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Supersaturation and solvent dependent nucleation of carbamazepine polymorphs during rapid cooling crystallization

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Polymorphic nucleation behavior of carbamazepine (CBZ) was investigated in terms of supersaturation in several solvents: nitromethane, acetonitrile, acetone, ethanol, 2-propanol and toluene. The solubility was measured and the effects of interaction between solvent and CBZ on solubility and polymorphic nucleation were discussed. It was found that the polymorphic forms of CBZ largely depended on the solvent type and supersaturation ratio. The carbonyl group in acetone blocked the NH…O interaction between dimer in form II by mimicking the same interaction with CBZ, then favored nucleation of form III. The aromatic-aromatic interaction between CBZ and solvent like toluene decreased the solute-solute interaction and favored formation of form II. The nucleation domains of CBZ polymorphs (forms II and III) were separated as a function of supersaturation ratio range in each solvent, and effects of solvents and supersaturation ratios on the induction time and transformation process were also explored. The interfacial energies of forms II and III in different solvents were calculated, and it was found that, at all investigated supersaturation ratios, the interfacial energy of form II in all solvents except acetone was always lower than that of form III, indicating that nucleation kinetics preferably favored formation of form II. However, at lower supersaturation ratios, thermodynamics was critical and form III was obtained.

Introduction

Crystal polymorphism is the ability of one molecule to adopt different molecular packing arrangements, or change its molecular flexibility in the crystalline structure, or include different co-formers in the crystal structure, such as solvent. These different forms can display significantly different physicochemical properties, such as melting point, solubility, stability, morphology and density[1]. Crystallization is a widely utilized purification step in pharmaceutical downstream processing, owing to it being a simple and the crystallization-filtration two step processes. The control over polymorphism in pharmaceutical crystallization is crucial, due to the different biological activities of the different polymorphs of the same pharmaceutical compound[2-4]. Additionally, it also influences the downstream operation of the particles due to the different morphology and density possessed by different polymorphs [5]. Therefore, it is of great significance to discover the potential polymorphic forms of active pharmaceutical ingredients (APIs) and to obtain the desired polymorph with high purity in the pharmaceutical industry[6, 7].

Solution crystallization is one of the most commonly used methods to prepare different polymorphs of one compound[8]. The final polymorph obtained in solution crystallization is largely determined by the nucleation and growth process[3, 9]. From the point view of thermodynamics, the crystal structure with the lowest lattice energy corresponds to the most stable polymorph, while crystal structures with higher energies result are metastable polymorphs. However, we should know that any given two polymorphs can be other monotropic or enantiotropic[10]. The relative kinetics of nucleation, growth and transformation of the metastable polymorph with respect to the stable polymorph influences the formation of a metastable polymorph[11]. Factors such as solvent[12], temperature[13], supersaturation ratio[5], seeding[14], pH[15] and template[16] can influence the polymorphic outcomes.

According to the Ostwald rule of stages, when leaving a system out of equilibrium, it will spontaneously go first to the 'nearest' metastable equilibrium. Then a cascade of metastable equilibrium can be observed before reaching the stable equilibrium [17, 18]. Therefore, the metastable forms should be observed before the stable form come out[19]. Recent research on polymorphic crystallization tends to focus on the nucleation and transformation process of metastable form to stable form by studying the influences of solvent and supersaturation ratio[20-22]. The role of the solvent is critical to the relative nucleation rate and sometimes influences the thermodynamic stability of solid solutions or solvates [23]. Furthermore, it was found that supersaturation ratio control was more effective than temperature control for isolation of the metastable form of paracetamol[24].

Carbamazepine (CBZ) is an anticonvulsant used to treat epilepsy and trigeminal neuralgia[25]. In pharmaceutical research, due to its diverse solid forms including five anhydrous

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polymorphs, one dihydrate form and many solvates and cocrystals, CBZ has been extensively studied as a model compound for polymorph screening and control[26-30]. *P*-monoclinic form III is thermodynamically stable below 70 ℃, whilst forms I, II and IV are metastable, though their crystallization kinetics can dominate in solution[31]. Currently, there are no data on the relative stability of form V, which is difficult to prepare by conventional crystallization.

It has been previously reported that both supersaturation ratio and solvent can determine the polymorphic nucleation of CBZ [32-34]. Florence et al. reported extensive experimental screening of the CBZ polymorphs in 66 solvents under 5 different conditions using an automatic parallel crystallization [30]. The result indicated that higher supersaturation ratios lead to higher crystallization rate, thus favoring the formation of form II, which is the least stable form of CBZ [30]. However, previous study of CBZ nucleation in toluene under quiescent condition disobeys the above conclusion, and it is found that form II nucleates in the lower supersaturation ratios while forms II and III concomitantly nucleate in the intermediate supersaturation ratios [5]. Hence, the polymorphic nucleation and transformation of CBZ in different solvents under different supersaturation ratios are not fully understood.

The aim of this work is to investigate the nucleation kinetics and transformation process of CBZ polymorphs in different solvents under a series of supersaturation ratios. To prepare supersaturated solutions, the solubility of stable form III in ethanol, 2-propanol, acetone, acetonitrile, nitromethane and toluene at temperature from 10 to 50 ℃ was measured using gravimetric method [35]. The effect of solvent polarity on the solubility of form III was evaluated. The crystallization experiments of CBZ were conducted in ethanol, 2-propanol, acetone, acetonitrile, nitromethane and toluene at 25 ℃ under different supersaturation ratios (S = 1.6 to 4.0), and magnetic stirring is considered during nucleation and transformation. The nucleation domains of CBZ polymorphs were determined with respect to supersaturation ratios and solvents. The induction time of different polymorphs was determined and the effects of interfacial energy on polymorphic nucleation were discussed. Polymorphic transformation process was characterized by microscope.

Experimental

Materials

CBZ ($C_{15}H_{12}N_2O$, CAS: 298-46-4) form III was purchased from ApolloScientific with a purity of 99%. Six solvents including ethanol, 2-propanol, acetonitrile, toluene, nitromethane and acetone, were chosen for crystallization experiments based on their range of boiling points and polarities. The polarity index of these solvents decreases in the order: nitromethane (6.8) > acetonitrile (6.2) > acetone (5.4) > ethanol (5.2) > 2-propanol (3.9) > toluene (2.3). All these solvents were analytically pure and purchased from VWR Chemicals.

Characterization methods

The crystal morphology of different polymorphs was visually examined by a light microscope Olympus CX41. The polymorphic form of CBZ crystals obtained at the initial nucleation onset and end of the crystallization experiment was confirmed by PXRD (PANalytical X'Pert PRO diffractometer).

Solubility measurement

The solubility of polymorph III in ethanol, 2-propanol, acetonitrile, nitromethane, toluene and acetone was determined at temperature from 10 to 50 ℃ using the gravimetric method [35], while the solubility of form II can be found in the previous article [36]. Excess amount of polymorph III was added to different solvents in a well-agitated 50 mL jacketed glass crystallizer. The temperature of the crystallizer was controlled by a water bath with an uncertainty of 0.05 ℃, and the solution was stirred for at least 12 h at each temperature to reach solid-liquid equilibrium. After settling excess solid solute without stirring, samples of the saturated solution were withdrawn and filtered through a 0.22 μm syringe filter into a previously weighed glass vial. The weight of the saturated solution was determined, then the solvent was allowed to evaporate in a vacuum oven at 25 ℃, and the polymorphic form and weight of dry CBZ crystals were determined. In this paper, the solubility is defined as grams of solute/gram of solvent on a solute-free basis.

Crystallization experiments

In these experiments, the aim is to study the polymorphic nucleation behavior and transformation of CBZ in different solvents at certain supersaturation ranges. The nucleation domains, induction time and polymorphic transformation with respect to solvent and supersaturation ratio were determined. Figure 1 shows the experimental apparatus, which consists of two water baths (F32, Julabo), two glass jacketed crystallizers, two thermometers, two magnetic stirrers (IKA) and two glass vials, where dissolution and crystallization took place. The purposes of the left bath and right bath are to control the temperature for dissolving and nucleating of CBZ in the glass vials, respectively.

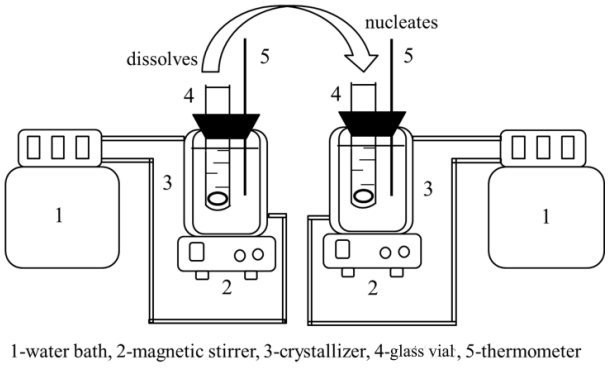

Figure 1. Schematic diagram of the experimental apparatus.

CBZ solutions with different supersaturation ratios ($S=C/C^*$, C being the initial concentration and C^* the solubility at the crystallization temperature T) were prepared by adding the required amount of CBZ form III into the 25 mL glass vial which contained the intended amount of solvents, including ethanol, 2-propanol, acetonitrile, nitromethane, toluene and acetone. The mixture was heated at 10 ℃ above the saturation temperature for 5 h at the stirring speed of 300 rpm until the solids dissolved. The solution was then rapidly cooled to the crystallization temperature to generate supersaturation by sending the left glass vial into the right crystallizer. The glass vial was hermetically sealed to avoid any evaporation of the solvent during the experiment. Crystallization experiments were carried out at initial supersaturation ratios from 1.6 to 4.0 at 25 ℃.

For each supersaturation ratio, the experiment was conducted at different solvents. The induction time was determined by naked eye observation and defined as the time interval between the instance when the left glass vial was introduced into the right crystallizer and the appearance of the first crystals in the solution [24, 37]. Upon nucleation, suspension samples withdrawn from the vial were placed under the microscope to determine their morphology, and the polymorphic forms were later confirmed by PXRD. The solution was kept stirred with the speed of 300 rpm, and samples were continually withdrawn at the time interval of 10 min. The morphology and polymorphic form of samples were examined.

Results and discussion

Identification of CBZ polymorphs

In our experiments, PXRD analysis and microscope characterization were performed to identify different polymorphs of CBZ, and it was found that only form III and II were crystallized out, and no other polymorphs and solvates were found. Figure 2 shows the PXRD patterns and microscope images of forms II and III obtained from ethanol. The two polymorphs had different crystal structures and displayed distinctly different PXRD patterns [38]. The microscope images show that forms III and II have the prismatic and needle shape, respectively [39].

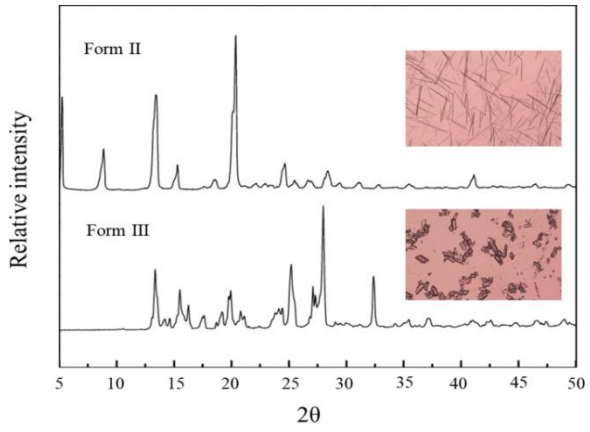

Figure 2. PXRD patterns and microscope images of CBZ forms II and III.

Solubility of CBZ form III

During solubility measurement, each solid phase in equilibrium with each solvent was characterized by XRD, and no other solid phase except form III was obtained, which is shown in Figure 3. Table 1 and Figure 4 show the solubility data of form III of CBZ in ethanol, 2-propanol, acetonitrile, toluene, nitromethane and acetone at temperature ranges from 10 to 50 ℃. The solubility of form III in these solvents increased with temperature, and at the same temperature solubility decreased in the order: nitromethane > acetonitrile > ethanol > acetone > 2-propanol > toluene. The polarity index of the solvents decreases in the order: nitromethane (6.8) > acetonitrile (6.2) > acetone (5.4) > ethanol (5.2) > 2-propanol (3.9) > toluene (2.3) [40]. Therefore, it is likely that the strong interaction between polar solvent and CBZ contributes to the higher solubility. The solubility data of form III in this paper is similar with the data reported by Liu et al. [41], which also shows that CBZ is most soluble in solvent with high polarity index.

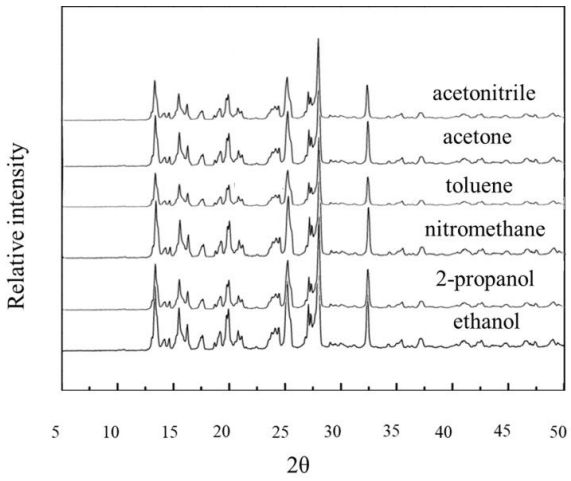

Figure 4. XRD patterns of CBZ solid phases in equilibrium with different solvents during solubility measurement.

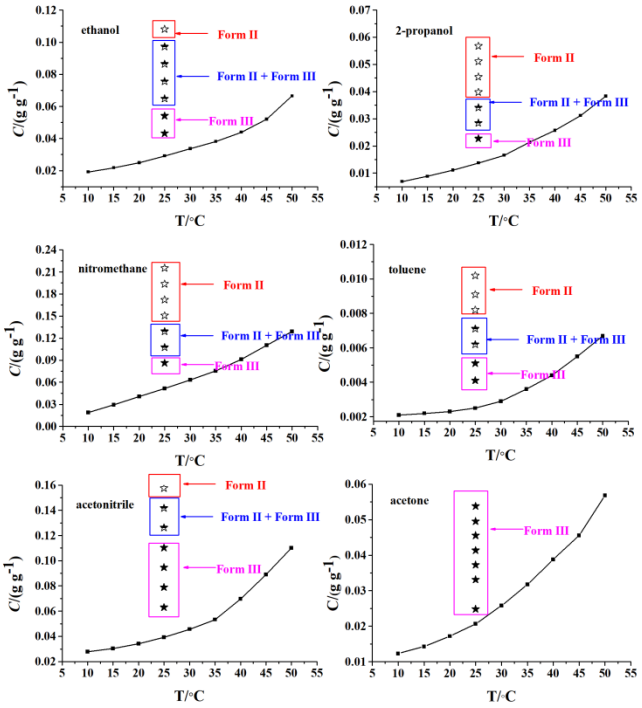

Figure 4. Solubility curves of form III and nucleation domains of CBZ polymorphs.

The effects of solvent on the solubility can be further evaluated by the solute-solvent interactions, including van der Waals force and hydrogen bonding [42]. The strength of solute-solvent van der Waals interactions can be evaluated by the dipolar polarizability, π* (Table 2) [43]. The strength of hydrogen bonding between the solvent and the solute can be evaluated by the hydrogen bond donor ability α, or the hydrogen bond acceptor ability β. According to the linear free energy approach for predicting solubility [43], the molar solubility of one compound in many solvents can be described by the following equation:

$$\ln x = a + b\delta^2 + c\alpha + d\beta + e\pi^* \quad (1)$$

where x is the molar solubility, δ is the solvent solubility parameter corresponding to the cohesive energy density, a, b, c, d, and e are (solvent-independent) coefficients characteristic of the process and indicative of its sensitivity to the accompanying solvent properties, and α, β, and π^* (Table 2).

Table 1. Solubility of form III in different solvents at different temperatures.

T/°C	Solubility-C*/(g g^{-1})					
	nitromethane	acetonitrile	acetone	ethanol	2-propanol	toluene
10	0.0188 ±0.0002	0.0278 ±0.0003	0.0123 ±0.0001	0.0192 ±0.0002	0.0069 ±0.0002	0.0021 ±0.0003
15	0.0295 ±0.0001	0.0305 ±0.0002	0.0143 ±0.0002	0.0218 ±0.0003	0.0088 ±0.0001	0.0022 ±0.0003
20	0.0406 ±0.0005	0.0343 ±0.0002	0.0172 ±0.0002	0.0249 ±0.0001	0.0111 ±0.0002	0.0023 ±0.0002
25	0.0517 ±0.0004	0.0394 ±0.0001	0.0207 ±0.0003	0.0292 ±0.0002	0.0137 ±0.0004	0.0025 ±0.0001
30	0.0633 ±0.0002	0.0457 ±0.0003	0.0258 ±0.0002	0.0337 ±0.0005	0.0166 ±0.0003	0.0029 ±0.0002
35	0.0753 ±0.0002	0.0533 ±0.0002	0.0318 ±0.0002	0.0381 ±0.0004	0.0214 ±0.0002	0.0036 ±0.0002
40	0.0911 ±0.0002	0.0698 ±0.0002	0.0388 ±0.0003	0.0439 ±0.0004	0.0257 ±0.0005	0.0044 ±0.0003
45	0.1102 ±0.0008	0.0891 ±0.0005	0.0456 ±0.0002	0.0521 ±0.0003	0.0312 ±0.0003	0.0055 ±0.0002
50	0.1292 ±0.0007	0.1102 ±0.0009	0.0568 ±0.0007	0.0665 ±0.0005	0.0383 ±0.0002	0.0067 ±0.0001

Table 2. Properties of the solvents

solvents	α	β	π^*
nitromethane	22	06	85
acetonitrile	19	40	75
acetone	08	43	71
ethanol	86	75	54
toluene	00	11	54
2-propanol	76	84	48

In eq (1), different solvents have different δ values (1.0, 0.5 and 0.0 for aromatic solvents, polychlorinated aliphatic solvents, and aliphatic solvents respectively) [44]. Hence, $b\delta^2$ should be equal to 0 in this study, and eq (1) can be simplified as follows.

$$\ln x = a + c\alpha + d\beta + e\pi^* \quad (2)$$

By fitting the solubility data obtained in this study to eq (2), we can express the solubility of form III at 25 °C by the following equation:

$$\ln x = 0.01627\alpha + 0.01553\beta + 0.09137\pi^* - 11.11714 \quad (3)$$

From eq (3), it can be seen that the coefficient for polarizability is higher than that for hydrogen bond acceptor ability and hydrogen bond donate ability by six times. This result further indicates that the solubility of form III is mainly affected by the polarizability of solvent, which can explain why the solubility of form III in acetonitrile and nitromethane with high π* values is higher than solubility in other solvents.

Role of solvent and supersaturation on the nucleation of CBZ polymorphs

The crystallization of CBZ polymorphs was conducted in ethanol, 2-propanol, acetonitrile, nitromethane, toluene and acetone under supersaturation range of 1.6 to 4 at 25 ℃. All nucleation experiments were carried out under the observation of naked eyes and microscope. Once nucleation was confirmed by naked eyes, the microscope was used to observe crystals and determine their polymorphs immediately. The first columns in Figures 5-10 show microscope images of CBZ polymorphs during nucleation onset in each solvent at different supersaturation ratios. Crystals with needle shape and prismatic shape represent form II and form III respectively. The nucleation domains of CBZ polymorphs are summarized in Figure 4 and Table 3. It is clear from Table 3 that form II nucleates at high supersaturation ratios in ethanol, acetonitrile, 2-propanol, nitromethane and toluene, indicating that high supersaturation ratios in these five solutions favor only the nucleation of comparatively less stable form II. Nucleation in the intermediate supersaturation ratios in ethanol, 2-propanol, nitromethane, toluene and acetonitrile shows the appearance of the stable prismatic shaped form III along with the metastable form II. The percentage of form III nucleation increased and that of form II nucleation decreased with decreasing supersaturation ratio in these five solvents. However, the nucleation results in toluene under low supersaturation ratios are inconsistent with those in previous literature [5], which reports the nucleation of less stable form II at the low supersaturation ratios. The main difference is that stirring was applied in this work while quiescent condition was applied in previous work, since the stirring effect on the polymorphic nucleation is tremendous and may result in different polymorphs nucleation [11]. Further decrease in the supersaturation ratio in ethanol, 2-propanol, nitromethane, toluene and acetonitrile favored only the nucleation of stable form III.

However, it should be noted that the nucleation of form III was favored in the whole supersaturation ratios in acetone, and no form II appeared. These results are somewhat agree with previous hypotheses that the aromatic-aromatic interactions are more important in the form III nucleation than form II [45, 46]. Due to their strong aromatic characters, nitromethane and toluene favor form II nucleation. For the absence of form II in acetone, it is because that the carbonyl group in acetone blocked the NH…O interaction between dimer in form II by mimicking the same interaction with CBZ, then favor form III [47]. Overall, it can be seen form Table 3 that the molecular weight of solvent also has a great impact on the nucleation result, since the number of pure form II occurrence in the whole supersaturation ratios range is high in nitromethane (61.04 g/mol), 2-propanol (60.09 g/mol) and toluene (92.14 g/mol), while it is low in ethanol (46.07 g/mol) and acetonitrile (41.05 g/mol).

Table 3. Nucleation results of CBZ in different solvents under different supersaturation ratios.

S	ethanol	toluene	2-propanol	acetonitrile	nitromethane	*S*	acetone
1.6	III	III	III	III	III	1.2	III
2.0	III	III	II+III	III	II+III	1.6	III
2.4	II+III	II+III	II+III	III	II+III	1.8	III
2.8	II+III	II+III	II	III	II	2.0	III
3.2	II+III	II	II	II+III	II	2.2	III
3.6	II+III	II	II	II+III	II	2.4	III
4.0	II	II	II	II	II	2.6	III

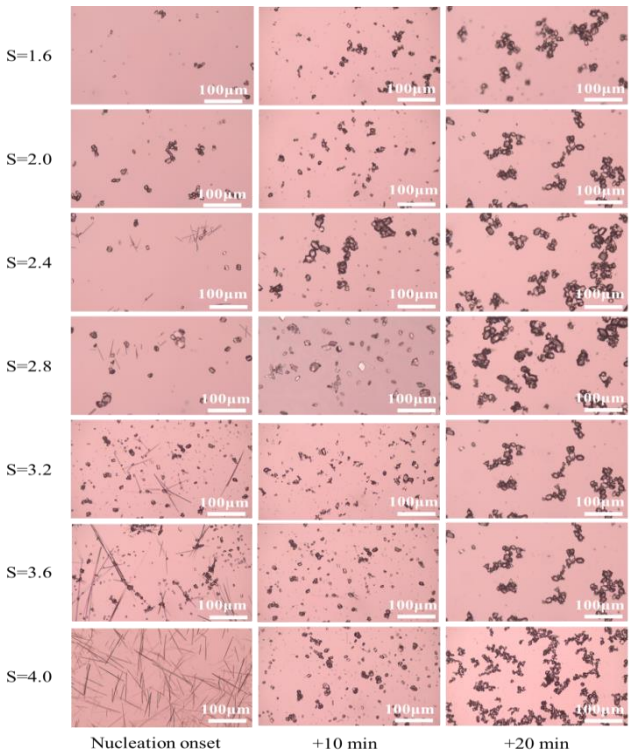

Figure 5. Polymorphic nucleation and transformation of CBZ with respect to initial supersaturation ratio and time in ethanol.

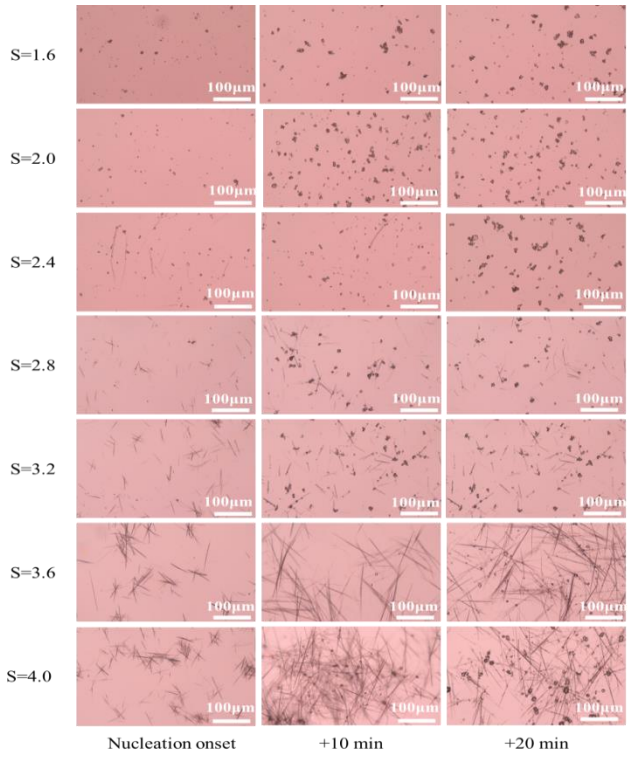

Figure 6. Polymorphic nucleation and transformation of CBZ with respect to initial supersaturation ratio and time in toluene.

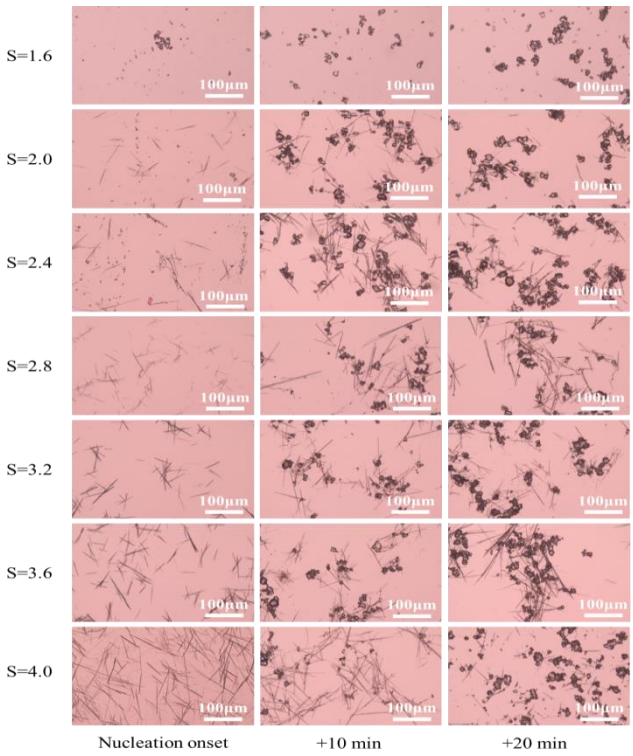

Figure 7. Polymorphic nucleation and transformation of CBZ with respect to initial supersaturation ratio and time in 2-propanol.

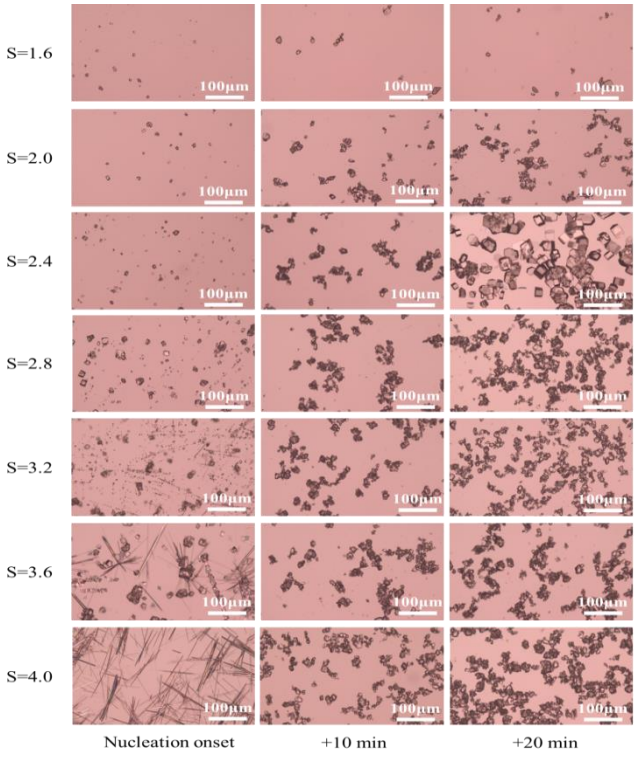

Figure 8. Polymorphic nucleation and transformation of CBZ with respect to initial supersaturation ratio and time in acetonitrile.

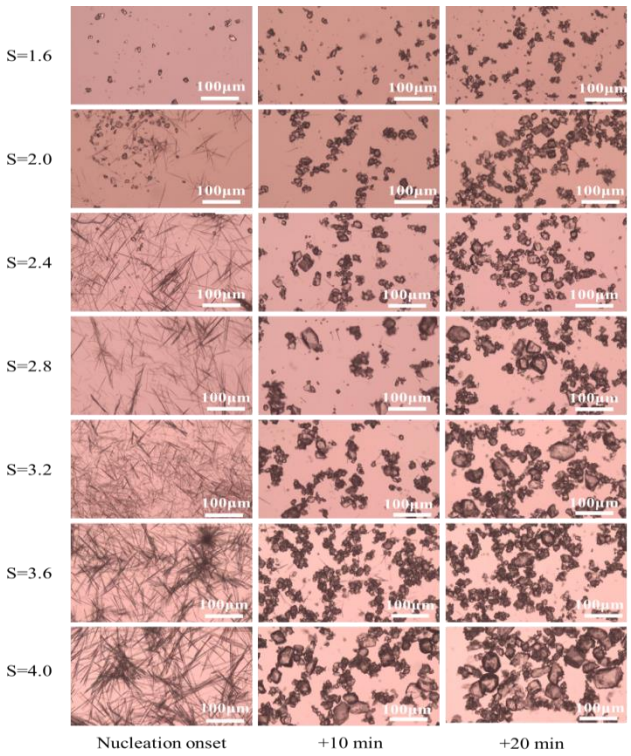

Figure 9. Polymorphic nucleation and transformation of CBZ with respect to initial supersaturation ratio and time in nitromethane.

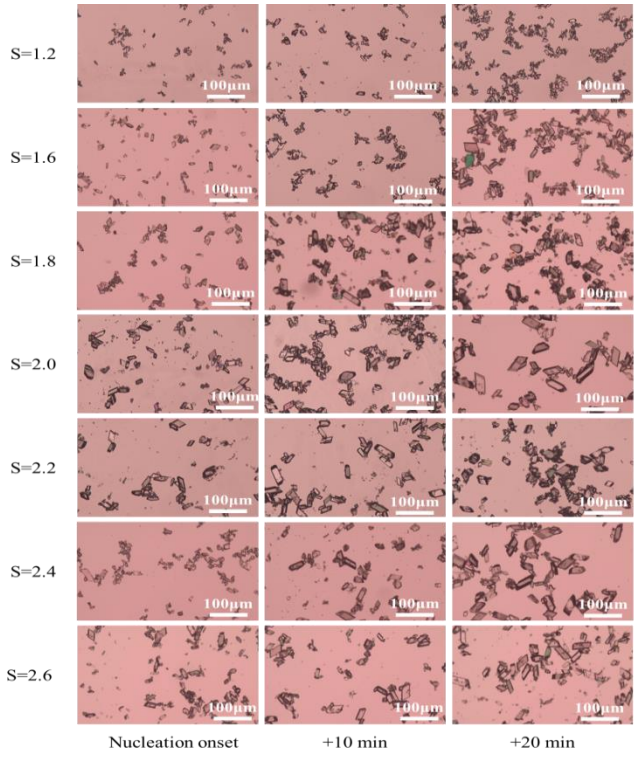

Figure 10. Polymorphic nucleation and transformation of CBZ with respect to initial supersaturation ratio and time in acetone.

Polymorphic nucleation kinetics

To investigate the effects of supersaturation ratio and solvent on the polymorphic nucleation, the kinetics was evaluated. The variation in the induction time of the different polymorphs of CBZ crystallized from solution at different supersaturation ratios is shown in Figure 11, which clearly shows that the induction time of different polymorphs changed with supersaturation. In the case of metastable form II nucleated at the supersaturation ratios range of 3.2 - 4.0 in 2-propanol, nitromethane and toluene, the induction time was less than 12 min when supersaturation ratio was 4.0 and the number of nucleation per unit volume was also high. The crystals obtained were observed under a polarizing microscope, and all of them were needle-like as shown in Figures 5-10. Whereas the induction time for concomitantly nucleation of forms II and III in the intermediate supersaturation ratios was more than those of pure form II, which could reach 20 min, and the number of nucleation per unit volume started to decrease.

In the case of nucleation of pure form III in the low supersaturation ratios, the induction time increased from 20 min to 200 min. It should be noted that the induction time of the stable form III in toluene increased from 1 min to 23 min when the supersaturation ratio decreased from 4.0 to 1.6. Figure 11 also confirms that the induction time changed without much variation until the supersaturation ratio decreased to 1.6. The number of prismatic-like particles nucleates of form III was also found increased remarkably as supersaturation ratio decreased.

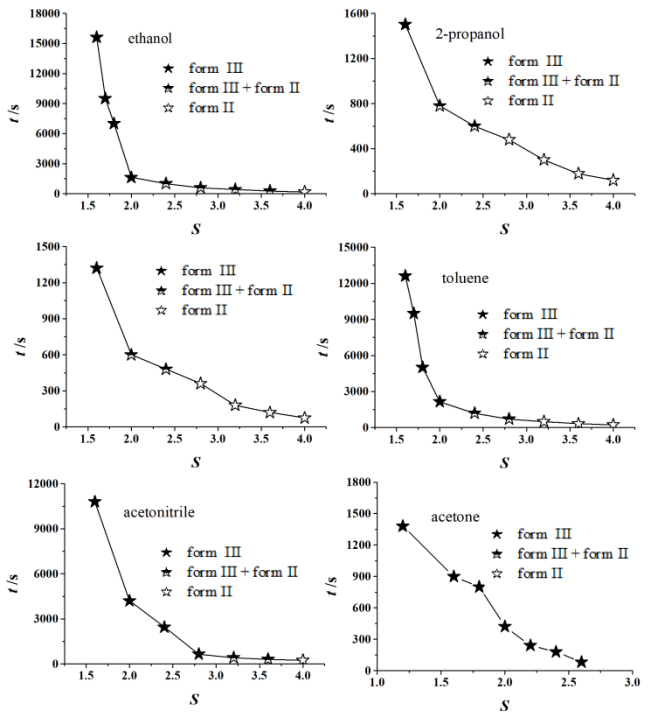

Figure 11. Induction time of CBZ polymorphs with respect to supersaturation ratios in different solvents at 25 °C.

To gain more insights into the polymorphic nucleation behavior of CBZ, the homogeneous nucleation was investigated. The classical theory of nucleation (CNT) assumes that solute clusters are formed in solution when the assembly clusters reach a critical size [48]. The clusters will dissolve if the clusters size is smaller than this critical size, or the clusters will grow into nuclei when clusters size exceeds this critical size. To simplify the CNT, the following assumptions are made:

1) the clusters are regarded ideally as spherical droplets, which have uniform interior densities and sharp interfaces;

2) the surface energy of a liquid droplet equals to that for a stable coexistence of liquid and solid phases at an infinite planar interface;

3) the clusters are incompressible and the surrounding vapor belongs to ideal gas with a constant pressure;

4) there is a quasi-equilibrium between nucleus and clusters;

5) the nucleus owns the same packing mode as the crystal;

6) f_s/f_v is used to characterize the shape of the nucleus.

Numerous authors [49-51] have discussed various assumptions inherent in CNT. Based on above assumptions, the crystal nucleation rate can be written as follows:

$$J = A\exp\left[-\frac{4f_s^3\gamma^3v^2}{27f_v^2k^3T^3\ln^2 S}\right] \quad (4)$$

where A refers to the pre-exponential factor, k is the Boltzmann constant, T is the absolute temperature, γ refers to the interfacial free energy, v is the molecular volume, S refers to the supersaturation ratio, f_s and f_v represent the surface and volume shape factors, respectively.

In terms of a homogeneous nucleation process, the induction time is considered to be inversely proportional to the crystal nucleation rate [48], as depicted in eq (5).

$$t_{ind}^{-1} \propto J \quad (5)$$

$$\ln t_{ind} = B + \frac{4f_s^3\gamma^3v^2}{27f_v^2k^3T^3\ln^2 S} \quad (6)$$

From eq (6), ln t_{ind} and $1/(\ln^2 S)$ have a linear relationship with line slope as follows:

$$a = \frac{4f_s^3\gamma^3v^2}{27f_v^2k^3T^3} \quad (7)$$

Then the interfacial free energy can be calculated from the slope:

$$\gamma = \left(\frac{27af_v^2k^3T^3}{4f_s^3v^2}\right)^{1/3} \quad (8)$$

In eq (8), parameters such as f_s, f_v and v can be calculated by the morphology information of CBZ polymorphs, and the values for forms II and III are f_s = 116.28, f_v = 28.57, v = 3.65 ·10^{-28} m^3 and f_s = 3.61, f_v = 0.42, v = 2.92 ·10^{-28} m^3 respectively.

A plot of ln(t_{ind}) vs $1/(\ln^2 S)$ was shown in Figure 12, and it can be seen that form III nucleated at low S while form II nucleated at high S in solvents except acetone. Therefore, the two straight lines in Figure 12 actually represent the primary nucleation of different polymorphs in ethanol, 2-propanol, nitromethane, toluene and acetonitrile. Based on Figure 12 and eq (8), the values of interfacial energies of the two polymorphs can be calculated from the slopes of the straight lines in the two regions of supersaturation ratio at 25 ℃, and the results are given in Table 4.

Table 4. Interfacial energies of CBZ polymorphs in different solvents at 25 ℃.

Polymorphs	Interfacial energy					
	nitromethane	acetonitrile	acetone	ethanol	2-propanol	toluene
Form II	1.8821	1.6264		1.7187	1.8125	1.6774
Form III	1.9326	1.6623	2.5166	2.532	1.8294	1.9612

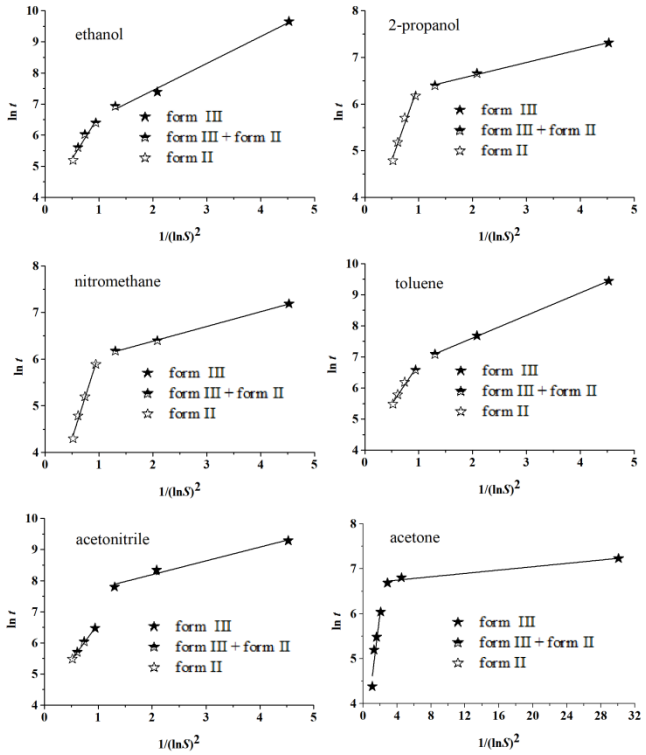

Figure 12. The plot of ln t vs $1/(\ln^2 S)$ of CBZ polymorphs in different solvents at 25 ℃.

From Table 4, it can be seen that the γ values for different polymorphs change with the solvents except acetone and the interfacial energies of the metastable form II were always less than those of stable form III. From the literature [52], the value of γ can serve as an indicator of the ability of solute to crystallize from solution spontaneously: the lower its value the preferable nucleation kinetics for the solute to crystallize. Therefore, the results in Table 4 indicate that nucleation kinetics preferably favored formation of form II. However, at lower supersaturation ratios, thermodynamics was critical and the stable form III was obtained.

Polymorphic transformation

The polymorphic transformation was observed for all the supersaturation ratios in different solvents. It confirms that the nucleated form III always retains the prismatic morphology in the solution at low supersaturation ratio. Due to the sudden increase in supersaturation ratio, the solution achieves a quasi-steady state distribution of molecular crystals favoring the nucleation of metastable form II for a short period of time, which then transform into more stable form III. Figures 5-10 show the morphology change during the polymorphic nucleation and transformation processes. In ethanol, the stable form III maintained its prismatic morphology from nucleation onset to the end of crystallization process at supersaturations ratio under 2.0, and metastable form II transformed into stable form III within 10 minutes at supersaturation ratios 2.0 - 4.0. After 10 min, it was observed that the nucleated needle shaped form II crystals started to dissolve at their edges. There was a significant reduction in size as well as the number of the needle shaped form II crystals because of dissolution. It indicates that the solution became undersaturated for form II with respect to its solubility and the concentration generated due to the dissolution of the form II provided the necessary supersaturation for the nucleation and growth of the form III in the solution. This led to the solution mediating the polymorphic transformation of the metastable form II to stable form III [53]. Figure 13 shows the polymorphic transformation results with respect to supersaturation ratio and solvent. It took more than 20 minutes to transform form II into form III in toluene and 2-propanol at the corresponding supersaturation ratio range of 2.8 - 4.0 and 2.0 - 4.0 respectively. The transformation kinetics of form II into form III in nitromethane and acetonitrile at the supersaturation ratio range of 2.0 - 4.0 and 3.2 - 4.0 was similar to those in ethanol, which needed less than 10 minutes to finish the transformation process. As the polymorph observed at the supersaturation ratio range of 1.6 - 4.0 in acetone from nucleation onset to the end was always form III, acetone favors the nucleation of stable form III despite high supersaturation ratio. Therefore, compared with other solvents, acetone is more suitable for crystallizing CBZ out with high purity of form III. The best way to separate form III from the polymorphic mixtures is to maintain a low initial supersaturation ratio or to wait until the transformation process is over under a high initial supersaturation ratio.

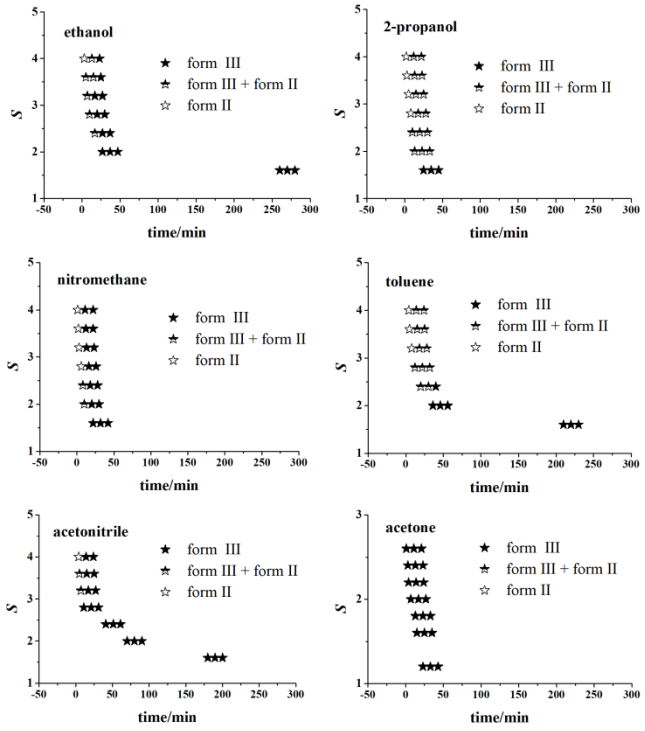

Figure 13. Polymorphic transformation vs time in different solvents at 25 ℃.

Conclusions

The polymorphic nucleation of CBZ in ethanol, 2-propanol, acetone, acetonitrile, toluene and nitromethane was studied in detail. It was found that the formation of different polymorphs of CBZ directly depended on the solvent and supersaturation ratio. The higher molecular weight solvents favored the formation of metastable form II, while the carbonyl group in acetone blocked the NH…O interaction between homodimer in form II by mimicking the same interaction with CBZ, then favored formation of stable form III. Although form III is the thermodynamically stable form, the results calculated from the induction time data showed that form II is the kinetically favored form with lower interfacial energy, which allows the initial nucleation of form II at high supersaturation ratios and transformation into form III. Thus, the subtle interplay between the solvent and supersaturation ratio determines the nucleation domains of these two polymorphs.

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