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RESEARCH PAPER

Carbamazepine/βCD/HPMC Solid Dispersions. I. Influence of the Spray-Drying Process and βCD/HPMC on the Drug Dissolution Profile

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ABSTRACT

The aim of this study was to compare carbamazepine (CBZ) solid dispersions prepared by spray-drying of aqueous dispersions with the corresponding physical mixtures. The influence of the association of β-cyclodextrin (βCD) and hydroxypropyl methylcellulose (HPMC) on the CBZ dissolution profile of the preparations was investigated. Results demonstrated that CBZ release from solid dispersions is dependent on the ratio of βCD and HPMC. The spray-drying process confers better homogeneity to CBZ polymeric dispersions than the physical mixture process. In summary, we demonstrated the feasibility of obtaining a homogeneous polymeric solid dispersion of CBZ from an aqueous media by spray-drying and a clear influence of the βCD:HPMC ratio on the release profile of CBZ.

INTRODUCTION

Carbamazepine (CBZ)—a tricyclic iminostilbene derivative—is a first-choice anticonvulsant drug used in the therapy of psychomotor epilepsy and in generalized tonic–clonic seizures (grand mal) in the treatment of trigeminal neuralgia, among other indications.[1] This drug is characterized by a dissolution rate-limited absorption due to its low-water solubility (<200 μg/mL). Intermittent side effects of CBZ have been correlated to fluctuations in plasma concentrations that suggests the study of modified release formulations as a powerful approach to improve its therapeutic use.[2]

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The poor water solubility of CBZ can be improved by complexation with cyclodextrins, as it has been reported by El-Nahhas[3] for β-cyclodextrin (βCD) complexes. CBZ complexation with 2-hydroxypropyl-βCD has also demonstrated an increase in the extent and rate of drug absorption.[4–6] In addition, the assessment of diffusional properties of polymeric materials can be an interesting approach to obtain a controlled delivery device of CBZ.

Hydroxypropyl methylcellulose (HPMC) has been used to produce tablets with extended release in view to reduce plasma fluctuations and side effects of CBZ.[7,8] Similarly, the spray-drying process can be used to produce controlled release solid dispersions either by coating the drug particles with polymers (e.g., in microcapsules)[9–12] or by dispersing the drug in a polymeric matrix (e.g., in microspheres).[13–15] However, in this process, organic solvents are currently used to incur risks of toxicity and explosions, reason why aqueous systems have been preferred.[11,16] In this regard, CBZ and βCD were associated with the purpose of improving CBZ solubility during the course of drug release from HPMC matrices.

The main goal of the present study was to investigate the technological feasibility of obtaining CBZ polymeric dispersions from aqueous media by spray-drying. Moreover, the influence of βCD and HPMC on the dissolution profile of CBZ from solid dispersions was investigated, and spray-dried solid dispersions were compared with corresponding physical mixtures.

EXPERIMENTAL

Materials

Carbamazepine, purchased from Galena (São Paulo, Brazil), was comminuted to obtain particle size lower than 250 μm. β-Cyclodextrin was obtained from Roquette (Genay, France), and HPMC (Methocel K100LV®, Dow Chemical Company, Midland, MI) was supplied by Blanver (São Paulo, Brazil). Methanol was HPLC grade, and all other reagents were of analytical grade.

Methods

Preparation of CBZ Solid Dispersions

Five formulations of CBZ solid dispersions were prepared by spray-drying aqueous dispersions containing CBZ associated with either βCD (SDCD) or HPMC (SDHPMC), or both excipients in different ratios as indicated in Table 1. Three batches of each formulation were prepared.

To prepare SDHPMC formulation, HPMC and CBZ were dispersed in 250 mL of water by shaking for 30 min at 80°–90°C. For SDCD preparation, βCD and CBZ were dispersed in the same volume of water, shaking for 30 min at 50°–60°C. SDA, SDB, and SDC formulations were obtained by the addition of the polymer dispersion to the CBZ-βCD aqueous mixture, as indicated in the SDCD preparation. The final volumes of SDA, SDB, and SDC aqueous dispersions were 250 mL. The total solids in the final liquid formulations were 2% (w/v). Spray-drying of the aqueous dispersions was performed in a mini-spray dryer Büchi 190 (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, feed dispersions were maintained at 40°C. Table 1 also indicates the compositions of the other three formulations (PMA, PMB, and PMC), prepared by simple physical mixture of CBZ, βCD, and HPMC. Drug and excipients were first mixed for 30 min and then ground in a mortar for 30 min. Three batches of each formulation were prepared.

CBZ Assay in Solid Dispersions

Carbamazepine assay was performed in all formulations by HPLC. The analytical system consisted of Shimadzu equipment with an SIL-10A autoinjector; a

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

wavelength detector SPD 10A set at 283 nm; column Nova-Pak® C_{18} (Waters, Milford, MA), 3.9 × 300 mm, 4 μm; mobile phase, 75% methanol and 25% water; and a flow rate of 0.7 mL/min. The retention time of CBZ was 4.5 min. The calibration curve was fitted by linear regression: $C = 2.37 \times 10^{-5}\ X + 2.57 \times 10^{-2}$, where C represents the CBZ concentration (μg/mL) and X the CBZ peak area (mV/sec). Standard curves for CBZ were linear ($r > 0.999$) over the examined concentration ranges of CBZ in methanol: 6.6–66 μg/mL. Evaluation of each point was repeated three times. The specificity of the analytical procedure was also validated, following ICH guidelines.[17] The procedure was repeated three times for each formulation and confirmed CBZ recoveries of 99.5 (±1.6%).

For the determination of the CBZ content, samples of 40 mg of solid dispersions were exactly weighed, extracted with methanol for 7 min, and the volume adjusted to 50.0 mL. A sample of 2.0 mL was diluted in methanol and filtered through a PVPD Millipore (Durapore), 0.22 μm membrane and injected in HPLC chromatograph.

In Vitro Dissolution Tests

Dissolution tests were carried out using a Pharma Test dissolution tester (USP XXIV) connected to a Hewlett-Packard 8452A UV spectrophotometer with multicell transport. The paddle speed was set at 100 rpm. USP-simulated gastric fluid and intestinal fluid without enzymes (1,000 mL) were employed at 37°C for 2 and 18 hr, respectively. To maintain sink conditions, samples of solid dispersions corresponding to 20 mg of drug were placed in gelatin capsules. Samples were automatically collected every 10 min, filtered through 0.45 μm membranes, and CBZ was assayed by UV spectrophotometry at 286 nm. All batches of SDHPMC, SDCD, SDA, SDB, SDC, PMA, PMB, and PMC were tested in gastric fluid. Dissolution profiles were compared with that of CBZ powder, which was also placed in gelatin capsules. Similar comparisons were performed by testing one batch of each formulation in simulated intestinal fluid.

RESULTS AND DISCUSSION

CBZ Solid Dispersions

The technological feasibility of producing solid dispersions SDHPMC, SDCD, SDA, SDB, and SDC by spray-drying was demonstrated. The yields of the processes were, respectively, 38%, 50%, 50%, 48%, and 44%. Considering the design of the mini-spray dryer system (nozzle 0.5 mm), the low solid concentration in the feed solutions (2%, w/v), and the fact that CBZ is not soluble in the aqueous dispersion, these yields were expected. Similar yields, 35–55%, have been reported by Conte et al.[18] and Bitz and Doelker.[19] The use of a "disk" spray system, in which feed solution containing higher total solid content (up to 20%, w/v) can be dispersed, would probably improve the yield. Unfortunately, this system is not available for laboratory-scale utilization.

Macroscopic characteristics of the solid dispersions were different, depending on the preparation method (spray-drying vs. physical mixture). The spray-dried products tended to form aggregates, especially when high amounts of HPMC were used.

In Vitro Dissolution Tests

Dissolution profiles of the five spray-dried formulations vs. bulk CBZ in USP-simulated gastric fluid are shown in Fig. 1. The in vitro dissolution tests demonstrated that while the formulation SDCD (containing only CBZ and βCD) presented the highest dissolution rate, the formulation SDHPMC (containing only CBZ and HPMC) showed the slowest CBZ release. Mixtures of βCD and HPMC in different ratios produced spray-dried polymeric dispersions with intermediate dissolution profile, as observed in Fig. 2. Within 1 hr, the rank order of release by these formulations was observed as follows: CBZ (~100%), SDA (~42%), SDB (~53%), and SDC (~93%). Within 2 hr, the amount of CBZ dissolved from formulations SDA and SDB reached approximately 77% and 87%, respectively, whereas that from the SDC formulation attached 100% dissolution.

Formulations prepared by spray-drying showed similar dissolution profiles to the corresponding formulations prepared by physical mixture. However, the higher standard deviations observed indicate a lack of homogeneity in the solid dispersions prepared by physical mixture (Fig. 3).

In USP-simulated intestinal fluid, similar patterns were observed. As in Fig. 1, SDCD formulation presented the fastest dissolution, whereas SDHPMC formulation presented the slowest (Fig. 4). Figure 5

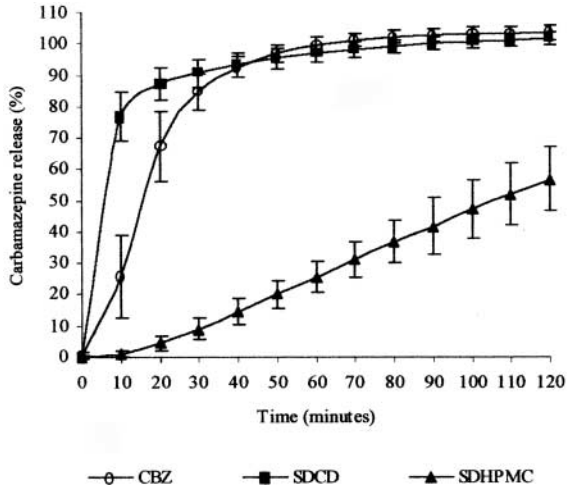

Figure 1. Dissolution profiles of CBZ and spray-dried formulations SDCD (CBZ:βCD, 50:50) and SDHPMC (CBZ:HPMC, 50:50) in gastric fluid.

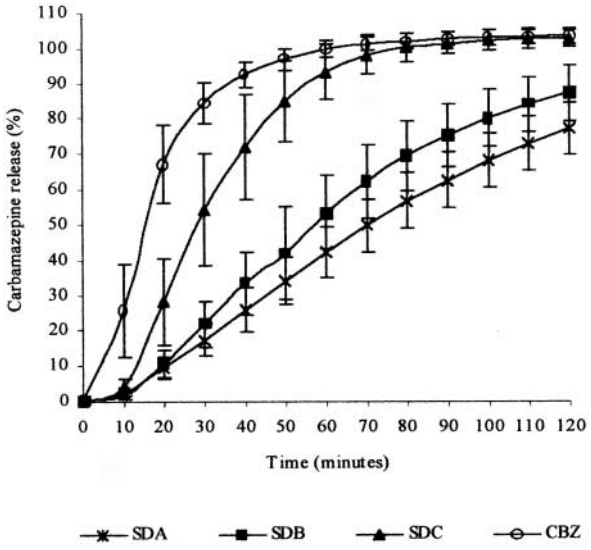

Figure 2. Dissolution profiles of CBZ and spray-dried formulations SDA (CBZ:HPMC:βCD, 50:35:15), SDB (CBZ:HPMC:βCD, 50:25:25), and SDC (CBZ:HPMC: βCD, 50:15:35) in gastric fluid.

presents the dissolution profiles of spray-dried formulations SDA, SDB, and SDC in comparison with CBZ, in which one can observe that the dissimilarity of SDA and SDB dissolution profiles seems to decrease. The lack of homogeneity observed in the corresponding physical mixtures PMA, PMB, and PMC is also evident (as shown in Fig. 6).

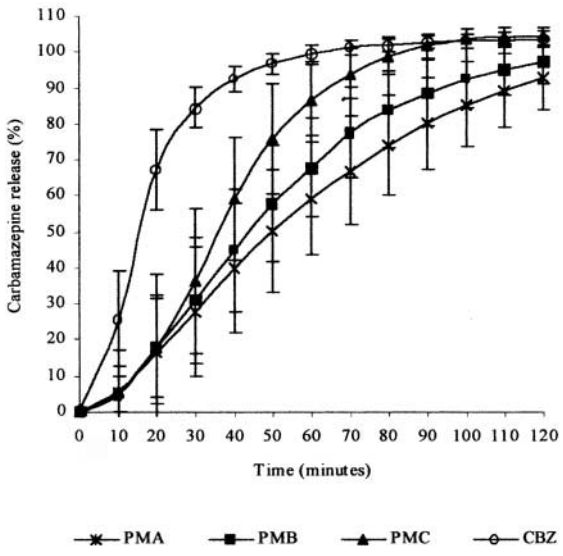

Figure 3. Dissolution profiles of CBZ and physical mixtures PMA (CBZ:HPMC:βCD, 50:35:15), PMB (CBZ:HPMC:βCD, 50:25:25), and PMC (CBZ:HPMC: βCD, 50:15:35) in gastric fluid.

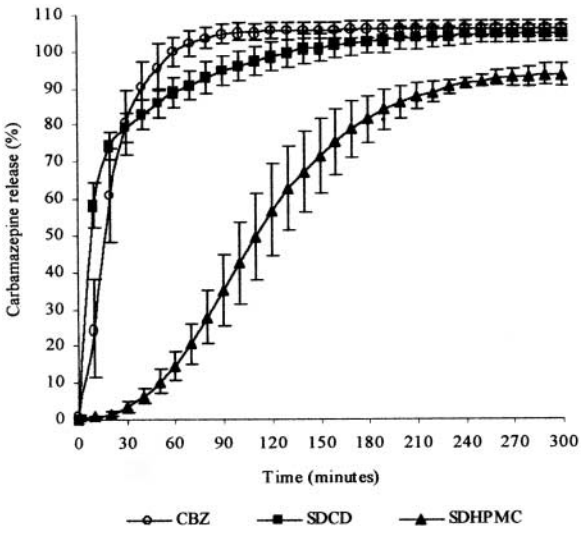

Figure 4. Dissolution profiles of CBZ and spray-dried formulations SDCD (CBZ:βCD, 50:50) and SDHPMC (CBZ:HPMC, 50:50) in intestinal fluid.

The influence of particle size on dissolution rate was minimized by the use of relative uniform particle sizes (SEM, $<4\,\mu m$, data not shown) for both dispersions, spray-dried and physical mixture.

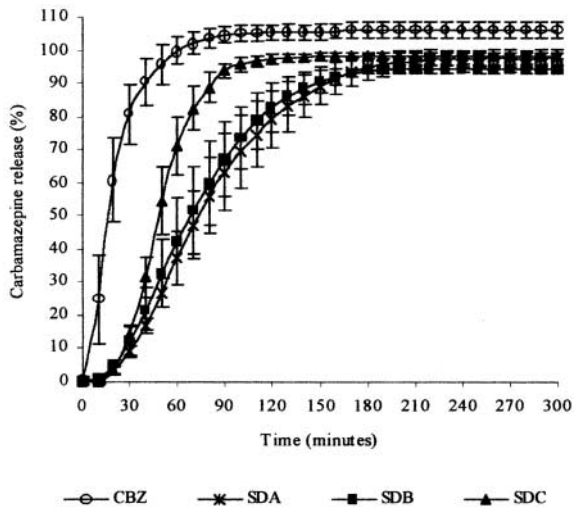

Figure 5. Dissolution profiles of CBZ and spray-dried formulations SDA (CBZ:HPMC:βCD, 50:35:15), SDB (CBZ:HPMC:βCD, 50:25:25), and SDC (CBZ:HPMC:βCD, 50:15:35) in intestinal fluid.

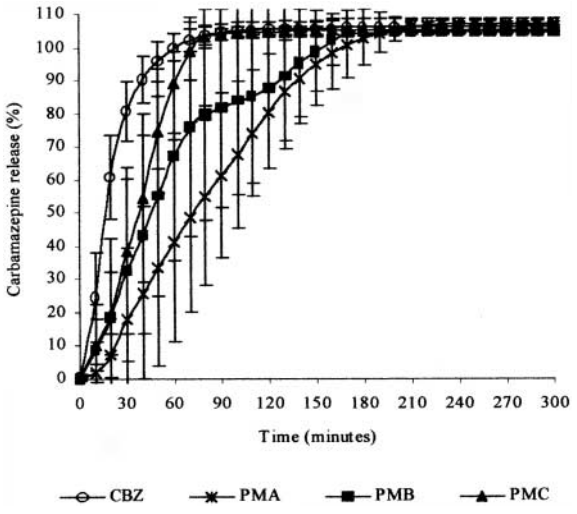

Figure 6. Dissolution profiles of CBZ and physical mixtures PMA (CBZ:HPMC:βCD, 50:35:15), PMB (CBZ:HPMC:βCD, 50:25:25), and PMC (CBZ:HPMC:βCD, 50:15:35) in intestinal fluid.

The different ratios of βCD and HPMC had a clear influence on the SDA, SDB, and SDC intermediate dissolution profiles. Nevertheless, it is worth mentioning that those profiles were not directly proportional, even though HPMC ratios were. In other words, decreasing HPMC ratios did not reflect an equivalent increase in CBZ dissolution from the formulations. This observation also leads to the evidence that βCD had a strong influence on CBZ release. Two hypotheses may be postulated to explain this phenomenon: (i) CBZ may be complexed with βCD and (ii) βCD could influence on CBZ diffusion throughout the polymeric matrix.

Spray-drying is known as a drying method that produces microparticles with high porosity and improves the dissolution rate of drugs.[20] In the presentwork, it was demonstrated that this method improved the homogeneity of the dispersion of CBZ, when compared with that obtained by physical mixtures.

CONCLUSIONS

The feasibility of obtaining spray-dried solid dispersions from aqueous dispersions of CBZ in combination with βCD and HPMC was demonstrated. The release profiles of CBZ from these solid dispersions were dependent on the ratio of βCD:HPMC.

Results indicate that CBZ microparticles, obtained by spray-drying, presented better homogeneity than the microparticles produced by the physical mixture. Physical characterizations, as well as studies including the investigation of the compression of the two solid dispersions and its effect on the differences in the dissolution profiles, are on course. In addition, we are investigating the influence of βCD on the extent and rate of CBZ absorption from HPMC matrices, as well as the establishment of in vitro–in vivo correlations.

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REFERENCES

1. *USP DI*, 17th Ed.; Rockville, 1997; Vol. 1, 714–720.
2. Levy, R.H.; Wilensky, A.J.; Anderson, G.D. Carbamazepine, valproic acid, phenobarbital, and ethosuximide. In *Applied Pharmacokinetics. Principles of Therapeutic Drug Monitoring*, 3rd Ed.; Evans, W.E., Schentag, J.J., Jusko,

W.J., Eds.; Applied Therapeutics: Vancouver, 1992; 26-1–26-29.
3. El-Nahhas, S.A. Physico-chemical characteristics of carbamazepine-β-cyclodextrin inclusion compounds and carbamazepine-PEG solid dispersions. Pharmazie **1996**, *51* (12), 960–963.
4. Betlach, C.J.; Gonzales, M.A.; McKiernan, B.C.; Neff-Davis, C.; Bodor, N. Oral pharmacokinetics of carbamazepine in dogs from commercialtablets and a cyclodextrin complex. J. Pharm. Sci. **1993**, *82* (10), 1058–1060.
5. Brewster, M.E.; Anderson, W.R.; Meinsma, D.; Moreno, D.; Webb, A.I.; Pablo, L.; Estes, K.S.; Derendorf, H.; Bodor, N.; Sawchuk, R.; Cheung, B.; Pop, E. Intravenous and oral pharmacokinetics evaluation of a 2-hydroxypropyl-β-cyclodextrin-based formulation of carbamazepine in the dog: comparison with commercially available tablets and suspensions. J. Pharm. Sci. **1997**, *86* (3), 335–339.
6. El-Zein, H.; Riad, L.; El-Bary, A.A. Enhancement of carbamazepine dissolution: in vitro and in vivo evaluation. Int. J. Pharm. **1998**, *168*, 209–220.
7. Giunchedi, P.; Maggi, L.; Conte, U.; La Manna, A. Linear extended release of a water-insoluble drug, carbamazepine, from erodible matrices. Int. J. Pharm. **1993**, *94*, 15–22.
8. Ikinci, G.; Capan, Y.; Senel, S.; Dalkara, T.; Hincal, A.A. Formulation and in vitro/in vivo investigation of carbamazepine controlled-release matrix tablets. Pharmazie **1999**, *54* (2), 139–141.
9. Takenaka, H.; Kawashima, Y.; Lin, S.-Y. Preparation of enteric-coated microcapsules for tableting by spray-drying technique and in vitro simulation of drug release from the tablet in GI tract. J. Pharm. Sci. **1980**, *69* (12), 1388–1392.
10. Broadhead, J.; Rouan, S.K.E.; Rhodes, C.T. The spray-drying of pharmaceuticals. Drug Dev. Ind. Pharm. **1992**, *18* (11–12), 1169–1206.
11. Wan, L.S.C.; Heng, P.W.S.; Chia, C.G.H. Spray drying as a process for microencapsulation and the effect of different coating polymers. Drug Dev. Ind. Pharm. **1992**, *18* (9), 997–1011.
12. Kristmundsdóttir, T.; Gudmundsson, Ó.S.; Ingvarsdóttir, K. Release of diltiazem from Eudragit microparticles prepared by spray-drying. Int. J. Pharm. **1996**, *137*, 159–165.
13. Palmieri, G.F.; Wehrlé, P.; Stamm, A. Evaluation of spray-drying as a method to prepare microparticles for controlled drug release. Drug Dev. Ind. Pharm. **1994**, *20* (18), 2859–2879.
14. Clarke, N.; O'Connor, K.; Ramtoola, Z. Influence of formulation variables on the morphology of biodegradable microparticles prepared by spray drying. Drug Dev. Ind. Pharm. **1998**, *24* (2), 169–174.
15. Ermis, D.; Yürksel, A. Preparation of spray-dried microspheres of indomethacin and examination of the effects of coating on dissolution rates. J. Microencapsulation **1999**, *16* (3), 315–324.
16. Wan, L.S.C.; Heng, P.W.S.; Chia, C.G.H. Preparation of coated particles using a spray drying process with an aqueous system. Int. Journal of Pharmaceutics **1991**, *77*, 183–191.
17. International conference on the harmonization of technical requirements for the registration of pharmaceuticals for human use (ICH) Q2B. Validation of analytical procedures. Methodology, 1996.
18. Conte, U.; Conti, B.; Giunchedi, P.; Maggi, L. Spray dried polylactide microsphere preparation: influence of the technological parameters. Drug Dev. Ind. Pharm. **1994**, *20* (3), 235–258.
19. Bitz, C.; Doelker, E. Influence of the preparation method on residual solvents in biodegradable microspheres. Int. J. Pharm. **1996**, *131*, 171–181.
20. López, C.R.; Fernández, M.J.A. Microencapsulación de medicamentos. In *Tecnología Farmacéutica. Aspectos Fundamentales de los Sistemas Farmacéuticos y Operaciones Básicas*; Jato, J.L.V., Ed.; Síntesis: Madrid, 1997; Vol. I, 577–608.