JOURNAL OF CHEMICAL & ENGINEERING DATA

ARTICLE

pubs.acs.org/jced

Solid−Liquid Phase Equilibrium and Phase Diagram for the Ternary Carbamazepine−Succinic Acid−Ethanol or Acetone System at (298.15 and 308.15) K

Shenmin Xu, Leping Dang, and Hongyuan Wei*

School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, People's Republic of China

ABSTRACT: In this work, the solubility of carbamazepine−succinic acid cocrystals in ethanol and acetone were measured at (298.15 and 308.15) K at atmospheric pressure. The solubility product (K_{sp}) which reflects the strength of cocrystal solid-state interactions of carbamazepine (CBZ) and succinic acid (SUC) relative to interactions with the solvent was determined. The solubility data show that significant complexation occurs in some solutions, and the relevant constants are derived. The ternary phase diagrams for the system of CBZ-SUC-ethanol or acetone at (298.15 and 308.15) K, which can provide the theoretical basis for crystallization processes, are presented.

1. INTRODUCTION

Pharmaceutical cocrystals can improve drug solubility and dissolution rates and increase the stability of drugs without compromising the structural integrity of the active pharmaceutical ingredient (API).[1] Carbamazepine (CBZ, CAS Registry No. 298-46-4, chemical name is 5*H*-Dibenz-[*b*,*f*]-azepine-5-carboxamide) is an anticonvulsant and mood-stabilizing drug used to treat epileptic and bipolar disorders. It has four different anhydrous polymorphs as well as many solvates and cocrystals.[2] Although the drug has been used for over 30 years, it is still confronted with multiple challenges related to solubility and polymorphism.[3] Therefore, CBZ cocrystals have recently been suggested to improve the physicochemical properties. Up to now, research of CBZ cocrystals mainly focused on the cocrystal solubility,[4] cocrystal screening,[5] the formation mechanism, and formation kinetics and stability,[3,6] and only a few phase diagrams have been reported.[7] So it is important to study the system and construct the phase diagram of the ternary system for the purpose of crystallization process control.

In this work, the ternary CBZ-SUC-solvent system was studied. The coformer, succinic acid (SUC, CAS Registry No. 110-15-6), is a common material in the pharmaceutical industry which can form cocrystals with CBZ.[2,7a] At first, the ratio of CBZ to SUC in the CBZ/SUC cocrystal was confirmed by dry grinding, wet grinding, and slurry experiments. Then the solubility of the cocrystal components in organic solvents were measured by a synthetic method at fixed temperatures [(298.15 and 308.15) K] and atmospheric pressure. Finally, the solubility product (K_{sp}) and complexation constants (K_{11} or K_{21}) could be obtained as follows.[6c]

Dissolution of a 2:1 CBZ/SUC cocrystal leads to 2:1 complex formation when:

$$[\mathrm{CBZ}]_T = \sqrt{\frac{K_{sp}}{[\mathrm{SUC}]_T}} + 2K_{21}K_{sp}$$

Dissolution of a 2:1 CBZ/SUC cocrystal leads to 1:1 complex formation when:

$$[\mathrm{CBZ}]_T = \sqrt{\frac{K_{sp}}{A_1}} + K_{11}\sqrt{A_1 K_{sp}}$$

where

$$A_1 = (2[\mathrm{SUC}]_T + K_{11}{}^2K_{sp} - 2K_{11}\sqrt{K_{sp}[\mathrm{SUC}]_T})/2$$

and

$$[\mathrm{CBZ}]_T = \sqrt{\frac{K_{sp}}{A_2}} + K_{11}\sqrt{A_2 K_{sp}}$$

where

$$A_2 = (2[\mathrm{SUC}]_T + K_{11}{}^2K_{sp} + 2K_{11}\sqrt{K_{sp}[\mathrm{SUC}]_T})/2$$

The solubility product (K_{sp}), which reflects the strength of cocrystal solid-state interactions of CBZ and SUC relative to interactions with the solvent, was determined.[4,8] The influence of complexation (K_{11} or K_{21}) on the solubility data is discussed, and relevant binding constants are determined. These constants were used to construct the cocrystal phase diagrams.[6c]

2. EXPERIMENTAL SECTION

2.1. Materials. Form III CBZ (99+ % purity) was obtained from the Suzhou Hengyi Pharmaceutical Co. Ltd., China. The cocrystal coformer SUC was obtained from Alpha Aesar (99+ % purity) and used as received. The ethanol and acetone (purchased from the Tianjin Kewei Chemical Reagent Co., China) used for experiments were of analytical grade (99+ % purity).

2.2. Procedure. CBZ (0.002 mol) and SUC (0.002 mol) were cocrystallized using dry grinding, wet grinding, and slurry

Received: September 8, 2010
Accepted: April 21, 2011
Published: April 29, 2011

ACS Publications © 2011 American Chemical Society

dx.doi.org/10.1021/je100918d | *J. Chem. Eng. Data* 2011, 56, 2746–2750

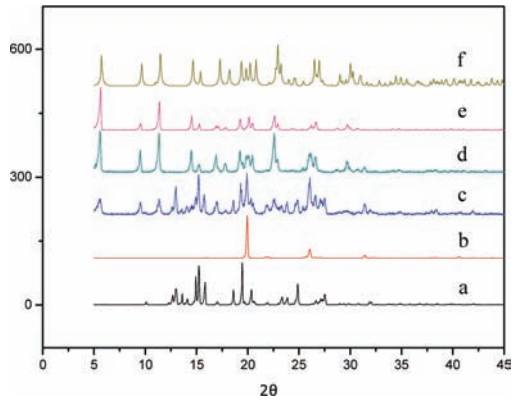

Figure 1. XRPD patterns of materials (a) CBZ, (b) SUC, and the solid phase from experiments (in ethanol) (c) dry grinding, (d) wet grinding, (e) slurry, and (f) 2:1 CBZ/SUC cocrystal structure reported in the CSD.

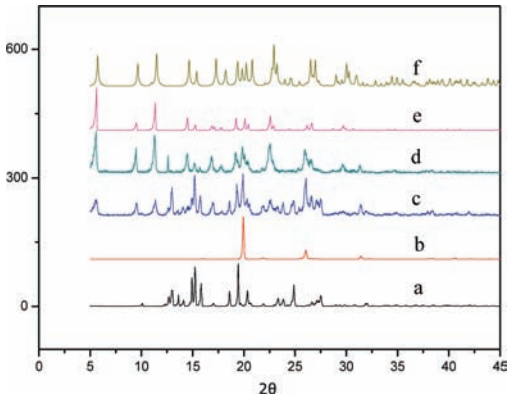

Figure 2. XRPD patterns of materials (a) CBZ, (b) SUC, and the solid phase from experiments (in acetone) (c) dry grinding, (d) wet grinding, (e) slurry, and (f) 2:1 CBZ/SUC cocrystal structure reported in the CSD.

experiments to confirm the form existing in the CBZ/SUC cocrystal (1:1 CBZ/SUC or 2:1 CBZ/SUC).[7a,9] The equilibrium solubility of CBZ and SUC in ethanol or acetone was determined by adding excess SUC and CBZ to each solvent while varying the SUC/CBZ ratio from 0 to 1. Experiments were carried out in several 50 mL sealed flasks that were tempered in a constant-temperature water bath with agitation over at least 24 h to make sure that the phase compositions reached thermodynamic equilibrium. The fluctuation of the temperature in the vessel was less than 0.1 K. Then the solid and liquid phases were separated by a 0.45 μm PTFE filter before the samples were analyzed.

2.3. Analysis. X-ray powder diffraction analyses (XRPD) were performed using a Rigaku D/max-2500 X-ray powder diffractometer using Cu Kα radiation (λ = 1.54 Å), a tube voltage of 40 kV, and a tube current of 100 mA was used to collect XRPD patterns of solid phases. Data were collected from 5° to 50° at a continuous scan rate of 1.2 deg·min^{-1}. The solution concentration of SUC was analyzed by an Agilent HPLC equipped with a UV−vis spectrophotometer detector. A ZORBAX SB-Aq Agilent column (5 μm, 4.6 × 250 mm) at 298.15 K was used to separate CBZ and SUC. A mobile phase consisting of 10 % volumes of methanol and a 50 mmol·L^{-1} solution of KH_2PO_4 previously adjusted to pH 1.54 with phosphoric acid was used with a flow rate of 1 mL·min^{-1}. The sample injection volume was 20 μL, and the absorbance of SUC was monitored at 210 nm. Data collection and processing were performed using the software from Agilent. Ultraviolet analyses of the CBZ content were carried out on a Hitachi-3100 UV−vis spectrophotometer. Samples were analyzed in 1 cm cells at 285 nm, and spectra were collected using the vendor-supplied software.

3. RESULTS

3.1. Ratio of SUC to CBZ in Cocrystal. Samples, prior to and after experiments, were analyzed by XRPD. XRPD patterns (Figure 1 and 2) were compared to diffraction patterns calculated from 2:1 CBZ/SUC cocrystal structures reported in the Cambridge Structural Database (CSD). The diffraction peaks at 5.7°, 11.5°, and 22.9° are unique to the 2:1 CBZ/SUC cocrystal in the XRPD patterns. They show that under the experimental conditions CBZ and SUC mixing only leads to the known cocrystalline phase. In this phase, one SUC molecule combines with two CBZ molecules by hydrogen bonding as indicated in Figure 3.[5a]

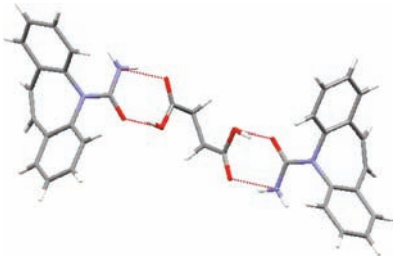

Figure 3. Diagram of the CBZ/SUC cocrystal structure.

3.2. Solubility. The mass fraction solubilities of single components, CBZ and SUC, and the cocrystal in the organic solvents at (298.15 and 308.15) K are presented in Table 1. These results indicate that the solubility of CBZ and SUC depends on the temperature and solvent. At same temperature, CBZ and SUC are more soluble in ethanol than in acetone. When in the same solvent, the solubility of CBZ and SUC exhibit the same trend following the temperature (308.15 K > 298.15 K). In Table 1, the solubility data show that the solubilities of SUC and CBZ are 2.5 to 3 times higher in ethanol than in acetone, yet the solubility of the cocrystal is only (4 to 15) % higher in ethanol than in acetone. As shown in the later section, the complexation constant of CBZ and SUC is low in ethanol and has a weak effect on the cocrystal solubility. But in acetone, CBZ and SUC lead to a higher solution complexation by hydrogen bonding. This shows that complexes of CBZ and SUC in acetone increase the solubility of the cocrystal. The solubilities of pure CBZ and SUC are a little different from those in the literature.[10] This results from the difference in the measuring method and temperature measurements. The small deviation of the experimental cocrystal solubility and the calculated data accounts for the analysis procedure and temperature of the water bath.

The solubility curves of CBZ to SUC in the two organic solvents, as shown in Figure 4, were obtained by stirring excess solid drug in a coformer solution. It is important for the crystallization of cocrystals by solvent evaporation or cooling methods. Results in Figure 4 show that the solubility of CBZ decreases nonlinearly with increasing SUC concentration in both ethanol and acetone.

A small amount of SUC clearly increases the solubility of CBZ, but it is not obviously in ethanol. Given these observations, it is of

Table 1. Mass Fraction Solubility of Single Components, SUC and CBZ, and the Cocrystal in Organic Solvents at Different Temperatures[a]

	SUC			CBZ			cocrystal		
T/K	$10^3\,x^e$	$10^3\,x^l$	$10^3(x^e - x^l)$	$10^3\,x^e$	$10^3\,x^l$	$10^3(x^e - x^l)$	$10^3\,x^e$	$10^3\,x^c$	$10^3(x^e - x^c)$
					Ethanol				
298.15	88.36	99.94	−11.58	30.72	26.49	4.23	16.46	16.50	−0.04
308.15	115.64	133.87	−18.23	48.60	35.39	13.21	24.15	25.78	−1.63
					Acetone				
298.15	35.82	35.89	−0.07	12.77	-	-	15.78	13.29	2.49
308.15	43.35	45.98	−2.63	20.65	-	-	21.23	20.65	0.58

[a] x^e, the experimental data; x^l, the data in the literature;[10] x^c, the data calculated by equation with parameters of Table 3.

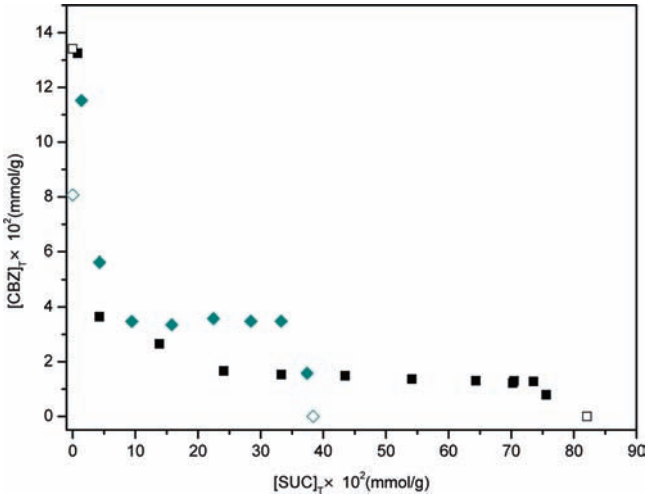

Figure 4. Phase solubility diagram for the 2:1 CBZ/SUC cocrystal. Filled symbols are experimental cocrystal solubility values in (■) 298.15 K ethanol and (◆) 308.15 K acetone. Open symbols are experimental CBZ and SUC solubility values in pure solvent.

Table 2. CBZ/SUC Cocrystal Solubility Product, K_{sp}, and 1:1 Solution Complexation Constant, K_{11}

solvent	T/K	K_{sp}	K_{11}
ethanol	298.15	$1.6685\cdot10^{-4}$	$8.0454\cdot10^{-14}$
ethanol	308.15	$3.7744\cdot10^{-4}$	$2.6085\cdot10^{-13}$
acetone	298.15	$1.1522\cdot10^{-4}$	$3.6652\cdot10^{-14}$
acetone	308.15	$2.0368\cdot10^{-4}$	$1.1302\cdot10^{-13}$

interest to consider how these might relate to the solution complexation. This predication is made using a solution complexation constant in a later section. In ethanol the calculated K_{21} was small, so solution complexation can be neglected in ethanol. But in acetone K_{21} values are larger than these in ethanol, so the solution complexation of cocrystal components increases the solubility.

According to the equations of the 1:1 complex formation, CBZ/SUC cocrystal solubility products and 1:1 solution complexation constants were calculated as shown in Table 2. From this table, these data show that the 1:1 solution complexation constants are very small, so the 1:1 solution complexation in ethanol and acetone can be neglected and only the 2:1 solution complexation needs to be considered. When there are only 2:1

Table 3. CBZ/SUC Cocrystal Solubility Product, K_{sp}, and 2:1 Solution Complexation Constant, K_{21}

solvent	T/K	K_{sp}	K_{21}
ethanol	298.15	$0.9025\cdot10^{-4}$	2.2161
ethanol	308.15	$3.5721\cdot10^{-4}$	0.6999
acetone	298.15	$0.3364\cdot10^{-4}$	105.5291
acetone	308.15	$1.5129\cdot10^{-4}$	21.1514

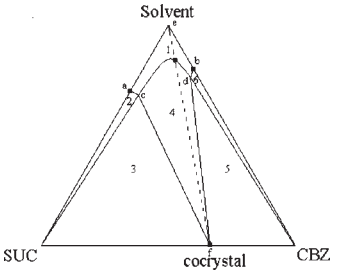

Figure 5. Schematic ternary phase diagram for the CBZ-SUC-solvent.

complexes in the solvents, the solubility product of the cocrystal can be obtained as shown in Table 3 according to the equation which is deduced from the solubility product theory.

Results illustrate that the solubility product has a relationship with the solvents and temperature. At the same temperature, the K_{sp} of the CBZ/SUC cocrystal in ethanol is greater than that in acetone. In the same solvent, when the temperature increases from (298.15 to 308.15) K, K_{sp} also increases obviously with an increase of solubility. That is to say that K_{sp} has the same order with the cocrystal solubilities as follows: ethanol > acetone, 308.15 K > 298.15 K. But the K_{21} follows an inverse trend as the cocrystal solubilities. Lower solubilities favor higher solution complexation. This indicates that complex formation is favored in solvents where these components have lower solubilities. In Table 3, the data show that the complexation between SUC and CBZ is evident in acetone but not in ethanol. This is because ethanol has a hydrogen-bonding ability to weaken the complex formation. So CBZ/SUC cocrystals in ethanol favor solute−solvent interactions, while in acetone they favor solute−solute interactions.

3.3. Ternary Phase Diagram. On the basis of the measurement of solubility and the XRPD results, it can be concluded that there are four phases, which are the liquid and the three solid

dx.doi.org/10.1021/je100918d |J. Chem. Eng. Data 2011, 56, 2746–2750

Table 4. Solubility Data of CBZ, SUC, and Solvent System

composition of liquid phase at 298.15 K (mass fraction)				composition of liquid phase at 308.15 K (mass fraction)			
SUC	CBZ	acetone	equilibrium solid phase	SUC	CBZ	acetone	equilibrium solid phase
0.0000	0.0128	0.9872	CBZ	0.0000	0.0206	0.9794	CBZ
0.0002	0.0143	0.9855	CBZ	0.0002	0.0230	0.9768	CBZ
0.0004	0.0157	0.9839	CBZ	0.0005	0.0267	0.9728	CBZ
0.0007	0.0178	0.9815	CBZ	0.0008	0.0303	0.9689	CBZ
0.0008	0.0186	0.9806	CBZ + 2:1 CBZ/SUC	0.0009	0.0319	0.9672	CBZ + 2:1 CBZ/SUC
0.0028	0.0108	0.9864	2:1 CBZ/SUC	0.0050	0.0130	0.9820	2:1 CBZ/SUC
0.0241	0.0049	0.9710	2:1 CBZ/SUC	0.0322	0.0079	0.9599	2:1 CBZ/SUC
0.0341	0.0028	0.9631	2:1 CBZ/SUC + SUC	0.0411	0.0047	0.9542	2:1 CBZ/SUC + SUC
0.0344	0.0024	0.9632	SUC	0.0416	0.0037	0.9547	SUC
0.0352	0.0011	0.9637	SUC	0.0426	0.0016	0.9558	SUC
0.0358	0.0000	0.9642	SUC	0.0434	0.0000	0.9566	SUC
SUC	CBZ	ethanol	equilibrium solid phase	SUC	CBZ	ethanol	equilibrium solid phase
0.0000	0.0307	0.9693	CBZ	0.000	0.0486	0.9514	CBZ
0.0006	0.0305	0.9689	CBZ	0.0009	0.0482	0.9509	CBZ
0.0017	0.0301	0.9682	CBZ	0.0023	0.0474	0.9503	CBZ
0.0028	0.0298	0.9674	CBZ	0.0037	0.0467	0.9496	CBZ
0.0034	0.0295	0.9671	CBZ + 2:1 CBZ/SUC	0.0043	0.0464	0.9493	CBZ + 2:1 CBZ/SUC
0.0050	0.0085	0.9865	2:1 CBZ/SUC	0.0164	0.0116	0.9720	2:1 CBZ/SUC
0.0599	0.0030	0.9371	2:1 CBZ/SUC	0.0752	0.0032	0.9216	2:1 CBZ/SUC
0.0809	0.0028	0.9163	2:1 CBZ/SUC + SUC	0.1033	0.0039	0.8928	2:1 CBZ/SUC + SUC
0.0824	0.0022	0.9154	SUC	0.1091	0.0020	0.8889	SUC
0.0858	0.0009	0.9133	SUC	0.1140	0.0005	0.8855	SUC
0.0884	0.000	0.9116	SUC	0.1156	0.000	0.8844	SUC

phases CBZ, SUC, and 2:1 CBZ/SUC cocrystal in the ternary CBZ-SUC-solvent system. A schematic ternary phase diagram is shown in Figure 5. It is divided into six regions by the solubility curves of the cocrystal and single components. Region 1 represents the undersaturated solution in which no crystalline phase can generate. Region 2/6 is the solution in equilibrium with SUC/CBZ crystals, and point a/b is the solubility of SUC/CBZ in the pure solvent. Region 3/5 means the solution in equilibrium with SUC/CBZ crystals and CBZ/SUC cocrystal. Region 4 is the solution in equilibrium with the CBZ/SUC cocrystal. The cocrystal component stoichiometric line (e to f) crosses the cocrystal solubility curve (c to d), and the point of intersection of these two lines stands for the cocrystal solubility. In the phase diagram, c and d are the invariant points for which experimental values are given in Table 4. All of the experiments were repeated three times at each temperature, and experimental uncertainties in the measured data were about 0.5 % for all mass fraction values measured over the mass fraction range from 0 to 1.

The four measured phase diagrams for the 2:1 CBZ/SUC cocrystal in ethanol or acetone at (298.15 or 308.15) K illustrate the influence of the temperature on the properties of the ternary system. When the temperature increases from (298.15 to 308.15) K, the trends of the solubility curves in the phase diagrams are similar, but the region of undersaturated solution becomes larger. In different solvents, the solubility curves trend differently suggesting solution complexation. In ethanol K_{21} values are small as shown in Table 3, so solution complexation is negligible. But in acetone K_{21} values are larger than those in ethanol; for this reason, the cocrystal solubility curves in acetone are different from those in ethanol. In summary, cocrystal solubility products and solution complexation constants calculated from solubility studies can be applied to estimate the crystallization diagrams.

4. CONCLUSIONS

In this work, solid−liquid phase equilibria for the ternary CBZ-SUC-ethanol or acetone system were measured at (298.15 and 308.15) K. Mathematical models were used to explain the cocrystal solubility behavior by considering the solubility products and solution complexation. Results show that the solubility of CBZ decreases with increasing SUC concentration, and K_{sp} and K_{21} can be determined from the solubility method. Solubility products are dependent on temperature and solvent. The solubility product of CBZ/SUC cocrystal in ethanol is $0.9025 \cdot 10^{-4}$ $mmol^3 \cdot g^{-3}$ at 298.15 K and $3.5721 \cdot 10^{-4}$ $mmol^3 \cdot g^{-3}$ at 308.15 K, while in acetone it is $0.3364 \cdot 10^{-4}$ $mmol^3 \cdot g^{-3}$ at 298.15 K and $1.5129 \cdot 10^{-4}$ $mmol^3 \cdot g^{-3}$ at 308.15 K. The solution complexation constants indicate that complex formation is favored in solvents where these components have lower solubilities. It is also confirmed that under the experimental conditions CBZ and SUC can only lead to the 2:1 CBZ/SUC cocrystal as indicated by the CSD. The ternary phase diagram which can provide the basis for the crystallization processes of the cocrystal was constructed.

AUTHOR INFORMATION

Corresponding Author

*Phone: +86022 27405754. Fax: +86022 27400287. E-mail: crystallization.wei@hotmail.com.

Funding Sources

We thank the National Nature and Science Foundation of China (NSFC, No. 20776098) and Tianjin University Independent Innovation Foundation for their financial assistance in this project.

■ ACKNOWLEDGMENT

We acknowledge Prof. Simon Black for helpful discussions and comments on the research work.

■ REFERENCES

(1) (a) Hickey, M. B.; Peterson, M. L.; Scoppettuolo, L. A.; Morrisette, S. L.; Vetter, A.; Guzmán, H.; Remenar, J. F.; Zhang, Z.; Tawa, M. D.; Haley, S. Performance comparison of a co-crystal of carbamazepine with marketed product. *Eur. J. Pharm. Biopharm.* **2007**, *67* (1), 112–119. (b) Schultheiss, N.; Newman, A. Pharmaceutical Cocrystals and Their Physicochemical Properties. *Cryst. Growth Des.* **2009**, *9* (6), 2950–2967.

(2) Childs, S. L.; Wood, P. A.; Rodríguez-Hornedo, N. R.; Reddy, L. S.; Hardcastle, K. I. Analysis of 50 Crystal Structures Containing Carbamazepine Using the Materials Module of Mercury CSD. *Cryst. Growth Des.* **2009**, *9* (4), 1869–1888.

(3) Chieng, N.; Hubert, M.; Saville, D.; Rades, T.; Aaltonen, J. Formation Kinetics and Stability of Carbamazepine−Nicotinamide Cocrystals Prepared by Mechanical Activation. *Cryst. Growth Des.* **2009**, *9* (5), 2377–2386.

(4) Good, D. J.; Rodríguez-Hornedo, N. R. Solubility Advantage of Pharmaceutical Cocrystals. *Cryst. Growth Des.* **2009**, *9* (5), 2252–2264.

(5) (a) Lu, E.; Rodríguez-Hornedo, N.; Suryanarayanan, R. A rapid thermal method for cocrystal screening. *CrystEngComm* **2008**, *10* (6), 665. (b) ter Horst, J. H.; Deij, M. A.; Cains, P. W. Discovering New Co-Crystals. *Cryst. Growth Des.* **2009**, *9* (3), 1531–1537.

(6) (a) Fleischman, S. G.; Kuduva, S. S.; McMahon, J. A.; Moulton, B.; Bailey Walsh, R. D.; Rodríguez-Hornedo, N.; Zaworotko, M. J. Crystal Engineering of the Composition of Pharmaceutical Phases: Multiple-Component Crystalline Solids Involving Carbamazepine. *Cryst. Growth Des.* **2003**, *3* (6), 909–919. (b) Friščić, T.; Jones, W. Recent Advances in Understanding the Mechanism of Cocrystal Formation via Grinding. *Cryst. Growth Des.* **2009**, *9* (3), 1621–1637. (c) Jayasankar, A.; Reddy, L. S.; Bethune, S. J.; Rodríguez-Hornedo, N. R. Role of Cocrystal and Solution Chemistry on the Formation and Stability of Cocrystals with Different Stoichiometry. *Cryst. Growth Des.* **2009**, *9* (2), 889–897.

(7) (a) Childs, S. L.; Rodríguez-Hornedo, N.; Reddy, L. S.; Jayasankar, A.; Maheshwari, C.; McCausland, L.; Shipplett, R.; Stahly, B. C. Screening strategies based on solubility and solution composition generate pharmaceutically acceptable cocrystals of carbamazepine. *CrystEngComm* **2008**, *10* (7), 856. (b) Gagnière, E.; Mangin, D.; Puel, F.; Rivoire, A.; Monnier, O.; Garcia, E.; Klein, J. P. Formation of co-crystals: Kinetic and thermodynamic aspects. *J. Cryst. Growth* **2009**, *311* (9), 2689–2695.

(8) (a) Nehm, S. J.; Rodríguez-Spong, B.; Rodríguez-Hornedo, N. Phase Solubility Diagrams of Cocrystals Are Explained by Solubility Product and Solution Complexation. *Cryst. Growth Des.* **2006**, *6* (2), 592–600. (b) Schartman, R. On the thermodynamics of cocrystal formation. *Int. J. Pharm.* **2009**, *365* (1−2), 77–80.

(9) Chiarella, R. A.; Davey, R. J.; Peterson, M. L. Making Co-Crystals The Utility of Ternary Phase Diagrams. *Cryst. Growth Des.* **2007**, *7* (7), 1223–1226.

(10) (a) Liu, W.; Dang, L.; Black, S.; Wei, H. Solubility of Carbamazepine (Form III) in Different Solvents from (275 to 343) K. *J. Chem. Eng. Data* **2008**, *53* (9), 2204–2206. (b) Yu, Q.; Black, S.; Wei, H. Solubility of Butanedioic Acid in Different Solvents at Temperatures between 283 and 333 K. *J. Chem. Eng. Data* **2009**, *54* (7), 2123–2125.