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Application of slurry bridging experiments at controlled water activities to predict the solid-state conversion between anhydrous and hydrated forms using theophylline as a model drug

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Abstract

The role of water activity (a_w), relative humidity (RH) and temperature on the hydration state of theophylline has been investigated. Slurry bridging experiments at controlled water activities, using powder X-ray diffraction (PXRD) and thermogravimetric analysis (TGA) to characterise the solid phase, established that the hydrate is the thermodynamically stable form of theophylline at $a_w \geq 0.5$ at 4 °C, $a_w \geq 0.64$ at 30 °C, and $a_w \geq 0.76$ at 40 °C. These data were used to produce a phase stability diagram for anhydrous/hydrate theophylline versus temperature. Anhydrous theophylline was spray dried in an attempt to reduce crystallinity. The spray dried theophylline was stored at a range of temperatures (4–40 °C) and humidities (22–89% RH). Samples were analysed at 3, 6, 9, 26 and 52 weeks using TGA and at the 26 and 52 weeks by PXRD. The solid state stability of the spray dried theophylline closely correlated to the phase stability diagram produced using the slurry bridging experiments. The data suggest that the slurry bridging technique at controlled water activities provides an accurate method of rapidly predicting the physically stable form in anhydrous/hydrate systems.

Keywords: Hydrate; Anhydrate; Water activity; Relative humidity; Solid-state physical stability; Theophylline

1. Introduction

Some pharmaceutical materials can exist in both anhydrous and hydrated forms. The presence of water within the crystal lattice of the hydrate results in the anhydrous and hydrated forms having different packing arrangements. Consequently a hydrate has different physical and chemical properties to that of an anhydrate (Khankari and Grant, 1995; Ahlneck and Zografi, 1990). These changes in the pharmaceutically active material could affect the quality, safety or

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efficacy of the final product (Shefter and Kmack, 1967; Shefter and Higuchi, 1963). It is, therefore, essential to understand the anhydrate–hydrate phase transformation of pharmaceutical materials to ensure that unwanted conversions do not occur during the shelf-life of the product.

Theophylline ($C_7H_8N_4O_2$, Fig. 1), a widely used bronchodilator in asthma therapy, can exist either as the anhydrate or the monohydrate depending on the conditions under which it is stored (Naqvi and Bhattacharyya, 1981). There are differences in the solubility (Fokkens et al., 1983), compaction, crystallinity (Adeyeye et al., 1995) and dissolution properties (Shefter and Higuchi, 1963; Ando et al., 1992) of the anhydrous and hydrated forms of theophylline. For example, it has been reported that the anhydrate of theophylline is more soluble than the monohydrate in aqueous systems (Shefter and Higuchi, 1963) and, therefore, if the anhydrate converts to the monohydrate then the bioavailability may also decrease (Otsuka et al., 1991). Thus theophylline provides a good model compound for assessing anhydrate/hydrate conversions.

Zhu et al. (1996) studied the thermodynamic equilibrium between the hydrate and the anhydrous forms of theophylline by slurrying either form of theophylline in a range of water activities in methanol and 2-propanol (isopropyl alcohol, IPA). They reported that the water activity of the crystallisation medium, calculated from previous reports (Gölles, 1961; Udovenko and Mazanko, 1967), determined the hydration state of the material. At 25 °C the theophylline anhydrate–hydrate was found to be in equilibrium at $a_w = 0.25$. Similar studies have also been carried out on nedocromil sodium in IPA/water mixtures (Khankari and Grant, 1993) and with ampicillin in methanol/water mixtures (Zhu and Grant, 1996).

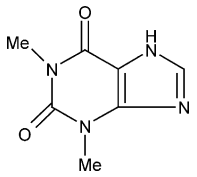

Fig. 1. Chemical structure of theophylline.

In addition the work of Zhu and Grant (1996) that anhydrous ampicillin was kinetically stable over the whole range of water activities, however, the addition of the trihydrate form ensured that the thermodynamically stable form was obtained. This process of equilibration of two or more solid forms in a slurry to generate the thermodynamically stable form is often referred to as a bridging experiment.

The anhydrous and monohydrate crystalline forms of theophylline have been extensively studied. To date there has only been one hydrated form identified; the monohydrate. The characteristics of anhydrous theophylline are more complex as shown in Table 1. Despite the multiple types of anhydrous theophylline there appears to be only one stable form (Form I), which can clearly exist in different morphologies. These different morphologies have been reported to give theophylline different levels of physical stability to hydration in the solid state (Otsuka et al., 1991).

Water activity is directly related to relative humidity in that $RH = a_w \times 100$. Therefore, it should be possible to directly relate the stability of an anhydrous/hydrate system in slurry bridging experiments to solid state stability in controlled RHs. Zhu et al. (1996) attempted to relate their work with that of Otsuka et al. (1991). However, their experiments gave a thermodynamic equilibrium water activity of 0.25 at 25 °C (which equates to 25% RH), whereas Otsuka et al. (1991) reported that in the solid state anhydrous theophylline Types I and II were both stable at up to 66% RH. Zhu et al. (1996) attributed this apparent discrepancy to the relatively slow kinetics of conversion in the solid state preventing true equilibrium of the anhydrous and hydrate forms and the difference in experimental temperatures.

More recently Beckmann and Winter (1999) have considered the stability of the anhydrate and hydrate forms of pyrazzocarnil hydrochloride in water/ethanol mixtures and moist air. This work indicated a temperature dependence of water concentration and equilibrium a_w. However, there did not seem to be a correlation between equilibrium a_w and RH of conversion in the solid state. This was attributed to the large hysteresis mea-

Table 1
Characteristics of anhydrous forms of theophylline which have been characterised in the literature

Type	Method of preparation	Characteristics	Relative stability	Reference
I	Crystallisation	Standard anhydrous form meets all pharmacopoeia standards	Stable anhydrous form. Will convert to monohydrate at elevated RHs (typically $\geq$ 75%)	USP, Ph. Eur.
II	Dehydration of monohydrate at 100 °C for 24 h	As Type I, but with different crystal morphology and a larger specific surface area	Kinetics of conversion to monohydrate are more rapid than Type I	Otsuka et al. (1990)
I*	Dehydration of monohydrate at 100 °C for $<$ 2 h	Different PXRD pattern to Type I. Can only be formed by dehydrating the monohydrate suggesting it is a dehydrated hydrate	Metastable to anhydrous Type I from − 150 °C to melting point (269 °C)	Phadnis and Suryanarayanan (1997)

sured for hydration/dehydration of pyrazzocarnil hydrochloride in the solid state.

The aim of the present study was to prepare a meaningful phase diagram of theophylline using slurry bridging experiments at controlled water activities and temperature, and then to determine whether this phase diagram could be used to predict the physical stability of theophylline. To investigate the physical stability of the anhydrous and hydrated phases samples were stored at a range of relative humidities for up to 52 weeks. Prior to storage the theophylline was processed by spray drying in order to increase surface area and reduce crystallinity in order to increase the kinetics of conversion in the solid state.

2. Materials and methods

2.1. Materials

Anhydrous theophylline (USP) was obtained from Sigma Chemicals (St. Louis, MO; lot 127H0539).

CH_3COOK, $MgCl_2 \cdot 6H_2O$, NaI, NaBr, NaCl and KNO_3 were supplied by Sigma as Analar grade.

2.1.1. Sample preparation

2.1.1.1. Theophylline monohydrate. Theophylline monohydrate was prepared by forming a saturated solution of anhydrous theophylline in hot distilled water. The solution was then filtered whilst hot and allowed to cool overnight. Theophylline monohydrate crystals were harvested.

2.1.1.2. Spray-dried theophylline. A 7 mg/ml theophylline aqueous solution was spray dried on an Aeromatic Strea-1 Fluid Bed Drier using the top spray method. The inlet temperature was set at 80 °C, outlet temperature at 55 °C with an air pressure of 1 bar. Samples were stored in a dessicator, over phosphorus pentoxide, after collection.

2.2. Methods

2.2.1. Slurry bridging experiments

Excess theophylline anhydrate was equilibrated in acetone and water mixtures (5 ml) and methanol and water mixtures (10 ml), of varying a_w values (0.1–0.9) and at varying temperatures (4, 22, 30 and 40 °C). Values of a_w were calculated from results previously reported (Sokolova and Morachevskii, 1967; Gölles, 1961). Samples were seeded with theophylline monohydrate after 16 h slurrying to ensure an excess of solid of both the anhydrous and monohydrate forms. The mixtures were constantly stirred for up to 14 days, using a spindle stirrer, in order to attain equilibrium. The excess solid phases were analysed by DSC, TGA and PXRD. The final water contents of the remaining solutions were measured using Karl Fischer analysis.

Theophylline has been shown to be chemically stable over short periods in aqueous solution (Baptista and Mitrano, 1988; Marti-Bonmati et al., 1986).

2.2.2. Differential scanning calorimetry (DSC)

A model 2910 differential scanning calorimeter (TA Instruments) was used to investigate the thermal properties of the samples. The DSC apparatus was calibrated with indium as the standard. Accurately weighed samples (2–5 mg) were transferred into crimped, aluminium pans (not hermetically sealed). Samples were run at a heating rate of 10 °C/min under a nitrogen purge.

2.2.3. Thermogravimetric analysis (TGA)

A TGA Model 2950 (TA Instruments) was used to determine the quantity of volatile material in the solid phases of the theophylline slurries. Samples were run in an open pan at a heating rate of 10 °C/min from ambient to 150 °C.

2.2.4. Karl Fischer analysis

The amount of water present in the organic solvent and water mixtures was determined using a Mitsubishi CA-06 Moisture meter. The samples were accurately measured and syringed into the moisture meter.

Table 2
Temperature and relative humidity conditions used in physical stability assessment (Nyqvist, 1983)

Salt	Temperature (°C) and corresponding relative humidity (%)		
	4 °C	30 °C	40 °C
CH_3COOK	23	22	22
$MgCl_2$	34	–	–
NaI	42	36	–
NaBr	64	56	53
NaCl	–	75	75
KNO_3	–	–	89

2.2.5. Powder X-ray diffraction (PXRD) analysis

The PXRD patterns of the theophylline samples were determined using a Bruker D5000 powder X-ray diffractometer fitted with an automatic sample changer, a θ–2θ goniometer, automatic beam divergence slits, a secondary monochromator and a scintillation counter. The samples were mounted on silicon wafer specimen mounts and rotated whilst being irradiated with copper Kα X-rays (wavelength = 1.5046 Å) with the X-ray tube operated at 40 kV/40 mA. The analyses were performed with the goniometer running in a continuous scan mode for a 5 s count per 0.02° step over a 2θ range of 2–55°.

For fast collection of data, from unstable samples, the goniometer was run in a continuous scan mode for a 0.5 s count per 0.02° step over a 2θ range 6–30°.

2.2.6. Solid state stability experiments

Saturated solutions of CH_3COOK, $MgCl_2 \cdot 6H_2O$, NaI, Na Br, NaCl and KNO_3 were prepared and stored at 4, 30 and 40 °C, producing relative humidity conditions detailed in Table 2. Once equilibrated samples of spray dried theophylline were placed at each condition. Samples were removed and analysed at 3, 6, 9, 26 and 52 weeks, as described previously.

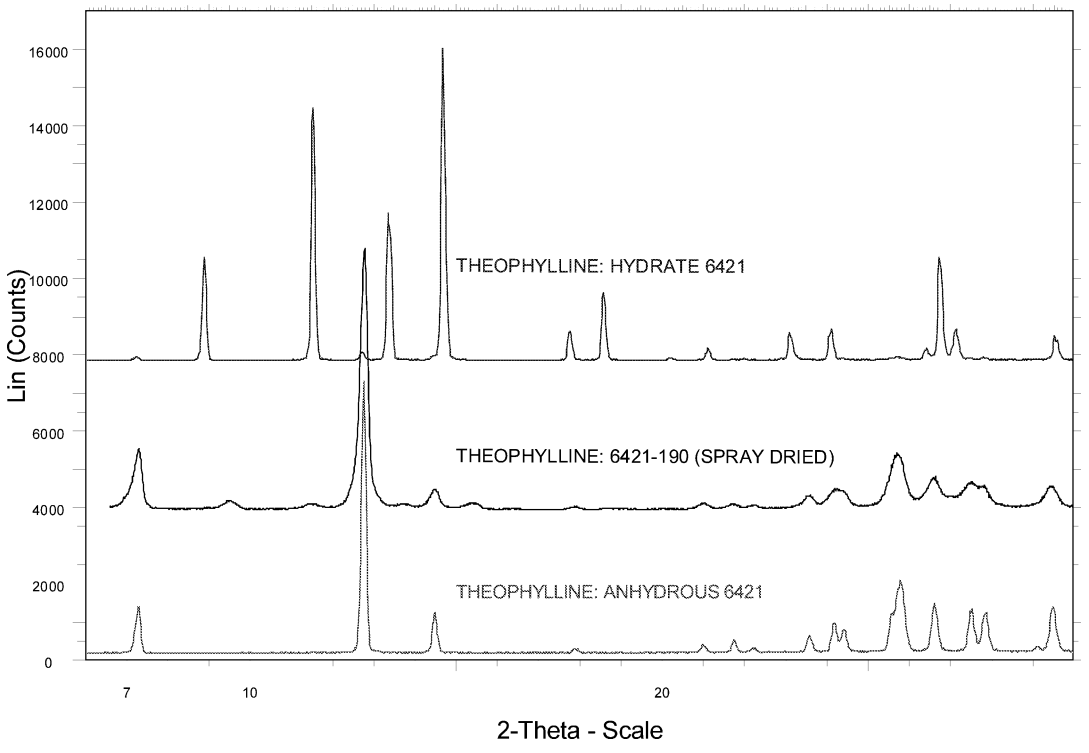

Fig. 2. PXRD analysis of theophylline anhydrous, theophylline monohydrate and spray-dried theophylline.

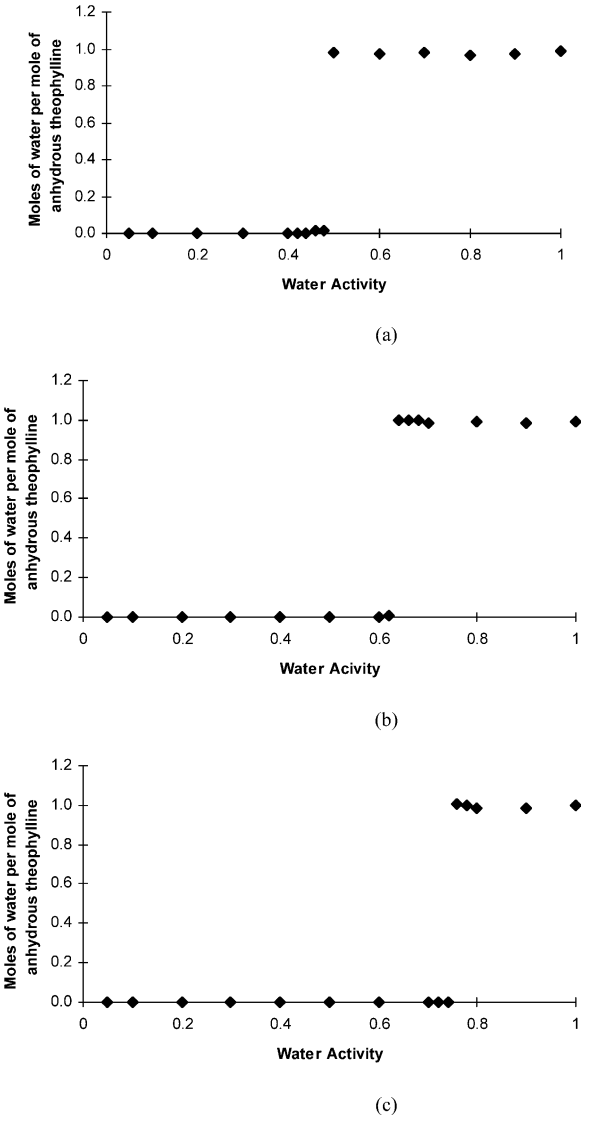

Fig. 3. Phase diagram after 14 days for theophylline in water and acetone slurries at 4 °C (a), 30 °C (b) and 40 °C (c).

3. Results and discussion

3.1. Characterisation of starting materials

The theophylline anhydrous and monohydrate were analysed using PXRD (Fig. 2) and were shown to have equivalent peak positions to those listed in the Powder Diffraction File (1998, ICDD, Pennsylvania) for anhydrous theophylline (ICDD No. 27-1977) and theophylline hydrate (ICDD No 26-1893). The PXRD pattern of the spray dried theophylline, shown in Fig. 2, has broad peaks suggesting a reduced level of crystallinity, which for the most part are consistent with the anhydrous pattern.

3.2. Slurry bridging experiments

The results of the acetone/water slurry bridging experiments showed the hydrate to be present at $a_w \geq 0.50$, ≥ 0.64 and ≥ 0.76 at 4 °C (Fig. 3a), 30 °C (Fig. 3b) and 40 °C (Fig. 3c), respectively. Above these water activities, at the specified temperatures, the TGA thermograms showed a weight loss of approximately 8.9%, which is stoichiometrically equivalent to the monohydrate. DSC and PXRD analysis confirmed the solid phases to be theophylline monohydrate. The increased water activity required to form a hydrate at higher temperatures can be explained by the weakening of H-bonds between the water and theophylline (Yoshihashi et al., 1998).

Samples of the anhydrate (Type I) and, in a separate experiment, the anhydrate (Type I) seeded with hydrate, were also slurried at room temperature in a range of methanol/water mixtures at different water activities. The results shown in Fig. 4 indicate that the hydrate was always present at $a_w \geq 0.6$ at 22 °C, after 5 days, which fits well with the results obtained from the acetone/water slurries. The results of the slurry bridging experiments are represented diagrammatically in Fig. 5.

Our results do not agree with those of Zhu et al. (1996) on the phase conversion of theophylline using methanol/water and IPA/water mixtures. Their results showed that theophylline monohydrate was present at $a_w > 0.25$ at 25 °C. The reason for the discrepancy between the two data sets is not clear despite detailed discussions between both sets of authors.

3.3. Solid-state physical stability

Spray dried theophylline was stored at 4, 30 and 40 °C over saturated salt solutions of varying relative humidities. The spray dried starting material in this experiment was predominantly anhy-

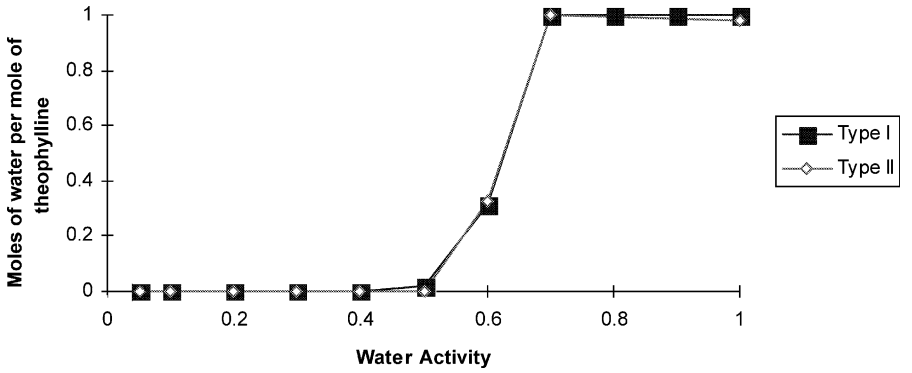

Fig. 4. Phase diagram of Type I (after 14 days) and Type II (after 5 days) anhydrous theophylline at equilibrium, at 22 °C.

drous theophylline with no evidence of theophylline hydrate. Hence the experiment was designed to purely monitor the hydration process.

The spray dried material was used in the solid state experiments in preference to the crystalline anhydrate because it was shown by XRD to be less crystalline than the original crystalline anhydrate, and hence the hydration kinetics would be expected to be increased. However, even with increased kinetics this solid-state experiment would not be expected to closely define the thermodynamic equilibrium between the anhydrous and hydrate forms.

The results of the TGA of the sample after 3, 6, 9, 26 and 52 weeks at controlled humidity and temperature are shown in Fig. 6. Fig. 6 also shows the results of the PXRD analysis after 52 weeks indicating where a detectable level of hydrate was present. The results clearly show hydration of the spray-dried material at the higher RHs for each temperature. Complete hydration of the spray dried material only occurred at 40 °C/89% RH. However, the initiation of hydrate formation at 4 °C/64% RH, 30 °C/56% RH, 30 °C/75% RH and 40 °C/75% RH was considered an indication that the hydrate was the more stable form and complete hydration would eventually occur. Otsuka et al. (1991) have observed that theophylline of different morphologies have different hydration kinetics. Hence a tentative reason for incomplete conversion is heterogeneity of the crystallinity/morphology in the batch of spray-dried material.

3.4. General discussion

Fig. 7 shows the solid state stability data for theophylline superimposed on the phase diagram produced from the slurry bridging experiments ($RH = a_w \times 100$). The results show that hydration has occurred in the solid state only under conditions at or near those where the hydrate is the thermodynamically stable form defined by slurry bridging experiments. The minor inconsistency of hydration at 30 °C/56% RH could be attributed to a slight inaccuracy in the slurry bridging experiments. The presence of a third component i.e. theophylline, could, depending on the solubility of the solute in the solvent mixture, lower the water activity by up to 6% (Zhu et al., 1996).

During the slurry bridging experiments there is dissolution of the more soluble (less physically stable) form of theophylline, leading to the supersaturation of the less soluble (more physically stable) form. Precipitation of the least soluble

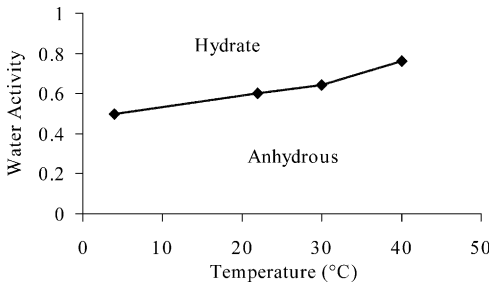

Fig. 5. Theophylline anhydrous/hydrate phase diagram from 4 to 40 °C.

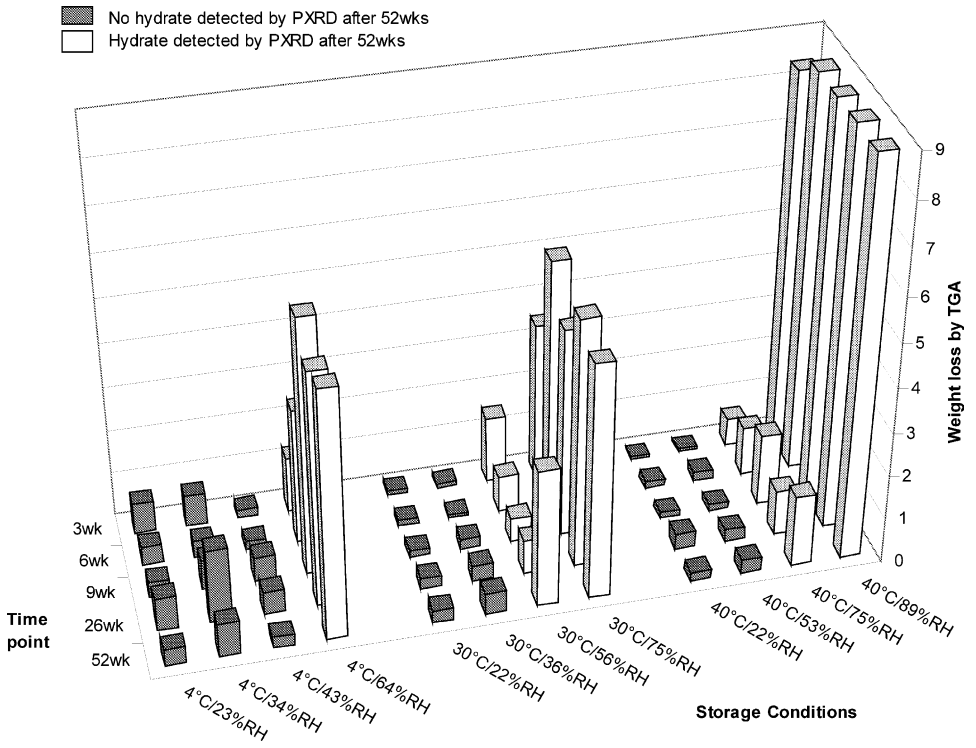

Fig. 6. Results of TGA and PXRD of samples of spray dried theophylline stored at different temperature/RH conditions.

form was ensured by having seeds of both forms present in the slurry (bridging). The kinetics of this process are controlled by the dissolution rate of the more soluble form, the rate of crystallisation of the less soluble form, their relative solubilities and whether seeds of both forms have been added. In contrast the hydration/dehydration process in the solid state requires water molecules to migrate either into or out of the crystal lattice. Phadnis and Suryanarayanan (1997) showed that the conversion of stable theophylline hydrate (II) to stable theophylline anhydrate (I) went through a metastable form (I*) (see Table 1 for a description of each Theophylline form). The transition between forms II and I* occurs at low humidities caused by the reversible loss of water through channels in the crystal lattice. The crystal lattice of Form I* was observed to collapse with time to produce form I. Interestingly the hydration of form I to the form II appears to go directly without a metastable intermediate (Yoshihashi et al., 1998) suggesting that the transformation is a dissolution/recrystallisation procedure.

The nature of the slurry experiments mean that the kinetics of hydration/dehydration are typically significantly faster than those of the solid-state.

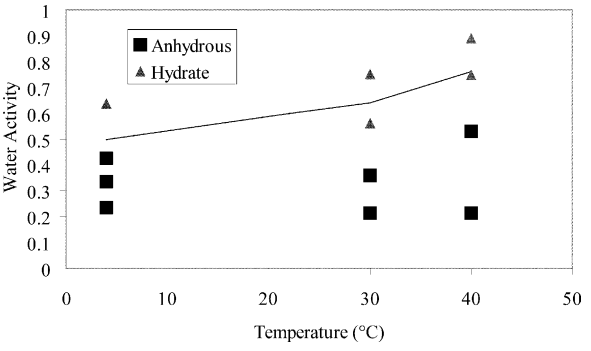

Fig. 7. Overlay plot of a line indicating equilibrium water activity for Theophylline anhydrous/hydrate forms from slurry bridging experiments compared with solid form at 52 weeks storage at controlled temperature and humidity (RH% = water activity × 100).

This is because with the slurry process the formation of the more stable form through recrystallisation means that there is a minimum barrier to addition or loss of water to or from the crystal lattice. Whereas, a solid-state conversion requires the migration of water through the crystal lattice and a potential change in the crystal structure.

The thermodynamic equilibrium defined by the slurry bridging experiments may be considered as the limiting case. That is if a form of a material is stored in its thermodynamically stable region (defined by the slurry bridging experiments) it will not convert. Indeed for some hydrate/anhydrous systems even if the form is stored outside its stable region the kinetics of conversion of the crystalline material may be so slow as to be negligible when compared with standard stability times. However, even in these cases the potential for disruption of the crystal lattice during processing such as milling (Ward and Schultz, 1995) or drying should be considered, as they may cause batch-to-batch variability in hydration/dehydration kinetics. For example Otsuka et al. (1991) highlighted this type of variability of physical stability for theophylline Type I and Type II which are the same polymorphic form but differ in method of manufacture.

In conclusion slurry bridging experiments at controlled water activities and temperatures have been used to produce a phase diagram for theophylline anhydrous and theophylline monohydrate forms. This phase diagram has been shown to be a useful tool for predicting the conversion of spray-dried anhydrous theophylline to the monohydrate form. The kinetics of hydration/dehydration in the solid state can be very slow and hydrate/anhydrous systems often have large hysteresis loops (Beckmann and Winter, 1999). In the early stages of drug development it is generally not possible to run an extended stability program and hence is often difficult to select the appropriate form of the material to progress. Slurry bridging experiments are not subject to the complex and typically slow kinetics of conversion, which are often observed in the solid-state (Richards et al., 2000), allowing them to be completed within a few weeks. Therefore, slurry bridging experiments at controlled water activities could prove a useful method to guide the choice of the preferred physical form for materials where anhydrous and hydrated forms are known to exist.

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