DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 20(17), 2741-2752 (1994)

EFFECT OF SOME POLYMERS ON THE PHYSICO-CHEMICAL AND DISSOLUTION PROPERTIES OF HYDROCHLOROTHIAZIDE II

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ABSTRACT

Different ratios of hydrochlorothiazide (HCT) and each of Polyethylene glycol (PEG) and B-cyclodextrin (B-CD) solid dispersions were prepared by melting and solvent method respectively. The solid dispersions were subjected to X-ray diffraction, I.R. spectroscopy, DSC and Dissolution from constant surface tablets. The drug was in the amorphous form when the ratios of the drug/PEG were less than 1:3. It formed hydrogen bond with both polymers. The dissolution of the drug from drug/PEG and drug/B-CD solid dispersions increased with the increase in the weight fraction of the polymers, reaching a maximum and then decreased with further increase of the latters.

INTRODUCTION

Several carriers have been used to enhance the dissolution behaviour of poorly water soluble drugs (1,2). Polyethylene glycols (PEG) are popular water soluble polymers, extensively used to enhance drugs dissolution (2,3). Cyclodextrins Alpha, Beta & Gamma, are cyclic oligosaccharides consisting of six, seven or eight glucose units respectively which can be obtained on large scale from starch. They form inclusion

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complexes with compounds or molecules which can fit into their cavity. The cyclodextrin complexes have a wide application in the field of pharmaceutics (4). One of these application is to enhance the in vivo absorption and hence bioavailability of a drug with low aqueous solubility.

Hydrochlorothiazide (HCT) is one of the poorly soluble and wetted drugs. It has a potential bioavailability/ bioequivalency problems (5). Thus, the main objective of this study was to investigate the effect of different ratios of PEG 6000 and B-CD on the physicochemical properties and dissolution of HCT.

EXPERIMENTAL

Material and Apparatus:

- Polyethylene glycol 6000 (PEG 6000), and B-cyclodextrin (B-CD), Sigma Chemical Company, St., Louis, Mo, USA.
- Hydrochlorothiazide (HCT), USP Standard by Sigma Chemical Company.
- Differential Scanning Calorimeter 700, DSC, and Infrared Spectrophotometer 283, Perkin Elmer, Germany, X-ray diffractometer (Norelco, Philips Electronic Instruments, Mount Vernon, NY, USA).

Preparation of Drug/Polymer Physical Mixtures:

Different ratios of HCT and each of PEG and B-CD were accurately weighed and mixed thoroughly in a porcelain mortar.

Preparation of HCT/B-CD Coprecipitates and HCT/PEG Solid Dispersion:

The different ratios of drug/B-CD coprecipitates, were prepared by the solvent method using 50% ethanol as the solvent and those of drug/PEG 6000 solid dispersions were prepared by the fusion method.

X-ray Diffraction of the Powder Mixtures:

Powder X-ray diffractometry was carried out using a philips X-ray diffractometer with Ni-filtered Cu-K alpha radiation.

Differential Scanning Calorimetry (DSC):

The DSC sample was prepared by weighing about 5 mg of the powder mixture into the aluminium pan which was then covered and placed in the instrument sample cell. The heating rate was 10°C/minute. Dry nitrogen at 20 ml/min. was used as the carrier gas.

Infrared Analysis:

The infrared sample was prepared by suspending the powder sample in nujol mull oil using a glass watch. The suspended sample was then, smeared as a thin film between two sodium chlorides plates and scanned.

Preparation of the Tablets:

Weighed quantities of each of pure drug or the previously prepared mixtures were compressed into tablets in the press using a 1-cm diameter die at a force of 3000 lb/sq inch. The tablets was not removed from the die and the other end of the die was sealed with a cork.

Dissolution Studies from Constant Surface Tablets:

The apparatus in all dissolution studies has been previously reported (6). The die containing the tablets was placed in a methylmethacrylate (Plexiglass) holder, This allows a constant surface throughout the dissolutiuon run. The dissolution medium used was 200 ml of distilled water at 37°C and the stirring rate was 60 rpm. Samples were removed at specified time intervals, suitably diluted with distilled water and analyzed spectrophotometrically at 272 nm. The volume of the dissolution medium was kept constant throughout the dissolution run by replacing the removed samples with an equal quantity of fresh media at 30°C.

RESULTS AND DISCUSSION

Powder X-ray Diffraction:

The X-ray diffractograms of HCT/B-CD coprecipitates in the 1:1, 1:2 and 1:3 drug/polymer ratios show the crystalline form of the drug (Figure 1). However, as the ratios of drug/polymer decreased, the drug

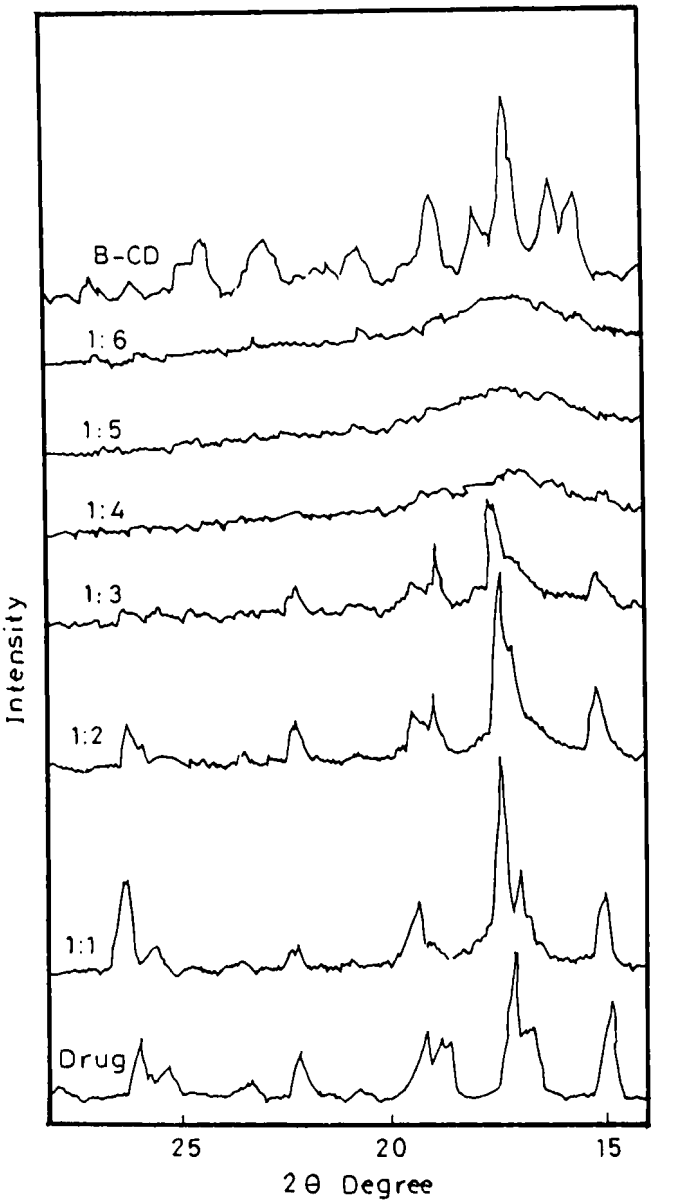

FIGURE 1

Powder X-ray diffractions of different ratios of HCT/B-CD coprecipitates.

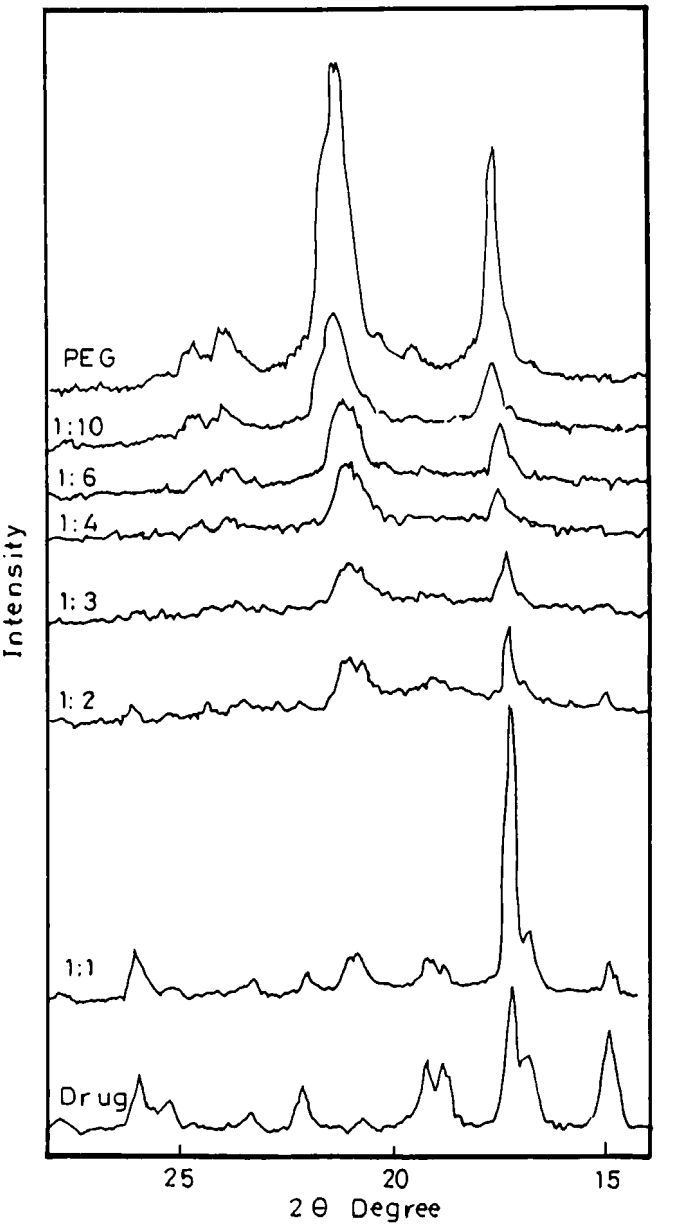

FIGURE 2

Powder X-ray diffractions of different ratios of PEG 6000 solid dispersions.

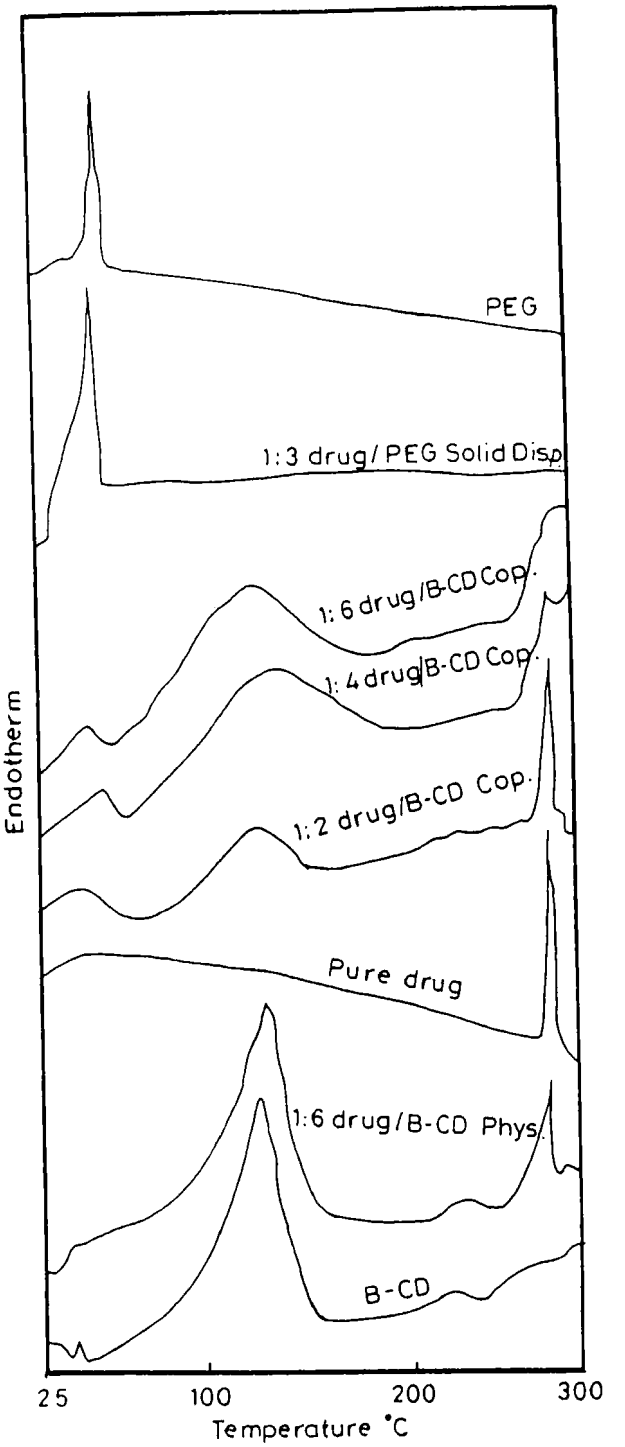

FIGURE 3

DSC thermograms of HCT, B-CD, drug/B-CD coprecipitates and physical mixtures and drug/PEG solid dispersions.

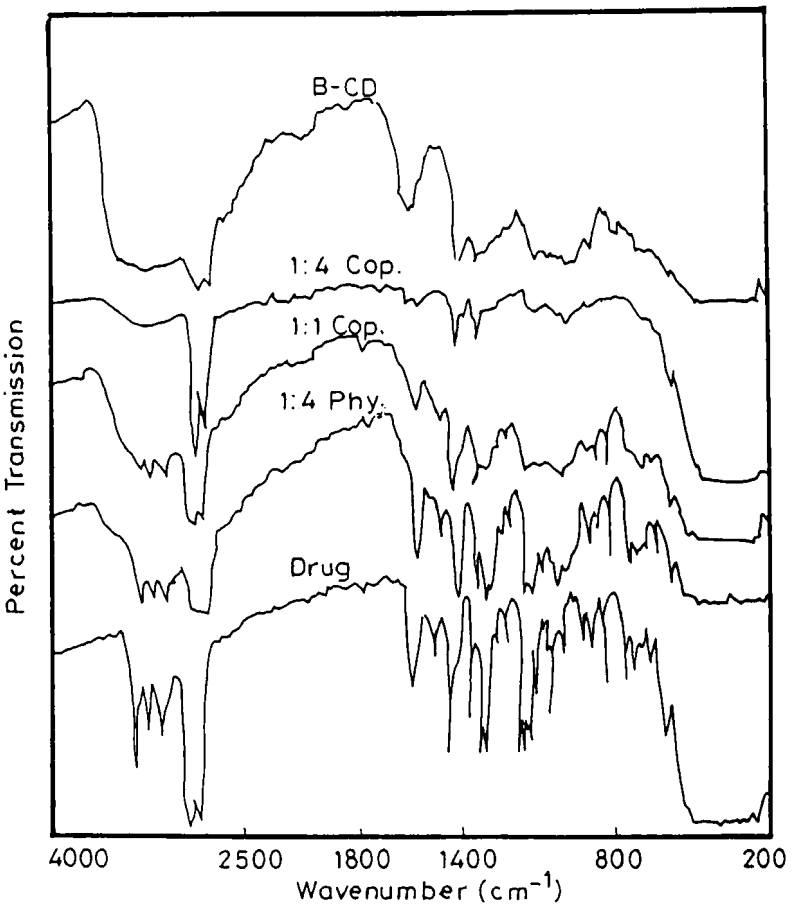

FIGURE 4

Infrared spectra of HCT, B-CD and drug/B-CD coprecipitates and physical mixture.

peaks completely disappeared indicating that the drug was present in the high energy amorphous form (6). Moreover, the crystalinity of the polymer completely disappeared in ratios of drug/B-CD less than 1:3. This indicated that; HCT and B-CD prevented the nucleation of each other. The solid dispersion of drug/PEG 6000 showed peaks of the PEG 6000 and an absence of those of the drug in the X-ray pattern (Figure 2), suggesting that a true molecular dispersion of the drug in the PEG matrix was formed (7). It should be

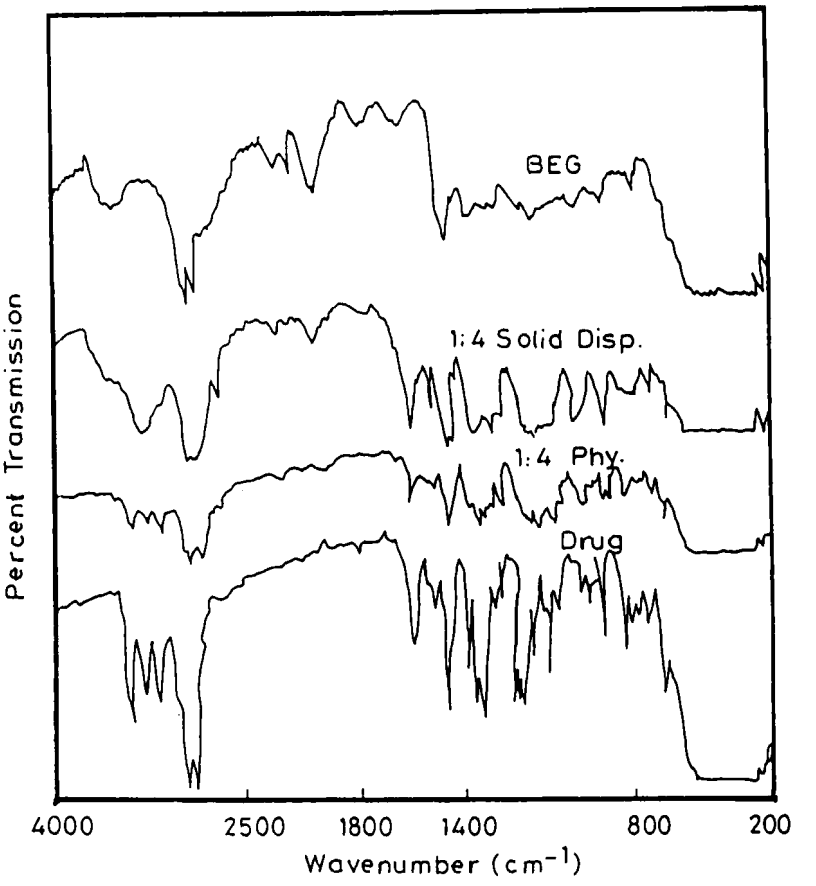

FIGURE 5

Infrared spectra, of HCT, PEG and drug/PEG solid dispersions and physical mixture.

noted that the drug, PEG 6000 and B-CD are crystalline. Also, physical mixing of HCT with each of PEG and B-CD did not affect drug crystallinity (8).

DSC Studies:

The DSC thermograms of pure drug, B-CD and 1:6 drug/B-CD physical mixture are show in Figure 3. From the figure the endothermic peaks corresponding to the melting point of pure HCT and B-CD were 265 and 126 °C respectively. The peaks of both pure drug and B-CD

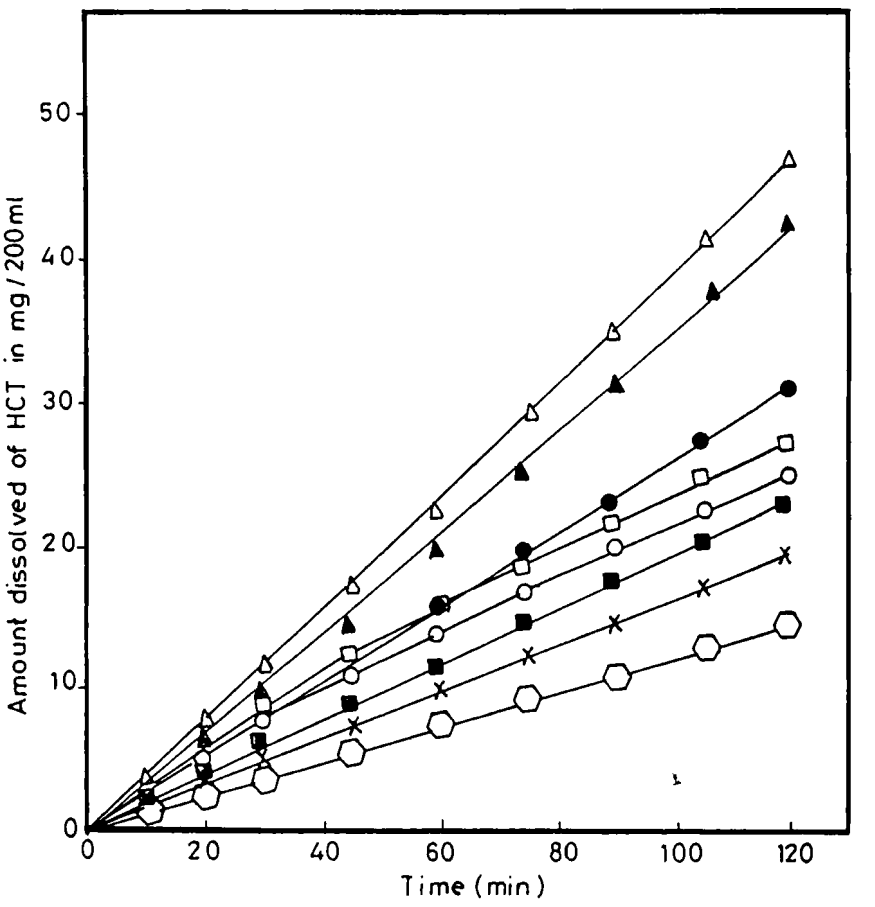

FIGURE 6

Dissolution profile of HCT from different ratios of drug/β-CD coprecipitates.

Keys:
Pure drug
1:1
1:3
1:5
2:1
1:2
1:4
1:6

are seen in the 1:6 physical system indicating that the presence of the polymer with the drug did not alter its crystallinity and vice versa. However, the thermograms of various ratios of HCT/B-CD coprecipitates in Figure 3 indicate that the drug and polymer peaks were reduced as the drug/polymer ratios decreased. This might indicate that the crystallinity of the drug and B-CD was reduced by coprecipitation.

The DSC thermograms of differnet ratios of drug/PEG 6000 solid dispersions in Figure 3, show the endothermic peak of PEG 6000 but not that of the drug. The appearance of the polymer's peak and disappearance of that of the drug in both physical mixtures (8) and solid dispersion, might indicate that HCT dissolved in the molten polymer during running the thermograms.

Infrared Studies:

The infrared spectra of 1:4 of both drug/B-CD and drug/PEG 6000 physical mixtures are simply the addition of the drug and polymer spectra (Figure 4 & 5 respectively). However, the spectra of either coprecipitate or solid dispersion in 1:4 drug-polymer ratio show that the drug bands at 3370, 3270, 3170 cm^{-1} corresponding to NH and NH_2 disappeared. This might be due to the formation of hydrogen bonding between the drug and the polymers during the dispersion and coprecipitation processes (9).

Dissolution Studies from Constant Surface Tablet:

The amount dissolved in mg of HCT from the different ratios of drug/B-CD coprecipitates was plotted as a function of time in Figure 6 as an example. The dissolution profiles of HCT were lienar from 1:2, 1:3, 1:4, 1:5 and 1:6 drug/B-CD coprecipitates. However, the 2:1 and 1:1 ratios have an initially rapid dissolution rate which tappered off to the same rate as that of pure crystalline drug. The initial rapid dissolution rate should be attributed to the presence of the polymer on the tablet surface (6) which acted as wetting and solubilizing agent (3,10). However, as the dissolution proceeded the tablet surface and the boundary layer became depleted of the polymer and therefore, the dissolution rate in the limiting region was equal to that of pure drug (6). Figure 6 shows also that the drug dissolution rate was significantly impr-

TABLE 1.
Dissolution Rates of HCT as a Function of Different Polymers Weight Fractions in Binary Mixtures.

D/P*	Polymer weight fraction	Absolute rate			Relative rate	
		PEG PM+	PEG SD++	B-CD**	PEG SD++	B-CD**
1:0	00000	0.117	0.117	0.117	1.00	1.00
2:1	0.333	-	-	0.218	-	1.86
1:1	0.500	0.120	0.434	0.245	3.71	2.09
1:2	0.667	0.217	1.056	0.376	9.03	3.21
1:3	0.750	-	1.545	0.346	13.21	2.96
1:4	0.800	-	1.181	0.215	10.09	1.89
1:5	0.833	-	-	0.205	-	1.75
1:6	0.857	-	1.141	0.167	9.75	1.43
1:10	0.909	-	0.774	-	6.62	-
1:20	0.952	-	0.479	-	4.09	-
1:40	0.976	-	0.183	-	1.56	-

* Drug/polymer ratios.
\+ Drug/PEG physical mixtures, low drug polymer ratios disintegrated upon contact with the dissolution medium.
++ Drug/PEG solid dispersions.
** Drug/B-Cyclodextrin coprecipitates, the physical mixture disintegrated upon contact with the dissolution medium.

oved by the presence of B-CD in the coprecipitates. This increase in dissolution rate migh be attributed to the reduction in drug crystallinity as indicated by the X-ray diffraction and the DSC thermal analysis. Table 1 shows the absolute and relative rates of dissolution of HCT from the coprecipitates and the solid dispersions. The drug dissolution rates from these systems were significantly improved as compared with the drug alone or the physical mixtures. As the polymer weight fraction increased the dissolution rate increased up till 1:2 and 1:3 drug polymer ratios in case of B-CD and PEG respectively. Further increase in the polymer weight fraction resulted in a decrease in dissolution rate. The polymer weight fraction-dissolution rate pattern could be described by the

same model reported before by Simonelli *et al.* (6) and Doherty & York (11).

CONCLUSION

It was found that the dispersion of HCT with PEG 6000 or coprecipitation with B-CD resulted in an amorphous form of the drug when the drug/polymer ratios were smaller than 1:3. The drug dissolution rate was greatly improved from drug/B-CD and drug/PEG 6000 solid dispersions. This enhancement was dependent on the drug/polymer ratios.

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