Drug Development and Industrial Pharmacy, 2011, 37(4): 373–386
© 2011 Informa Healthcare USA, Inc.
ISSN 0363-9045 print/ISSN 1520-5762 online
DOI:10.3109/03639045.2010.513984

informa
healthcare

ORIGINAL ARTICLE

Solid dispersion of prednisolone: solid state characterization and improvement of dissolution profile

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Abstract

Background: Dissolution testing is an important test for judging the effectiveness of a pharmaceutical dosage form. Many drugs create adverse effect because of insufficient solubility at the physiological pH. This study is aimed to improve the dissolution properties of prednisolone (PRD) that falls under the category of class II biopharmaceutics system. *Methods*: In this study, preparation of solid dispersions with various water-soluble carriers was studied to improve the dissolution of PRD. To obtain the optimized formulation, solid dispersions were prepared employing different methods using different carriers with various drug:carrier ratios. Their dissolution behaviors were also compared. Fourier transform infrared (FTIR) spectroscopy, powder X-ray diffraction, and thermal analysis were studied to characterize the prepared solid dispersion. *Results*: PRD formed stable complexes with carriers as indicated by the stability constants (K_a) of 9.5–597.2 M^{-1}. The results indicated that in vitro dissolution rate of PRD was remarkably improved in the solid dispersion of the drug compared with physical mixture and drug alone. This can be attributed to improved wettability, dispersibility, decrease in crystallinity, and increase in amorphous fraction of the drug. The results obtained from Fourier transform infrared spectroscopy and powrer X-ray diffraction showed good evidence of drug–carrier interaction while using carriers such as hydroxypropyl-β-cyclodextrin (HP-βCD) and polyethylene glycol (PEG). Crystallinity of the drug was reduced in the solid dispersions prepared with hydroxypropyl-β-cyclodextrin, polyvinylpyrrolidone-co-vinyl acetate 64, and PEG as revealed from the differential scanning calorimetry thermograms. *Conclusion*: The results suggested that the solid dispersion with selected excipients is a powerful tool to accelerate the dissolution of poorly water-soluble drugs.

Key words: Dissolution enhancement, prednisolone, solid dispersion, solubility, wettability

Introduction

Research on combinatorial chemistry and high-throughput screening of potential therapeutic agents generated quite a large number of drugs with poor water solubility. The impact of biopharmaceutical properties, including solubility, has become an industry-wide concern in the design of proper dosage form[1,2]. Therefore, the improvement of dissolution and solubility of poorly soluble drugs is a major field of interest for formulation scientists. The various physical and chemical approaches adopted to improve the solubility include increase in the surface area, solubility and wettability of the powder particles by micronization[3], nanosizing[4], generation of amorphous states[5], and soluble prodrugs[6] and salts[7]. The solid dispersion technique has been used widely to enhance the solubility and dissolution characteristics of drugs with low aqueous solubility[8,9]. A solid dispersion is 'the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting, solvent evaporation, or melting-solvent methods'[10]. The mixture of drug and carrier is converted from semisolid/liquid to solid state. The solid is pulverized in most cases and then sieved. Various carriers were investigated such as polymers, sugars, polyols, urea, organic acids, and emulsifiers. There had been a great deal of interest in using solid dispersion technique to improve the dissolution rate and the bioavailability of poorly water-soluble drugs[11–13]. Prednisolone (PRD) was chosen in this study as a typical example of a very slightly soluble drug (0.22–0.24 mg/mL at 25°C)[14]. It is a synthetic steroid that is chemically defined as 11,17,21-trihydroxypregna-1,4-diene-3,20-dione. Bioavailability of its conventional oral

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(Received 29 Jan 2010; accepted 3 Aug 2010)

dosage form is limited and it causes gastric irritation[15,16]. It does not ionize over wide range of pH. Hence, it is a neutral substance and no reference to a pK_a value was found[14]. Its high lipophilicity (log P = 1.68) will not hinder permeation if it is in more soluble state. Several attempts have been proposed to overcome its disadvantages[16,17]. Various water-soluble inert materials have shown to improve the dissolution rate and bioavailability of many drugs[18–20].

In this article, we explore the influence of several hydrophilic carriers on the dissolution behavior and hence absorption of PRD by applying the solid dispersion approach. The chosen hydrophilic carriers are β-cyclodextrin (βCD), hydroxypropyl-β-cyclodextrin (HP-βCD), polyvinylpyrrolidone-co-vinyl acetate 64 (PVP-VA64), skimmed milk powder (SMP), PEG 4000, mannitol (MNT), Cremophor EL (EL), and Cremophor RH 40 (RH 40).

This investigation was aimed at (i) use of various carriers in the preparation of solid dispersion of PRD, (ii) study of thermodynamic parameters, and (iii) characterization of solid dispersion using dissolution and instrumental analysis such as Fourier transform infrared (FTIR) spectroscopy, powder X-ray diffraction (XRD), thermogravimetric (TG) analysis, and differential scanning calorimetry (DSC).

Materials and methods

Materials

PRD was kindly donated by Medopharm (Karnataka, India). Following chemicals were purchased: PEG 4000 (Merck Specialties Private Ltd., Mumbai, India), lactose (BD Pharmaceutical Works, Howrah, India), MNT (SD Fine Chem. Pvt. Ltd., Boisar, India), and SMP (Aavin, Tamil Nadu Cooperative Milk Product Producers, Erode, India). Chemicals received as gift samples were βCD and HP-βCD (Roquette, Lestrem, France), PVP-VA64, Cremophor EL, and Cremophor RH 40 (Albert David, Kolkata, India). All other chemicals and reagents were of analytical grade.

Phase solubility studies

The solubility study was performed in aqueous solution of selected carriers such as βCD, HP-βCD, PVP-VA64, PEG 4000, SMP, MNT, EL, and RH 40 at 25°C and 37°C. The experiments were carried out by adding an excess amount of drug to 100 mL aqueous solutions containing different concentrations of carriers (1%, 2%, 3%, 4%, 5%, 10%, 12%, and 15%). The volumetric flasks were placed in a water bath at a constant temperature and shaken at 30-minute intervals until equilibrium was attained (~12 hours). Then, these solutions were filtered through a 110-mm Whatman filter paper (pore size: 11 μm), diluted suitably, and absorbance was measured at 247 nm with UV-spectrophotometer. Each data point for the concentration of the solubilized drug was calculated as the average of three experimental trials. The apparent complexation constant ($K_{1:1}$) of the complex was calculated using Equation (1) from phase solubility slope, where the intercept is the intrinsic solubility of drug in the absence of carrier at 25°C and 37 ± 0.5°C;

$$K_{1:1} = \frac{\text{Slope}}{\text{Intercept}\,(1 - \text{Slope})} \tag{1}$$

Also, the change in enthalpy (ΔH) on complexation was determined using van't Hoff equation, (Equation 2)

$$\ln\left(\frac{K_2}{K_1}\right) = \Delta H \frac{T_2 - T_1}{RT_2T_1} \tag{2}$$

where K_2 and K_1 are the stability constants at 37°C and 25°C, respectively. T_2 and T_1 are the corresponding temperatures in Kelvin.

The change in Gibbs free energy (ΔG) and entropy (ΔS) upon complexation was also determined using Equations (3) and (4), respectively.

$$\Delta G = -RT \ln K \tag{3}$$

where R is the gas constant (R = 8.314 J/mol K)

$$\Delta S = \frac{(\Delta H - \Delta G)}{\Delta T} \tag{4}$$

Preparation of physical mixtures

Physical mixtures (PM) were prepared by mixing the drug and the carrier substances at various ratios (1:3 to 1:7) using a mortar and pestle according to the rules of geometrical blending, followed by screening with a sieve (mesh no. 120).[21] In each preparation, 100 mg of drug was used.

Preparation of solid dispersions

Solid dispersions (SD) were prepared at various ratios (1:3 to 1:7) of the drug and the carrier. In each preparation 100 mg of drug was used.

Solvent evaporation technique with βCD, HP-βCD, and PVP-VA64

First, PRD was dissolved in methanol to produce a clear solution. Then, the carrier was dispersed in this solution by stirring at 38 ± 0.5°C using a magnetic stirrer (REMI-2MLH, Remco, Kolkata, India)[22]. Next, the clear solution was poured into the petri dish and the solvent was removed by evaporation at 50 ± 0.5°C using a hot plate. The resultant mass was dried at 40°C for 24 hours, pulverized, and passed through a sieve (mesh no. 120).

Melting method with PEG 4000 and MNT

Melting method was adopted to prepare solid dispersion using PEG 4000 (m.p. 58°C)[23] and MNT (m.p. 166–168°C)[24]. The required quantity of the respective carrier was weighed into a china dish and heated first to 80°C on a water/oil bath, and stirred until the carrier melts. Then the drug was dispersed in the melted carrier and stirred continuously for 15 minutes using a magnetic stirrer (REMI-2MLH). The resultant melt was poured onto an aluminum foil spread on a petri dish to obtain a thin layer and then allowed to cool at room temperature (28°C). Approximately 1 hour later, the solidified dispersions were milled using a pestle and mortar. The prepared samples were stored at 25°C in desiccators.

Kneading technique with SMP, EL, and RH 40

The calculated amounts of PRD and the corresponding carriers were weighed and moistened with a small volume (1 mL) of ethanol/water solution (50:50, v/v)[22]. The mixtures were ground thoroughly in a pestle and mortar following addition of solvent drop wise until the mixture reached a granular appearance and then the slurry was kneaded thoroughly for about 45 minutes and dried at room temperature (28 ± 2°C) overnight. The dried mass was pulverized and sieved through a 120-mesh sieve. It was then stored in a desiccator at 25°C. Lactose was added as an inert carrier to the drug while using Cremophor EL or Cremophor RH 40 followed by the same method as mentioned above.

Assay procedure

Prepared solid dispersion (50 mg) of each composition was dissolved in 5 mL of methanol and diluted up to 50 mL with double-distilled water in a volumetric flask and then the necessary dilution was made. Maximum absorbance of the sample was noted at wavelength 247 nm and the content of the drug was determined using standard calibration curve at this wavelength. The material balance was calculated with respect to the drug content.

Dissolution rate studies

A USP dissolution apparatus II (TDT 06P, Electro Lab, New Mumbai, India) was used for all dissolution studies. The dissolution test was carried out at 37 ± 0.5°C in 900 mL dissolution media (double-distilled water) at 50 rpm[25]. At every 5-minute time interval up to 30 minutes, 5 mL of samples were withdrawn periodically and filtered using Whatman filter paper (pore size: 11 μm) and the dissolved amount of drug was determined at 247 nm spectrophotometrically. A correction was accounted for the cumulative dilution caused by replacement of the sample with an equal volume of original medium to maintain the sink condition. Each test was repeated at least three times.

Mathematical comparison of dissolution profiles

Two mathematical methods for the comparison of dissolution profiles from the solid dosage forms were described by Moore and Flanner[26] as the difference factor (f_1, Equation 5) and similarity factor (f_2, Equation 6)

$$f_1 = \frac{\sum_{t=1}^{n} (R_t - T_t)}{\sum_{t=1}^{n} (R_t)} \times 100 \tag{5}$$

where R_t is the reference assay at time point t, T_t is the test assay at time point t, n is the number of samples. The difference factor (f_1) calculates the percent difference between two curves at each time point and is a measurement of the relative error between the two curves. If difference factor (f_1) between two curves is zero indicating the identical dissolution profile. The similarity factor (f_2) is a logarithmic transformation of the sum of the squared error. It is a measurement of the similarity in the percent dissolution between the test and the reference profiles by taking the average sum of squares and fit the result between 0 and 100.

$$f_2 = 50 \log \left[\left\{ 1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right\}^{-0.5} \times 100 \right] \tag{6}$$

f_2 value ranges from 50 to 100 ensure similarity of the two curves.

Fourier transform infrared spectrophotometric analysis

FTIR spectroscopic analysis was carried out on the solid dispersions to evaluate possible interactions between the drug and the polymers using FTIR-8300, Shimadzu Co., Kyoto, Japan, combined with Quick Snap sampling modules. Infrared spectra of the samples were recorded in the solid state using the KBr disc method over wave number range of 4000–400 cm^{-1}. Individual polymers, drug (PRD), and drug/polymer physical mixtures were run as controls.

Powder X-ray diffraction analysis

Phase analysis was done using powder X-ray diffraction using Rigaku Miniflex diffractometer (Rigaku Co., Ltd., Osaka, Japan) with a Kb filter, Cu radiation, a voltage of 30 kV, and a 15-mA current. The powder samples were packed in the X-ray holder from the top before analysis. These samples were continuously spun and scanned at a rate of 1°min^{-1} over a 2θ range of 5–70°, and the results processed by a preloaded computer program.

Thermogravimetric analysis

Thermogravimetric analysis was performed with a SDT Q600 V8.2 build 100 DST/TG analyzer using a dry nitrogen purge of 100 mL/min. Approximately 3 mg of PRD and/or solid dispersion sample was placed in a 100-μL platinum cup and the percentage weight loss of the samples was monitored from 30°C to 700°C with a heating rate of 10°C/min.

Differential scanning calorimetric analysis

The DSC measurements were performed on a differential scanning calorimeter (Pyris diamond TG/DTA; P, Perkins Elmer Instruments, Mumbai, India) with a thermal analyzer. Under nitrogen flow of 25 mL/min, approximately 3 mg of PRD, carriers, their physical mixtures, or solid dispersion with respective carriers were placed in a sealed aluminum pan and heated at a scanning rate of 10°C/min over the temperature range of 30–300°C.

Results and discussion

The phase solubility authorizes to study the binding constant between drug and carrier at various temperatures such as 25°C and 37 ± 0.5°C. Solubility profiles were obtained by plotting solubility of drug (%) against concentration of polymer (%) in aqueous solution. All the carriers produced A_L-type isotherm (graph not shown) whereby the solubility of drug increased with the increase in temperature and concentration of carrier, probably because of the changes in the interaction forces, such as van der Waals and hydrophobic forces between drug and carriers[27]. Intercept value was obtained by intersecting the extrapolated curve with y-axis (Table 1). This value theoretically represents solubility of a drug in a polymer-free aqueous solution. This theoretical value does not always comply with the actual solubility of pure drug in pure water. Actual aqueous solubility of PRD at 25°C and 37 ± 0.5°C are 0.674 and 1.2 mM, respectively[14]. Carrier along with drug molecules is bound to water molecules with hydrogen bonding. This binding varies with the nature of polymer. So, the intercept values reported in Table 1 were all different and it differs from the drug's aqueous solubility. Slope varied with the extent of binding of drug with each carrier. The slope of the phase solubility diagram (<1) indicated the 1:1 complex stoichiometry[28]. The stability constant $K_{1:1}$ of PRD in aqueous polymer solution ranges between 9.5 and 597.2 M^{-1}. Stability constants (M^{-1}) depend on slope and intercept, which in turn depends on molecular weight of drug and polymer and their binding capacity. The stability constants obtained from different drug:carrier complex ranked in the order of PEG > RH 40 > HP-βCD > βCD > EL > PVP > MNT > SMP. Among all the carriers HP-βCD, PEG, and RH 40 showed ideal complexation constant within the ranges of 100–1000 M^{-1} [28]. Except these carriers, rest of the carriers showed weak interaction with the drug. The various thermodynamic parameters are listed in Table 1. The calculated values of Gibbs free energy change (ΔG) were found negative that ensured spontaneity of binding between the drug and the carrier. ΔG (kJ/mol) decreased with increasing molecular weight of the carrier. The calculated values of ΔH were found negative (exothermic) in all drug–carrier complexes except in the solubility system with PEG 4000. The ΔS value in drug–PEG 4000 system was very high (15 J/mol K). So, the reaction type is expected to be endothermic. Thermodynamic values confirmed the drug–carrier polymer interaction that was driven by enthalpy change. Enhancement factor is a measure of enhancement of solubility of each drug–carrier (15%) system with respect to that of the pure drug. Enhancement factor was greatest in drug–HP-βCD system.

Comparison of different methods and mechanisms for preparation of solid dispersions

With the advent of solvent evaporation, thermolabile substances and polymers with high melting point (e.g., PVP) could be utilized efficiently in this method[8]. This method is very simple. However, ecological and economical factors because of use of solvent cannot be ignored. An important prerequisite for using this method is that both drug and carrier must dissolve

Table 1. Thermodynamic parameters of prednisolone with various carriers.

Carrier	T (°C)	Intercept (mM)	Slope (M)	K_a (M^{-1})	G (kJ/mol)	H (kJ/mol)	S (kJ/mol K)
PVP-VA64	25	1.30×10^{-3}	0.01974	15.4 ± 0.545	−6.78 ± 0.087	−2.27 ± 0.764	0.01512 ± 0.002
	37	2.07×10^{-3}	0.03005	14.9 ± 0.351	−6.96 ± 0.060		
MNT	25	1.55×10^{-3}	0.01561	10.2 ± 1.129	−5.76 ± 0.262	−4.32 ± 1.770	0.00483 ± 0.005
	37	2.09×10^{-3}	0.01966	9.5 ± 0.802	−5.81 ± 0.201		
SMP	25	1.27×10^{-3}	0.0156	12.4 ± 1.214	−6.25 ± 0.240	−4.04 ± 2.488	0.00742 ± 0.007
	37	1.99×10^{-3}	0.02289	11.7 ± 0.717	−6.34 ± 0.156		
EL	25	1.59×10^{-3}	0.09311	64.2 ± 4.927.	−10.31 ± 0.191	−3.61 ± 1.888	0.0224 ± 0.005
	37	2.35×10^{-3}	0.12486	60.7 ± 2.988	−10.58 ± 0.125		
RH 40	25	1.21×10^{-3}	0.1275	120 ± 12.718	−11.86 ± 0.256	−6.23 ± 4.564	0.01888 ± 0.014
	37	2×10^{-3}	0.1788	108.8 ± 3.569	−12.08 ± 0.083		
βCD	25	1.77×10^{-3}	0.1291	83.7 ± 2.145	−10.97 ± 0.062	−5.26 ± 1.076	0.01913 ± 0.003
	37	2.92×10^{-3}	0.1838	77.1 ± 1.592	−11.19 ± 0.052		
HP-βCD	25	2.08×10^{-3}	0.187982	111.2 ± 3.997	−11.674 ± 0.089	−5.11 ± 1.307	0.0220 ± 0.004
	37	3.34×10^{-3}	0.255747	102.7 ± 2.024	−11.93 ± 0.050		
PEG	25	1.69×10^{-3}	0.38174	363.6 ± 13.131	−14.6 ± 0.088	31.73 ± 2.623	0.1555 ± 0.008
	37	2.93×10^{-3}	0.63698	597.2 ± 4.992	−16.47 ± 0.021		

adequately in an inert and nontoxic solvent and the solvent removal should be possible using any suitable method. βCD and HP-βCD have been widely used to form inclusion complex for the solubilization and stabilization of poorly soluble drugs[29]. A variety of noncovalent forces such as van der Waals forces, hydrophobic interaction, dipole moment, and other forces are responsible for the formation of a stable complex[30]. PRD, a nonpolar drug, associates readily with the apolar cavity of cyclodextrin than with water. Here water provides a driving force[29].

Until the advent of the solvent method, solid dispersions were prepared using the melting method[24]. An important prerequisite to the manufacture of solid solutions using the melting method is the miscibility of the drug and carrier in the molten form[23]. The fusion should not cause any decomposition or evaporation of drug. Molten carriers solubilize the drug and then solidify. PEG 4000 was suitably selected because it is not hygroscopic, it is not sticky, and its moderate chain length does not hinder release rate. Crystalline drug turns to amorphous with the increase in percentage of the carrier up to an optimum level and the release rate also increases accordingly. At higher concentration a highly viscous gel is formed in the dissolution medium when increase in percentage of the carrier increases beyond the optimum level. Melting point of sugars is generally very high, making the preparation using hot melting method difficult and because these substances have poor solubility in organic solvent. It makes difficult to prepare co-evaporates by solvent evaporation[8]. In spite of these properties, sugars such as sorbitol and MNT can be employed in making hot melt of poorly soluble drugs. After the carrier has been dissolved, the drug is molecularly dispersed in the dissolution medium. The drug's crystal state disappears. During dissolution no energy is spent to break the crystal structure[8]. After dissolution, the drug is present as supersaturated solution in the boundary layer and precipitation of the drug is inhibited because of the viscosity of wet carrier. Wettability and dissolution of drug are improved by the carrier[31].

Kneading technique is a low-cost, simple method for the preparation of solid dispersion[22]. In this study, kneading is done manually. Here, the limitation of hot melt and solvent evaporation method was overcome. Kneading causes size reduction of drug particles and drug–carrier interaction by shearing[32]. Preparation of inclusion complex of PRD in skimmed milk by lyophilization had been reported earlier[16]. Skimmed milk is composed of alpha, beta, and kappa casein. It is assumed that hydrophobic core of casein micelles entrap hydrophobic PRD inside and surface activity of β-casein improves its solubility. Drug is released through porous inclusion complex at the hydrophilic surface that is occupied by κ-casein. Enhancement of solubility by improving wettability and surface activity is a common technique[33]. The release rate of PRD from solid solution in Cremophor (surface active) was reported to be identical with that of the physical mixture[18]. In this study, use of Cremophor EL and Cremophor RH 40 caused higher release of drug from solid dispersion compared with that of the physical mixture.

Drug content and material balance

The amount of PRD present in the prepared solid dispersion varied from 83% to 98% as shown in Table 2. The material balance with respect to the drug content was found to be 1.24–13% loss of material. The percent loss of material was minimized by increasing the percentage of carrier. After recovery of product, higher material loss was observed in some cases (PVP-VA, CR-EL). This may be because of hydrophobicity, and/or sticky nature of the carrier in liquid state. When this type of material was dissolved in the organic solvent, it formed a film with high sticky property. Thus, it led to adherence on the wall of the preparation chamber. The minimum loss was observed in PEG 4000 and MNT, because of its greater hydrophilic nature. When solid dispersion of HP-βCD was compared with βCD, the % loss was more in HP-βCD, owing to the hydroxypropyl substitution that induces some change in the hydrophobic characteristics[34]. From the obtained data, we observed that the method of preparation and improper recovery of product from vessel also contribute to the loss of material. Solid dispersion prepared using melting method had shown minimum percent loss of material. The kneading and solvent evaporation methods follow it with respect to yield. Drug content in solid dispersion was determined at 247 nm spectrophotometrically. Total amount of loss of solid dispersion was calculated on the basis of drug content and the ratio of drug and carrier. The slight difference between theoretical and practical yield may arise because of accuracy of measurement.

Dissolution studies

The mean dissolution curves of PRD from various binary systems are presented in Figures 1–6. In Figure 1, it was evident that dissolution rate of pure PRD was very slow. Only 60% of drug was dissolved at the end of 30 minutes. In case of PM, there was a marginal improvement in dissolution as compared with pure PRD powder. These accredited to both improvement in drug wettability and formation of readily soluble complex in the dissolution medium[35].

The dissolution rate of PRD solid dispersion with respective carriers showed high burst release (80–90%) in the first 5–6 minutes indicating ideal complex formation with the carrier. After the burst release the constant rate release profile was observed in all dissolution studies. These may owe to the metastable super saturation of drug in the viscous wet carrier matrix during dissolution[36]. After burst release, very low amount of drug was released in the steady state in which it was observed that the solid dispersion with βCD and PEG

Table 2. Drug content and mass balance.

Carrier (C)	Drug:carrier ratio (mg)	Drug content (mg)	Total loss theoretical (mg)	Practical % yield SD
PVP-VA64	1:03	86.88 ± 2.76	52.46 ± 11.043	86.52 ± 3.092
	1:04	87.51 ± 1.115	62.4 ± 5.576	88.16 ± 1
	1:05	88.51 ± 1.571	68.93 ± 9.429	89.75 ± 1.293
	1:06	88.28 ± 2.012	81.99 ± 14.086	88.84 ± 1.451
	1:07	90.72 ± 1.306	74.22 ± 10.454	90.31 ± 1.186
MNT	1:03	89.1 ± 4.785	43.59 ± 19.14	91.25 ± 1.909
	1:04	92.99 ± 1.682	35.02 ± 8.41	92.6 ± 1.25
	1:05	96.66 ± 1.781	19.99 ± 10.688	97.06 ± 1.449
	1:06	96.44 ± 1.682	24.86 ± 11.777	97.37 ± 1.143
	1:07	97.62 ± 1.777	18.99 ± 14.217	98.08 ± 1.519
SMP	1:03	90.78 ± 16.424	36.85 ± 11.502	91.25 ± 1.527
	1:04	91.98 ± 2.059	40.09 ± 10.299	92.44 ± 1.822
	1:05	91.52 ± 1.841	50.85 ± 11.051	92.41 ± 1.328
	1:06	92.52 ± 3.645	52.33 ± 25.52	90.6 ± 2.805
	1:07	92.03 ± 2.053	63.68 ± 16.424	90.62 ± 1.268
EL[a]	1:03:06	83.68 ± 1.898	163.2 ± 18.983	72.08 ± 1.192
	1:04:12	86.72 ± 1.933	225.76 ± 32.872	78.97 ± 1.03
	1:05:20	91.41 ± 2.864	223.34 ± 74.473	86.15 ± 1.003
	1:06:25	92.52 ± 3.986	239.36 ± 27.565	84.76 ± 2.089
	1:07:30	93.27 ± 4.097	255.74 ± 15.718	83.23 ± 1.723
RH 40[a]	1:03:10	87.57 ± 1.978	173.88 ± 27.693	95.14 ± 2.581
	1:04:10	89.8 ± 1.08	152.92 ± 16.204	95.41 ± 1.321
	1:05:15	90.57 ± 2.221	197.82 ± 26.651	93.52 ± 1.415
	1:06:20	92.85 ± 4.313	192.88 ± 16.473	92.09 ± 1.113
	1:07:25	93.35 ± 2.488	219.31 ± 22.121	90.26 ± 2.015
βCD	1:03	91.42 ± 2.431	34.31 ± 9.724	92.75 ± 2.466
	1:04	94.94 ± 1.152	25.27 ± 5.764	95.64 ± 1.161
	1:05	94.44 ± 1.614	33.3 ± 9.689	93.66 ± 1.601
	1:06	92.18 ± 1.199	54.69 ± 8.395	91.42 ± 1.189
	1:07	93.26 ± 1.565	53.86 ± 12.525	91.5 ± 1.536
HP-βCD	1:03	90.8 ± 2.182	36.78 ± 8.73	88 ± 1.04
	1:04	91.31 ± 1.166	43.42 ± 5.832	90.2 ± 1.101
	1:05	91.91 ± 1.219	48.49 ± 7.319	90.53 ± 0.985
	1:06	91.03 ± 1.765	62.73 ± 12.361	86.01 ± 1.371
	1:07	91.1 ±1.854	71.16 ± 14.832	87.78 ± 1.329
PEG	1:03	96 ± 2.362	15.96 ± 9.448	96.5 ± 1.941
	1:04	98.21 ± 1.334	8.91 ± 6.674	97.8 ± 1.616
	1:05	98.6 ± 1.627	8.35 ± 9.766	96.33 ± 1.357
	1:06	98.75 ± 1.174	8.74 ± 8.219	98.57 ± 1.033
	1:07	98.75 ± 1.358	9.99 ± 10.867	98.12 ± 1.063

[a] Cremophor EL and RH 40 represent ratio as drug:carrier:lactose.

4000 released greater amount compared with others. Hydrophilic carriers dissolved more rapidly in the dissolution medium followed by the drug. Rapid dissolution of the drug in case of physical mixture may be explained as in situ complex formation leading to reduction in interfacial tension[37]. The increment in drug dissolution from the HP-βCD:PRD system was higher than that of βCD as shown in Figure 1. In HP-βCD:PRD system 93.36% of drug was released at the end of 30 minutes with the initial burst release of 88.39% whereas the release of 75.48% at 5 minutes and then 84.63% at 30 minutes was observed in the βCD:PRD solid dispersion. These data proved high solubilization capability of substituted cyclodextrin. Also, the higher cavity size leads to improve amorphous behavior of drug, wetting and complexing power[22,34].

Dissolution profiles of PEG and MNT solid dispersion are displayed in Figure 2. The PEG solid dispersion showed higher release rate of about 86% at the end of 30 minutes. The dissolution rate was significantly improved compared with the pure drug and the physical mixture because of appearance of glassy matrix of the drug in the molten carrier that induced dissolution rate[38]. The mechanism involved in the improvement of dissolution rate was drawn from the following factors: (1) decrease in particle size while the drug is dispersed in the molten

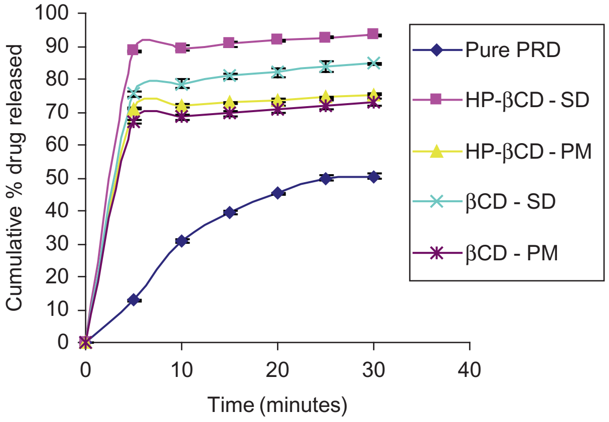

Figure 1. Dissolution profile of prednisolone in solid dispersions versus physical mixtures of HP-βCD (1:5) and βCD (1:6).

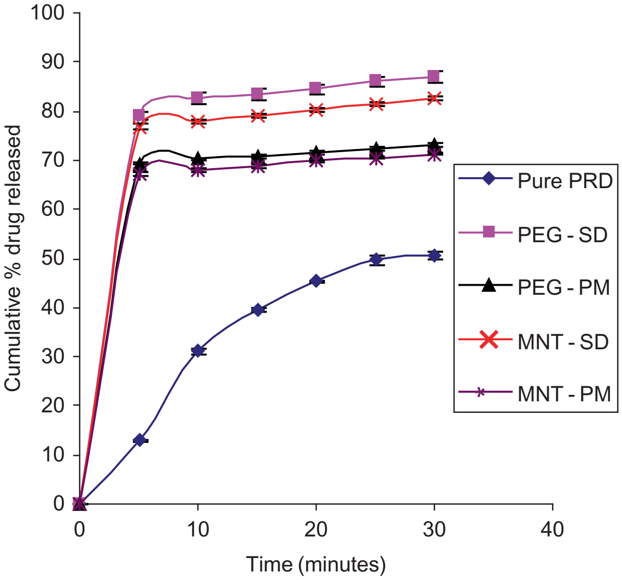

Figure 2. Dissolution profile of prednisolone in solid dispersions versus physical mixtures of PEG (1:4) and MNT (1:7).

carrier and (2) sudden solidification of the carrier[10]. Formation of MNT:PRD solid dispersion showed the nominal drug release rate over 82% at end of 30 minutes. Enhanced solubilization using MNT was caused because of its wetting ability and its ability to prevent the aggregation of the drug particles when exposed to dissolution medium[38]. Also, the formation of hydrogen bond with the polar group present in MNT[20] may improve solubilization. The results obtained from the MNT solid dispersion were not satisfactory compared with other carriers because the result of X-ray diffractometric analysis showed the incomplete amorphization of drug particles compared with the pure drug powder.

The solid dispersion with PVP-VA64 and SMP showed nominal release with respect to other carriers as shown in Figure 3. The substituted PVP with vinyl acetate exhibited

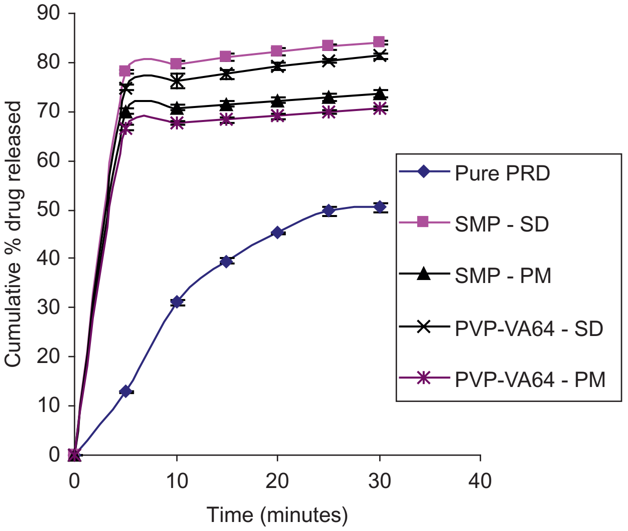

Figure 3. Dissolution profile of prednisolone in solid dispersions versus physical mixtures of SMP (1:7) and PVP-VA64 (1:6).

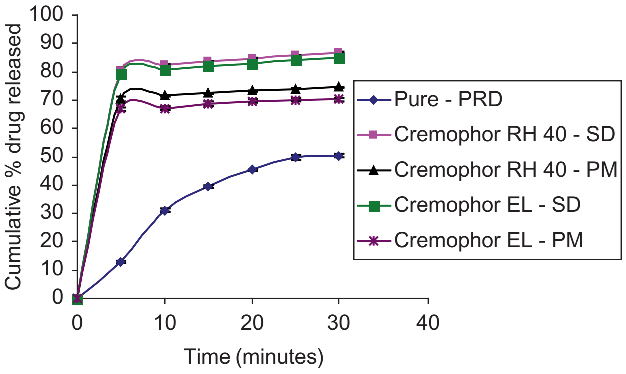

Figure 4. Dissolution profile of prednisolone in solid dispersions versus physical mixtures of Cremophor RH 40 (1:7) and Cremophor EL (1:7).

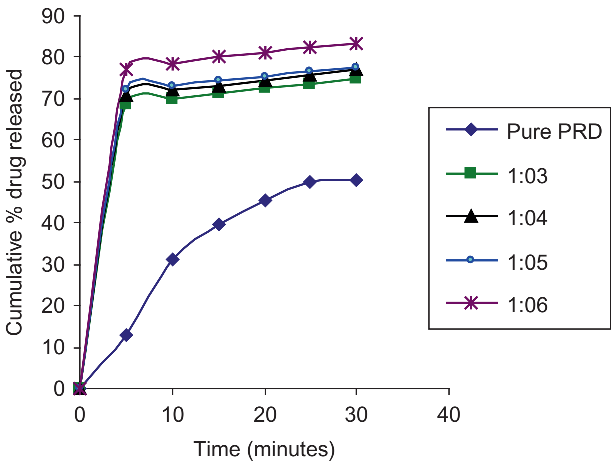

Figure 5. Dissolution profiles of various compositions of prednisolone–Cremophor EL solid dispersions.

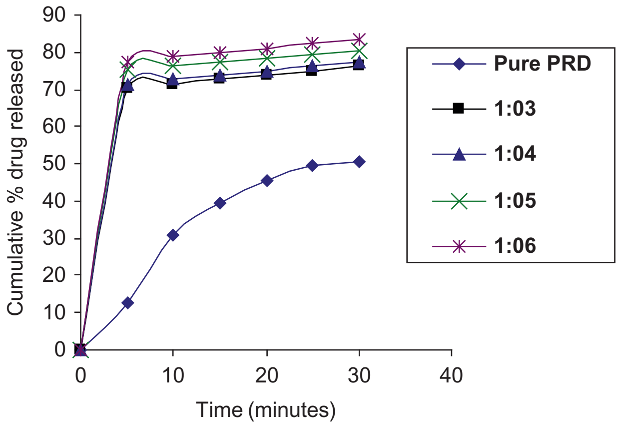

Figure 6. Dissolution profiles of various compositions of prednisolone-Cremophor RH 40 solid dispersions.

enhancement of release compared with pure drug. Even though the polymer is hydrophobic in nature because of the filming effect on the surface of the solids, it results in increased wettability owing to the hygroscopic nature of the polymer[35]. Incorporation of PRD in SMP significantly improved the dissolution of the drug compared with PM and pure drug. Enhancement of dissolution of drug in SMP proved its stronger interaction. The presence of proteins and amino acids influenced the solubility of the drug by forming inclusion complex[16].

Figure 4 showed the dissolution rate of PRD solid dispersion with surfactants (Cremophor EL and RH 40). The dissolution rates were enhanced with increasing concentration of surfactants. An initial burst release was obtained in the dissolution profiles, which then reached the saturated solubility through the study. It is well known that the surfactants increase the wettability and spread ability of the precipitated drug by reducing aggregation in the readily soluble state[39]. Higher solubility and dissolution rate were shown by the solid dispersion of drug with Cremophor RH 40 hydrophilic lipophilic balance (HLB) value 14–16) compared with that of Cremophor EL (HLB value 12–14). This may be because of higher HLB value of RH 40. Apart from nonionic characteristics, viscosity played an ideal role in the dissolution of drug by prolonging the contact of drug with the dissolution medium[40]. When compared with the EL, viscosity of RH 40 is lower (20–40 mPa.s).

Solid dispersion of drug with HP-βCD and PEG 4000 showed improved dissolution profile up to the ratio of 1:5, then it decreased at higher percentage of carrier (data not shown). In other cases the drug dissolution increased as the function of carrier concentration as depicted in Figures 5 and 6.

Mathematical comparison of dissolution profiles

The mathematical comparison of dissolution profiles using two comparison factors f_1 and f_2 is displayed in Table 3. The cumulative % release was used to calculate the two factors by keeping the PEG solid dispersion dissolution data as a reference, because of its higher stability constant value as shown in Table 1. Generally f_1 values up to 15 (0–15) and f_2 values greater than 50 (50–100) signify the average difference ≤10% of the sample points[41]. f_2 similarity factor for all carriers gave values between 47 and 99. The dissolution profiles of solid dispersion obtained with HP-βCD (1:7) and PVP-VA64 (1:4) vary slightly (f_2, $47 < 50$) where others were considered to be similar ($f_2 > 50$). The difference factor f_1 ranges from 0.66 to below 15 approximately; this ensured equivalence of the two curves. From the obtained results, we conclude that the drug:carrier ratio and the type of carrier selected would affect the dissolution characteristics of the solid dispersion.

Fourier transform infrared spectrophotometric analysis

FTIR spectrum revealed the functional groups of PRD involved in the complexation with the carrier. These spectra depicted in Figures 7 and 8 show important stretch vibrations of the molecules of pure substances and mixed substances in transmittance mode. Table 4 shows important functional groups and its stretching vibration caused hydrogen bonding. Pure PRD displayed peak characteristics of O–H stretch vibration at 3357 cm^{-1}, 3454 cm^{-1}, and 3496 cm^{-1} indicative of the presence of

Table 3. Values for comparison factors (f_1 and f_2) for solid dispersion.

	Drug:carrier ratio									
	Difference factor f_1[a]					Similarity factor f_2[b]				
Carriers	1:3	1:4	1:5	1:6	1:7	1:3	1:4	1:5	1:6	1:7
HP-βCD	11.01	5.61	9.88	14.08	8.48	53.08	65.71	54.18	47.95	58.16
βCD	3.11	4.67	2.73	4.09	1.86	75.07	68.51	77.98	72.55	86.18
PVP-VA64	8.61	13.15	9.54	0.66	4.85	58.33	47.75	54.92	96.92	69.6
SMP	1.07	7.56	3.22	0.89	1.92	93.08	59.51	77.07	95.04	86.18
MNT	6.22	11.69	7.6	0.27	0.47	65.17	50.26	59.75	99.19	97.81
RH 40	6.13	11.07	6.05	3.53	5.07	65.51	51.45	64.57	76.64	68.89
EL	8.06	11.71	9.49	3.44	3.1	59.73	50.25	55.04	77.08	78.2

[a] Drug-PEG 4000 solid dispersion was considered as reference. [b] Calculated values obtained from average of three dissolution data ± SD ($n = 3$).

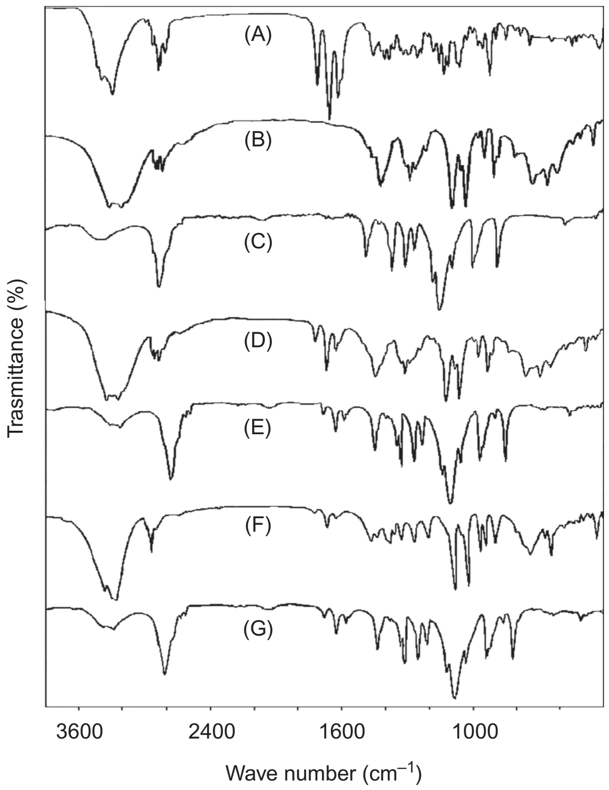

Figure 7. FTIR of (A) prednisolone; (B) MNT; (C) PEG 4000; (D) MNT PM; (E) PEG 4000 PM; (F) PRD:MNT solid dispersion; (G) PRD:PEG solid dispersion.

three hydroxyl groups and peaks showed at 1710 cm^{-1} and 1654.8 cm^{-1} for the presence of carbonyl groups in its structure. The presence of C–H stretching (alkanes), C–C stretch (in ring) and aromatics was depicted in Table 4 by the appearance of bands at respective wave numbers.

From the structure of PRD, PEG 4000, HP-βCD, MNT, SMP, and PVP-VA64, it can be assumed that the possible interaction could occur between the hydroxyl group (proton donor) and carbonyl group (proton acceptor) of the drug and the carriers. A strong absorption peak at 3396 cm^{-1} (O–H stretching vibration) and 2929 cm^{-1}(for C–H stretching vibration) was found in HP-βCD raw material. In the solid dispersion, the peak corresponding to O–H stretching vibration disappeared and C–H band was broadened. Reduced frequency in C=O stretching vibration peak corresponding to drug was the evidence of strong complexation of drug with the carrier molecules[22,35]. In PM, functional groups of PRD were dominantly exposed, though its intensity was reduced. FTIR spectra of PEG (physical mixture) and PEG (solid dispersion) (Figure 7) revealed that O–H stretching vibration corresponding to PEG disappeared and C=O stretching vibration owing to PRD was found with reduced intensity. This suggested the formation of complex by hydrogen bonding. Single peak observed at

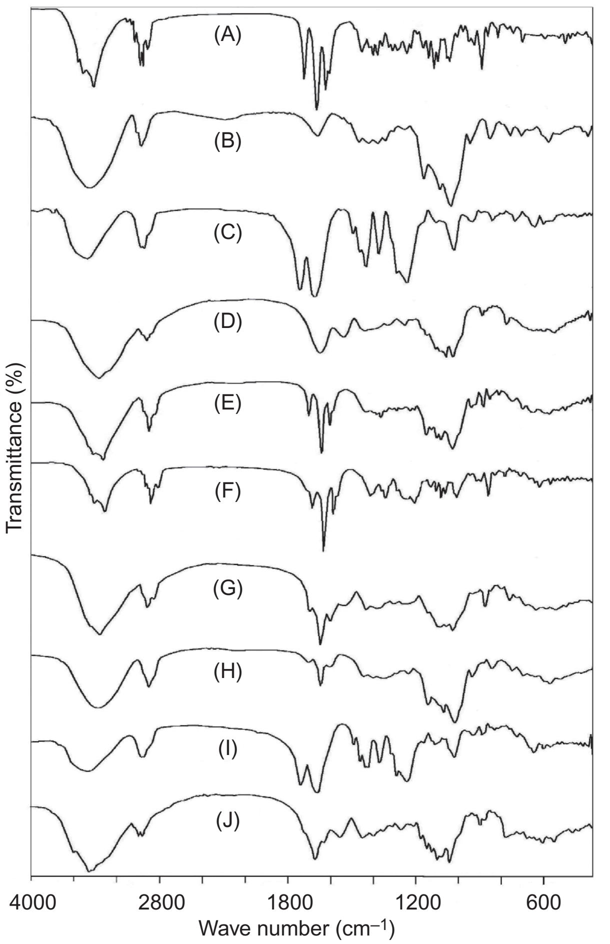

Figure 8. FTIR of (A) prednisolone; (B) HP-βCD; (C) PVP-VA64; (D) SMP; (E) PRD:HP-βCD PM; (F) PRD:PVP-VA64 PM; (G) PRD:SMP PM; (H) PRD:HP-βCD solid dispersion; (I) PRD:PVP-VA64 solid dispersion; (J) PRD:SMP solid dispersion.

Table 4. Overview of the most important stretch vibration of the pure substances that can be affected by hydrogen bonding.

Substance	Wave number (cm^{-1})	Function
PRD	3357, 3454, 3496	O–H (alcohol)
	1710, 1654	C=O (carbonyl)
	2866, 2912, 2929	C–H (alkanes)
	1596	C–C (aromatics)
HP-βCD	3396	O–H (alcohol)
	2929	C–H (alkanes)
PEG	3436	O–H (alcohol)
	1110	C–O–C (ether)
	2887	C–H (alkanes)
MNT	3238, 3288, 3346, 3400	O–H (alcohol)
	2906, 2948, 2970, 2983	C–H (alkanes)
SMP	3386	O–H (alcohol)
	1656	C=C (alkenes)
	1037, 1068, 1095, 1114	C–N (aliphatic amines)
	1542	N–O (nitro compounds)
PVP-VA64	1660, 1739	C=O (carbonyl)

2884 cm^{-1} (C–H stretching) with reduced intensity may be an alternative complexing site of drug with carrier. In case of using MNT–drug, for the preparation of physical mixture and solid dispersion of the drug, O–H stretching vibration was dominantly exhibited with reduced intensity. C–H stretching vibration owing to MNT was evidenced both in PM and in SD. Drug peak corresponding to C=O showing much reduced intensity suggested hydrogen bond interaction. Incorporation of PRD into SMP (Figure 8) showed a broad O–H band at 3386.77 cm^{-1} and the band at 1656.74 cm^{-1} (alkenes) indicated the amorphous nature of the product. Some variation in the drug's peak corresponding to O–H stretch and C–H stretch was observed in both PM and SD of SMP. Disappearance of peak owing to C=O group of drug suggested some interaction. The PVP-VA64 copolymer has two regions of interest for potential drug interaction. The characteristic carbonyl band was observed at 1668 cm^{-1} (vinyl pyrrolidone monomer) and 1737 cm^{-1} (vinyl acetate monomer) having higher proton affinity[42]. The broad single O–H stretching vibration peak observed at 3448 cm^{-1}, 2952 cm^{-1}, and 2935 cm^{-1} in SD indicated interaction between O–H group of drug and carbonyl groups of polymers that showed slightly altered peak position. In physical mixtures, characteristics of the drug were prominent. C=O stretching vibration owing to PRD disappeared in SD, suggesting its interaction with the carrier because of hydrogen bonding.

Powder X-ray diffraction analysis

The XRD patterns of the drug (PRD) and different carriers (HP-βCD, PEG 4000, PVP-VA64, SMP, and MNT), their physical mixture and solid dispersions are exhibited in Figures 9–11. The characteristic peaks for PRD and their intensities are listed in Table 5. Carriers SMP, HP-βCD, and PVP-VA64 showed amorphous characteristics in their XRD chart[27,35]. PEG 4000 exhibited sharp peaks showing its crystallinity. In Figure 9, we observed that amorphous nature was prominent in both physical mixture and solid dispersion of drug–SMP when compared with that of SMP, though the characteristic peak at 2θ of 15.47° of PRD was found with reduced intensity and overlapped with the peak of SMP. Peak overlapping was also reported in lyophilization technique by Sahin and Arslan[16]. In Figure 10, PEG exhibited a distinct pattern with diffraction peaks at 2θ of 19.1° and 23.3°. In the case of physical mixture, the XRD pattern showed the peaks of both PRD and PEG 4000 at 2θ of 15.47°, 19.1°, and 23.3° with lower intensities. It indicated that the crystallinity of PRD remained unchanged in the physical mixture. In its solid dispersion, PEG peaks were the same and superimposable, but the intensity of drug peaks at 2θ of 15.47° was reduced indicating a decrease in crystallinity. Many diffraction peaks with high intensity were observed in the X-ray chart of MNT raw material, because of its crystallinity (Figure 10) (2θ of 14.5°,

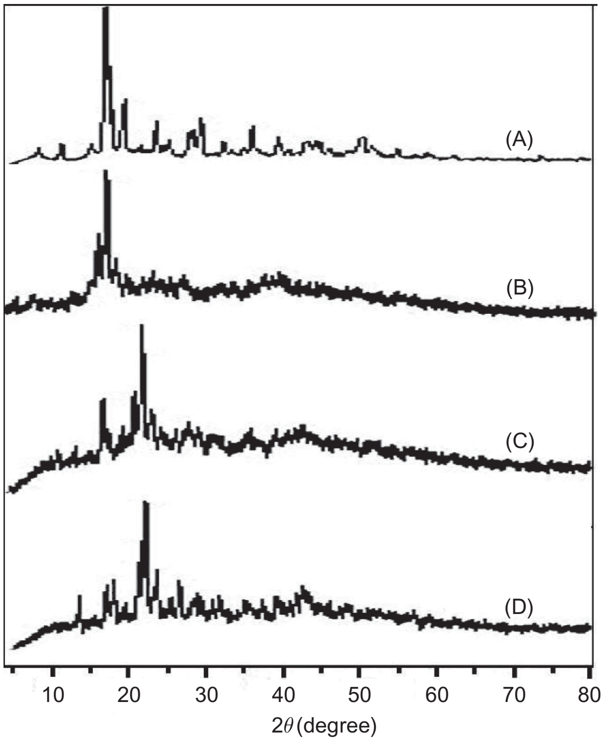

Figure 9. Powder X-ray diffraction pattern of (A) prednisolone; (B) SMP; (C) PRD:SMP PM; (D) PRD:SMP solid dispersion.

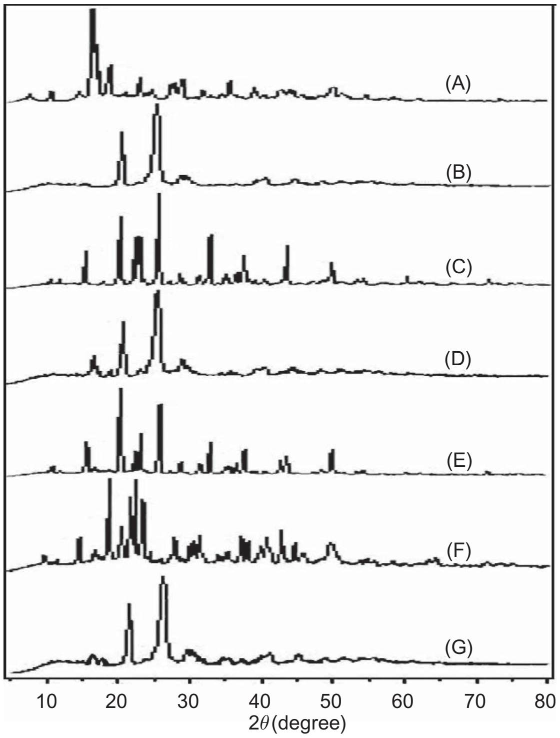

Figure 10. Powder X-ray diffraction pattern of (A) prednisolone; (B) PEG; (C) MNT; (D) PRD:PEG PM; (E) PRD–MNT PM; (E) PRD–MNT solid dispersion; (G) PRD:PEG solid dispersion.

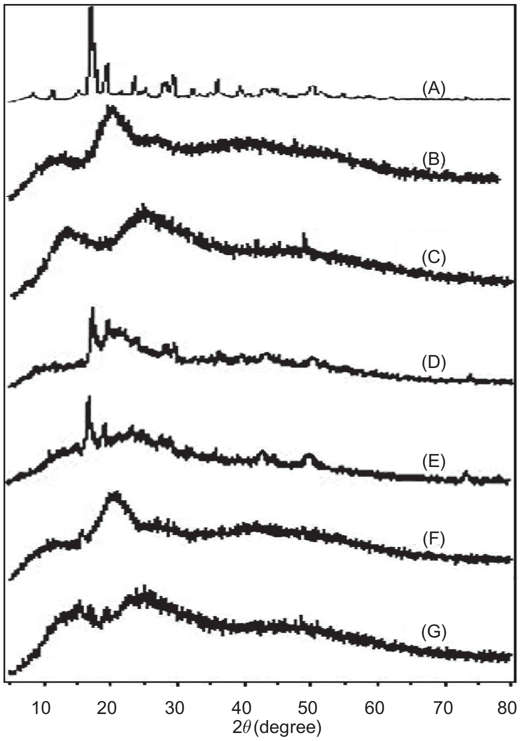

Figure 11. Powder X-ray diffraction pattern of (A) prednisolone; (B) HP-βCD; (C) PVP-VA64; (D) PRD:HP-βCD PM; (E) PRD:PVP-VA64 PM; (F) PRD:HP-βCD solid dispersion; (G) PRD:PVP-VA64 solid dispersion.

Table 5. Intensities at characteristic diffraction angles 2θ (degree) and d-values (Å) for prednisolone.

2θ	d-Value	Intensity
8.03	11	86
10.52	8.4	161
13.91	6.36	119
15.47	5.72	1462
15.83	5.59	805
16.25	5.44	353
17.6	5.03	553
19.49	4.55	78
21.2	4.18	316
22.07	4.02	66
22.64	3.9	140
24.8	3.58	198
25.22	3.52	195
26.18	3.4	354
28.7	3.1	144
29.6	3.01	46
30.95	2.88	73
31.94	2.79	296
34.79	2.57	182
35.99	2.49	54
37.94	2.36	59
38.96	2.3	87
39.5	2.27	92
44.15	2.04	48
45.29	2	94
48.29	1.88	88
64.37	1.44	54

18.6°, 21°, 23.3°, and 29.4°). The same diffraction pattern additionally with drug peak at 2θ of 15.47° was observed in the PM that showed unchanged crystallinity of the drug whereas in the solid dispersion, the intensity of drug peak at 2θ of 15.47° was gradually reduced and the peak corresponding to the carrier remains unchanged indicating less interaction between drug and carrier. In Figure 11, the physical mixture of both PRD–HP-βCD and PRD–PVP-VA64 exhibited crystallinity with reduced intensity at 2θ of 15.47° when compared with that of PRD. Amorphous nature had been established in their solid dispersion completely in their respective diffractogram. These were found to be superimposable with the X-ray diffractogram of pure carriers. Crystallinity of drug was reduced because of complex formation with the carriers. This was found most prominent in case of solid dispersion of drug with HP-βCD and PVP-VA64.

Thermogravimetric analysis

TG can be used for qualitative and quantitative analysis[43]. Quantitative analysis is useful to determine the loss of volatile components such as water from the sample as a function of temperature[43]. The onset temperature, T_{onset}, is the temperature at the initiation of mass loss. It is measured by extrapolating to intersection the linear portions of the thermal curve recorded before and during the mass loss. The T_{onset} can be used to compare between the reference and the sample. In Figure 12, T_{onset} of PRD, solid dispersion of PRD–HP-βCD, PRD:PEG, and PRD–PVP-VA64 was 30°C. The mass loss was obtained from the vertical distance on the thermal curve between the horizontal portions before and after the mass loss. The measurement was done over the wide range of 30–700°C. From the thermal curve (Figure 12) we found that only 1.77% of its total weight was lost at 225°C for pure PRD, which is close to the drug's melting point (232°C—experimental value). Similar value was reported in an earlier paper[16]. This may be because of the volatilization of hydroxyl group present in PRD. Weight loss gradually increased as the function of temperature. It lost 98.1% of weight at end of 700°C. Variation in weight loss was observed in solid dispersion as well. In HP-βCD solid dispersion 0.4307°C/mg weight loss was observed up to 96.83°C. The percentage weight loss was about 6.567% up to 96.83°C. This weight loss was attributed to dehydration[44]. Then, the constant weight was maintained up to the temperature slightly above the melting point of the drug. The weight loss gradually increased with the rate of 0.3191°C/mg up to 693.94°C and then became constant. In PVP-VA64 solid dispersion, sample lost mass of 2.191% at 198.17°C and 94.56% with the weight loss rate of 0.2242°C/mg up to 695.01°C. It was evident that amount of volatile substance increased with increasing content of PVP in the dispersion. Weight loss initiates above 250°C in PEG solid dispersion. The continuous weight loss with rate of

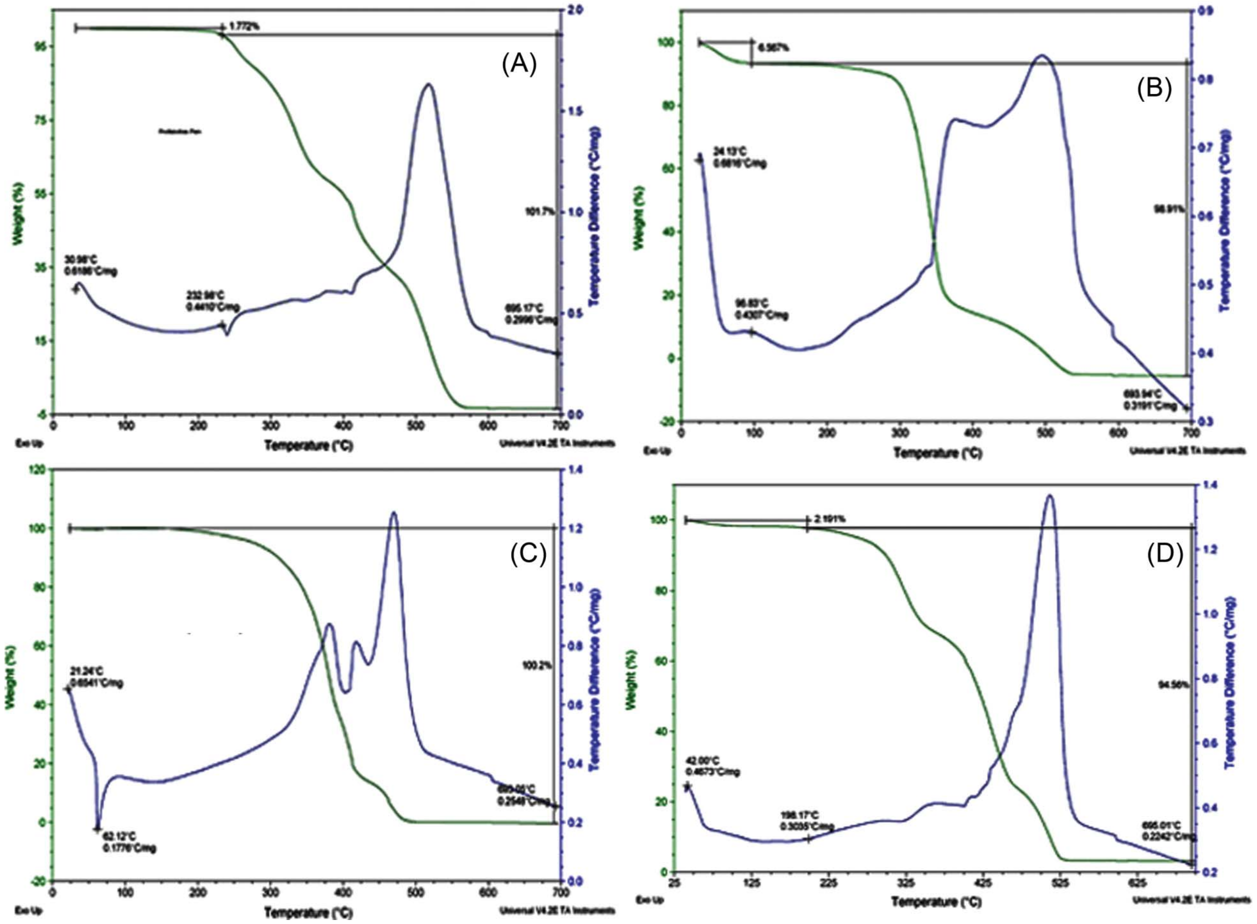

Figure 12. TGA curve of (A) prednisolone; (B) PRD:HP-βCD (1:5) solid dispersion; (C) PRD:PEG (1:4) solid dispersion; (D) PRD:PVP-VA64 (1:6) solid dispersion.

0.2548°C/mg up to 693.05°C was observed. The result of the TG analysis was taken into consideration for undertaking the DSC thermogram.

Differential scanning calorimetric analysis

The DSC curves reported in Figure 13 revealed the solid-state interaction of PRD with carriers. Thermogram of PRD exhibited sharp endothermic peak at 239.5°C that complies with the reported data[16]. The physiochemical properties such as melting, boiling, or sublimation point were generally altered when the guest molecules interacted with the host molecules. The thermogram of HP-βCD showed very broad endothermic effect at 50°C, because of release of water molecules and in the case of PVP-VA64, endothermic peak was observed at 100–140°C and 260–340°C. This may be because of residual moisture content[22]. A very small broad peak near 250°C was observed in solid dispersion of PRD–HP-βCD. This may correspond to melting of PRD (m.p. 235°C) shifted slightly to higher temperature. This indicated reduction in crystallinity of the drug. Thermogram of solid dispersion of PRD–PVP-VA64 showed a big broad peak near 200°C that did not comply with the melting point of the

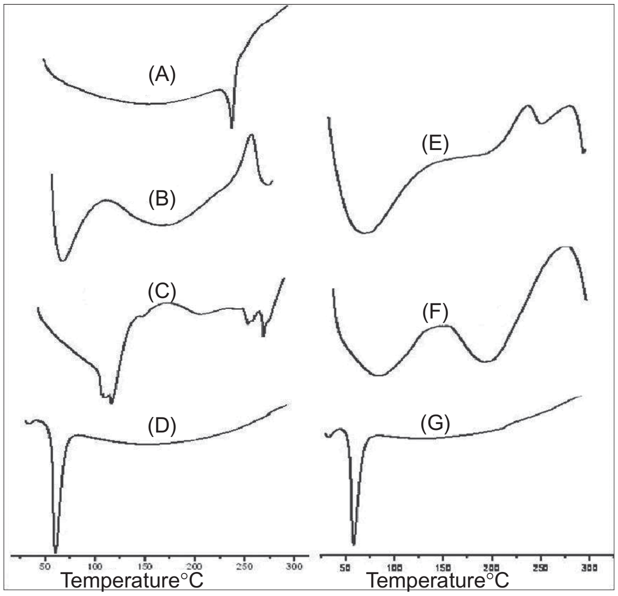

Figure 13. DSC thermograms of (A) prednisolone; (B) HP-βCD; (C) PVP-VA64; (D) PEG 4000; (E) PRD:HP-βCD (1:5) solid dispersion; (F) PRD:PVP-VA64 (1:6) solid dispersion; (G) PRD:PEG (1:4) solid dispersion.

drug. This exposed complete amorphous behavior of the drug. In case of PEG the sharp endothermic peak appeared at 58°C because of melting of PEG[45]. The complete disappearance of peak because of melting point of the drug (239°C) was observed in PEG solid dispersion; only peak because of melting of the carrier (58°C) appeared[23]. This thermogram indicated that PRD completely converted to amorphous state in the solid solution.

Conclusion

The dissolution characteristics of PRD in water may be improved by the formation of solid dispersions with various carriers. The complexation constant was up to 519 that may be influenced by the molecular weight of a carrier but principally depended on concentration of the carrier content in the mixture and the system preparation method. The decrease of crystallinity of the drug is an indication of its complex formation that resulted in enhancement of solubility of the drug. Among all carriers, HP-βCD showed a better dissolution rate of about 93.36% at the end of 30 minutes. The FTIR spectroscopy of PRD solid dispersion showed stronger interaction with the carrier, HP-βCD, because of hydrogen bonding. The XRD and DSC substantiated the claim of amorphization of PRD in solid dispersion form resulting in better dissolution rate. Overall, the solid dispersion using HP-βCD as carrier provides a promising approach to improve the solubility and dissolution rate of PRD. Future studies concern with the development of controlled drug delivery system by incorporating PRD solid dispersion.

Acknowledgment

We are grateful to Medopharm, Karnataka, India, for their interest and supply of prednisolone as a gift sample. We wish to thank Dr. S. Nath, Deputy General Manager (R&D) of Albert David, whose valuable suggestion helped us to select carrier polymers.

Declaration of interest

The authors are thankful to University Grants Commission (UGC), New Delhi, India, for financial support through a grant project number 34-132\2008 (SR). The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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