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Short communication

Influence of beta-cyclodextrin on the phase transition in carbamazepine polymorphs

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Introduction

Carbamazepin (CBZ), a widespread used antiepileptic drug, branded as Tegretol, firstly was launched in form of Active Pharmaceutical Ingredient (API) as a commercially available polymorphic form III. Additionally, crystallographic studies on crystal packing motifs of carbamazepine molecules in crystal lattices, reveal that, a part of the firstly confirmed structure of polymorphic form III, this drug exists in three other polymorphic forms I, II and IV, as well as pseudopolymorph, dihyrdate form. (Grzesiak et al., 2003). Further solid-state testing confirmed that in terms of thermodynamical stability CBZ III and I are related as enantiotropic pair, former exerting higher stability at ambient temperatures, up to phase transition temperature (Tt≈71℃) when it is transformed in the later with melting temperature at 193 ℃. Due to the polarity of the CBZ molecule that is carbamylated derivative of iminostilbene, consequently that determine its lipophilicity, CBZ belongs to BCS class II of low water solubility and high permeability drug. Compromising the differences in crystal packing between CBZ polymorphs III and I that exert differences in density and solubility with the requirements for sufficient plasma concentration available for favorable crossing the blood-brain barrier (BBB) and reaching receptor sites, remain the challenge for crystal engineering CBZ polymorphs with functional excipients which, based on their molecular structures, are appropriate for formation either of inclusion complexes (IC) or co-crystals (CC). In terms of processing the CBZ polymorph, either with solvents or by mechanochemical treatments, both technologies impose phase transition; the first one causes transformation of anhydrous polymorphs to CBZ dihydrate, and second lead to interconversion of stable to metastable forms by thermomechanical activation on crystal particle surface (Li et al., 2000). The outlined research objectives address the testing of the influence of beta cyclodextrin (BCD), native cyclic oligosaccharide, on controlling the phase transition of CBZ form III to form I, respectively toward the formation of inclusion complex by non-covalent interactions between nonpolar part of CBZ molecule and hydrophobic CBD cavity that interact each other in stoichiometric ratio**.**

Materials and methods

CBZ form III was prepared by recrystallization of the commercially available CBZ in methanol. CBZ form I was made by heating of column packed with powder of CBZ III at 180 ℃ for 10 min. Beta cyclodextrin, BCD ((Kleptose®) with 13 ±1.5 m/m crystalized water content was gifted by Roquette Fröres (FR). Binary solid samples CBZ III and CBZ I with BCD, respectively in molar ratio 1/1 were processed both by grinding and kneading. Grinding method was performed manually by grounding the mixtures during the 30 min in mortar with pestle, while for manual kneading 50 % V/V water ethanol solution was used for wetting and kneading the powders during the 30 min, then leaving to dry on ambient temperature. The CBZ pseudopolymorph, dihydrate form was prepared by slurry method, steering overnight the powder of CBZ form III in purified water, followed by filtering and drying the sediment. Differential Scanning Calorimetry (DSC) was used for monitoring the thermal profiles of the samples, while modified USP Dissolution apparatus 1 with ring for controlling surface area for dissolution, in order to minimize the effect of particle size and habits, was utilized for measuring Intrinsic Dissolution Rate (IDR).

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Results and discussion

The presented results of the values for enthalpy of fusion for two groups of binary solid systems CBZ III and I with BCD, respectively that were processed by kneading and grinding (Table 1), in correlation with values for their Intrinsic dissolution rates (IDR) imply that grinded samples of CBZ form I/BCD, formed with metastable form I i.e. less stable then form III at room temperature, underway to higher kinetics of transition to dihydrate form during the course of dissolution testing. Consequently, it impacts the lower value of IDR of 94.84 $\mu g \cdot cm^{-2} \cdot min^{-1}$ for CBZ form I/BCD grinded samples compared to much more higher values of 287.36 $\mu g \cdot cm^{-2} \cdot min^{-1}$ for ICR for CBZ form III/BCD which thermal profile in DSC scanned in situ course reveals that higher value of enthalpy of fusion compared to pure form III is due to interacting the CBC with melted phase of CBZ form III and formation of IC CBZ form III/BCD. Thermomechanical activation on the surfaces of crystal particle during the mechanochemical processing of the binary powdered mixtures of polymorphic form and BCD leads to heat generation and milling effect that leads to releasing of 13 % m/m crystallized water from the CBD hydrophobic cavity, thus transforming the previously crystalline CBD phase into amorphous as a much energetically reach and favorable form for setting noncovalent interaction with the drug molecules from the surface of crystal particles that obey to deformation.

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

CBZ form	Treatment	Onset ℃	Enthalpy J/g	Onset ℃
III	Grinded	173.6	101.7 (2.4)	188.6
III	Kneaded			181.5
I	Grinded			186.3
I	Kneaded			181.9

Thermal profiles for kneaded CBZ III/CBD and CBZ I/CBD samples relate to transition of anhydrous form III and I in the similar extent to the dihydrate, respectively. CBZ dihydrate as the least water soluble form compared to anhydrous CBZ III and I inhibits the efficiency of formation of the IC, that was contributed with the low, but similar values for their IDR for CBZ III/BCD and CBZ I/BCD of 77.11 and 72.02 $\mu g \cdot cm^{-2} \cdot min^{-1}$, respectively (Cvetkovski et al., 2002; Khoo et al., 2013; Li et al., 2000).

Conclusion

These results confirm that phase transition of CBZ polymorphs, anhydrous form III and I leading to less water soluble CBZ pseudopolymoprph, dihydrate form during the kneading and formation of IC with BCD occur simultaneously. Less water soluble and stable at ambient temperature CBZ III, thus less favorable for transition in CBZ dihydrate, in grinded binary sample with BCD exerts higher water solubility due to formation of IC. BCD in high extent retains inhibition of phase transition of CBZ III to CBZ I during the DCS heating cycle. ICs as immediate release drug delivery systems offer further opportunities for design modified release formulations that may include IC in combination with a polymeric matrix formation compound for additional control of both the drug release profile and drug phase transition.

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