Available online at www.sciencedirect.com
ScienceDirect
International Journal of Pharmaceutics 348 (2008) 3–9
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

One-solvent polymorph screen of carbamazepine

A. Getsoian [1], R.M. Lodaya *, A.C. Blackburn

Pharmaceutical Sciences, Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, MI 48105, USA

Received 8 December 2006; received in revised form 26 June 2007; accepted 27 June 2007
Available online 22 October 2007

Abstract

To emphasize the fact that solvents can be either critical or immaterial in crystallizing specific polymorphs, a method for obtaining multiple polymorphs of a compound using only one solvent is demonstrated. By varying the crystallization temperature and level of supersaturation, three of the four polymorphs of carbamazepine (CBZ; 5*H*-dibenz [*b*,*f*]azepine-5-carboxamide) were crystallized from cumene (isopropyl benzene). Form III, also referred to as the primitive monoclinic form, was produced at temperatures below 60 °C from supersaturated solutions concentrated at less than twice the solubility of that form. When the supersaturation was increased to twice the solubility of form III at temperatures below 60 °C, form II, also referred to as the trigonal form, was produced. Form I, also referred to as the triclinic form, was produced regardless of the level of supersaturation at temperatures above 80 °C. Between 60 °C and 80 °C, mixtures of forms were produced. Competition slurries were employed to establish the transition temperature to be between 79 °C and 82 °C for the enantiotropically related forms III and I. These results indicate that crystallization of CBZ from cumene can either be under thermodynamic control or affected by the kinetics of crystallization of metastable forms. This raises the question about the importance of solvent diversity when looking for polymorphs, suggesting that a rational experimental design can be used to greatly reduce the number of solvents and crystallization conditions. The results of this one-solvent polymorph screen correlate somewhat with a phase–solubility diagram for CBZ.

Keywords: Carbamazepine; Polymorphism; Polymorph screen; Supersaturation; Crystallization; Cumene; Enantiotropic transition temperature

1. Introduction

Polymorphism is defined as the ability of a compound to assume more than one crystalline form. The relevance of polymorphism has been covered elsewhere (Suryanarayanan and Byrn, 2001; Grant, 1999; Byrn et al., 1995). In spite of the significance of polymorphism and the need for solid-form screening of pharmaceuticals, there is no industry-standard approach for conducting a comprehensive polymorph screen of a new chemical entity. New polymorphs are often discovered by trial-and-error, primarily by recrystallizing the compound of interest from a wide variety of solvents. Solvent diversity is thought to be an important factor, and important solvent parameters have been delineated by Gu et al. (2004). While it is known that such diverse factors as solubility, solvent viscosity, solvent polarity, evaporation rate, cooling rate, and initial solution concentration can affect the outcome of a crystallization, approaches to vary these contributing factors are typically not systematic. Solvent diversity without varying degrees of supersaturation and crystallization temperatures has limited utility when screening for polymorphs. Varying degrees of supersaturation are usually achieved by crystallization techniques such as antisolvent addition, rapid cooling, or rapid evaporation. As many as 100 or more solvents, combinations of those solvents, and multiple crystallization techniques may be used in an attempt to cover the wide range of possible crystallization conditions (Morissette et al., 2004; Hilfiker et al., 2006). The temperature of crystallization and degree of supersaturation achieved using such techniques is often not being controlled by the screener, and even with automation (Storey et al., 2004), discovering new polymorphs is a time-consuming and resource–intensive process. Still, no polymorph screen can guarantee that all possible, or even pharmaceutically relevant, forms have been found regardless of the effort.

Threlfall (Threlfall, 2000) has suggested that of the many factors influencing crystallization outcomes, temperature and

* Corresponding author. Tel.: +1 919 240 55642; fax: +1 919 315 4220.
E-mail address: ritalodaya@yahoo.com (R.M. Lodaya).
[1] Present address: Department of Chemical Engineering, University of California, Berkeley, CA, USA.

0378-5173/$ – see front matter © 2007 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2007.06.053

concentration are of utmost significance, as those factors place the crystallization under either kinetic or thermodynamic control. For this reason, often seen statements that a given polymorph will crystallize from a given solvent may not be absolutely correct. A corollary to Threlfall's 2000 paper would be the possibility of generating multiple polymorphic forms of a compound using a single solvent. This suggests that a much more systematic approach to polymorph screening, using a limited number of solvents is possible. Some degree of simultaneous control of supersaturation and temperature of crystallization would be required for such an approach. The work described herein is an attempt to test this approach on the antiepileptic drug carbamazepine, using cumene as the solvent. Results should provide guidance towards a more rational design for polymorph screening.

2. Experimental

2.1. Materials

Carbamazepine (CBZ; 5*H*-dibenz[*b*,*f*]azepine-5-carboxamide) USP grade and cumene 98% were obtained from Sigma–Aldrich (St. Louis, MO) and used as received.

2.2. Preparation of CBZ polymorphs (reference standards)

Reference standards of the four known anhydrous polymorphs of CBZ were desired to enable direct comparison of their PXRD patterns and thermal data with those of experimental samples run on the same instruments. CBZ form III (P-monoclinic), known to be the stable form at room temperature, was used as provided from Sigma–Aldrich. CBZ form I (triclinic), known to be enantiotropically related to form III, was prepared by holding form III at 185 °C for 10 min, which induced complete phase transformation. CBZ form II (trigonal) was crystallized from highly supersaturated solutions of CBZ in ethanol at 0 °C. Attempts to make a reference standard for form IV by crystallization from solution were unsuccessful. Form IV was obtained by desolvating a form obtained from methanol solution. The methanol was likely to contain water, based on the fact that the powder pattern of this solvate matches that of the dihydrate.

To validate these reference standards, the identity and phase-purity were confirmed by comparing their measured PXRD patterns to PXRD patterns simulated from the known crystal structures of each of these four polymorphs; crystal structures were taken from the Cambridge Structural Database. Thermal analysis results were also compared to those available in the literature (Grzesiak et al., 2003; Rustichelli et al., 2000; Behme and Brooke, 1991; Krahn and Mielck, 1987).

2.3. Methods

2.3.1. Sample preparation: RS-12 reaction block

Trials were conducted in an RS-12 Electrothermal Stem Reaction Block (Barnstead International, Dubuque, IA). The block is a 12-zone reaction system allowing users to perform multiple experiments at individually set temperatures. Each zone comprises a block with four vessel positions, heated electrically and cooled by a Peltier device. Each zone is under independent temperature control; adjacent zones may differ in temperature by up to 60 °C without significant interference. The device has a minimum operating temperature of −30 °C, a maximum operating temperature of 150 °C, and a maximum heating and cooling rate of 5 °C/min. It allows samples to be stirred between 250 rpm and 1200 rpm.

Samples were prepared by weighing out the desired amount of CBZ, then transferring the material into a 2-mL HPLC vial with a Teflon-coated stir bar. The desired amount of cumene (0.5–1.5 mL) was then added using an Eppendorf pipette. Vials were capped and placed in the RS-12 reaction block. These samples were heated to a temperature sufficient to ensure total dissolution of CBZ (80–140 °C depending on concentration), and held at this temperature for 2 h, during which time samples were visually inspected to ensure complete dissolution. Samples were then cooled to target temperature at the maximum allowed cooling rate (5 °C/min) and maintained at the target temperature thereafter. Time to crystallization varied between a few seconds for highly supersaturated solutions to a few hours for slightly supersaturated solutions. Once CBZ crystallized, the resulting slurry was transferred to a pre-heated, filter-equipped glass syringe using a pre-heated transfer pipette. The recrystallized material collected on the filter was dried under a fume hood and analyzed by PXRD.

2.3.2. Sample preparation: Reacti-therm heating/stirring module

Additional trials were conducted using two Reacti-Therm Heating/Stirring modules (Pierce, Rockford, IL), which were better suited for low-concentration trials, as the higher solvent volume would allow for recovery of sufficient material for subsequent analyses. These devices were equipped with aluminum heating blocks designed to hold six 20-mL vials.

Samples were prepared by weighing a desired amount of CBZ and transferring it into a 20-mL glass scintillation vial equipped with a Teflon-coated stir bar. The desired amount of cumene (2–20 mL) was added using a volumetric pipette. Recrystallizations were then conducted as described above for the RS-12 reaction block.

2.3.3. Filtration equipment

Micro-mate Pressure Control Syringes with interlocking filter tips (Popper & Sons, New Hyde Park, NY) equipped with 0.2-μm filter paper (VWR Scientific Products, West Chester, PA) were used for filtration. Syringes were pre-heated to the desired temperature in an oven before use.

2.3.4. Crystal form determination

The crystal form for recrystallized solids isolated from the above sample preparations was determined by powder X-ray diffraction (PXRD). The PXRD patterns of the recrystallized solids were overlaid on the reference standards prepared previously for CBZ forms I–IV. Differential scan-

ning calorimetry (DSC) was performed on selected samples and DSC thermograms were compared with that of the reference standards.

2.3.4.1. Powder X-ray diffraction (PXRD). PXRD analysis was conducted on a Bruker AXS D8 Discover diffractometer equipped with GADDS (Bruker AXS, Madison, WI) using a Cu (Kα radiation) tube powered at 40 kV and 40 mA. Samples were prepared on nickel holders and scanned from 4.5° to 38.7° 2θ using a scan time of 60 s and a sample oscillation of 1.5 mm. When necessary, samples were gently ground with a mortar and pestle before analysis. Diffractograms were evaluated using DiffracPlus software with Eva version 8.0.

2.3.4.2. Differential scanning calorimetry (DSC). DSC analysis was performed using a DSC Q1000 (TA Instruments, New Castle, DE). Unless otherwise noted, scans were conducted at 10 °C/min from ambient temperature to 300 °C. All samples were analyzed in closed aluminum pans with a vent hole. Nitrogen was used as the purge gas at a flow rate of 50 mL/min for the DSC cell and 110 mL/min for the refrigerated cooling system. The calorimeter was calibrated for temperature and cell constant using indium (melting point 156.61 °C, enthalpy of fusion 28.71 J/g). Data analyses were performed using TA Instruments' Universal Analysis 2000 software for Windows, Version 3.8B.

2.3.5. Solubility determination (forms III and I)

Semi-empirical solubilities for CBZ (forms III and I) in cumene as a function of temperature were calculated from the Margules equation (Frank et al., 1999). Calculation of solubilities using this method, takes into consideration solute parameters such as solubility in the solvent at room temperature, molecular weight, melting point, and heat of fusion. The solvent parameters taken into account are density and molecular weight of the solvent.

In order to determine the solubility at room temperature, an excess of CBZ form III was slurried in cumene for 24 h. The saturated solution was filtered and a measured aliquot was transferred to a preweighed aluminum boat. The weigh boat was then transferred to a vacuum oven to allow total evaporation of the solvent. The solubility in cumene was determined gravimetrically, upon reweighing the boats containing dried sample.

The solubility of form I in cumene at room temperature was determined from the known ratio of solubilities of forms I and III in isopropanol (Behme and Brooke) and *n*-pentanol (our data). Solubility of forms I and III in *n*-pentanol was determined to be 15.8 mg/mL and 12.6 mg/mL, respectively. The rates of dissolution in isopropanol and *n*-pentanol are significantly higher, allowing determination of the actual ratio of the solubility of form I to form III (∼1.2). The actual solubility of form I at ambient temperature was unmeasurable in cumene because not all of the form I present in slurry would dissolve before extensive conversion to form III occurred.

3. Results

3.1. Solvent selection

This work required a solvent that avoids solvation with CBZ, provides a wide range of temperature in the liquid state, provides moderate solubility, and is safe to handle. The specific criteria used were: (1) boiling point above 150 °C, to allow complete dissolution of very high concentrations relative to saturation at room temperature; (2) freezing point below 0 °C, to allow crystallization at that temperature; (3) solubility low enough to reduce consumption of CBZ, but high enough that the amount of material crystallized be sufficient for analysis and (4) low hazard to human health. As shown in Table 1, several high-boiling solvents were tested for solubility. Initial experimentation suggested that a practical range of solubility would be 1–2 mg/mL. Based on these results, cumene (isopropylbenzene, mp −96 °C, bp 153 °C, CBZ solubility 1.13 mg/mL at 20 °C) was chosen.

3.2. Transition temperature for forms III and I

CBZ forms III and I were combined in a 1:1 ratio in HPLC vials equipped with Teflon-coated magnetic stir bars. One milliliter of cumene was added to each vial. Vials were placed on the RS-12 reaction block and held at 60 °C, 70 °C, 77 °C, 86 °C, 94 °C, and 105 °C for 1 week, after which contents were filtered and analyzed by PXRD. The diffraction patterns for samples at 60 °C, 70 °C, and 77 °C confirmed the presence of form III only, while the diffraction patterns for samples at 86 °C, 94 °C, and 105 °C confirmed the presence of form I only. Based on these results, a second set of samples were prepared and held at 77.3 °C, 79.6 °C, 81.4 °C, and 83.0 °C for 1 week. PXRD confirmed the presence of form III only at 77.3 °C and 79.6 °C, and the presence of form I only at 81.4 °C and 83.0 °C.

Based on experimental results described above we report the transition temperature for forms III and I to be between 79 °C and 82 °C. There has been some discrepancy regarding this in earlier

Table 1
Temperature dependence of carbamazepine form III solubility in various high-boiling solvents

Solvent	bp (°C)	Solubility (mg/mL)		
		RT	40 °C	60 °C
N-Methyl-2-pyrrolidone	202	294.0	457.9	701.9
N,*N*-Dimethylacetamide	166	231.0	377.9	604.4
N,*N*-Dimethylformamide	153	91.1	174.4	328.1
Cyclohexanone	155	50.7	99.9	194.1
Anisole	154	17.9	37.7	78.6
Bromobenzene	156	13.0	27.9	59.3
1-Hexanol	156	9.6	20.7	44.2
2-Heptanone	150	8.5	18.3	38.9
1-Heptanol	176	7.9	18.4	39.3
Phenetole	170	7.7	16.8	36.1
1-Octanol	196	7.4	15.7	33.7
n-Butyl acetate	126	6.3	13.6	29.2
Cumene	153	1.1	2.6	6.0
Mesitylene	163	0.66	1.6	3.8
cis-Decalin	190	0.13	0.34	0.9

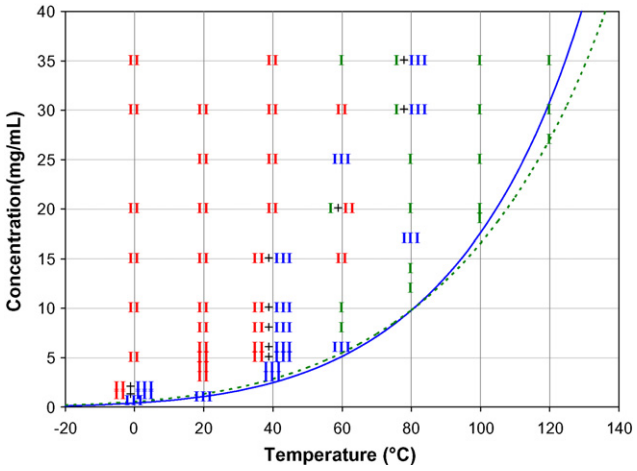

Fig. 1. Polymorphic outcome for carbamazepine in cumene: Numerals I–III indicate the polymorph initially obtained at various temperature–concentration conditions. The blue (solid) line and the green (dotted) line represent the temperature–solubility curves of polymorph III and polymorph I, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

reports. Krahn and Mielck (1987) reported that the transition temperature is slightly greater than 100 °C but a number or range was not given. Behme and Brooke (1991) reported the transition temperature to be 71 °C from heats of fusion and solubility data. Our result is in good agreement with the calculated value of 77.6 °C obtained from heats of solution and solubility data of Urakami et al. (2002).

3.3. Exploration of temperature–concentration space

Hot, undersaturated solutions of CBZ were prepared at elevated temperatures and then cooled rapidly down to the desired crystallization temperatures. Concentrations tested and results obtained are given numerically in Table 2 and shown graphically in Fig. 1.

Phase-space was explored between temperatures ranging from 0 °C to 120 °C and concentrations ranging from 1 mg/mL to 35 mg/mL. At lower concentrations, form III was obtained from 0 °C to 60 °C and form I was obtained at temperatures between 80 °C and 120 °C. At concentrations greater than or equal to 15 mg/mL, metastable form II was predominantly obtained up to 40 °C, mixtures of polymorphs were obtained between 60 °C and 80 °C, and form I was obtained at temperatures higher than 80 °C. Form IV was not observed in the temperature–concentration space explored with cumene. Fig. 2 shows the PXRD patterns of the reference standards (CBZ forms I–IV) obtained for this study. Fig. 3 shows representative PXRD patterns of polymorphs I–III as well as a mixture of forms I + III obtained within the explored grid.

4. Discussion

The objective of this work was to examine if most or all known polymorphs of a given compound could be obtained without resorting to several thousand experiments using a large

Table 2
Experimental conditions and results for exploring temperature–concentration space in the recrystallization of carbamazepine from cumene

Temperature (°C)	Concentration (mg/mL)	Preparation	Result
0	0.6	Reacti-therm	III
0	1.356	Reacti-therm	II + III
0	1.695	Reacti-therm	II + III
0	5.0	Reacti-therm	II
0	10.0	Reacti-therm	II
0	15.0	RS-12	II
0	20.0	RS-12	II
0	30.0	RS-12	II
0	35.0	RS-12	II
20	1.3	Reacti-therm	III
20	2.0	Reacti-therm	–
20	3.0	Reacti-therm	II
20	4.0	Reacti-therm	II
20	5.0	Reacti-therm	II
20	6.0	Reacti-therm	II
20	8.0	Reacti-therm	II
20	10.0	RS-12	II
20	15.0	RS-12	II
20	25.0	RS-12	II
20	30.0	RS-12	II
40	3.0	Reacti-therm	III
40	4.0	Reacti-therm	III
40	5.0	Reacti-therm	II + III
40	6.0	Reacti-therm	II + III
40	8.0	Reacti-therm	II + III
40	10.0	Reacti-therm	II + III
40	15.0	RS-12	II + III
40	20.0	RS-12	II
40	25.0	RS-12	II
40	30.0	RS-12	II
40	35.0	RS-12	II
60	6.0	RS-12	III
60	8.0	RS-12	I
60	10.0	RS-12	I
60	15.0	RS-12	II
60	20.0	RS-12	I + II
60	25.0	RS-12	III
60	30.0	RS-12	II
60	35.0	RS-12	I
80	10.0	RS-12	I
80	12.0	RS-12	I
80	14.0	RS-12	I
80	17.0	RS-12	III
80	20.0	RS-12	I
80	25.0	RS-12	I
80	30.0	RS-12	I + III
80	35.0	RS-12	I + III
100	16.0	RS-12	–
100	17.0	RS-12	I
100	18.0	RS-12	I
100	19.0	RS-12	I
100	20.0	RS-12	I
100	25.0	RS-12	I
100	30.0	RS-12	I
100	35.0	RS-12	I
120	27.0	RS-12	I
120	30.0	RS-12	I
120	35.0	RS-12	I

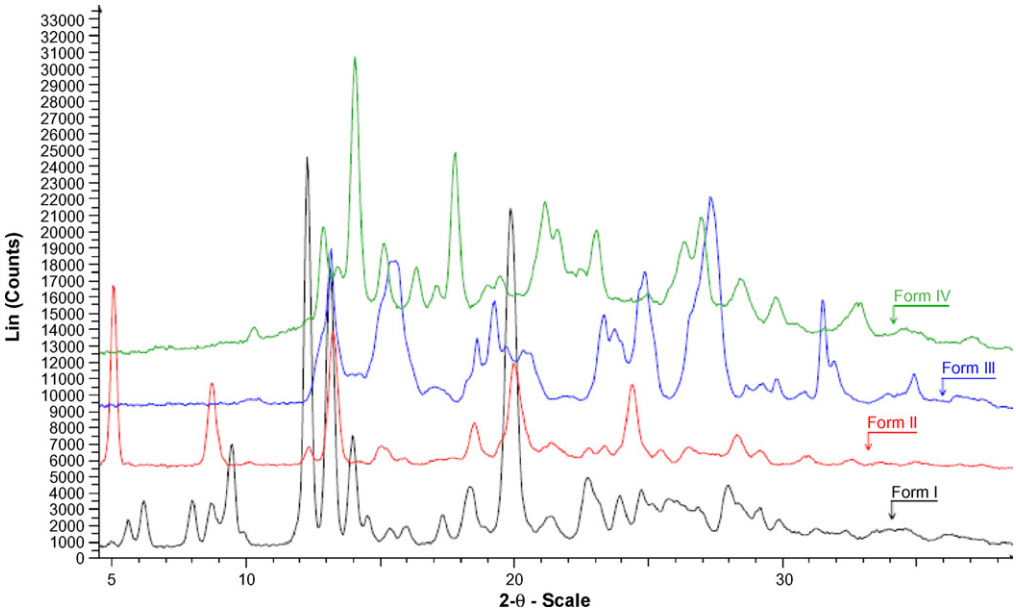

Fig. 2. Powder X-ray diffractograms from bottom to top: CBZ reference standards forms I–IV. The preparation of these standards is described in Section 2.

number of solvents. CBZ was chosen as the model compound as its polymorphs have been extensively studied. To date, four anhydrous polymorphs (forms I–IV) of CBZ are known to have single crystal structure determinations. At least four pseudopolymorphs (solvates) are known to exist (Hilfiker et al., 2003), but in this one-solvent polymorph screen, psuedopolymorphs were purposely avoided. Literature abounds with studies on CBZ polymorphism, and the differences in nomenclature for the forms studied have led to some confusion regarding the identity of these polymorphs (Grzesiak et al., 2003; Rustichelli et al., 2000; Behme and Brooke, 1991; Krahn and Mielck, 1987). For the purpose of this paper and for clarity, we have referred to the nomenclature by Grzesiak et al. (2003).

After careful selection of a suitable solvent and consideration of some experimental limitations, a temperature–concentration grid was constructed and experiments were carried out within this grid. The grid consisted of a practical range of temperatures and concentrations, such that upon cooling, varying degrees of supersaturation were attained. For each point on the grid, hot undersaturated solutions were rapidly cooled to the desired temperature and the resulting crystals were quickly isolated and characterized.

Based on practical constraints, the experimental grid comprised of temperatures ranging from 0 °C to 120 °C on the abscissa and concentrations ranging from 1 mg/mL to 35 mg/mL on the ordinate. Within the phase-space that was explored using

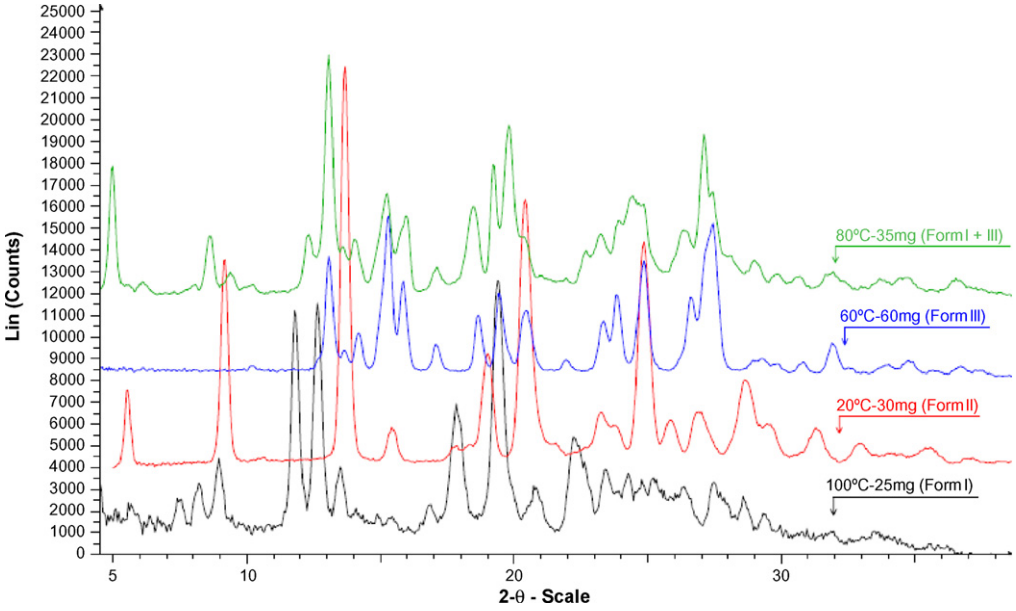

Fig. 3. Powder X-ray diffractograms representing coordinates on the experimental temperature–concentration grid from Fig. 1 and Table 2. From bottom to top: CBZ I (100 °C–25mg/mL); CBZ II (20 °C–30mg/mL); CBZ III (60 °C–6 mg/mL); CBZ I + III (80 °C–35 mg/mL).

this temperature–concentration grid, the observed crystallization behavior is depicted in Table 2 and Fig. 1. The results correlate somewhat with a phase–solubility diagram. At low supersaturation levels, the crystallization appears to be thermodynamically controlled over the entire temperature range, producing form III below and form I above the enantiotropic transition temperature for these two forms. The results are different at higher concentrations. At high supersaturation levels (more than twice the solubility of form III), the metastable form II is produced below the enantiotropic transition temperature, possibly indicating some means of kinetic control in which the solution-phase conformation favored by CBZ under these conditions is more similar to that of the metastable solid state. However, crystallization from ethanol at low temperature and high supersaturation also favors form II, thus molecular recognition by the solvent (cumene) may not be responsible for the kinetically driven crystallization of form II. The somewhat unpredictable polymorphic outcome observed between 60 °C and 80 °C suggests that near the transition temperature, especially at higher supersaturation levels, there is no thermodynamic control. Based on Threlfall's discussion (Threlfall, 2000) this is also the region where concomitant crystallization of enantiotropic polymorphs is likely to occur, which is consistent with our observation of obtaining mixtures of forms. Form IV was not observed in the one-solvent polymorph screen. This is not surprising since this was also the only form for which a reference standard could not be crystallized directly from solution. Form IV was reported to have been crystallized from a solution in methanol using hydroxypropyl cellulose in a molecular recognition role to direct its crystallization (Lang et al., 2002). In this work, a reference standard for form IV was reproducibly generated by desolvating a form obtained from wet methanol solution; solvates were purposely avoided in this study with cumene, thus the desolvation pathway was not available.

As with any method, there are limitations to the notion of using only one solvent to perform a comprehensive polymorph screen. In order to select a solvent that meets some of the criteria listed above, the solubility of the compound has to be determined in several high-boiling and safe solvents. Of course, solubility determinations should precede any type of polymorph screen. Although the results for CBZ were straightforward, interpretation of results could be more difficult without *apriori* knowledge of the physicochemical properties and thermodynamic relationships between different polymorphs of a compound. Comparing the one-solvent screen with a polymorph screen performed on CBZ using about 13 different solvents and five different crystallization conditions (Hilfiker et al., 2003), the obvious disadvantage of the one-solvent screen would be the inability to find solvates, including hydrates. In addition to the known dihydrate and acetone solvate, Hilfiker et al. found dioxane and DMSO solvates.

It should be clarified here that it is not the authors' intent to state that the polymorphic behavior of an API can be appropriately understood using just one solvent. Applying this technique, a comprehensive screen would likely involve exploring a relevant temperature–concentration grid using two to three appropriate solvents, and would need to be coupled with the technique of solution-mediated phase transformation (aging or slurry experiments) in about 15–20 commonly used process solvents (Miller et al., 2005). This combination of experiments will still be resource saving compared to more traditional polymorph screening, and should uncover all the relevant crystal forms. The one-solvent polymorph screen, repeated with two to three solvents, should identify relevant metastable forms by PXRD analysis of the crystallized solids. A plot of the PXRD results on a temperature–concentration grid, combined with thermal analyses of those solids, will provide a strong start to establishing energy relationships. The stable polymorph and/or solvates at room temperature would be identified by the slurry experiments. Any suspected enantiotropic polymorphs would require additional work to establish transition temperatures.

Nonetheless, the work presented herein provides a practical, rational design for polymorph screening. Confirming Threlfall's assertion (Threlfall, 2000), results presented in Fig. 1 delineate portions of the temperature–concentration grid for which crystallization of CBZ polymorphs from cumene are under thermodynamic control or being driven by kinetics. An obvious extension of this work would be to use a structurally different solvent, e.g., a straight chain alcohol such as pentanol and compare the results with those obtained from cumene. Additional studies with structurally diverse solvents as well as solute molecules would provide further insight into the interplay of thermodynamics, kinetics and influence of solvents (molecular recognition) in the crystallization of polymorphs.

5. Conclusion

The reported one-solvent polymorph screen of CBZ demonstrates how solvents can be either critical or immaterial in crystallizing specific polymorphs. By targeting multiple crystallization temperatures and supersaturation levels, three of the four polymorphs of carbamazepine (CBZ; 5*H*-dibenz [*b*,*f*]azepine-5-carboxamide) were crystallized from cumene (isopropyl benzene). Additionally, the transition temperature was determined to be between 79 °C and 82 °C for the enantiotropically related forms III and I. The results of this approach to polymorph screening raise questions about the importance of solvent diversity when searching for polymorphs. While the CBZ study pushed solvent diversity to the extreme by using only one solvent, it may be advantageous in general to repeat temperature–concentration grids with two to three solvents per compound. It is also suggested that this type of screening, which purposely avoids solvates, be combined with a solution-mediated phase transformation study under ambient conditions, using approximately 20 solvents. This combination of rational and purposeful polymorph screens would be expected to identify the stable polymorph at room temperature and all relevant polymorphs/pseudo polymorphs with an appropriate resource burn.

Acknowledgements

The authors would like to acknowledge Dr. Adam Matzger for providing the single crystal X-ray diffraction data (.cif file)

for CBZ form IV. The authors would also like to acknowledge members of the Materials Science group at Pfizer Global R&D, Ann Arbor, Michigan, for their insight and support.

References

Behme, R.J., Brooke, D., 1991. Heat of fusion measurement of a low melting polymorph of carbamazepine that undergoes multiple-phase changes during differential scanning calorimetry analysis. J. Pharm. Sci. 80, 986–990.

Byrn, S., Pfeiffer, R., Ganey, M., Hoiberg, C., Poochikian, G., 1995. Pharmaceutical solids: a strategic approach to regulatory considerations. Pharm. Res. 12, 945–954.

Frank, T.C., Downey, J.R., Gupta, S.K., 1999. Quickly screen solvents for organic solids. Chem. Eng. Prog. 95, 41–61.

Grant, D.J.W., 1999. Theory and origin of polymorphism. In: Brittain, H.G. (Ed.), Polymorphism in Pharmaceutical solids, 95. Marcel Dekker, New York, pp. 1–33.

Grzesiak, A.L., Lang, M., Kim, K., Matzger, A.J., 2003. Comparison of the four anhydrous polymorphs of carbamazepine and the crystal structure of form I. J. Pharm. Sci 92, 2260–2271.

Gu, C., Li, H., Gandhi, R.B., Raghavan, K., 2004. Grouping solvents by statistical analysis of solvent property parameters: implication to polymorph screening. Int. J. Pharm. 283, 117–125.

Hilfiker, R., Berghausen, J., Blatter, F., Burkhard, A., De Paul, S.M., Freiermuth, B., Geoffroy, A., Hofmeier, U., Marcolli, C., Siebenhaar, B., Szelagiewicz, M., Vit, A., von Raumer, M., 2003. Polymorphism—integrated approach from high-throughput screening to crystallization optimization. J. Therm. Anal. Calorim. 73, 429–440.

Hilfiker, R., De Paul, S.M., Szelagiewicz, M., 2006. Approaches to polymorphism screening. In: Hilfiker, R. (Ed.), Polymorphism: in the Pharmaceutical Industry. Wiley–VCH, Weinheim, pp. 287–308.

Krahn, Mielck, 1987. Relationships between several polymorphic forms and the dihydrate of carbamazepine. Pharm. Acta Helv. 62, 247–254.

Lang, M., Kampf, J.W., Matzger, A.J., 2002. Form IV of carbamazepine. J. Pharm. Sci. 91, 1186–1190.

Miller, J.M., Collman, B.M., Greene, L.R., Grant, D.J.W., Blackburn, A.C., 2005. Identifying the stable polymorph early in the drug discovery–development process. Pharm. Dev. Technol. 10, 291–297.

Morissette, S.L., Almarsson, O., Peterson, M.L., Remenar, J.F., Read, M.J., Lemmo, A.V., Ellis, S., Cima, M.J., Gardner, C.R., 2004. High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids. Adv. Drug Del. Rev. 56, 275–300.

Rustichelli, C., Gamberini, G., Ferioli, V., Gamberini, M.C., Ficarra, R., Tommasini, S., 2000. Solid-state study of polymorphic drugs: carbamazepine. J. Pharm. Biomed. Anal. 23, 41–54.

Storey, R., Docherty, R., Higginson, P., Dallman, C., Gilmore, C., Barr, G., Dong, W., 2004. Automation of solid form screening procedures in the pharmaceutical industry-how to avoid the bottlenecks. Cryst. Rev. 10, 45–56.

Suryanarayanan, R., Byrn, S.R. (Eds.), 2001. Characterization of the solid state. Adv. Drug Deliv. Rev. 48, 136.

Threlfall, T., 2000. Crystallization of polymorphs: thermodynamic insight into the role of solvent. Org. Process Res. Dev. 4, 384–390.

Urakami, K., Shono, Y., Higashi, A., Umemoto, K., Godo, M., 2002. A novel method for estimation of transition temperature for polymorphic pairs in pharmaceuticals using heat of solution and solubility data. Chem. Pharm. Bull. 50, 263–267.