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Solution-mediated phase transformation of anhydrous to dihydrate carbamazepine and the effect of lattice disorder

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Abstract

This paper describes the kinetics of the solution-mediated phase transformation of the anhydrous monoclinic polymorph of carbamazepine (CBZ(A)) to the dihydrate crystal form (CBZ(D)). Monitoring both solution concentration and solid phase composition identified the steps and mechanisms that control the kinetic processes, and regulate the concentration of drug achieved during dissolution of the metastable solid phase, CBZ(A). The results show that the kinetics and the rate-controlling step for the transformation depend on grinding and storage conditions of CBZ(A). Grinding CBZ(A) shortened the transformation times and changed the rate-controlling step from crystallization of CBZ(D) to dissolution of CBZ(A). Grinding may cause various degrees of disorder in the form of lattice defects and/or amorphous regions. These disordered regions promote the anhydrous to dihydrate transformation by facilitating the surface nucleation of CBZ(D) on freshly ground CBZ(A) and on amorphous CBZ. The concentration-time profiles revealed aging effects on the solution-mediated transformation of ground CBZ(A) that were undetectable by diffraction and thermal analysis. These results have significant consequences on the concentration-time profiles of active pharmaceutical ingredients during dissolution of metastable solid phases, crystalline or amorphous.

Keywords: Crystallization; Transformation rate; Polymorphs; Amorphous solids; Grinding; Solubility

1. Introduction

Compounds that exist in various solid-state forms, crystalline or amorphous, offer unique challenges in product development and manufacturing (Morris et al., 2001). Pharmaceutical development of thermodynamically metastable forms is often desired because of their enhanced biopharmaceutical properties as a result of higher solubilities and faster dissolution rates. In other cases,

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metastable forms are unacceptable because of crystallization and transformation to a more thermodynamically stable form during processing, storage, or dissolution (Byrn et al., 1995; Zhu et al., 1996; Rodríguez-Hornedo and Murphy, 1999; Shekunov and York, 2000). In many cases of pharmaceutical importance, transformations take place in solution during dissolution of a metastable active form that compromise the delivery and therapeutic effect of a product by decreasing the concentration of drug available for absorption (Rodríguez-Hornedo et al., 1992; Kobayashi et al., 2000; Vippagunta et al., 2001). This behavior leads to erratic dissolution and is of special concern for drug compounds in which the range of therapeutic efficacy is narrow, such as carbamazepine (CBZ), an anticonvulsant routinely used in the treatment of epilepsy. Transformation to the more thermodynamically stable solid phase in water will decrease the concentration of drug dissolved and increase the risk of seizures.

CBZ, 5H-dibenz(b,f)azepine-5-carboxamide, exists as several anhydrous polymorphs, three have been well characterized by X-ray methods, the monoclinic or β-polymorph (Himes et al., 1981), the trigonal or α-polymorph (Lowes et al., 1987), and the triclinic or γ-polymorph (Ceolin et al., 1997). Two solvates, the dihydrate (Kahela et al., 1983; Reck and Dietz, 1986) and an acetone solvate (Terrence et al., 1983) have also been identified. The monoclinic and triclinic anhydrous forms are enantiotropic (Behme and Brooke, 1991) and the trigonal and triclinic forms are monotropic (Edwards et al., 2001). The monoclinic polymorph is the most stable and least soluble of the anhydrous forms at room temperature while the trigonal is the least stable and most soluble form (Edwards et al., 2001). Due to the confusion in the nomenclature of the various CBZ solid forms in the literature, the forms relevant to this work, the anhydrous monoclinic form is CBZ(A) and the dihydrate form is CBZ(D). Tablets of CBZ are formulated with the CBZ(A) polymorph because of its higher solubility and faster dissolution rate relative to the hydrated form CBZ(D). However, during storage at room temperature at relative humidities greater than 97% (Kaneniwa et al., 1984) and during dissolution in aqueous solutions, CBZ(A) transforms to CBZ(D) (Kahela et al., 1983; Kaneniwa et al., 1987; Young and Suryanarayanan, 1991; Kobayashi et al., 2000). This phase transformation results in a reduction in dissolution and bioavailability and explains the observed erratic dissolution from anhydrous CBZ tablets stored at different temperatures and relative humidities (Wang et al., 1993). Furthermore, the anhydrous to dihydrate CBZ transformation may be the cause for the reported changes in dissolution characteristics and clinical failures which initiated a major recall in 1988 of CBZ tablets (Meyer et al., 1992).

Solution-mediated transformations involve three essential processes: (a) dissolution of metastable solid, (b) self-recognition of the molecular units to nucleate a more stable solid phase, and (c) growth of the stable phase. These processes determine the concentrations achieved during a dissolution test of a thermodynamically metastable drug. Although there have been several studies on the anhydrous monoclinic to dihydrate CBZ transformation in solution (Young and Suryanarayanan, 1991; Luhtala et al., 1990; Kobayashi et al., 2000), there is little understanding of the consequences that both the solid phase and solution composition have on the transformation kinetics. A critical question is whether the presence of the anhydrous phase facilitates the heterogeneous nucleation or even epitaxial growth of the dihydrate form. In heterogeneous nucleation, the surface of the metastable phase acts as a nucleation substrate for the stable form. Epitaxial growth is a specific case of heterogeneous nucleation in which close values of crystal lattice parameters between the solid forms results in the oriented growth of the stable phase. This mechanism has been reported during dissolution of metastable solid phases (Rodríguez-Hornedo et al., 1992) and in the selective nucleation of polymorphs (Mitchell et al., 2001). The heterogeneous nucleation of dihydrate CBZ on the surface of CBZ(A) has been indicated (Laine et al., 1984; Lowes et al., 1987), although the conditions (i.e. solid phase composition and supersaturation) under which this occurs are unknown.

Mechanically induced structural changes of solid drug substances can occur unintentionally

during processing and can affect the pharmaceutical properties of a compound (Florence and Salole, 1976; Elamin et al., 1994; Mosharraf and Nystrom, 1999; Otsuka et al., 1999). The crystal structure can be disrupted to various degrees of disorder from lattice defects at molecular level dislocations to amorphous regions when the disorder is more extensive. Disorder induced by grinding or milling has been reported to increase the dissolution rate and metastable or dynamic solubility of poorly water-soluble compounds (Elamin et al., 1994; Mosharraf and Nystrom, 1999). Previous studies describe the solubility enhancement in terms of the ratio of crystalline and amorphous phases with little emphasis on the kinetics of dissolution and crystallization and on the rate-controlling steps that determine the concentration profile. A description in terms of amorphous to crystalline ratios is correct as long as the dissolution rate of the amorphous phase is faster than the crystallization rate i.e. a crystallization rate limited process. Models that explain the concentration-time profiles during a solution-mediated transformation have been developed (Cardew and Davey, 1985) and applied to polymorphic and anhydrous to hydrate transformations (Davey et al., 1986; Rodríguez-Hornedo et al., 1992; Bernstein et al., 1999; Rodríguez-Hornedo and Murphy, 1999).

This paper describes a study of the solution-mediated transformation of anhydrous monoclinic CBZ, CBZ(A) to the dihydrate form, CBZ(D). The goals of this study are to identify the rate-controlling processes and determine how mechanical activation of the anhydrous solid phase affects the kinetics and mechanism of the transformation.

2. Materials and methods

2.1. Materials

Anhydrous CBZ (CBZ(A); Lot # 28F0109) was purchased from Sigma Chemical Company (St. Louis, MO), stored at room temperature under 0% relative humidity, and used as received. Anhydrous CBZ was also recrystallized from methanol (Fisher Scientific, HPLC grade). Ten grams of CBZ were dissolved in 70 ml of methanol at 65 °C. The solution was cooled to 10 °C in an ice bath, and after 20 min, the crystals were filtered off and dried in an oven for 3 h at 65 °C under reduced pressure (25 mmHg). Ground CBZ was prepared by grinding CBZ(A) in a mortar and pestle for 15 min. Amorphous CBZ was formed by quench-cooling the melt of CBZ(A) in liquid nitrogen.

CBZ dihydrate CBZ(D) was prepared by crystallization from aqueous solutions supersaturated with respect to the dihydrate form and used for solubility and dissolution studies. Supersaturation was created by dissolving CBZ(A) (0.31 mg/ml) between 50–65 °C under constant stirring, filtering the solution to remove any extraneous particulates, and cooling the filtrate to 5 °C. CBZ(D) crystals were filtered and stored at 100% RH at room temperature. Water used in this study was filtered through a double deionized purification system (Milli Q Plus Water System from Millipore Co., Bedford, MA).

2.2. Solubility of anhydrous and dihydrate CBZ

The solubility of dihydrate CBZ, S_D, was determined from undersaturation by adding an excess of CBZ(D) solid phase to aqueous solutions. The suspensions were placed in a shaker water bath (Precision Scientific Model 25, Winchester, VA) set at 100 rpm and a temperature of 25 ± 1 °C. Samples were withdrawn at 24, 48, and 72 h. Aliquots were withdrawn using plastic syringes and filtered with 0.22 μm filters (Millipore, Bedford, MA). CBZ concentration in solution was measured by UV spectrophotometry using a Perkin-Elmer Lambda 7 UV/VIS spectrophotometer (Shelton, CT) at 284.5 nm. In all systems, the equilibrium concentration was achieved by 72 h and the average sample concentration at 48 and 72 h differed by $< 2\%$. Solubility studies were done in triplicate. Solid phases at equilibrium were characterized by X-ray powder diffraction (XRPD), thermal gravimetric analysis and differential scanning calorimetry (DSC).

Since the anhydrous form undergoes a phase conversion to the dihydrate, the solubility of anhydrous CBZ, S_A, was estimated from the initial

disk dissolution rates of anhydrous and dihydrate CBZ under sink conditions, and from the measured equilibrium solubility of dihydrate CBZ using the method described by Shefter and Higuchi (1963).

2.3. Disk dissolution

Intrinsic dissolution rates of anhydrous monoclinic and dihydrate CBZ were measured with a rotating disk apparatus in a die of 10 mm diameter. Solids were compressed in a Carver hydraulic press at 5000 psi for 45 min. Preparation of the disk at lower compression pressures and at shorter times resulted in fracture of the compact parallel to the surface of the disk after initial wetting by the dissolution media. Powder X-ray diffraction analysis under these conditions confirmed that no measurable conversion had taken place during preparation of the disk. Dissolution studies were done at 10, 25 and 37 °C and the temperature controlled to ±0.1 °C by a circulating water bath (Neslab RTE 210, Portsmouth, NH). The dissolution medium consisted of 400 ml of water. The die containing the compacted sample was rotated at 100 rpm. The concentration of CBZ was determined every 30 s for a total of 120 min by means of a peristaltic pump that continuously circulated the dissolution medium through a 1 cm cell inside a UV spectrophotometer (Perkin-Elmer 3B) at 284.5 nm. Sink conditions were maintained throughout the experiment.

2.4. Solution-mediated transformation of anhydrous to dihydrate CBZ

The transformation from anhydrous to dihydrate CBZ was studied from suspensions of CBZ(A) in solutions initially supersaturated with respect to the dihydrate phase at 25 °C. Solutions supersaturated with respect to CBZ(D) were prepared by completely dissolving anhydrous CBZ(A) in water under constant stirring at a temperature between 50–65 °C. In this report, relative supersaturation refers to the ratio of CBZ concentration in solution to the solubility of CBZ(D), C/S_D, and supersaturation refers to $\sigma_D = (C/S_D) - 1$. The amount of CBZ(A) added and dissolved was sufficient to achieve a supersaturation with respect to CBZ(D) of 1.5 at 25 °C. The solution was filtered and rapidly cooled in an ice bath to 25 °C to avoid crystallization of CBZ(D). Two-hundred and fifty milliliters of the solution supersaturated with CBZ(D) was placed in a jacketed beaker at 25±1 °C. At the start of an experiment, ground or unground CBZ(A) was added to the solution, forming a suspension. To investigate the effects of the mass and total surface area of ground and unground CBZ(A), experiments were done at constant initial mass, 500 mg, or constant surface area, 0.25 m^2. The suspension was stirred at 400 rpm. Aliquots of the suspension were withdrawn at various time intervals with a plastic syringe and filtered through a 0.45 μm Millipore filter in a 13 mm Swinex disc filter holder. The filtrate was appropriately diluted and the concentration of CBZ in solution determined by the method described in the solubility section.

At periodic intervals during the transformation of anhydrous to dihydrate CBZ, 5–10 ml of the suspension were filtered under reduced pressure (25 mmHg) for 40 min to remove physically bound water (Young and Suryanarayanan, 1991). Approximately 2–10 mg of solid phase were accurately weighed using a Mettler ultra-microbalance (Columbus, OH) with an accuracy of ±0.1 μg. The solid phase was dried in a vacuum oven at ~60 °C under reduced pressure (25 mmHg) to constant weight. The weight fraction of anhydrous and dihydrate CBZ was quantified by comparing the percent weight loss of dried samples to a standard curve based on physical mixtures of known composition of CBZ(A) and CBZ(D). To test whether the anhydrous transformed to dihydrate during the filtration and drying procedure, CBZ(A) was dispersed in water, immediately filtered for 40 min, and dried to constant weight at ~60 °C under reduced pressure (25 mmHg). The percent weight loss measured was 0.55±0.11. To confirm that filtration does not remove water in the crystal hydrate, aliquots of a 1.25 mg/ml suspension of CBZ(D) were filtered for 40 min and dried to constant weight at ~60 °C under reduced pressure (25 mmHg). The percent weight loss measured was 13.12±0.05 (mean±SD, $n = 3$) in good agreement with the theoretical value of

13.2%. Ground and unground CBZ(A) solid samples were found to contain $0.06 \pm 0.01\%$ and $0.05 \pm 0.02\%$ of water based on weight loss on drying at 60 °C to constant weight. Young and Suryanarayanan (1991) developed this weight loss method and showed to be in good agreement with the results from XRPD.

2.5. Surface area determination

The specific surface areas of ground and unground anhydrous CBZ samples were measured with a Quantasorb® surface area analyzer (Quantachrome Co., Syosset, NY) using nitrogen gas as the adsorbate and applying the BET equation. The measured specific surface areas for the unground and ground anhydrous solid forms was 0.07 and 0.50 m^2/g.

2.6. Chemical stability

The stability of ground and unground samples of CBZ was determined by thin layer chromatography (TLC) according to a method reported in the literature (Krahn and Mielck, 1989). A solution of 10 mg of CBZ in 1 ml of methanol was added onto TLC plates. Plates were developed with a mixture of methanol, ethyl acetate, and toluene (1:5:4 volume parts). After drying in an air stream, CBZ was visually detected under a UV lamp.

2.7. X-ray powder diffraction

The powder patterns of CBZ solid phases were recorded using a Scintag X-ray diffractometer (Franklin, MA) using Cu Kα radiation ($\lambda = 1.5418$ Å), tube voltage of 35–45 kV, tube current 20–40 mA, 2θ from 2° to 50°, scan rate of 5°/min, and step size of 0.020°.

2.8. Differential scanning calorimetry

The thermal properties of CBZ were determined by DSC using a Perkin-Elmer DSC-7. Samples were accurately weighed into aluminum pans and sealed with a crimper. The thermal behavior was studied in sealed aluminum pans under a dry nitrogen purge (20 cc/min) at a heating rate of 10 °C/min.

2.9. Microscopy

CBZ solid was examined during the transformation while suspended in the transformation medium with an inverted light microscope (Nikon, Diaphot-TMD, Nikon Inc., Melville, NY) with $10\times$ and $40\times$ Nomarski objectives. Solid phases were also examined using scanning electron microscopy (SEM) (Hitachi S-3200N, Tokyo, Japan). Samples were prepared by transferring the CBZ solid to a strip of double-sided carbon tape (Ted Pella, Inc., Redding, CA) attached to a standard SEM mounting stub. The samples were subsequently coated with gold for 200 s (Desk II, Denton Vacuum, Moorestown, NJ) to prevent charging at the surface. The microscope was operated with 15 kV beam current.

3. Results

3.1. Solubility of anhydrous and dihydrate CBZ

The solubility of anhydrous monoclinic CBZ, S_A, was estimated from the disk dissolution rates of anhydrous and dihydrate CBZ under sink conditions and from the measured equilibrium solubility of CBZ(D), S_D, using the method of Shefter and Higuchi (1963). The anhydrous solubility was estimated according to

$$S_A = \frac{(dC/dt)_A}{(dC/dt)_D} S_D$$

This equation is valid when the dissolution rate constant is equal for both crystal forms and is proportional to the diffusion coefficient, the boundary layer thickness, and the surface area of the dissolving solid (i.e. dissolution is diffusion-controlled). A diffusion-controlled dissolution mechanism has been reported for CBZ(D) based on the linear relationship between the square root of the rotational speed and disk dissolution rate under sink conditions at 37 °C (Crison et al., 1997). Since the hydrodynamic conditions and

surface area are constant during disk dissolution, both the anhydrous and dihydrate crystal forms have the same dissolution rate constant.

During disk dissolution in aqueous media, CBZ(A) has been shown to undergo a phase change to the dihydrate form (Kaneniwa et al., 1987; Kobayashi et al., 2000). This transformation results in a change in slope of the concentration-time profile (Fig. 1). Therefore, the dissolution rate of CBZ(A) was calculated from the initial linear portion of the concentration-time profile. Although the concentration of CBZ in the bulk solution is below saturation with respect to the dihydrate phase, a solution-mediated transformation during disk dissolution of CBZ(A) is possible if the solution adjacent to the disk is supersaturated with respect to the dihydrate form. Crystallization of CBZ(D) could then occur on the surface of the disk or within the boundary layer resulting in a decrease in the dissolution rate of CBZ(A). The presence of CBZ(D) on the surface of anhydrous CBZ disk after dissolution has been confirmed by SEM and DSC thermograms (Lowes et al., 1987; Kaneniwa et al., 1987; Kobayashi et al., 2000). The intrinsic dissolution rates for anhydrous monoclinic and dihydrate are shown in Table 1. Heats of dissolution calculated from the slope of ln (dissolution rate) versus ($1/T$) line, were 37 and 50 kJ/mole for CBZ(A) and CBZ(D), respectively.

Table 1
Intrinsic dissolution rates (μg/(cm^2 min)) of CBZ anhydrous monoclinic, CBZ(A), and dihydrate, CBZ(D)

T (°C)	CBZ(A)	CBZ(D)
10	9.45 ± 0.05[a]	2.58 ± 0.02
25	22.00 ± 1.73	7.24 ± 0.05
37	37.60 ± 0.69	16.60 ± 0.07

[a] Standard deviation.

The dissolution rate and solubility ratios of anhydrous monoclinic to dihydrate CBZ range from 3.67 at 10 °C to 2.26 at 37 °C (Fig. 2). At 25 °C the solubility of the anhydrous form is 0.379 mg/ml whereas the dihydrate form has a solubility of 0.125 mg/ml. The heats of solution calculated from a Van't Hoff-type plot were 18 and 33 kJ/mole for CBZ(A) and CBZ(D), respectively. Kaneniwa et al. (1987) reported 38 kJ/mole for both forms in the temperature range of 20–50 °C. The discrepancy in the heat of solution of CBZ(A) may be a result of the effect of the transformation kinetics on the solubility estimates and the lower temperature range included in our work. The transition temperature at which the hydrate and anhydrous forms have the same solubility was calculated to be 100 °C.

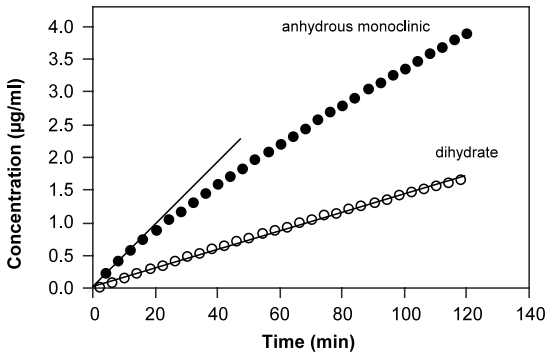

Fig. 1. Typical concentration profiles during the dissolution of anhydrous monoclinic CBZ (●) and dihydrate CBZ (○) from a disk in water at 25 °C.

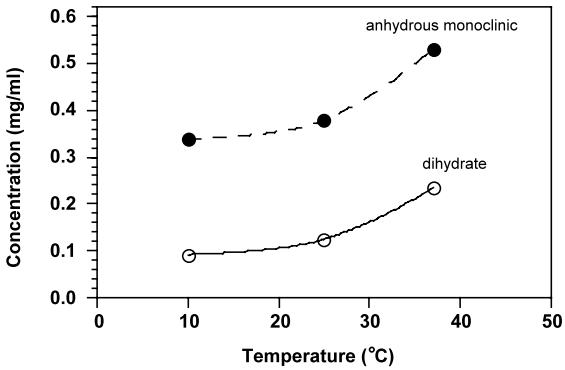

Fig. 2. Solubility dependence on temperature for anhydrous monoclinic CBZ (●) and dihydrate CBZ (○). Anhydrous CBZ solubility estimated from initial dissolution rate and dihydrate CBZ solubility determined by equilibrium method.

3.2. Effect of grinding anhydrous monoclinic CBZ on the solution-mediated transformation to dihydrate

The effects that grinding and initial surface area of CBZ(A) have on the rate and extent of transformation to the dihydrate form are shown in Fig. 3. The initial surface area was increased from 0.04 to 0.25 m^2 by two methods: (1) grinding CBZ(A) for 15 min in a mortar and pestle, and (2) increasing the initial mass of unground CBZ(A) added to the solution. All systems show a plateau supersaturation. The unground systems achieved a supersaturation with respect to CBZ(D) consistent with the solubility of CBZ(A) while the ground solid achieved a lower supersaturation half the way between the solubilities of the dihydrate and anhydrous forms. Grinding shortened the anhydrous to dihydrate transformation times.

Dissolution of unground CBZ(A) crystals maintained the concentration in solution close to the solubility of the anhydrous form despite a concentration of CBZ in solution of three times the dihydrate CBZ solubility, $\sigma_D = 2.0$ (Fig. 3). Increasing the initial surface area of unground CBZ(A), did not promote crystallization of CBZ(D). This behavior was observed with both unground CBZ(A) crystals used as received and CBZ(A) recrystallized from methanol. Microscopic examination showed that there were very few dihydrate crystals present ($< 5\%$) and mostly the anhydrous solid phase remained suspended in solution at around 20 h.

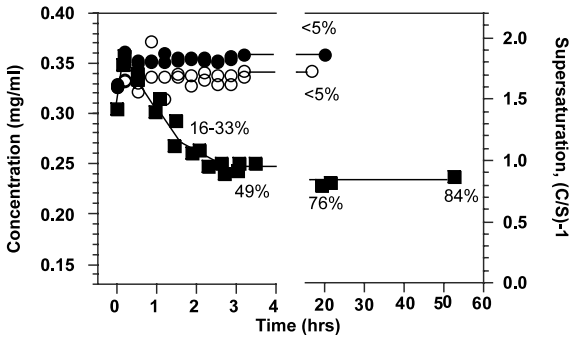

Fig. 3. Effects of grinding and initial surface area of CBZ(A) solid phase on the supersaturation profile and solid phase composition (% CBZ(D)) during the transformation of anhydrous to dihydrate CBZ at 25 °C. *Key:* unground 0.004 m^2 (500 mg) (○); unground 0.25 m^2 (3.4 g) (●); ground 0.25 m^2 (500 mg) (■).

Ground CBZ(A) transformed to the dihydrate form at a faster rate than the unground solid. CBZ(D) crystallized from solution resulting in a decrease in solution concentration to a supersaturation plateau of 0.85, 1.85 times the solubility of the dihydrate form (Fig. 3). Microscopy studies were carried out to determine if specific crystal faces of ground CBZ(A) promoted nucleation of CBZ(D). Dihydrate crystals were observed microscopically as long needles and plates in the bulk solution and on the surface of large and agglomerated crystals of CBZ(A) (Fig. 4). This observation confirms the heterogeneous nucleation of CBZ(D) on the surface of ground CBZ(A). Preferential nucleation on a given crystal face of CBZ(A) was not observed. A similar kinetic profile was observed for unground and ground anhydrous CBZ using a 106–150 μm sieve fraction. Monitoring the solid phase composition during the transformation of ground CBZ(A) indicates that the decrease in solution concentration corresponds to an increase in the fraction of CBZ(D). The initial dip in supersaturation corresponded to 50% of the transformation in 3 h (Fig. 5). At the plateau supersaturation (20–50 h) the percent of dihydrate in the solid phase was 76–84%.

While grinding CBZ(A) increased the transformation rate to CBZ(D), this effect was dependent on aging of ground CBZ(A) (Fig. 6). The transformation profile of ground anhydrous CBZ became similar to that of unground CBZ(A) upon storage for a period of 28–29 days at room temperature (~ 23 °C) and 0% relative humidity after grinding. Similar to the unground system, only crystals of CBZ(A) remained suspended in solution after a period of 35 h. The effect of aging ground anhydrous CBZ on the transformation rates was dependent on the grinding time. Grinding for a longer time (40 min) increased the storage time required for the aging effect to be manifested.

To explain the differences in the transformation and nucleation behavior of ground CBZ(A), the physical and chemical stability of the solid phase after the grinding process were investigated.

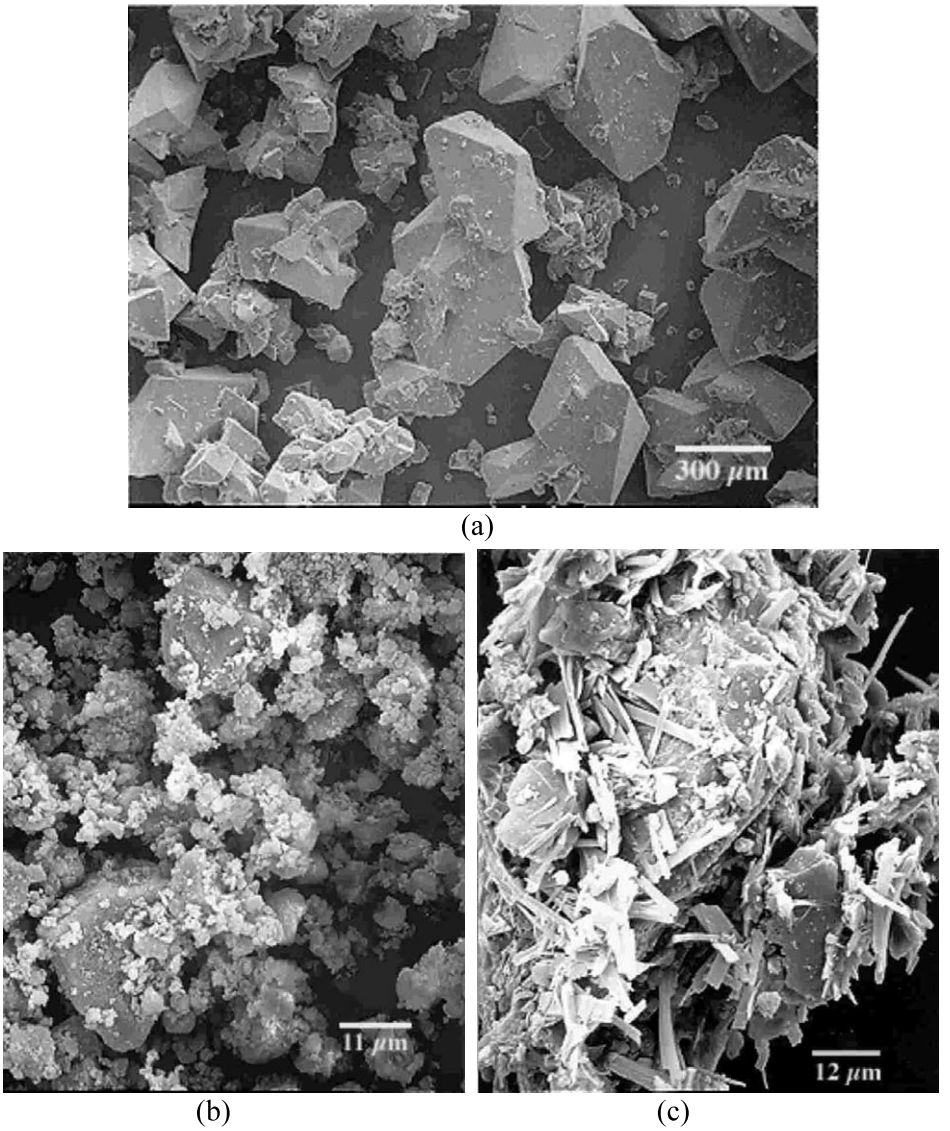

Fig. 4. Scanning electron photomicrographs of CBZ solid phases: (a) unground CBZ(A); (b) ground CBZ(A); (c) solid phase collected 20 min during the transformation of ground CBZ(A), needle-shaped crystals are CBZ(D).

Ground CBZ(A) samples were found to be chemically stable for at least 3 months after grinding by TLC. The XRPD patterns of freshly ground CBZ(A) and the calculated powder patterns of the trigonal anhydrous CBZ, CBZ(A), and CBZ(D) are shown in Fig. 7. Two of the most intense reflections at $2\theta = 5.1$ and 8.8° in the powder pattern of the trigonal polymorph are absent in the XRPD pattern of ground CBZ(A). This suggests that grinding did not induce the anhydrous monoclinic to trigonal polymorphic transformation beyond the 5–10% detection limit. Lefebvre et al. (1986) have also shown that CBZ(A) does not convert to CBZ(T) after grinding in a ball mill for 15 and 60 min. Similarly, grinding did not induce the solid-state conversion of anhydrous to dihy-

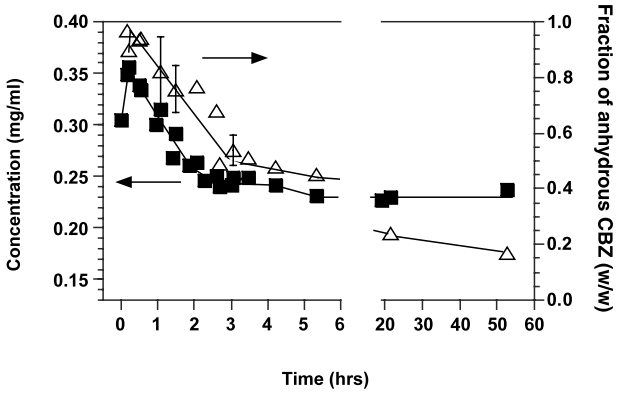

Fig. 5. CBZ concentration in solution and solid phase composition during the anhydrous to dihydrate phase transformation of ground CBZ(A) at 25 °C.

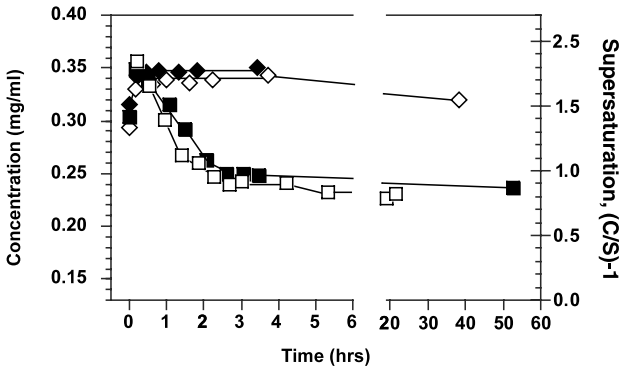

Fig. 6. Effect of batch age of ground CBZ(A) on the supersaturation profile during the transformation of anhydrous to dihydrate CBZ at 25 °C. *Key:* storage time after grinding (days): 0 (□), 3 (■), 27 (◇), 28 (◆).

drate CBZ as evidenced by the absence of peaks at $2\theta = 6.2$ and 9.0° in the powder pattern of the ground anhydrous form.

A comparison between the XRPD patterns of unground and freshly ground anhydrous CBZ (Fig. 8) shows a reproducible and significant decrease in the intensities of all reflections and an increase in the line broadening of freshly ground CBZ(A) samples. An amorphous halo was sometimes observed in the powder patterns of freshly ground samples (Fig. 7), even though neither a glass transition nor a crystallization exotherm were detected in the DSC thermograms of ground CBZ(A) samples.

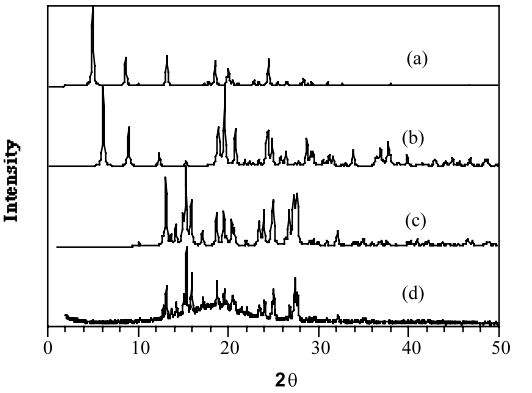

Fig. 7. Calculated XRPD patterns from single crystal structure data for (a) dihydrate CBZ(D) (Reck and Dietz, 1986), (b) trigonal anhydrous CBZ (Lowes et al., 1987), and (c) monoclinic anhydrous CBZ (Himes et al., 1981); experimental X-ray powder pattern of (d) freshly ground anhydrous monoclinic CBZ (Scintag XRPD Tube Voltage: 45.0 kV; Tube Current: 40.0 mA; scan rate: 5°/min; step size: 0.020°).

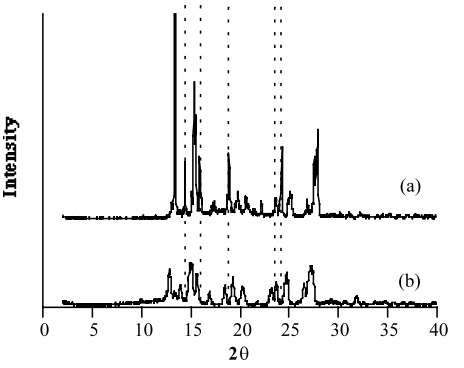

Fig. 8. X-ray power diffraction patterns of (a) unground and (b) freshly ground, anhydrous monoclinic CBZ. (Scintag XRPD Tube Voltage: 35.0 kV; Tube Current: 20.0 mA; scan rate: 5°/min; step size: 0.020°.)

In order to determine whether disordered regions in the CBZ crystals would promote the nucleation of the dihydrate form, amorphous CBZ was formed by quench-cooling the melt of CBZ(A) in liquid nitrogen and suspended in solutions supersaturated with respect to dihydrate CBZ. A DSC thermogram for the quench-cooled melt of CBZ(A) (Fig. 9) showed a glass transition at 52 °C and crystallization at 100 °C, followed by an endotherm corresponding to the melting point of the trigonal polymorph. Amorphous CBZ

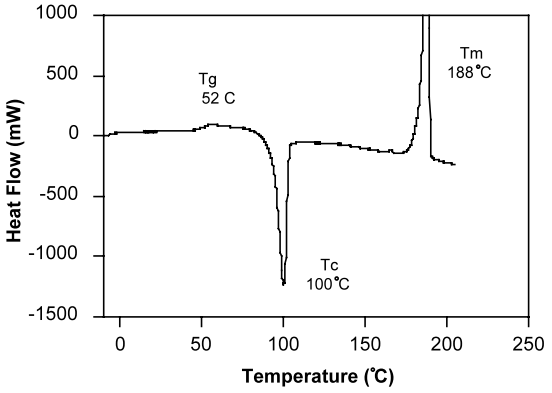

Fig. 9. DSC thermogram of the quench-cooled melt of anhydrous monoclinic CBZ. Glass transition temperature (T_g), crystallization temperature (T_c) and melting temperature (T_m) are indicated.

prepared by in situ dehydration of CBZ(D) in the DSC according to the method of Li et al. (2000) exhibited similar thermal behavior. When amorphous CBZ was placed in solutions supersaturated with respect to CBZ(D) ($\sigma_D = 1.5$) for 20 min, needles of the dihydrate form grew on the surface (Fig. 10). These needles grew mostly in patches and along cracks on the surface.

4. Discussion

The kinetic data for the anhydrous to dihydrate transformation of CBZ(A) in water shows that the transformation is solution-mediated and that the kinetics and the rate-controlling step for the transformation depend on the processing and storage conditions of CBZ(A). A solution-mediated transformation involves three processes: (a) dissolution of the metastable form, CBZ(A), (b) nucleation of the stable form, CBZ(D), and (c) crystal growth. Grinding CBZ(A) shortened the transformation times by at least 4-fold and changed the rate determining step from crystallization of the stable phase to dissolution of the metastable phase. In the presence of unground CBZ(A) the rate determining step is crystallization of the stable phase while in the presence of freshly ground CBZ(A) the rate limiting step is dissolution of the metastable phase. Thus higher concentration levels

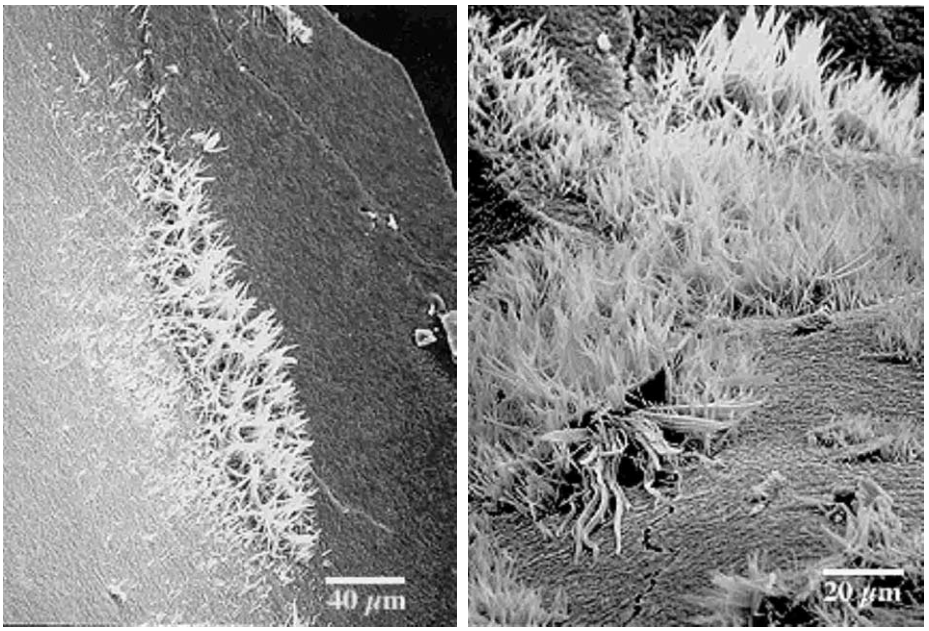

Fig. 10. Scanning electron photomicrographs of needles of dihydrate CBZ growing from the surface of amorphous CBZ (quench-cooled melt of anhydrous monoclinic CBZ) after being placed in a supersaturated solution ($\sigma_D = 1.5$ or 2.5 times the solubility of dihydrate) for 20 min at 25 °C.

are reached and maintained with the unground solid. Although in the initial stage of the transformation of freshly ground CBZ(A) the crystallization rate is faster than the dissolution rate, the solution concentration reaches a steady-state value (at a concentration 1.85 times the solubility of the stable phase) in which the rate of dissolution of CBZ(A) and crystallization of CBZ(D) are slow and equal. Monitoring the solid phase composition during this transformation confirms that the decrease in solution concentration corresponds to an increase in the fraction of CBZ(D). Investigations in our laboratory on the growth rates of single crystals of dihydrate CBZ have shown that growth is very slow at a supersaturation corresponding to the steady-state concentration. Therefore, the elevated plateau concentration is due to the growth rate dependence of CBZ(D) on supersaturation.

The faster transformation rate of ground CBZ(A) can be attributed to a change in surface energetics during grinding. This surface activation facilitates the surface nucleation of CBZ(D) on both ground and quenched CBZ(A) (Figs. 4 and 10). The surface nucleation may be a consequence of lattice disorder or amorphous regions that have greater affinity for the crystallizing solid and higher dissolution rates resulting in local regions of high supersaturations. Similar observations have been reported for ground and quenched samples of various drugs with emphasis on the effects of processing on their metastable solubilities, maximum and/or plateau concentrations achieved during dissolution (Corrigan et al., 1984; Otsuka et al., 1986; Elamin et al., 1994; Mosharraf and Nystrom, 1999). The independence of the transformation rate with increasing mass (total surface area) of unground CBZ(A) indicates that the unground surface does not promote CBZ(D) nucleation.

The XRPD patterns of the processed CBZ(A) crystals strongly suggest that grinding damaged the lattice structure and caused disordered or amorphous regions. Amorphous halo, line broadening and decrease in intensity of XRPD reflections were observed in some of the freshly ground samples, suggesting that grinding CBZ(A) reduces the crystal quality by introducing residual stress and non-uniform strain. These observations are consistent with the findings of Otsuka et al. (1999) in which 20% of CBZ(A) converted into an amorphous solid during the first hour of ball milling at room temperature at 17 and 90% relative humidity.

Grinding could also expose new crystal faces and functional groups that may affect the transformation rates. A material may fracture along a cleavage plane or a molecular layer that is most weakly bound within the crystal lattice. The dihydrate and anhydrous (monoclinic and trigonal) forms of CBZ share the same dimer motif between carboxamide groups, a proton donor (NH_2) and a proton acceptor (C=O). In the monoclinic and trigonal polymorphs the packing of the dimers is governed by van der Waals interactions. The cleavage plane for the monoclinic polymorph, CBZ(A), has been predicted to be the [0 1 1] (Sunkersett et al., 2001) which is dominated by edge and facial portions of the benzene rings. While these faces may have been created by grinding CBZ(A) in our work, the observed aging effects indicate that they were partially or fully disordered, since morphology did not change upon storage.

It is clear from the transformation profiles that although the transformation of ground CBZ(A) is initially much faster than that of the unground material, it reverts to that of the crystalline unground CBZ(A) after storage at 25 °C and 0% RH for 4 weeks. This can be explained by crystallization of the disordered regions despite a storage temperature 27 °C below T_g. The T_g of CBZ(A) was determined to be 52 °C, in good agreement with the value reported by Li et al. of 56 °C (Li et al., 2000). Crystallization from the amorphous state during storage has also been observed for indomethacin ($T_g = 47$ °C) over a time scale of a few weeks at temperatures as low as 30 °C below its T_g (Yoshioka et al., 1994). Amorphous glibenclamide with the same T_g as indomethacin, has been reported to recrystallize during prolonged dry mixing for 75 h at room temperature (Mosharraf and Nystrom, 1999).

The solubility enhancement or metastable solubility of amorphous phases is often described in terms of the solubility ratio of the amorphous to

crystalline forms with little attention to the relative rates of dissolution and crystallization (Corrigan et al., 1984; Otsuka et al., 1986; Elamin et al., 1994; Mosharraf and Nystrom, 1999; Hancock and Parks, 2000). Because the metastable solubility is determined by kinetic processes, it is dependent on the variables that control dissolution and crystallization rates: solubility, interaction between solute and solvent molecules, total solid surface area (mass and specific surface area), hydrodynamic conditions and temperature. Nucleation and crystal growth models predict that the rates for both processes in solution will increase with increasing solubility (Boistelle and Astier, 1988; Rodríguez-Hornedo and Murphy, 1999; Gu et al., 2001). This is generally observed, as long as solute-solvent interactions do not interfere with the formation of molecular clusters that precede nucleation or with the integration of growth units into the crystal lattice. In the case of crystallization-controlled transformations or when an initial steady-state concentration is established, increasing the mass of amorphous solid will increase the plateau supersaturation as a result of higher dissolution rates relative to crystallization rates. This has been observed for ground or quenched griseofulvin and glibenclamide (Elamin et al., 1994; Mosharraf and Nystrom, 1999). Glibenclamide reached plateau supersaturation ratios of 3–14 with a 40-fold increase in mass while for griseofulvin these values were from 1.2 to 5 with a 174-fold increase in mass. In both cases the plateau supersaturations were maintained over a time course greater than 3 days. Although the crystallization kinetics of these compounds have not been reported, their solubilities in water at 21 °C are very low, 5.9 μg/ml for glibenclamide and 8.6 μg/ml for griseofulvin. In contrast to these compounds, dihydrate CBZ has a higher water solubility, 125 μg/ml at 25 °C, and exhibits greater rates of crystallization relative to dissolution when milled. Comparing the maximum or critical supersaturations for spontaneous nucleation (negligible surface nucleation) among these compounds, it is observed that CBZ dihydrate has the lowest critical supersaturation ratio at 5, consistent with its higher solubility and faster nucleation rate.

It is reasonable to expect that: (a) the level of solubility enhancement is dependent on the amorphous to crystalline transformation mechanisms and rates, (b) the level of solubility enhancement is proportional to the amorphous to crystalline ratio if the transformation is crystallization controlled, and (c) the importance of a solid-state or solution-mediated mechanisms depends on the T_g and the solubility of the drug in the solvents under consideration. The farther below T_g is the temperature at which the transformation is studied, and the higher the solubility in the solvent studied, the more significant is a solution-mediated transformation. It would be expected that with either mechanism initiating crystallization, the least soluble compounds would achieve higher solubility ratios (metastable solubilities relative to their stable state solubilities) for longer times due to their slower crystallization rates. While the T_g's of glibenclamide, 47 °C (Mosharraf and Nystrom, 1999), and CBZ, 52–56 °C, are lower than the T_g of griseofulvin 75–80 °C (Mosharraf and Nystrom, 1999), the supersaturation or solubility ratios achieved during dissolution of ground or quenched material are consistent with the order of their solubilities. This trend is also observed for various thiazide compounds with amorphous to crystalline solubility ratios increasing from 1.2 to 9.7 with decreasing solubilities (Corrigan et al., 1984). Although metastable solubilities are reported for a larger number of compounds, it is difficult to compare results from different laboratories, given the kinetic nature of these processes and the varying experimental conditions considered.

5. Conclusion

Kinetic studies of the anhydrous monoclinic to dihydrate transformation of CBZ in aqueous suspensions indicate that the transformation kinetics and the rate-controlling step for the transformation depend on the processing and storage conditions of anhydrous monoclinic CBZ. Grinding anhydrous monoclinic CBZ shortened the transformation times and changed the rate-limiting step from crystallization of the dihydrate form

to dissolution of the anhydrous form. While undetectable limits (by XRPD and DSC) of amorphous anhydrous CBZ did not increase the concentration in solution above the solubility of the anhydrous monoclinic form, the crystallization rate of CBZ dihydrate was significantly increased. Crystallization of dihydrate CBZ was facilitated by surface nucleation on freshly ground anhydrous monoclinic CBZ and on the amorphous phase. Monitoring both solution and solid phase composition identified the steps and mechanisms that control the kinetic process, and that regulate the concentration of drug achieved during dissolution of metastable solid phases. This method also revealed aging effects on the solution-mediated transformation of ground CBZ(A) that were undetectable by diffraction and thermal analysis.

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