ELSEVIER

International Journal of Pharmaceutics 160 (1998) 251–255

international journal of pharmaceutics

Note

Physical characterization and optimisation of dissolution parameters of prochlorperazine maleate coevaporates

M.S. Nagarsenker *, S.D. Garad

Department of Pharmaceutics, Bombay College of Pharmacy, Kalina, Mumbai 400 098, India

Received 30 June 1996; received in revised form 20 August 1997; accepted 12 September 1997

Abstract

Coevaporates of prochlorperazine maleate were prepared using different polymers by solvent evaporation technique. Ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose phthalate were used in preparation of coevaporates. The coevaporates were characterized by X-ray diffraction studies, IR spectrophotometry and Differential scanning calorimetry. Dissolution behavior of coevaporates was studied using buffer solution with pH 1.2 and 6.8 by half change method. A two level, two factor factorial design was used to quantitate effect of polymers on dissolution profile of PCPM. Dissolution of drug in pH 6.8 buffer improved with increasing content of hydroxypropyl methyl cellulose phthalate in coevaporates. © 1998 Elsevier Science B.V.

Keywords: Prochlorperazine; Coevaporates; Dissolution

Prochlorperazine maleate, a weak base, has good solubility in acidic pH but in alkaline pH its solubility is significantly reduced. When a conventional formulation containing weak base is given orally precipitation of poorly soluble free base occurs within formulation in intestinal fluid. Precipitated drug is no longer capable of release from formulation (Thomma and Zimmer, 1990; Naonori et al., 1991) A possible approach for ensuring maximum bioavailability with controlled release dosage form of a weak base is preparation of 'coevaporate system' incorporating a carrier with solubilizing effect in intestinal fluid which may operate in the microenvironment, immediately surrounding the drug particle. This study was planned to prepare coevaporates of prochlorperazine maleate (PCPM) with the objective of controlling release of PCPM in gastrointestinal tract. The carrier used for solubilization of drug in alkaline medium was Hydroxypropyl methyl

* Corresponding author.

PII S0378-5173(97)00318-9

Table 1
Composition of the coevaporates: a two factor, two level factorial design

Experiment	PCPM (mg)	EC (X_1) (mg)	PMCP (X_2) (mg)	HPC (mg)
1	10	10 (28.57%)	10 (28.57%)	5
a	10	30 (54.54%)	10 (18.18%)	5
b	10	10 (18.18%)	30 (54.54%)	5
ab	10	30 (40.00%)	30 (40.00%)	5

cellulose phthalate and the polymers used for controlling the dissolution rates were ethyl cellulose and hydroxypropyl cellulose.

Coevaporates containing PCPM, (Rhone Poulenc, India) EC, (Colorcon, India) HPMCP and HPC (Shin-Etsu Chemicals, Japan) were prepared using alcohol as solvent by solvent evaporation method (Chiou and Riegelman, 1971) at temperature not exceeding 55°C. A two level, two factor experimental design (Davis, 1978), as shown in Table 1, describes the proportion in which the polymers were used in preparation of coevaporates. For e.g. coevaporate-1/physical mixture-1 had composition described for experiment (1) in Table 1. Physical mixtures were prepared by spatulation.

Ratio of quantity of EC to that of drug was varied at two levels, 1 and 3. Ratio of quantity of HPMCP to that of drug was also studied at the same level of 1 and 3. Percent content of polymers in coevaporates are indicated in bracket. Coevaporates were passed through sieve no. 30 mesh and used for further investigation.

Powder X-ray diffraction patterns of coevaporates were recorded using Phillips X-ray diffractometer with a copper target, voltage 40 kV, current 20 mA, at a scanning speed of 2° per min. Powdered samples of PCPM and physical mixtures were also studied by diffractometry for comparison.

The X-ray diffraction patterns of PCPM, physical mixtures, and coevaporates are illustrated in Fig. 1. The diffraction spectra of pure PCPM revealed that the drug was highly crystalline in nature as indicated by numerous distinctive peaks in the X-ray diffractogram. The spectra of physical mixtures showed sharp distinct peaks for PCPM whereas in spectra of coevaporates the number and intensity of peaks was reduced indicating partial amorphization of the drug.

Jasco Fourier transform spectrophotometer was used to obtain IR spectra of the pure drug, polymers, physical mixtures and coevaporates (KBr disc). The IR spectra of PCPM, physical mixtures and coevaporates showed all characteristic bands of prochlorperazine, excluding possibility of any interaction of polymers with prochlorperazine.

The differential scanning calorimetry (DSC) thermogram of PCPM, physical mixtures, and coevaporates were obtained by heating up to 290°C on Shimadzu thermal analyzer DT-40. Weighed samples were sealed in aluminum pans and scanned at a rate of 10°C/min. The thermogram of PCPM, physical mixture and coevaporates, showed the melting endotherm for PCPM (Fig. 2) at 207.6°C. The DSC thermogram of the coevaporates exhibited broadened endotherm due to amorphization.

When dissolution of PCPM powder was studied in medium of pH 1.2, PCPM dissolved to the extent of 95.84% in 2 h but in pH 6.8 as much as 81.68% of PCPM dissolved in 2 h. No significant increase was observed in amount dissolved there after in pH 6.8.

Dissolution patterns of coevaporates were studied using samples equivalent to 10 mg of PCPM in 900 ml buffer solution of pH 1.2 and buffer of pH 6.8 by half change method using USP XXIII dissolution test apparatus, type 1 at 100 rpm. The drug content in the withdrawn aliquots was estimated spectrophotometrically at 254 nm on Shimadzu UV spectrophotometer, with reference to a suitably constructed standard curve.

Dissolution profiles of different coevaporates, studied by half change method are shown in Fig. 3. Based on the dissolution studies two response

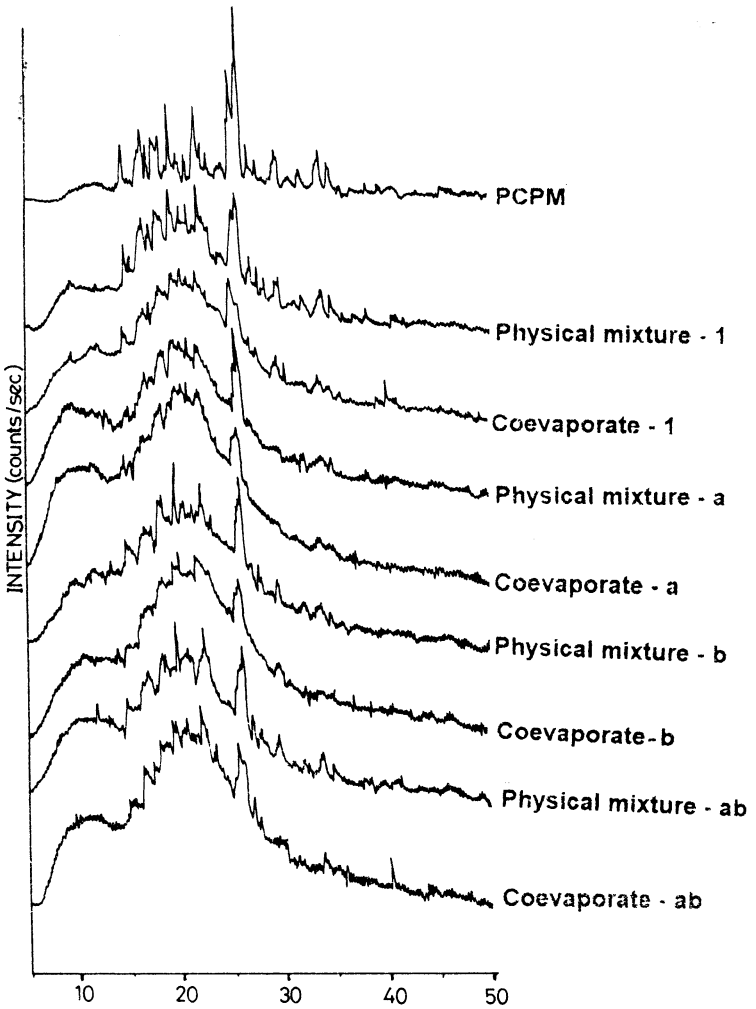

Fig. 1. X-ray diffraction patterns of PCPM, physical mixtures and coevaporates.

parameters were selected for evaluation, (i) $t_{50\%}$, time required for 50% of PCPM to dissolve, which indicated controlled dissolution of PCPM in initial stages of study, (ii) DE, dissolution efficiency (Banakar et al., 1992) which indicated extent of dissolution. DE was calculated as

$$\mathrm{DE} = \frac{\text{area under dissolution curve}}{\text{total area}} \times 100$$

Dissolution profile of coevaporate of experiment (b) exhibited sustained release of 42.80% of PCPM in 2 h and almost complete dissolution of 94.50% in 12 h. It was observed that lower percent content of HPMCP in coevaporates of experiment (1) and (a) resulted in a greater amount of PCPM dissolved in the first 2 h, whereas higher percent content of HPMCP improved dissolution of PCPM in pH 6.8 buffer and at the same time checked amount of PCPM dissolved in pH 1.2 buffer. Increasing percent content of EC from 18.18 to 54.54 in coevaporates of experiment (a) and (ab) did not significantly sustain release of PCPM in initial 2 h.

Values of $t_{50\%}$ (Y_1) and DE (Y_2) for these coevaporates are given in Table 2. Relationship between the response variables ($t_{50\%}$/DE) and the

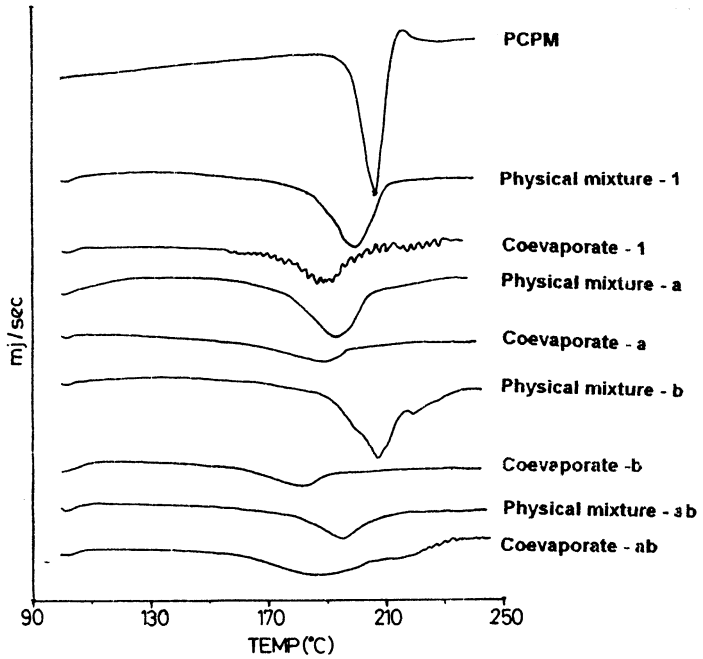

Fig. 2. DSC thermograms of PCPM, physical mixtures and coevaporates.

independent variables X_1 (percent content of EC) and X_2 (percent content of HPMCP) is described by including an interaction term in the following equation.

$$Y = B_0 + B_1X_1 + B_2X_2 + B_{12}X_1X_2$$

mathematical treatment and solving of simultaneous equations led to

$$Y_1 = 0.32 - 0.017X_1 + 0.0245X_2 + 0.000778X_1X_2 \quad (1)$$

$$Y_2 = 35.85 + 0.6142X_1 + 0.6725X_2 - 0.00889X_1X_2 \quad (2)$$

where Y_1 is the $t_{50\%}$ in h and Y_2 is dissolution efficiency of the coevaporates. Eqs. (1) and (2) were made use of to construct contour plot which are shown in Figs. 4 and 5, respectively. Each line in the contour plot represents number of combination of percent content of EC and that of HPMCP in the coevaporates which will have the same value of $t_{50\%}$/dissolution efficiency.

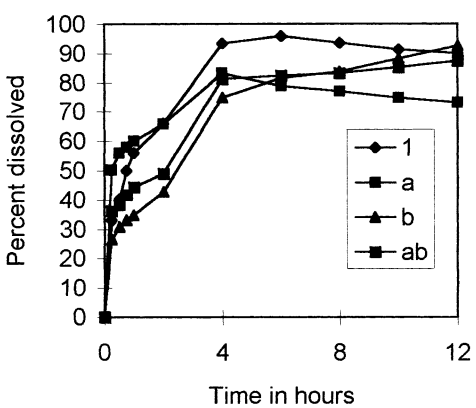

Fig. 3. Cumulative amounts of PCPM released from coevaporates of experiment 1, a, b, and ab.

Table 2
Values of $t_{50\%}$ and dissolution efficiency of the coevaporates

Coevaporates of experiment	$t_{50\%}$ (Y_1) (h)	Dissolution efficiency (DE), (Y_2)
1	1.15	65.33
a	0.57	72.74
b	2.11	74.86
ab	1.84	73.09
d	1.69	76.50

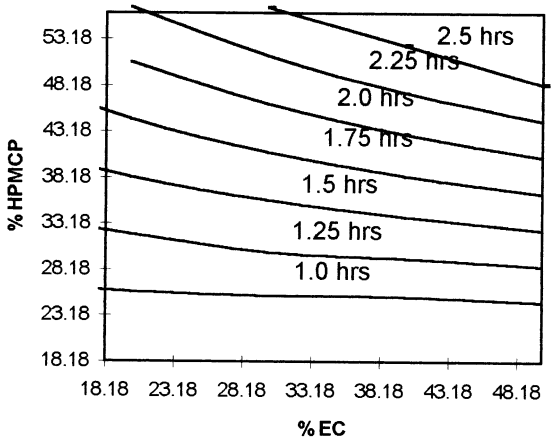

Fig. 4. Contour plots of $t_{50\%}$ of coevaporates of PCPM.

To test the validity of the design and the equation derived from it, a combination of independent variables X_1 and X_2 not studied in the design was selected and coevaporate of PCPM containing EC (20%) and HPMCP (48.7%), experiment (d), was prepared and evaluated for dissolution behavior. The observed value and calculated value of $t_{50\%}$ were 1.69 and 1.84 h, respectively, and those for DE were 76.50 and 71.65%, respectively.

In conclusion dissolution of PCPM in pH 6.8 buffer improved with increased content of HPMCP in coevaporates. Various combinations of EC and HPMCP can be selected, from equations generated by factorial design, to optimize values of $t_{50\%}$ and DE of coevaporates.

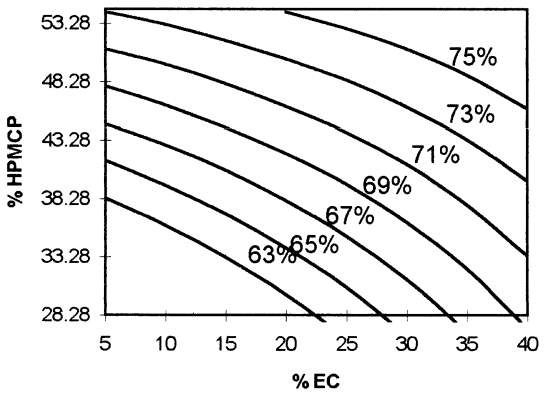

Fig. 5. Contour plots of dissolution efficiency of coevaporates of PCPM

References

Banakar, U.V., Lathia, C.D., Wood, J.H., 1992. Interpretation of dissolution rate data and technique of in vivo dissolution. In: Banakar, U.V. (Eds.), Pharmaceutical Dissolution Testing. Marcel Dekker, New York, 1992, pp. 189–250.

Chiou, W.L., Riegelman, S., 1971. Pharmaceutical application of solid dispersion system. J. Pharm. Sci. 60, 1281–1302.

Davis, O.L., 1978. Factorial experiment: elementary principles. In: Davis, O.L., (Eds.), The Design and Analysis of Industrial Experiments, 2nd ed. Longman group, London, pp. 247–289.

Naonori, K., Yatabe, H., Iseki, K., et al., 1991. A new type of pH independent controlled release tablet. Int. J. Pharm. 68, 255–264.

Thomma, K., Zimmer, T., 1990. Retardation of weakly basic drug with diffusion tablet. Int. J. Pharm. 58, 197–202.