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RESEARCH PAPER

Carbamazepine/βCD/HPMC Solid Dispersions. II. Physical Characterization

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ABSTRACT

Solid dispersions containing carbamazepine (CBZ) associated with β-cyclodextrin (βCD) and/or hydroxypropyl methylcellulose were prepared by two different methods, spray-drying or physical mixture, and characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), infrared (IR) spectroscopy, and x-ray powder diffraction analysis (XRPD) studies. Scanning electron microscopy pictures showed that spray-drying produced a mixture of hollow, spherical, and partially shrunken microparticles of homogeneous materials, whereas the physical mixtures yielded heterogeneous systems in which all individual components could be identified. Thermal and IR analyses suggest the existence of a strong interaction between CBZ and excipients in spray-dried solid dispersions, but no CBZ polymorphic transition was detected by either IR spectroscopy or XRPD analysis after the spray-drying process.

INTRODUCTION

Carbamazepine (CBZ) is widely used in the treatment of psychomotor epilepsy[1] and is known to exist in several polymorphic forms.[2–5] It is very slightly soluble in water and has a dissolution rate-limited absorption.[6] One way to increase its dissolution and consequently improve its absorption is to associate CBZ to cyclodextrins, as previously reported for β-cyclodextrin (βCD)[7] and for its 2-hydroxypropyl derivative.[8] On the other hand, controlled release dosage forms containing CBZ

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have been currently investigated to avoid fluctuations in plasma concentrations, as well as to extend the drug action.[9–13] In this regard, hydroxypropyl methylcellulose (HPMC) has been used to extend drug release.[11,14] Thus, CBZ and βCD were associated with the aim of improving CBZ solubility when CBZ is released from HPMC matrices.

This work was designed to characterize solid dispersions that had CBZ associated with βCD and/or HPMC and to evaluate the influence of the dispersion method, spray-drying or simple physical mixture, on the interaction of the constituents, polymorphic transition of the drug, as well as on the morphological characteristics of the microparticles. Scanning electron microscopy (SEM), differential scanning calorimetry (DSC), infrared (IR) spectroscopy, and x-ray powder diffraction (XRPD) analysis were used to analyze the aforementioned characteristics.

EXPERIMENTAL

Materials

Carbamazepine was supplied by Galena (São Paulo, Brazil) and comminuted to obtain particles up to 250 μm. HPMC (Methocel K100LV®, Dow Chemical Company, Midland, MI) was supplied by Blanver (São Paulo, Brazil), and βCD was obtained from Roquette (Genay, France).

Methods

Preparation of Solid Dispersions

Carbamazepine solid dispersions containing either βCD or HPMC or both materials were prepared by two different methods. In the first one, five different aqueous dispersions with 2% (w/v) total solids were spray-dried in Büchi 190 equipment (Büchi, Göppingen, Germany) in the following operational conditions: aspirator scale value, 10; nozzle, 0.5 mm diameter; flow rate, 3 ± 0.5 mL/min; inlet temperature, 140 ± 5°C; and outlet temperature, 105 ± 5°C. During the drying process, the feed aqueous dispersions were kept at 40°C. Three batches of each formulation were prepared. The composition of each formulation is presented in Table 1, as well as the composition of the other three formulations (PMA, PMB, and PMC) prepared by the simple physical mixture of CBZ, βCD, and HPMC. In this second method, drug and excipients were blended for 30 min and ground in a mortar for 30 min. Three batches of each formulation were prepared.

Table 1. Composition of solid dispersions produced by either spray-drying or physical mixture.

Solid dispersion	CBZ [% (w/w)]	βCD [% (w/w)]	HPMC [% (w/w)]
Spray-drying			
SDA	50	15	35
SDB	50	25	25
SDC	50	35	15
SDCD	50	50	—
SDHPMC	50	—	50
Physical mixture			
PMA	50	15	35
PMB	50	25	25
PMC	50	35	15

SEM

The morphological characteristics of raw material and solid dispersions (SDHPMC, SDCD, SDA, SDB, SDC, PMA, PMB, and PMC) were analyzed by scanning electron photomicrographs, recorded in a JSM 5800 SEM, using a voltage of 15 or 20 kV. Samples were analyzed after gold sputtering.

DSC

Thermal analysis was recorded with PL-DSC (Polymer Laboratories) equipment. Samples corresponding to around 2.5 mg of CBZ were placed in open pans, and the operating conditions were as follows: heating rate, 10°C/min, from 0° to 300°C; N_2 gas environment; and temperature calibrated with indium (melting point 156°C).

IR Spectroscopy

The IR spectra were obtained using Shimadzu equipment. Blends corresponding to 1.5 mg of samples and 150.0 mg of KBr were gently produced and compressed. Spectra were recorded in the region of 4,600–400 cm^{-1}.

XRPD Analysis

Diffractograms were taken at room temperature with a Shimadzu XD-7A x-ray diffractometer. The setting parameters of the diffractometer were: Ni-filtered CuKα radiation ($\lambda = 1.5418$ Å); high voltage, 40 kV; tube current, 30 mA; step of 0.2° per minute; angular speed, 1° (2θ) per min; 1, 1, and 0.3° slits; and angular range, $2° < 2\theta < 45°$.

RESULTS AND DISCUSSION

Scanning Electron Photomicrographs (SEM)

The SEM of raw materials reveals different morphological characteristics of CBZ, ground CBZ, βCD, and HPMC (Fig. 1, A–D). Figure 2 (A–C) shows photomicrographs of the physical mixtures PMA, PMB, and PMC, in which it is possible to identify individual components—CBZ, βCD, and HPMC—used to prepare these solid dispersions.

Photomicrographs of spray-dried solid dispersions are given in Fig. 3 (A and B) (SDCD and SDHPMC) and Fig. 4 (nos. 1–3) (SDA, SDB, and SDC). The purpose of spray-drying CBZ with either βCD or HPMC, separately, was to investigate the influence of the excipient on particle shapes. In fact, the spray-dried microparticles containing CBZ and βCD (formulation SDCD) showed, predominantly

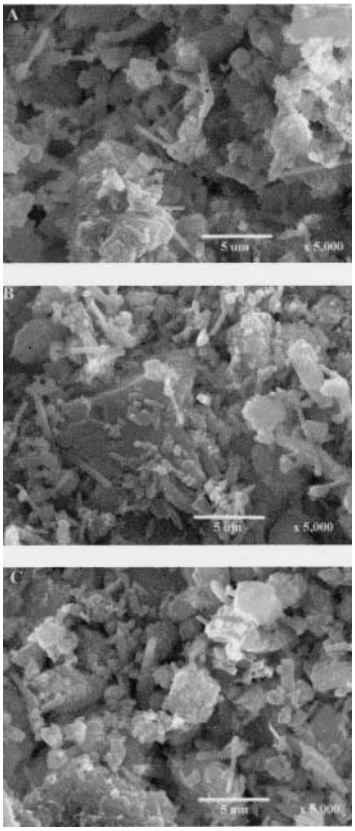

Figure 2. Photomicrographs of physical mixtures: (A) PMA (CBZ:βCD:HPMC, 50:15:35); (B) PMB (CBZ:βCD:HPMC, 50:25:25), and (C) PMC (CBZ:βCD:HPMC, 50:35:15).

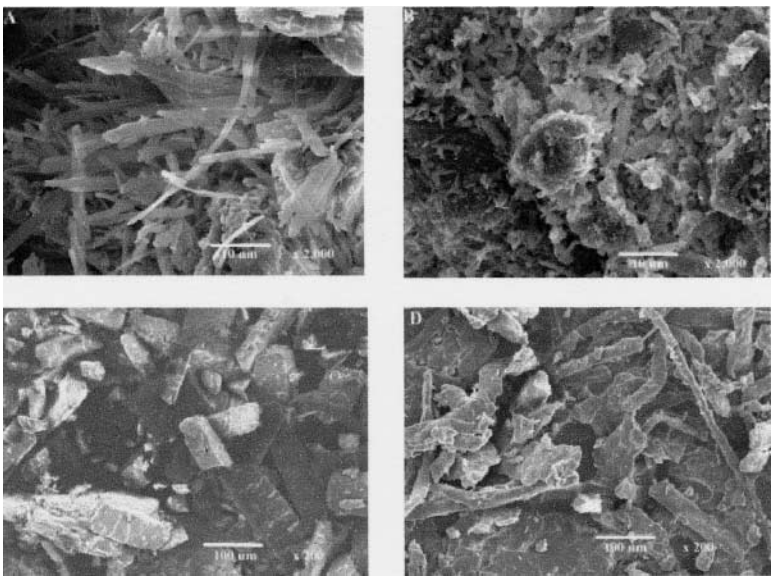

Figure 1. Photomicrographs of (A) CBZ, (B) ground CBZ, (C) βCD, and (D) HPMC.

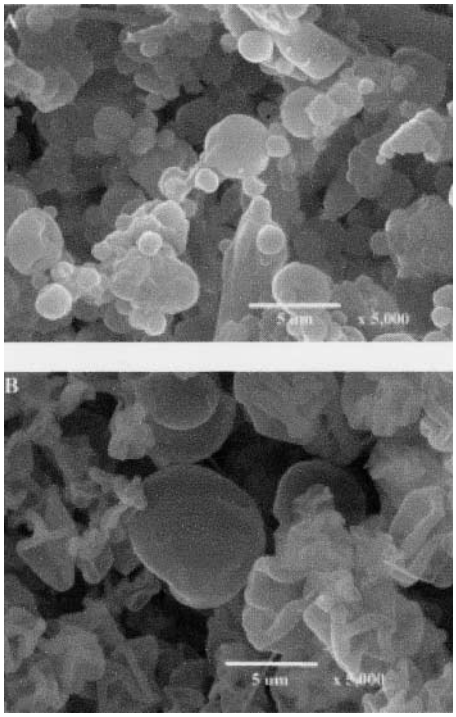

Figure 3. Photomicrographs of spray-dried microspheres: (A) SDCD (CBZ:βCD, 50:50) and (B) SDHPMC (CBZ:HPMC, 50:50).

spherical shape, whereas the microparticles containing CBZ and HPMC (formulation SDHPMC) showed more irregular shape and were partly shrunken. These two kinds of particle shapes can be observed in the formulations containing the association of CBZ, βCD, and HPMC (Fig. 4, nos. 1–3). However, it is important to observe that it was not possible to identify the raw materials in these spray-dried microparticles (Fig. 4, nos. 1–3), except for the presence of few crystals presenting a needle shape, like CBZ particles. In Fig. 4 (no. 1), it is possible to observe for SDA the presence of hollow particles. Similar structures have also been reported by Vidgren et al.[15] and Giunchedi et al.,[16] respectively, to microparticles of disodium cromoglycate and nonsteroidal anti-inflammatory drugs obtained by the spray-drying technique. Taken together, SEM demonstrates the existence of significant morphological differences among the microparticles according to the dispersion method used (i.e., in the case of spray-drying, a more homogeneous polymeric matrix was formed instead of the heterogeneous dispersions obtained by simple physical mixture of CBZ, βCD, and HPMC).

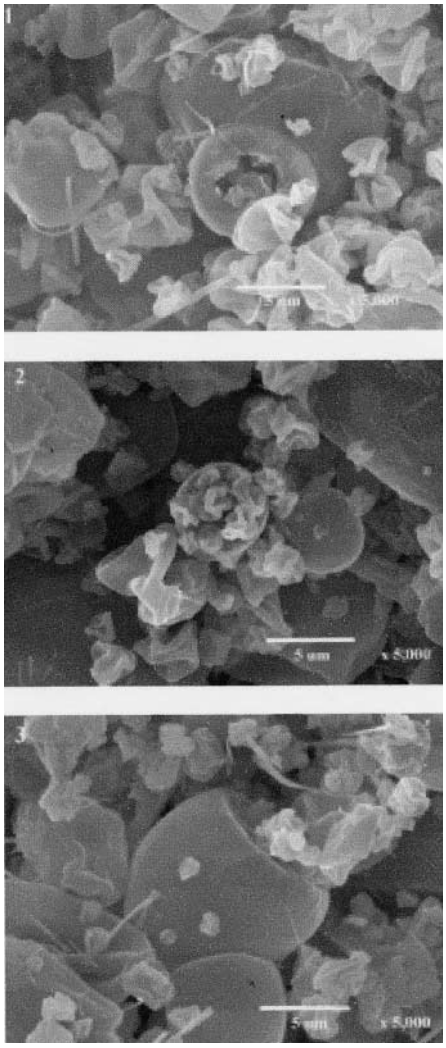

Figure 4. Photomicrographs of spray-dried microspheres: (1) SDA (CBZ:βCD:HPMC, 50:15:35), (2) SDB (CBZ:βCD:HPMC, 50:25:25), and (3) SDC (CBZ:βCD:HPMC, 50:35:15).

DSC

It is currently known that commercial monoclinic CBZ polymorph III (also called β form) melts at ~175°C. However, before it completely liquefies, a new solid phase begins to crystallize, and a new solid phase melts at ~190°C, which is classified as trigonal polymorph I, or as α form.[2,3] Figure 5A shows the DSC thermogram of ground CBZ, which was used as raw material for all formulations. Based on the previous statement, the sharp peak at ~190°C could represent the melting point of form I. Nevertheless, it is not possible to state that this

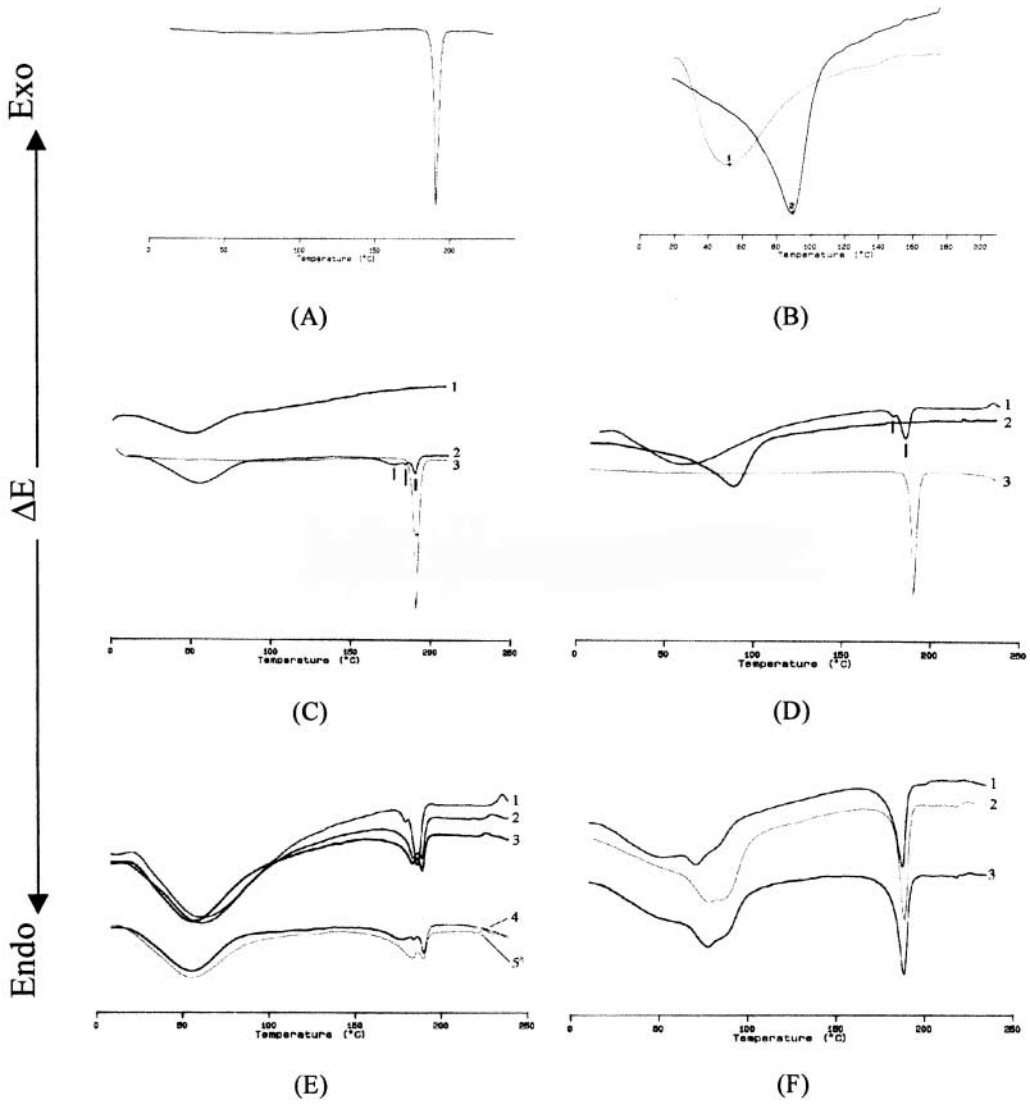

Figure 5. DSC of (A) ground CBZ, (B_1) spray-dried βCD, (B_2) βCD, (C_1) HPMC, (C_2) SDHPMC (spray-dried CBZ:HPMC, 50:50), (C_3) ground CBZ, (D_1) SDCD (spray-dried CBZ:βCD, 50:50), (D_2) βCD, (D_3) ground CBZ, (E_1) SDCD, (E_2) SDC (spray-dried CBZ:βCD:HPMC, 50:35:15), (E_3) SDB (spray-dried CBZ:βCD:HPMC, 50:25:25), (E_4) SDHPMC, (E_5) SDA (spray-dried CBZ:βCD:HPMC, 50:15:35), (F_1) PMA (physical mixture of CBZ:βCD:HPMC, 50:15:35), (F_2) PMC (physical mixture of CBZ:βCD:HPMC, 50:35:15), and (F_3) PMB (physical mixture of CBZ:βCD:HPMC, 50:25:25).

sample is constituted by form I, because Lowes and coworkers,[2] as well as Rustichelli and coworkers,[4] have already verified the influence of the operative heating rate on thermal analysis of CBZ. As reported by Lowes and coworkers,[2] the DSC thermograms of monoclinic CBZ (β form) recorded at 10°C/min exhibited only one sharp peak at ~192°C. At a heating range of 30°C/min, an additional peak was present at ~177°C. On the other hand, the DSC thermograms for the α form recorded at 10° and 30°C/min exhibited only one peak, at 191°–192°C. According to Rustichelli and coworkers,[4] slow heating rates lead to a sharp endotherm (melting of form I). Otherwise, an extensive melting process is observed due to the melting of form III, followed by recrystallization and further melting of form I. Because DSC itself does not provide enough evidence of the existence of polymorphism, as stated by

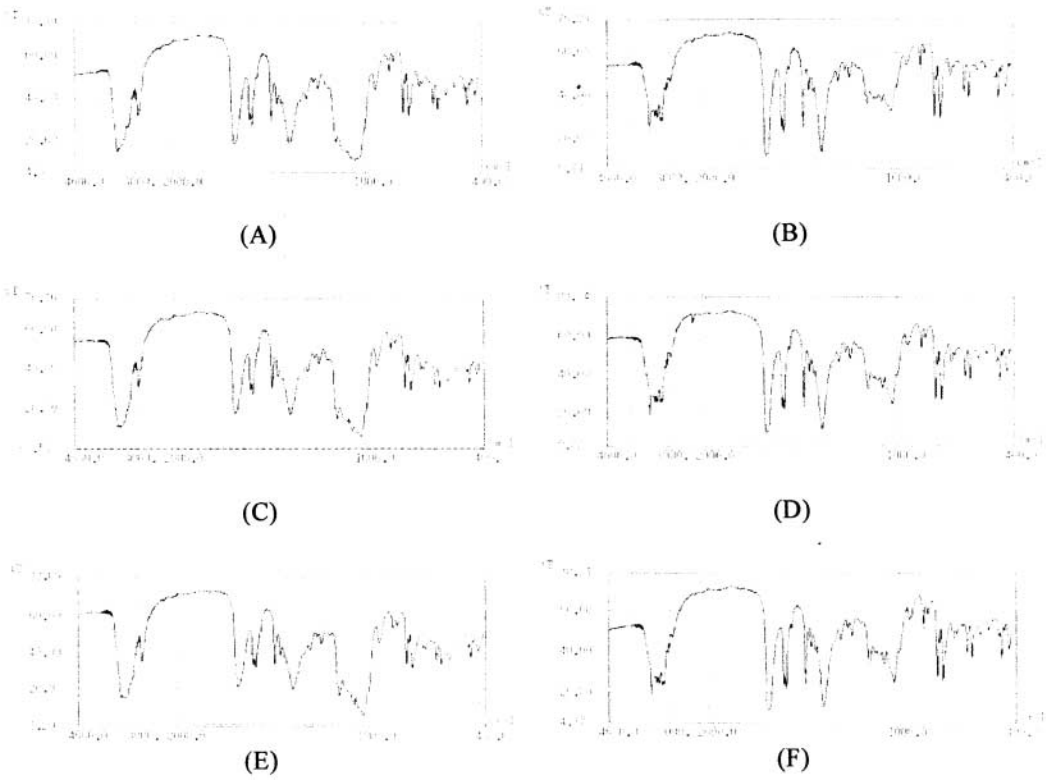

Figure 6. IR spectra of (A) SDA (spray-dried CBZ:βCD:HPMC, 50:15:35), (B) PMA (physical mixture of CBZ:βCD:HPMC, 50:15:35), (C) SDB (spray-dried CBZ:βCD:HPMC, 50:25:25), (D) PMB (physical mixture of CBZ:βCD:HPMC, 50:25:25) (spray-dried CBZ:βCD:HPMC, 50:25:25), (E) SDC (spray-dried CBZ:βCD:HPMC, 50:35:15), and (F) PMC (physical mixture of CBZ:βCD:HPMC, 50:35:15).

Rustichelli and coworkers,[4] IR spectroscopy and XRPD analysis were preferred to analyze this phenomenon, and the results are presented in the next section. DSC analysis was therefore focused on showing CBZ/βCD/HPMC interactions in both spray-dried and physical mixtures.

Figure $5B_{1-2}$ presents βCD dehydration endotherm (no. 2), which usually starts at 50°C. Nevertheless, when βCD is spray-dried (no. 1), this temperature shifts to 20°C. The same pattern was observed for βCD heated up to 200°C.[17] The difference in shapes was attributed to the release of water from the cyclodextrin cavity, which occurred during heat treatment. Figure $5C_{1-3}$ presents the thermograms of HPMC (C_1), formulation SDHPMC (C_2), and ground CBZ (C_3). The SDHPMC thermogram illustrates the broad depression that corresponds to the loss of water from HPMC. It is worth citing that dehydration of HPMC (no. 1) takes place in the same graph position, regardless of whether it was spray-dried or not. Nevertheless, the main interesting finding is the presence of three weak endothermic peaks at 177°, 184°, and 190°C. Once the amount of CBZ in this sample corresponded to the same 2.5 mg of pure ground CBZ, the thermogram suggests the existence of a strong interaction between HPMC and CBZ in the spray-dried formulation. The same pattern could be observed in formulation SDCD (Fig. $5D_1$) even though only two weak endothermic points could be observed at 179° and 186°C. It is also worth noting the presence of a different βCD pattern, when it is in a spray-dried matrix (as shown in Fig. $5B_1$).

Figure $5E_{1-5}$ shows the thermograms of all spray-dried formulations, SDCD (E_1), SDC (E_2), SDB (E_3), SDHPMC (E_4), and SDA (E_5), respectively. In addition to the broad peaks of HPMC and βCD dehydration, which should have overlapped, formulations SDA, SDB, and SDC displayed two more weak endothermic depressions, at ~183° and ~189°C.

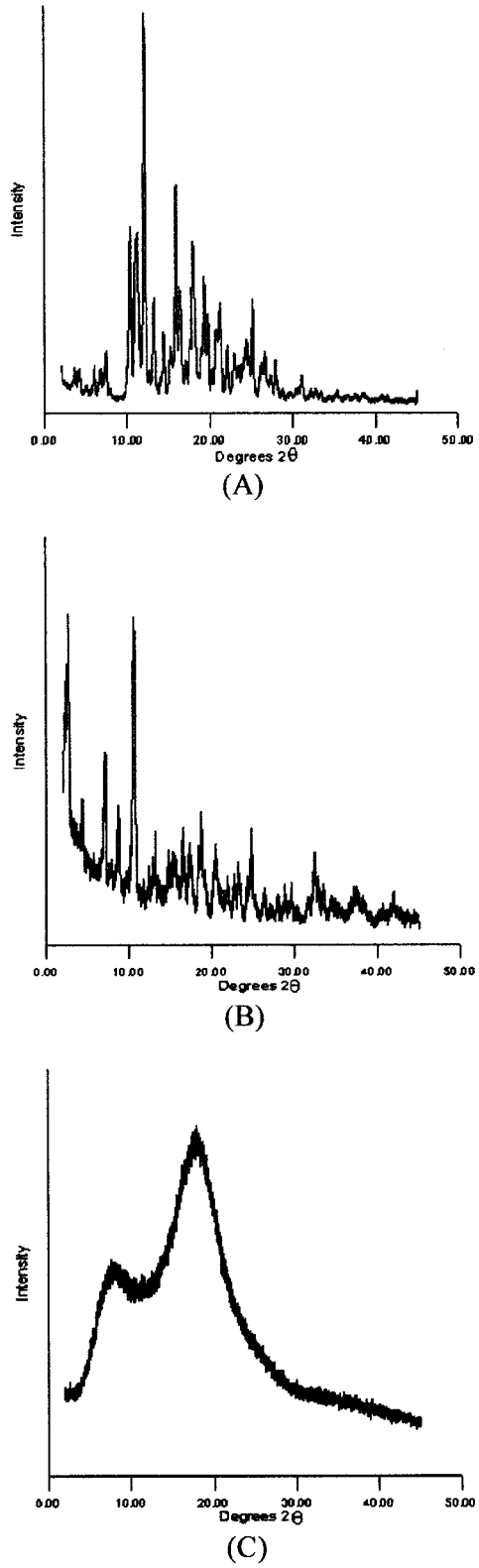

Figure 7. Patterns (XRPD) of (A) ground CBZ, (B) βCD, and (C) HPMC.

As in SDCD (E_1) and SDHPMC (E_4), those peaks are split and, therefore, decreased in intensity, which indicate an interaction βCD–CBZ and/or a polymorph modification of CBZ in the spray-dried matrices. The hypothesis of polymorph transition was investigated by XRPD analysis, and the results are presented further. On the other hand, formulations PMA, PMB, and PMC (Fig. $5F_{1-3}$) displayed only one endothermic band at ~188°C, whose intensity was nearly the same as that of the CBZ sharp peak. In addition, the large bands (20°–100°C) are broader and bimodal when compared with the bands corresponding to HPMC and βCD in spray-dried formulations.

Taken together, DSC data of CBZ solid dispersions revealed a stronger interaction between CBZ and excipients in the spray-dried formulations than that in formulations obtained by physical mixture. This can be partially responsible for the more homogeneous release profiles, as previously reported in part I.

IR Spectroscopy

The IR spectra of CBZ presented characteristic signals at 3,474 cm^{-1}, 1,678 cm^{-1}, 1,393 cm^{-1}, 1,271 cm^{-1}, and 1,250 cm^{-1}, which are quite the same described for polymorph II.[4] The presence of a −NH valence vibration at an intermediate wave number (3,474 cm^{-1}) was the major indicative sign that CBZ could be neither polymorph III (3,464 cm^{-1}) or polymorph I (3,484 cm^{-1}). IR spectra of both βCD and HPMC display a large band and a peak in the region of 2,900–3,900 cm^{-1}, a short band between 1,600 and 1,750 cm^{-1}, and a large band, which presents three distinct peaks in βCD spectrum, in the region of 900–1,200 cm^{-1}.

Figure 6 (A–F) shows IR spectra of spray-dried and physical mixture formulations. Because no shift of band positions was observed, no polymorphic changes seem to be characterized. Nevertheless, IR analysis supports DSC data, which indicated a stronger interaction between CBZ, βCD, and HPMC in the spray-dried formulations. Analyzing Fig. 6 (A and B), it is possible to observe that, while in SDA, the peak at 3,474 cm^{-1} was completely hidden by the broad band of βCD/HPMC. This peak could be detected in PMA, despite being partially covered by the same band. Besides that, the peaks at 1,678 cm^{-1} and 1,599 cm^{-1} are less intense in formulation SDA. Additionally, the band corresponding to

either βCD or HPMC at 900–1,200 cm^{-1} is much more intense in SDA than it is in formulation PMA. This could be explained by an interaction between both excipients after spray-drying. Nevertheless, SDHPMC formulation presented the same band broadening, whereas SDCD formulation did not (spectra not shown). Thus, the enlargement and intensity of the band denotes that the spray-drying process may cause a stronger interaction between CBZ and HPMC. The same pattern described for SDA/PMA was observed comparing SDB/PMB and SDC/PMC formulations, with very slight differences, such as a more pronounced presence of βCD characteristic peaks in the formulation that contains 35% of this excipient (SDC/PMC).

XRPD Analysis

A ground CBZ XRPD pattern is presented in Fig. 7A. The absence of a characteristic intense peak at 5° 2θ excluded the possibility of the presence of α form. The observed characteristic peaks at 17.9° and 21.2° 2θ, which are absent in polymorph III (β form), indicate that the raw material could be polymorph II,[4] confirming IR analysis. Once the same pattern was obtained with nonground CBZ, we infer that, in this case, grinding did not cause any polymorphic modification. Figure 7 (B and C) shows the diffractograms of βCD and HPMC, respectively. As observed, βCD has high intensity peaks at 2.7°, 7.0°, and 10.6° 2θ, whereas HPMC presents a

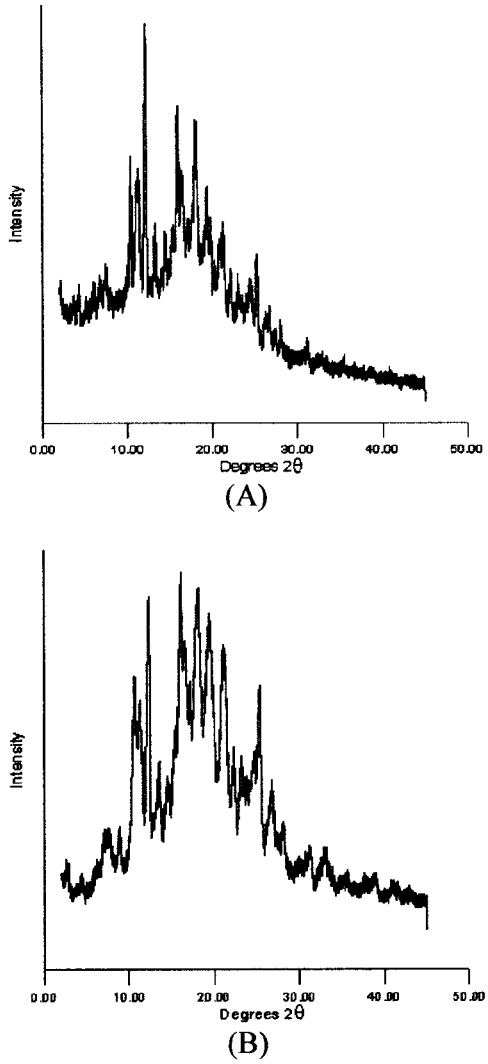

Figure 8. Patterns (XRPD) of (A) SDA and (B) PMA.

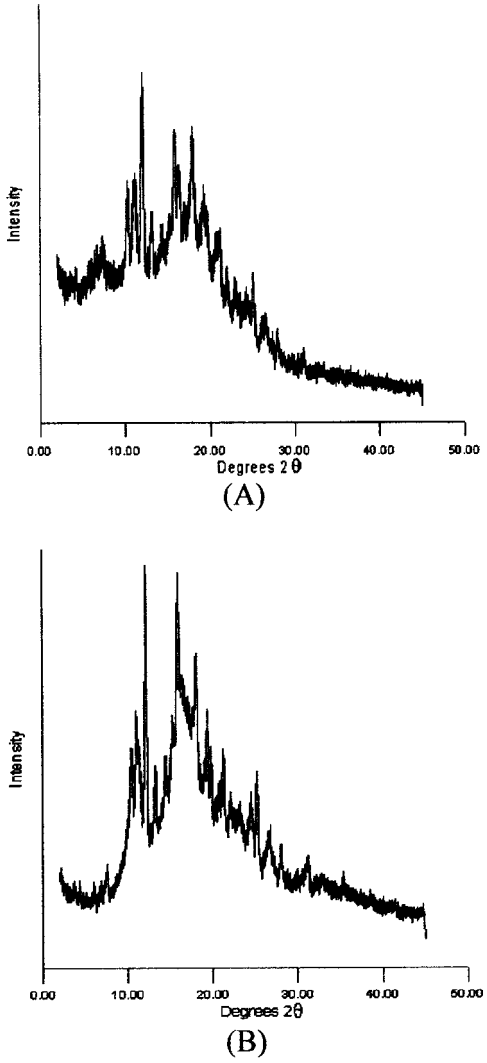

Figure 9. Patterns (XRPD) of (A) SDHPMC and (B) SDCD.

very amorphous structure. The XRPD patterns observed in both SDA and PMA formulations [Fig. 8 (A and B)] were found to be the same and did not present any βCD characteristic peak. They are also less crystalline than CBZ, demonstrating the influence of HPMC on the samples. The same pattern was observed comparing SDB/PMB and SDC/PMC. SDHPMC (Fig. 9A) also presented quite an amorphous structure, and βCD peaks were not available in the SDCD diffractogram (Fig. 9B). Maintenance of the CBZ original polymorphic form, which was characterized as being polymorph II, does not give support to the hypothesis of polymorph transition of CBZ in spray-dried formulations.

CONCLUSIONS

Results obtained in this study demonstrated that, in both spray-dried and solid-state mixtures, no polymorphic transition of CBZ was observed. Whereas the physical mixture produced heterogeneous systems, dispersion by spray-drying produced microparticles of homogeneous matrices. Stronger interactions between CBZ, βCD, and HPMC were observed in spray-dried solid dispersions rather than in physical mixtures. In part I, CBZ microparticles obtained by spray-drying presented more regular dissolution profiles, and these results were corroborated by the physical characterization presented in the current study.

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