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Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods

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Abstract

This study compares the physicochemical properties of carbamazepine (CBZ) solid dispersions prepared by either a conventional solvent evaporation versus a supercritical fluid process. Solid dispersions of carbamazepine in polyvinylpyrrolidone (PVP) K30 with either Gelucire 44/14 or Vitamin E TPGS, NF (D-α-tocopheryl polyethylene glycol 1000 succinate) were prepared and characterized by intrinsic dissolution, differential scanning calorimetry, powder X-ray diffraction and Fourier transform infrared spectroscopy. CBZ/PVP K30 and CBZ/PVP K30/TPGS solid dispersions showed increased dissolution rate. The best intrinsic dissolution rate (IDR) was obtained for supercritically processed CBZ/PVP K30 that was four-fold higher than pure CBZ. Thermograms of various solid dispersions did not show the melting peak of CBZ, indicating that CBZ was in amorphous form inside the carrier system. This was further confirmed by X-ray diffraction studies. Infrared spectroscopic studies showed interaction between CBZ and PVP K30 in solid dispersions. The amorphous state of CBZ coupled with presence of interaction between drug and PVP K30 suggests fewer, if any, stability problems. Because the supercritical-based process produced solid dispersions with IDR better than conventional solid dispersions augmented with amphiphilic carriers, stability issues associated with lipid carriers do not apply, which, in turn, implies easier scale up under current Good Manufacturing Practice for this technique.

Keywords: Supercritical fluid; TPGS; PVP K30; Carbamazepine; Amorphous; Solid dispersions

1. Introduction

Carbamazepine (CBZ) is an antiepileptic with different crystalline (Rustichelli et al., 2000) forms, all of which have variable dissolution leading to irregular and delayed absorption (Bertillson, 1978). CBZ has an experimental log *P* value of 2.45 and is practically insoluble in water (∼113 μg/ml at 25 °C). CBZ and similar drugs of low solubility and high permeability, i.e. "Class II" in the Biopharmaceutical Classification System (Löbenberg and Amidon, 2000) are more likely to display dissolution-dependent oral bioavailability; solid dispersion techniques have been developed to address these problems. Formation of eutectic mixtures, molecular dispersion, amorphous dispersion, and metastable polymorph dispersion are strategies shown to benefit dissolution behavior (Ford, 1986; Leuner and Dressman, 2000). Conventional methods for preparation of solid dispersions include either the fusion or solvent processes, with supercritical fluid processing (SCP) emerging as an alternative solvent-evaporation method for formulating coprecipitates of smaller particle size (Moneghini et al., 2001), lower residual organic solvent (Beach et al., 1999), and better flowability. A supercritical fluid exists as a single fluid phase above its critical

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temperature (T_c) and pressure (P_c). Carbon dioxide is currently the most commonly used supercritical fluid because of its low critical temperature and pressure ($T_c = 31.1\,^{\circ}C$, $P_c = 73.8$ bar). Apart from being non-toxic, non-flammable, and inexpensive, the low critical temperature of carbon dioxide makes it attractive for processing heat labile pharmaceuticals. In the context of manufacturability, rate of cooling and solvent removal is stringently controlled, resulting in acceptable batch to batch variation (York, 1999). In this investigation gas antisolvent crystallization technique (Gallagher et al., 1989) using supercritical carbon dioxide as a processing medium was used.

Historically, water-soluble carriers such as high molecular weight polyethylene glycols and polyvinylpyrrolidones (PVP) have been the most common carriers used for solid dispersions. For solid dispersions PVP K12 to K30 (MW 2500–50,000) has been widely used. The high molecular size of the polymers favors the formation of solid solutions. The use of lipid-based amphiphilic carriers with solubilizing properties like Gelucire 44/14 and Vitamin E TPGS (TPGS) has recently attracted much interest (Serajuddin, 1999). Gelucire 44/14 is a saturated polyglycolized glyceride consisting of a well-defined mixture of mono-, di- and tri-glycerides and mono- and di-fatty acid esters of polyethylene glycol. It has a hydrophilic–lipophilic balance (HLB) value of 14. TPGS (D-α-tocopheryl polyethylene glycol 1000 succinate) is a water-soluble derivative of Vitamin E consisting of a hydrophilic polar head group (polyethylene glycol) and a lipophilic tail (tocopherol succinate) resulting in amphiphilic properties (HLB value ∼13). TPGS has a relatively low critical micelle concentration of 0.02 wt.% above which this carrier offers the advantage of spontaneously solubilizing lipophilic drugs upon contact with an aqueous medium to form a fine emulsion that, in turn, further facilitate drug absorption. Gelucire 44/14 and TPGS have relatively low melting temperatures of 44 °C and a range of 37–41 °C, respectively and it was anticipated that solid dispersions with these two alone would more likely produce long-term stability problems. The use of new formulation technique in conjunction with PVP might reduce the rate of crystallization in carriers with low melting temperatures. Postprandial "food effect" (increase in bioavailability) might be another advantage offered by these lipid-based formulations (Khoo et al., 2000).

Very few comparisons of the in vitro performance of conventional and supercritical-based solid dispersions are found in literature. Attempts have been done in this study to evaluate the physicochemical properties of the solid dispersions of CBZ in PVP K30 with or without TPGS or Gelucire 44/14. Solid dispersions were prepared by conventional solvent evaporation and novel SCP methods and characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (XRD) and Fourier transform infrared (FTIR) spectroscopy.

2. Materials and methods

2.1. Materials

CBZ was purchased from Sigma Chemical Company, St. Louis, MO. PVP K25 and K30 were obtained from BASF Corporation, Ledgewood, NJ. Vitamin E TPGS was obtained from Eastman Chemical Company, Kingsport, TN. Gelucire 44/14 was received from Gattefossé Corporation, Westwood, NJ. All organic solvents were high-performance liquid chromatography (HPLC) grade. All other chemicals were reagent grade.

2.2. Solubility measurements of CBZ

Solubility measurements of CBZ were performed according to a published method (Higuchi and Connors, 1965). An excess amount of CBZ was added to 10 ml of aqueous solutions having different concentrations of PVP K25 or PVP K30. The samples were sonicated for 1 h at room temperature. Thereafter, the capped test tubes were shaken at 25 °C for 48 h in a water bath. Subsequently, the suspensions were filtered through a 0.45-μm membrane filter, and the filtered solutions were properly diluted with methanol. The diluted solutions were analyzed for CBZ by using HPLC.

2.3. Preparation of solid dispersions

Solid dispersions of CBZ in PVP K30 alone or in combination with either TPGS or Gelucire 44/14

Table 1
Composition (w/w) of various solid dispersions of CBZ prepared by conventional and SCP method

Formulation	CBZ	PVP K30	Gelucire 44/14	TPGS
CBZ/PVP K30	1	5	–	–
CBZ/PVP K30/Gelucire 44/14	1	4	1	–
CBZ/PVP K30/TPGS	1	4	–	1

were prepared in different ratios (Table 1) both by conventional solvent evaporation method and SCP as described in our previous work (Sethia and Squillante, 2002). Briefly, in conventional solvent evaporation method, drug and carrier were dissolved in minimum volume of methanol and the solvent was removed under vacuum in a rotavapor at 40 °C and 45 rpm for 24 h. The resultant solid dispersion was kept in refrigerator for 2 days to harden. Dispersions were then pulverized in mortar and pestle, passed through a 250-μm sieve (mesh size 60), and then stored in a desiccator at room temperature. In the SCP method, the drug and polymers were dissolved in minimum volume of methanol, processed in stainless steel reactor with supercritical CO_2 at 135 bar, 40 °C and mild stirring. End point of drying was measured by gas chromatography headspace analysis. Handling and storage conditions for SCP were identical to the conventional processed solid dispersion.

2.4. Measurement of the apparent intrinsic dissolution rates

The intrinsic dissolution rate (IDR) of each solid dispersion as well as plain CBZ were measured in triplicate using the Wood's apparatus attached to a USP II apparatus (VK 7000, VanKel) at 150 rpm and 37 ± 0.5 °C. Two hundred and fifty milligrams of powder was compressed using a Carver hydraulic press to form a pellet at 3000-lb force for 2 min. The Wood's apparatus containing the compressed pellet was submerged in 400-ml of distilled water contained in a 900-ml dissolution vessel to one-half of the height of the die. The constant surface area of the pellet exposed was 0.5 cm^2. At different time points, 3-ml aliquot samples were withdrawn with media replacement, filtered, and analyzed by a reversed-phase HPLC.

2.5. Drug analysis

Chromatographic analyses were performed on a Waters HPLC system consisting of a pump (model 515), an auto-sampler (ULTRA WISP 715), UV detector (model 486), and Millennium 32 software. CBZ was analyzed at 212 nm by using a C_{18} reversed-phase column (LiChrosorb, 10 μm, 4 mm inside diameter × 25 cm; Phenomenex, Torrance, CA) at ambient temperature. The mobile phase, a mixture of acetonitrile (35%) and water (65%) was pumped at 1 ml/min. Standard curves for CBZ were measured over a range of 0.125–20 μg/ml and shown to be linear. The detection limit was 0.05 μg/ml.

2.6. DSC

Thermal analyses of various solid dispersions were performed in a Perkin-Elmer DSC-7 differential scanning calorimeter with a TAC 71DX thermal analysis controller (Perkin-Elmer, Norwalk, CT). Samples were accurately weighed (5–8 mg) into aluminum pans and thermograms obtained at a heating rate of 10 °C/min over a temperature range of 25–210 °C. Temperatures below ambient were obtained by using an ice–water mixture inside the cooling assembly of the calorimeter. Pyris software 2.04 (Perkin-Elmer) was used for analysis.

2.7. Powder XRD

Samples were evaluated by using a Rigaku D/Max 2200 diffractometer to assess the solid state of CBZ. The samples were radiated using a Cu target tube and exposed to all lines. A monochromator was used to select Kα 1 line ($\lambda = 1.54056$). The scanning angle ranged from 2° to 40° of 2θ, steps were 0.02° of 2θ, and the counting time was 0.6 s per step. The current used was 40 mA and the voltage 40 kV.

2.8. FTIR spectroscopy

A Perkin-Elmer Spectrum 1000 FTIR spectrometer equipped with a DTGS detector was used for infrared analysis. Samples were prepared by KBr disc method (2 mg sample in 100 mg KBr) and examined in the transmission mode. A resolution of 4 cm^{-1} was used and 64 scans were co-added for each spectrum over

a frequency range of 4000–450 cm^{-1}. The software used for the data analysis was Perkin-Elmer Spectrum 3.02.

2.9. Data analysis

Results are expressed as mean values and standard deviation (±S.D.) and the significance of the difference observed was analyzed by the Student's *t*-test. In all tests, a probability value of $P < 0.05$ was considered statistically significant.

3. Results and discussion

3.1. Solubility studies

Fig. 1 shows the solubility phase diagram representing the effect of increasing the concentrations of PVP K25 and K30 on the apparent solubility of carbamazepine in water at 25 °C. Between the two polymers, aqueous solutions of PVP K30 increased the solubility of CBZ more, though the increase was marginal. The solubility of CBZ did not increase appreciably below 1% concentration of polymer. The increase in solubility was linear with respect to the weight fraction of the carrier above 1%. At 15% concentration of PVP K25 and K30, the increase in CBZ solubility was approximately 11- and 12-fold, respectively. The increase in solubility of CBZ by PVP may probably be due to the formation of soluble complexes between water-soluble polymeric carrier and poorly soluble drug. The increase in CBZ solubility at 15% concentration of Gelucire 44/14 and TPGS was seen to be approximately 27- and 33-fold, respectively (Sethia and Squillante, 2002). PVP K30 was selected for formulation of solid dispersions because of its higher molecular weight and better solubility of CBZ in its aqueous solution.

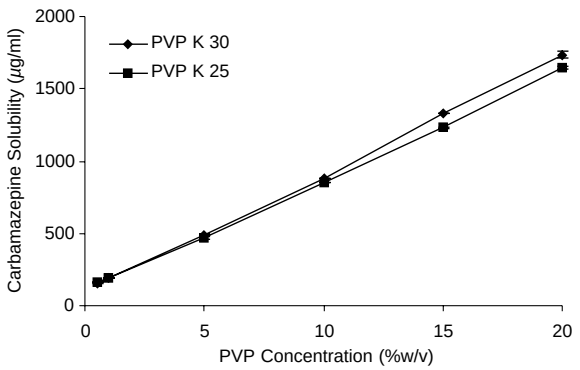

Fig. 1. Phase solubility diagram of CBZ in aqueous solutions of PVP at 25 °C. Error bars indicate the standard deviation, $n = 3$.

3.2. Intrinsic dissolution studies

In powder dissolution, factors such as rate of wetting, effect of particle size and hence specific surface area, disintegration, clumping etc., are unnecessarily complicating. To avoid these complications mounted tablets in Wood's apparatus were utilized in these studies as they provide a constant surface area, permit a constant hydrodynamic system and in general avoid many of the problems associated with powders (Mayersohn and Gibaldi, 1966). In the sink condition, the concentration of drug, C at time t can be obtained from the following expression (Nogami et al., 1966),

$$C = \left(\frac{S}{V}\right) k \times C_s \times t \quad (1)$$

where S is the surface area of the disk, V is the volume of test solution, k is the intrinsic dissolution rate constant, and C_s is solubility. The dissolution rate from the unit surface area, i.e. IDR, can be calculated by the following rearranged equation,

$$\text{IDR} = \left(\frac{C}{t}\right)\left(\frac{V}{S}\right) = k \times C_s \quad (2)$$

Apparent IDR of various solid dispersions were measured and compared to that of pure CBZ. Kaplan noted that compounds with IDR below 0.1 mg/min/cm^2 usually exhibited dissolution rate-limited absorption (Kaplan, 1972). The IDR of pure CBZ being 0.048 mg/min/cm^2 falls into this category. Table 2 shows the IDR of various formulations prepared by conventional and supercritical processing. As expected the increase in IDR was sensitive to the particular ratio of the drug to polymers utilized and the method of preparation. CBZ/PVP K30-SCP formulation showed the best IDR that was ~4-fold greater than pure CBZ, followed by CBZ/PVP K30/TPGS-SCP and CBZ/PVP K30/TPGS-Rotavap that were both about 2.9 times greater than pure CBZ ($P < 0.005$). Surprisingly,

Table 2
Intrinsic dissolution rates of various solid dispersions (mean±S.D.; $n = 3$)

Formulation	Intrinsic dissolution rate (mg/min/cm^2)
Pure CBZ	0.048 ± 0.005
CBZ/PVP K30-Rotavap	0.128 ± 0.009
CBZ/PVP K30-SCP	0.187 ± 0.005
CBZ/PVP K30/Gelucire 44/14-Rotavap	0.080 ± 0.007
CBZ/PVP K30/Gelucire 44/14-SCP	0.065 ± 0.002
CBZ/PVP K30/TPGS-Rotavap	0.139 ± 0.002
CBZ/PVP K30/TPGS-SCP	0.141 ± 0.008

formulations having Gelucire 44/14 showed least increase in IDR compared to other formulations. CBZ is a class II drug according to the Biopharmaceutical Classification System (BCS), with low solubility and high intestinal permeability (Löbenberg and Amidon, 2000). For Class II drugs, the luminal dissolution rate is most likely the rate limiting step in the intestinal absorption. Because all solid dispersions of CBZ except those having Gelucire 44/14 showed IDR greater than 0.1 mg/min/cm^2 and thus expected to show better bioavailability than pure CBZ. Remarkably, the method of preparation for CBZ/PVP K30 formulation proved significant with the SCP formulation giving 1.5 times better IDR (∼4-fold) compared to its conventional counterpart (∼2.6-fold); $P < 0.005$.

3.3. DSC studies

Figs. 2 and 3 show the DSC traces of CBZ and various formulations prepared by both conventional and SCP method. DSC trace of pure CBZ shows a polymorphic transition with two endotherms at around 171–174 and 191 °C. It is well known that CBZ exhibits enantiotropic polymorphism, i.e. there exists a transition temperature below the melting point of either of polymorphs at which both these forms have the same free energy (Behme and Brooke, 1991). Above the transition temperature, the higher melting Form I has the lower free energy and is more stable. Below the transition temperature, however, the lower melting Form III is more stable since it has lower free energy. The transition temperature of CBZ enantiotropic forms has been reported to be around 71 °C (Behme and Brooke, 1991). Hence at room

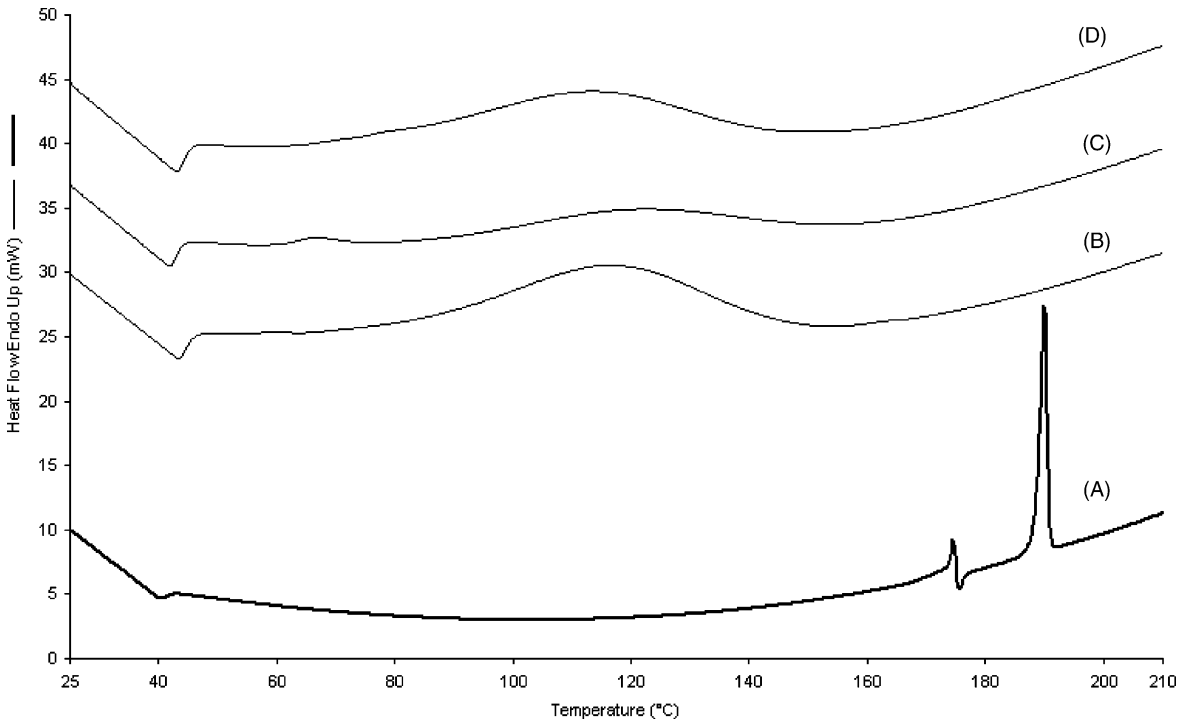

Fig. 2. DSC traces of pure CBZ (A), PVP K30 (B), CBZ/PVP K30-Rotavap (C), and CBZ/PVP K30-SCP (D) at a scanning rate of 10 °C/min.

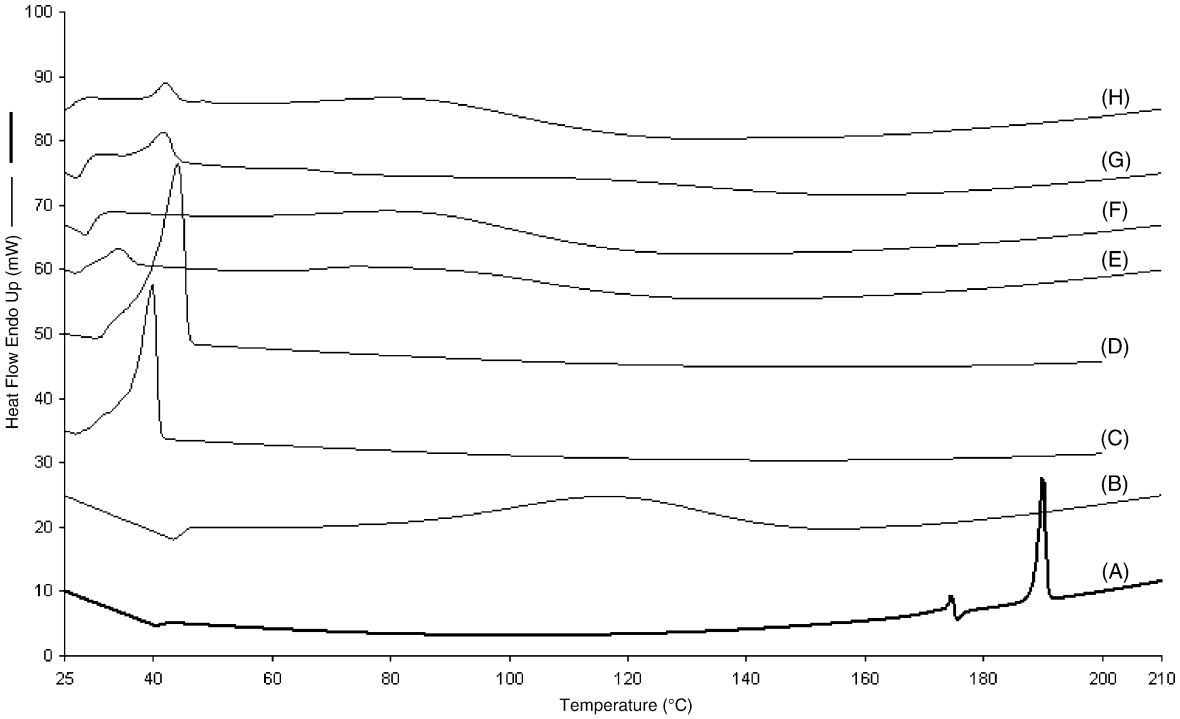

Fig. 3. DSC traces of pure CBZ (A), PVP K30 (B), TPGS (C), Gelucire 44/14 (D), CBZ/PVP K30/TPGS-Rotavap (E), CBZ/PVP K30/TPGS-SCP (F), CBZ/PVP K30/Gelucire 44/14-Rotavap (G), and CBZ/PVP K30/Gelucire 44/14-SCP (H) at a scanning rate of 10 °C/min.

temperature, Form III is the most stable form and is the one possessed by most commercially available CBZ. In Fig. 2A, the endotherm around 171 °C corresponds to the melting of Form III, followed by immediate recrystallization to Form I and subsequent melting of Form I at 191 °C. It is important to note that the analytical heating rate has a profound effect on DSC traces. Different curves as well as melting point values can be seen owing to differences in the rate of transformation (Sethia and Squillante, 2002). During scanning of PVP K30, a broad endotherm ranging from 90 to 140 °C was observed indicating the loss of water due to extremely hygroscopic nature of PVP polymers. Repeated scanning led to the disappearance of the endotherm. The thermograms of both CBZ/PVP K30-Rotavap and CBZ/PVP K30-SCP formulations (Fig. 2C and D) also showed similar broad endotherm, but no endotherms were observed around the melting point of both forms of CBZ. This indicates that CBZ might be in amorphous state. The corresponding physical mix of CBZ/PVP K30 showed endotherm corresponding to the melting point of CBZ indicating the presence of crystallinity. The thermograms of TPGS and Gelucire 44/14 (Fig. 3C and D) showed a single endothermic peak corresponding to their melting point; TPGS (39 °C) and Gelucire 44/14 (44 °C). DSC traces of solid dispersions having Gelucire 44/14 as one of the component (Fig. 3G and H) showed a broad endotherm around 42 °C, close to the melting point of Gelucire 44/14. Similarly, CBZ/PVP K30/TPGS-Rotavap formulation showed melting endotherm around 35 °C. Surprisingly, the melting endotherm for TPGS in CBZ/PVP K30/TPGS-SCP formulation was not observed. Even after a year of storage of all the solid dispersions in vacuum desiccator at room temperature, no endothermic peaks corresponding to CBZ were detected, indicating that CBZ was still present in amorphous form.

Various studies (Matsumoto and Zografi, 1999; Van den Mooter et al., 2001) have shown that PVP inhibits crystallization of drugs in solid dispersions resulting in amorphous form of the drug in the solid dispersions.

Crystallization inhibition is attributed to two effects: interactions, such as hydrogen bonding between the drug and the polymer and the entrapment of the drug molecules in the polymer matrix during solvent evaporation or a combination of both. As the solvent is removed during the preparation of solid dispersions, viscosity of the system increases very rapidly leading to a decrease in drug mobility. When the solvent is evaporated completely, drug molecules are frozen in the polymer matrix. A crystal lattice is not formed, but the drug molecules are randomly "ordered" comparable to the liquid state and exhibit short-range order over only a few molecular dimensions.

3.4. Powder XRD studies

The solid state of CBZ, various carriers and differently processed solid dispersions of CBZ were studied by XRD (Figs. 4 and 5). PVP being amorphous did not show any peaks. The powder diffraction patterns (pdp) of pure CBZ showed characteristic high-intensity diffraction peaks at 2θ values of 15.04°, 15.38°, 15.87°, 27.38°, 27.60°, and 32.10° that matched the known pdp of CBZ Form III (Krahn and Mielck, 1987; Lowes et al., 1987). The pdp's of all the formulations did not show peaks corresponding to CBZ thus indicating that CBZ was in amorphous form. The formulations having Gelucire 44/14 showed some lines at 2θ values of 19.5° and 23.5° that corresponded with the lines found in pure Gelucire 44/14. The same was true for the TPGS formulation prepared by rotavap method. The CBZ/PVP K30/TPGS-SCP formulation did not show the lines corresponding to TPGS and was thus amorphous with respect to both CBZ and TPGS. This was in line with our findings from thermal analysis.

3.5. FTIR spectroscopy

FTIR studied were done to detect the possible interactions between the CBZ and PVP in the solid dispersions leading to amorphous state of CBZ. Fig. 6 shows the IR spectra of CBZ, PVP K30 and their formulations. The FTIR spectra of CBZ corresponded with those previously reported for Form III by various researchers (Krahn and Mielck, 1987; Lowes et al., 1987; Rustichelli et al., 2000). Characteristic bands of polymorph III were found at 3466 and 3161 cm^{-1}

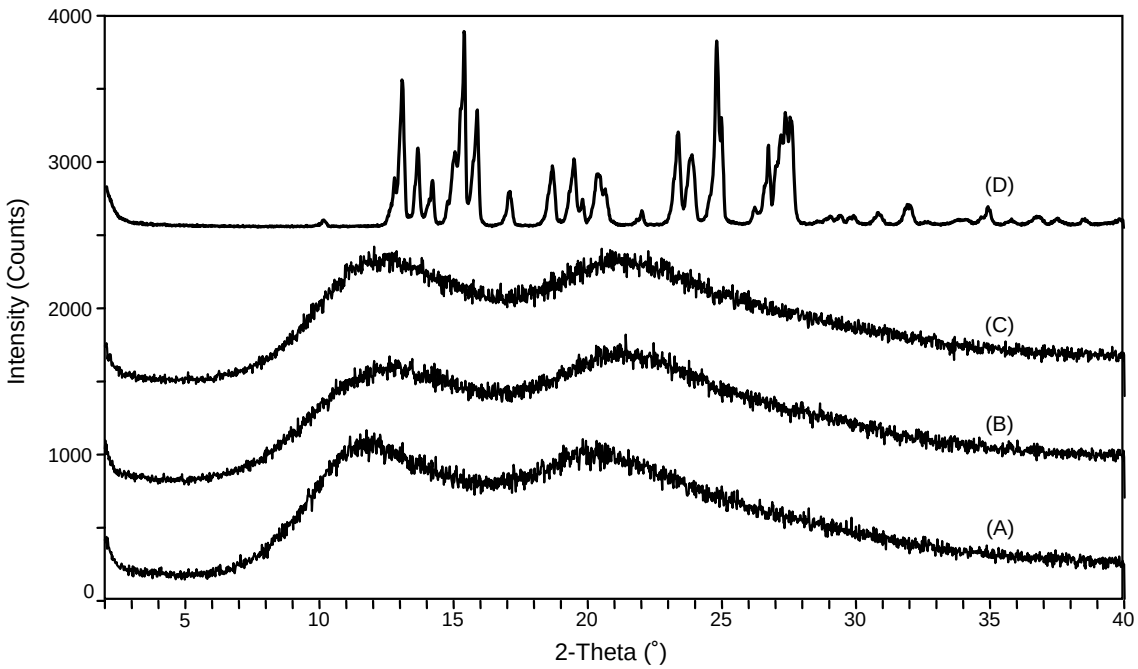

Fig. 4. XRD patterns of solid dispersions of CBZ. PVP K30 (A), CBZ/PVP K30-Rotavap (B), CBZ/PVP K30-SCP (C), and pure CBZ (D).

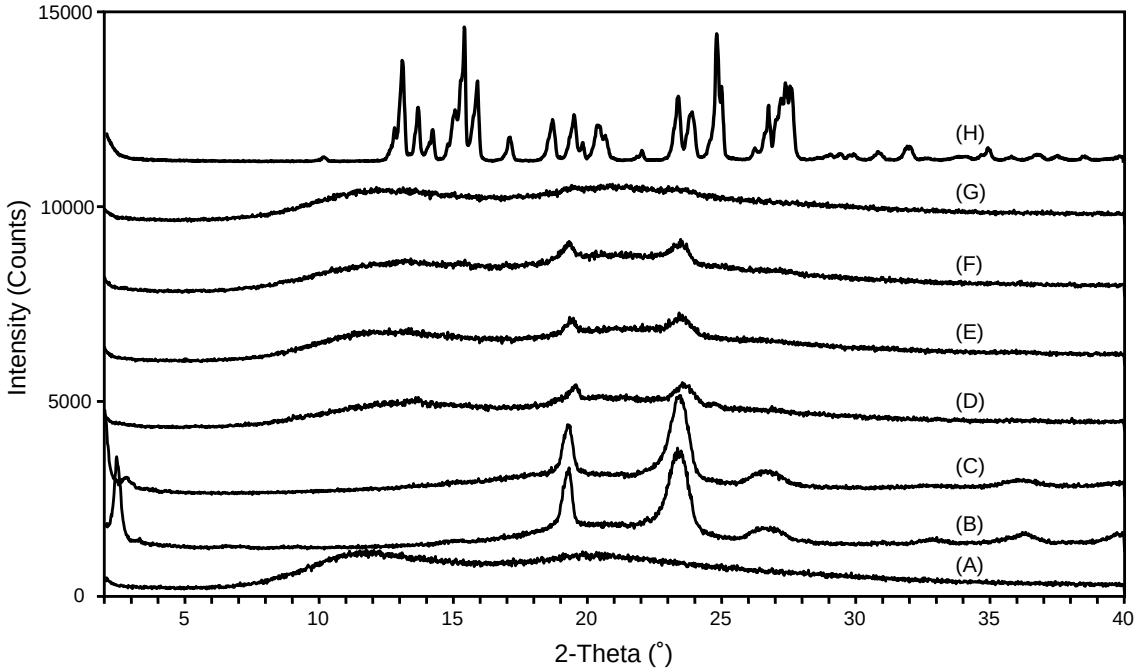

Fig. 5. XRD patterns of solid dispersions of CBZ. PVP K30 (A), Gelucire 44/14 (B), TPGS (C), CBZ/PVP K30/Gelucire 44/14-Rotavap (D), CBZ/PVP K30/Gelucire 44/14-SCP (E), CBZ/PVP K30/TPGS-Rotavap (F), CBZ/PVP K30/TPGS-SCP (G), and pure CBZ (H).

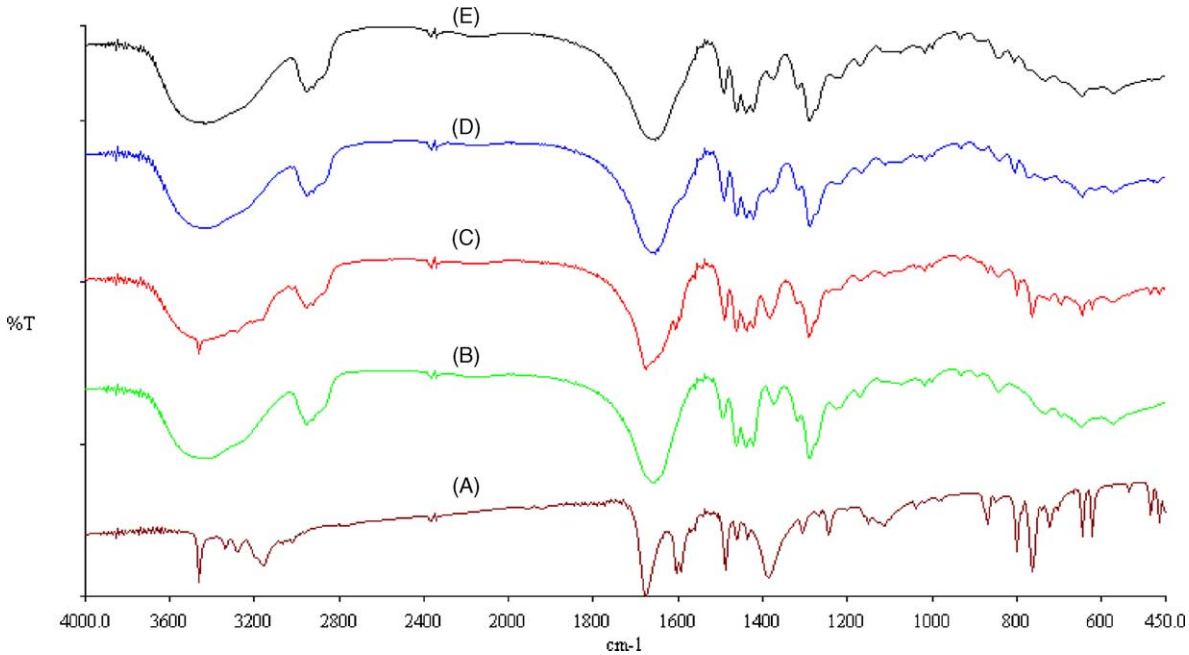

Fig. 6. FTIR spectra of solid dispersions of CBZ and PVP K30. Pure CBZ (A), PVP K30 (B), physical mixture of CBZ/PVP K30 (C), CBZ/PVP K30-Rotavap (D), and CBZ/PVP K30-SCP (E).

(–NH valence vibration), 1677 cm^{-1} (–CO–R vibration), 1605 and 1595 cm^{-1} (range of –C=C– and –C=O vibration and –NH deformation). The spectrum of PVP K30 showed, among others, important bands at 2955 cm^{-1} (C–H stretch) and 1654 cm^{-1} (C=O). A very broad band was also visible at 3435 cm^{-1} that was attributed to the presence of water (Van den Mooter et al., 1998) confirming the broad endotherm detected in the DSC experiments. In spite of the broad peak at 3435 cm^{-1} from PVP K30, the FTIR spectra of physical mixture still showed small peak of –NH valence vibration. Also –CO–R and –C=O vibration peaks were detected at the same position as that of drug. The FTIR spectra of physical mixtures seemed to be only a summation of drug and PVP K30 spectra. This result suggested that there was no interaction between drug and PVP K30 in physical mixture and CBZ maintained its crystallinity as observed in thermal analysis. If the drug and PVP K30 interact, then the functional groups in the FTIR spectra will show band shifts and broadening compared to the spectra of the pure drug and PVP (Silverstein et al., 1991). Each pyrrolidone moiety of PVP has two groups (=N– and C=O) that can potentially form hydrogen bond with the drug. However, steric hindrance precludes the involvement of nitrogen atom in intermolecular interactions, thus making the carbonyl group more favorable for hydrogen bonding (Taylor and Zografi, 1997). The two bands at 3466 and 3161 cm^{-1} corresponding to the symmetrical and asymmetrical N–H stretching vibrations of primary amide groups of CBZ, seen in physical mixture, are replaced by a broader band indicating the possible involvement of $–NH_2$ group in hydrogen bonding with C=O group of PVP K30. Similar interactions were seen in PVP K90 films containing CBZ (Nair et al., 2001). Thus, a combination of interaction and decreased mobility of CBZ during preparation of solid dispersions may be the cause for stable amorphous form of the drug inside the polymer.

A discussion of the advantages of supercritical fluid technology as compared to other methods for formulation of solid dispersions can be found in a recent review (Sethia and Squillante, 2003). Transformation of these reviewed methods from laboratory curiosity to viable commercial process requires scale-up to produce large batch sizes. The potential for scale up of supercritical-based processes has been long recognized by the food industry; the classic example being the decaffeination process which is totally enclosed, free of moving parts and constructed from easily maintained high-grade stainless steel. SCP methods adopted by pharmaceutical industrial facilities, such as Bradford Particle Design, Plc., report annual productions on the order of 1 ton of cGMP material and costs of manufacturing comparable to conventional techniques. Improvements in dissolution rate, speed and efficiency of drying, and stability of PVP dispersions prepared by supercritical processing illustrate the overwhelming advantages of this emerging method.

4. Conclusions

Solid dispersions of CBZ with PVP K30 with or without amphiphilic carrier gave higher intrinsic dissolution rates. In contrast to physical mixture, CBZ in the solid dispersions was present in amorphous form and was found to interact with PVP suggesting greater stability for the drug. The most important finding was that CBZ/PVP K30-SCP showed best IDR, i.e. a simpler formula gave better results compared to more complicated formulae with lipid carriers. Because lipid carriers are plagued by stability issues and are notoriously hard to manufacture by conventional methods, the simpler supercritical-based process is noteworthy. Presently in vivo studies are being performed to support our in vitro findings.

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