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THERMAL PROPERTIES OF BINARY MIXTURES OF β-CYCLODEXTRIN WITH CARBAMAZEPINE POLYMORPHS

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Abstract

The thermal behaviour of binary mixtures between β-cyclodextrin (β-CD) and either carbamazepine polymorphic Form I (CBZ I), Form III (CBZ III) or dihydrate was investigated in order to assess possible interactions of CBZ solid phases with β-CD. Physical mixtures and kneaded binaries of β-CD and different CBZ crystal forms were studied by differential scanning calorimetry, thermogravimetric analysis and hot stage microscopy. The pattern of transition of CBZ Form III into Form I is strongly influenced by β-CD. The liquid-solid transition is practically absent when anhydrous CBZ/β-CD mixes are tested, as a consequence of an interaction between β-CD and liquid CBZ that hinders CBZ recrystallisation as Form I occurring after CBZ Form III melting.

Water loss on heating of CBZ dihydrate in the presence of β-CD leads in all cases to the formation of CBZ Form I.

Keywords: betacyclodextrin, carbamazepine dihydrate, carbamazepine polymorphs, polymorphic transition

Introduction

Carbamazepine (CBZ), 5H-dibenz [b,f] azepine-5-carboxamide, is an anticonvulsant drug practically insoluble in water extensively studied for polymorph formations [1–3]. CBZ Form III (the stable form at ambient temperature) and Form I represent an enantiotropic pair (transition temperature ~71°C) extensively investigated in terms of solid state and biopharmaceutical characteristics [4]. CBZ can also exist as a crystalline dihydrate [5–10].

It is well known that polymorphism and pseudopolymorphism may have a profound influence on technological and biopharmaceutical performances of drugs. In

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particular, polymorphism influences CBZ bioavailability by affecting powder wettability, solubility and dissolution rate [11, 12] and the physicochemical stability of the drug product [13–15].

Polymorphic transformation of CBZ at high relative humidity or in aqueous suspension was investigated and it was concluded that all polymorphic forms transform into the dihydrate, though with different kinetics [16, 17]. The interconversion dihydrate–anhydrous crystalline CBZ is still matter of debate [5, 18]. McMahon *et al.* [5] presented evidence that on heating CBZ dihydrate can give rise to different anhydrous polymorphs depending both on the starting material and the experimental conditions. Interestingly, Katzhendler *et al.* [19] showed that polymeric excipients, such as hydroxypropylmethylcellulose (HPMC), in matrix drug delivery systems inhibited the transformation of CBZ Form III into the dihydrate, mainly by changing the nucleation process and the morphology of crystal surface.

Therefore, the crucial role played by the hydration-dehydration process can be deduced, especially considering possible interactions with pharmaceutical excipients in the presence of water. Since this interaction implies preliminary CBZ dissolution for occurring at a molecular level, it is expected that different kinetics could be involved as a function of water solubility of the CBZ solid phase.

Cyclodextrins (CD) are currently used in pharmaceutical technology as excipients able to improve aqueous solubility of drugs either via the formation of inclusion complexes or as a consequence of the physical stabilisation of a more soluble solid phase [20].

Formation of inclusion complexes of parent CD or derivative with CBZ has been reported [20, 21]. Possible differences in interaction between CD and different CBZ crystal forms were not considered.

In this work we investigated the thermal behaviour of binary mixtures between β-CD and either CBZ I, CBZ III or dihydrate, aiming to assess whether CBZ solid phases could interact with β-CD in different ways.

Experimental

Materials and methods

Materials

CBZ Form III (batch no; 97001203, Recordati S.p.A., Milan, Italy) and β-CD (Kleptose, batch no. 410716, Roquette Frères, Lille, France, water content 13±1% by mass), were a generous gift of producers. All other chemicals were of analytical grade.

Preparation of CBZ Form I and CBZ dihydrate

CBZ Form I was prepared by heating Form III at 185°C for 10 min according to the method described by Borka *et al.* [1]. The transformation III→I was verified by FT-IR spectroscopy (FT/IR – 300E, JASCO, Japan) [1] and by DSC (DSC 821^e, Mettler Toledo, USA) [4].

CBZ dihydrate was prepared by dispersing Form III in distilled water at room temperature for 24 h. The slurry was filtered under suction and dried in air stream for 2 h at room temperature.

Preparation of solid and kneaded CBZ samples

One-gram samples of CBZ Form III or Form I were thoroughly ground in a china mortar with pestle for 5, 15 or 30 min.

Each polymorph, 1 g, was kneaded singly in a china mortar with pestle using 10 mL of a 1:1 *v*/*v* water–ethanol solution added drop-wise in 5 or 30 min.

Preparation of binary mixtures

Kneaded CBZ/β-CD mixtures were obtained by kneading CBZ Form III or Form I with β-CD in 1:1 molar ratio, adding 10 mL of a 1:1 *v*/*v* water–ethanol solution in 5 or 30 min.

Physical mixtures were prepared in same molar ratios by gently blending in a β-CD with either CBZ Form III, Form I or dihydrate.

Thermal analysis

Differential scanning calorimetry (DSC) was performed on an indium calibrated Mettler DSC 821^e (Mettler Toledo, USA) driven by a STAR^e software (Mettler Toledo). DSC traces were recorded by placing precisely weighed quantities (3–7 mg) in an aluminium pan sealed and twice pierced. Scans were performed between 25 and 250°C at 40 K min^{-1} under a flux of dry nitrogen (100 mL min^{-1}). Each preparation was analysed at least in triplicate. Data are expressed as mean value (standard deviation).

Thermogravimetric analysis (TG) (TG 50, Mettler Toledo, USA) was carried out on samples placed in alumina pans with a pierced cover. The samples were heated at 5 K min^{-1} in the 25–150°C temperature range under a flux of dry nitrogen (200 mL min^{-1}).

Hot stage microscopy (HSM) with polarised light was performed with an Optiphot2-Pol microscope (Nikon, Japan) equipped with a Linkam hot stage (HFS 91, Linkam, UK). Powder samples, suspended in silicon oil, were heated from ambient temperature up to 200°C at 10 or 40 K min^{-1}.

Results and discussion

In DSC runs high scanning rate (40 K min^{-1}) was adopted in order to put into evidence and properly estimate the enthalpy associated with the endotherm relevant to Form III→liquid transition [1]. Since Form III→Form I solid-solid transition occurs at temperature values (~71°C) much lower than the melting temperature of Form III (177°C) [1], low heating rates would result in almost flat traces. DSC curves obtained from CBZ Form I and III are reported in Fig. 1. The thermal profile of CBZ III (curve 1) shows a first peak at about 177°C, corresponding to the melting as Form III,

Table 1 Peak temperatures and fusion enthalpy of CBZ samples. Mean values (S.D.) (n=3)

Sample		Onset/°C	Peak/°C	Enthalpy/J g^{-1}	Onset/°C	Peak/°C	Enthalpy/J g^{-1}
CBZ form	Treatment						
III		175.1	177.6	40.7 (0.4)	190.7	193.8	134.1 (1.4)
III	ground 5 min	175.0	177.4	40.6 (0.6)	190.4	193.5	133.6 (1.3)
III	ground 15 min	176.0	178.8	39.5 (0.5)	191.4	193.8	129.8 (0.5)
III	ground 30 min	175.5	178.2	41.2 (4.3)	190.6	193.1	128.6 (2.2)
III	kneaded 5 min	145.6	162.4	8.9 (2.2)	190.2	192.6	120.7 (0.9)
III	kneaded 30 min	146.8	159.7	6.0 (2.1)	191.6	194.3	127.7 (9.5)
I					190.8	192.9	138.9 (6.6)
I	ground 5 min				190.6	192.5	138.0 (6.1)
I	ground 15 min				190.9	193.1	133.5 (5.7)
I	ground 30 min				191.2	193.9	131.3 (1.2)
I	kneaded 5 min				189.6	192.0	120.3 (1.6)
I	kneaded 30 min				190.3	192.6	125.0 (6.3)
III	slurry method	144.2	157.9	4.4 (0.05)	191.1	193.7	122.9 (3.9)

Table 2 Peak temperatures and fusion enthalpy of CBZ/β-CD 1:1 molar ratio binary mixtures. Mean values (S.D.) (n=3)

Sample		Onset/°C	Peak/°C	Enthalpy/J g^{-1}	Onset/°C	Peak/°C	Enthalpy/J g^{-1}
CBZ form	Treatment						
III	physical mixture	173.6	177.7	101.7 (2.4)	188.6	192.5	7.3 (4.8)
III	kneaded 30 min				181.5	187.2	100.7 (4.7)
I	physical mixture				186.3	192.0	91.3 (5.0)
I	kneaded 30 min				181.9	187.6	104.2 (14)

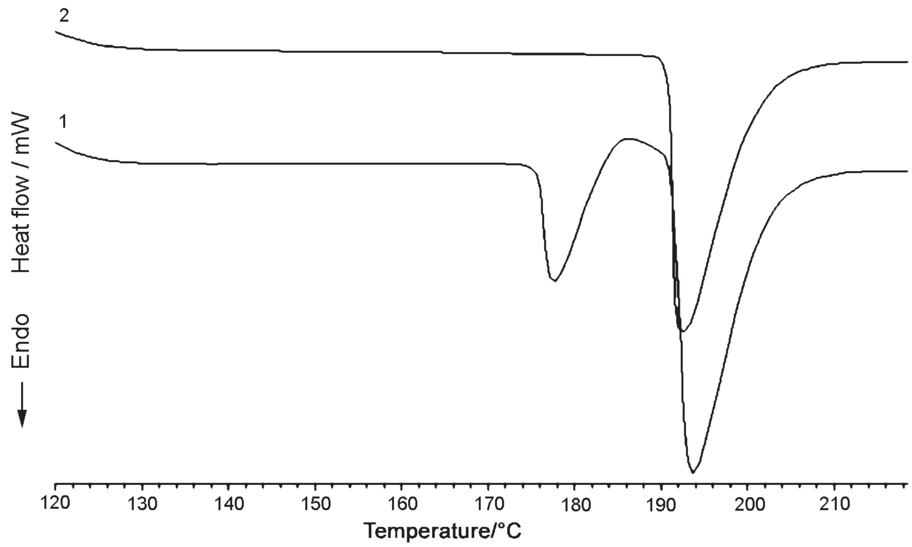

Fig. 1 DSC traces of CBZ Form III (curve 1) and CBZ Form I (curve 2)

followed by an exothermic effect due to the recrystallisation as CBZ Form I which subsequently melts at about ~193°C.

CBZ Form I (curve 2) presents only the endothermic peak at 193°C relevant to fusion.

Grinding of CBZ Forms I or III for 5, 15, 30 min altered significantly neither peak positions nor fusion enthalpy values (Table 1). This suggests a satisfactory physical stability of both crystal forms [3], thus excluding possible changes of CBZ solid state characteristics as a consequence of the mechanical stress applied during the preparation of binaries.

The DSC curve for CBZ dihydrate, obtained by the slurry method starting from CBZ Form III, is reported in Fig. 2 along with the traces of CBZ Form I and III samples obtained by kneading with ethanol–water for 5 min. CBZ dihydrate (curve 1) shows a broad endothermic effect in the 40–120°C interval due to water removal. This was confirmed also by TG in the same temperature interval: the mass loss percent, 12.8 (2.1), corresponds to the elimination of 2 molecules of water (calculated, 13.2) [8]. A barely visible endotherm (~9 J g^{-1}) was observed in the 130–180°C temperature range followed by a sharp endotherm with a peak at 193°C, corresponding to Form I melting. The fusion enthalpy (ΔH^f) of this latter endotherm was lower (by ~10%) than that measured when testing anhydrous Form III (Table 1). These results are in good agreement with previously published data [5, 19]. The decrease of ΔH^f value has been attributed by McMahon *et al.* [5] to a reduction in the degree of crystallinity for Form I as a consequence of dehydration, while by Katzhendler and co-workers [19] to the mass change of the specimen due to dehydration. In our case,

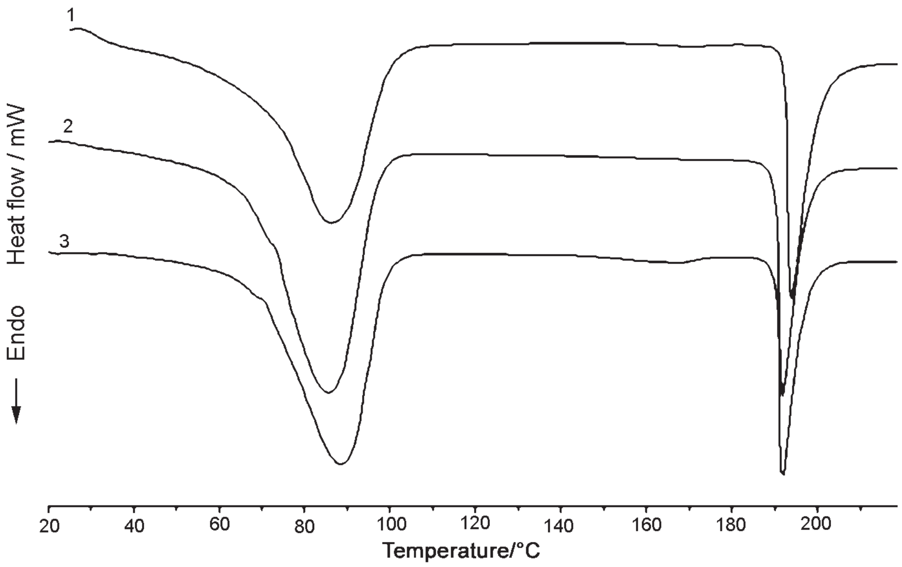

Fig. 2 DSC traces of CBZ dihydrate (curve 1), kneaded CBZ Form I (curve 2) and kneaded CBZ Form III (curve 3)

the enthalpy decrease was roughly corresponding to the water content percent by mass of the specimen.

DSC traces of kneaded CBZ Form I and III (curves 2 and 3, respectively) evidenced a broad endotherm in the 40–120°C interval indicating the water elimination from the hydrate formed as a consequence of the kneading procedure. The mass loss

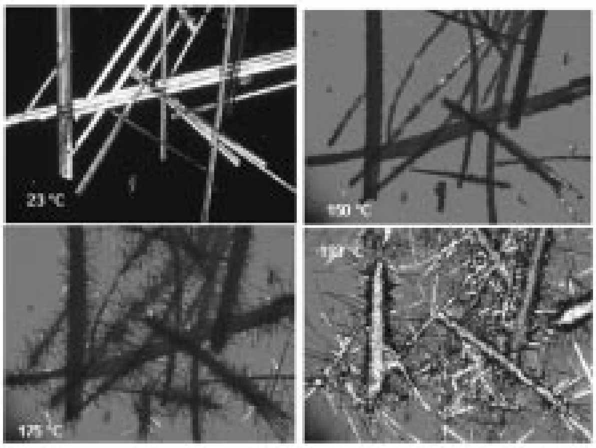

Fig. 3 Micropictures of CBZ hydrate taken at 23, 150, 175 and 193°C

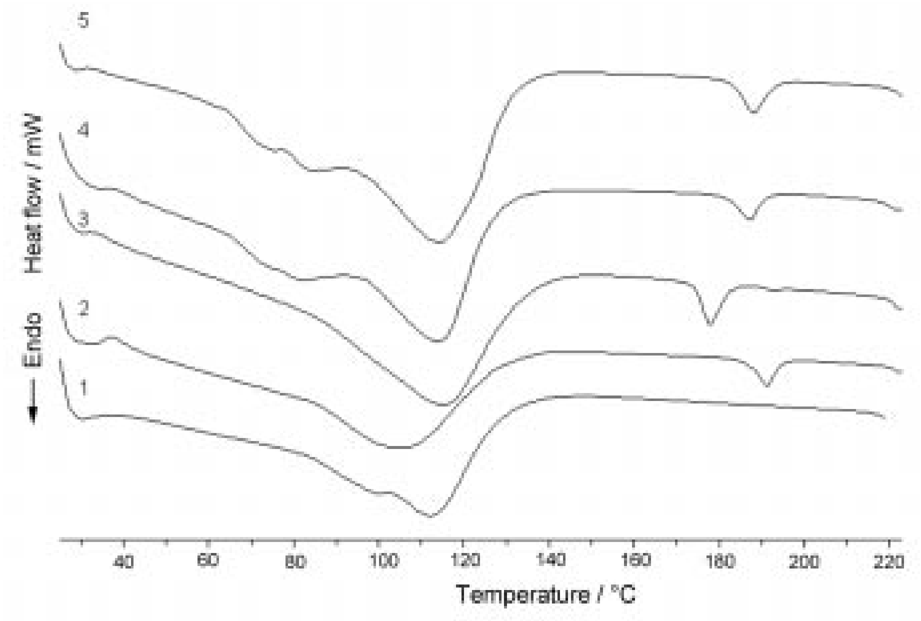

Fig. 4 DSC traces of β-CD (curve 1), CBZ I/β-CD physical mixture (curve 2), CBZ III/β-CD physical mixture (curve 3), kneaded CBZ I/β-CD (curve 4), kneaded CBZ III/β-CD (curve 5)

percent in the same temperature interval determined by TG on samples kneaded for 5 min was 14 (0.7) for Form I and 15.7 (0.7) for Form III suggesting that the formation of the hydrate was completed even with low kneading times. The DSC trace of kneaded CBZ Form III (curve 3) was similar to that obtained from the sample prepared by the slurry method. The DSC profile of kneaded CBZ Form I, after the large endotherm due to water removal, exhibited only one endotherm corresponding to melting of anhydrous Form I.

By HSM it was noted that, in the 40–90°C range, dark crystals appeared as a result of water loss. On further heating the appearance of needle shaped crystals of CBZ Form I could be observed above 150°C (Fig. 3).

The thermal behaviour of binary mixtures of β-CD ad CBZ polymorphs is reported in Fig. 4. β-CD eliminated water in the 40–120°C interval with a broad endothermic effect (curve 1).

When physical mixtures of CBZ Form I and β-CD were scanned (curve 2), the large β-CD dehydration endotherm was followed only by the melting peak of Form I at 192°C. However, the corresponding heat of fusion (Table 2) was about 35% lower with respect to that measured for CBZ Form I alone (Table 1).

When examining DSC patterns of physical mixtures of CBZ Form III and β-CD (curve 3) some interesting considerations can be drawn. First of all, the β-CD dehydration endotherm was not substantially different, as for peak temperature and associated enthalpy value, from that observed when testing mixtures containing CBZ Form I.

Secondly, the melting enthalpy of CBZ Form III (Table 2) was significantly higher than that of Form III alone (101.7 *vs.* 40.7 J g^{-1}). No exothermic effect was recorded after Form III fusion and, finally, the enthalpy associated to the fusion of CBZ Form I was very low, hardly measurable and poorly reproducible (7.3±4.8 J g^{-1}). A similar behaviour has been already reported in the case of HPMC-CBZ mixtures [19]. These authors interpreted the observed results as a consequence of the capability of HPMC of altering the CBZ Form III→Form I transition from solid-solid to solid-liquid. However, we have already shown (Fig. 1) for CBZ Form III alone that, by applying high scanning rates, this transformation occurs, at least in part, via melting of Form III and subsequent recrystallisation as Form I.

This peculiar behaviour may suggest that, after melting of Form III, the interaction of liquid CBZ with β-CD hinders the recrystallisation of CBZ as Form I.

It can be speculated that the small amount of CBZ melting at 192°C (about 5.3% of the theoretical amount, as calculated from the ratio of ΔH of fusion) is a fraction of the initial CBZ Form III that converted into Form I by solid-solid transition before melting.

In the case of the binaries obtained by kneading, DSC curves were very similar (Fig. 4 curves 4 and 5). A broad endotherm was recorded in the 40–130°C interval with two peaks. The first one at about 80°C can be attributed to dehydration of CBZ hydrate formed during the kneading process, while the second one, at about 120°C, can be ascribed to the elimination of β-CD crystal water. Rather surprisingly, no endotherm in the region of Form III melting could be detected for the mixture prepared with this polymorph. Furthermore, for both binaries an endothermic peak was observed at 187°C (ΔH~100 J g^{-1}, Table 2).

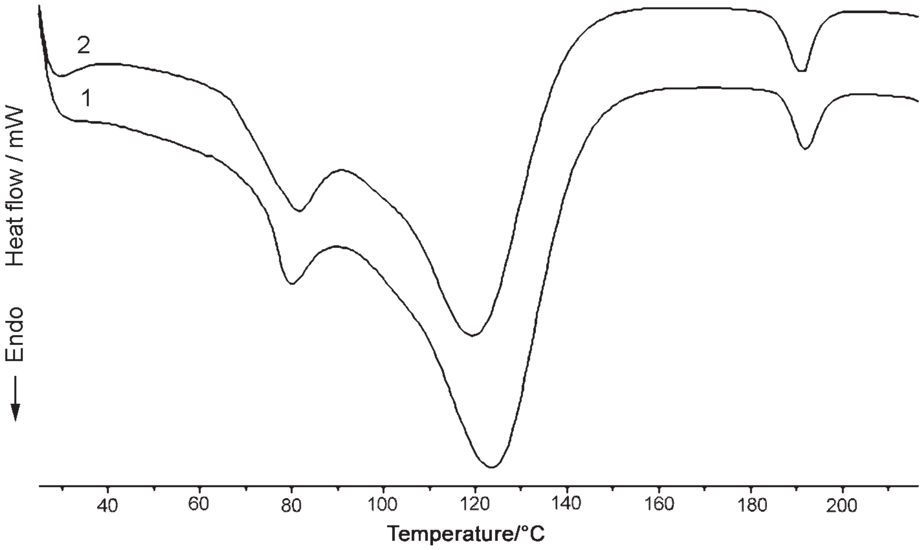

Fig. 5 DSC traces of physical mixtures of β-CD with CBZ hydrate prepared from CBZ III (curve 1) and β-CD with CBZ hydrate prepared from CBZ I (curve 2)

Differently from HPMC [11], β-CD seemed not to interfere with the CBZ-water interaction. In fact, as for CBZ alone, the kneading process in the presence of β-CD leads to the formation of the CBZ hydrate with both polymorphs. However, contrarily to what observed with CBZ alone, the heating of CBZ hydrate in the presence of β-CD gave rise to the formation of CBZ Form I, irrespective of the CBZ crystal form from which the hydrate Form has been prepared.

Finally, the thermal behaviour of the physical mixture of β-CD and CBZ hydrate was investigated. The thermal profiles obtained are reported in Fig. 5. Similarly to the case of kneaded mixtures, almost identical curves were obtained, independently of the CBZ Form from which the hydrate had been prepared. In fact, after dehydration during DSC runs of both CBZ and β-CD at about 80 and 125°C respectively, only the melting endotherm of CBZ Form I was recorded. In this case, however, melting of CBZ occurred at 192°C, indicating that the decrease of CBZ I melting temperature observed with the kneaded product was a consequence of a possible β-CD/CBZ interaction due to the preparation method.

Conclusions

From the presented results it can be concluded that CBZ Forms I and III interact in a different way with β-CD upon heating. This probably occurs because CBZ, molten as Form III, is able to interact with β-CD.

When CBZ dihydrate is considered, heating in the presence of β-CD always leads to the formation of CBZ Form I as a consequence of CBZ dehydration, regardless of the CBZ crystal form from which the hydrate has been prepared.

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