AAPS PharmSciTech, Vol. 10, No. 3, September 2009 (© 2009)
DOI: 10.1208/s12249-009-9274-6

Research Article

Studies on the Effect of Water-Soluble Polymers on Drug–Cyclodextrin Complex Solubility

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Received 25 August 2008; accepted 10 June 2009; published online 27 June 2009

Abstract. The effect of complexation of irbesartan (IRB), a practically water-insoluble drug, with cyclodextrins in presence of different concentrations of water-soluble polymers (PEG 4000 and PVP K-90) on the dissolution rate of the drug has been investigated. Phase solubility studies were carried out to evaluate the solubilizing power of βCD in association with water-soluble polymers towards IRB and to determine the apparent stability constant (K_S) of the complexes. Improvement in K_S value for ternary complexes (IRB–βCD–polymers) clearly proved the benefit on the addition of water-soluble polymer to increase complexation efficiency. The dissolution rate of the drug from ternary systems containing PEG 4000 and PVP K-90 was higher as compared to the binary system. An optimum increase in the dissolution rate of the drug was observed at a polymer concentration of 5% *w/w* for PVP K-90 and 10% *w/w* for PEG 4000. DSC, FTIR, SEM, and XRD studies were carried out to characterize the complexes.

KEY WORDS: dissolution; hydrophilic polymers; irbesartan; solubility; β-cyclodextrin.

INTRODUCTION

Cyclodextrins (CDs) form a group of structurally related oligosaccharides with cylinder-shaped cavities that have the capacity to form inclusion complexes with many drugs by taking a whole drug molecule or a part of it into the cavity. CDs have wide applications mainly because of their effect on enhancing the solubility and bioavailability of many lipophilic drugs (1–3).

Irbesartan (IRB), used orally for treatment of hypertension, is a nonpeptide, specific competitive antagonist of the Angiotensin II receptor (AT_1 subtype) (4,5). The drug is lipophilic and practically insoluble in water. The low aqueous solubility and slow dissolution may lead to irreproducible clinical response or therapeutic failure (6). The rationale of this study was to improve the dissolution and solubility of IRB utilizing the approach of inclusion complexation of the drug in CDs in presence of water-soluble polymers like PEG 4000 and PVP K-90.

The ability of water-soluble polymers to enhance the solubilizing effect of cyclodextrins in a given dosage form has been demonstrated by Loftsson *et al.* (7). Such results are attributed to a synergistic effect of polymer and cyclodextrin believed to be due to formation of ternary complexes or co-complexes between drug, cyclodextrin, and polymer (8). Polymers such as water-soluble cellulose derivatives can form complexes with cyclodextrin that have different physicochemical properties than those of cyclodextrin alone. The solubility of the cyclodextrin or the apparent binding constant between the drug and cyclodextrin can be changed in this manner (1). When added in small amounts, water-soluble polymers or ion-pairing agents enhance CD solubilizing effect by increasing the apparent complex stability constant. The polymers, due to their direct participation in drug complexation, improve both pharmaceutical and biological properties of drug–CD complexes, independent of drug's physiochemical properties (9).

Characterization of the complexes was performed by differential scanning calorimetry (DSC), Fourier transformation infrared spectroscopy (FTIR), X-ray diffraction (XRD), and scanning electron microscopy (SEM).

EXPERIMENTAL

Materials

Irbesartan was kindly supplied by Aarti Drugs Ltd, Mumbai, India as a gift sample.

β-cyclodextrin (M.W. 1,135) was gifted by Signet, India. All the polymers and reagents used were of analytical grade. Freshly prepared distilled water was used throughout the experiments.

Phase Solubility Studies

Phase solubility studies were carried according to the Higuchi and Connors (10) method in distilled water at room

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ABBREVIATIONS: IRB, irbesartan; βCD, beta-cyclodextrins; DSC, differential scanning calorimetry; FTIR, Fourier transform infrared spectroscopy; XRD, X-ray diffraction; SEM, scanning electron microscopy; K_S, apparent stability constant; CE, co-evaporation; HCl, hydrochloric acid.

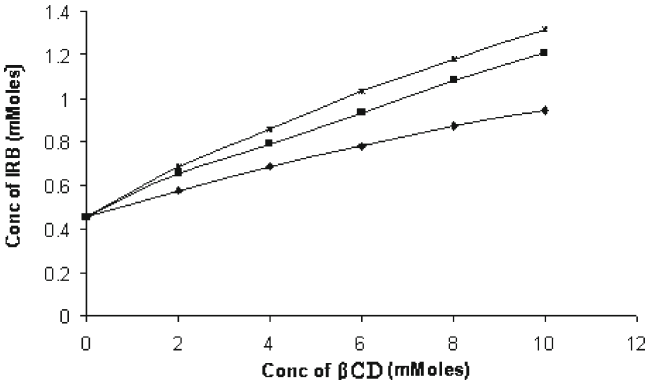

Fig. 1. Phase solubility diagram IRB–βCD system in water at 25±2°C (n=3). *Closed diamonds* IRB–βCD, *closed squares* IRB–βCD–PEG 4000, *asterisks* IRB–βCD–PVP K-90

temperature (25°C). Excess amounts of IRB was weighed in stoppered glass vials to which were added 5 ml of aqueous solutions containing increasing amounts of βCD (0–0.01 mol) with or without a fixed polymer (PVP K-90 and PEG 4000 at 1% *w/v* w.r.t. to final solution) concentration. The polymer concentration was selected on the basis of preliminary studies carried between IRB, polyethylene glycol (PEG), and polyvinyl pyrrolidone (PVP) as no further improvement in the solubility values of IRB was achieved by increasing polymer concentration. The glass vials were mechanically shaken until equilibrium was achieved (48 h). Aliquots were drawn, filtered, and spectrophotometrically (Shimadzu UV 1601 Japan) analyzed at 244 nm for IRB content. The apparent stability constant K_S was calculated from the slope of the linear plot of the phase solubility diagram according to the equation:

$$K_S = \frac{slope}{S_0(1 - slope)}$$

Where S_0 is the solubility of the drug in absence of βCD.

Preparation of Drug–βCD complexes

Coevaporation Method

Binary and ternary systems of IRB with βCD were prepared in 1:1 molar ratio. For binary system, drug and βCD and, for ternary systems, IRB, βCD, and either PVP K-90 or PEG 4000 were added in required amount of ethanol–water 50% *v/v* mixture to obtain a suspension. Each polymer was used at a concentration of 2%, 5%, 10%, and 15% *w/w* with respect to drug and βCD complex. The suspensions were further sonicated. The clear solution was subjected to coevaporation (11,12) at temperature 50–70°C on a magnetic stirrer till all the solvent got evaporated. The complex obtained was dried at 50°C and kept under vacuum overnight. The mass obtained was sieved through no.80 sieve.

Table I. Values of Apparent Stability Constant K_S in Presence of Various Concentration of Polymers

System	Curve Type	Binding constant (K_S) (M^{-1})
IRB–βCD	A_L	129.73
IRB–βCD–0.25% *w/v* PEG 4000	A_L	127.4
IRB–βCD–0.5% *w/v* PEG 4000	A_L	136.7
IRB–βCD–1.0% *w/v* PEG 4000	A_L	158.76
IRB–βCD–2.0% *w/v* PEG 40000	A_L	156.63
IRB–βCD–0.25% *w/v* PVP K-90	A_L	131.4
IRB–βCD–0.5% *w/v* PVP K-90	A_L	164.2
IRB–βCD–1.0% *w/v* PVP K-90	A_L	201.2
IRB–βCD–2.0% *w/v* PVP K-90	A_L	199.7

Table II. Solubility Profile of Plain IRB, Dry Powder Admixture, and Inclusion Complexes of IRB, βCD, and Water-Soluble Polymers

Sample	Solubility in distilled water at 25°C (n=3; μg/ml)
IRB	67.8
IRB–βCD (dry powder admixture)	109.8
IRB–βCD–PEG 4000 (dry powder admixture)	189.7
IRB–βCD–PVP K-90 (dry powder admixture)	210.4
IRB–βCD (inclusion complexes)	137.6
IRB–βCD–PEG 4000 (inclusion complexes)	331.19
IRB–βCD–PVP K-90(inclusion complexes)	345.63

Saturation Solubility Studies

Excess amounts of inclusion complexes (72.9 mg for binary and 76.81 mg for ternary systems equivalent to 20 mg of IRB) were added to 5 ml of distilled water in glass vials which were subsequently tightly closed and shaken for 24 h in

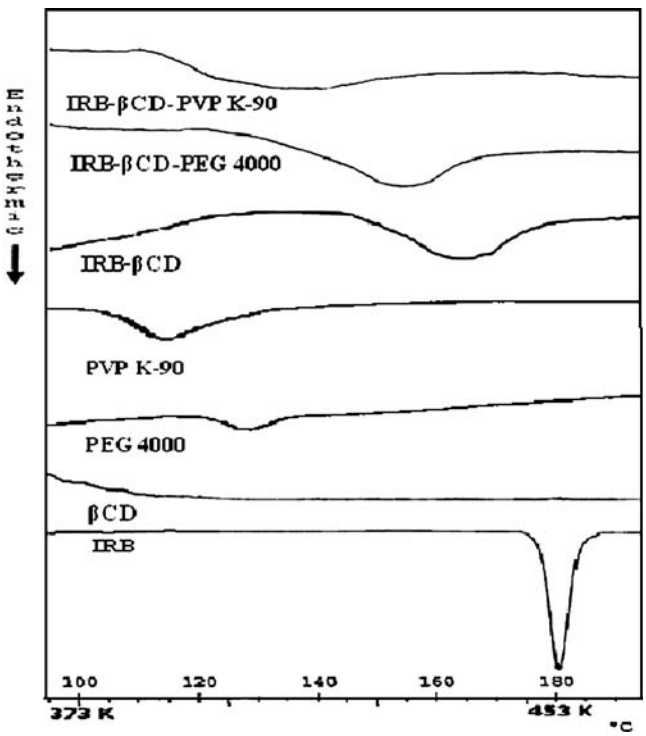

Fig. 2. DSC spectra of IRB–βCD complexes

a mechanical shaker at room temperature to achieve the equilibrium. Appropriate aliquots were then withdrawn, filtered, and diluted and were analyzed spectrophotometrically at 244 nm.

Differential Scanning Calorimetry

The DSC curves of drug, βCD, binary, and ternary systems were recorded on METTLER TOLLEDO-DSC-822^e (USA) model of differential scanning calorimeter. The thermal behavior was studied by heating all samples (5–10 mg of drug or its equivalent) in sealed aluminum pans, using an empty sealed pan as a reference, over a temperature range of 30–200°C at heating rate of 10°C/min.

Fourier Transformation Infrared Spectroscopy

FTIR spectra were recorded on Jasco-700 FT-IR spectrophotometer (UK) using KBr discs. The instrument was operated under dry air purge, and the scans were collected at scanning speed of 2 mm/s with resolution of 4 cm^{-1} over the region of 4,000–400 cm^{-1}.

X-Ray Diffraction

Powder X-ray diffraction patterns were recorded using Phillips P Analytical X'Pert PRO (Netherlands) powder X-ray diffractometer using Ni-filtered, CuKα radiation, a voltage of 40 kV, and a current of 30 mA. The scanning rate employed was 1°/min, and samples were analyzed between 2θ angles of over 5–45°.

Scanning Electron Microscopy

The surface morphology of the drug, binary, and ternary systems were examined by a Philips 500 scanning electron microscope (Japan). The samples were fixed on a brass stub using double-sided tape and made electrically conductive by coating with a thin layer of gold by sputter coater Palaron E 5100. The photographs were taken at an electric voltage of 20 kV and a magnification of ×500 and ×2,500.

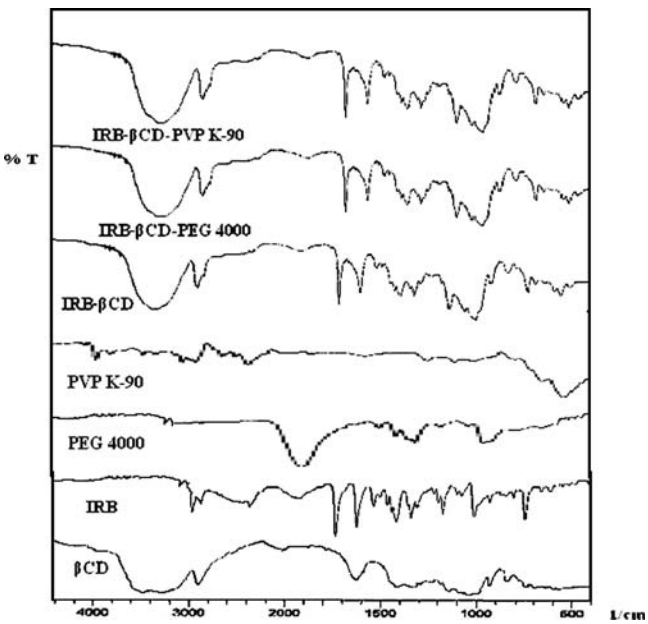

Fig. 3. FTIR spectra of IRB–βCD complexes

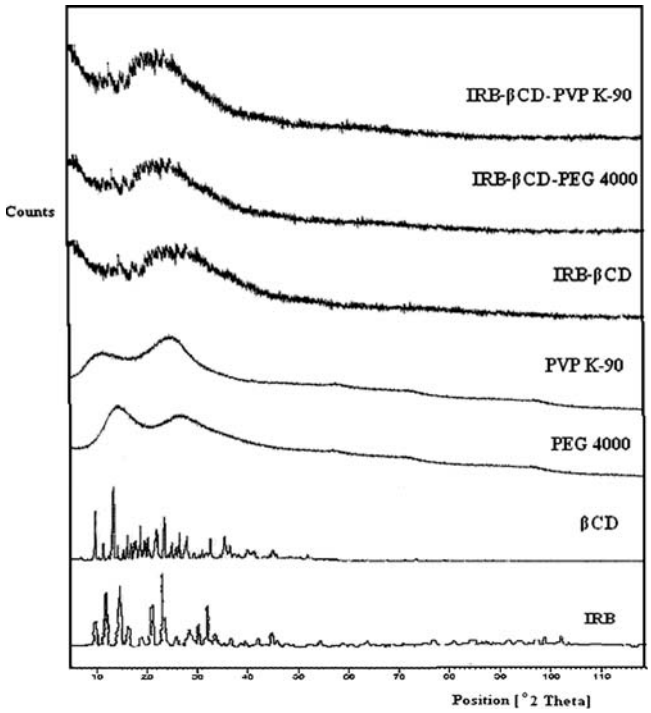

Fig. 4. XRD spectra of IRB–βCD complexes

Dissolution Studies

Dissolution studies of the complexes was carried out using type II (paddle type) dissolution test apparatus (Model: Veego VDA-6DR tablet dissolution test apparatus, India) USP XXIII at 50 rpm using 1,000 ml 0.1 N hydrochloric acid (pH 1.2) as dissolution medium maintained at 37±0.5°C. Five milliliters of sample was withdrawn at time intervals of 0, 5, 10, 20, 30, 45, and 60 min and filtered through Whatman filter paper (0.45 μm size). The volume of dissolution fluid was adjusted by replacing 5 ml of dissolution medium after each sampling. The absorbance of withdrawn samples was measured at 244 nm.

RESULTS

Phase Solubility Studies

The phase solubility diagram (Fig. 1) of IRB in aqueous solutions at 25°C of βCD with or without 1% *w/v* polymers was of Higuchi and Connors A_L type: that is, a linear increase of drug concentration with increase in cyclodextrin concentration was observed. The slopes in all cases were less than unity, thus confirming the formation of 1:1 complexes.

The phase solubility studies of IRB in aqueous solution of βCD with various concentrations (0.25%, 0.5%, 1.0%, and 2.0% *w/v*) of PEG 4000 and PVP K-90 were carried out. The values of stability constant of IRB–βCD complex, either when no polymers were present or in the presence of 1% *w/v*

polymers, are shown in Table I. IRB showed solubility enhancement of 68.9% at 10 mM concentration of βCD with 1% *w*/*v* of water-soluble PVP K-90 and 201.2 M^{-1} as the apparent stability constant (K_S).

Saturation Solubility Studies

The solid ternary systems of IRB and βCD in presence of water-soluble polymers showed an increase in aqueous solubility as compared to the binary system and to the pure drug alone with IRB–βCD–PVP K-90 complex showing highest solubility than all other systems as shown in Table II.

Differential Scanning Calorimetry

The DSC curves for irbesartan alone and its binary and ternary mixtures with the carrier are shown in Fig. 2. A sharp endothermic peak at 182°C in thermal curve of IRB corresponds to its melting point, whereas the DSC thermogram of βCD showed a broad endotherm in the region of 90–120°C, which can be attributed to the release of water molecule from the cavity as explained by Liu *et al.* (13). In the case of binary system, a very shallow peak was observed which disappeared completely in case of ternary systems.

Fourier Transformation Infrared Spectroscopy

Figure 3 shows the infrared (IR) spectra of drug alone and different complexes. The IR spectra of IRB–βCD binary and ternary systems (IRB–βCD–PEG 4000 and IRB–βCD–PVP K-90) showed differences when compared with those of their corresponding constituents. In case of binary system, the peak at 1,176 cm^{-1} [C–N vibrations] was reduced and shifted to a lower wave number 1,157 cm^{-1}, and the peak at 1,533 cm^{-1} [N–H bending] was shifted to a higher wave number 1,541 cm^{-1}.

X-Ray Diffraction

The records of XRD pattern are shown in Fig. 4. The sharp and intense peaks observed in the diffractograms of irbesartan and βCD indicated a crystalline phase. Prominent peaks of IRB and βCD disappeared, and the remaining peaks were less intense in the case of binary system confirming the

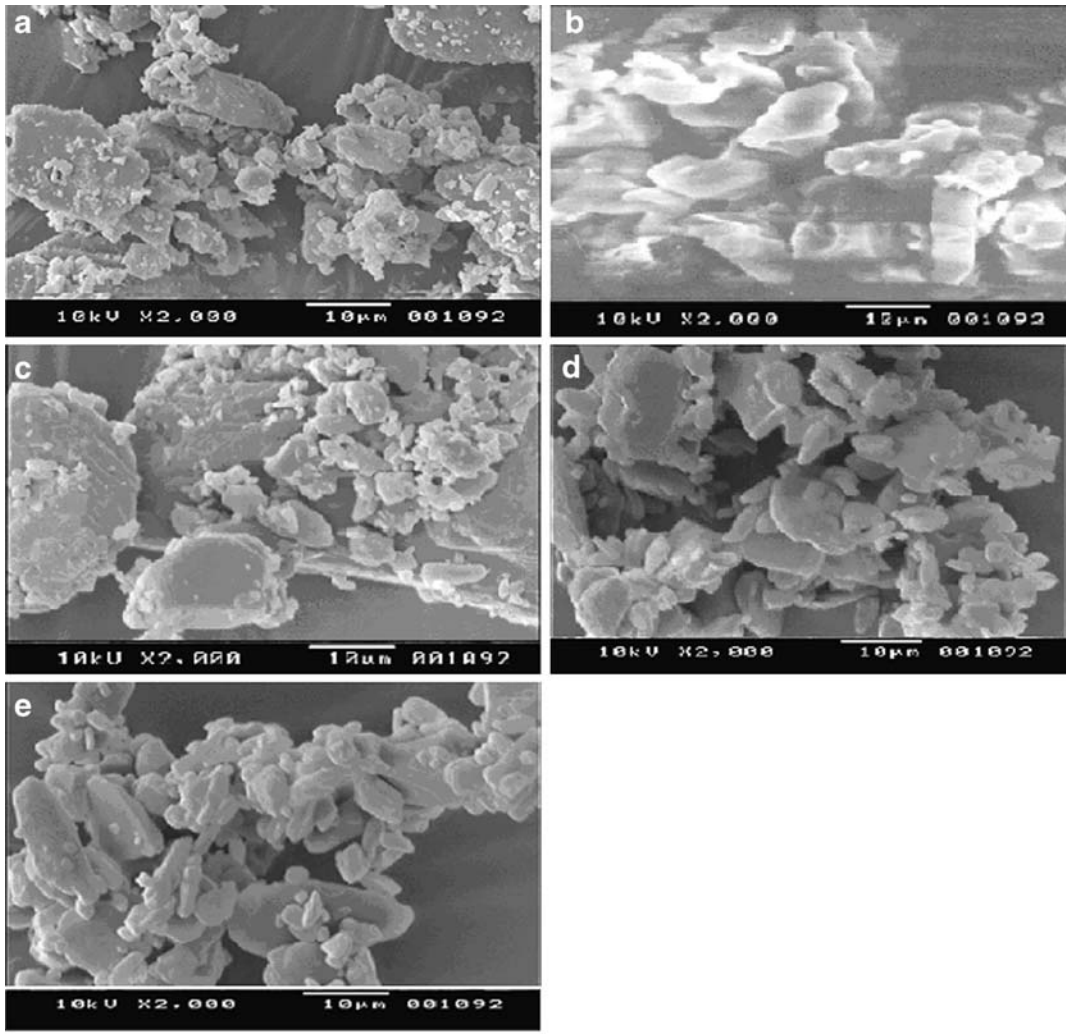

Fig. 5. Scanning images of **a** irbesartan, **b** β-cyclodextrin, **c** IRB–βCD, **d** IRB–βCD–PEG 4000, **e** IRB–βCD–PVP K-90

Table III. Dissolution Profile of IRB–βCD–PVP K-90 and IRB–βCD–PEG 4000 at Various Concentrations in 0.1 N HCl at 37±0.5°C (n=3)

Sample	% Drug dissolved						
	5 min	10 min	15 min	20 min	30 min	45 min	60 min
IRB–βCD—2% *w/w* PVP K-90	86.78±1.7	90.45±2.3	93.23±0.7	96.58±2.2	98.41±0.8	100.19±1.6	100.19±1.6
IRB–βCD—5% *w/w* PVP K-90	96.94±1.8	99.698±1.3	99.49±2.1	100.41±0.6	100.41±0.6	100.41±0.6	100.41±0.6
IRB–βCD—10% *w/w* PVP K-90	96.31±0.9	97.98±1.7	99.31±2.1	100.12±0.1	100.12±0.1	100.12±0.1	100.12±0.1
IRB–βCD—2% *w/w* PEG 4000	84.56±0.8	87.63±1.6	91.89±1.9	93.32±2.3	96.48±0.7	99.23±0.8	100.12±1.8
IRB–βCD—5% *w/w* PEG 4000	85.23±1.9	86.17±1.1	89.61±1.9	93.37±2.3	97.97±0.8	99.45±1.6	100.87±1.3
IRB–βCD—10% *w/w* PEG 4000	94.73±0.7	96.12±1.8	98.46±2.0	99.91±0.4	101.32±1.6	101.32±1.6	101.32±1.6
IRB–βCD—15% *w/w* PEG 4000	95.64±0.9	96.89±1.8	97.56±1.4	99.96±2.1	100.12±1.4	100.89±0.8	100.65±1.7

formation of new solid phase. The intensity and sharpness of the peaks were further diminished in case of ternary systems.

Scanning Electron Microscopy

From SEM scans as seen in Fig. 5a, pure IRB particles appeared as irregular-shaped crystals (10–30 μm); βCD particles [Fig. 5b] consisted of three-dimensional crystals of irregular sizes. Drug–βCD binary product as seen in Fig. 5c showed small and irregular pieces with a change from crystalline to amorphous nature. The morphology of the ternary systems of drug–βCD–water-soluble polymers showed loss of smooth surface and reduced size of the particles [Fig. 5d, e]. The formations of undifferentiated particles were clearly different from those of IRB and βCD.

Dissolution Studies

Effect of Polymers on the Dissolution Rate of IRB–βCD Complexes

Data of dissolution study of ternary systems revealed an enhancement of dissolution of IRB compared to binary system. PVP K-90 was used in 2%, 5%, and 10% *w/w* concentrations, and for PEG 4000, 2%, 5%, 10%, and 15% *w/w* concentrations were used for preparation of ternary system. In presence of the polymers, the enhancement of dissolution rate was found to increase with increasing polymer concentration as seen in Table III.

In presence of PVP K-90, the dissolution rate of the drug showed optimum increase at 5% *w/w* polymer concentration as seen in Fig. 6.

In case of ternary system containing PEG 4000, the optimum increase was at 10% *w/w* polymer concentration (Fig. 7). There was no further improvement in the dissolution profile of the drug when the polymer concentrations were improved, and hence, the optimum polymer concentration was selected.

The investigated polymers increased the dissolution rate of the drug in order of IRB–βCD 5% *w/w* PVP K-90 > IRB–βCD 10% *w/w* PEG 4000 > IRB–βCD > IRB. Ternary complex containing 5% *w/w* PVP K-90 showed 99.69% drug release as compared to 70.63% from IRB–βCD binary system and 21.86% from the plain drug at the end of 10 min. IRB–βCD 10% *w/w* PEG 4000 showed 96.12% drug release at the end of 10 min. The increase in the dissolution of IRB might be related to the increase of complexation efficiency and solubilizing effect of CD in presence of water-soluble polymers.

DISCUSSIONS

As seen from phase solubility studies, the higher K_S value for ternary complexes in comparison with the corresponding binary one suggested a significant improve-

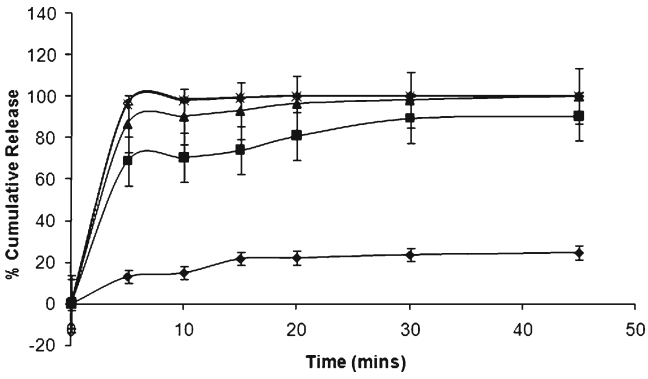

Fig. 6. Dissolution profile of IRB–βCD-PVP K-90 complexes at 37±0.5°C (n=3). *Closed diamonds* IRB, *closed squares* IRB–βCD, *closed triangles* IRB–βCD–2% PVP K-90, *open diamonds* IRB–βCD–5% PVP K-90, *asterisks* IRB–βCD–10% PVP K-90

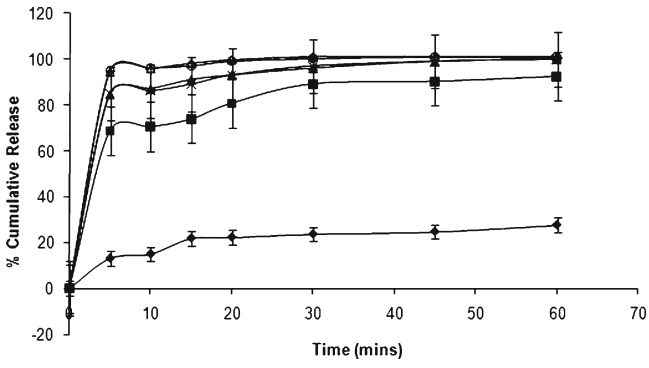

Fig. 7. Dissolution profile of IRB–βCD-PEG 4000 complexes at 37±0.5°C (n=3). *Closed diamonds* IRB, *closed squares* IRB–βCD, *closed triangles* IRB–βCD–2% PEG 4000, *asterisks* IRB–βCD–5% PEG 4000, *open triangles* IRB–βCD–10% PEG 4000, *open diamonds* IRB–βCD–15% PEG 4000

ment in drug complexation and solubility by addition of small amounts of water-soluble polymer.

Addition of the polymer resulted in an increase in the stability constant, which could be attributed to the increase of the cyclodextrin complexing power towards IRB. PVP K-90 exhibited the highest solubilizing effect at 1% *w*/*v* as compared to PEG 4000, as evident by a large increase in stability constant. Results of the saturation solubility studies indicated enhancement in solubility of IRB in presence of βCD which was further improved on addition of water-soluble polymers. This is in accordance with the observation made by Patel *et al*. that, when polymer and cyclodextrin are present together, one achieves an extent of drug solubilization greater than drug–βCD or of drug alone (14).

In DSC thermogram, presence of a very shallow peak in case of binary system with its complete disappearance in ternary systems indicated formation of inclusion complex as explained by Diaz *et al.* (15)

The minor changes in the FTIR scans of the binary system indicate the presence of host–guest interactions and suggest the formation of hydrogen bonds between IRB and βCD. Due to complex formation, it could result in inclusion of tetrazole moiety into the hydrophobic cavity of βCD. These findings were in full agreement with earlier author Veiga *et al*. (11), who reported similar behavior for vinpocetine–βCD complex. The shift in characteristic bands of IRB in ternary systems was similar to that of binary system, indicating that water-soluble polymers played no role in interaction involved in complex formation.

Disappearance of prominent peaks in XRD of binary system scans indicate the strong interaction between drug and βCD (12), suggesting formation of stable hydrogen bonds as explained by Figueiras *et al*. (16). Appearance of more diffused patterns in case of ternary systems indicated further amorphization due to addition of polymers, as explained by Ammar *et al.* (12).

Naidu *et al.* (17) have found that a modification in the shape of drug particles was indicative of a new solid state. Hence, the changes in the particle shape and size as observed in SEM scans of binary and ternary systems suggested the change in the physical properties of the drug and CD, which concludes the formation of drug–CD–water-soluble polymer complex.

In case of PVP K-90, increasing the concentration from 2% *w*/*w* to 5% *w*/*w* improved the dissolution profile of drug which remained unchanged with further improvement of polymer concentration. In PEG 4000, maximum dissolution rate was found at 10% *w*/*w* polymer concentration. Comparing the effect of polymers on the dissolution of IRB–βCD complexes, it is evident that PVP K-90 at a lower concentration of 5% *w*/*w* as compared to 10% *w*/*w* PEG 4000 exhibited the highest dissolution rate, and hence, it is the selected polymer.

The ternary system showed a 3.38- and 4.55-fold increase in dissolution rate as compared to the binary system and drug alone, respectively. The dissolution rate of glimeperide–β-cyclodextrin was improved by incorporation of 20% *w*/*w* of PVP. These results indicated the effectiveness of hydrophilic polymers on improving dissolution rate of the complex (18).

CONCLUSIONS

From the results of the characterization studies of binary and ternary systems, it can be concluded that IRB forms inclusion complex with βCD. Incorporation of hydrophilic polymer can further aid in amorphization and particle size reduction of the complex, leading to further improvement in the dissolution rate of the complex. Thus, hydrophilic polymers can be utilized to enhance the solubility conferred by CD complexation.

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