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Comparison Between Hydroxypropyl β-Cyclodextrin and Polyvinylpyrrolidone as Carriers for Carbamazepine Solid Despersions

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Solid dispersions of carbamazepine were prepared in order to improve its aqueous solubility by simple kneading procedure. Hydroxypropyl β-cyclodextrin and polyvinyl pyrrolidone were used as carriers. Solid dispersions were stored at room temperature in a dessicator over anhydrous calcium chloride for one month. The changes in dispersions during storage were assessed by X-ray diffraction studies and dissolution studies. It was concluded from this study that hydroxypropyl β-cyclodextrin, as a carrier, reduced crystalline nature of carbamazepine in solid dispersions to a greater extent than polyvinyl pyrrolidone as a carrier and resulted in better and predictable dissolution profiles.

Carbamazepine (CBZ), a major antiepileptic drug, exhibits extremely poor water solubility[1]. The influence of crystal modification on the bioavailability and dissolution of two crystalline forms of CBZ is reported. The slower absorption of the thermodynamically more active anhydrous form was attributed to rapid transformation, in aqueous milieu, of this form to the dihydrate, resulting in a fast growth in particle size. The transition between the two crystalline forms is highly dependent on the temperature and the relative humidity[2]. Therefore prevention of crystal growth during storage is particularly important for predictable dissolution and bioavailability.

It has been reported that carbamazepine-polyvinylpyrrolidone coprecipitate gives higher dissolution rate than the solid dispersions with anhydrous lactose, mannitol, galactose and polyethylene glycol 6000[3]. Hydroxypropyl β-cyclodextrin (HPB), a chemically modified β-cyclodextrin, is highly water soluble, stable and its safety and tolerance has been well documented[4,5]. Its ability to improve aqueous solubility has been attributed to the formation of inclusion complex between cyclodextrins and 'guest' drug molecule[6]. Formulation of solid dispersions of CBZ with HPB can be expected to form inclusion complex and reduce crystallinity of CBZ by preventing conversion of anhydrous form to dihydrate.

In the present study, HPB and polyvinyl pyrrolidone (PVP) were studied as carriers for solid dispersions in order to compare their ability to improve aqueous solubility and to control crystal growth of CBZ.

MATERIALS AND METHODS

Carbamazepine was obtained as a gift from Ciba-Geigy Limited, Mumbai. Hydroxypropyl β-cyclodextrin was generously donated by American Maize Products Co., USA. Polyvinyl pyrrolidone and microcrystalline cellulose were obtained as gift samples from Khandelwal Laboratories, Mumbai. Double distilled water (DDW) and Methanol AR (S. D. Fine Chemicals, Mumbai) were used throughout the study.

Preparation of solid dispersions :

Two grams of CBZ and 13.6 g of HPB (1:1 molar proportion) were mixed together. The mixture was kneaded together to get a dough like consistency with 1:1 methanol-DDW mixture. It was triturated in mortar for 30 min and was almost completely dried in vacuum oven at 45°. It was stored overnight in a dessicator over anhydrous calcium chloride. The dry kneaded product was then

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seived through a # 85 to obtain a powder. The powder was then transferred to a dry tared sample tube which was closed tightly and stored in a desiccator over anhydrous calcium chloride. A similar procedure was followed for preparing kneaded solid dispersion of 2 g of CBZ and 13.6 g of PVP so that proportion by weight of drug to carrier remained the same.

Evaluation of solid dispersions

Powder X-ray Diffraction patterns were recorded using Phillips X-ray diffractometer with a copper target, voltage 40 KV, current 30 mA at a scanning speed of 2°/min. To estimate extent of crystalline nature of CBZ in the solid dispersions, X-ray diffraction calibration curve for mixtures of CBZ and amorphous diluent of known composition was prepared. CBZ alone was considered 100% crystalline and its relative intensity as 1.

Dissolution studies were carried out using a USP XXII dissolution apparatus type II with 500ml phosphate buffer (pH 7.4±0.2) as dissolution medium at 37±0.5° and 100 rev min^{-1} for 3 h. The aliquots were diluted and analysed for drug content spectrophotemetrically at 285 nm on a Shimadzu UV-160A UV-vis recording spectrophotometer with reference to a suitably constructed standard plot. X-ray diffraction studies and dissolution studies for both the dispersions were carried out on days 1, 3, 7, 15, 21 and 28 of storage.

RESULTS AND DISCUSSION

Crystalline state is characterized by perfectly ordered lattice whereas non-crystalline (amorphous) state is characterized by perfectly disordered lattice. The term degree of crystallinity or extent of crystalline nature is useful in attempts to quantify these intermediate states of lattice order. X-ray powder diffractometry is widely used to determine the crystallinity of pharmaceuticals.

As there is a possibility of interaction between CBZ and HPB or CBZ and PVP even in physical mixture, for calibration of relative intensity, CBZ-HPB mixture or CBZ-PVP mixture cannot be used. Physical mixtures containing known weight fractions of CBZ and microcrystalline cellulose (MCC) were made. The samples were scanned from 5-35°2θ. In mixtures containing CBZ and MCC, the amorphous halo of MCC interfered with the lines of CBZ in 2θ range of 13.6885-24.2°[7]. Therefore the lines in this angular range could not be used for quantitative analysis.

Table I - Calibration Plot

Weight fractions of CBZ in mixtures and their relative intensity in XRD studies

Weight fraction of CBZ	Relative Intensity (I/I_o)
0.00	0.0000
0.10	0.0676
0.25	0.1641
0.50	0.4394
0.75	0.8749
1.00	1.0000

Equation of line : $y = (1.082)x + (-0.044)$

$r = 0.988$

Table II - X-ray Diffraction Study

Changes in relative intensity (I/I_o) for CBZ-HPB and CBZ-PVP kneaded solid dispersions on various days

Day	Relative Intensity (I/I_o)	
	CBZ-HPB dispersion	CBZ-PVP dispersion
1	0.0391	0.0553
3	0.0471	0.0603
7	0.0614	0.0619
15	0.0360	0.0609
21	0.0344	0.0580
28	0.0387	0.0595

Table III - Dissolution Study

Time required 50% release of CBZ from CBZ-HPB and CBZ-PVP kneaded solid dispersions on various days of storage.

Day	$T_{50\%}$(Minutes)	
	CBZ-HPB dispersion	CBZ-PVP dispersion
1	4.2	11.1
3	2.8	26.4
7	2.1	25
15	2.8	8.3
21	2.8	4.2
28	2.6	5.6

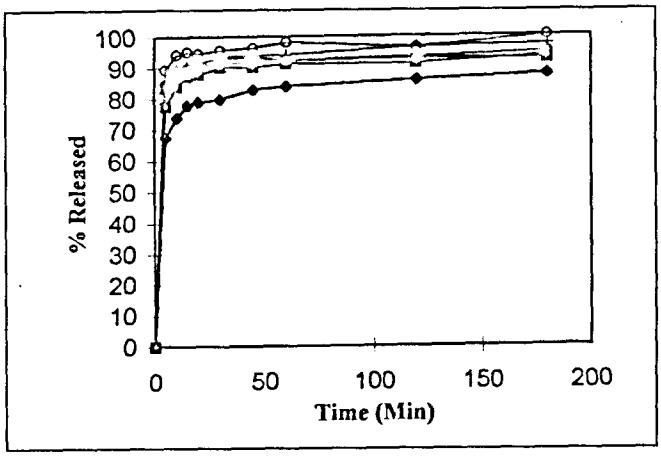

Figure 1a

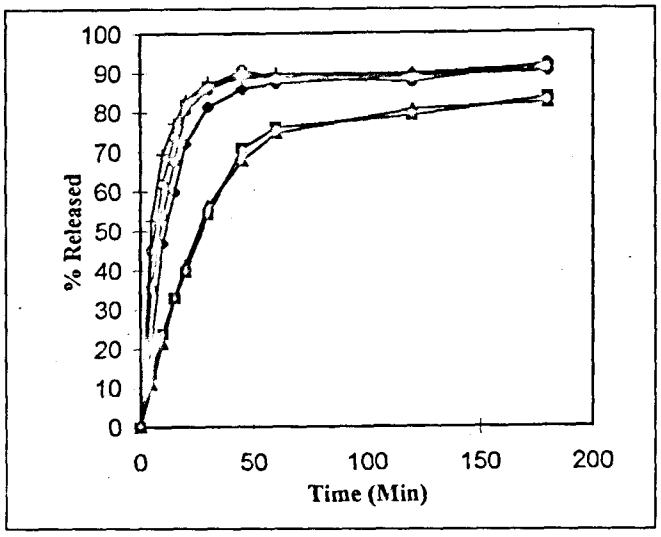

Figure 1b

Fig. 1 a & b : Dissolution profile of carbamazepine from (a) carbamazepine-hydroxypropyl β-cyclodextrin and (b) carbamazepine-polyvinyl pyrrolidone solid dispersions on different days of storage

Key words : ◇ First day, □ Third Day, △Seventh day, ○ Fifteenth day, | Twenty first day, ○Twenty eighth day

In order to experimentally determine relative intensity, the integrated intensities of the appropriate lines were determined in mixture containing only CBZ and the intensity values were summed up. The sum of the integrated intensities of the same lines was also determined in the mixtures containing different weight fractions of the active ingredient (CBZ) and the excipient (MCC). This

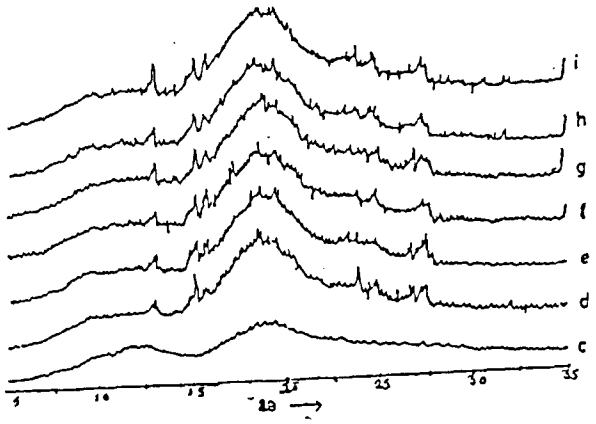

Figure 2a

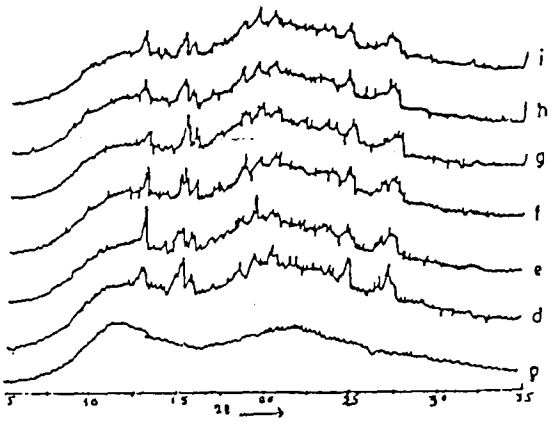

Figure 2b

Fig. 2 a & b : X-ray diffraction pattern of solid dispersions of (a) carbamazepine-hydroxypropyl β-cyclodextrin and (b) carbamazepine-polyvinyl pyrrolidone solid dispersions on different days of storage

Key words : c. Hydroxypropyl β-cyclodextrin, p. Polyvinyl pyrrolidone, d. First day, e. Third day, f. Seventh day, g. Fifteenth day, h. Twenty first day and i. Twenty eighth day

permitted the experimental determination of the intensity ratio as a function of the weight fraction of the active ingredient in the mixtures. Table 1 gives values for the intensity ration and corresponding weight fractions of CBZ used in Calibration Plot. CBZ alone was considered 100% crystalline and its relative intensity as 1. Equation of line was,

$$y = (1.082)\ x + (-0.044)$$

where, Y = Weight fraction of CBZ

x = Relative intensity(I/I_0)

Value of correlation coefficient, r was found to be 0.998 which is indicative of good correlation. Value of relative intensity is indicative of extent of crystalline nature.

X-ray diffraction patterns of CBZ-HPB and CBZ-PVP solid dispersions on various days of storage is shown in figs 2a and 2b respectively. In X-ray diffraction studies, increase in crystalline nature in CBZ-HPB dispersion was apparent in first seven days as shown in table 2 but it did not affect release profile adversely. After seven days relative intensity (I/I_0) was almost constant as shown in table 2 and dissolution profile (Fig. 1 a) continued to improve as storage in dessicator was continued.

But CBZ-PVP dispersion showed increase in crystalline nature in first seven days and showed decrease in dissolution of CBZ. As storage in desiccator was continued further, this dispersion showed decrease in crystalline nature as shown by values of relative intensities in table 2 and release profiles (Fig. 1 b) were improved considerably which was in good accordance with XRD studies.

As samples were kept in desiccator, solid dispersions lost their moisture content to maximum possible extent, which may have resulted in increased hydrophilic nature of dispersion and faster dissolution as shown by CBZ-HPB dispersion despite of increase in values of relative intensities from 0.0391 to 0.0614. For CBZ-PVP dispersion, in first seven days, values of relative intensities indicated increase in crystallinity correspondingly $t_{50\%}$ value increased from 11.5 to 25 min in dissolution studies of this dispersion as shown in table 3. Both the dispersions CBZ-HPB and CBZ-PVP required more than 7 days storage in desiccated condition to check increase in crystallinity as is evident from values of relative intensities of dispersions in Table 2.

As shown in Fig. 1a, 1b and Table 3, dissolution of CBZ from CBZ-HPB dispersion was always greater than that from CBZ-PVP dispersion. At any particular time point in the study, crystalline nature of CBZ in CBZ-HPB dispersion was always less than that of CBZ-PVP dispersion. Storage in desiccated condition appeared to be more essential in case of CBZ-PVP dispersion. Therefore it can be concluded from this study that as compared to PVP, use of HPB as a carrier for solid dispersion of CBZ, exhibits better and predictable dissolution profiles and reduces crystalline nature of CBZ to a greater extent.

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