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MONITORING HYDRATION STATE CONVERSION BY TG-DTA

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Characterization of the solid-state form (hydrate or polymorph) of a pharmaceutical active is a key scientific and regulatory requirement during development of and prior to seeking approval for marketing of the drug product. A variety of analytical methods are available to perform this task. By nature of the fundamental information it provides, TG-DTA offers advantages over other methods in regards to monitoring and quantitation of hydration state changes. In a single experiment with only a few milligrams of sample, TG-DTA perceives minor changes in phase, quantitates total water content and percent conversion, and illustrates hydrate type. All of this is accomplished without the necessity of generating time-consuming standard curves representing the differing ratios of hydrated to anhydrous forms. This study describes the use of TG-DTA to monitor and quantitate humidity induced solid–solid phase conversion of nitrofurantoin and risedronate. Percent conversion was qualitatively observed by both TG and DTA signals and quantitated by the TG.

Keywords: *DTA, hydrate, phase conversion, polymorph, TG, TG-DTA, thermal analysis*

Introduction

Active pharmaceutical ingredients (API) may crystallize in different solid-state phases known as polymorphs and/or hydrates. Polymorphs and hydrates can display different chemical, physical and mechanical behaviors which can affect product quality and performance [1, 2]. Although some forms are more stable than other, the most thermodynamically stable form of an active pharmaceutical ingredient may not be the best candidate for development. If the most stable form of a drug has a low solubility and its absorption is solubility dependent, the desired therapeutic dosage may be difficult to achieve and a more soluble form chosen for advancement; or, a metastable form may impersonate the most stable form and mistakenly be chosen for advancement [3, 4].

As water is common in manufacturing, hydrates are especially pertinent in pharmaceutics. Depending on the characteristics of the drug, processing events, storage conditions, and dosage form, an active pharmaceutical ingredient can undergo solid-state phase changes, including incorporation of water into or release of water from the molecule [5, 6]. In either circumstance, a hydrate phase different from the original compound, and most likely the incorrect phase of the API, is formed. Phase transitions (and the rate of these transitions) can be influenced by impurities, particle size, crystal imperfections, the presence of seed of the stable form, excipients, pressure, relative humidity, and temperature [2, 3, 7]. As the hydration state of the molecule changes, the unit cell is altered, affecting the molecular interactions and crystalline order. The alterations in the unit cell modify the thermodynamic activity of the molecule which can lead to the cascade of adjustments in the pharmaceutically pertinent properties, such as manufacturability, solubility, density, physical stability, chemical stability dissolution rate, and bioavailability [5]. In addition, the hydrate phase used in a formulation as well as a change in hydrate phase upon processing or storage can effect other properties such as powder flow, tabletting ability, and tablet characteristics [3–5]. Due to the effects of hydration state on various solid-state properties, the solid-state chemistry of an API must be characterized under long term relevant processing and storage conditions to determine the conditions under which the hydration state could change and to ensure consistent product performance [2–7].

Typical analytical techniques for solid-state characterization of hydrates include X-ray diffraction (XRD); thermal analysis, including differential scanning calorimetry (DSC), differential thermal analysis (DTA), and thermogravimetric analysis (TG); vibrational spectroscopy, including Raman, FTIR and near IR spectroscopies; nuclear magnetic resonance (NMR); microscopy with polarized light and/or hot stage, and Karl Fischer (KF) titrimetry [3, 6–12]. Each technique employed has advantages and disadvantages.

XRD is non-destructive and considered the definitive confirmation of phase as it can usually show significant differences among crystal forms, gives in depth understanding of the structure, and provides a fingerprint of the solid phase. However, other identity methods are needed to link a specific powder pattern to the proper hydration state. Until the powder diffraction pattern is assigned to a specific hydrate, XRD does not give information on how materials differ, just that they

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are different. Care must also be taken with crystals to minimize preferred orientation issues so that a pattern is representative of the entire bulk material and not just of the preferentially ordered material. For quantitative work in a mixture of phases, at least one high intensity peak unique to each form must exist, the intensity of unique peaks must be proportional to concentration, and an extensive set of samples and standards are needed to build a standard calibration curve. The limit of detection (LOD) and limit of quantitation (LOQ) may vary with each material and tend to be higher than other methods [3, 7–10].

Vibrational spectroscopy is non-destructive, needs only a small amount of sample (<10 mg), and has little to no sample preparation as it is possible to perform some types of spectroscopy through a clear sample container [8, 10, 11]. Each phase must have a unique spectral feature to distinguish it from the other phases, overlap of the majority of the spectral features often exists, and chances of finding random spectral information which relates to an analytical property is high, therefore interpretation can be difficult. A large number of standards and samples are required to create standard calibration curves for quantitative work of mixtures and complicated analysis, such as multivariate analysis, must be applied to the standard curve [11]. Additionally, the response of some forms is particle size dependent or moisture sensitive and/or the forms can cause localized heating, and therefore change the material during measurement [8, 10, 13].

Solid-state NMR provides information regarding the connectivity and local environment of atoms and therefore helps determine structure. Interpretation of spectra and signal assignment can be difficult as experimental artifacts, such as the development of sidebands or peak broadening due to high speed spinning, can occur and determining the correct experimental conditions may take extensive amounts of time. For each measurement, a large amount of sample (>100 mg) is necessary and data acquisition time may be long. Additionally, generation of standard curves for quantitative work takes a large number of samples and standards [3, 7–10].

While Karl Fisher obtains a quantitative water value to be used for stoichiometric calculations of hydration level, it gives no information as to the nature of the type of hydrate (channel *vs*. lattice) and cannot distinguish between adsorbed water and water of hydration. The compound of interest may also not be soluble in the solvents commonly used for KF.

Microscopy needs only a small amount of material (<10 mg) but provides information only on morphology and size, not on the nature of the hydration level. When used with a hot stage, thermal transitions can be assigned [7, 8]. Unfortunately, morphology is not necessarily correlated to phase [1] as different phases may have similar habits or a single phase may have more than one habit.

Although TG-DTA is a destructive technique, it provides distinct advantages over all of the other techniques described above. Like most of them it requires only a small amount of material per test (<10 mg) [14, 15]. TG-DTA generates a thermal profile unique to each hydrate phase which can be used to identify each phase as well as quantitatively determine water content for stoichiometric determination of hydration level. When differing hydration states exhibit unique TG-DTA signatures, TG-DTA alone can determine quantitatively the content of each phase within a binary mixture with comparison of the experimental mass loss to the theoretical mass loss [16] and can be used to determine the amount of a specific material in the whole material [17] without a standard curve. Information on phase transitions can also be obtained from the thermal profile as well as the type of water in the hydrate (channel *vs*. lattice).

Risedronate and nitrofurantoin were used to examine the use of TG-DTA to monitor conversion between hydration states.

Experimental

Nitrofurantoin

Samples of nitrofurantoin anhydrate were seeded with 5% monohydrate by shaking physical mixtures for 3 min then placed into 97% relative humidity (RH) and 85% RH chambers. Humidity chambers were prepared as per ASTM E104-02 [18] and kept at room temperature throughout the study. Phase pure samples of both forms were also shaken using the same conditions as above and placed into 85 and 97% RH chambers. At appropriate intervals, 5–10 mg samples were analyzed for phase conversion on a Seiko TG-DTA 220. Samples were run in aluminum sample pans from 25 to 275°C at 5°C min^{-1} with a dry nitrogen purge rate of 200 mL min^{-1}. The instrument was temperature calibrated with tin and gallium and mass calibrated with certified masses. After conversion, sample phase was further confirmed by XRD.

Risedronate

Samples of risedronate anhydrate, monohydrate, and variable hydrate were seeded with 5% hemipentahydrate and physically mixed by hand shaking for 3 min then placed into 97 and 85% RH chambers. Phase pure samples of both forms were shaken using the same conditions as above and placed into 85 and 97% RH chambers. At appropriate intervals, 5–10 mg samples were analyzed on a Seiko TG-DTA 220 from 25 to 250°C

at 10°C min^{-1} with a dry nitrogen purge rate of 200 mL min^{-1}. Other instrument conditions were as described above. If samples showed conversion at 97 and 85% RH, additional samples were prepared as described above and placed into 75 and 54% RH chambers and analyzed as previously described. After conversion, sample phase was additionally confirmed by XRD.

Additional samples of risedronate monohydrate and variable hydrate were seeded with 5% hemipentahydrate and concomitantly reduced in size by ball milling physical mixtures on a Spex Certiprep 5300 mixer/mill in stainless steel vials with 2 stainless steel mixing balls at level 5 for 3–5 min intervals (total time: 15 min). Phase pure samples were also milled in a similar manner. All samples were placed into 97, 85, 75 and 54% RH chambers. Samples were analyzed immediately after milling to assess the effect of milling on the samples then at appropriate intervals as described above. After milling and conversion, samples were submitted for XRD analysis.

Humidity chambers were prepared as per ASTM E104-02 [18] and kept at room temperature throughout the study.

Results and discussion

Nitrofurantoin conversion

Nitrofurantoin, 1-{[(5-nitro-2-furanyl)methylene]amino}-2,4-imidizolidinedione, empirical formula $C_8H_6N_4O_5$, is recognized to exist in both anhydrate and monohydrate forms [19–22] (Fig. 1 for structure). While both monohydrate and anhydrate are used in commercial production, the monohydrate is the water equilibrium form at room temperature; therefore, a possibility exists that the anhydrate would convert to the monohydrate under certain conditions at room temperature. The conversion between the forms at various humidity levels and temperatures has been previously investigated using XRD standard calibration curves to measure the anhydrate and monohydrate contents in the samples [23–26]. In this paper, the use of TG-DTA to monitor the conversion of anhydrate to monohydrate under high relative humidity was explored. The difference in the hydrate forms was easily distinguished in the thermal profiles; the monohydrate form exhibited only a single step mass loss of 7.0% due to dehydration *vs*. no mass loss for the anhydrate. This enabled the use of TG-DTA to quantitate conversion directly from the measured

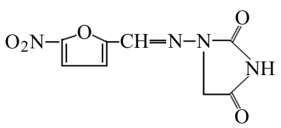

Fig. 1 Nitrofurantoin anhydrate structure

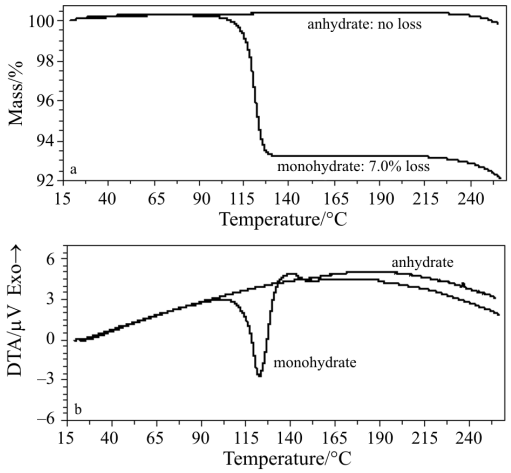

Fig. 2 Nitrofurantoin anhydrate and monohydrate thermal profiles: a – TG and b – DTA signal

mass loss without generating a standard curve. Figure 2 shows the TG and DTA profiles of both forms.

TG-DTA was successfully employed to examine phase conversion. The conversion was tracked by the water content of the TG signal and the magnitude of dehydration endotherm in the DTA signal. Both the water content and the dehydration endotherm increased with time for samples in the 97% RH conditions and conversion was complete within 5 weeks. Figure 3 shows the TG-DTA scans for phase pure nitrofurantoin anhydrate at 97% RH. The samples seeded with monohydrate showed a similar progression from anhydrate to monohydrate at 97% RH. At 85% RH, the conversion was slower than at 97% RH and had begun, but was not complete, by 6 weeks for both the phase pure and seeded samples.

Estimated % monohydrate during conversion was determined by the % mass loss at each interval *vs*. the theoretical value for dehydration of the monohydrate (7.0%) as illustrated in Eq. (1).

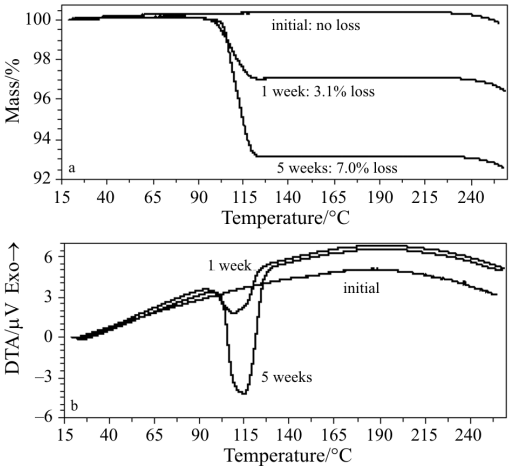

Fig. 3 Phase pure nitrofurantoin anhydrate conversion to monohydrate at 97% RH: a – TG and b – DTA signal

Table 1 Summary for nitrofurantoin anhydrate conversion to monohydrate (MH)

Conditions	Phase pure anhydrate		Anhydrate seeded with 5% monohydrate	
	time/week	monohydrate/%	Time/week	monohydrate/%
97% RH	1	44	1	not determined
	3	96	3	96
	5	100	5	100
85% RH	6	4	6	7

$$\frac{\text{mass loss}_{obs}\,\%}{7.0\%}\cdot 100 = \text{monohydrate}\% \qquad (1)$$

Table 1 gives a summary of conditions and conversion results for nitrofurantoin anhydrate in this study. Although not performed under equivalent conditions as previous studies, these results are in general agreement with those studies [23–26].

Risedronate conversion

Risedronate monosodium, [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt, empirical formula $C_7H_{10}NO_7P_2Na$, the active in Actonel™, also has multiple hydrate forms: anhydrate, monohydrate, hemipentahydrate, and variable hydrate. Hemipentahydrate (Fig. 4 for structure), the commercial form, is the water equilibrium form from room temperature to 37°C [13]; therefore, the anhydrate, monohydrate, and variable hydrate might be expected to undergo a solid-state conversion to the hemipentahydrate form under certain RH conditions. Although the risedronate hydrate system is much more complicated than the nitrofurantoin hydrate system, observing conversion from the anhydrate, monohydrate, or variable hydrate form was possible by TG-DTA as each phase had unique thermal signatures. Quantitating conversion was possible for all forms, although more difficult for some hydrate forms than others.

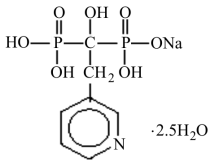

Fig. 4 Risedronate sodium hemipentahydrate structure

Risedronate monohydrate

Figure 5 shows the differences between the thermal profiles of risedronate hemipentahydrate and monohydrate. The detailed evaluation of these thermal curves was provided in a previous publication [27]. The first step mass loss of the hemipentahydrate is due to the stoichiometric loss of the first mole of water. The final mass loss due to dehydration is followed immediately by degradation, rendering it difficult to separate degradative mass loss from dehydration mass loss. Because the monohydrate has no mass loss until the dehydration above 200ºC, the

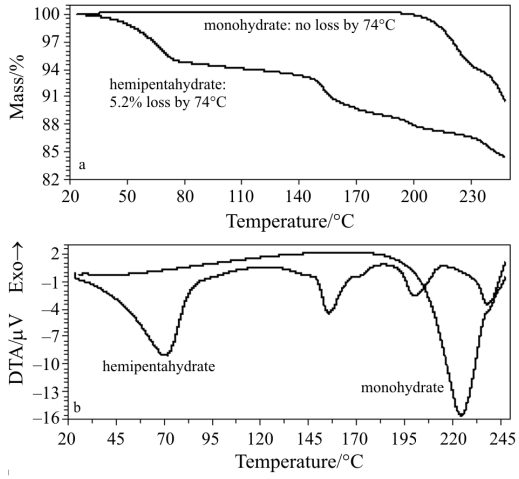

Fig. 5 Thermal profiles of risedronate hemipentahydrate and monohydrate: a – TG and b – DTA signal

increase of the hemipentahydrate phase in the monohydrate was easily observed, especially in the temperature range where the first mole of water is lost from the hemipentahydrate. The mass loss of the first mole of water from the hemipentahydrate is easy to measure, is lost stoichiometrically, and is proportional to the amount of hemipentahydrate present; therefore this transition was used to calculate the conversion of the monohydrate to hemipentahydrate. Likewise, the magnitude of the DTA curve may be used for qualitative assessment of phase conversion.

No changes were observed for phase pure monohydrate or for monohydrate seeded with 5% hemipentahydrate in conditions as extreme as 97% RH for 4 months. As process milling can cause unexpected phase changes [3], phase pure samples and samples seeded with 5% hemipentahydrate were ball milled for 15 min and subjected to the same conditions as the gently mixed samples. Samples analyzed directly after milling showed a profile different from the unmilled monohydrate, with onset of dehydration starting near 150 rather than 200ºC. XRD confirmed the phase pure samples to be pure monohydrate and the seeded samples to be monohydrate with small amounts of hemipentahydrate so the decrease in dehydration temperature is interpreted to be the natural consequence of significantly decreasing the particle size (Fig. 6). Because this occurs at a temperature outside the region used for quantitation, it was not expected to impact ability to quantitate conversion to hemipentahydrate.

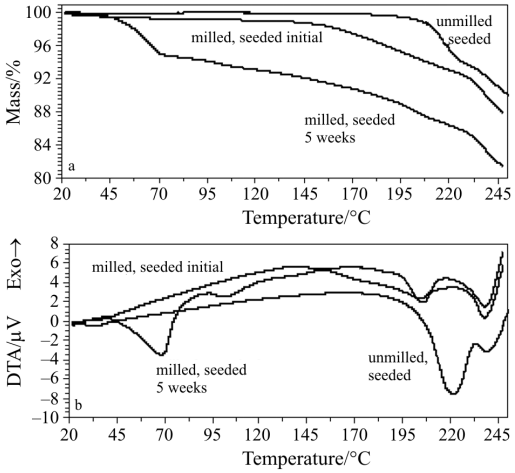

Fig. 6 Conversion of milled seeded risedronate monohydrate to hemipentahydrate at 97% RH and comparison of seeded milled and unmilled monohydrate: a – TG and b – DTA signal

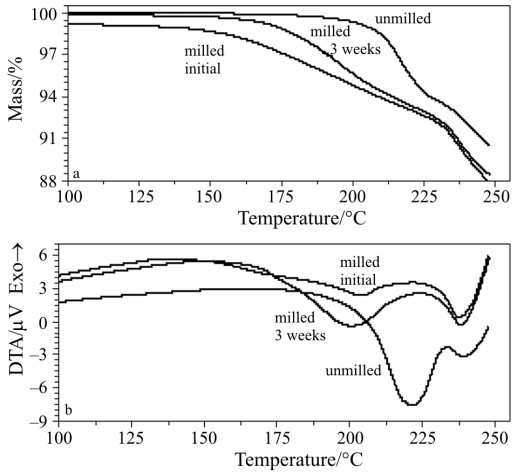

Fig. 7 Comparison of unmilled and milled seeded risedronate monohydrate at 85% RH: a – TG and b – DTA signal

At 97% RH conditions, milled seeded monohydrate samples converted to hemipentahydrate within 5 weeks (Fig. 6). In the DTA signal, conversion was observed by the growth of an endotherm below 100ºC associated with the dehydration of the first mole of water from the hemipentahydrate; in the TG signal, conversion was observed by the development and increase in mass loss also corresponding to the loss of the first mole of water from the hemipentahydrate. Estimated % hemipentahydrate during conversion was determined by the TG mass loss of the first mole of water *vs*. the theoretical value of 5.2% as expressed in Eq. (2).

$$\frac{\text{mass loss}_{\text{obs}}\%}{5.2\%}\cdot 100 = \text{hemipentahydrate}\% \qquad (2)$$

Neither the seeded milled monohydrate at 85% RH nor the phase pure milled monohydrate at 97% RH showed conversion to hemipentahydrate within 3 weeks; rather the monohydrate crystals annealed themselves and the profile shifted slightly toward the unmilled monohydrate profile (Fig. 7). These results indicate that solid-state conversion of the monohydrate to the hemipentahydrate may be dependent upon very high humidity and particle size. Table 2 gives a summary of conditions and conversion results for risedronate monohydrate in this study.

Variable hydrate

The variation between the thermal profiles of the variable hydrate and hemipentahydrate are shown in Fig. 8. The water content in the channels of the variable hydrate fluctuates with RH, causing the total water content of this phase to vary with RH. At equivalent RH conditions, the total water content for the variable hydrate is greater than the hemipentahydrate; therefore, the water content of the variable hydrate is expected to decrease with conversion to hemipentahydrate. The conversion was observed in the DTA signal as a sharpening of the dehydration endotherm for the dehydration of the first mole of water and the growth of the endotherm of the final dehydration around 206ºC. In the TG signal, the conversion was observed by an overall mass loss and a sharpening of the mass loss below 100ºC associated with the first mole of water.

Like the monohydrate, no conversion was observed for the variable hydrate after 4 months at 97% RH. To analyze the ability of processing (pressure and particle size reduction) to cause a phase change, the variable hydrate was also milled using the same conditions as the monohydrate. Milling did not impact the profile of the variable hydrate as it did on the monohydrate. Within 3 days, the seeded milled samples at 75, 85 or 97% RH were completely or mostly converted. At 54% RH, the conversion process occurred more slowly and was therefore easier to

Table 2 Summary for risedronate monohydrate conversion to hemipentahydrate (HPH)

Condition	Phase pure monohydrate			Monohydrate with 5% hemipentahydrate		
	treatment	time	hemipentahydrate/%	treatment	time	hemipentahydrate/%
97% RH	ball miled	3 weeks	no conversion	ball milled	18 days 34 days	88.5% HPH 100% HPH
	none	4 months	no conversion	none	4 months	no conversion
85% RH	ball milled	4 weeks	no conversion	ball milled	4 weeks	no conversion

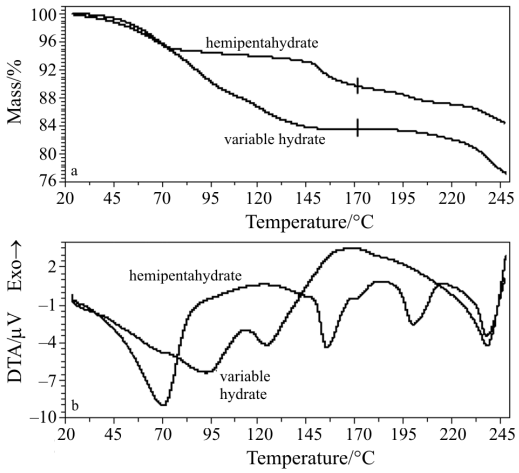

Fig. 8 Thermal profiles of risedronate hemipentahydrate and variable hydrate: a – TG and b – DTA signal

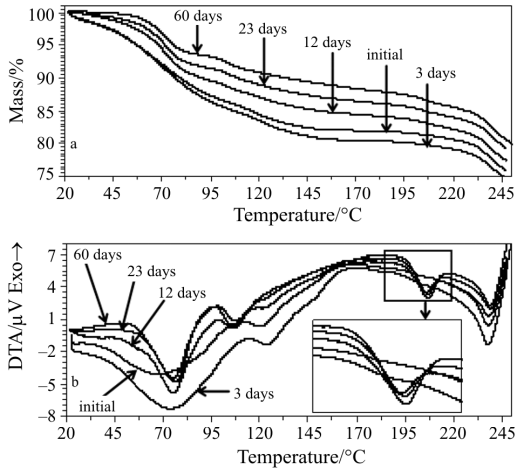

Fig. 9 Conversion of seeded milled risedronate variable hydrate (VH) to hemipentahydrate at 54% RH: a – TG and b – DTA signal

monitor. After 3 days at 54% RH, there was some evidence of conversion in the DTA signal but, because the variable hydrate had been equilibrated to a lower RH before mixing, the sample gained water, masking any conversion visible in the TG signal. After 9 days, the TG signal did not change *vs*. initial but had decreased from the previous reading. However, the DTA signal clearly showed a difference from initial as the dehydration endotherm from the loss of the first mole of water was sharper and the dehydration endotherm around 210ºC increased with time. After 12 days, the TG mass loss had clearly decreased as expected and continued to decrease through the conversion process (Fig. 9 for the progression). Conversion to hemipentahydrate from the ball milled phase pure variable hydrate was partially complete within 3 weeks at 97, 85 and 75% RH, and was evident by 4 weeks at 54% RH. These results indicate that conversion from variable hydrate to hemipentahydrate is a function of particle size and is independent of the presence of hemipentahydrate.

Unlike the anhydrate, which contains no water, and monohydrate, which contains only lattice water, but like the hemipentahydrate, the variable hydrate contains both channel and lattice water; consequently, the variable hydrate does not have an area in the profile where it does not lose water but the hemipentahydrate does. Therefore, the % hemipentahydrate present during conversion is determined by the change in total water content of the variable hydrate with time *vs*. the difference in the total variable hydrate mass loss and the hemipentahydrate mass loss at the equivalent temperature as expressed in Eq. (3). The total water content of the variable hydrate was determined at the point on the TG curve at which the final DTA dehydration endotherm was complete but before the degradation endotherm began as marked in Fig. 8. As explained above, the water content of the variable hydrate sample will change with RH.

All variable hydrate samples initially gained mass when placed into the RH chambers because the ambient humidity to which they had equilibrated was lower than the stress condition humidity. Therefore, the total water content possible at each RH condition was not known before seeding and the start of conversion. Quantitative amounts of hemipentahydrate in the variable hydrate conversion were not obtained in this study as the estimated conversion relied on the use of the initial water content of the variable hydrate; however, it was possible to observe the changes associated with conversion and the approximate time to complete conversion. To obtain an accurate initial water content on the variable hydrate and therefore an accurate change in water content to be used to quantitate the amount of hemipentahydrate present during conversion, the variable hydrate sample would need to be equilibrated to the appropriate RH conditions before use. Additionally, the ball milled hemipentahydrate lost more water at equivalent temperatures than the intact hemipentahydrate and the ball milled variable hydrate profile was more similar to the ball milled hemipentahydrate during conversion. Therefore, the % hemipentahydrate present should be based on the mass loss in the ball milled hemipentahydrate at the same temperature as the variable hydrate onset in the initial analysis. Table 3 gives a summary of conditions and conversion results for risedronate variable hydrate in this study.

$$\frac{\text{variable hydrate mass loss}_{\text{initial}}\,\% - \text{mass loss observed}_{T=n}\,\%}{\text{variable hydrate mass loss}_{\text{initial}}\,\% - \text{hemipentahydrate mass loss}\%} \cdot 100 = \text{hemipentahydrate}\% \qquad (3)$$

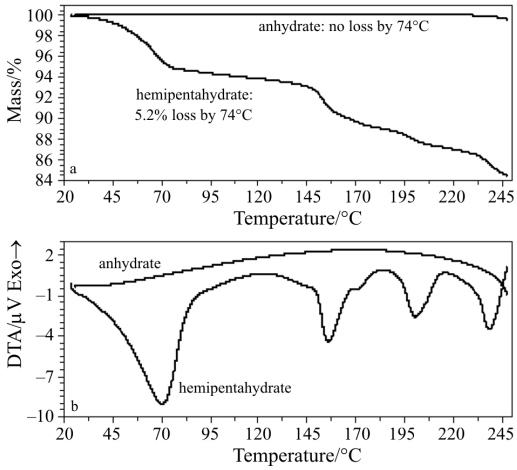

Fig. 10 Thermal profiles of risedronate hemipentahydrate and anhydrate: a – TG and b – DTA signal

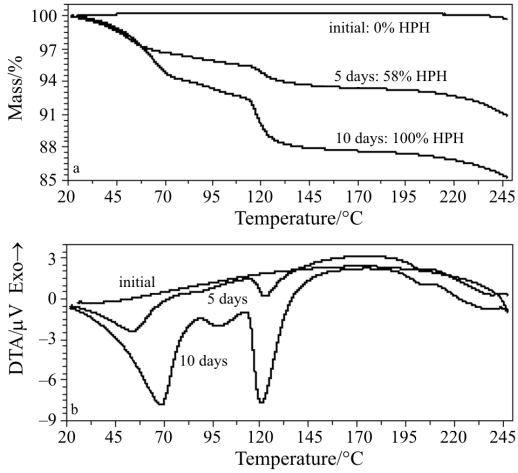

Fig. 11 Conversion of phase pure risedronate anhydrate to hemipentahydrate: a – TG and b – DTA signal

Table 3 Summary for risedronate variable hydrate conversion to hemipentahydrate

Condition	Phase pure variable hydrate		Variable hydrate with 5% hemipentahydrate	
	treatment	comments	treatment	comments
97% RH	none ball milled	no conversion in 4 months conversion evident by 3 days	none ball milled	no conversion in 4 months complete conversion by 3 days
85% RH	ball milled	conversion evident by 3 days	ball milled	partial conversion by 3 days
75% RH	ball milled	conversion evident by 3 weeks	ball milled	partial conversion by 3 days
54% RH	ball milled	conversion evident by 4 weeks	ball milled	conversion evident by 3 days; complete conversion >3 weeks

Table 4 Summary for risedronate anhydrate conversion to hemipentahydrate (HPH)

Conditions	Phase pure anhydrate		Anhydrate with 5% hemipentahydrate	
	time	hemipentahydrate/%	time	hemipentahydrate/%
97% RH	5 days 10 days	58% HPH 100% HPH	4 days 7 days	65% HPH 100% HPH
85% RH	11 weeks 4 months	26% HPH 100% HPH	4 weeks 11 weeks	23% HPH 98% HPH
75% RH	4 months	no conversion	4 months	no conversion

Anhydrate

The differences between the thermal profiles of risedronate hemipentahydrate and anhydrate are shown in Fig. 10. As expected, no mass loss or dehydration is evident in the TG or DTA signals of the anhydrate, making the conversion to hemipentahydrate very obvious in all regions and the same calculation used for the monohydrate was applied to the anhydrate.

At 97% RH, the phase pure anhydrate sample converted to hemipentahydrate within 10 days. Conversion was observed in the DTA signal by endotherm growth and in the TG signal by the development of mass losses associated with the dehydration endotherms. Figure 11 shows the progression from phase pure anhydrate to phase pure hemipentahydrate at 97% RH. At 85% RH, the conversion was slower than at 97% RH. The phase pure sample was only 26% hemipentahydrate by 11 weeks. At 97 and 85% RH, the anhydrate seeded with hemipentahydrate showed a similar but more rapid conversion process than the phase pure samples. After 3 months, the samples at 75 and 54% RH showed no signs of conversion. The estimated % hemipentahydrate during conversion was determined by Eq. (2). Table 4 gives a summary of conditions and conversion results for risedronate anhydrate in this study.

Conclusions

TG-DTA was successfully demonstrated to be a valuable tool to observe phase conversion. In a binary system, quantitation is possible without the need to generate standard curves. For nitrofurantoin, a simple hydrate system comprised of anhydrate and lattice

monohydrate, the application was uncomplicated. Quantitation of conversion of anhydrate to monohydrate was accomplished directly by measuring the mass loss obtained from the TG curve and rationing the observed loss to the theoretical loss.

For risedronate, a system which includes mixed channel and lattice hydrates in four hydrate forms, the quantitation was more difficult but was possible due to the unique mass loss signature exhibited by each form. The conversion of anhydrate to hemipentahydrate was quantitated by monitoring the dehydration of the initial, most labile mole of water from the hemipentahydrate present. Because this initial mole of water was removed cleanly and stoichiometrically, the ratio of the mass loss observed in this region to theory for loss of the first mole provided the percent hemipentahydrate present. Quantitation of conversion of the monohydrate to the hemipentahydrate was performed in the same manner. This was possible because loss of the first mole of water from the hemipentahydrate occurred at a temperature far below and completely separated from that observed for loss of water from the monohydrate form. Estimation of the amount of hemipentahydrate present in the variable hydrate required identification of a temperature for consistently measuring water loss from *hemipentahydrate* at a temperature on the thermal curve where all moisture would be expected to be removed from the variable hydrate. In this study, the unexpected initial gain of water in the samples indicated a need to pre-equilibrate future study samples to the stress humidity prior to initiating the study.

In each example, the TG portion of the TG-DTA curve was used to quantitate percentage of equilibrium form present. In addition to enabling this quantitation, the TG curve also provided insight into the impact of milling upon the chemical stability of the monohydrate form of risedronate. After milling the onset of degradation as observed by degradative mass loss occurred at lower temperature than for the unmilled sample. XRD observations confirmed that milling had not caused a change in solid-state form so the decrease in degradation onset temperature was attributed to the larger surface area. Interestingly, some crystal annealing appeared to have occurred at the high humidity as the degradation onset temperature of the milled material increased over time.

DTA curve provided qualitative evidence for the phase conversions. In the instance of the variable hydrate conversion to hemipentahydrate, the appearance in the DTA curve of the final dehydration endotherm in the hemipentahydrate was the most sensitive marker for early conversion to hemipentahydrate.

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