in controlling the release, making the overall release rate faster. The values of the exponent n in the range 5–60% dissolved were around 1 for these particular formulations (Table 1) and indicate that the release of propranolol approached zero order. This confirms the hypothesis of erosional release. It seems that this effect on the matrix structure was greater when the total amount of HPMC in the matrix was low because, in the formulations containing 140 mg of polymer, the burst release was only found in the 0:1 HPMC/carbopol matrices. The amount of HPMC (35 mg) in the formulation 1 : 3 HPMC/carbopol (140 mg of total polymer) would be sufficient to maintain the integrity of the matrix.

4. Conclusions

The total amount of polymer included in the matrix was the main factor which controlled the release of the propranolol hydrochloride. The ratio of both polymers only had a major effect in matrices containing 1: > 3 HPMC/carbopol. In these matrices, a burst release of propranolol hydrochloride was found to be due to the formation of a complex between the drug and carbopol which would give imperfect, more easily erodible matrices. Due to a reduction in the hydration states of the polymers, the values of the cloud points of the mixtures of HPMC and carbopol were reduced and the amounts of free water in their gels were increased.

Acknowledgements

We are grateful to B.F. Goodrich, U.S.A. for their generous supply of carbopol 974. Financial assistance for the studies received from FAR 91–0239 Comision Interministerial de Ciencia y Tecnologia, Spain.

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