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Research paper

Influence of β-cyclodextrin complexation on carbamazepine release from hydroxypropyl methylcellulose matrix tablets

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Abstract

The in vitro release profiles of carbamazepine and β-cyclodextrin either complexed or simply mixed and subsequently incorporated in hydrophilic matrix tablets containing 15 or 30% hydroxypropyl methylcellulose were evaluated. Solubility studies revealed a linear relationship between the increase in carbamazepine solubility and the increase in β-cyclodextrin concentration. Drying methods (spray-drying and freeze-drying) were used to obtain carbamazepine/β-cyclodextrin solid complexes in order to prepare tablets. The results demonstrated that matrix tablets containing carbamazepine/β-cyclodextrin solid complexes displayed faster carbamazepine and β-cyclodextrin release compared to that containing simple physical mixture. Gelling and matrix formation was impaired in formulation containing 15% hydroxypropyl methylcellulose and spray-dried complex. The comparison of spray-drying and freeze-drying revealed no significant influence of both drying methods on carbamazepine and β-cyclodextrin dissolution rate when carbamazepine/β-cyclodextrin complexes were incorporated in 30% hydroxypropyl methylcellulose matrix tablets. The results point to the possibility of modulating carbamazepine release using a hydroxypropyl methylcellulose matrix associated to the drug complexed with β-cyclodextrin.

Keywords: Carbamazepine; β-Cyclodextrin; Hydroxypropyl methylcellulose; Complexes; In vitro dissolution; Matrix tablets; Spray-drying; Freeze-drying

1. Introduction

Cyclodextrins can be used to increase the solubility and bioavailability of many low water soluble drugs. The incorporation of cyclodextrins into polymeric drug delivery systems can influence the mechanisms by which drug is released. They have the potential to enhance drug release by increasing the concentration of diffusible species within the matrix. On the other hand, they may also enhance drug release by acting as channeling or wicking agents or by promoting erosion of the matrix [1]. Possible in situ formation of a drug-cyclodextrin complex, and an improvement in apparent drug solubility, has been suggested by some authors [2,3]. Nevertheless, it is difficult to evaluate whether both free and complexed drug are capable of diffusing from the matrix. The investigation of whether cyclodextrin releases from the matrix in the same ratio as the drug does is also arduous due to the fact that cyclodextrins cannot be easily assayed by simple methods, as ultraviolet spectrophotometry. Recently, Rao and co-workers [2] used an indirect fluorescence method to assess $(SBE)_{7M}$-β-cyclodextrin release from hydroxypropyl methylcellulose matrix tablets and found some differences between formulations containing either pre-complexed or physical mixtures of prednisolone and this cyclodextrin. High-performance liquid chromatography (HPLC) coupled to refractive index detector (RID) is universally applicable, but only moderately sensitive. The detection limit depends on the retention time and column quality. Methods consisting of amino-bonded stationary phases and refractive index detector [4], as well as classical reversed phase chromatography with polarimetric detector [5] have been successfully employed on β-cyclodextrin determination (βCD), depending on the concentration range of interest.

Carbamazepine (CBZ) is an anticonvulsant drug practically insoluble in water (<200 μg/ml) and its absorption is limited by the dissolution rate [6]. CBZ was found to form an inclusion complex with βCD [7], which could improve the biological performance of the drug. On the other hand, hydroxypropyl methylcellulose (HPMC) has been used with the aim to extend CBZ release [8–10], once the drug is also characterized by a short half-life on chronic dosing, due to

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autoinduction of its metabolism. Giunchedi and co-workers [8] have pointed out that a sustained release formulation should be able to smooth out plasma fluctuations and side effects of the drug. In this regard, the possibility of modulating CBZ release using the drug complexed with βCD and associated to a HPMC matrix seems to be an approach to obtain, besides drug release control, better bioavailability.

The main purpose of this work is, therefore, to evaluate the in vitro release profiles of CBZ and βCD either complexed or simply mixed in hydrophilic matrix tablets containing 15 or 30% of HPMC (Methocel K 100 LV®). Following optimization of an HPLC/RID method to achieve βCD assessment in a low concentration range, the rate of βCD release from the matrix tablets could be also investigated. An additional objective of this work was to investigate the influence of the drying methods used to obtain CBZ/βCD solid complexes, spray-drying and freeze-drying, on the dissolution rate of CBZ and βCD from HPMC matrix tablets.

2. Materials and methods

2.1. Materials

Carbamazepine was purchased from DEG (São Paulo, Brazil). βCD was obtained from Roquette (France) and HPMC (Methocel K100LV®, DOW Chemical Company) was supplied by Blanver (São Paulo, Brazil). All reagents were of analytical quality.

2.2. Phase solubility studies

Solubility studies were carried out according to the method reported by Higuchi and Connors [11]. Nineteen fold excess amounts of CBZ (16 mM) were added to water containing increasing concentrations of βCD (8–48 mM), performing the following CBZ:βCD molar ratios: 1:0.5, 1:1, 1:2 and 1:3. At least tree samples of each molar ratio were prepared. The suspensions were stirred for 2 days at 37°C, after which equilibrium was reached. After cooling to room temperature (25°C), samples were filtered. The drug present in the liquid phase was assayed by ultraviolet spectrophotometry at 286 nm.

Table 1
Formula composition (%, w/w)[a]

Formulation	CBZ/βCD complex	CBZ + βCD	HPMC	MgSte[b]
SD 15	84	–	15	1
FD 15	84	–	15	1
PM 15	–	84	15	1
SD 30	69	–	30	1
FD 30	69	–	30	1
PM 30	–	69	30	1

[a] SD15 and SD30: spray-dried complex; FD15 and FD30: freeze-dried complex; and PM15 and PM30: physical mixture.
[b] Magnesium stearate.

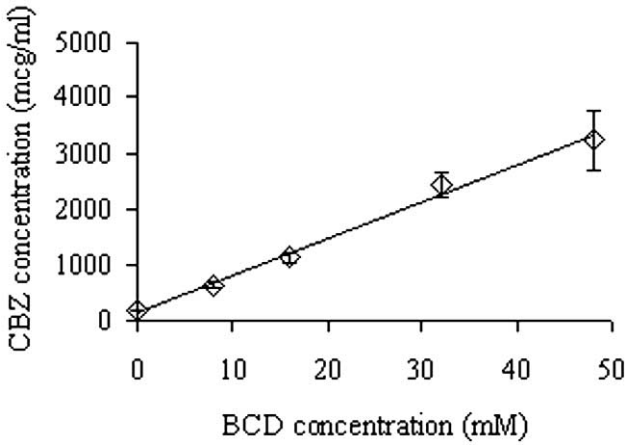

Fig. 1. Phase solubility diagram of CBZ:βCD in aqueous media at 25°C.

2.3. Preparation of CBZ/βCD solid complex

Preparation of the complex followed the same procedure as for the solubility study, using a molar ratio of 1:1 (3.78 g CBZ: 18.158 g βCD), which in fact produces a solution containing approximately 1.1 mg of CBZ complexed with βCD per ml of solution. One batch of this solution was subsequently spray-dried in a Büchi 190 equipment and another was freeze-dried in a Edwards Freeze Dryer. CBZ content in the solid complexes was assayed by a spectrophotometric method at 286 nm.

2.4. Preparation of physical mixtures

Drug and excipients were first blended for 10 min and then mixed with magnesium stearate for further 5 min, according to the compositions described in Table 1. The amounts are presented as percentage in order to clear up

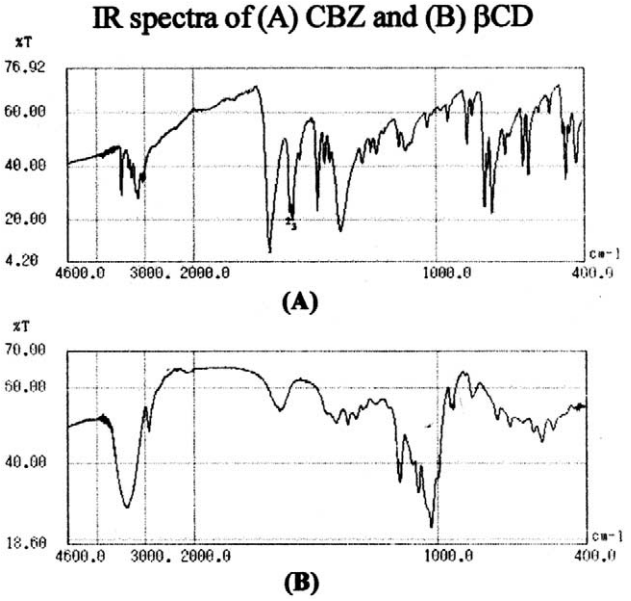

Fig. 2. IR spectra of (A) CBZ; and (B) βCD.

the data. The required CBZ loads should correspond to the amount present in the solid complexes, that is, 20 mg of CBZ correspond to approximately 266 mg of βCD. CBZ content in the mixtures was further assayed by a spectrophotometric method at 286 nm.

2.5. Infrared spectroscopy (IR)

Complex formation was evaluated by comparing the IR spectra of the solid complexes and of a simple physical mixture containing the same amount of CBZ assayed in the spray-dried or freeze-dried powders. Samples were analyzed on a Shimadzu DR-8001 equipment. Blends corresponding to 1.5 mg of samples and 150.0 mg of KBr were produced, compressed and recorded in the region of 4600–400 cm^{-1}.

2.6. Differential scanning calorimetry (DSC)

Complex formation was also investigated by DSC. Ther-

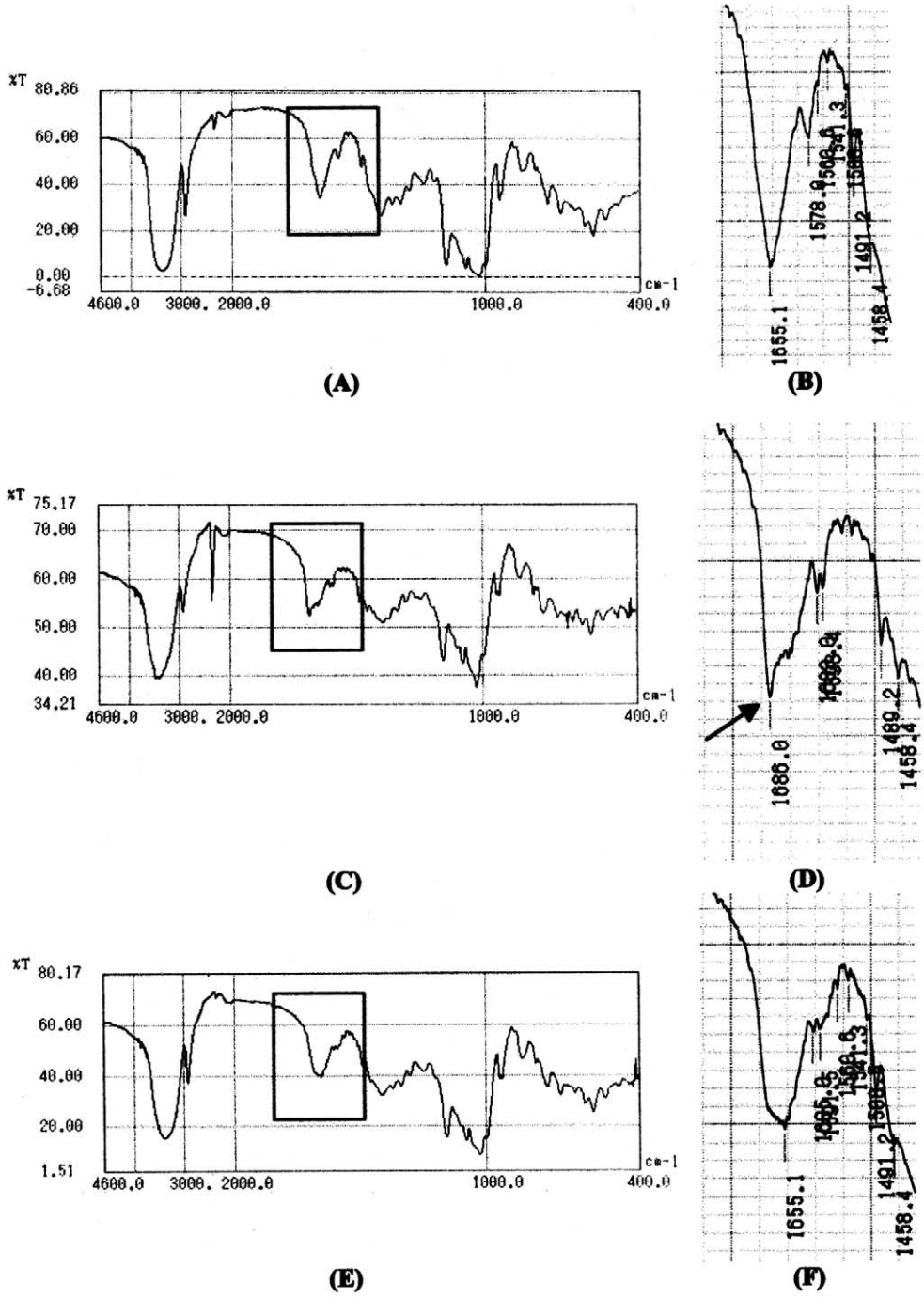

Fig. 3. IR spectra of (A) and (B) CBZ/βCD spray-dried complex; (C) and (D) CBZ/βCD physical mixture; and (E) and (F) CBZ/βCD freeze-dried complex.

mal analysis was performed on a DSC-4 Perkin Elmer. Samples (10.0 mg) of solid complexes and simple physical mixture contained the same amount of CBZ. CBZ and βCD samples were of 4.0 and 10.0 mg, respectively. The samples were heated at a scanning rate of 10°C/min, from 40°C up to 250°C. Temperature calibration was performed using Indium as standard.

2.7. Preparation of tablets

The powder mixtures (Table 1) were directly compressed in a single punch Korsch EK-0 machine, equipped with flat-punches of 12.0 mm, in order to manufacture tablets weighing 398 ± 49 mg with a thickness of 4.1 ± 0.8 mm. The amount of drug and βCD in the physical mixtures corresponded to that assayed in the complex, and all tablets contained 20 mg of CBZ. By holding CBZ content constant, and avoiding the use of fillers, the surface area of the compacts varied, as stated above. The composition of the tablets is described in Table 1.

2.8. In vitro dissolution testing

Release tests were carried out in a Pharma Test dissolution tester (USP XXII) coupled to a Hewlett Packard 8452A spectrophotometer. The paddle speed was set at 75 rpm and 1000 ml of distilled water was employed, as dissolution medium at 37°C. In order to avoid floating, tablets were placed in baskets (mesh diameter 1 mm), which were placed at the bottom of the vessels. Samples (six replicates) were automatically collected each 30 min, during the first 2 h, and then each 1 h, and filtered through 0.45 μm. CBZ was assayed by spectrophotometric method at 286 nm using a multicell transport whereas βCD was assayed by HPLC method.

2.9. βCD assay

An HPLC method was validated following ICH guidelines [12] for the quantitative analysis of βCD released during dissolution tests. Filtered samples were injected (50 μl) in a Shimadzu CTO-10A HPLC coupled to a RID-10 A refractive index detector. The analytical system consisted of an octadecyl column (Nova-Pak®), 3.9 × 300 mm, 4 μm, mobile phase, 93% water, 7% ethanol, flow rate of 0.85 ml/min. Retention time of βCD was 5.5 min. Standard curves for βCD were linear ($r^2 > 0.999$) over the examined concentration ranges of βCD: 27–324 μg/ml. The linearity was not influenced by the presence of HPMC on a concentration up to 120%, and the specificity of the analytical procedure confirmed βCD recoveries of 101.8 (±2.1%). Detection and quantitation limits were determined based on the standard deviation of the response and the slope of the calibration curve, and they were found to be 5.8 and 17.5 μg/ml, respectively.

2.10. Scanning electron microscopy (SEM)

Raw material, physical mixture and solid complexes were analyzed by scanning electron photomicrographs, recorded in a JSM 5800 SEM, using a voltage of 10 or 20 kV, after they have been gold sputtered.

3. Results and discussion

Fig. 1 shows the phase solubility diagram of CBZ/βCD, which was obtained by plotting the increase in CBZ solubility as a function of βCD concentration. The graphical representation reveals a linear relationship ($R^2 > 0.99$) between the increase in CBZ solubility and the increase in βCD concentration. The curve can be classified as the A_L type, according to Higuchi and Connors [11]. The extent of complexation is characterized by the apparent 1:1 stability constant Ks, which was calculated based on the solubility diagram, using the equation described by Higuchi and Connors [11]. Ks value was found to be 376.5 M^{-1}, indicating a labile association of CBZ and βCD, which would be desirable in case only free drug is capable of leaving the matrix. These results are in agreement with the effect of βCD on the solubility of CBZ, reported by El-Nahhas [7], for smaller molar portions (2–25 mM) of βCD and approximately fourfold excess amount of CBZ, resulting in a stability constant of 404 mol^{-1}.

The preparation of CBZ/βCD solid complexes yielded, either by spray-drying or by freeze-drying, powders containing approximately 7.0% of CBZ. In this way, the actual stoichiometry ratio of the complex, after all steps, was 1:2.8 CBZ:βCD.

IR spectra of CBZ and βCD are shown in Fig. 2. In Fig. 2A, bands characteristic of CBZ are observed at 3484 cm^{-1} (—NH valence vibration), 1686 cm^{-1} (—CO—R vibration), 1603 and 1593 cm^{-1} (range of —C=C— and —C=O vibra-

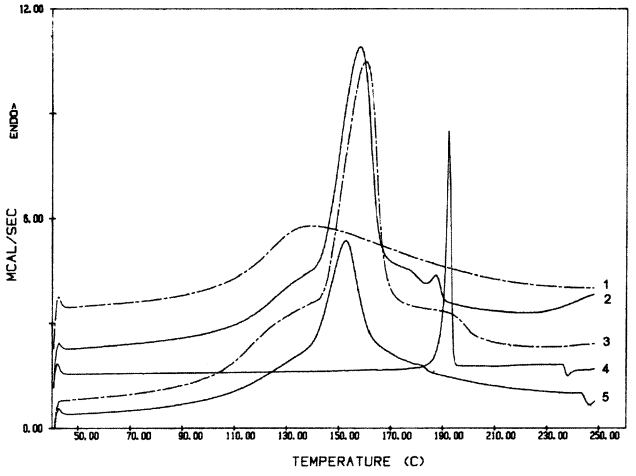

Fig. 4. Differential scanning calorimetry (DSC) of: (1) CBZ:βCD spray-dried complex; (2) CBZ:βCD physical mixture; (3) βCD; (4) CBZ; and (5) CBZ:βCD freeze-dried complex.

tion and —NH deformation), and 1395 cm^{-1} [13]. βCD spectrum (Fig. 2B) presents a large band and a peak in the region of 2900–3900 cm^{-1}, a shorter band between 1600 and 1700 cm^{-1}, and a large band which displays distinct peaks, in the region of 900–1200 cm^{-1}. Fig. 3 presents IR spectra of the spray-dried complex (A), physical mixture (C) and freeze-dried complex (E). As one can observe, βCD broad bands overlap CBZ main characteristic peaks. This was expected since CBZ content is around 7.0% in the freeze-dried complex. Nevertheless, the CBZ characteristic peak at 1686 cm^{-1} could only be detected in the physical mixture that contains the same amount of CBZ in the complexes (detail pictures B, D and F).

Thermal analysis was carried out on CBZ, βCD, spray-dried complex, freeze-dried complex and physical mixture. Respective thermograms are shown in Fig. 4. CBZ thermogram (4) presents an endothermic peak at 192°C, which represents the melting point of the drug. The broad band observed in βCD thermogram (3) corresponds to the loss of water. The thermogram of the physical mixture (2) presents two peaks corresponding, respectively, to the dehydration band of βCD as well as to the melting point of CBZ, which is reduced and to some extent displaced. The peak reduction may be explained by the small CBZ content (7.0%), but its displacement is supposed to be caused by an interaction with the cyclodextrin, during heating. The thermograms of both spray-dried (1) and freeze-dried (5) complexes displayed no peak corresponding to CBZ melting. It is

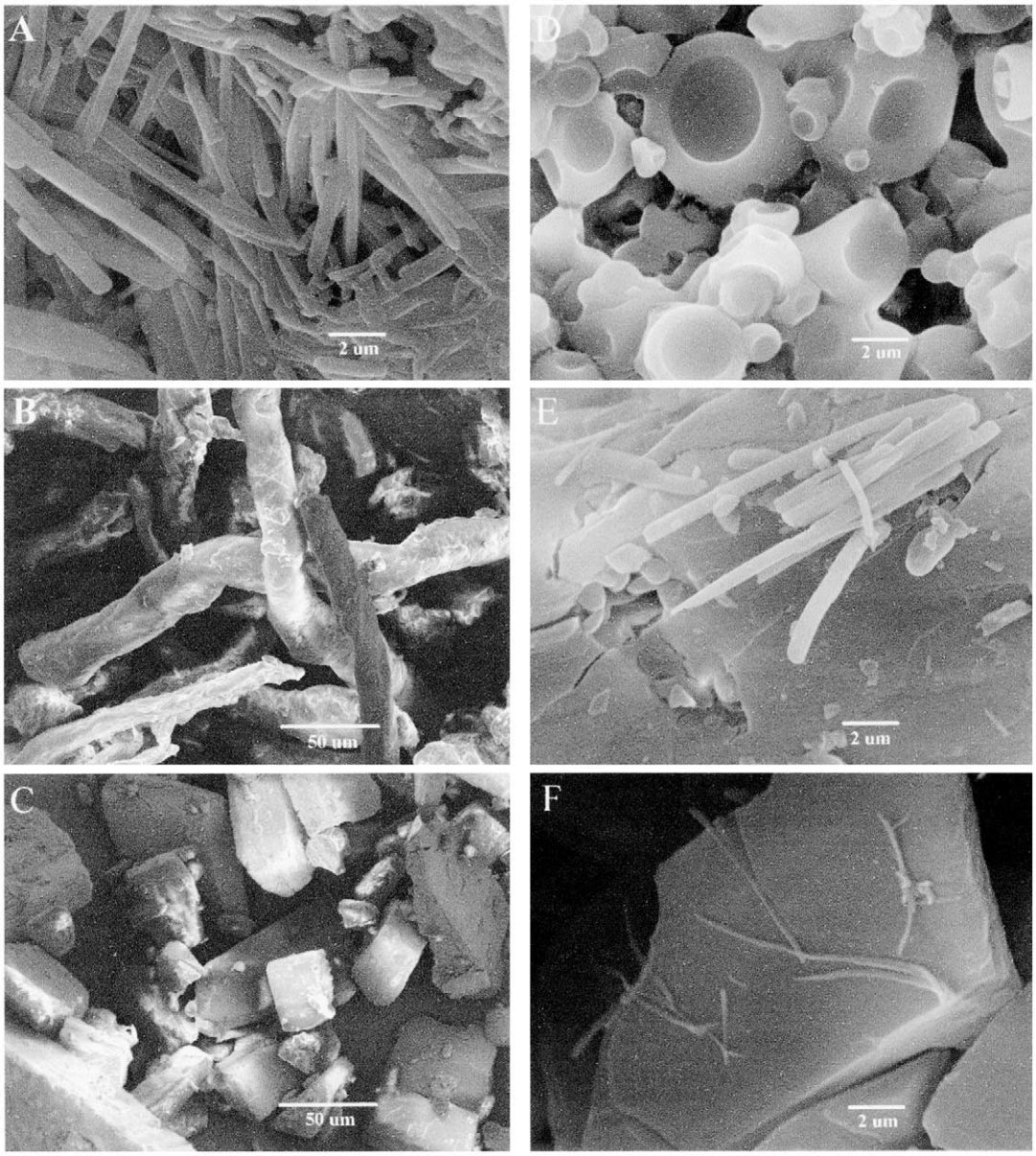

Fig. 5. Photomicrographs of (A) carbamazepine; (B) hydroxypropyl methylcellulose; (C) β-cyclodextrin; (D) spray-dried complex; (E) simple physical mixture of CBZ; and βCD and (F) freeze-dried complex. B and C magnification 500×. A, D, B and D magnification 7000×.

worth mentioning that the dehydration region of the spray-dried formulation shifted to lower temperatures. Such displacement was observed by Wulff and Aldén [14] for β-cyclodextrin heated up to 200°C. In the same way, the loss of water from the freeze-dried complex was smaller compared to that of βCD sample. The difference in dehydration patterns concerning freeze-dried and spray-dried powders can be attributed to the level of water elimination during drying processes.

Taken together, IR and DSC analysis suggest stronger interaction between drug and cyclodextrin in the solid complexes rather than in a simple physical mixture, probably as a consequence of CBZ/βCD complexation.

In order to investigate whether the drying process could have some influence on the particle morphology and further on its dissolution, SEM was performed for the raw materials and for the particles obtained by spray-drying and freeze-drying as well as for a simple physical mixture (Fig. 5). It may be inferred from SEM that spray-dried powder is composed of small, spherical and probably hollow particles, once they seem to be partially withered. On the other hand, freeze-dried complex and physical mixture morphologies seem to be at some extent alike. Physical mixture presents βCD particles surrounded and covered by smaller and sharp CBZ particles. Upon freeze-drying of the CBZ/βCD complex, βCD seems to have acquired the same shape, presenting some sticks covering its surface, with a shape similar to that of the drug.

Tablets were produced with 20 mg of CBZ in order to assure *sink* condition in the dissolution testing, what means 20 mg of drug to 1000 ml of water. The hardness of all tablets was quite similar (60.8 ± 3.1 N). Figs. 6A,B show CBZ and βCD release from each of all six formulations.

Analyzing the in vitro dissolution profiles, one can infer that SD15 and FD15 showed faster CBZ release compared to the corresponding PM15, as well as SD30 and FD30 showed faster CBZ release compared to PM30. This increase on CBZ release is related to an improvement in its solubility, caused by CBZ/βCD complexation. Despite the different particle shapes and sizes, spray-dried and freeze-dried complexes once incorporated in 30% HPMC matrix tablets (SD30 and FD30) presented the same CBZ release profile, as one can clearly observe in Fig. 6B. A mathematical comparison was performed by applying f_1 and f_2 equations [15], and a 10% average difference between two dissolution profiles would lead to a f_2 limit of 50 and to a f_1 limit of 15. The comparison confirmed that tablets containing SD30 and FD30 could be considered equivalent to each other. This phenomenon was not observed when HPMC content is smaller (15%). In fact, analyzing Fig. 6A, one can infer that SD15 showed faster CBZ release when compared to FD15. Nevertheless, CBZ release from SD15 was not so homogeneous, according to the error bars. During the in vitro dissolution testing we could observe that some of the tablets began to disintegrate while others did not show pronounced erosion. The most likely explanation is that 15% HPMC content was not enough to insure gelling and matrix formation. Thus, the release regulation did not take place when 15% HPMC and CBZ/βCD complexes are present and therefore, admitting a difference, the morphology of the particles could have influence on the dissolution of the complexes. Therefore, when 30% HPMC is present, it may be inferred that diffusion throughout the matrix is the limiting step of CBZ/βCD release.

No filler was added to the mixtures, since this procedure could have an influence on βCD release. We have also aimed at holding the CBZ amount constant. Both factors led to an increase in the surface are of tablets containing 30% HPMC. Nevertheless, we believe that the difference of tablet thickness did not have a significant effect on CBZ release, once variables such as the amount of polymer [16,17] and drug load [18,19] are known to have a considerable influence on the drug release.

According to the CBZ solubility determined by βCD complexation and based on Rao and co-workers findings [2], we may not rule out that in situ complexation occurs

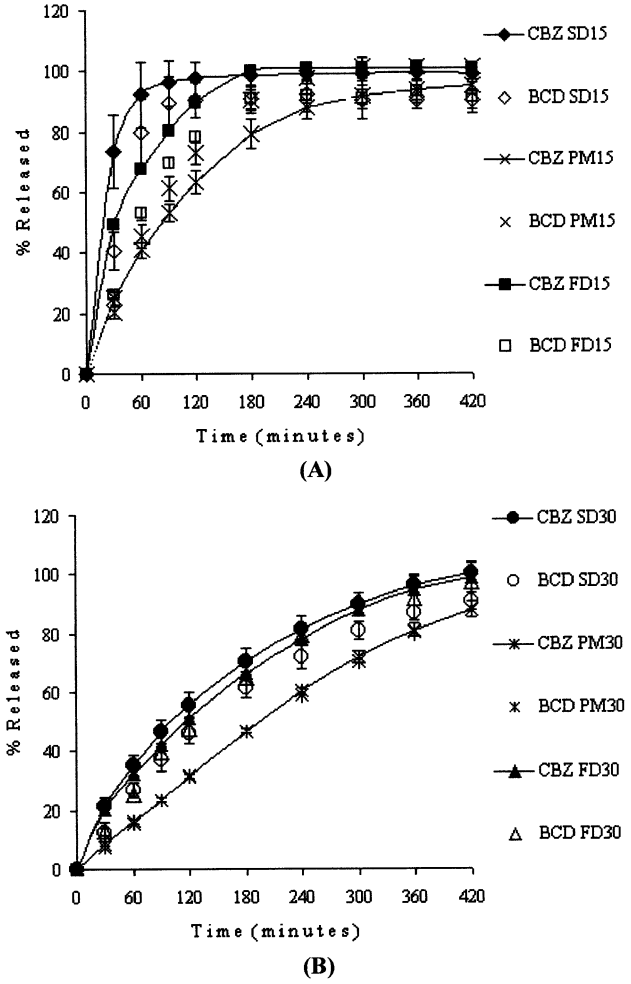

Fig. 6. In vitro dissolution profiles of CBZ (line) and βCD (symbol without line) from (A) SD15, PM15, FD15; and (B) SD30, PM30, FD30 matrix tablets.

in the tablet containing simple physical mixture of CBZ/βCD (PM30). PM30 presented slower CBZ release profile than the corresponding SD30 and FD30 formulations, but faster than CBZ in absence of βCD, which could denote that the increase on CBZ solubility would be related to the amount of complex formed in situ.

4. Conclusions

In the present work an enhancement of CBZ solubility was obtained by its complexation with βCD. The incorporation of CBZ previously complexed with βCD influenced its dissolution profile. Formulations containing spray-dried or freeze-dried CBZ/βCD complexes presented faster dissolution rates compared to those containing simple physical mixtures. The analysis of CBZ and βCD release in matrix tablets containing 30% of HPMC demonstrate that diffusion throughout the matrix is the limiting step of CBZ/βCD release. The development of an HPLC method coupled to refractive index detector allowed βCD assay during dissolution test. In this way, we demonstrated that βCD release from the matrices was almost simultaneous to CBZ release. This is an important finding once it points to the outlook for modulation of drug release and improvement on the bioavailability.

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