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A method for the rapid evaluation of the physical stability of pharmaceutical hydrates

Jun Han[1], Raj Suryanarayanan[*]

College of Pharmacy, University of Minnesota, 308 Harvard Street SE, Minneapolis, MN 55455, USA

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Abstract

The object of this project was to develop a simple kinetic method to rapidly assess the physical stability of pharmaceutical hydrates. Humidity controlled thermogravimetric analysis (TGA) and X-ray powder diffractometry (XRD) were used to study the dehydration of amoxicillin trihydrate. Dehydration resulted in a poorly crystalline phase and could be described by the phase boundary controlled model at all the conditions studied. The relationship between the dehydration rate constant, k, and water vapor pressure, p, was described by the equation: $k = k_0 \times (1 - p/p_t)$, where k_0 is the rate constant when the water vapor pressure is 0 Torr and p_t is the transition water vapor pressure at the temperature studied. When the dehydration rate constant was plotted as a function of water vapor pressure, the intercept on the x-axis was the transition water vapor pressure, p_t. Using this relationship, the transition water vapor pressure of amoxicillin trihydrate was determined to be ~10.5 Torr at 68°C. At water vapor pressures>p_t, the hydrate is the stable phase. Published by Elsevier Science B.V.

Keywords: Thermogravimetric analysis (TGA); Amoxicillin; Solid state; Dehydration; X-ray diffractometry (XRD); Water vapor pressure

1. Introduction

Hydrates are molecular complexes that incorporate water molecules, usually stoichiometrically, in their crystal lattice [1–3]. The current edition of the United States Pharmacopeia [4] includes over 150 compounds that exist as hydrates. During pharmaceutical processing and storage, hydration and dehydration processes can occur [2]. It is becoming increasingly clear that the solid-state properties (polymorphic form, state of solvation, degree of crystallinity) of the active ingredient can profoundly influence the in vivo performance of the dosage form [5]. In order to control the state of hydration of the active ingredient[2], it is necessary to understand the kinetics and mechanism of hydration and dehydration processes under the appropriate conditions.

Byrn et al. [5] have comprehensively summarized the approaches to study pharmaceutical hydrates. In order to determine the physical stability of hydrates, the anhydrous and hydrated forms of a compound are stored in chambers (desiccators) maintained at various relative humidities. After the system attains equilibrium, the solid phase is characterized. This permits

*Corresponding author. Tel.: +1-612-624-9626; fax: +1-612-626-2125; e-mail: surya001@maroon.tc.umn.edu

[1]Current address: Wyeth-Ayerst Research, 401 N. Middletown Road, Pearl River, NY 10965 USA.

[2]For the sake of simplicity, in all our discussions we will assume that there is only one hydrated state of the drug. However, the approach discussed in this publication can also be used, with appropriate modification, for drugs existing in multiple states of hydration.

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the determination of the conditions (i.e. water vapor pressures) under which the anhydrous and hydrated forms are stable. However, such an approach has a few drawbacks:

1. Since the experiments are carried out under isothermal conditions, the phase diagram is valid only for that temperature.
2. The experiment is very time consuming and attainment of equilibrium may take a very long time.
3. In numerous systems, there is resistance to achievement of equilibrium and as a result the phase diagram exhibits pronounced hysteresis [6].
4. Since only a limited number of relative humidity chambers are used in such studies, the phase diagram generated may not be very accurate.

Many other approaches to determine the equilibrium water vapor pressure have been used in the literature, which include one-way flow systems [7], mercury manometery [8], water and organic cosolvent method [9,10], dew point hygrometry [11], thermocouple psychrometry (wet bulb depression) [12], the Fett–Vos method [13,14], graphic interpolation method [15] and calorimetric and IR spectroscopic methods [16].

Recently, automated controlled microbalance systems have been constructed wherein the sample can be subjected to a controlled relative humidity program [17]. Such instruments are commercially available and they can be used to assess the stability of pharmaceutical hydrates. However, because of their high cost, the availability to academic institutions has been limited.

The goal of this project was to develop a simple method to rapidly assess the physical stability of pharmaceutical hydrates. The method is based on a simple humidity controlling device which was originally attached to the sample chamber of a powder X-ray diffractometer [18]. By suitable modifications, we have developed the capability to perform humidity controlled XRD, TGA and DSC. This permitted simultaneous control of *both* the temperature and the water vapor pressure.

The experimental techniques used: thermogravimetric analysis (TGA), and variable temperature X-ray powder diffractometry (VTXRD), respectively, provide information about the change in weight and solid-state (phase) during the dehydration process. By combining the two techniques, it was possible to develop a mechanistic understanding of the dehydration process. Amoxicillin trihydrate ($C_{16}H_{19}N_3O_5S\cdot 3H_2O$) a widely used antibiotic was used as the model compound. Dehydration of the crystalline trihydrate resulted in a poorly crystalline ''dehydrated'' phase which could be rehydrated to the trihydrate phase by storage under high relative humidity [19]. Shefter et al. [20] had observed that dehydration of ampicillin trihydrate resulted in an amorphous anhydrate. However, there are no systematic studies which have examined the effect of temperature *and* water vapor pressure on the physical stability of amoxicillin trihydrate.

2. Theory

Unlike reactions in the liquid and gaseous states, solid-state reactions tend to be much more complicated and difficult to study. Though the kinetics of solid-state reactions are governed by the basic principles of physical chemistry, they can be affected by numerous factors including sample size and packing, particle size and solid-state of the reactant, and the nature and concentration of impurities [21,22]. The dehydration of pharmaceutical hydrates is a widely studied solid-state reaction [2,23]. Assuming that the water liberated on dehydration undergoes immediate vaporization, the conversion of a hydrate, $D\cdot nH_2O$, into the corresponding anhydrate, D, can be described by the equation:

$$D\cdot nH_2O_{(solid)} \rightarrow D_{(solid)} + nH_2O_{(gas)} \quad (1)$$

The dehydration reaction can be treated as a decomposition reaction and represented by the general equation:

$$AB_{(solid)} \rightarrow A_{(solid)} + B_{(gas)} \quad (2)$$

In decomposition reactions of inorganic compounds, the effect of the pressure of the gaseous product phase, B, on the reaction kinetics has been studied [24,25]. These studies assume that the sample size as well as the sample packing do not vary from one experiment to another and that the vapor pressure of the gaseous product does not change during the isothermal studies. It is also assumed that the reaction mechanism and the solid-state of the product phase are identical under all the experimental conditions, and

that the diffusion of the gaseous product to the solid-vapor interface is not the rate limiting step in the reaction. The decomposition rate constant, k, at a vapor pressure p of the gaseous product was then described by the equation,

$$k = k_0 \times (1 - p/p_t), \quad (3)$$

where k_0 is the rate constant when the vapor pressure is zero and p_t is the transition vapor pressure. This equation was used in the study of decomposition reactions of inorganic compounds which released CO_2 gas as a decomposition product [24,25]. We have attempted to extend this equation to dehydration processes. In such reactions, when the water vapor pressure>p_t, the hydrate phase will be stable. Since the solid-states of the anhydrous and hydrated phases will affect the value of p_t, it is necessary to define these. The unique advantage of Eq. (3) is that it can be used to rapidly assess the physical stability of pharmaceutical hydrates.

3. Materials and methods

3.1. Materials

Amoxicillin trihydrate was obtained from Sigma Chemical Company (St. Louis, MO). The precise characterization of the particle habit was not possible and they can best be described as rod shaped. The particle size distribution was determined with a particle size analyzer (model 2010, Brinkman) which is a laser based Time of Transition analysis system. A saturated aqueous solution of amoxicillin trihydrate was prepared and the amoxicillin trihydrate particles were dispersed in this solution. The particle size was expressed as the surface-volume mean diameter±SD. The surface-volume mean diameter, d, is defined as: $\sum nd^3 / \sum nd^2$ where n is the number of particles.

3.2. Humidity controlling device

The general scheme of the humidity controlling device is given in Fig. 1. This device included a flowmeter, flasks, waterbath and necessary valves. Dry nitrogen was allowed to flow in at a controlled rate of 250 ml/min using a gas pressure regulator (Fisherbrand). This was split into two routes. In one route, the nitrogen was undisturbed and continued to be dry. In the other route, nitrogen was bubbled through a conical flask containing water. The flask was placed in a waterbath maintained at ~27°C. This was connected to a second conical flask containing water, which was maintained under ambient conditions. The room temperature was ~24.5°C and since the building was air conditioned, only small fluctuations in temperature (≤1°C), if any, were observed during the experiments. There was a small temperature drop between the first and second conical flasks. This served two purposes.

1. It ensured that the nitrogen was saturated with water vapor at ambient temperature.
2. Condensation of water past the second conical flask was avoided.

The 'dry' and 'wet' nitrogen were mixed so as to obtain the desired water vapor pressure which was measured with a traceable digital hygrometer/thermometer (Model 111-661-7B, Control Company, TX). The water activity could be measured either as a % RH value or as a dew point. The accuracy in this measurement was ~±1.5%. The setup allows the relative

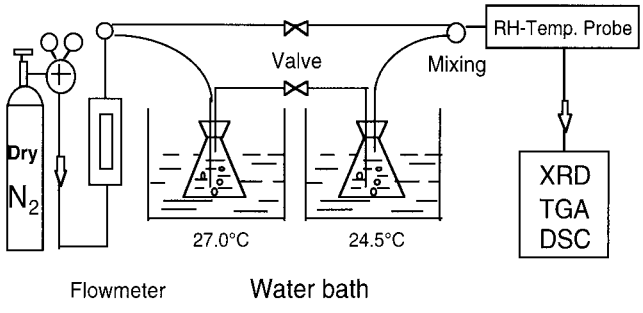

Fig. 1. The scheme of the humidity controlling device.

humidity to range from 0% to 100% at room temperature. At a temperature of 24.5°C, the saturated water vapor pressure is ~23.0 Torr. This device permitted us to produce an atmosphere with a constant and predetermined water vapor pressure. TGA and XRD studies were carried out under controlled water vapor pressures using this device. Since the goal of the project was to study the effects of temperature and water vapor pressure on the dehydration kinetics, experiments were carried out under two conditions:

1. isothermally at different water vapor pressures, and
2. at a defined water vapor pressure but at different temperatures.

The high nitrogen flow rate of 250 ml/min ensured the rapid removal of the liberated water from the sample surface so as to maintain a constant water vapor pressure above the sample.

3.3. Thermal analysis

For the isothermal TGA studies, either 8 or 16(±1) mg of sample was weighed into a platinum pan, very rapidly heated to the desired temperature where it was maintained under isothermal conditions. The sample was purged with nitrogen gas at a controlled water vapor pressure from the humidity controlling device.

3.4. Powder X-ray diffractometry

A variable temperature powder X-ray diffractometer (Model XDS 2000, Scintag) was used to study the phase formed at different temperatures. A HIGHTRAN SYSTEM, which included a heat and temperature controller (Micristar®, Model 828D, R.G. Hansen and Associates) was used to control the sample temperature. The working temperature range of the variable temperature XRD is −190°C to +300°C. The sample was exposed to CuKα radiation (45 kV×40 mA) in the continuous temperature step scan operation mode, at a heating rate of 10°C/min. During the XRD run, the sample was maintained under isothermal conditions. The samples were scanned over the angular range of 5–35°2θ (unless otherwise stated) at 5°2θ/min. The step size was 0.03°2θ.

For the isothermal XRD under different water vapor pressures, an aluminum chamber was designed and used to control the environment around the sample. This chamber had a thin polyester film (Mylar®, Du Pont) window which allowed the passage of the incident and the diffracted radiation. During the experiment, the water vapor pressure in the chamber was maintained constant by purging humidified nitrogen through this chamber.

4. Results

4.1. Solid-state characterization

The powder X-ray diffraction pattern of amoxicillin trihydrate was identical to that of amoxicillin trihydrate reported in the literature [26]. When heated in the TGA up to 120°C (at 10°C/min under nitrogen purge), a weight loss of 12.7% was observed, which agreed with the theoretical weight loss of 12.8% for complete dehydration. The particle size (expressed as surface, volume mean diameter) was determined to be 29.4±32.0 μm.

4.2. Isothermal dehydration at 0 Torr water vapor pressure and at different temperatures

Amoxicillin trihydrate was subjected to isothermal TGA at 40°C, 49°C, 59°C and 68°C. The experiments were carried out under dry nitrogen purge. Therefore the water vapor pressure was 0 Torr (0% RH). The results obtained with a sample size of 8 mg are given in Fig. 2. When the data was fitted to the most commonly used solid state reaction kinetic models, the zero-order kinetics (one dimensional phase boundary controlled model) resulted in the best fit [27]. This model is described by the equation:

$$1 - x = kt, \tag{4}$$

where x is the weight fraction of the hydrate phase remaining at time t, and k is the reaction rate constant. It is recognized that fitting of data alone cannot form the basis for deducing reaction mechanism. However, the kinetic analysis has been used as the starting point to understand the mechanism of dehydration. It has been shown that the initial rate data ($x \leq 0.5$) result in a reliable determination of the rate constant and

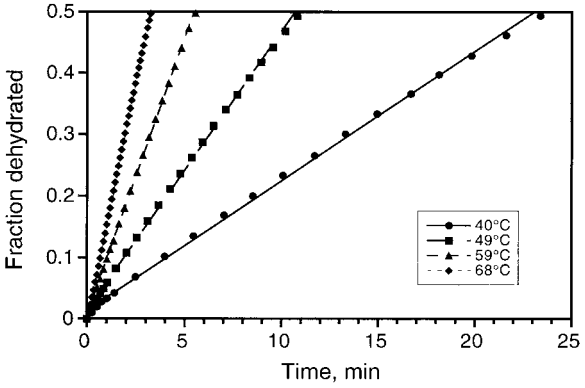

Fig. 2. Isothermal TGA curves of amoxicillin trihydrate at different temperatures and at a water vapor pressure of 0 Torr. The experimental data points as well as the fitted profiles (one-dimensional phase boundary controlled model) are presented. For the sake of clarity, only every tenth data point is shown. However, all the data points were used to obtain the fitted profiles. Sample weight=8 mg.

activation energy [28]. The fitted profiles ($x \leq 0.5$) are presented in Fig. 2, for a sample size of 8 mg. When the sample size was increased to 16 mg, the dehydration rate decreased though it continued to follow zero-order kinetics (fitted profiles are not shown). Isothermal VTXRD permitted characterization of the solid-state of the powder *during* the dehydration process. Dehydration, at a water vapor pressure of 0 Torr, resulted in a poorly crystalline anhydrous phase which supported the phase boundary controlled kinetics (Fig. 3). While the mechanism of dehydration does not appear to change over the temperature range of 40–68°C, the dehydration rate constant exhibited a pronounced increase as a function of temperature. The activation energy of dehydration, determined using the Arrhenius relationship, were 65.5 and 63.3 kJ/mol for sample sizes of 8 and 16 mg, respectively (Fig. 4). Thus the sample size does not seem to influence the activation energy of dehydration of amoxicillin trihydrate.

4.3. Isothermal dehydration at 68°C and at different water vapor pressures

The next objective was to study the effect of water vapor pressure on the dehydration process. These studies were carried out isothermally at 68°C, at water vapor pressures ranging from 0 to 9.2 Torr. At this temperature, complete dehydration was achieved in<4 h at all the water vapor pressures investigated. As expected, the dehydration rate was inversely related to the water vapor pressure (Fig. 5).

5. Discussion

Despite its obvious significance, the effect of water vapor pressure on the dehydration of hydrates has

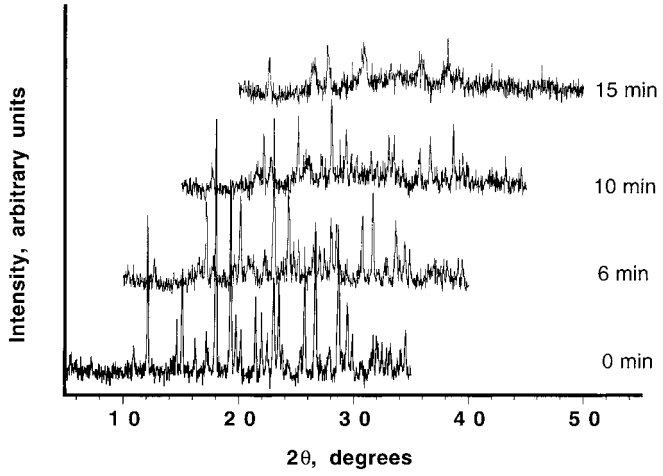

Fig. 3. Isothermal XRD patterns of amoxicillin trihydrate at 68°C and at a water vapor pressure of 0 Torr. Similar results were obtained when the water vapor pressure was increased to 9.2 Torr.

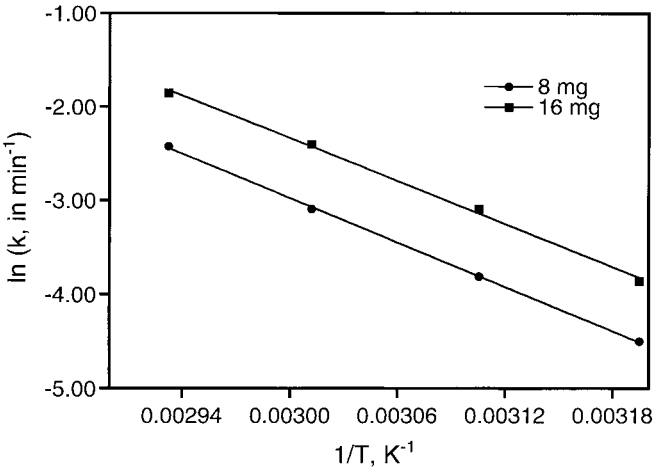

Fig. 4. Arrhenius plots of the dehydration rate constants of amoxicillin trihydrate. The activation energy of dehydration was ~65.5 and 63.3 kJ/mol for sample sizes of 8 and 16 mg, respectively.

received inadequate attention in the pharmaceutical literature [29]. Since water vapor is one of the products of the dehydration reaction, an increase in the water vapor pressure should decelerate the dehydration reaction. We attempted to use Eq. (3) to assess the physical stability of hydrates. When the dehydration rate constant, k, was plotted as a function of water vapor pressure, p, a linear relationship was observed (Fig. 6). While the dehydration rate constant values were influenced by the sample size, the transition water vapor pressure was not. It is a measure of the physical stability of the hydrate and its value is expected to be unaffected by the experimental conditions.

The transition water vapor pressure (p_t) was obtained by extrapolation (Fig. 6). Our experimental setup also permitted us to directly determine p_t. Amoxicillin trihydrate was subjected to isothermal TGA at 68°C and at a water vapor pressure of ~11 Torr (just above p_t). It did not undergo dehydration during the time course of the experiment (>48 h). The experiment was repeated at a water

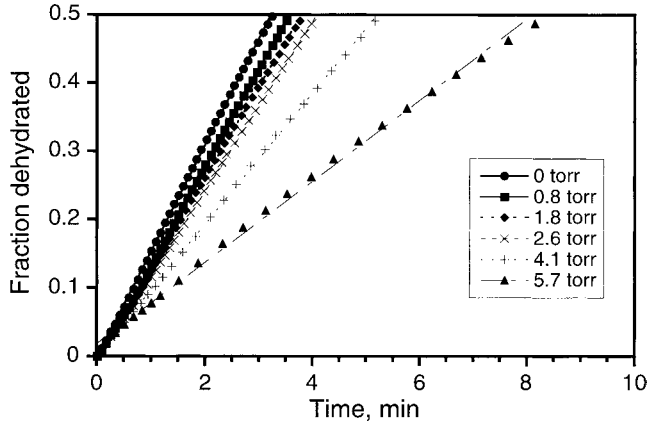

Fig. 5. Isothermal TGA curves of amoxicillin trihydrate at 68°C and at different water vapor pressures. The experimental data points as well as the fitted profiles (one-dimensional phase boundary controlled model) are presented. For the sake of clarity, only every tenth data point is shown. However, all the data points were used to obtain the fitted profiles. Sample weight=8 mg.

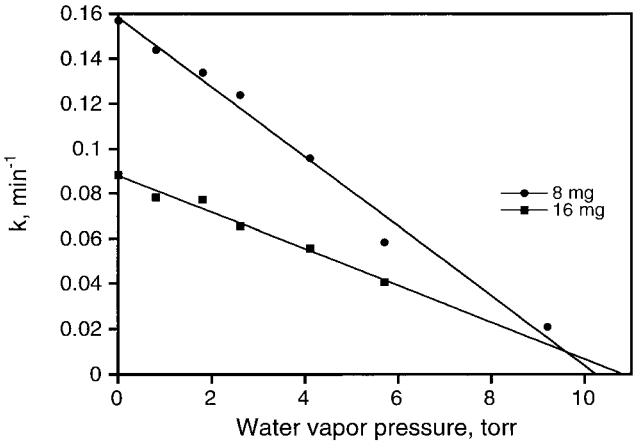

Fig. 6. Plot of dehydration rate constant of amoxicillin trihydrate as a function of water vapor pressure. The intercept on the *x*-axis is the transition water vapor pressure, p_t.

vapor pressure of 9.2 Torr. Though dehydration occurred slowly, there was significant weight loss in 48 h, indicating dehydration. Thus we were able to bracket the p_t between 9.2 and 11 Torr and this was in excellent agreement with the extrapolated value of ~10.5 Torr.

This extrapolation method will be valid only when the following conditions are met. First, the mechanism of dehydration should be the same at all the water vapor pressures of interest. In case of amoxicillin trihydrate, the one-dimensional phase boundary controlled model best described the dehydration kinetics under all the study conditions. Irrespective of the temperature and water vapor pressure, the dehydrated phase was observed to be poorly crystalline (Fig. 3). This also suggests that the mechanism of dehydration is the same at all water vapor pressures. Second, the processes of dehydration and removal (vaporization) of the liberated water should occur concomitantly. In light of the very high nitrogen flow rate used (250 ml/min), this is a reasonable assumption.

While a plot of the dehydration rate constant as a function of the water vapor pressure was linear for amoxicillin trihydrate (Fig. 6), a number of hydrates exhibit more complex relationships. Such a plot for $ZnSO_4H_2O$ contained two minima while that of carbamazepine dihydrate revealed a minimum [30,31]. It is postulated that there is a change in the dehydration mechanism after each minimum. In such hydrates, the use of Eq. (3) will be inappropriate.

6. Conclusions

A simple and rapid method has been developed to assess the physical stability of pharmaceutical hydrates. A humidity controlling device was fabricated which permitted thermogravimetric analysis and powder X-ray diffractometry under controlled water vapor pressures. As a result, it was possible to study the dehydration kinetics of amoxicillin trihydrate as a function of both temperature and water vapor pressure. When the dehydration rate constant (at 68°C) was plotted as a function of water vapor pressure, the intercept on the *x*-axis was the transition water vapor pressure, p_t. At water vapor pressures>p_t, the hydrate is the stable phase. The humidity controlling device has been used to predict the stability of hydrates at different temperatures [32].

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