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Research Paper

Influence of β-Cyclodextrin and Hydroxypropyl-β-Cyclodextrin on Enhancement of Solubility and Dissolution of Isradipine

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ABSTRACT

The content of this investigation was to study the influence of β-cyclodextrin and hydroxy propyl-β-cyclodextrin complexation on enhancement of solubility and dissolution rate of isradipine. Based on preliminary phase solubility studies, solid complexes prepared by freeze drying method in 1:1 molar ratio were selected and characterized by DSC for confirmation of complex formation. Prepared solid dispersions were evaluated for drug content, solubility and *in vitro* dissolution. The physical stability of optimized formulation was studied at refrigerated and room temperature for 2 months. Solid state characterization of optimized complex performed by DSC and XRD studies. Dissolution rate of isradipine was increased compared with pure drug and more with HP-β-CD inclusion complex than β-CD. DSC and XRD analyzes that drug was in amorphous form, when the drug was incorporated as isradipine β-CD and HP-β-CD inclusion complex. Stability studies resulted in low or no variations in the percentage of complexation efficiency suggesting good stability of molecular complexes. The results conclusively demonstrated that the enhancement of solubility and dissolution rate of isradipine by drug-cyclodextrin complexation was achieved.

KEYWORDS: Isradipine; complexation; β-cyclodextrin; hydroxypropyl-β-cyclodextrin; solubility; dissolution.

Introduction

Drug absorption from the gastrointestinal (GI) tract is often limited by a variety of factors with the most significant contributors being poor aqueous solubility and/or poor membrane permeability. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption (Amidon et al., 1995). Oral bioavailability of drugs improved by two approaches namely, enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly permeable drugs. Solubility can be improved by various techniques such as micronization (Chaumeil, 1998), modification of the crystal habit like polymorphs (Blagden et al., 2007), solid dispersions (Sinha et al., 2010), micellar solubilization (Rangel-Yagui et al., 2005), inclusion complex formation (Uekama et al., 1998) and cryogenic techniques such as spray freeze drying (Rogers et al., 2002) and lyophilization (Cao et al., 2005).

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of usually six, seven, or eight glucose units (α-, β- and γ-CDs, respectively) bound by 1,4-glycosidic linkages (Gao et al., 2006). CDs are known to form inclusion complexes with hydrophobic drugs and improve their water solubility, dissolution rate and bioavailability (Loftsson and Brewster, 1996). It is also used to stabilize unstable medicine, improve taste, suppress volatility, atomize liquid materials, provide content uniformity, prevent hemolysis in the injection and improve stimulant properties (Matsuda and Arima, 1999).

Isradipine (ID) is a calcium channel blocker used to treat hypertension. It works by relaxing the blood vessels so your heart does not have to pump as hard (Chrysant and Cohen, 1997). ID having low oral bioavailability (15-24%) due to poor aqueous solubility (0.01mg/mL) and hepatic first-pass metabolism. Previously, the oral bioavailability of ID was enhanced by using nanoparticles was reported (Thirupathi et al., 2017). Hence, the solubility and dissolution of ID was increased by complexed with β-cyclodextrin (β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD). Previously, solid dispersions prepared with physically mixing of drug and surfactant (De Waard et al., 2008).

The objective of this investigation was to evaluate the possibility of increasing the solubility of isradipine through complexation with β-CD and HP-β–CD by using freeze-drying method.

Materials and Methods

Isradipine was a kindly gifted sample from Dr. Reddy's laboratories, Hyderabad, India. β-cyclodextrin and hydroxypropyl-β-cyclodextrin are kindly gifted samples from M/s. Aurobindo Labs, Hyderabad, India. All chemicals and reagents used were of analytical grade.

Phase Solubility Studies

Phase solubility studies with increasing concentration of β-cyclodextrin and hydroxypropyl-β-cyclodextrin (0.1, 0.25, 1, 1.5, 2, 5, 4 and 5-millimole ratio) were performed according to the method described by Higuchi and Connors. Briefly, excess amount of the drug was added to 10mL of double distilled water containing various concentrations of β-cyclodextrin and hydroxy propyl β-cyclodextrin taken in a stoppered glass vials. The suspensions were vigorously shaken at 25 ± 1°C for 3 days on a rotary shaker. After equilibrium was attained, the samples were filtered through a 0.45 µm Millipore membrane filter and suitably diluted. These samples were assayed for the drug content by spectrophotometer against blank in same concentration of HP-β-CD in water. The solubility experiments were conducted in triplicate. The apparent 1:1 stability constant, Ks, was calculated from the phase solubility diagrams using the following equation: The complexation constant ($K_{1:1}$) and complex efficiency (CE) were calculated from linear proportionality of phase solubility diagrams, according to equations (1) and (2) respectively

$$K_{1:1} = \text{slope}/S_0\,(1 - \text{slope}) \qquad .....(1)$$

Where, S_0 is drug solubility in the absence of HP-β-CD (intercept).

$$\text{CE} = S_0 \times K_{1:1} = \text{slope}/S_0(1 - \text{slope}) \qquad .....(2)$$

Preparation of CD Solid Dispersions

Solid dispersion by lyophilization: Based on phase solubility graphs an A_L-type means that the complexation ratio of CD: isradipine is on 1:1 molar basis. Briefly, 1mM cyclodextrin derivative was initially dissolved in distilled water and a 30% methanolic solution containing ID was then added stepwise to the aqueous solution of cyclodextrin derivative. It was stirred at 600 rpm for 6h until a stable suspension was formed on magnetic stirrer to obtain complexation equilibrium. All the clear solutions were frozen at -20°C and the frozen solutions were lyophilized in a freeze-dryer (Lyodel, Delvac Pumps Pvt. Ltd, India) to obtain a solid complex for 72 h and obtain a dry powder of CD solid dispersion formulations of isradipine-HP-β-CD-lyophilized.

Preparation of physical mixture: Physical mixtures (PM) of ID-β-CD and ID-HP-β-CD in the ratio of 1:1 were prepared by mixing weighed amount of isradipine, β-CD and HP-β-CD in a glass mortar until a homogeneous mixture was obtained. Then these mixtures were taken and were stored in the desiccators. This mixture was used for the comparative study with respect to ID-β-CD and ID-HP-β-CD-lyophilized products.

Drug content: The drug content of freeze-dried products and PM was assayed to calculate the equivalent amount of isradipine to be taken. To analyze the drug content in the prepared solid dispersion and physical mixture formulations by taking an appropriate weighed quantities (in triplicate) and then dissolved in 25 mL of methanol in a conical flask and kept on a rotary shaker for 1 h. After this time, samples were centrifuged for 15 minutes and supernatant was filtered through 0.45µ membrane filter and diluted suitably and analysed spectrophotometrially (SL-159, Elico, Hyderabad, India) at 330nm.

Inclusion efficiency: The prepared solid dispersion complex and physical mixtures were placed in 25mL volumetric flasks. Methanol (10mL) was added, mixed thoroughly and sonicated for 30 min. The volume was made up to the mark with methanol. The solution was suitably diluted with the same solvent and analysed spectrophotometrically.

Solid State Characterization

Differential scanning calorimetry (DSC): DSC thermal analysis of freeze-dried solid dispersions, physical mixtures, β-CD, HP-β-CD and pure drug were performed using Perkin Elmer (DSC 4000, Perkin Elmer, CT). Differential scanning calorimeter calibrated with indium. samples were accurately loaded into aluminum pans, sealed and heated at a temperature ranging from 30°C to 200°C with a constant nitrogen gas at a heating rate of 20°C/min (De Waard et al., 2008).

Powder X-ray Diffractometry (PXRD): Powder X-ray diffractometer (Multiflex, M/s. Rigaku, Japan) was used for diffraction studies and reveals the PXRD patterns of pure drug, HP-β-CD and solid dispersions. Powder XRD studies were performed on the samples by exposing them to nickel filtered CuKα radiation (40kV, 30mA) and scanned from 2° to 70°, 2θ at a step size of 0.045° and step time of 0.5s.

In vitro dissolution study: To role of cyclodextrin in enhancing the dissolution behavior of poorly water-soluble drug, solid dispersions, physical mixtures and pure drug were ascertained by *in vitro* dissolution tests. The tests were run in triplicate using USP type II (paddle) apparatus (TDT-06P, Eletrolab, Hyderabad, India) in pH 6.8 phosphate buffer as dissolution medium maintained at 37±0.5°C temperature with paddle speed set at 50 rpm right through the study. Relevant quantities of formulations (solid dispersions and physical mixture) and pure drug equivalent to 5mg dose were placed into dissolution media. Aliquots of 5mL were withdrawn at predetermined time intervals followed by refilling with fresh media to retain fixed volume and analyzed by spectrophotometer.

Analysis of Dissolution Data

The percentage cumulative amount of drug released in 15 and 60 minutes (Q15 and Q60 respectively) were derived from the *in vitro* dissolution release profile.

Dissolution efficiency (DE%): Dissolution efficiency (DE) is defined as the area under the dissolution curve up to a certain time (t), expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. It was calculated by using the following equation:

$$\text{D.E.} = \frac{\int_0^t y \times dt}{y_{100} \times t} \times 100\% \qquad .....(3)$$

Mean dissolution rate (MDR): The sum of drug coming into bulk of dissolution media per unit time under *in vitro* dissolution conditions is defined as the mean dissolution rate (MDR). This was calculated by following equation

$$\mathrm{MDR} = \frac{\Sigma_{j=1}^{n} \Delta M_j / \Delta t}{n} \qquad .....(4)$$

Where, ΔMj is the additional amount of drug dissolved between tj and t−1, n is the number of *in vitro* dissolution sample times, Δt the midpoint time between tj and t−1 which can be easily calculated with (t + t−1)/2.

Mean dissolution time MDT (min): In order to assess the comparative extent of the dissolution rate enhancement from SDs, mean dissolution time (MDT) was calculated. It defined as the time taken for dissolving a molecule from solid dosage form and following equation was used to calculate MDT:

$$\mathrm{MDT}_{\text{in vitro}} = \frac{\sum_{i=1}^{n} t_{\text{mid}} \Delta M}{\sum_{i=1}^{n} \Delta M} \qquad .....(5)$$

Where, *i* is the *in vitro* dissolution sample number, n defines number of sample time points, t_{mid} is the midpoint of the *i*th time period easily calculated with [t + (t-1)]/2 and ΔM is the additional amount of drug dissolved between t_i and t-1.

Initial dissolution rate (IDR): Initial dissolution rate isthe first 15 minutes dissolution rate of the *in vitro* dissolution study and also called dissolution rate.

Stability studies: The aliquots of phase solubility studies were placed in stability chambers at 25°C/60% RH and 40°C/75% RH for period of 60days. Samples were withdrawn at 0, 30 and 60 days from the study, processed and estimated for the content of drug by spectrophotometer.

Results and Discussion

Phase Solubility Study β-Cyclodextrin

The phase solubility of ID was constructed by using β-cyclodextrin and propyl hydroxy β-cyclodextrin carried out by taking varied concentrations.The solubility of ID was increased with increase in the concentration of β-CD and HP-β-CD. The Gibbs free energy for the resulting solution decreases as the concentration of the carrier increases. The decrease in Gibbs free energy indicates increase in the solubility of the drug. The stability constant was calculated as to indicate the stability of the complex formed between the drug and the carrier. The A_L type phase solubility curve indicates the linear increase in solubility of ID. The stability constant (69.44 for β-CD), 115.8 (optimum stability constant for HP-β-CD) values indicated the weak complexation of drug and cyclodextrin. Comparing the solubility of drug without carrier and with 25% of carrier in water the solubility of the drug was increased by 2.4 and 4.18 folds with β-CD and HP-β-CD, respectively (Loftsson and Brewster, 1996). The results are shown in Table 1.

TABLE 1

Solubility of isradipine in different millimolar ratios of β-CD and HP-β-CD (mean±SD, n=3).

Solution	Amount of drug dissolved (mg/mL)	
	β-CD	HP-β-CD
Water	0.089 ± 0.013	1.01 ± 0.03
0.1 mM	0.82 ± 0.35	1.28 ± 0.41
0.25 mM	1.26 ± 0.19	1.82 ± 0.52
0.5 mM	1.61 ± 0.31	1.91 ± 0.40
1 mM	2.13 ± 0.32	2.44 ± 0.62
2 mM	2.43 ± 0.27	2.59 ± 0.52
2.5 mM	2.75 ± 0.39	2.99 ± 0.38
4 mM	1.66 ± 0.39	3.12 ± 0.50
5 mM	1.20 ± 0.28	1.52 ± 0.22

Based on the results obtained from phase solubility studies, HP-β-CD were selected as suitable CD for formulation development due to their superior solubilizing capacity. Moreover, earlier reports suggests that the chemically modified beta cyclodextrin (HP-β-CD) have greater applicability in development of oral solid dosage forms due to higher efficiency of complexation and lower toxicity over native β-cyclodextrin (Zeng et al., 2011).

Drug content: Drug content from all the formulations of β-cyclodextrin was found to be 89.55 ± 2.41 to 91.82 ± 2.04% and hydroxy propyl β-cyclodextrin was 90.27 ± 1.85 to 97.94 ± 2.66%. From the results, more amount drug present in the HP-β-CD of ID than β-CD because of solubility difference (Table 2).

TABLE 2

Drug content and inclusion efficiency of physical mixtures, β-CD and HP-β-CD isradipine solid dispersions (mean±SD, n=3).

Formulations	Drug content (%)	Inclusion efficiency (%)
PM β-CD	92.05 ± 1.63	87.12 ± 1.99
PM HP-β-CD	93.12 ± 1.95	92.88 ± 2.01
ID β-CD (1:1)	90.13 ± 1.84	79.16 ± 2.43
ID β-CD (1:2.5)	91.82 ± 2.04	81.02 ± 1.74
ID β-CD (1:4)	90.09 ± 2.95	80.65 ± 3.72
ID β-CD (1:5)	89.55 ± 2.41	81.53 ± 2.63
ID HP-β-CD (1:1)	95.83 ± 1.84	90.11 ± 2.11
ID HP-β-CD (1:2.5)	94.31 ± 2.75	92.22 ± 1.88
ID HP-β-CD (1:4)	97.94 ± 2.66	96.75 ± 3.61
ID HP-β-CD (1:5)	90.27 ± 1.85	89.77 ± 0.86

Inclusion efficiency: Inclusion efficiency of prepared solid dispersions were found to be 79.16 ± 2.43 to 81.53 ± 2.63% and 89.77 ± 0.86 to 96.75 ± 3.61 for β-CD and HP-β-CD, respectively (Table 2). More amount of drug should be included in hydroxy propyl cyclodextrin.

In vitro dissolution study: Dissolution profiles of β-CD and HP-β-CD shown in Figure 1 & 2. The *in vitro* dissolution study performed in case of β-CD and HP-β-CD shows maximum release of drug at the end of 1h. At the end of 1 h pure drug showed a maximum release of 32.82 ± 1.09% of the drug where as solid dispersion of β-CD with 1:1, 1:2.5, 1:4, and 1:5 showed 65.23 ± 0.98%, 75.27 ± 1.22%, 88.94 ± 1.86% and 93.57 ± 2.01%, respectively. However, physical mixture of β-CD (1:5) showed 40.75 ± 1.11% of drug release. In case of HP-β-CD solid dispersions, HP-β-CD (1:1, 1:2.5, 1:4, and 1:5) exhibited

72.82 ± 1.04%, 78.34 ± 1.74%, 89.95 ± 2.31% and 99.1 ± 2.13% during 1h period and PM of HP-β-CD showed 43.85 ± 1.55%. The dissolution efficiency in solid dispersions suggests that increased solubility and dissolution rate of ID in solid dispersions. The initial dissolution rate of β-CD and HP-β-CD was found to be 4.91 and 5.29 higher than other solid dispersions and physical mixtures indicates higher dissolution rate at 15 mins. However, the increase in dissolution characteristics of ID in solid dispersions is further compared from Mean Dissolution Time and Mean Dissolution Rate values (Table 3 & 4). Based on the solubility, drug content, inclusion efficiency and dissolution studies HP-β-CD with 1:4 formulation considered as optimized and used for further studies.

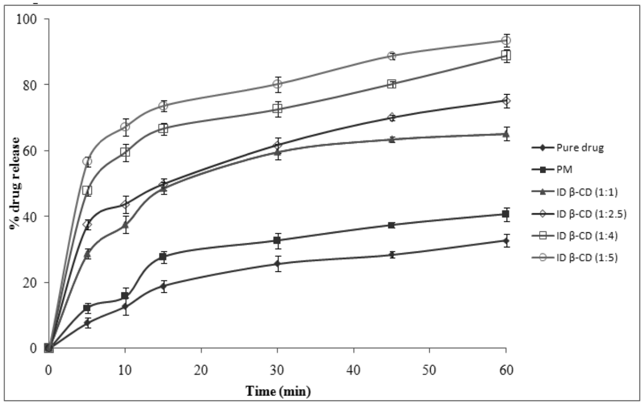

Fig. 1. Dissolution profile of pure drug, physical mixture and β–CD solid dispersions (mean±SD, n=3).

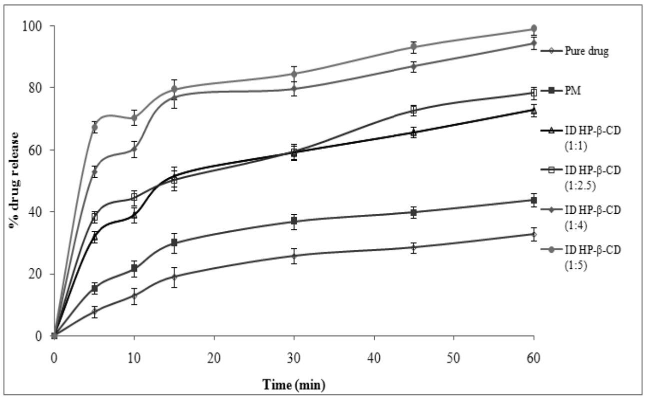

Fig. 2. Dissolution profile of pure drug, physical mixture and HP-β-CD solid dispersions (mean±SD, n=3).

TABLE 3

Dissolution parameters of Isradipine, β–cyclodextrin solid dispersions and physical mixture.

Parameters	Q_{15}	Q_{60}	DE_{15}	DE_{60}	MDT	MDR	IDR
PD	18.94	32.82	28.94	21.13	38.38	0.21	1.26
PM-β-CD	27.74	40.75	21.98	31.25	29.55	0.54	1.84
ID β-CD (1:1)	48.71	54.79	16.6	44.98	21.48	0.84	3.24
ID β-CD (1:2.5)	49.88	56.85	17.65	46.28	25.62	0.88	3.32
ID β-CD (1:4)	66.72	66.29	28.47	59.46	12.36	1.32	4.44
ID β-CD (1:5)	73.72	90.45	38.81	80.35	13.04	1.78	4.91

TABLE 4

Dissolution parameters of Isradipine, hydroxypropyl-β–cyclodextrin solid dispersions and physical mixture.

Parameters	Q_{15}	Q_{60}	DE_{15}	DE_{60}	MDT	MDR	IDR
PD	18.94	32.82	28.94	21.13	38.38	0.21	1.26
PM HP-β-CD	29.85	43.85	26.33	66.28	21.38	1.28	1.99
ID HP-β-CD (1:1)	51.43	72.82	25.58	61.29	18.74	1.24	3.42
ID HP-β-CD (1:2.5)	54.21	78.34	27.95	66.75	21.87	1.52	3.61
ID HP-β-CD (1:4)	76.88	94.44	35.34	72.46	18.37	1.62	5.12
ID HP-β-CD (1:5)	79.45	99.1	36.85	79.00	18.75	1.71	5.29

Solid-state characterization

Differential Scanning Calorimetry (DSC) of OM-SLNs

The compatibility status of the excipients in the solid dispersion formulation was investigated by differential scanning calorimetry (DSC). DSC thermograms of pure drug, β-CD, HP-β-CD physical mixtures of β-CD and HP-β-CD and lyophilized β-CD and HP-β-CD inclusion complex formulations were showed in Figure 3. The DSC thermogram of isradipine exhibited a sharp endothermic peak at 165.8°C corresponding to its melting point. The DSC thermogram of β-CD and HP-β-CD showed a polymeric transisition melting range. Physical mixture of ID and β-CD showing endothermic peak at 161.7°C of ID and physical mixture of ID and β-CD (1:1) shown endothermic peaks at 159.9°C (De Paula et al., 2007) and it indicates the complex formation between the drug and cyclodextrins. Freeze dried formulations showed absence of endothermic peak of ID indicating that drug was encapsulated, and/or molecularly dispersed in the β-CD and HP-β-CD (Timko et al., 1984).

X-Ray Diffraction

The diffraction pattern of pure drug showed high intensity peaks at 2θ values of 10.8ºC, 14.9ºC, 15.7ºC, 16.3ºC, 17.8ºC, 21.4ºC and 29.9ºC respectively (Figure 4). Sharp intense peaks may be due to presence of crystalline form of the drug. Diffraction patterns of physical mixture exhibited intensity of peaks at 21.05ºC, 28.07ºC and 29.38ºC. In case of solid dispersion exhibited intensity peaks at 21.06ºC, 28.28ºC and 29.35ºC. The lack of numerous distinctive peaks of the drug in the physical mixture as well as solid dispersions demonstrated that high concentration of the drug was dissolved in the solid-state carrier matrix in an amorphous structure suggesting the transformation of crystalline form of ID to amorphous form in the solid dispersions and physical mixtures (Ramasahayam et al., 2015).

Stability studies: The stability studies were performed by storage at 25°C and 40°C for period of two months. Samples were withdrawn at 0, 30 and 60 days from the study, processed and the drug content was found to be 90.23 ± 1.32% and 96.85 ± 2.66% in β-CD (1:5) and HP-β-CD (1:5) formulation. There was no significant change in the complex efficiency values with respect to day 0 in the aqueous solid dispersions of β-CD and HP-β-CD by the end of 60th day. Hence, prepared solid dispersions were stable at 25°C and 40°C for two months time.

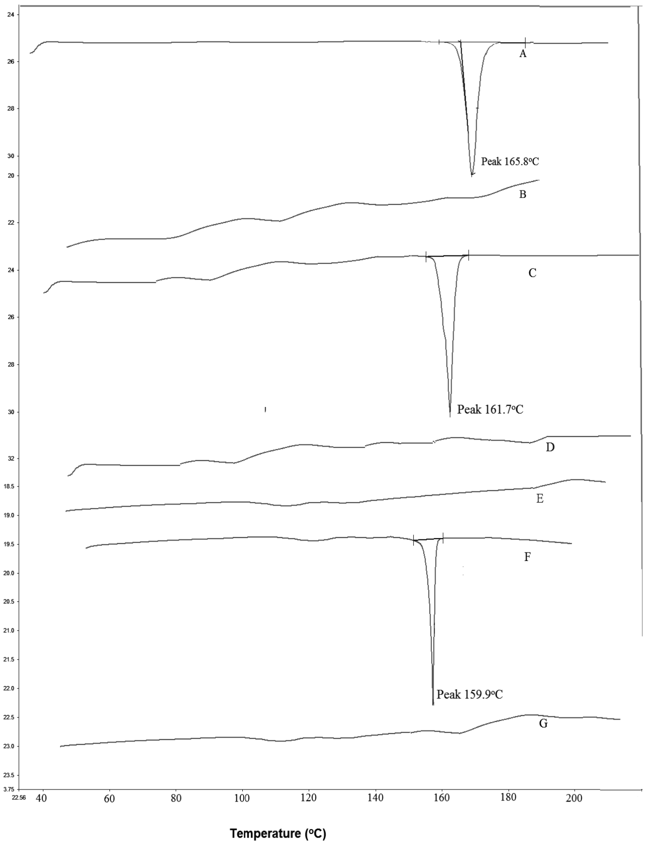

Fig. 3. DSC thermograms of A) pure drug, B) β–CD, C) physical mixture of drug and β–CD (1:1 ratio), D) inclusion complex of β-CD, E) HP-β–CD, F)) physical mixture of drug and HP-β–CD (1:1 ratio) and G) inclusion complex of HP-β-CD.

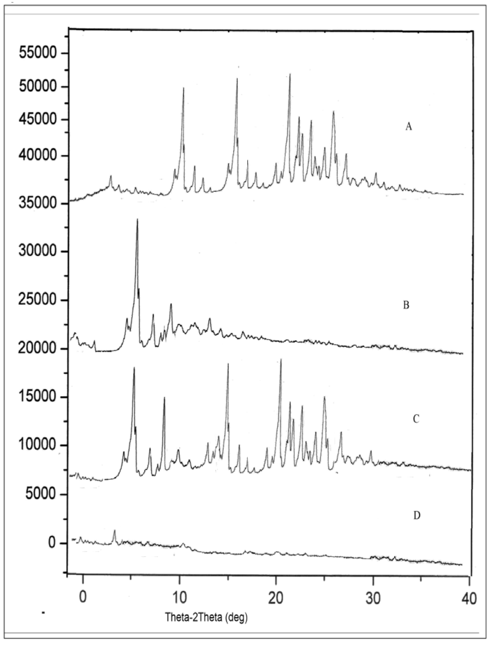

Fig. 4. XRD spectra of A) pure drug, B) HP-β–CD, C) physical mixture of drug and HP-β–CD and D) inclusion complex of HP-β-CD.

Conclusions

The solubility of poorly water soluble drug isradipine was improved by complexation formation with β-cyclodextrin and hydroxypropyl-β-cyclodextrin by solid dispersion approach. Solid dispersions were prepared by freeze drying method. Solubility of ID in β-cyclodextrin and hydroxypropyl-β-cyclodextrin was studied at increasing concentrations indicating A_L type phase solubility diagram. The dissolution parameters indicated increased dissolution of ID in solid dispersions. The characterization using DSC and XRD studies revealed transformation of crystalline drug to amorphous formandindicated there is no evidence of interaction between the drug and carriers studied. Thus the enhancement of solubility of I and dissolution rate of ID was achieved.

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