International Journal of Pharmaceutics 431 (2012) 237–240

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Note

Formation mechanism of a new carbamazepine/malonic acid cocrystal polymorph

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ARTICLE INFO

Article history:
Received 6 February 2012
Received in revised form 26 March 2012
Accepted 9 April 2012
Available online 16 April 2012

Keywords:
Cocrystal
Polymorphism
Grinding
Carbamazepine
Transition

ABSTRACT

A new 2/1 carbamazepine (CBZ)/malonic acid (MA) cocrystal polymorph form C was formed using a vibrational rod mill, whereas the known cocrystal polymorph form A was prepared using a ball mill. IR measurements showed that the interaction between CBZ and MA in cocrystal form C was formed by amide–carboxylic acid heterosynthons, similar to that in cocrystal form A. However, NMR results showed that the molecular states of CBZ at the dibenzazepine ring appeared to be different, which could be due to variation in either the conjugation of the aromatic rings or the π–π interaction of CBZ. Factors affecting the formation of cocrystal polymorphs, such as heat and force, were investigated to clarify the formation mechanism.

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Carbamazepine (CBZ) is classified as a class II drug, i.e., low water solubility and high permeability, in the biopharmaceutics classification system. Improving its solubility or dissolution rate can enhance the bioavailability of CBZ. Many methods are available to improve the dissolution of poorly water-soluble drugs, such as solid dispersion, complexation, and cocrystal formation. The cocrystallization of active pharmaceutical ingredients (APIs) with pharmaceutically acceptable coformers is a method that can sometimes yield new crystalline forms of APIs with desirable physical properties (Qiao et al., 2011). Cocrystals of CBZ with various coformers, including carboxylic acids and nicotinamide, have been reported (Childs et al., 2009; Rahman et al., 2011). The different methods used for preparing cocrystals, such as evaporation and coprecipitation, sometimes result in cocrystal polymorphs that affect their physicochemical properties (e.g., solubility and stability) (Aitipamula et al., 2010). Cocrystals that have many polymorphic forms may change into other undesirable forms during the manufacturing processes. Therefore, the formation mechanism of cocrystal polymorphs is of interest to the pharmaceutical industry. The purposes of this study were to characterize the CBZ/malonic acid (MA) cocrystal phases yielded via two different cogrinding methods and to investigate the formation mechanism of any new polymorphs identified.

The 2.5 g physical mixtures (PMs) of CBZ/MA at a molar ratio of 2/1 were coground using different conditions: (1) with a ball mill (model PM100, Retsch GmbH, Germany; conditions: ten 10 mm ZrO_2 balls, 300 rpm, 120 min); and (2) with a vibrational rod mill (model TI-200, CMT Co. Ltd., Japan; grinding time, 60 min), to obtain the ground mixtures (GMs) GM-B and GM-R, respectively. The powder X-ray diffraction (PXRD) pattern of GM-R was different from that of GM-B and the starting materials (Fig. 1), indicating that a potential new cocrystal was formed by the different cogrinding condition. Two CBZ/MA cocrystal polymorphs, i.e., form A and B, have been reported (Childs et al., 2008; Lu et al., 2008). The diffraction pattern of cocrystal form A was shown to have characteristic peaks at 5.8°, 11.6°, and 14.6°, while the characteristic peaks of cocrystal form B were observed to be at 6.6° and 8.8°. Compared with our results, the GM-B pattern corresponded to that of cocrystal form A, while the pattern of GM-R was different from cocrystal form A or B, suggesting a novel cocrystal polymorph. Cocrystal form B has been reported to be a hydrate (Childs et al., 2008). As measured by the Karl–Fischer method, GM-R had water content of less than 1%, which showed that GM-R was not in hydrate form. Hereafter, GM-B and GM-R were referred to as cocrystal forms A and C, respectively.

The interaction between CBZ and MA was examined using Fourier transform infrared (FT-IR) spectroscopy (Fig. 2). Compared with the starting materials, cocrystal form C showed changes in the C═O stretching peak of MA and in N─H and C═O stretching, C═C and C═O vibration, and the NH deformation peaks of CBZ. Each

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Abbreviations: CBZ, carbamazepine; API, active pharmaceutical ingredient; MA, malonic acid; PM, physical mixture; GM, ground mixture; PXRD, powder X-ray diffraction; FT-IR, Fourier transform infrared; DSC, differential scanning calorimetry; Cryo, cryogenic; RH, relative humidity.

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http://dx.doi.org/10.1016/j.ijpharm.2012.04.027

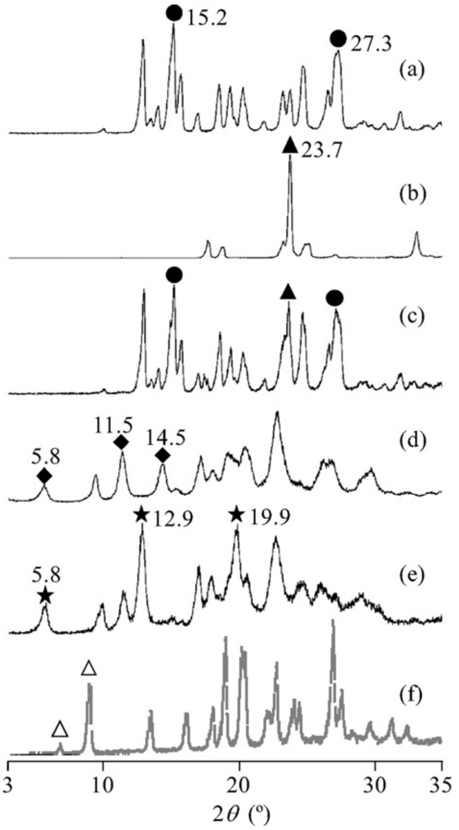

Fig. 1. The PXRD patterns of the 2/1 CBZ/MA system: (a) CBZ, (b) MA, (c) PM, (d) GM-B, (e) GM-R, and (f) cocrystal form B*. ●: CBZ, ▲: MA, ◆: cocrystal form A, ⋆: cocrystal form C, △: cocrystal form B.

*Cocrystal form B was prepared by storage cocrystal form C at 40 °C, 96% RH for 1 week. Its PXRD diffraction pattern was in accordance with that reported by Childs et al. (2008).

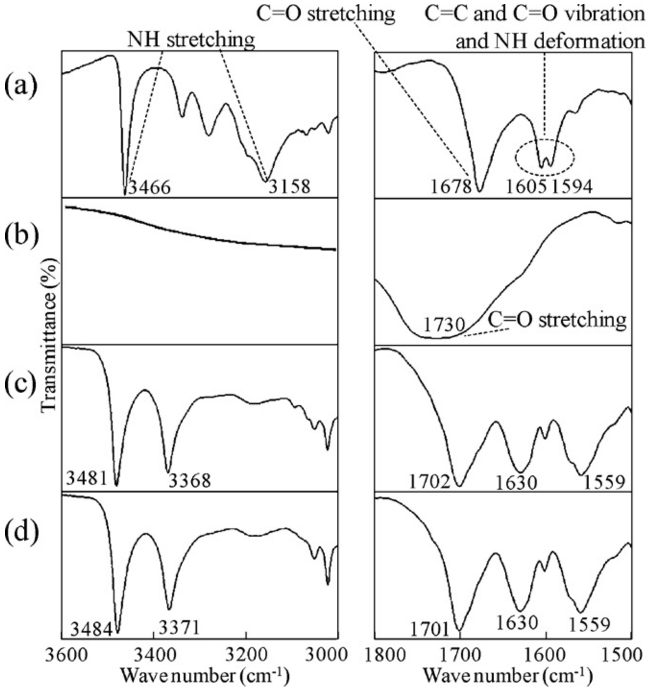

Fig. 2. FT-IR spectra of the CBZ/MA system: (a) CBZ, (b) MA, (c) cocrystal form A, and (d) cocrystal form C.

CBZ and MA forms dimers in their structures (Reboul et al., 1981; Jagannathan et al., 1994). Changes in IR spectrum of cocrystal form C indicated that the dimers of both CBZ and MA were broken and new hydrogen bonds between CBZ and MA were formed. The IR spectrum of cocrystal form A was the same as that of cocrystal form C, suggesting similar interaction modes.

^{13}C solid-state NMR was used to evaluate the difference in the molecular states of the polymorphic cocrystal forms A and C (Fig. 3). The peaks derived from MA and the carbon atom at the amide group of CBZ in the cocrystal form C spectrum were similar to those in cocrystal form A. However, chemical shifts of carbons at the dibenzazepine ring were apparently distinguished. The CBZ/MA cocrystal polymorphs A and C were formed by the same hydrogen bonding, but displayed some differences in the molecular states of CBZ at the dibenzazepine ring.

The thermal behavior of cocrystal forms A and C was investigated using differential scanning calorimetry (DSC) and shown in Fig. 4. The DSC curve of cocrystal form C gave an endothermic peak at 146 °C following by the decomposition, similar to that of cocrystal form A. The thermal behavior of both cocrystal forms A and C is assumed to be similar. The information from the thermal analysis can be used to classify the polymorphs into enantiotropic or monotropic (Burger and Ramberger, 1979). Burger and Ramberger's heat of transition rule states that if an endothermic phase change is observed at a particular temperature and the transition point lies below that temperature, the two polymorphs are related enantiotropically. On the contrary, the polymorphs are monotropically related when there is an exothermic transition. However, it could not apply the heat of transition rule to our results. At present, it is difficult to determine how cocrystal form A relates to cocrystal form C as monotropic or enantiotropic relationship. Although the thermal analysis did not show difference of these two polymorphs, the results from PXRD and solid-state NMR measurements revealed that cocrystal form C is a true polymorph to cocrystal form A.

To determine the structure of cocrystal form C at an atomic level, a single crystal of cocrystal form C is required. However, obtaining a single crystal is difficult because to date cocrystal form C has only been prepared using the cogrinding method, not the solvent method. Several solvents such as acetonitrile and ethyl acetate were used to prepare cocrystal form C but it yielded only cocrystal form A. Thus, to gain an understanding about the structure, the integration of characterization techniques was necessary. The almost identical IR spectra of cocrystal forms A and C indicated that the interaction between CBZ and MA in cocrystal form C was formed by hydrogen bonding through amide–carboxylic acid heterosynthons, as observed in cocrystal form A (Lu et al., 2008). The difference between the cocrystal polymorphs was observed by NMR measurements. The π–π interaction between adjacent CBZ molecules was observed in cocrystal form A (Lu et al., 2008). Therefore, the difference between cocrystal forms C and A may be due to changes in either the conjugation of the aromatic rings or the π–π interaction of CBZ.

Factors affecting the formation of cocrystal polymorphs, such as force, heat, and humidity, were investigated to elucidate their formation mechanism (Figs. 5 and 6). The temperature of the grinding chamber in ball and rod mills usually increases during grinding. Cryo-GM was prepared by grinding the PM in a vibrational rod mill (model TI-500ET, CMT Co. Ltd., Japan) at −180 °C for 30 min to eliminate the heat associated with grinding. Cryo-GM was in an amorphous state (Fig. 5a). Mechanical force from cogrinding CBZ with MA facilitated the breaking of the crystal structures into an unstable state. The halo pattern became similar to that of cocrystal form A after storage at 25 °C, 0% relative humidity (RH) for 18 h (Fig. 5b), indicating the formation of crystalline form A. Thus, mechanical force and thermal activation were necessary for CBZ/MA cocrystal formation by cogrinding method.

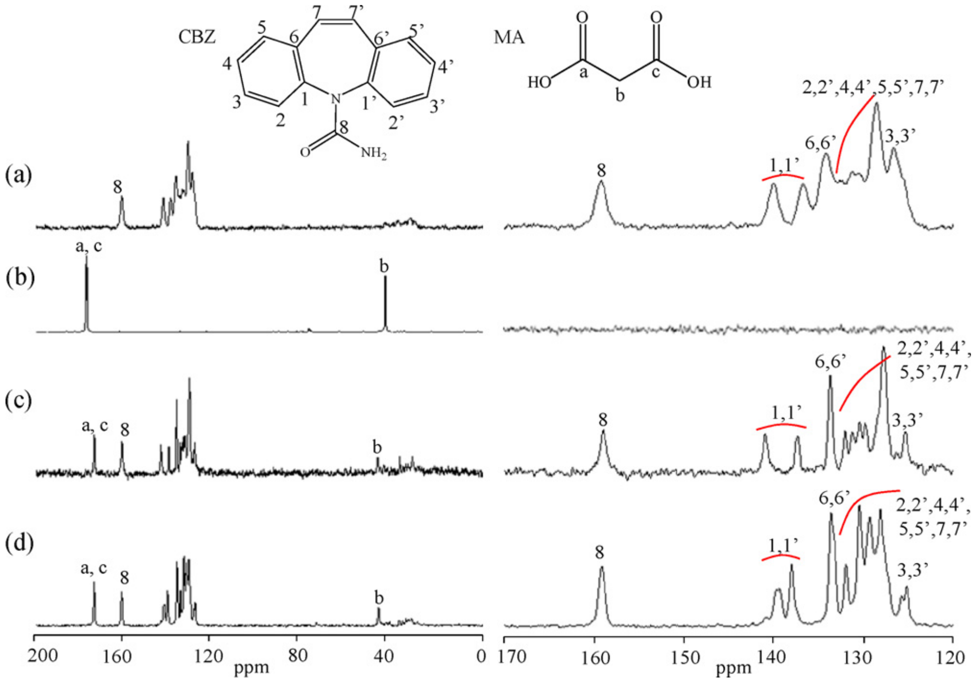

Fig. 3. ^{13}C solid-state NMR spectra of the CBZ/MA system between 0 and 200 ppm (left): (a) CBZ, (b) MA, (c) cocrystal form A, and (d) cocrystal form C. Expanded spectra in the range of 120–170 ppm are shown on the right.

Cocrystal form A prepared by coprecipitation (Childs et al., 2008) was ground for 60 min using a vibrational rod mill or a ball mill (Fig. 5d and e). The PXRD of the sample ground by ball mill showed no change, while the PXRD of the sample ground by rod mill was similar to that observed for cocrystal form C, indicating that polymorph transition (A → C) had occurred. In contrast, when cocrystal form C was ground for 30 min by ball mill, no transition was observed. The PXRD pattern was the same as that of cocrystal form C even after grinding for 60 min (Fig. 5f). The force/heat associated with the vibration rod mill is generally higher than that experienced with a ball mill. The formation of cocrystal form C should require higher energy than cocrystal form A. When cocrystal

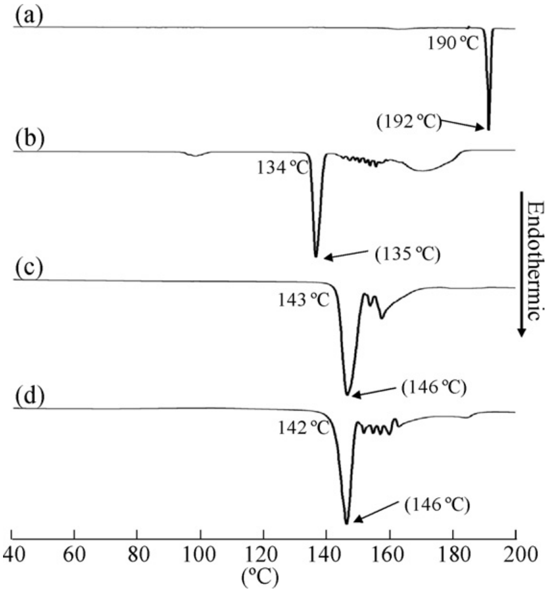

Fig. 4. DSC curves of (a) CBZ, (b) MA, (c) cocrystal form A, and (d) cocrystal form C. Conditions: heating rate: 5 °C/min, crimp aluminum pan; number in parenthesis means the temperature at peak top.

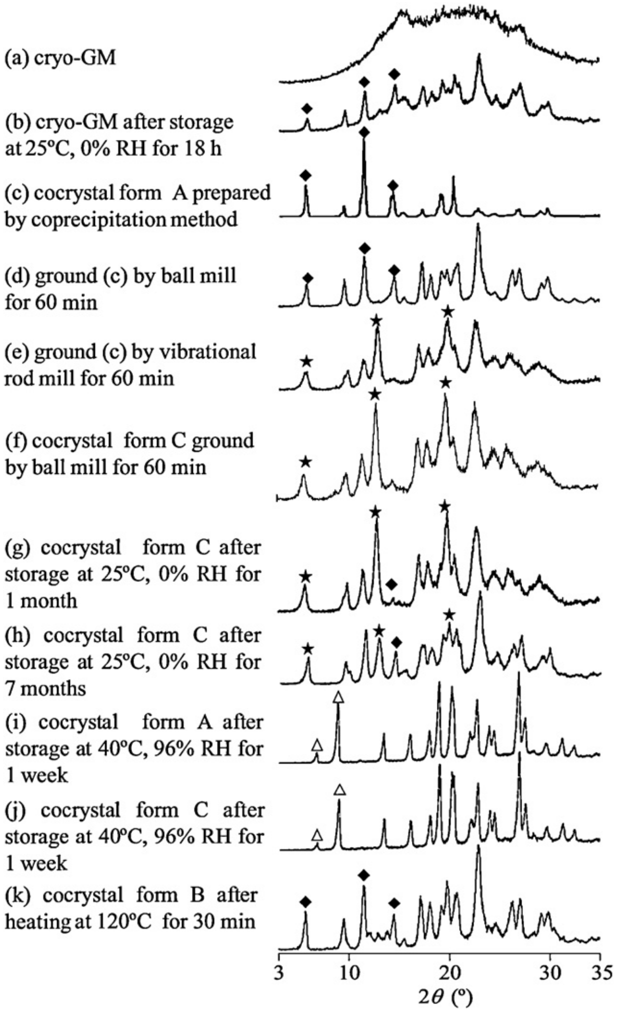

Fig. 5. Changes in the PXRD patterns of the 2/1 CBZ-MA system under different conditions. ◆: cocrystal form A, △: cocrystal form B, ★: cocrystal form C.

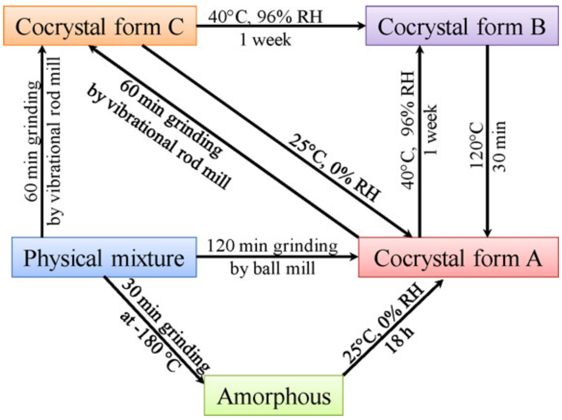

Fig. 6. Preparation methods and the transitions of 2/1 CBZ/MA cocrystal polymorphs.

forms A and C were heated at 100 °C for 60 min, both PXRD patterns showed no change, indicating their stability at high temperature and confirming that heat alone did not facilitate cocrystal form C formation.

The effect of humidity was evaluated by storing cocrystal forms A and C at 25 °C, 0% RH. Cocrystal form A was stable during observation, whereas a characteristic peak of cocrystal form A was observed in the cocrystal form C sample after storage for 1 month. The intensity of this peak became stronger after 7 months (Fig. 5g and h), indicating a mixture of the cocrystal forms A and C. The storage conditions were then changed to 40 °C, 96% RH for 1 week (Fig. 5i and j). Both diffraction patterns were similar to that of cocrystal form B, the hydrate form, and then changed to the pattern of cocrystal form A after heating at 120 °C for 30 min (Fig. 5k). Cocrystal form C could be formed only using a vibrational rod mill, while cocrystal form A could be prepared by several methods and under varied conditions (i.e., heat, force, and humidity), as shown in Fig. 6.

In conclusion, solid-state grinding by vibrational rod mill resulted in the novel CBZ/MA cocrystal polymorph C, which to date has not been obtained by solution-state crystallization methods. Cocrystal form C was formed by the same amide–carboxylic acid heterosynthons, but with a different arrangement of the CBZ dibenzazepine ring compared with that in cocrystal form A due to changes in the conjugation of the aromatic rings or the π–π interaction of CBZ. The formation of cocrystal form C required higher mechanical force and thermal activation simultaneously. Changing the grinding conditions of CBZ and MA resulted in the formation of cocrystal polymorphs. Therefore, attention should be given to the possibility of polymorphism during manufacturing processes such as milling and compaction.

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