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Dehydration of Crystalline Theophylline Monohydrate and Ampicillin Trihydrate

ELI SHEFTER▲, HO-LEUNG FUNG, and OLIVIA MOK

Abstract □ The dehydration kinetics of theophylline monohydrate and ampicillin trihydrate were measured by an X-ray powder diffraction technique in an open system. In the case of theophylline, the hydrate transforms directly to a crystalline anhydrous form with apparent zero-order kinetics. The loss of water from ampicillin trihydrate results in an amorphous state. Commercial micronized ampicillin trihydrate, which contains a small amount of excipients, exhibits a different kinetic order and a faster rate of transformation.

Keyphrases □ Theophylline monohydrate—dehydration kinetics measured using X-ray powder diffraction technique □ Ampicillin trihydrate—dehydration kinetics measured using X-ray powder diffraction technique □ Solid-state phase transformations—dehydration of theophylline monohydrate and ampicillin trihydrate studied using X-ray powder diffraction technique □ X-ray powder diffraction technique—used to measure dehydration kinetics for theophylline monohydrate and ampicillin trihydrate □ Phase stability, theophylline monohydrate and ampicillin trihydrate—dehydration kinetics studied using X-ray powder diffraction technique

The solid-state phase transformation of the active ingredient in a dosage form could dramatically alter the pharmaceutical properties of the preparation. The solid phase of the administered drug can influence such important properties as bioavailability (1). Where highly energetic (metastable) forms are incorporated into the formulation, it is exceedingly important that, in addition to chemical stability, the phase integrity of the pharmaceutical be monitored.

Many organic medicinal agents are known to crystallize with solvent molecules as an integral part of their structure. The most widely found group of solvates are the hydrates. The phase stability of these multicomponent solids is governed by temperature, pressure, and the concentration of solvent in the system. However, even though thermodynamics might indicate that a particular solvate is metastable under normal storage conditions, the conversion rate to a desolvated phase could be relatively slow in pharmaceutical terms. The rates at which these desolvation processes take place are exceedingly important to the formulation.

The desolvation process of two crystalline hydrates (theophylline monohydrate and ampicillin trihydrate) was studied using an X-ray powder diffraction method. This investigation is part of a continuing study to delineate the various physical parameters controlling the kinetics of solid-state phase transformations. The principal point of this study is to demonstrate the scope of

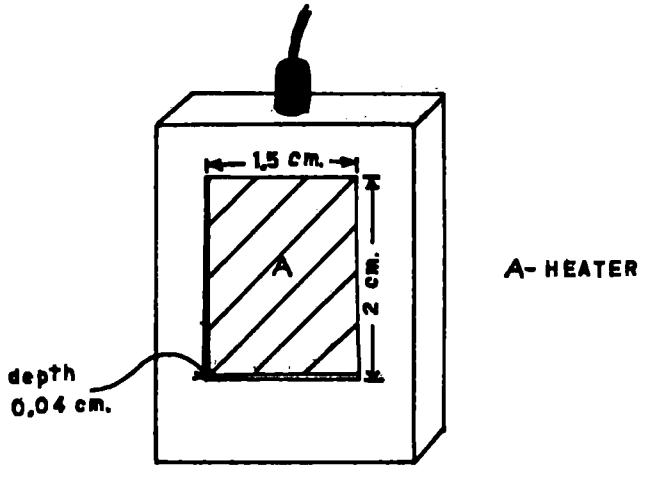

Figure 1—*The powder holder.*

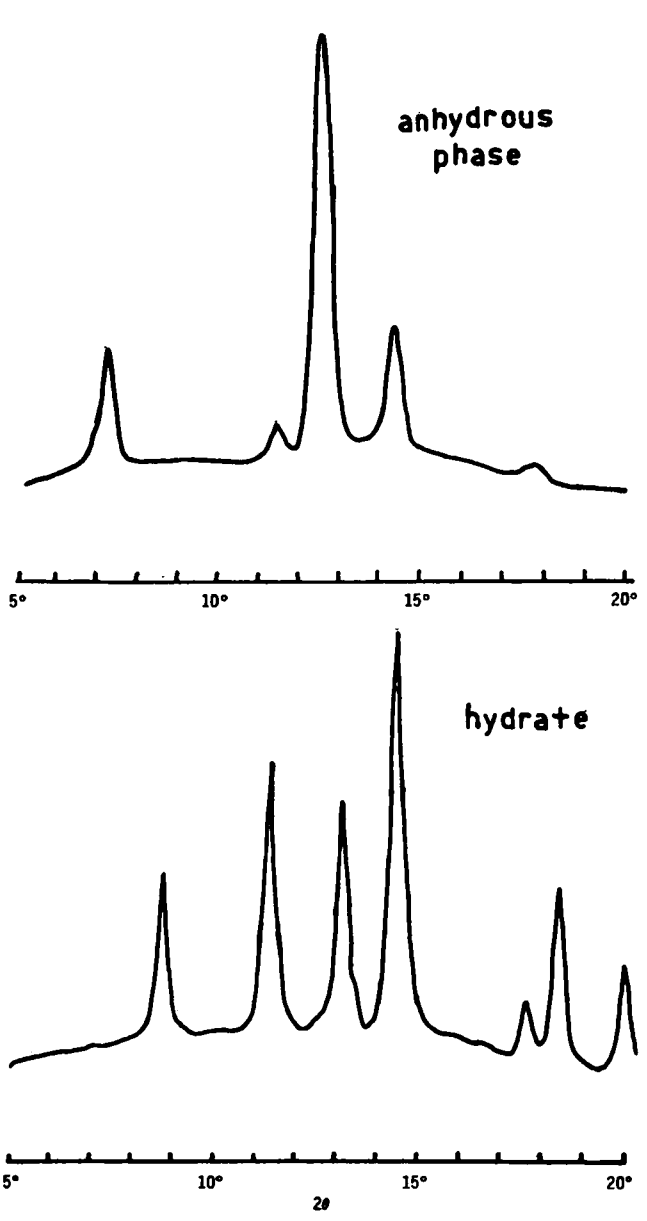

Figure 2—*Portions of the X-ray powder patterns for theophylline monohydrate and an anhydrous form.*

the X-ray powder technique for routine control of phase stability.

EXPERIMENTAL

Materials—Theophylline USP was recrystallized from water. After filtering, the crystals were ground to a fine powder in a mortar and stored in a tightly stoppered container.

Ampicillin trihydrate and the two anhydrous polymorphs were used[1]. The trihydrate sample consisted of very small needles and had a measured potency of 842 mcg./mg. (biological assay based on anhydrous ampicillin). A commercial sample of ampicillin trihydrate[2] (capsule form) was also used. Microscopic examination revealed that the ampicillin material was in a micronized state in the capsules. Weight analysis of the capsules indicated that a small amount of excipient was present (approximately 7% by weight).

No attempt was made to measure the particle-size distribution in each batch of material, but the same batch was used for each set of kinetic studies.

[1] Batch Nos. 71F1064 (trihydrate), 67F3041 (form I), and 68F2199 (form II), supplied by Bristol Laboratories, Syracuse, N. Y.

[2] Penbritin, Batch No. A60410L, 500-mg. capsules, supplied by Ayerst Laboratories, Rouses Point, N. Y.

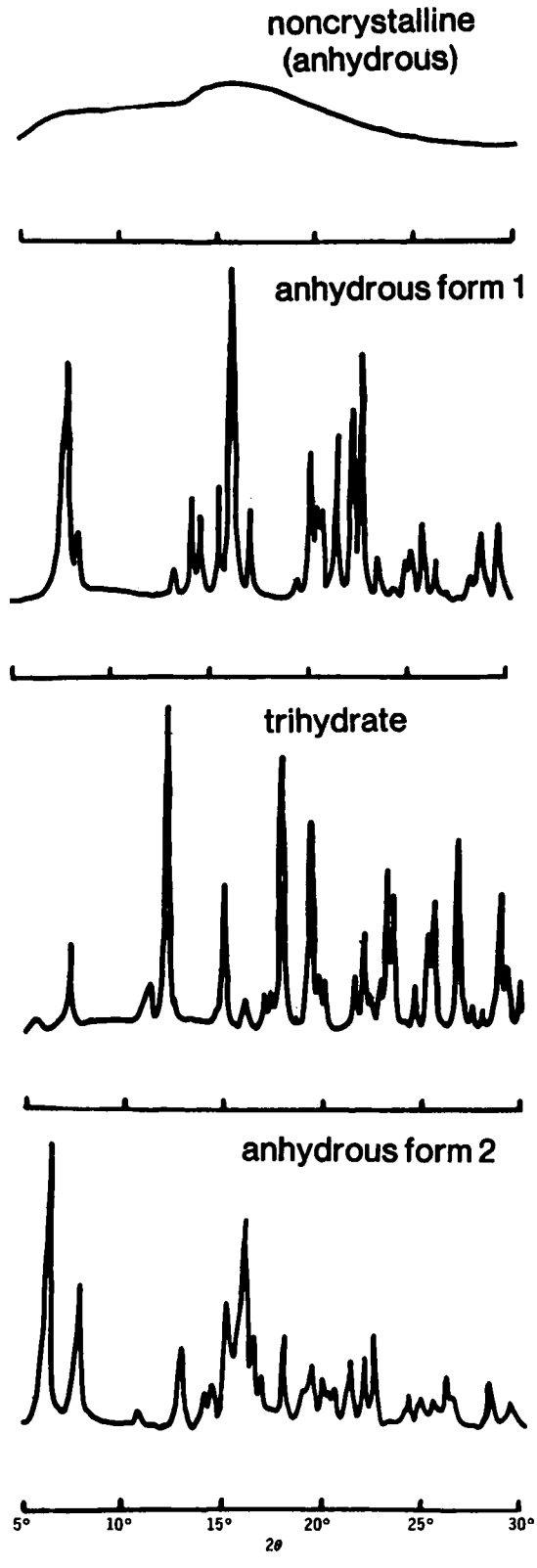

Figure 3—*Diffractograms for various forms of ampicillin.*

X-ray diffraction patterns run on all starting materials were used as controls. In the case of the hydrates, no evidence of any anhydrous form was observed.

Apparatus—All X-ray powder patterns were collected on a diffractometer[3]. Nickel-filtered CuKα radiation was used.

[3] Toshiba ADG-301 Diffpet. The detector used was a Geiger–Mueller type.

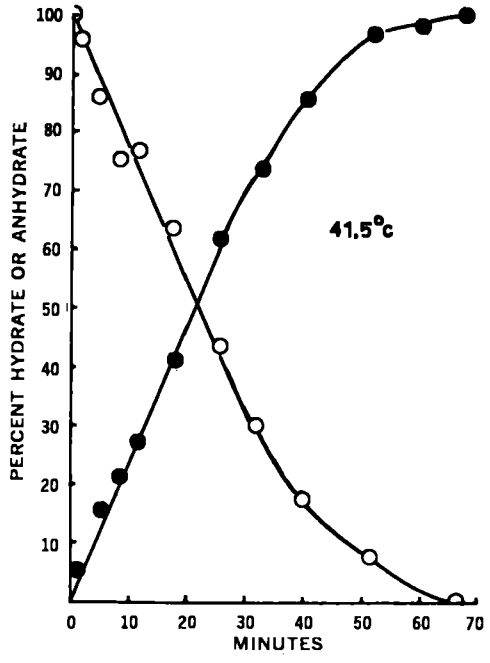

Figure 4—*Fraction (in percent) of monohydrate* (○) *and anhydrous* (●) *forms in powder as a function of time.*

A sample holder, made of Bakelite, was designed to maintain the powder bed at a relatively constant temperature (Fig. 1). The temperature on the underside of the powder was maintained to ±0.5° of the set temperature. By placement of a thermocouple on the powder surface, the temperatures on the two sides were monitored. Since the atmospheric temperature in the diffraction chamber was not controlled in these experiments (room conditions 25 ± 3°), the surface material exhibited a lower temperature than those particles in contact with the heater. The temperature differential remained fairly constant throughout each experiment. The difference was greater at higher temperatures: approximately 10° when the heater was maintained at 95° and less than 2° when set at 38°.

X-Ray Powder Patterns—The X-ray powder diffraction patterns for theophylline monohydrate and the crystalline anhydrous form into which it directly converts are shown in Fig. 2. Ampicillin trihydrate was found to transform to an amorphous anhydrous state. (Diffraction patterns for these forms are shown in Fig. 3.) During the experiment with ampicillin, it was of interest to see if the two crystalline anhydrous forms entered into a phase transformation in the temperature range studied; their X-ray diffractograms are also illustrated in Fig. 3.

Kinetic Study—The sample to be studied was firmly packed into the holder with a spatula. After placing the holder in the diffraction chamber, a zero-time diffractogram of the material was recorded and then the heater and timer were initiated. The diffraction pattern for theophylline (between 10.5 and 14.5° in 2θ) was recorded at various time intervals. For the theophylline studies, the disappearance of a hydrate diffraction maximum at 11.3° (2θ) and the appearance of an anhydrate crystal peak at 12.6° (2θ) were simultaneously followed as a function of time. In the case of ampicillin, only the disappearance of a trihydrate peak could be followed (maximum at 12.2° in 2θ was selected) because the material transformed to an amorphous powder. The fractional amount of each species relative to the zero time (100% hydrate) was derived from the ratio of peak intensities over background in a manner similar to that described by Alexander and Klug (2). The linear absorption coefficients and

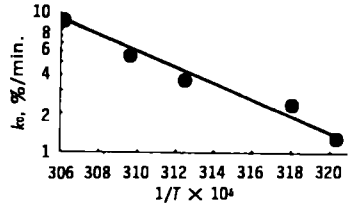

Figure 5—*Arrhenius plot of zero-order dehydration of theophylline monohydrate.*

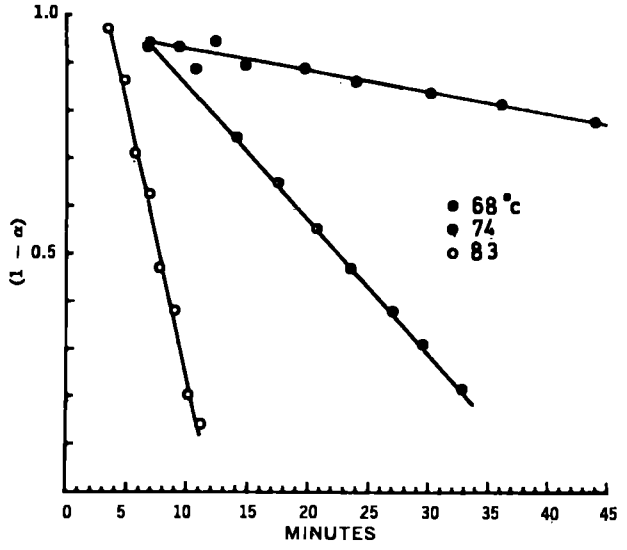

Figure 6—*Fraction of crystalline ampicillin trihydrate remaining in heated sample as a function of time.*

density of the dehydrated material were assumed to be approximately equal to the hydrated samples.

The time necessary for the sample holder to reach a prescribed temperature was approximately 5 min. at 95° and much less at lower temperatures. Thus, the initial points on the dehydration plots could not be relied on. In general, the kinetic plots indicated a lag time that reasonably reflected the lag time required to achieve temperature equilibrium. The temperature ranges (lower surface) used in these studies were 68–95° for ampicillin and 38–54° for theophylline.

RESULTS AND DISCUSSION

A typical experimental dehydration plot for theophylline is shown in Fig. 4. The observed rates of appearance of the anhydrous form

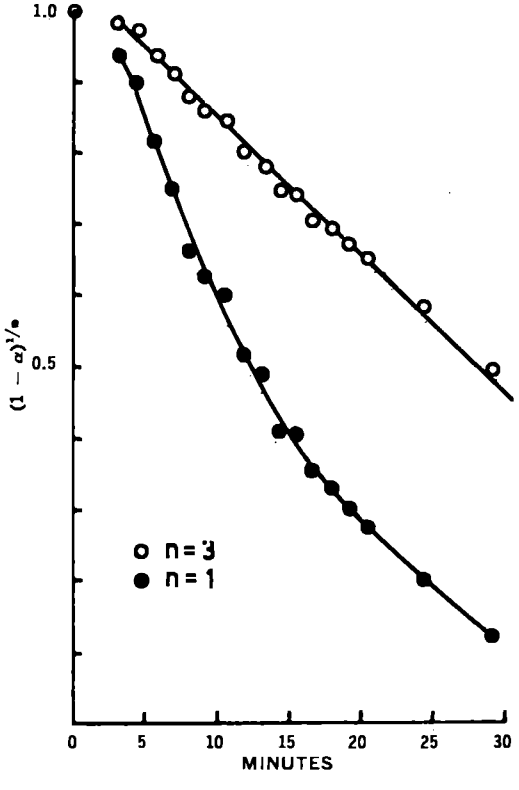

Figure 7—*Fraction of ampicillin trihydrate present in the capsule formulation (1 − α) at various times at 74.5° (plotted in two ways).*

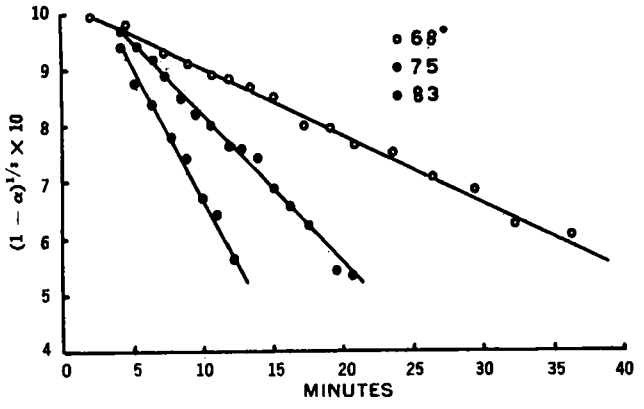

Figure 8—*Kinetic data for ampicillin trihydrate capsule formulation plotted by diminishing sphere model.*

and the disappearance of the hydrate were essentially the same. The 1:1 relationship need not occur because physical intermediates can form in some systems (3). The initial transformation rate appeared to be zero order for at least 1 half-life at all of the temperatures studied. Many solid-state dehydrations typically show a decrease in rate as the anhydrous material accumulates on the surface (4). Since the theophylline hydrate used in these studies was composed of fine needles, the retardation of the dehydration process did not appear to take place as rapidly as it probably would for spheres and flat platelets. The activation energy for the dehydration process can be estimated from an Arrhenius plot (Fig. 5). A value of approximately 140 kJ./mole was obtained.

In a few experiments carried out with nitrogen (dried over sulfuric acid) constantly flushed through the reaction chamber vessel, the zero-order rate constant increased slightly. This observation is expected inasmuch as any decrease in water vapor pressure should promote the reaction: theophylline hydrate ⇄ theophylline (anhydrous) + water (vapor).

The needle-shaped crystals of ampicillin trihydrate generally exhibited zero-order decomposition (Fig. 6). In the case of the capsule formulation, this was not found (Fig. 7). A good fit of the experimental data was obtained using the "diminishing sphere" model (4) for this material. The equation for this model is:

$$(1 - \alpha)^{1/3} = -k_{d_s} \cdot t + A \qquad \text{(Eq. 1)}$$

where α is the fraction transformed, k_{d_s} is the transformation rate constant, t is the time, and A is a constant associated with the lag time involved in the attainment of thermal equilibrium. The data plotted in this manner are shown in Fig. 8.

Microscopic examination of the ampicillin trihydrate samples showed that the commercial preparation contained micronized particles which were fairly equiaxial (spherical).

Both ampicillin trihydrate samples are converted to an amorphous anhydrous light-yellow powder. A bioassay run on an ampicillin trihydrate sample (capsule formulation held at 65° until it turned amorphous) suggested that a significant amount of decomposition (approximately half) had taken place[4]. It was of interest to see if, in the temperature range of this study, any physical or chemical degradation takes place in the two anhydrous forms. No significant changes in the diffractograms (distribution of peaks and their intensities) were found on maintaining these two forms at 90° for 24 hr. A detailed analysis of the decomposition mechanism which takes place in the trihydrate is contemplated.

At room temperature the trihydrate is the most stable form in water (5). It was, therefore, of interest to look at the relative stabilities of the two anhydrous forms in the presence of water. Slurries of the two forms were prepared and their X-ray diffraction patterns

[4] Assay carried out by A. P. Granatek of Bristol Labs., Syracuse, N. Y.

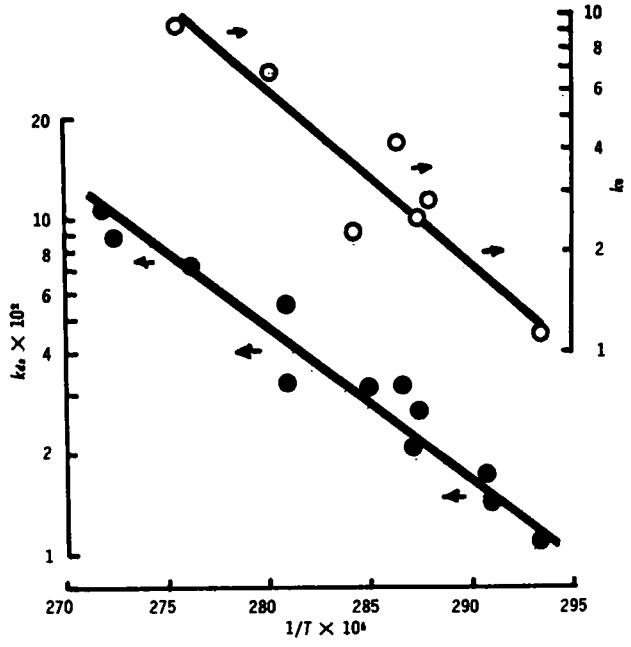

Figure 9—*Arrhenius plots for ampicillin trihydrate dehydration. Key: ●, zero-order k_0 for small needle crystals; and ○, k_{d_s} (diminishing sphere model) of capsule formulation.*

were measured. Form II was found to convert to the trihydrate very rapidly (converted while making slurry). Form I, on the other hand, showed no significant change in its diffraction pattern for 2 days (time of study), which is in agreement with the Poole and Bahal (5) findings.

The activation energies for the two trihydrate samples are essentially the same (estimated to be approximately 95 kJ./mole from the Arrhenius plots shown in Fig. 9). The gradients in these plots are parallel within the limits of experimental error. On a zero-order basis, the commercial preparation exhibits a significantly faster transformation rate; the zero-order rate constant at any temperature studied for the capsule material is nearly twice the value found for the other sample. The observed differences could result from the marked differences in particle size and/or the presence of the small amount of excipients in the capsule preparation.

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