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Dehydration kinetics of theophylline-7-acetic acid monohydrate

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Abstract A hydrated form of theophylline-7-acetic acid obtained by recrystallization from water is described and characterized in terms of thermal properties, physical stability with respect to relative humidity and dehydration kinetics. The hydrate resulted to be stable at ambient conditions. Fitting of experimental dehydration data to solid state reaction equations suggests a three dimensional phase boundary reaction proceeding from the surface of the crystal inward along three dimensions. The relevant activation energy calculated from the Arrhenius plot is 173 kJ/mol.

Keywords Dehydration kinetics · Hydrate · Physical stability · Theophylline-7-acetic acid

Introduction

The rational design and development of a solid dosage form necessarily entail the selection of the appropriate physical form of both active ingredients and excipients. In fact, since different crystal forms, polymorphs and/or solvates, can show distinctive physical properties, they may have a remarkable effect on the biopharmaceutical performance as well as the manufacturability and the stability of the dosage form. For this reason, preformulation studies, aiming at an early identification of all possible crystalline modifications, are nowadays a fundamental step in the pharmaceutical development of new drugs and drug products [1].

Theophylline-7-acetic acid (1,2,3,6-tetrahydro-1,3-dimethyl-2,6-dioxopurine-7-acetic acid, CAS no. 652-37-9, Fig. 1) is a derivative of theophylline, an extensively used xanthine with diuretic, cardiac stimulating and smooth muscle relaxing pharmacological effects. With respect to its precursor, theophylline-7-acetic acid has shown similar but more specific bronchodilating activity [2] and is therefore a potential candidate for medicinal products for the treatment of asthma.

To date, information on the solid state properties of this compound reported in the literature is limited to the structure of one crystalline anhydrous form [3, 4].

The present work describes a new hydrated form of theophylline-7-acetic acid obtained by recrystallization from water. In particular this study is aimed towards the characterization of the new form as well as providing information on its physical stability and dehydration kinetics.

Materials and methods

Anhydrous theophylline-7-acetic acid (purity 99.2%, m.p. 272 °C, residual solvents <10 ppm, TAA) was provided by Erregierre SpA (San Paolo d'Argon BG, I) and was used as supplied. The monohydrate ($TAA{\cdot}H_2O$) was prepared by crystallization from a hot (60 °C) saturated aqueous solution (~1% w/v) slowly cooled and allowed to stand overnight at room temperature. The separated crystals were filtered and exposed to room temperature in vacuo for 24 h to allow removal of superficial moisture. The resulting solid was stored in a closed glass flask (yield = 76%).

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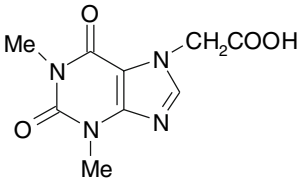
Fig. 1 Structural formula of theophylline-7-acetic acid



Powder X rays diffractometry (PXRD)

X-rays powder diffraction profiles were recorded at room temperature with a Philips PW1050/25 diffractometer (Philips Analytical Inc., Natick, MA, USA) using Cu–K_α radiation ($\lambda = 1.5418$ Å) generated with 40 kV and 20 mA. The system was calibrated with a silicon standard which yielded peak positions of 28.45 ± 0.01° 2θ. Samples were packed in the same aluminum sample holder in order to minimize errors of reproducibility. The powders were gently ground in order to minimize preferred orientation effects. The operating conditions were as follows: scan speed 1.0° 2θ/min, step size 0.1° 2θ, 2θ-range 5–40°.

Fourier transform infrared spectroscopy (FT-IR)

FT-IR spectra were recorded with a Paragon 1000 FT-IR spectrometer (Perkin-Elmer Instruments, Shelton, CT, USA). The samples were prepared as physical mixtures of about 1.5% w/w drug in potassium bromide; the mixtures were then compressed into pellets and scanned. Samples were analyzed as KBr discs from 500 to 4,000 $cm^{-1.}$

Karl-Fischer titrimetry (KFT)

The water content was determined by KFT employing a Mettler DL50 Graphix equipment (Mettler Toledo GmbH, Schwerzenbach, CH).

Thermal analysis

Differential Scanning Calorimetry (DSC) and Thermogravimetric analysis (TG) were conducted with TA Instruments equipment (DSC2010 calorimeter, TG2050 thermobalance, New Castle, DE, USA) under nitrogen purging of 70 mL/min. DSC runs were performed on 2–3 mg samples in non-hermetically sealed aluminum pans at a scanning rate of 10 K/min; TG was performed on 15–20 mg samples at 10 K/min. Data presented are the mean of 6 replicates.

Water vapour sorption

Solid samples (~1 g, 90–125 μm sieved fraction) were stored at room temperature (25 ± 2 °C) in closed glass containers together with P_2O_5 or saturated aqueous solutions of CH_3COOK, NaI (samples of TAA·H_2O), NaBr, KBr, KNO_3 and K_2SO_4 (samples of TAA) in order to produce relative humidity values of 0, 22, 38, 58, 81, 94 and 97, respectively [5]. The control of relative humidity was performed by a calibrated hygrometer.

The weight change of each sample was monitored over a period of 6 months and the solid recovered at the end of the study was characterized by PXRD and thermal analysis.

Isothermal TG experiments

Isothermal TG was performed on samples of solid (~20 mg, 90–125 μm sieved fraction) at 68, 70, 72, 75, 80 and 85 °C, under dry N_2 purging of 100 mL/min. Samples were introduced in the furnace pre-heated at the desired temperature and their weight loss was monitored until equilibrium was reached.

Data fitting

Dehydrated fractions (α) from 0.2 to 0.9 were selected for the fitting according to the equations for solid state reactions reported in Table 1. The following general integrated equation was applied:

$$g(\alpha) = kt$$

where k is the rate constant, t is the reaction time and g(α) is a function of the reaction mechanism. Conformity to a specific kinetic model was quantified using correlation coefficient, standard deviation of the regression, and standard deviation of the slope of the regression line. Dehydration rate constants (the slopes of the linear plots), obtained from the equations giving the best fits, were plotted versus the reciprocal of the absolute temperature, according to the Arrhenius plot. The activation energy for the dehydration process was then estimated from the slope of the plot.

Results and discussion

A hydrated form of theophylline-7-acetic acid was isolated by recrystallization from water, producing a dense network of needle-like crystals in the mother liquor. Unfortunately, the crystals recovered from these experiments were in all cases very thin, and therefore unsuitable for single-crystal X-rays diffraction studies.

Water content of the solid was consistent with the theoretical value for a monohydrate (7.03% w/w). The PXRD pattern generated for the new form (TAA·H_2O) is presented in Fig. 2 and compared with that of the anhydrous form (TAA). Differences in peak positions and intensities indicate different crystal lattices. Extensive differences

Table 1 Kinetic equations for the most common mechanisms of solid-state reactions [12]

Model notation	Equation	Mechanism
P1	$\ln [\alpha/(1-\alpha)] = kt$	Random nucleation (Prout-Tompkins eq.)
A2	$[-\ln (1-\alpha)]^{1/2} = kt$	Two-dimensional growth of nuclei (Avrami-Erofeev eq.)
A3	$[-\ln (1-\alpha)]^{1/3} = kt$	Three-dimensional growth of nuclei (Avrami-Erofeev eq.)
F1	$-\ln (1-\alpha) = kt$	Random nucleation (first order mechanism)
R1	$1-\alpha = kt$	One-dimensional phase boundary reaction (zero order mechanism)
R2	$1-(1-\alpha)^{1/2} = kt$	Two-dimensional phase boundary reaction (cylindrical symmetry)
R3	$1-(1-\alpha)^{1/3} = kt$	Three-dimensional phase boundary reaction (spherical symmetry)
D1	$\alpha^2 = kt$	One-dimensional diffusion
D2	$(1-\alpha)\ln (1-\alpha)+\alpha = kt$	Two-dimensional diffusion
D3	$[1-(1-\alpha)^{1/3}]^2 = kt$	Three-dimensional diffusion (Jander eq.)
D4	$1-(2/3)\alpha-(1-\alpha)^{2/3} = kt$	Three-dimensional diffusion (Ginstling-Brounshtein eq.)

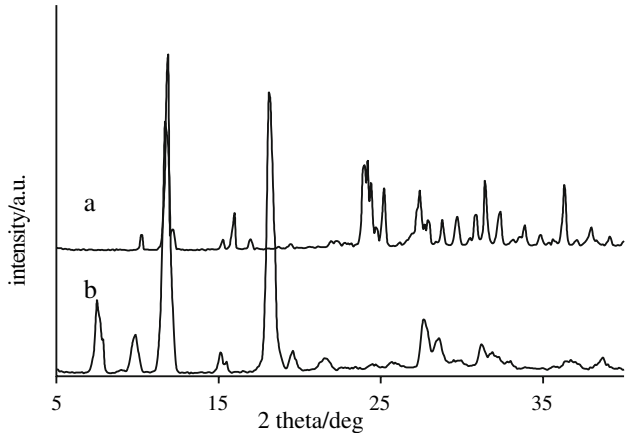


Fig. 2 PXRD patterns of TAA (a) and TAA·H_2O (b)

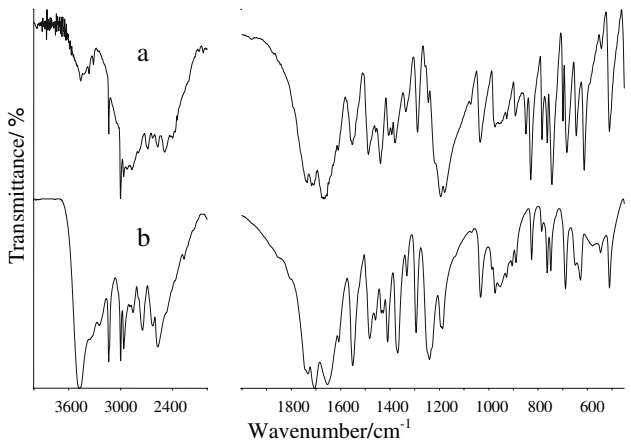


Fig. 3 FT-IR spectra of TAA (a) and TAA·H_2O (b)

also exist between the FT-IR spectra of the two forms (Fig. 3), especially in the range of frequencies 3,500–2,000 cm^{-1} and in the fingerprint region. Specifically TAA·H_2O spectrum is characterized by the presence of

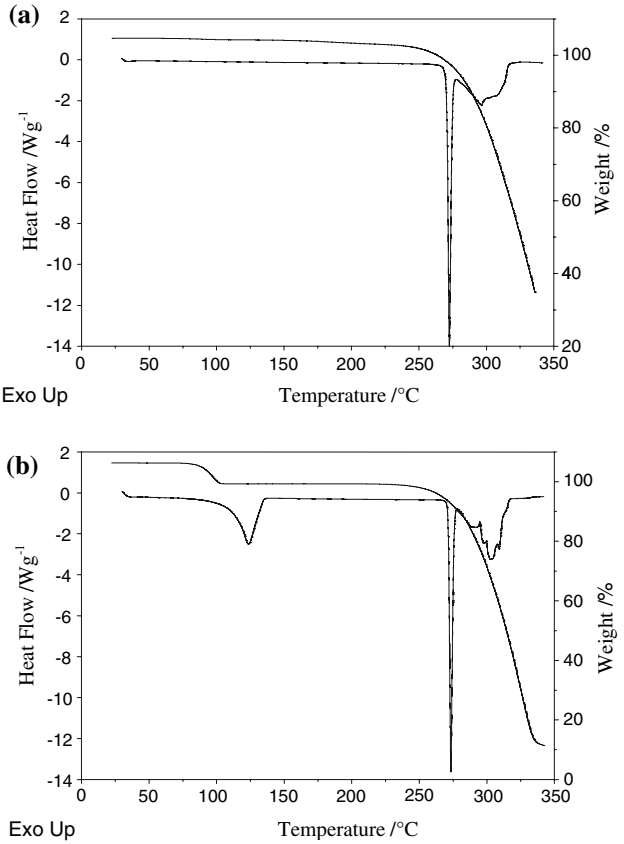


Fig. 4 DSC and TG curves of TAA (**a**) and TAA·H_2O (**b**)

sharp and structured bands in the OH stretching region due to the tightly bound water.

DSC and TG traces are shown in Fig. 4. TAA shows a single endothermic event, due to fusion, at 271 °C (T_{onset}), followed by decomposition as evidenced by the relevant weight change in the TG experiment. The thermal profile of TAA·H_2O is characterized by a dehydration endotherm at 107 °C (heat of dehydration of 58.4 ± 1.5 kJ/mol) associated with a weight loss of 6.9 ± 0.1% in the TG

curve. After dehydration, melting and decomposition are observed at the same temperatures recorded for the anhydrous form.

The nature of the dehydration product was independently confirmed by performing a PXRD scan on a solid sample previously stored at 120 °C for 1 h. The relevant pattern (data not shown) was found to be superimposable on that of the anhydrous form in terms of peak positions, thus confirming that water subtraction leads to the formation of TAA.

Knowledge of the hydration–dehydration behavior of a drug showing solvatomorphism is important in pharmaceutical development since a change in the hydration state can cause an alteration of the physicochemical, processing, and biopharmaceutical properties [6].

The stability of the solid forms of theophylline-7-acetic acid as a function of both relative humidity and temperature was evaluated in distinct experiments.

The tendency of the TAA for water uptake was studied by storing solid samples at room temperature in closed glass containers together with saturated solutions of various salts within the 58–97% relative humidity (RH) range. On the other hand, the stability of TAA·H_2O with respect to dehydration was tested at 0%, 22% and 38% RH values. Figure 5 illustrates the relevant weight change versus time profiles over a 6-month period. Remarkable water uptake was observed for the anhydrate at 94% and 97% RH with equilibrium weight gain being reached within 60 days. For these samples the complete conversion to TAA·H_2O was assessed by PXRD analysis at the end of the storage period. As for the sample maintained at 81% RH, a weight gain of approximately 2% of the initial value was recorded and the recovered solid was only partially hydrated. On the contrary, the sample stored at 58% RH was found to still consist of TAA so that the negligible weight gain recorded in this case (<0.5%) must be attributed exclusively to surface moisture sorption. Conversely, TAA·H_2O remained

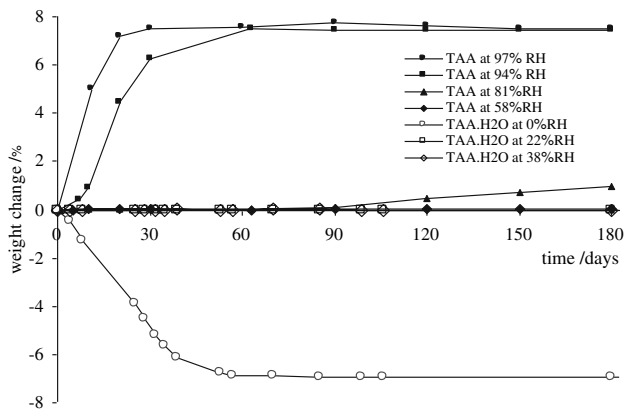


Fig. 5 Sorption and desorption profiles at room temperature

stable at 22% and 38% RH and completely transformed to the anhydrous form at 0% RH in 2 months.

In order to evaluate the rate and possible mechanism of thermal dehydration of TAA·H_2O, kinetic studies were carried out by isothermal TG at different temperatures. As the dehydration kinetics are known to be influenced by factors such as the sample characteristics (surface properties, particle size, degree of crystal disorder and weight) as well as the environmental conditions (RH, flow rate and temperature of the purging gas) [7–11], the TG scans were conducted under controlled experimental setting (see experimental section). Prior to each run the furnace was rapidly equilibrated to the selected temperature and the sample was maintained at that temperature until dehydration was complete. TG data expressed as fraction of dehydrated product (α) as a function of time are reported in Fig. 6.

A sigmoidal profile is observed at all temperatures, dehydration rates, as expected, increasing with temperature. Thermal dehydration was treated as a reaction of solid-state decomposition producing water vapour and a solid anhydrous phase. Dehydrated fractions in the 0.2–0.9 range were fitted according to the common kinetic equations for solid-state reactions (see Table 1). At all considered temperatures the results of the fitting parameters suggest that equation R3 ($g(\alpha) = 1 - (1 - \alpha)^{1/3}$) is the best applicable to the kinetics of the process. Therefore, the model is that of a three dimensional phase boundary reaction assumed to proceed from the surface of the crystal inward along three dimensions [5]. Good linearity in the Arrhenius plot was obtained, thus indicating a single dehydration mechanism of TAA in the temperature range considered. The activation energy (Ea) for dehydration calculated from the slope of the Arrhenius plot (Fig. 7) was 173 kJ/mol. In this respect, some differences were found between TAA and its parent compound theophylline. Several studies reported in the literature indicate that dehydration of theophyllline monohydrate occurs with different mechanisms over different temperature ranges, shifting from diffusion type to phase boundary type reaction model at temperatures below 40 °C and above 42 °C, respectively [8, 13, 14]. Accordingly, Ea values of 125 ± 10 and 84 ± 4 kJ/mol were found for lower and higher temperature ranges, respectively.

Whilst recognizing the limitations of this approach and the strict dependence of the relevant outcome on the selected experimental conditions, the estimation of Ea for dehydration is still considered a useful tool for the assessment of the thermal stability of medicinal hydrates.

In this respect, TAA·H_2O can be considered stable. In fact, the derived Ea value for dehydration is actually relatively high compared to those reported for other pharmaceutical hydrates, specifically xanthine derivatives [8],

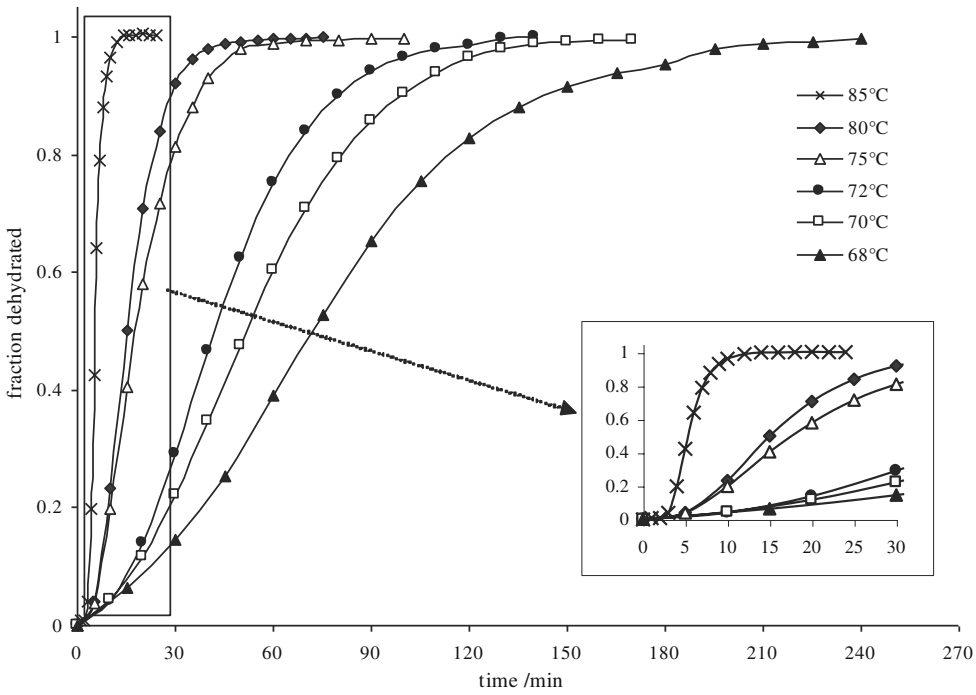


Fig. 6 Isothermal dehydration curves of TAA·H_2O at different temperatures. The *inset* shows a magnification of the profiles in the 0–30 min time range

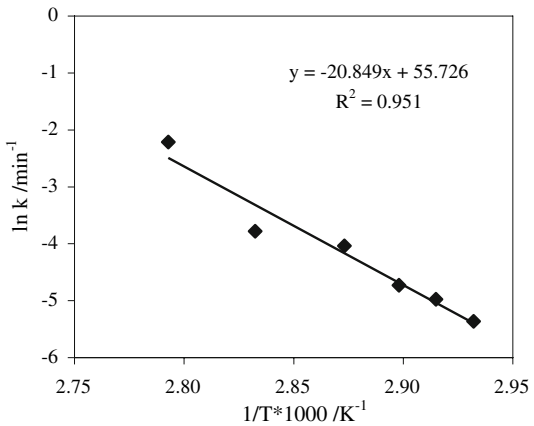


Fig. 7 Arrhenius plot for dehydration of TAA·H_2O

and is consistent with the data of dehydration temperature and enthalpy recorded by DSC. Moreover, at room temperature, dry conditions (0%RH) seem to be required for its dehydration.

Conclusions

A new monohydrate form of theophylline-7-acetic acid has been successfully isolated by recrystallization from water. Physical stability with respect to dehydration was highlighted both with respect to the relative humidity as well as temperature, making this form suitable for future pharmaceutical development.

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