



RESEARCH ARTICLE

BINARY AND TERNARY SOLID SYSTEMS OF CARVEDILOL WITH 2-HYDROXYPROPYL- β -CYCLODEXTRIN AND PVP K30

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The present investigation undertook a study on BCS class II drug, Carvedilol (CRL), a nonselective beta-blocker indicated in the treatment of congestive heart failure, angina pectoris, hypertension, using 2-Hydroxypropyl- β -cyclodextrin (HP β CD) as carrier and Kollidon[®] 30 as auxiliary substance. The formulations were prepared using physical mixing, kneading and freeze drying method and evaluated for percent drug incorporation, solubility studies, *in vitro* dissolution studies, DSC, XRD and FTIR studies. Among all solid systems, formulation prepared by freeze drying method using equimolar ratio of CRL to HP β CD with 0.5% *w/v* of Kollidon[®] 30 showed significant modifications in the physicochemical properties and exhibited almost complete drug release within 10 min. The studies concluded that the addition of small amount of water soluble polymer as third auxiliary substance during complexation could display tremendous enhancement in release characteristics of poorly water soluble drugs exhibiting significant pharmaceutical potential in the development of better commercial products over existing dosage forms.

Key words: Inclusion complex, Ternary complex, Binary complex, Dissolution.

INTRODUCTION

Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development. A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. Orally administered drug completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. Bioavailability depends on several factors, drug solubility in an aqueous environment and drug permeability through lipophilic membranes being the important ones. The techniques generally employed for solubilization of drug include micronization, chemical modification, pH adjustment, solid dispersion, complexation, co solvency, micellar solubilization, hydrotrophy etc.

Only solubilized drug molecules can be absorbed by the cellular membranes to subsequently reach the site of drug action (vascular system for instance). Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption. As solubility and permeability are the deciding factors for the *in vivo* absorption of the drug, these can be altered or modified by employing one of many available enhancement techniques. Poorly soluble compounds also present many *in vitro* formulation obstacles, such as severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to the *in vivo* absorption (Sachan *et al* 2011). These poorly water soluble drugs generally suffer from slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal

toxicity (Naidu *et al* 2004). Carvedilol (CRL), chemically (\pm) -1-(Carbazol-4-yloxy)-3-[[2-(*o*-methoxyphenoxy) ethyl] amino]-2-propanol is a nonselective beta-blocker indicated in the treatment of congestive heart failure, angina pectoris, hypertension. According to BCS, CRL is classified as class II compound that possesses poor aqueous solubility and high permeability which leads to low dissolution rate limited absorption and reduced bioavailability. Therefore, improving the aqueous solubility and dissolution rate of CRL is of therapeutic significance. Complexation with cyclodextrins has been widely used to improve the solubility and dissolution rate of poorly water soluble drug (Duchene and Wouessidjewe, 1990; Bekers *et al* 1991; Dahiya and Pathak, 2006a; 2006b). Many researchers have reported effect of cyclodextrins with addition of water soluble polymers in order to enhance effectiveness of complexation (Mura *et al* 2003; Ribeiro *et al* 2003; Dahiya and Pathak, 2007; Sami *et al* 2010; Singh *et al* 2012; Taupitz *et al* 2013; Wang *et al* 2013). The present study aims to employ HP β CD as carrier and PVP K30 as an auxiliary polymer in order to investigate the influence of third component for solubility enhancement.

EXPERIMENTAL

Materials

Carvedilol was provided by Microlabs, Bangalore as gift sample. 2-HP β CD (Kleptose HPB) was obtained ex-gratia from Roquette, France. PVP K30 (Kollidon[®] 30) was obtained from BASF, Germany. All other chemicals used were of analytical grade. Double distilled water was used

throughout the studies.

Methods

Solubility study of pure drug with different concentrations of PVP

Excess amount of drug (20 mg) was added to 25 ml conical flasks containing 0.1 to 0.5% w/v PVP in distilled water. The flasks were shaken at 37 \pm 5 °C for 72 h. At the end of 72 h, samples were filtered through the Whatman filter paper. One ml of filtered samples were suitably diluted and analyzed at 243 nm.

Phase solubility studies

Excess amount of CRL was added to 10 ml of distilled water containing increased concentration of HP β CDs and placed in a mechanical shaker at 37 \pm 5 °C for 72 h. Samples were filtered through the whatman filter paper. One ml of filtered samples were suitably diluted and analyzed at 243 nm.

Phase solubility studies with optimized concentration of different polymers

Excess amount of CRL was added to 10 ml of distilled water containing increasing concentration of HP β CDs with fixed polymer concentration (0.5% w/v for PVP). The above suspensions were allowed to equilibrate for 72 h on a water bath shaker and analyzed spectrophotometrically at 243 nm.

Preparation of binary and ternary solid system

All solid systems were prepared using 1:1 Drug: CD molar ratio with/without PVP (**Table 1**).

Table 1. Composition of solid systems formulations

Formulation code	CRL (g)	HP β CD (g)	PVP % (w/w)
F1 (PMB)	4.065	1.4	-
F2 (PMT)	4.065	1.4	0.5
F3 (KNB)	4.065	1.4	-
F4 (KNT)	4.065	1.4	0.5
F5 (FDB)	4.065	1.4	-
F6 (FDT)	4.065	1.4	0.5

Physical mixing

The physical mixtures of CRL and HP β CD in 1:1 molar ratio was obtained by mixing individual components that has previously been sifted (75-150 μ m) together with a spatula (PMB). For a ternary system, 0.5% PVP was added along with CRL and HP β CD and the same procedure was followed (PMT).

Kneading method

A physical mixture of drug and HP β CD in 1:1 molar ratio was triturated in motar with a small volume of water ethanol (1:1 v/v) solution. The thick slurry was kneaded for 45 min and then dried at room temperature. The dried mass was pulverized and sieved and a (75-150 μ m) granulometric sieve fraction was collected

(KNB). For a ternary system 0.5 % PVP K30 was added along with drug and HP β CD and the same procedure was followed (KNT).

Freeze drying method

Freeze drying product was prepared by dissolving an equimolar mixture of CRL and HP β CD (FDB) and CRL-HP β CD-PVP (FDT) in distilled water and shaken for 24 h. Ammonia solution (25% v/v) was added to it drop wise till a clear solution was obtained. The solution was frozen overnight in petri dishes at -40 °C and lyophilized in a freeze dryer at -40 °C for 48 h. Secondary drying was carried out at room temperature.

Determination of drug content

Ten mg of each solid dispersion was accurately weighted and dissolved in 10 ml of volumetric flask with hydrochloric acid buffer (pH 1.2), assayed spectrophotometrically for CRL at 243 nm. Results were expressed both as the drug content (mg incorporated drug) and percent incorporation (actual amount of drug in formulation vs initially added amount). The studies were conducted in triplicate.

In vitro drug release studies

In vitro dissolution was studied using USP XXVII Apparatus 2 in 900 ml of hydrochloric acid buffer (pH 1.2) at an agitation rate of 50 rpm. The temperature of medium was maintained at 37 \pm 0.5°C. Ten mg of drug or its equivalent weight of the prepared solid system was taken and analyzed for dissolution.

A sample was withdrawn at specific time period and equal volume of fresh dissolution medium was used to maintain a constant volume. The aliquot samples were filtered and the concentration was determined spectrophotometrically at 243 nm (IP, 1996).

Characterization of solid dispersion systems

FTIR spectroscopy

Infrared spectra were obtained using a Shimadzu FTIR spectrophotometer. The samples were previously ground and mixed thoroughly with KBr, an infrared transparent matrix. The KBr disk were prepared by compressing the power. The scanning range was 400-4000 cm⁻¹.

Differential scanning calorimetry analysis

Thermograms of pure materials, their treated components and all binary and ternary systems were recorded on a (Perkin Elmer-Jude DSC)

model differential scanning calorimeter. About 1-5 mg samples were sealed in aluminum pans and an empty aluminum pan was used as reference. The experiment was carried out under nitrogen flow (20 ml/min) at scanning rate of 10 °C/min in the range of 30 to 400 °C.

X-Ray powder diffractometry

Diffraction pattern of CRL, physical mixtures, kneading, and freeze drying product, an polymers were recorded. A voltage of 40 kV and a current of 30 mA for the generator was used, with Cu as the tube anode material. The solids were exposed to Cu-K α radiation ($\alpha_1=1.54060$ A and $\alpha_2=1.54439$ A, with an α_1/α_2 ratio of 0.5), over a range of 2θ angles from 10 °C to 30 °C, at an angular speed of 1° (2θ) per minute.

RESULTS AND DISCUSSION

Solubility studies

Solubility studies of CRL in solution containing different concentration of PVP in distilled water at 37°C showed that PVP (the most) was effective polymer in improving CRL solubility at 0.5% w/v concentration (**Figure 1**).

Phase-solubility studies

Phase-solubility studies of CRL in binary and ternary system without and with PVP K30 were then performed to obtained more information about the drug solubilization mechanism and the multicomponent complex formation (**Figure 2a, 2b**).

Solubility diagrams obtained by adding increasing amounts of HP β CD to excess amounts of CRL or CRL-PVP K30 mixture were both of A_L type according to the Higuchi classification, showed a linear increased of drug solubility, indicative of the formation of soluble complexes. The solubility calculated for CRL in distilled water was 8.5 μ g/ml at 37°C. The solubility of CRL increased linearly with an increase in the concentration of HP β CD, giving A_L type solubility diagrams. The increase in solubility in the systems was due to one or more molecular interaction between CRL and HP β CD to form distinct species or complexes. The solubilizing efficiency of HP β CD was higher. The cavity size of the HP β CD seemed to be optimal for entrapment of CRL molecule and consequently provides the greatest solubilization effect. The stability constant value calculated was 1630 \pm 1.26 M⁻¹, for HP β CD. The larger constant that was observed with HP β CD indicated that CRL interacted more strongly with the HP β CD.

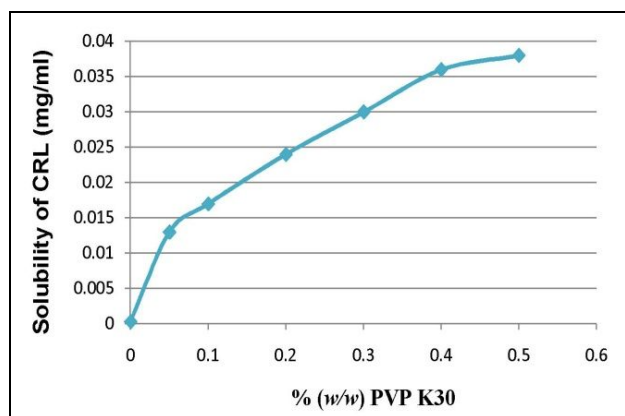


Fig. 1. Solubility study of CRL with PVP K30 to screen the polymer concentration in distilled water

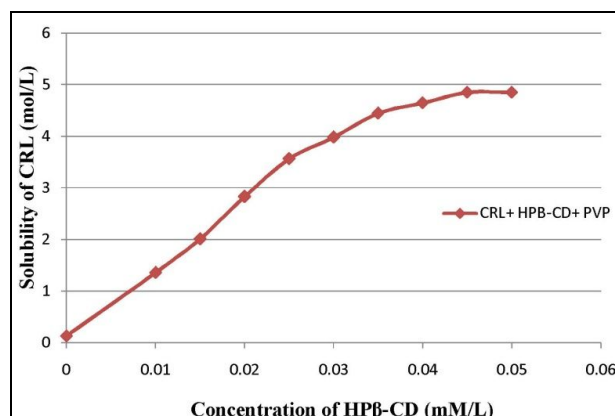


Fig. 2b. Phase solubility of CRL with fixed conc. of PVP K30 (0.5 % w/v)

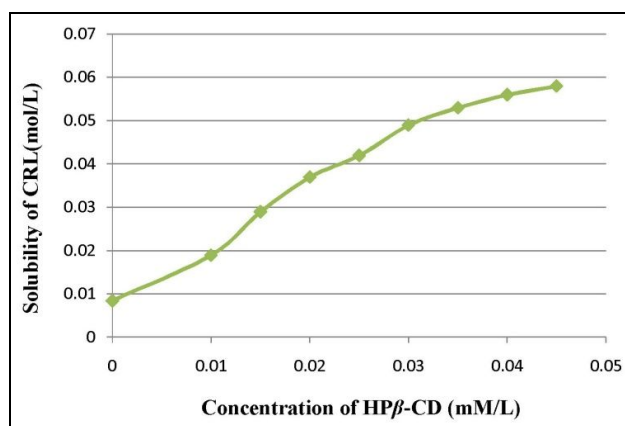


Fig. 2a. Phase solubility study of CRL with HPβCD in distilled water

Drug content estimation

Drug content studies suggested that actual drug content values were in good agreement with theoretical values with percent drug incorporation in range of 90.66-91.11% of expected values (Table 2).

In vitro drug release studies of solid system

The dissolution rates of CRL in the form of powder, PM, KN and FD of binary and ternary systems were examined in hydrochloric acid buffer pH 1.2. The dissolution of pure CRL was extremely low, with only 75% of drug released during 120 min of dissolution run in hydrochloric acid buffer (pH 1.2) (Figure 3).

Table 2. Percent drug content of solid systems

S. No.	Formulation	Loading efficiency (mg)		Percent incorporation
		Theoretical drug content (%)	Actual drug content	
1.	F1	22.5	20.4 ± 0.115	90.66
2.	F2	22.5	20.3 ± 0.057	90.22
3.	F3	22.5	20.5 ± 0.100	87.55
4.	F4	22.5	19.7 ± 0.602	88.88
5.	F5	22.5	20.2 ± 0.152	89.77
6.	F6	22.5	20.0 ± 0.100	91.11

This might be attributed to poor wettability and particle agglomeration during the run that caused the powder to float on the surface of dissolution medium. The mean dissolution curves of CRL from various binary systems (PMB, KNB, FDB) CRL, HPβCD and ternary systems (PMT, KNT, FDT) were studied and the relevant dissolution data are presented in Table 3. The increase in dissolution rate was higher for the ternary than the respective binary compositions. Due to the very strong affinity of CRL and HPβCD, it was reasonable to assume

that CRL-HPβCD interaction in ternary products occurred in a similar way as in the binary system. Therefore, in ternary preparations, the molecules of the CRL-HPβCD inclusion complex were supposed to be present in a more or less intimate dispersed state within the PVP matrix through interactions between the exterior of the complex and PVP, and this state could be responsible for the higher dissolution rate with respect to binary preparations. The results in terms of relative dissolution rate (RDr) at 5 and 30 min and the percent of active ingredient

dissolved at 30 min (DP_{30}) are presented in (Table 3). Overall, the ternary system of HP β CD with PVP (F6/FDT) FD product showed the best dissolution among all the formulation of the HP β CD.

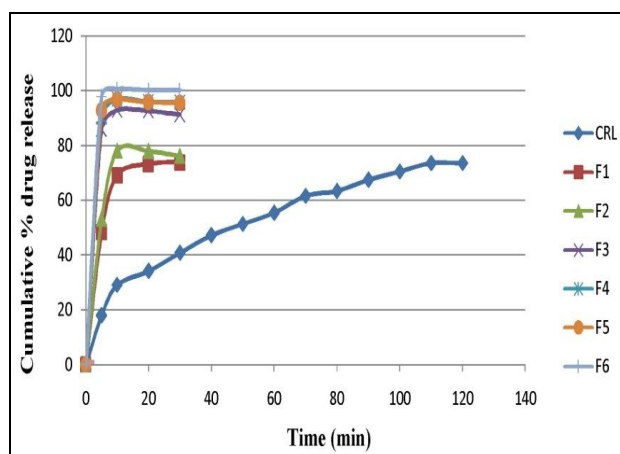


Fig. 3. Comparative drug release profile of pure drug and formulation F1 to F6

Table 3. Model independent parameters of solid systems

Formulation code	$t_{50\%}$	$t_{85\%}$	PD _{10min}	PD _{30min}	Rdr _{5min}	Rdr _{30min}
CRL	36.6	62.3	29.16	40.88	-	-
F1	20.3	34.5	70.12	73.81	2.68	1.83
F2	19.6	33.4	78.04	76.15	2.94	1.89
F3	16.4	27.9	92.85	91.20	4.76	2.26
F4	15.6	26.6	96.87	95.72	5.01	2.37
F5	15.6	26.6	96.83	95.55	5.14	2.37
F6	14.9	25.4	100.52	100.16	5.42	2.48

indicating that overall symmetry of the molecule was not significantly affected even though the vibration and bending of the drug were restricted due to the formation of an inclusion complex.

Differential scanning calorimetry

DSC was used to identify the inclusion ternary complex between the CRL-HP β CD and PVP K30. As seen from the DSC thermograms, CRL alone showed a sharp endothermic peak at 114 °C, corresponding to the melting point of the crystalline CRL. The physical mixture showed a sharp endothermic peak corresponding to CRL (114 °C) PVP, HP β CD, indicated no complex formation. In case of the kneaded complex, a broad endotherm was obtained around 120°C. The thermo gram of the inclusion ternary complex prepared by the FD method shifted towards lower temperature showed a broad endotherm between 90 and 100°C. Lower

Characterization of solid system

FTIR spectroscopy

Infrared spectra of pure drug, physical mixture, kneaded complex and complex obtained by freeze drying. Carvedilol showed characteristic peak at 3344.5 cm^{-1} (O-H and N-H stretching vibration peaks merged together) 2922.16 cm^{-1} (C-H stretching vibration). 1591.34 cm^{-1} (N-H bending vibrations) and 1257.59 cm^{-1} (OH bending and C-O stretching vibrations). The intensity and shape of these bands changed dramatically for the inclusion ternary complex compared to the physical mixture and Carvedilol (CRL).

The complex showed broadening of OH and N-H stretching vibration peaks (3383.45 cm^{-1}). Differences were found in the 1450-1606 cm^{-1} region which were attributed to skeleton vibrations of the C=C bonds in the aromatic ring. In the low frequency regions (4000-400 cm^{-1}), all the spectra were almost unchanged (Figure 4),

temperature of the inclusion ternary complex can be attributed to the melting point depression in the complex. Also in the case of complex obtained by freeze drying, it can be concluded that amorphization of the drug might occurred in the presence of HP β CD and PVP and trapping of carvedilol inside the HP β CD cavity, led to the broad nature of the endotherm (Figure 5).

X-Ray powder diffraction

Powder X-ray diffractometry is a useful method for the detection of cyclodextrin complexation in powder or microcrystalline states. The diffraction pattern of the complex should be clearly distinct from that of the superposition of each of the components if a true inclusion complex has been formed. The XRD patterns of CRL, HP β CD, PVP the physical mixture, and the ternary system are showed in Figure 6. The complexation products were identified by comparing their diffractograms with those of

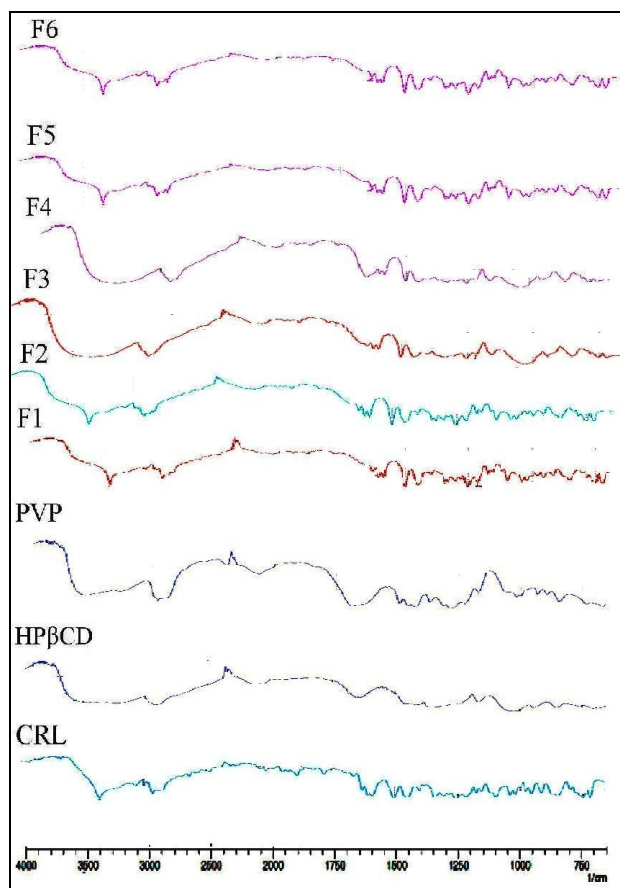


Fig. 4. FTIR spectra of pure components and formulations

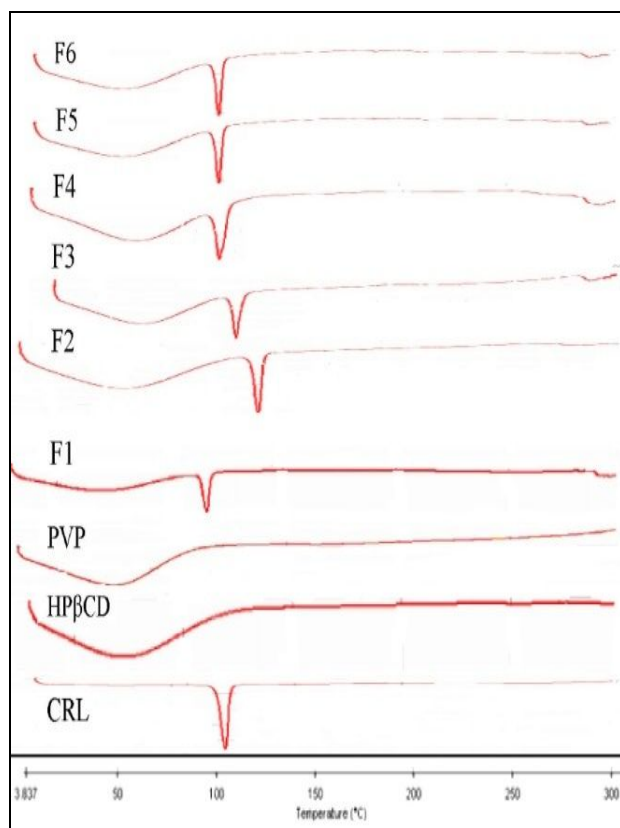


Fig. 5. Comparison among DSC thermograms of CRL, HPβCD, PVP and formulations

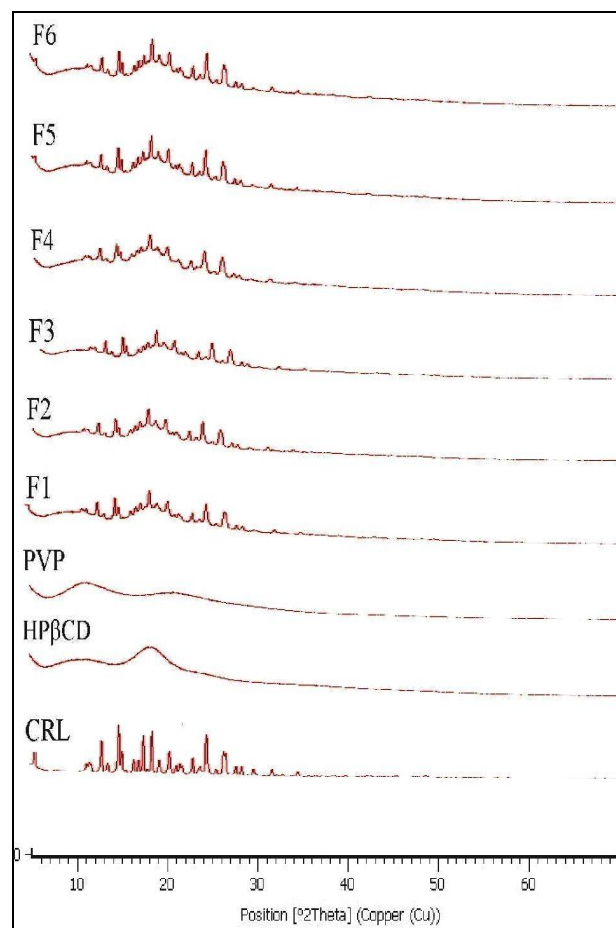


Fig. 6. X-ray diffraction patterns of CRL, HPβCD, PVP and formulations

pure CRL, HPβCD and PM. The XRD pattern of the PM contained the principal diffraction peaks of CRL and HPβCD. This can be attributed to the reduction in particle size as a consequence of the preparation method and to the dilution of the drug in the PM. A reduced number of signals were noticeable in the complexes, with a markedly reduced intensity, demonstrating the nature of the inclusion compounds compared with that of the drug. This was also in agreement with the results of the FTIR and DSC studies.

CONCLUSION

The study demonstrated the possibility of significantly improving the dissolution performance of CRL by complexation using HPβCD with PVP as third auxiliary substance; as evidenced by synergistic effect when used in combination with HPβCD. Among preparation methods used, freeze drying technique was the most suitable for obtaining solid homogeneous equimolar CRL-HPβCD-PVP complexes. These systems could be useful for formulating better dosage forms with rapid onset of action and improved bioavailability.

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