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Applications of pressure differential scanning calorimetry in the study of pharmaceutical hydrates I. Carbamazepine dihydrate

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Abstract

The dehydration of carbamazepine dihydrate ($C_{15}H_{12}N_2O \cdot 2H_2O$) was studied by both conventional differential scanning calorimetry (DSC) and by pressure differential scanning calorimetry. Variable temperature powder X-ray diffractometry (VTXRD) and thermogravimetric analysis were used as complementary techniques. By performing DSC at elevated pressures, the dehydration and vaporization endotherms were separated and it was possible to determine the enthalpy of dehydration. Over the range of 100–600 psi, the enthalpy of dehydration was unaffected by pressure. However, the solid-state of the anhydrous phase formed was influenced by the DSC conditions. At ambient pressure, dehydration resulted in the formation of the γ-form of anhydrous carbamazepine while at elevated pressures, the anhydrous β-form appeared which converted to the γ-form at higher temperatures. At high pressures, the water liberated on dehydration is not immediately removed and its presence appears to be responsible for the formation of β-carbamazepine. VTXRD permitted in situ study of dehydration and this confirmed the DSC results. A specially fabricated sample holder permitted VTXRD studies at elevated pressures. © 1997 Elsevier Science B.V.

Keywords: Pressure differential scanning calorimetry (PDSC); Carbamazepine dihydrate; Powder X-ray diffractometry; Hydrate; Dehydration

1. Introduction

Hydrates are molecular complexes that have water molecules incorporated, usually stoichiometrically, into their crystal lattice (Haleblian, 1975; Zografi, 1988). Hydrates are formed during the preparation (for example during crystallization) or processing (such as wet granulation or spray–drying) of pharmaceutical solids. The anhydrous and hydrated forms of a drug can show differences in physicochemical properties, such as

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heat capacity, density, crystal structure, chemical stability, hygroscopicity, powder flow and dissolution rate (Byrn, 1982; Khankari and Grant, 1995). About 150 compounds listed in the USP are capable of existing as hydrates (The United States Pharmacopeia, 1994). If the hydrate phase is present in the finished dosage form, its quantification may become an important issue (Byrn et al., 1995).

Differential scanning calorimetry (DSC) is routinely used for the characterization of pharmaceutical hydrates (Byrn, 1982; Ford and Timmins, 1989). Based on the temperature of dehydration, the nonisothermal dehydration reaction may be generally classified into two types: (i) reactions which occur below the boiling point of water, and (ii) those that occur above or near the boiling point of water.

The different steps in the dehydration process could be described as follows: (D = drug; s = solid; l = liquid; v = vapor)

$$D \cdot nH_2O(s) \rightarrow D(s) + nH_2O(l)$$

Enthalpy of dehydration (ΔH_d) Step 1

$$D(s) + nH_2O(l) \rightarrow D(s) + nH_2O(v)$$

Enthalpy of vaporization of water (ΔH_v) Step 2

$$D \cdot nH_2O(s) \rightarrow D(s) + nH_2O(v)$$

Enthalpy of overall transition (ΔH_t)

$$\Delta H_t = \Delta H_d + \Delta H_v \quad (1)$$

For the first type of reaction, it is usually possible to measure the ΔH_d and ΔH_v separately by conventional DSC. However, for the second type of reaction, the dehydration and vaporization (of water) endotherms overlap and are not completely separated from one another. Under such circumstances, it is almost impossible to measure the ΔH_d by conventional DSC. By carrying out the DSC experiments at elevated pressures, the two processes may be completely separated. The temperature of dehydration is unlikely to be significantly influenced by pressure while the boiling temperature of water is pressure dependent. The Clausius Clapeyron equation can be used to ascertain the influence of pressure, P, on the boiling temperature, T, of water.

$$\ln P = \frac{\Delta H_v}{RT} + C \quad (2)$$

In Eq. (2), R is the gas constant and C is a constant. The boiling temperature of water is strongly dependent on pressure because of the large difference in specific volume between the liquid and the gaseous states. In comparison, the solid–solid and solid–liquid transition temperatures are much less influenced by pressure (Levy et al., 1970; Sawada et al., 1987). The boiling point of water as a function of pressure has been reported in the literature and the results obtained by pressure differential scanning calorimetry (PDSC) were in excellent agreement with the reported values (Table I in Levy et al., 1970).

Before the availability of PDSC, hydrates were characterized by heating in hermetically sealed pans (Suryanarayanan and Mitchell, 1986). There are two major limitations of this method. (i) The pressure inside the pan is uncontrolled. (ii) Above the boiling point of water, an increase in temperature will result in a dramatic increase in the pressure. This is likely to result in the rupture of the pan. These problems are avoided in PDSC. In addition, the technique offers some unique capabilities. (i) The pressure can be precisely controlled. (ii) Solids can be subjected to a controlled temperature program while under substantially elevated pressures (Levy et al., 1970).

The dehydration reactions of inorganic hydrates were studied by differential thermal analysis (DTA), a technique similar to DSC, at pressures ranging from 1 to 170 atmospheres (Williams and Wendlandt, 1973). At ambient pressure, there were overlapping endothermic events due to dehydration and vaporization which were resolved into individual peaks at elevated pressures. Similar results were obtained in our preliminary studies with pharmaceutical hydrates. By separating the dehydration and vaporization endotherms, a precise determination of the enthalpy of dehydration will be possible.

Studies with inorganic compounds suggest that the dehydration conditions can influence the solid-state of the phase formed. According to Frost et al. (1951), drying cupric sulfate pentahydrate at very low water vapor pressures (≤ 0.21 mm Hg) resulted in the formation of X-ray amor-

phous cupric sulfate monohydrate while at higher pressures (≥ 1.51 mm Hg), the crystalline monohydrate was observed. In pharmaceutical solids, the influence of the condition of dehydration on the solid-state of the dehydrated phase has not been thoroughly studied. This is unfortunate for two reasons. First, drying is a commonly encountered unit operation in pharmaceutical processing. Secondly, it is well recognized that the solid-state of the active ingredient can influence the in vivo performance of the dosage forms. Thus the influence of drying conditions can go beyond processing and ultimately affect the product performance.

Our first objective was to demonstrate the applicability of PDSC in the characterization of pharmaceutical hydrates using carbamazepine dihydrate as the model compound. In this context, we wish to point out that though PDSC has been commercially available for a long time period, it has found very limited application in the study of pharmaceuticals (Dwivedi et al., 1990). The second objective was to determine the influence of dehydration conditions on the solid-state of the anhydrous phase formed. The dehydration experiments were carried out at ambient and at elevated pressures and the solid-state of the dehydrated phase was characterized. For these studies, variable temperature powder X-ray diffractometry (VTXRD) was used as a complementary technique.

The model compound selected for this study was carbamazepine dihydrate ($C_{15}H_{12}N_2O \cdot 2H_2O$). Carbamazepine (CBZ) is widely used in the treatment of epilepsy. Several polymorphic forms of anhydrous CBZ as well as the dihydrate and monoacetonate forms have been prepared and characterized (Dugue et al., 1991; Kaneniwa et al., 1984; Lowes et al., 1987; Krahn and Mielck, 1987). In a study aimed at preparing different CBZ solid phases, it was observed that the solid-state of the anhydrous phase depended on the conditions of dehydration of the dihydrate (Krahn and Mielck, 1987). It is therefore of interest to perform an in-depth investigation of the influence of temperature and water vapor pressure on the solid-state of the anhydrous phase formed. By combining PDSC with VTXRD, mechanistic information regarding the process of dehydration can be obtained.

2. Materials and methods

2.1. Materials

CBZ dihydrate was prepared by dispersing anhydrous CBZ (Sigma Chemical Company, St. Louis, MO) in water at room temperature for 24 h. The slurry was filtered and stored at room temperature in a chamber maintained at 52% relative humidity (RH) until it attained constant weight. The sample was then ground using a pestle and mortar for 5 min and stored at room temperature at 52% RH.

2.2. Methods

2.2.1. Thermal analysis

A conventional differential scanning calorimeter (Model 910, TA Instruments), or a pressure differential scanning calorimeter (Model 910 cell enclosed in a specially designed pressure chamber, TA Instruments) and a thermogravimetric analyzer (model 951, TA Instruments) were connected to a thermal analysis operating system (Thermal Analyst 2000, TA Instruments). The differential scanning calorimeters were calibrated with indium (TA Instruments). The pressure cell was calibrated at ambient pressure and also at all elevated pressures at which the samples were run. The entire calibration work was carried out with the same three indium samples in order to minimize the errors associated with sample weighing. In the conventional DSC, about 3 mg of sample was weighed into an aluminum pan, the pan was crimped nonhermetically and heated under nitrogen purge. The heating rate was 10°C/min, unless otherwise stated. Levy et al. (1970) have described in detail the pressure DSC cell. The unit is pressurized with nitrogen and is designed to operate at a maximum pressure of 1000 psi. In all cases, the peak temperature, i.e. the point on the temperature scale of maximum deviation from the baseline, was determined. For the thermogravimetric analysis (TGA), about 10 mg of sample was

weighed into platinum pans and heated, at a rate of 10°C/min, under nitrogen purge.

2.2.2. Powder X-ray diffractometry (XRD)

The samples were exposed to CuKα radiation (45 kV $\times$ 30 mA) in a wide-angle powder X-ray diffractometer (model D500, Siemens). The instrument was operated in the step scan mode in increments of 0.05°2θ. The angular range was 5–40°2θ and counts were accumulated for 1 s at each step.

2.2.3. Variable temperature powder X-ray diffractometry (VTXRD)

In an effort to identify the transitions that occur in the DSC, the samples were subjected to a controlled temperature program and X-ray powder patterns were obtained as a function of temperature. The temperature controller (Micristar®, Model 828D, Hansen), could be used over the temperature range of -195 to $+300$°C. The sample was subjected to a continuous temperature program wherein the heating rate was 10°C/min. The XRD patterns were obtained by exposing to CuKα radiation (45 kV $\times$ 40 mA) in a wide angle powder X-ray diffractometer (Model XDS 2000, Scintag). However, during the XRD runs, the samples were maintained under isothermal conditions at the selected temperatures. The angular range was 5–35°2θ, at increments of 0.03°2θ per step. Since the scanning rate was 5°2θ/min, the entire scan took 6 min.

The XRD experiments were carried out under a variety of conditions. This necessitated the use of different types of holders. Samples heated in the DSC and PDSC were cooled back to room temperature and subjected to XRD. In these cases, because of the small sample size, a quartz holder (also referred to as a 'zero background' holder) was used. The samples subjected to the controlled temperature program were heated in an open copper holder. Finally, it was of interest to obtain XRD patterns in a 'closed' environment in an effort to simulate the conditions in the PDSC. A specially fabricated holder was used for this purpose. The holder consisted of two aluminum plates which were held together with several screws. The powder sample was sprinkled in the central circular region ($\sim$26 mm in diameter) of the bottom plate. A circular hole, 26 mm in diameter, was cut in the top plate so as to enable exposure of the sample to X-rays. In an effort to obtain a sealed environment, a polyester (Mylar®, Type 142A, Du Pont) film was placed over the sample and sandwiched between the two aluminum plates. An O-ring assembly facilitated the maintenance of the seal. The inert film can be used over a wide temperature range (-73 to $+149$°C) and is resistant to moisture permeation (Du Pont Films, 1995). The XRD pattern of the film consisted of a broad peak between 20 and 30°2θ.

3. Results and discussion

3.1. Characterization of CBZ dihydrate

The powder X-ray diffraction pattern was identical to that of CBZ dihydrate reported in the literature (PDF-2, 1996; Suryanarayanan, 1989; McMahon et al., 1996). Though the existence of two crystal modifications of CBZ dihydrate has been suggested, all the batches of CBZ dihydrate prepared in our laboratory had identical XRD patterns (Reck and Dietz, 1986). The relative peak intensities were close to one another in all these samples suggesting that CBZ dihydrate existed in one crystalline structure (Suryanarayanan, 1989). When heated in the TGA up to 125°C, a weight loss of 13.5% was observed, which agreed with the theoretical weight loss of 13.2% for complete dehydration.

3.2. Pressure differential scanning calorimetry (PDSC)

3.2.1. Effect of pressure

CBZ dihydrate was first subjected to DSC in a conventional cell. The DSC profile (at ambient pressure with nitrogen purge) consisted of two overlapping endotherms in the temperature range of 85–100°C and these were attributed respectively to dehydration (Step 1 of Eq. (1)) and vaporization (Step 2 of Eq. (1)) processes (Fig. 1a). This was then followed by the melting of the

anhydrous CBZ at ~189°C (Lowes et al., 1987). The DSC profile of CBZ dihydrate obtained in a pressure cell at ambient pressure was similar to that obtained in a conventional cell (Fig. 1b). The pressure cell could therefore be used as a conventional cell if operated at ambient pressure. When the DSC was carried out at elevated pressures (100–600 psi), the dehydration endotherm (at ~ 90°C) was well separated from the other thermal events that occur between 120 and 150°C (explained later) and finally the solid melted at ~189°C (Fig. 1c–g). At higher pressures (≥ 200 psi), the noisy baseline could be attributed to the gradual and continuous vaporization of water. The enthalpy (ΔH_d) and temperature of dehydration were determined as a function of pressure (Table 1). In the range of 100–600 psi, there appeared to be no systematic effect of pressure on the enthalpy and temperature of dehydration of CBZ dihydrate.

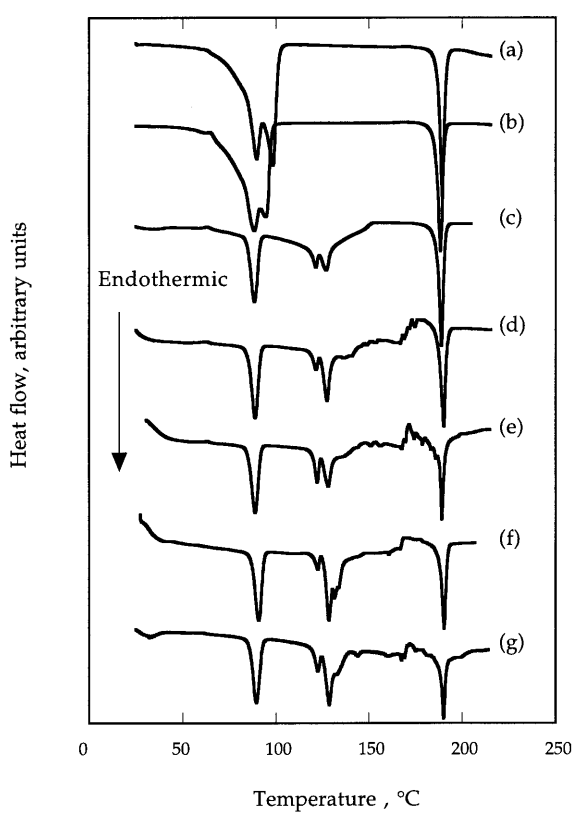


Fig. 1. DSC of CBZ dihydrate at different pressures. (a) At ambient pressure in a conventional DSC cell, (b) at ambient pressure in a PDSC cell, (c) 100 psi, (d) 200 psi, (e) 300 psi, (f) 400 psi, and (g) 600 psi.

3.2.2. Effect of heating rate

These experiments were carried out at a constant pressure of 100 psi (Fig. 2). At a heating rate of 2.5°C/min, the vaporization of water appears to be complete by ~115°C (Fig. 2a). The boiling point of water at 100 psi is 170°C (Williams and Wendlandt, 1973). However, in this case, the small amount of water released (only 130 mg of water is released due to dehydration of 1 mg of CBZ dihydrate) coupled with the slow heating rate appears to cause complete vaporization at a temperature substantially below the boiling point of water. As the heating rate was increased, the vaporization was shifted to a higher temperature range. For example, at a heating rate of 5°C/min, the vaporization appeared to be complete only at ~135°C (Fig. 2b). However, after the dehydration (at ~90°C) and before the final melting (at ~185°C) there appear to be two overlapping thermal events (explained later). These events were more clearly discernible when the heating rate was increased to 10°C/min (Fig. 2c). At heating rates of 15 and 20°C/min, the water vaporization does not appear to be complete until about 170°C. These profiles revealed that the faster the heating rate, the wider the temperature range over which the vaporization of water occurred (Fig. 2a–e).

The effect of heating rate on the enthalpy and temperature of dehydration is presented in Table 1. The major fraction of CBZ dihydrate was expected to dehydrate over a narrow temperature range. However, the dehydration process is expected to be initiated as soon as the sample is placed in the DSC cell. This is because of the 'dry' (~0% RH) environment created by the nitrogen used to pressurize the DSC cell. At slow heating rates, the fraction of sample that dehydrates (before reaching the temperature of dehydration) can be significant. This is clearly revealed by the increase in the enthalpy of dehydration as the heating rate is increased from 2.5 to 5°C/min. Further increases in the heating rate, have generally resulted in a less dramatic increase in the enthalpy of dehydration (Table 1). At all heating rates, it

Table 1
Effect of pressure and heating rate on the enthalpy and temperature of dehydration of CBZ dihydrate

Effect of pressure[a]			Effect of heating rate[b]		
Pressure (psi)	Enthalpy of dehydration (ΔH_d) (J/g)	Temperature of dehydration (°C)	Heating rate (°C/min)	Enthalpy of dehydration (ΔH_d) (J/g)	Temperature of dehydration (°C)
100	71.3 ± 2.3[c]	89.2 ± 0.7	2.5	62.6 ± 2.2	85.0 ± 0.5
200	65.6 ± 3.5	90.4 ± 0.6	5.0	68.6 ± 1.0	86.9 ± 0.7
300	67.5 ± 2.6	89.7 ± 0.8	10.0	71.3 ± 2.3	89.2 ± 0.7
400	69.1 ± 2.3	90.2 ± 0.7	15.0	71.6 ± 0.8	90.8 ± 0.5
600	68.3 ± 4.3	90.3 ± 0.7	20.0	74.6 ± 0.8	91.4 ± 0.5

[a] The heating rate was maintained constant at 10°C.
[b] The pressure was 100 psi.
[c] Mean $\pm$ SD; $n = 3$.

was possible to measure the enthalpy of dehydration with a high degree of precision (coefficient of variation ranged between 1.1 and 3.5%). The temperature of dehydration also increased as a function of the heating rate and this effect is attributed to thermal lag (Wendlandt, 1986).

3.2.3. Advantage of PDSC

As mentioned previously, in conventional DSC, the dehydration and vaporization endotherms overlap. As a result, it is often not possible to determine the enthalpy of dehydration (ΔH_d). However, as demonstrated for CBZ dihydrate (Fig. 1), PDSC permitted direct measurement of enthalpy of dehydration (ΔH_d). Ambient pressure DSC and PDSC were observed to be excellent complementary techniques. At ambient pressure, the enthalpy of the overall transition (ΔH_t) was measured. In case of CBZ dihydrate, the enthalpy of the overall transition (ΔH_t) and the enthalpy of dehydration (ΔH_d) were determined to be ~380 and ~70 J/g respectively. The difference, ~310 J/g, was very close to the calculated enthalpy of vaporization (calculated $\Delta H_v = 304$ J/g) of two moles of water per mole of CBZ dihydrate. Thus PDSC and DSC can potentially complement Karl Fischer titrimetry (KFT) and thermogravimetric analysis (TGA) for water content determination. In the past, conventional DSC has been used to determine the water content in hydrates by assuming that the enthalpy of binding of n moles of water molecules in the hydrate is the same as that of n moles of water molecules in liquid water ($\Delta H_t \approx \Delta H_v$) (Khankari et al., 1992). Using PDSC, we were able to calculate the ΔH_v from ΔH_d and ΔH_t. The water content could be obtained from ΔH_t.

3.3. Solid-state of anhydrous phase-role of water

3.3.1. Variable temperature X-ray powder diffractometry (VTXRD)

Powder diffractometry is a powerful technique for the unambiguous identification of solid phases. Since VTXRD permits powder patterns to be obtained as a function of temperature, it is an excellent complement to DSC. Unfortunately, our current capabilities permit XRD patterns to be obtained only at ambient pressure. XRD patterns of CBZ dihydrate obtained at 30 and 50°C were virtually identical (Fig. 3). However, at 70°C, an abrupt change was observed and a poorly crystalline intermediate phase was formed. At this temperature, crystalline CBZ dihydrate was not detectable. Therefore it had completely disappeared between 50 and 70°C. In the DSC (at ambient pressure) the dehydration peak was observed at a higher temperature of ~85°C (Fig. 1a). While the sample was heated in a crimped pan in the DSC, in the powder X-ray diffractometer an 'open' holder was used. This difference in sample environment could be responsible for the observed discrepancy in the temperature of dehydration.

The XRD pattern of the poorly crystalline phase formed at 70°C did not match that of any of the CBZ solid phases reported in the literature. This phase is likely to be unstable since it rapidly transformed to anhydrous γ-CBZ at 80°C (Fig. 3). Anhydrous γ-CBZ is characterized by peaks at 13.1, 13.9, 18.1 and 19.9°2θ. These peaks are pointed out in Fig. 3. Between 80 and 180°C, there was a progressive increase in the degree of crystallinity of γ-CBZ and this could be at least partially attributed to annealing. Thus dehydration of CBZ dihydrate resulted in a poorly crystalline intermediate phase (not characterized so far) at 70°C which then transformed to anhydrous γ-CBZ at 80°C (Scheme 1). Though these experiments were carried out under ambient conditions, the heating would have made the atmosphere

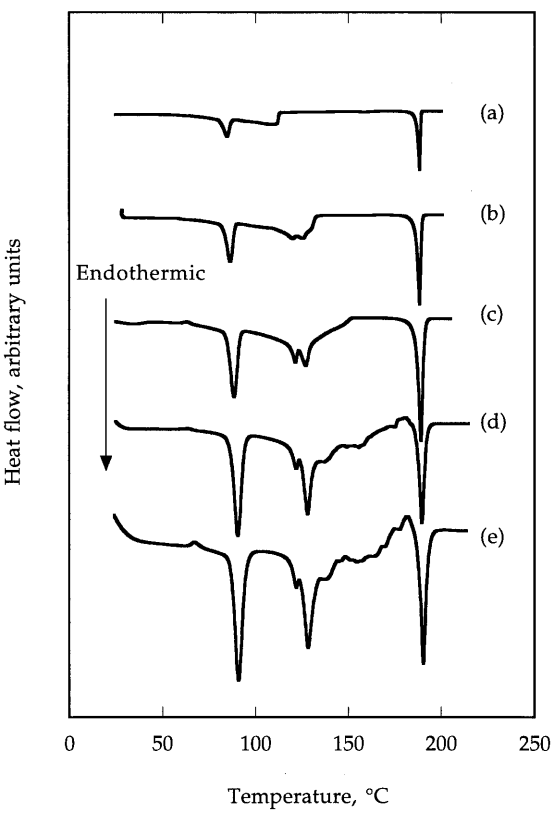


Fig. 2. DSC of CBZ dihydrate at different heating rates. (a) 2.5°C/min, (b) 5°C/min, (c) 10°C/min, (d) 15°C/min, and (e) 20°C/min. These experiments were carried out at a constant pressure of 100 psi.

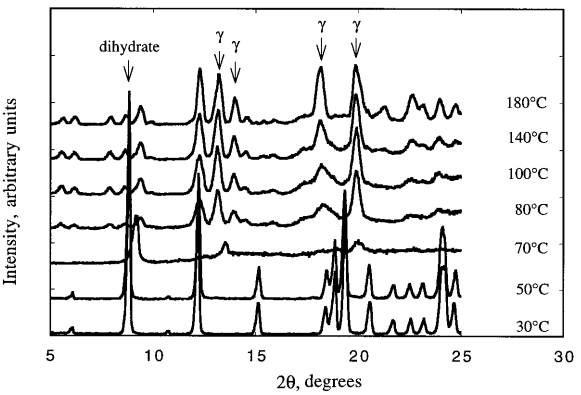


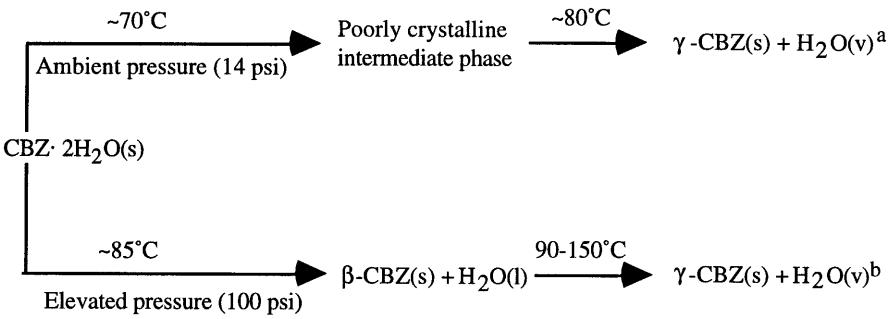
Fig. 3. VTXRD of CBZ dihydrate. The sample was heated in an open copper holder and XRD patterns were obtained at 30, 50, 70, 80, 100, 140 and 180°C. Some peaks unique to CBZ dihydrate and γ-CBZ are pointed out.

around the sample dry (particularly at higher temperatures) and as a result, the water liberated on dehydration would have been rapidly removed. The XRD pattern observed at temperatures $\geq$ 80°C were identical to that of γ-CBZ reported in the literature (PDF-2, 1996; Kaneniwa et al., 1984). Two other anhydrous CBZ phases—α- and β-CBZ have been widely reported. The former and the latter are characterized by intense peaks at 5.0 and 18.7°2θ respectively. The absence of peaks at these angular values, strongly suggested that the anhydrate formed was polymorphically pure and consisted only of γ-CBZ.

3.3.2. XRD of samples subjected to PDSC

In an effort to characterize the transitions observed in the PDSC, CBZ dihydrate was heated (at 100 psi) up to 100°C so that the dehydration was complete. The sample was removed from the DSC and subjected to XRD. The solid phase was identified to be anhydrous β-CBZ. Similar experiments were carried out after heating CBZ dihydrate to 150°C. The solid phase in this case was anhydrous γ-CBZ. The results are summarized in Scheme 1.

In order to perform the XRD, it was necessary to remove the sample from the differential scanning calorimeter. At these temperatures, if the sample is exposed to ambient pressure, the vaporization of all the water is inevitable. It would be



Scheme 1. Transitions of carbamazepine dihydrate at ambient and elevated pressures. (a) The DSC experiments were carried out in a nonhermetically crimped pan under nitrogen purge. The VTXRD experiments were performed in an open copper holder. Therefore, in both cases, rapid vaporization of water is expected. (b) Based on the DSC results (Fig. 1c), the vaporization of water appears to be complete by 150°C.

much more meaningful to delay the removal of the water liberated by the dehydration process (in order to simulate the PDSC) and simultaneously obtain the XRD patterns. This was accomplished by performing the VTXRD in a sealed holder.

3.3.3. VTXRD in a sealed holder

This was carried out in a specially fabricated holder containing the Mylar® film (details in the experimental section). The advantage of this approach is that the XRD patterns are obtained *while* the sample is in a 'closed' environment. However, unlike the PDSC, it is recognized that in this assembly the pressure is uncontrolled.

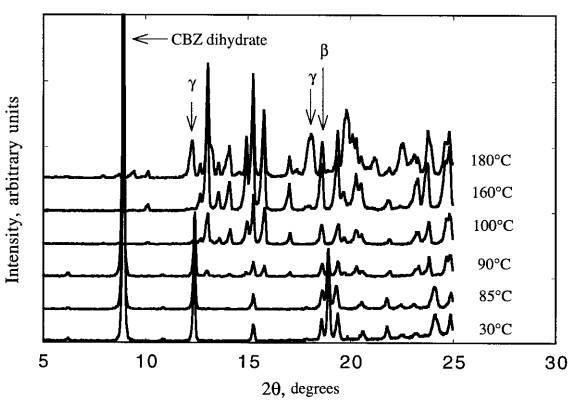


Fig. 4. VTXRD of CBZ dihydrate. The sample was heated in a 'closed' aluminum holder and XRD patterns were obtained at 30, 85, 90, 100, 160 and 180°C. Some peaks unique to CBZ dihydrate, anhydrous β- and γ-CBZ are pointed out.

Up to 85°C, only the crystalline CBZ dihydrate was observed (Fig. 4). At 90°C, several characteristic peaks of β-CBZ (for example at 13.1, 15.3 and 18.7°2θ) were observed indicating the initiation of sample dehydration. At 100°C, the characteristic peaks (8.9 and 12.3°2θ) of CBZ dihydrate had completely disappeared suggesting that dehydration was complete. There was also a pronounced increase in the intensities of the β-CBZ peaks. At 160°C, several characteristic peaks of γ-CBZ (for example at 18.1, 19.9 and 23.1°2θ) were observed indicative of a solid–solid β- to γ-CBZ transition (Kaneniwa et al., 1984). At 180°C, there was a pronounced increase in the intensities of the γ-CBZ peaks and a concomitant decrease in the intensities of the β-CBZ peaks. Based on these results, it is possible to postulate the events observed in the PDSC (Fig. 1c–g and Fig. 2b–e). Usually four endotherms are observed. The first endotherm is attributed to the dehydration of CBZ dihydrate at ~90°C. The VTXRD results (of the previous paragraph) indicate that in presence of water, dehydration of CBZ dihydrate results in the formation of β-CBZ. At these pressures, a significant fraction of the liberated water is expected to exist in the liquid state. On further heating, two more overlapping endothermic transitions occur at ~123 and ~125°C. Those are attributed to transitions of β-CBZ to γ-CBZ and to vaporization of water. However we are unable to assign the sequence of the thermal events here. At high pressures ($\geq$ 200

psi) and at rapid heating rates ($\geq$ 15°C/min), the dehydrated water is not completely removed by 150°C, resulting in a noisy baseline at higher temperatures. Finally the melting of the γ-CBZ is responsible for the fourth endotherm at ~189°C. Though the polyester film cover placed above the XRD holder did not permit precise control of the pressure, it enabled the water liberated on dehydration to be in intimate contact with the dehydrated phase. The presence of this water appears to have a significant influence on the solid-state of the anhydrous phase. It appears to facilitate the nucleation and growth of the stable anhydrous phase which is β-CBZ at the dehydration temperature. These observations demonstrate that the drying condition can influence the solid-state of the dehydrated phase of a hydrate.

4. Conclusion

Using CBZ dihydrate as a model compound, we have demonstrated that DSC at elevated pressures is an excellent complement to conventional DSC in the characterization of pharmaceutical hydrates. The technique has the potential to separate the dehydration and vaporization endotherms when dehydration occurs at a temperature $\geq$ 100°C. As a result, it was possible to determine the enthalpy of dehydration. More interestingly, the technique permits the dehydrated water to be in intimate contact with the anhydrous phase formed. This can significantly influence the solid-state of the anhydrous phase formed. VTXRD permitted in situ observation of the various phase transitions as a function of temperature. By combining this technique with DSC (both ambient and high pressure), the role of the liberated water on the solid-state of the anhydrous phase was delineated.

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