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Thermodynamic Investigation of Carbamazepine-Saccharin Co-Crystal Polymorphs

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ABSTRACT

Polymorphism in active pharmaceutical ingredients can be regarded as critical for the potential that crystal form can have on the quality, efficacy, and safety of the final drug product. The current contribution aims to characterize thermodynamic interrelationship of a dimorphic co-crystal, FI and FII, involving carbamazepine (CBZ) and saccharin (SAC) molecules. Supramolecular synthesis of CBZ-SAC FI and FII has been performed using thermokinetic methods and systematically characterized by differential scanning calorimetry, powder X-ray diffraction, solubility, and slurry measurements. According to the heat of fusion rule by Burger and Ramberger, FI (ΔH_{fus} = 121.1 J/g; melting point, 172.5°C) and FII (ΔH_{fus} = 110.3 J/g; melting point, 164.7°C) are monotropically related. The solubility and van't Hoff plot results suggest FI stable and FII metastable forms. This study reveals that CBZ-SAC co-crystal phases, FI or FII, could be stable to heat-induced stresses; however, FII converts to FI during solution-mediated transformation.

Introduction

Co-crystals[1-3] are crystalline entities that comprise more than 1 component in a defined stoichiometric ratio and are held together by noncovalent interactions. Co-crystals of active pharmaceutical ingredients (APIs) show great promise in improving pharmaceutically relevant properties, such as dissolution,[4-7] bioavailability,[8-11] compressibility,[12,13] physical stability,[14-17] and photostability.[18,19] Thus, pharmaceutical companies are focusing on development aspects of co-crystals that include physicochemical characterization,[20-22] scale-up,[23,24] processing, and formulations of these novel materials.[25,26] Polymorphism in APIs is well known and regarded as critical for the potential that crystal form can have on the quality, efficacy, and safety of the final drug product.[27] As an example, ritonovir, an antiviral drug found to exist in 2 polymorphic forms (forms I and II), showing significantly different bioavailabilities between these crystalline phases has forced Abbott to change its formulation.[28] In the last 2 decades, there is an increasing interest in the pharma industry for a thorough evaluation of polymorphs of APIs.[29-31] Along the lines, polymorphic behavior of API co-crystals can influence the drug development process.[32,33] Polymorphism in co-crystals can be defined as the different co-crystal structures with the same stoichiometric ratio.[34] Initial reports on co-crystals stated that these materials have fewer tendencies to show polymorphism compared with the single-component APIs and salts. Recent findings, however, suggest that the difficulty in the method of co-crystal preparation limits the polymorphism in co-crystals.[34,35] Jones et al.[35] have suggested multiple technique approach for the co-crystal screening and successfully demonstrated its application in polymorph screening of phenazine-mesaconic acid co-crystal. This multiple screening approach includes techniques such as solution crystallization, crystallization at interface, dry and liquid-assisted grinding, sublimation, and thermal methods. Recently, few reports have been published about the preparation of metastable forms of co-crystal using thermokinetic methods, such as spray drying[36] and rotary evaporation.[37] In addition, rapid heating differential scanning calorimetry (DSC) and controlled cooling crystallization approaches have showed their potential for getting co-crystal polymorphs.[38]

Although new methods have been developed for obtaining co-crystal polymorphs, there are limited reports on the systematic evaluation, characterization, and classification of the co-crystal polymorphs. The most important parameter in the characterization

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of polymorphs is the thermodynamic stability relationship between polymorphic forms.[39] Burger and Ramberger[40,41] have developed thermodynamic relationship between the polymorphic forms and classified them as monotropes or enantiotropes based on the heat of fusion and the melting event of polymorphs. The transition temperature is measured as the temperature where free energy of both the polymorphs is 0; if the transition temperature falls between 0 K and melting point of polymorphs, then it is referred to as enantiotropes. For monotropic polymorphs, the transition temperature is either less than 0 K or higher than the melting point of the polymorphs. The thermodynamic stability relationship of polymorphs can be determined from the solubility curves and the van't Hoff plot. In general, if solubility curves intersect at a temperature below the melting point, then the polymorphic pair is enantiotropic, whereas in the case of monotropic pair, solubility curves would not intersect between 0 K and the melting point.[42] Accordingly, metastable form can be susceptible to heat or solvent-induced transformation to a thermodynamically stable crystal form. Therefore, the knowledge of crystal form stability and their thermodynamic interrelationship is an important factor for the pharmaceutical processing and formulation development.

The 1:1 co-crystal involving carbamazepine (CBZ) and saccharin (SAC) is by far one of the most extensively studied pharmaceutical co-crystal systems (Scheme 1). CBZ-SAC co-crystal exists in 2 polymorphs, form I (FI) and form II (FII). Compared with FI, there are fewer reports for synthesis and characterization of FII. Matzger et al.[43] have reported the discovery, thermal, and structural characterization of FII. However, the study was not focused on the thermodynamic interrelationship between FI and FII. Rager and Hilfiker[44] demonstrated the preparation of CBZ-SAC FI or FII using solvent mixtures. Recently, Pagire et al.[45] have reported the preparation of FII using spherical crystallization technique, and focus of that work was on the separation of co-crystal forms based on surface energy. Accordingly, the objective of the present contribution was set out to delineate the thermodynamic relationship of 1:1 CBZ-SAC co-crystal polymorphs (Scheme 1).

Herein, we report the supramolecular synthesis of FI and FII using thermokinetic methods and a systematic thermodynamic investigation of interrelationship between FI and FII using solubility and thermodynamic models.

Experimental

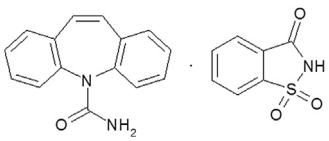
Materials

CBZ and SAC were obtained from Sigma-Aldrich and used as received. The solvents were of chromatographic grade.

Methods

Preparation of CBZ-SAC Co-Crystal Polymorphs

CBZ-SAC co-crystal forms, FI was prepared using the slow evaporative solution crystallization method reported by Fleischman et al.,[46,47] where CBZ and SAC have been considered in 1:1 molar ratio, and the solvent used for co-crystallization was ethanol. FII was prepared using rotary (fast) evaporation technique, where 0.557 g of CBZ and SAC in 1:1 stoichiometric ratio was dissolved in 10 mL of solvent mixture consisting of 62.5% methanol and 37.5% ethanol, respectively. The mixture was heated to 60°C to get a clear solution. Next, it was transferred to a round bottom flask and concentrated using rotary evaporator. The process parameters include reduced pressure from 500 to 100 mbar over a period of 5 min, water bath temperature was kept at 60°C, and 100 rpm revolution speed was used. After evaporation of the solvents, vacuum was decreased to 50 mbar and held for 10 min to ensure the removal of residual solvent.



Scheme 1. Molecular structures of carbamazepine and saccharin.

Powder X-ray Diffraction

The X-ray powder diffraction patterns for CBZ-SAC FI and FII were recorded at a scanning range of 4-40° 2θ with step size of 0.02° and a 1 s per step time by a Philips automated diffractometer. Cu Kα radiation was used with a voltage of 40 kV and a current of 35 mA.

Scanning Electron Microscopy

The morphology of crystal forms was studied using scanning electron microscopy (SEM). Self-adhesive carbon mounts were used to mount samples on aluminum pin stubs (Agar Scientific, Stansted, UK). SEM images of the mounted samples were collected using a FEI Quanta 400 scanning electron microscope (Cambridge, UK) under vacuum and XTM microscope control software, version 2.3.

Differential Scanning Calorimetry

DSC for FI and FII was performed using DSC Q2000 from TA instruments. Approximately, 2-4 mg of the sample was heated in the sealed standard aluminum pan from 25 to 200°C at heating rate of 10°C/min under nitrogen atmosphere. DSC data were analyzed using the TA Universal analysis 2000 software, version 4.5A (TA Instruments, Inc.).

Solubility Curves

The profiles were generated based on the solubility of CBZ-SAC FI and FII in the deionized water at different temperatures ranging from 10 to 45°C. Thermodynamic solubilities of FI and FII were determined by taking excess of FI or FII aliquot in 2 mL of deionized water, and stirring was performed. After 6 h, samples were filtered using syringe filter (0.45 μM), and filtrate was subjected to solubility analysis. The solubility of FI and FII was measured in terms of concentration of CBZ using HPLC, and Waters e-2695 equipped with PDA detector (PDA-2998). The HPLC analysis was performed using Waters symmetry C18 column with 5 μ column packing material and 4.6 × 250 mm column dimensions. The HPLC method used is an isocratic and mobile phase comprising 30% water and 70% acetonitrile containing 0.1% trifluroacetic acid as well as flow rate and injection volume used is 1 mL/min and 10 μL, respectively. Thermodynamic models (van't Hoff plots) were constructed using DSC and solubility curves. Accordingly, thermodynamic interrelationship between FI and FII was fully determined.

Lattice Energy Calculations

The lattice energies of CBZ-SAC co-crystal forms, FI and FII, were performed using the Forcite module in the Materials Studio.[48] The coordinates of single-crystal X-ray diffraction experiments performed at 200 K were minimized by the COMPASS force field. The charges were assigned by the force field. The Ewald summation used to compute the nonbonded interactions that include van der Waals and electrostatic interactions and the single-point energy were determined for FI and FII using fine quality convergence. Finally, lattice energies were computed per molecule based on the number of molecules present in the unit cell.

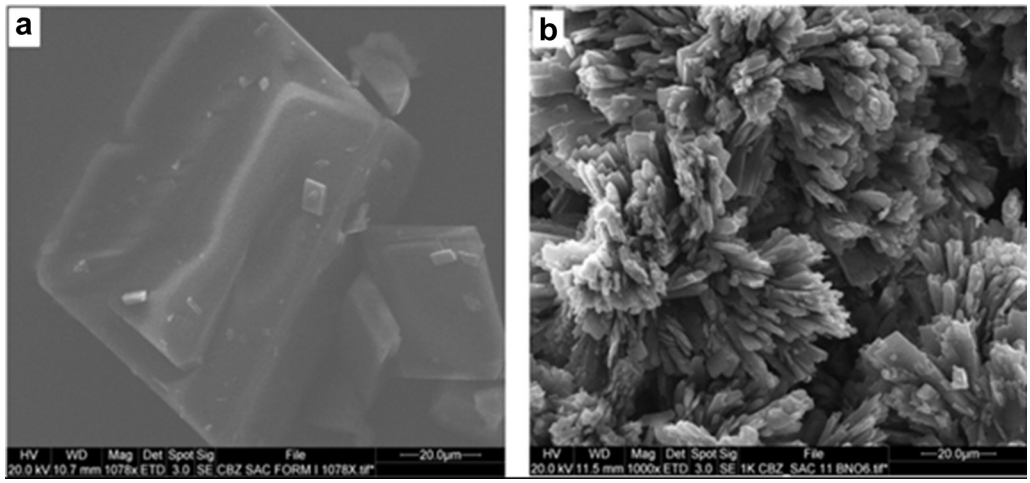


Figure 1. SEM images depicting crystal morphologies from (a) slow and (b) rotary evaporative crystallization methods.

Results and Discussion

CBZ-SAC co-crystal forms, FI and FII, were prepared using slow evaporative crystallization and rotary (fast) evaporative methods, respectively. These were initially characterized using various analytical techniques, such as SEM, powder X-ray diffraction (PXRD), and DSC to confirm integrity of a crystal form, and detailed thermodynamic investigations were carried out.

Physical Characterization

Crystal morphologies obtained either from slow (evaporative) crystallization or rotary evaporation are provided in Figure 1. The PXRD patterns determined at ambient conditions (298 K) of these crystalline materials were compared with simulated powder patterns, which were generated from reported single-crystal X-ray diffraction data sets of CBZ-SAC co-crystal forms, FI and FII at 200 K (Fig. 2). The PXRD pattern of slow crystallization product corresponds to that of stable FI, whereas rotary evaporation product obtained from 62.5% methanol and 37.5% ethanol was in agreement with that of metastable FII (Fig. 2).[40,41] It reveals that PXRD and simulated patterns match well at low 2θ values than at high 2θ values because of temperature difference for data collection of PXRD (298 K) and simulated patterns (200 K), and such observations were reported elsewhere for other compounds.[49]

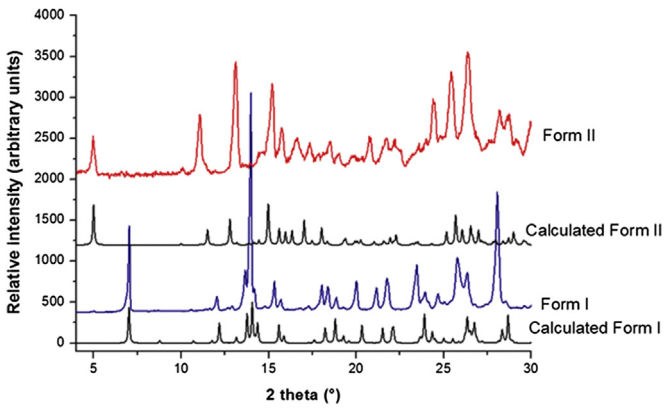


Figure 2. PXRD patterns for CBZ-SAC forms I and II compared with that of respective simulated powder patterns.

In comparison to slow crystallization method, there is relatively less probability of transformation of metastable to stable form during rotary evaporation as the solvent is removed rapidly from the mother liquor.

In rotary evaporation experiments, it was also observed that the different crystalline forms, such as FII, mixture of FI and FII, were obtained per solvent composition (SI). This could be due to the solubility difference of reacting components in a particular solvent composition led to metastable product phases.

DSC analyses reveals the presence of a single melting endotherm for each of the co-crystal phase of CBZ-SAC, FI at 172.45°C and FII at 164.7°C, respectively (Fig. 3). These results matched with that of the literature findings.[43] Accordingly, it confirms the phase purity of FI and FII (see also SI). A detailed investigation of DSC traces of FI and FII showed respective single melting endotherm with a difference of 8°C between them. Interestingly, we observed that DSC profiles of FI and FII did not show any solid-solid phase transitions during heating of phase pure forms. This finding from thermal analysis has motivated us for the detailed thermodynamic investigations to unequivocally ascertain the thermodynamic interrelationship between FI and FII.

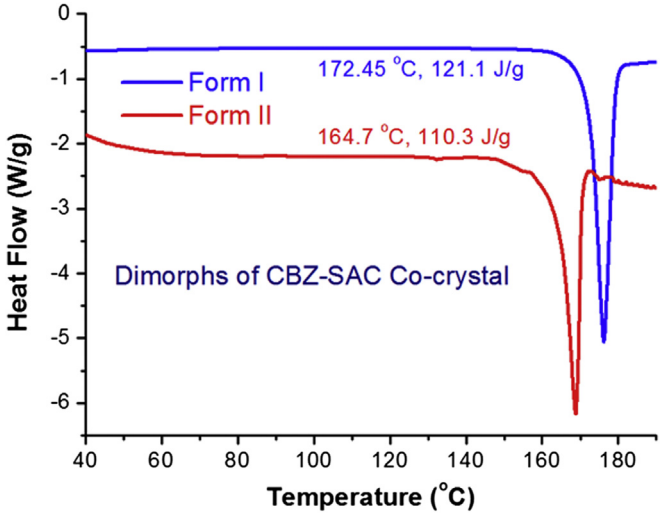


Figure 3. DSC profiles of CBZ-SAC co-crystal phases, FI and FII.

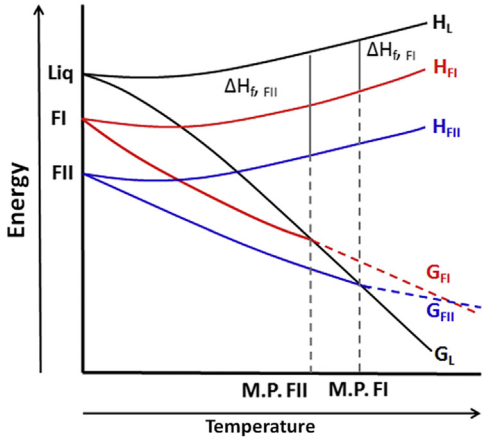


Figure 4. Variation of energy with temperature for monotropic CBZ-SAC co-crystal system. Curves HFI, HFII, and HL represent enthalpy, whereas ΔH_f, FI and ΔH_f, FII are enthalpy of fusion.

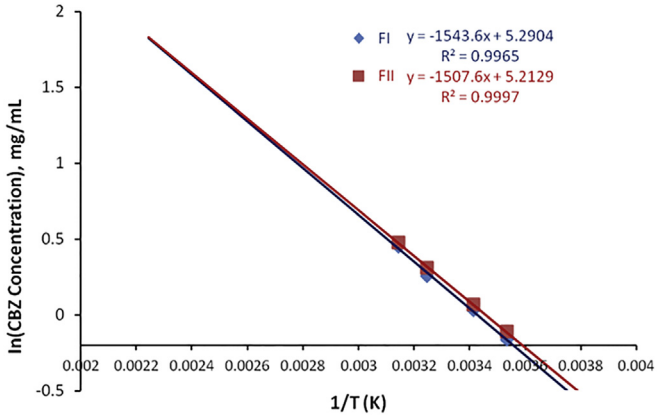


Figure 6. van't Hoff plots for CBZ-SAC co-crystal forms, FI and FII. Note the differences between the slopes of the solubility curves in the plots.

Thermodynamic Investigation

To understand the stability relationship between the polymorphs, it is essential to determine if a given polymorphic system is enantiotropic or monotropic. The most commonly used method for estimating thermodynamic relationship between polymorphs is by means of the heat of fusion rule. According to the heat of fusion rule by Burger and Ramberger, for the polymorphs, higher melting polymorph should have higher heat of fusion to relate them monotropically; otherwise, they are enantiotropic.[40,41] In the case of CBZ-SAC co-crystal polymorphs, heat of fusion values were obtained from DSC analyses, which suggest that FI (ΔH_{fus} = 121.1 J/g) and FII (ΔH_{fus} = 110.3 J/g) are monotropically related.

Accordingly, energy-temperature diagram is constructed based on the thermodynamic parameters such as heat of fusion and melting temperature from the DSC analysis (Fig. 4). In general, the energy-temperature diagram of enantiotropic polymorphs shows transition temperature between 0 K and lowest melting polymorph, whereas monotropic polymorphs show transition temperature above the melting point, which could be an extrapolated hypothetical transition temperature.[40,41] In the present study, energy-temperature plot suggests that FI and FII are monotropically related as there is no transition temperature in the practically acceptable region.

The development of solubility curves in water at different temperatures and van't Hoff plots are reliable methods to distinguish the stability and the thermodynamic relationship of polymorphs to understand whether they are enantiotropically or monotropically related to each other.[40] The solubility curves and van't Hoff plots constructed for FI and FII are shown in Figures 5 and 6 (see SI for the values used for solubility curve and van't Hoff plot). The solubility curves show the complete solubility dominance of FII over FI throughout the selected temperature range, and curves are not intersecting in the measurement area. The results suggest that FII is a metastable form and FI is a stable form. On the other hand, van't Hoff plots show the different slopes for the solubility curves of FI and FII. In general, solubility curves would intersect with each other at a particular temperature, transition temperature, where the solubility of both polymorphs is same. Herein, transition temperature has been calculated by extrapolating the van't Hoff plot. In this study, an extrapolated transition temperature was found to be 464.68 K (191.68°C), which is well above the melting temperature of both the polymorphs, an unrealistic value. Thus, FI and FII considered as monotropic polymorphs as transition temperature do not fall within the realistic temperature range.

In an effort to understand the solution-mediated phase transformations of CBZ-SAC dimorphs, FI and FII, slurry state studies were performed in 3 different solvents; water, ethanol, and methanol at 25°C. The slurry containing excess solid of FI or FII was stirred at 500 rpm. The resulting powders were collected, filtered, and dried during regular time intervals (30 min, 1 h, 2 h, 4 h, 6 h, 12 h, and 24 h). Analysis of the solids by PXRD revealed that FI remained intact in 3 of the tested solvents over the period of 24 h,

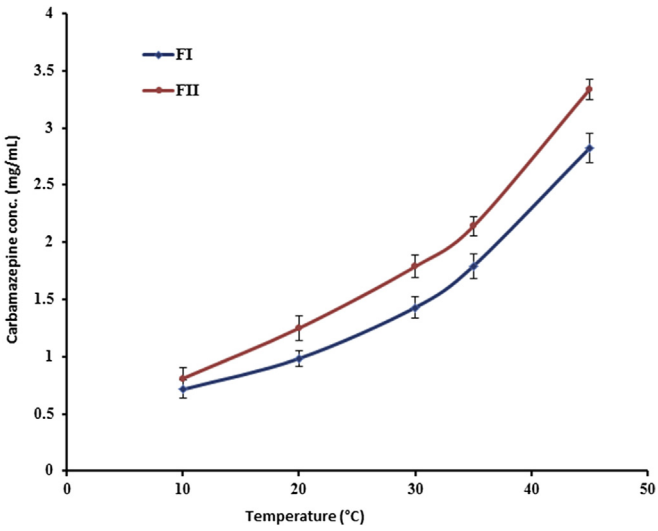


Figure 5. Solubility versus temperature curves for CBZ-SAC co-crystal phases, FI and FII.

Table 1
Summary of Slurry State Stability of CBZ-SAC Co-Crystal Polymorphs in Water, Methanol, and Ethanol at 25°C Over a Period of 24 h

Solvent	Time Intervals						
	30 min	1 h	2 h	4 h	6 h	12 h	24 h
Slurry of FI							
Water	FI	FI	FI	FI	FI	FI	FI
Methanol	FI	FI	FI	FI	FI	FI	FI
Ethanol	FI	FI	FI	FI	FI	FI	FI
Slurry of FII							
Water	FII	FII	FII	FII	FII	FII	FII
Methanol	**FI**	**FI**	**FI**	**FI**	**FI**	**FI**	**FI**
Ethanol	FII	**FI**	**FI**	**FI**	**FI**	**FI**	**FI**

Bold text indicates a form conversion from **FII** to **FI**.

Table 2
Physical Properties of CBZ-SAC Co-crystal Forms, FI and FII

Modification	FI	FII
Mp (°C) DSC onset temperature	172.5	164.7
Enthalpy of transition/J g^{-1}[a]	121.1	110.3
Calculated density/g cm^{-3}[a]	1.4556 (3)	1.4302 (1)
Packing co-efficient C_{k*}[a]	70.2	69.0
Stability	Stable	Metastable
Lattice energies/kcal mol^{-1}[a]	−70.601	−68.784

[a] Determined using the reported single-crystal X-ray diffraction data for FI[46] and FII.[43]

meaning FI is a stable form. However, slurry studies of FII show that it has converted to FI within 30 min in methanol or within 1 h in ethanol, meaning FII is a metastable form (Table 1). Notably, FII intact in water for more than 24 h could be ascribed to the poor solubility of CBZ-SAC in water at 25°C, and also the number of molecules entered into the liquid phase is too little to form the nuclei and crystal growth of FI at the tested conditions. The overall observations suggest that the transformation of the metastable FII to the stable FI is mediated by the solvent.

The calculated densities, packing fractions, and lattice energies for FI and FII were also determined using the reported single-crystal X-ray diffraction data sets (Table 2).[48] As per the density rule, the crystal form with the greatest density is often the most stable form. The calculated density of FI was found to be higher than FII, which is in line with the close packing observed in FI (70.2%) over FII (69%). The lattice energies further confirm that FI has lower free energy (~1.82 kcal/mole) compared with FII; accordingly, FI stable and FII metastable forms.

Conclusions

Polymorphism in molecular crystals involving one-component systems, such as APIs, has been widely investigated, but limited reports are available on the multicomponent systems such as co-crystals of APIs and their thermodynamic behavior. In the present study, we have successfully investigated the thermodynamic stability and interrelationship between FI and FII of CBZ-SAC co-crystal using thermal, solubility, and slurry methods. According to the heat of fusion rule by Burger and Ramberger, FI and FII are monotropically related. The solubility and van't Hoff plot results confirm that FI is a stable form and FII is a metastable form, and these are monotropically related polymorphs. Slurry tests, density rule, and lattice energy results further confirm the FI stable and FII metastable forms. This study reveals that there was no phase transformation of FII and FI during heating. It should be mentioned, however, that FII converts to FI during solution-mediated transformation, which would potentially impact formulation development.

Acknowledgments

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