

Dissolution Enhancement and Physicochemical Characterization of Valsartan in Solid Dispersions with β -CD, HP β -CD, and PVP K-30

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ABSTRACT

Solid dispersions (SDs) and physical mixtures (PMs) of valsartan in β -cyclodextrin (β -CD), hydroxypropyl β -cyclodextrin (HP β -CD), and polyvinyl pyrrolidone (PVP K-30) were prepared to increase its solubility characteristics. The drug formulations were characterized in the solid state by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). By these physical determinations, drug-polymer interactions were found. Both the solubility and the dissolution rate of the drug in these formulations were increased. Drug contents were determined by UV spectrophotometry at a λ_{max} of 249.5 nm. The phase solubility behavior of valsartan in various concentrations of β -CD, HP β -CD, and PVP K-30 (0.25–1.0% w/v) in distilled water was obtained at 37 ± 2 °C. The dissolution of valsartan is increased with increasing amounts of the hydrophilic carriers (i.e., β -CD, HP β -CD, and PVP K-30). Gibbs free energy ($\Delta G_{\text{tr}}^{\circ}$) values were all negative, indicating the spontaneous nature of valsartan solubilization. The SDs of valsartan with β -CD and HP β -CD were prepared at 1:1, 1:3, and 1:5 drug/carrier ratios by a kneading method, and PVP K-30 SDs were prepared at the same ratios (i.e., 1:1, 1:3 and 1:5 drug/carrier) by a lyophilization technique. The FTIR spectroscopic studies show the stability of valsartan and the absence of well-defined drug-polymer interaction. Compared with β -CD, HP β -CD showed better enhancement of dissolution rate; compared with HP β -CD, PVP K-30 showed better solubility and dissolution enhancement.

INTRODUCTION

From an economic point of view, low oral bioavailability results in the wasting of a large portion of an oral dose and adds to the cost of drug therapy, especially for expensive drugs (1). No matter how active or potentially active a new molecular entity (NME) is against a particular molecular target, if the NME is not available in solution at the site of action, it is not a viable candidate. As a result, the development of many exciting NMEs is stopped before their potentials are realized or confirmed because pharmaceutical companies cannot afford to conduct rigorous preclinical or clinical studies on molecules that do not have sufficient pharmacokinetic profiles due to poor water solubility (2). The rate of oral absorption of poorly soluble or BCS Class II drugs is often controlled by the dissolution rate in the gastrointestinal tract. Thus solubility and dissolution rate are the key determinants of oral bioavailability, which is the concluding point drawn for fate of oral bioavailability (3).

Solubility is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature, and in a qualitative way, it can be defined as

the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion (4). McBain (5) has stated, "Any material can be solubilized in any solvent by proper choice of solubilizing agent." Final selection of solubilizing agent should be based on phase solubility studies.

Among the various approaches to improve solubility, the solid dispersion technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble active pharmaceutical ingredients because it is simple, economic, and advantageous (6). The solid dispersion technique provides a means of reducing particle size to a nearly molecular level. As the soluble carrier dissolves, the insoluble drug is exposed to the dissolution medium as very fine particles for quick dissolution and absorption. In particular, polymers such as polyethylene glycols and polyvinylpyrrolidone have been used extensively as carriers for dispersions because of their low melting points and their hydrophilic environments (7).

Cyclodextrins (CDs), with lipophilic inner cavities and hydrophilic outer surfaces, are capable of interacting with a large variety of guest molecules to form noncovalent inclusion complexes (8). CDs can have both stabilizing and destabilizing effects on chemically labile compounds, they

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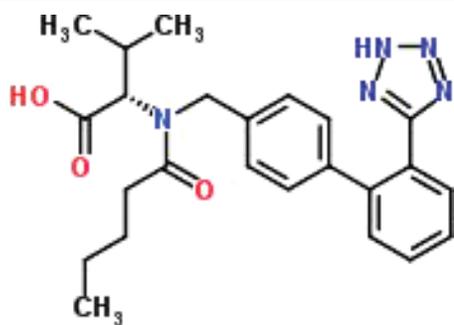


Figure 1. Structure of valsartan.

can be used as enzyme models, and they can solubilize lipophilic water-insoluble compounds (9). The presence of water-soluble drug–cyclodextrin complexes at the hydrated epithelial surface will frequently increase the availability of dissolved drug molecules, especially lipophilic drugs with poor aqueous solubility.

Polyvinylpyrrolidone (PVP) has been used for the preparation of solid dispersions as a component of binary systems for various drugs such as sulindac, fenofibrate, tenoxicam, tacrolimus, and flurinazine (10).

Valsartan, N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl] methyl]-L-valine (Figure 1), is used in the treatment of hypertension. It is an angiotensin II receptor blocker (ARB). Valsartan is one of the recently introduced, poorly water-soluble ARBs and is administered orally. In this study, the solid dispersions of valsartan were prepared with β -CD and HP β -CD using a kneading technique and with PVP K-30 using a lyophilization technique. The SDs were characterized by dissolution, Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC).

MATERIALS AND METHODS

Materials

Valsartan, β -CD, HP β -CD, and PVP K-30 were received from Alembic Ltd. (Baroda, Gujarat, India) as gift samples. Distilled water was used for all dissolution experiments and all other chemicals and reagents were of analytical grade.

Methods

Analytical Method

The absorbance maximum (λ_{max}) was determined to be 249.5 nm by UV spectrophotometry. A linear regression line was drawn by plotting absorbance against concentration (from 5 to 40 ppm); the correlation coefficient was 0.9994.

Solubility Measurements and Phase Solubility Study

Solubility measurements were performed according to the method of Higuchi and Connors (11). Various aqueous solutions (0.25%, 0.5%, 0.75%, and 1% w/v) of β -CD, HP β -CD, and PVP K-30 were prepared, and 20 mL of

each solution was taken into separate glass vials. An excess amount of drug was added to these vials. The vials containing drug–hydrophilic polymer carrier mixtures were shaken at 37 ± 0.1 °C for 48 h in a water bath shaker (Remi Pvt Ltd, Mumbai). After 48 h, samples were filtered through 0.45- μ m filter paper. The filtrate was suitably diluted with corresponding polymer carrier solution (0.25%, 0.5%, 0.75%, or 1% w/v) and analyzed spectrophotometrically at 249.5 nm using a UV spectrophotometer (Shimadzu 1601PC, Japan). Solubility studies were performed in triplicate ($n = 3$) (12).

The saturation solubility of drug in pure water without hydrophilic carrier was also determined. An indication of the process of transfer of valsartan from pure water to the aqueous solutions of β -CD, HP β -CD, and PVP K-30 was obtained from the values of Gibbs free energy change. The Gibbs free energy of transfer (ΔG_{tr}°) of valsartan from pure water to the aqueous solution of carriers was calculated using the following equation:

$$\Delta G_{tr}^\circ = -2.303 RT \log S_0/S_s$$

where S_0/S_s is the ratio of molar solubility of drug in aqueous solution of carrier to that in pure water (13, 14).

Preparation of Solid Dispersions by Kneading Technique

Inclusion complexes of valsartan with β -CD and HP β -CD in the weight ratios of 1:1, 1:3, and 1:5 were prepared by a kneading technique. Solid dispersions were prepared by mixing drug with β -CD or HP β -CD and then kneading the same with a mixture of ethanol–water (1:9) to obtain a mass with a pasty consistency. This was then dried in a tray dryer at 45–50 °C. All the dispersions were prepared in triplicate, sieved through British Standard Sieve (BSS) 60# (180- μ m diameter), and stored over anhydrous calcium chloride in a desiccator.

The physical mixtures (PM) were prepared by geometric mixing of drug and β -CD or HP β -CD in a mortar and pestle with simple trituration for 15–20 min and then passing the mixture through a 60# sieve (15).

Preparation of Lyophilized Formulations

Drug formulations were processed using ultra-rapid freezing technology. Hydrophilic excipient PVP K-30 was dissolved in methanol. Valsartan, which is poorly water soluble, was added to this separately and dissolved. The resulting ternary system of organic solvent, hydrophilic carrier, and drug was freeze-dried by filling glass vials with the solutions and positioning the vials in a lyophilizer. During operation, the freeze-drier was maintained at -45 °C and a compressional pressure of 0.5 Torr. After complete drying, the vials were taken out, and the dried products were scraped from the vials. The formulations were powdered and packaged in glass vials (16).

In Vitro Dissolution Studies

Dissolution studies of valsartan in powder form, SDs, and PMs were performed using a digital USP dissolution

Apparatus 2 (Lab India, Mumbai) at a paddle rotation speed of 50 rpm in pH 6.8 phosphate buffer as dissolution medium at 37 ± 0.5 °C. SDs or PMs equivalent to 80 mg of valsartan were weighed using a digital balance (Sartorius, Germany) and added to the dissolution medium. At specified times (every 15 min for 1 h), 10-mL samples were withdrawn using a 0.45- μ m syringe filter (Sepyrane, Mumbai) and then assayed for the valsartan content by measuring the absorbance at 249.5 nm using a UV-vis spectrophotometer (Shimadzu UV-1700, Pharm Spec). Fresh medium (10 mL) that was maintained at 37 °C was added to the dissolution medium after each sampling to maintain a constant volume throughout the test. Dissolution studies were performed in triplicate ($n = 3$), and calculated mean values of cumulative drug release were used to plot the release curves (13).

Fourier Transform Infrared Spectroscopy

Infrared spectra were obtained using an FTIR spectrometer (Model 430, Shimadzu, Japan). The samples (valsartan or SDs) were ground and mixed thoroughly with potassium bromide, an infrared-transparent matrix, at 1:100 (sample/KBr). The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained from 4000 to 400 cm^{-1} at a resolution of 2 cm^{-1} .

Differential Scanning Calorimetry

The DSC measurements were performed on a DSC-6100 (Seiko Instruments, Japan) differential scanning calorimeter with a thermal analyzer. All accurately weighed samples (about 1 mg of valsartan or its equivalent) were placed in sealed aluminum pans before heating under nitrogen flow (20 mL/min) at a scanning rate of 10 °C min^{-1} from 50 to 300 °C. An empty aluminum pan was used as reference.

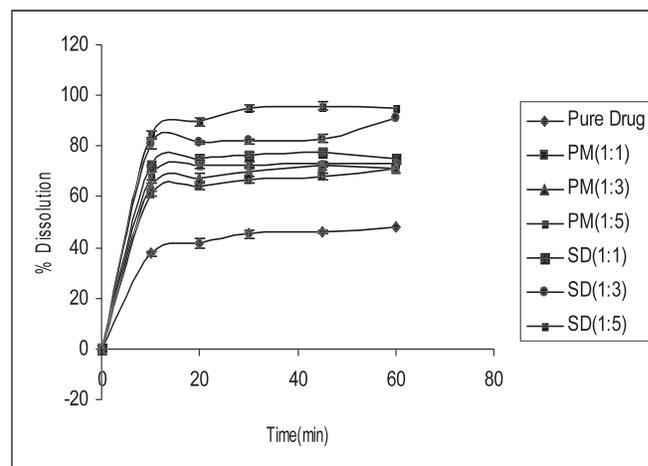


Figure 2. In vitro dissolution profiles of pure valsartan, valsartan SDs, and PMs with PVP K-30.

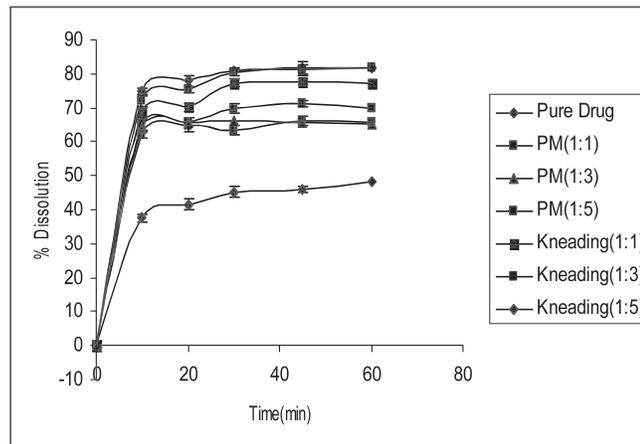


Figure 3. In vitro dissolution profiles of pure valsartan, valsartan SDs, and PMs with β -CD.

RESULTS

Solubility Studies

Phase solubility diagrams showed a linear increase in drug solubility with an increase in the concentration of each examined carrier. At 1% w/v concentration of β -CD, HP β -CD, and PVP K-30, the solubility of valsartan increased significantly. Analogous results were found for these same carriers, probably due to the formation of weakly soluble complexes. Hydrophilic carriers mainly interact with drug molecules by electrostatic bonds (ion-to-ion, ion-to-dipole, and dipole-to-dipole bonds), even though other types of forces, such as van der Waals forces and hydrogen bonds, can frequently play a role in the drug-carrier interaction (17). The drug solubility increased linearly with increasing polymer concentration, indicative of the A_L type of phase solubility diagram (10). The values of Gibbs free energy (ΔG_{tr}°) associated with the aqueous solubility of valsartan in presence of carrier were all negative for carriers at various concentrations, indicating

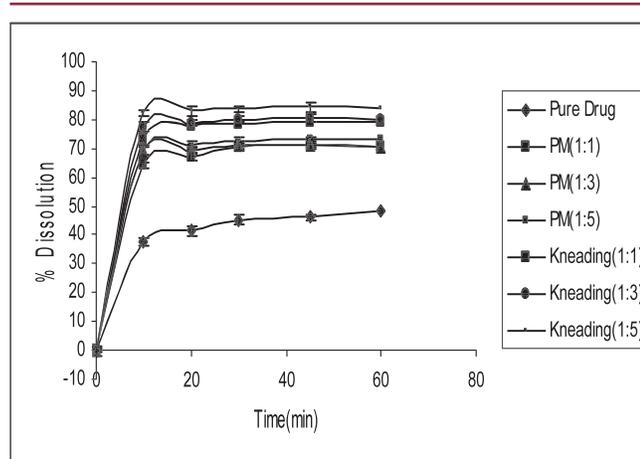


Figure 4. In vitro dissolution profiles of pure valsartan, valsartan SDs, and PMs with HP β -CD.

Table 1. Percent Drug Dissolved within 60 min for Pure Valsartan and Valsartan with β -CD, HP β -CD, and PVP K-30 Binary Systems

Sample	Drug/Polymer Ratio	Valsartan Dissolved (%)				
		Q ₁₀	Q ₂₀	Q ₃₀	Q ₄₅	Q ₆₀
Valsartan	-	37.57 ± 0.74	41.54 ± 1.12	45.21 ± 1.74	46.15 ± 1.51	48.26 ± 0.91
Valsartan: β -CD (PMs)	1:1	62.12 ± 0.93	64.60 ± 0.95	63.34 ± 0.99	66.09 ± 1.44	65.90 ± 1.27
	1:3	63.86 ± 1.68	65.81 ± 1.57	66.34 ± 1.58	65.85 ± 1.20	65.43 ± 0.91
	1:5	64.85 ± 1.54	65.84 ± 1.38	69.81 ± 1.28	71.02 ± 1.88	69.86 ± 0.59
Valsartan: β -CD (Kneading)	1:1	68.32 ± 0.89	70.06 ± 0.38	77.25 ± 0.66	77.75 ± 1.05	77.25 ± 0.89
	1:3	72.04 ± 1.62	75.32 ± 1.77	80.47 ± 0.39	81.22 ± 1.23	81.72 ± 1.59
	1:5	74.77 ± 0.17	78.00 ± 1.06	80.72 ± 1.29	81.72 ± 1.19	81.90 ± 1.69
Valsartan: HP β -CD (PMs)	1:1	64.19 ± 0.56	67.33 ± 0.93	70.56 ± 0.99	71.25 ± 0.99	70.28 ± 1.49
	1:3	68.90 ± 1.69	69.12 ± 1.16	71.05 ± 1.89	71.30 ± 1.57	70.36 ± 1.65
	1:5	69.30 ± 0.64	71.29 ± 1.05	72.52 ± 0.89	73.02 ± 1.18	72.95 ± 1.29
Valsartan: HP β -CD (Kneading)	1:1	73.28 ± 1.63	77.75 ± 0.95	78.24 ± 1.89	79.5 ± 1.76	79.04 ± 1.06
	1:3	77.50 ± 0.98	78.74 ± 1.5	79.98 ± 0.98	80.48 ± 1.44	79.73 ± 1.79
	1:5	82.46 ± 1.74	82.96 ± 1.23	83.70 ± 1.23	84.44 ± 1.88	83.95 ± 0.59
Valsartan: PVP K-30 (PMs)	1:1	61.19 ± 0.56	64.33 ± 0.93	66.56 ± 0.99	68.25 ± 0.99	71.28 ± 1.49
	1:3	63.90 ± 1.69	67.12 ± 1.16	70.05 ± 1.89	72.30 ± 1.57	71.36 ± 1.65
	1:5	68.30 ± 0.64	72.29 ± 1.05	72.52 ± 0.89	73.02 ± 1.18	73.15 ± 1.29
Valsartan: PVP K-30 (SDs)	1:1	72.39 ± 1.74	75.35 ± 0.94	76.59 ± 0.64	77.58 ± 1.22	75.28 ± 1.88
	1:3	80.72 ± 1.04	81.47 ± 1.33	81.96 ± 1.91	82.91 ± 1.09	90.89 ± 1.01
	1:5	84.69 ± 1.24	89.65 ± 1.69	94.85 ± 1.32	95.81 ± 0.77	95.04 ± 1.21

PM: Physical Mixture.
SD: Solid Dispersion.

the spontaneous nature of drug solubilization. The values decreased with increasing carrier concentration, demonstrating that the reaction became more favorable as the concentration of carrier increased (13).

In Vitro Dissolution Studies

All formulations of valsartan were subjected to in vitro dissolution studies using phosphate buffer at pH 6.8 as the dissolution medium to assess various dissolution properties. All SD formulations with various polymers exhibited higher rates of dissolution than valsartan pure drug and corresponding physical mixtures.

The pure drug showed up to 50% dissolution over 60 min, but its solid dispersions prepared by lyophilization with PVP K-30 (1:3 and 1:5 w/w) showed dissolution of greater than 84% over 10 min (Figure 2).

Solid dispersions of β -CD and HP β -CD prepared by kneading and physical mixture showed nearly similar dissolution profiles (Figures 3 and 4). Compared with β -CD, HP β -CD solid dispersions showed better results of about 82% within 10 min of dissolution study, but only about

70% for β -CD. The dissolution enhancing effect of various carriers used in this study followed the order: PVP K-30 > HP β -CD > β -CD.

The dissolution rate of valsartan from physical mixtures (1:5) with all three carriers was up to 75% higher than that of pure valsartan (59%) within 45 min. In this case (physical mixture), the increased dissolution rate observed can be attributed to several factors such as a solubilization effect of these carriers, improved wettability of the drug, and inhibition of particle aggregation. The results of dissolution studies for the different formulations in terms of percent dissolved at 15 min (Q_{15}), 30 min (Q_{30}), and 45 min (Q_{45}) are shown in (Table 1).

Fourier Transform Infrared Spectroscopy

The interaction between the drug and carrier often leads to identifiable changes in the IR profile of SDs. The IR spectra of SDs were compared with the standard spectrum of valsartan. In the IR spectrum of valsartan (Figure 5), a broad band at 3300 cm^{-1} indicates the presence of an N-H functional group. The band at 2962 cm^{-1}

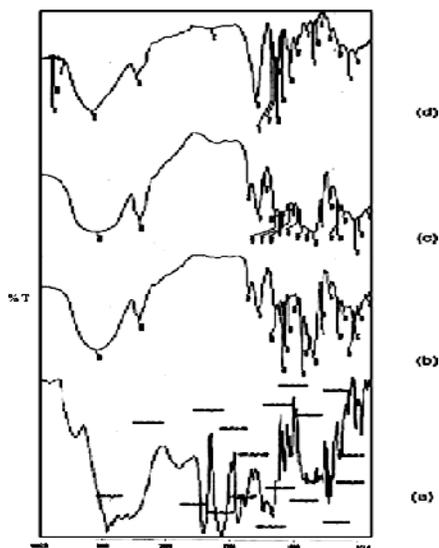


Figure 5. Infrared spectra of (a) valsartan, (b) valsartan SDs with β -CD, (c) valsartan SDs with HP β -CD, and (d) valsartan SDs with PVP K-30.

indicates a C–H group stretching vibration. Bands in the range of 1206–1035 cm^{-1} confirm the presence of a tetrazole ($-\text{CN}_4$) ring. The presence of a band at 1502 cm^{-1} indicates an N=N bond. The peak at 1337 cm^{-1} is due to

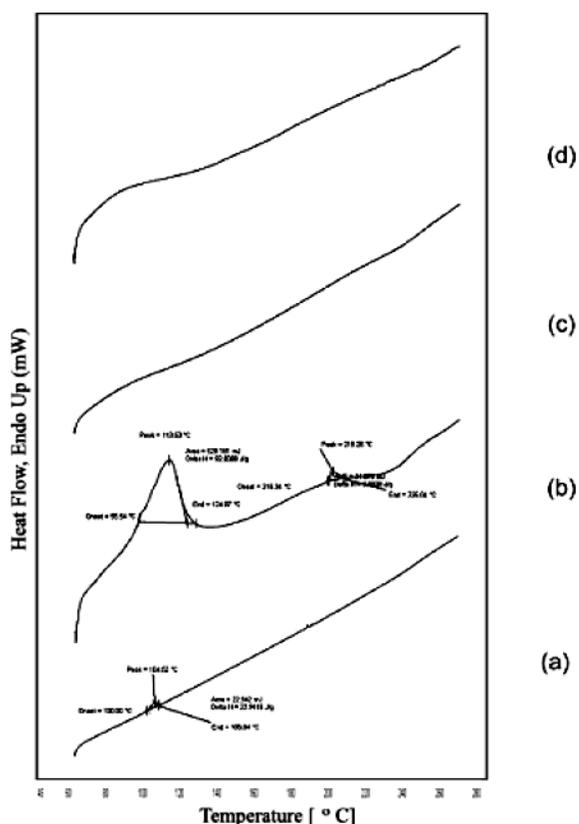


Figure 6. DSC thermogram of (a) valsartan, (b) valsartan SDs with β -CD, (c) valsartan SDs with HP β -CD, and (d) valsartan SDs with PVP.

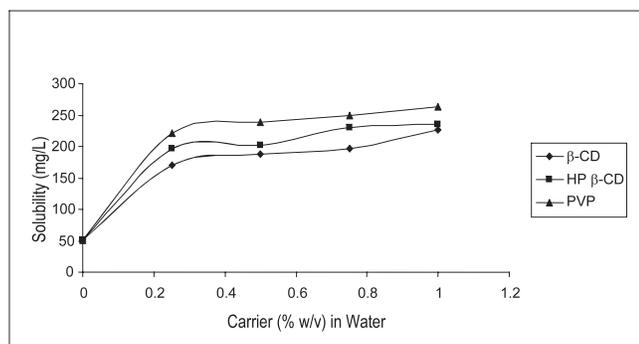


Figure 7. Phase solubility plot of valsartan with β -CD, HP β -CD, and PVP K-30.

C=N. The peak at 1731 cm^{-1} confirms the presence of a carboxylate functional group. The characteristic peak at 1682 cm^{-1} is for stretching of a C=O functional group present in the drug structure. The peak at 1050 cm^{-1} indicates the presence of a C–N bond. The complex region of 900–600 cm^{-1} indicates skeletal vibration and an aromatic ring in the drug substance. The IR spectrum for drug– β -CD SDs reveals a broad peak at 3383 cm^{-1} due to N–H bond stretching. A peak at 2925 cm^{-1} indicates C–H vibrational stretching. A peak in the region of 1202–1028 cm^{-1} indicates the tetrazole (CN_4) ring. A significant broad peak at 3383 cm^{-1} in the IR spectrum of drug–HP β -CD SDs is due to O–H functional group of HP– β -CD, which overlaps the N–H peak (at 3300 cm^{-1}) present in the pure drug. The characteristic peak for a tetrazole (CN_4) ring is located in the same range for the SDs as for the pure drug. Solid dispersions with PVP K-30 showed a broad peak in the range of 3850–3300 cm^{-1} , which indicates N–H bond stretching. The spectrum reveals the characteristic peaks in the typical range (CN_4 at 1219–1034 cm^{-1} , C–H stretching at 2959 cm^{-1} , and an aromatic ring at 900–600 cm^{-1}) inferring no significant interaction between drug and carrier in the solid dispersions.

Differential Scanning Calorimetry

Differential scanning calorimetry enables the quantitative detection of all processes in which energy is required

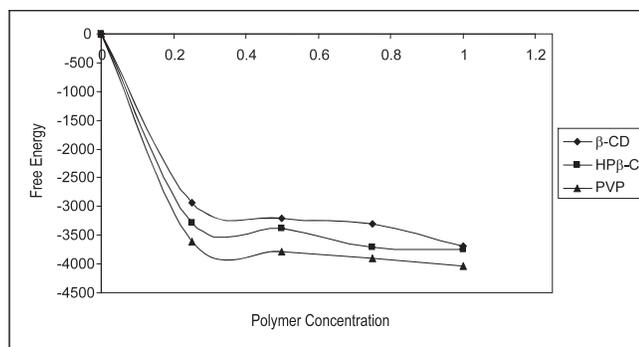


Figure 8. Free energy change with aqueous solution of polymer in different concentrations.

or produced (i.e., endothermic and exothermic phase transformations). The DSC thermograms for pure drug and SDs are shown in Figure 6. The DSC thermogram of valsartan shows a less intense endothermic peak at 104.52 °C corresponding to its melting point. The onset of melting was observed at 100.9 °C. The DSC thermogram of valsartan with β -CD showed a broad peak at 113.53 °C for the drug and another peak at 219.26 °C for β -CD, indicating drug amorphization. With HP β -CD and PVP K-30, peaks for drug or polymer are absent, indicating that the drug is homogeneously distributed in the polymer backbone and is amorphous in the formulations.

DISCUSSION

The phase solubility study with water and various hydrophilic carriers shows an increase in the solubility of the drug in the presence of the carriers (Figure 7). The values of Gibbs free energy (ΔG_{tr}°) associated with the aqueous solubility of valsartan in the presence of carrier were all negative for carriers at various concentrations indicating the spontaneous nature of drug solubilization. The values decreased with increasing carrier concentration (Figure 8), demonstrating that the reaction became more favorable as the concentration of carrier increased. All SD formulations with various polymers exhibited higher rate of dissolution values than valsartan pure drug and corresponding physical mixtures. The pure drug showed up to 50% dissolution over 60 min, but its solid dispersions prepared by lyophilization with PVP K-30 (1:3 and 1:5 w/w) showed dissolution of more than 80% over 10 min. The dissolution enhancing effect of various carriers used in this study followed the order: PVP K-30 > HP β -CD > β -CD. This enhancement of valsartan dissolution from drug carrier systems can be ascribed to several factors. Lack of crystallinity (i.e., amorphization), increased wettability and dispersibility, and particle size reduction are considered important factors for dissolution rate enhancement (18). FTIR spectroscopy shows that individual peak characteristics are retained in the spectra of drug and hydrophilic carriers, indicating there is no interaction between the drug and the carriers. The DSC study with HP β -CD and PVP K-30 shows no peaks for drug or polymer, indicating that the drug is homogeneously distributed in the polymer backbone and is of an amorphous nature in the formulations. The DSC study reveals no significant interaction between valsartan and the hydrophilic carriers used; there is change in the crystallinity of pure valsartan to amorphous state in the solid dispersions.

CONCLUSIONS

The solubility and dissolution rate of valsartan can be enhanced by the use of valsartan SDs with β -CD, HP β -CD, and PVP K-30. Compared with β -CD, HP β -CD showed better enhancement of dissolution. The lyophilized formulation of valsartan with PVP K-30 showed better dissolution enhancement than that with HP β -CD. From FTIR spectroscopy it was concluded that there were no

well-defined chemical interactions between valsartan and β -CD, HP β -CD, or PVP K-30 in the SDs because no important new peaks could be observed. The DSC study reveals no significant interaction between valsartan and the hydrophilic carriers used; however, there is a change in crystallinity of pure valsartan to amorphous state in the solid dispersions. The experience with solid dispersions indicates that this is a very fruitful approach to improve the dissolution rate and oral bioavailability of poorly soluble drugs.

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