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Dehydration of theophylline monohydrate powder – effects of particle size and sample weight

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Abstract

From isothermal thermogravimetric analysis, the dehydration mechanism and activation energy of dehydration of theophylline monohydrate powder were found to be dependent on both the particle size and sample weight. With a large sample weight (i.e., 17.0 mg), the dehydration process was best described by the Avrami-Erofeev equation ($n = 1/4$) for both the unfractionated samples (needles of length ≤ 3 mm) and the < 500 μm sieve fraction. In contrast, dehydration for the < 150 μm sieve fraction was consistent with a two-dimensional phase boundary mechanism. However, with a smaller sample weight (i.e., 6.0 mg), dehydration in both the unfractionated samples and the < 150 μm fraction conformed to the same mechanism, the Avrami-Erofeev model ($n = 1/4$). The activation energy of dehydration, E_a, estimated from these mechanisms was 70–90 kJ mol^{-1}, depending on the mechanism of dehydration, sample weight and particle size. These analyses suggest that both the mechanism and the activation energy of dehydration of a hydrate could be significantly influenced by sample pre-history such as particle size, sample weight, crystal defects and surface characteristics. Therefore, meaningful comparisons of kinetic parameters should relate data acquired under similar experimental conditions.

Key words: Theophylline monohydrate; Dehydration kinetics; Particle size effect; Sample weight effect; Processing; Activation energy; Drug hydrate

1. Introduction

Knowledge of the dehydration behaviour of a medicinal hydrate is relevant in pharmaceutical formulation since the physicochemical, processing, mechanical, compaction and bioavailability properties of hydrates can differ from those of the anhydrous material. This has been ascribed to the different crystal structure in the hydrate conferred by the presence of water molecules in the crystal lattice (Byrn, 1982; Brittain et al., 1988). The differences in thermodynamic properties associated with both crystalline modifications are believed to be responsible for observed variation in physical and chemical properties (Higuchi, 1958; Shefter and Higuchi, 1963).

The aqueous dissolution rate, and in some cases solubility, of the anhydrous form of some drug substances have been shown to be greater than those of the corresponding hydrate (Shefter and Higuchi, 1963; Botha et al., 1988). Differ-

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ences in the in vivo absorption rate and plasma concentration of products containing both crystalline forms have also been demonstrated (Poole et al., 1968; Hill et al., 1972).

The role of water of hydration on the compressional behaviour of some pharmaceutical powders has been investigated (Jaffe and Foss, 1959; Fell and Newton, 1970). Water of hydration could act as a 'built in' binding agent and promote both lubricity and plasticity, its removal causing a disruption of the crystal structure and preventing tablet formation (Jaffe and Foss, 1959). In other situations, a rigid network of hydrogen bonding between water molecules and the parent compound could inhibit inter-planar slippage, reducing plasticity and bond strength in the hydrate (Beevers and Hansen, 1971; Lerk et al., 1983, 1984).

These differences between a drug hydrate and its anhydrous forms have necessitated research effort directed to understand both the mechanisms of dehydration and the experimental, environmental and sample variables influencing hydrate/anhydrous transitions.

In the kinetic approach employed in this work, thermal dehydration is treated as a solid-state reaction of the type shown in Eq. 1, the hydrate existing as a solid, which on heating evolves water vapour leaving the anhydrous solid (Byrn, 1982; Otsuka and Kaneniwa, 1983). The experimental fractional dehydration at different temperatures is then plotted according to the kinetic models of reaction mechanisms known to occur in the solid state (Sharp et al., 1966; Byrn, 1982) (see Table 1). Whilst recognising the limitations of this mechanistic approach, it does provide insight into the kinetic effects of processing variables (e.g., temperature) and sample pre-history (e.g., particle size and sample weight) on the dehydration process.

$$A \cdot H_2O_{(s)} \rightarrow A_{(s)} + H_2O_{(v)} \quad (1)$$

This study examines the effects of particle size and sample weight, on both the dehydration mechanism and the activation energy of dehydration, E_a, of theophylline monohydrate.

2. Experimental

2.1. Preparation of theophylline monohydrate samples by controlled crystallisation

An automated 5-l chiller thermocirculator (Conair Churchill Ltd, Uxbridge, U.K.) with a Eurotherm controller/programmer (Type 818, Eurotherm, Worthing, U.K.) was used for the crystallisation of the hydrate. This equipment has been described by Brown et al. (1990). The liquor temperature was continuously monitored by a

Table 1
Kinetic equations of most common mechanisms of solid state decompositions (compiled from Sharp et al. (1966))

Symbol [a]	Equation	Rate-controlling process
P1	$\ln\frac{x}{1-x} = kt$	random nucleation (Prout-Tompkins equation)
A2	$[-\ln(1-x)]^{1/2} = kt$	two-dimensional growth of nuclei (Avrami-Erofeev, $n = 1/2$)
A3	$[-\ln(1-x)]^{1/3} = kt$	three-dimensional growth of nuclei (Avrami-Erofeev, $n = 1/3$)
F1	$-\ln(1-x) = kt$	random nucleation; first-order mechanism
R1	$1-x = kt$	one-dimensional phase boundary reaction (zero-order mechanism)
R2	$1-(1-x)^{1/2} = kt$	two-dimensional phase boundary reaction (cylindrical symmetry)
R3	$1-(1-x)^{1/3} = kt$	three dimensional phase boundary reaction (spherical symmetry)
D1	$x^2 = kt$	one-dimensional diffusion
D2	$(1-x)\ln(1-x)+x = kt$	two-dimensional diffusion
D3	$[1-(1-x)^{1/2}]^2 = kt$	three-dimensional diffusion (Jander equation)
D4	$1-(2/3)x-(1-x)^{2/3} = kt$	three-dimensional diffusion (Ginstling-Brounshtein equation)

Note: The Avrami-Erofeev equation can also have $n = 1/4$, $2/3$ and 1.
[a] After Sharp et al. (1966).

thermocouple connected to a calibrated chart recorder to enable the mean cooling rate to be calculated.

A known weight of anhydrous theophylline (Sigma Chemicals Ltd, Poole, U.K.) was dissolved in distilled water at 50°C using a stirring rate of 175 rpm. Crystalline needles of the hydrate (length ≤ 3 mm) were harvested after 1 h at 30°C, following a cooling cycle operated at 45°C/h. The product was vacuum-dried at 600 mbar for 6 h at room temperature (23–25°C). Samples so prepared are referred to in the text as unfractionated. When necessary, the dried material was gently ground with pestle and mortar and with the aid of a fine powder brush passed through a 500 or 150 μm sieve to obtain other size fractions (i.e., < 500 μm and < 150 μm). All samples were stored in closed jars until used.

2.2. Water content determination

The water content of the samples was determined by thermogravimetric analysis (Perkin-Elmer TGA7 analyser, Perkin-Elmer, Norwalk, U.S.A.)

2.3. Isothermal dehydration of samples

A Perkin-Elmer TGA 7 Thermogravimetric Analyser and TAS 7 Thermal Analysis software (Perkin-Elmer, Norwalk, U.S.A.) were used for the dehydration studies. Samples (6.0 and 17.0 mg) were placed in a platinum holder and isothermal scans of the dehydration obtained at 60, 65, 70, 75 and 80°C, respectively. The TGA furnace was rapidly heated to the required temperature at 150°C/min and the sample was maintained at the study temperature until dehydration was complete.

For the particle size investigation, three size ranges were used (i.e., unfractionated, < 500 and < 150 μm sieve fractions) with a sample weight of approx. 17.0 mg. In addition, two sample weights (i.e., 6.0 mg and 17.0 mg) were used for both the unfractionated and < 150 μm samples to examine the effects of sample size on the dehydration kinetics.

2.4. Dehydration kinetics

Fractional dehydration, x, in the range 10–90%, was determined at the corresponding time, t, at the various isothermal temperatures and data were plotted according to the kinetic equations shown in Table 1. Minitab software (Minitab Inc., U.S.A.) was used to calculate three statistical parameters on which decisions about conformity to the kinetic models were based. These were the standard deviation of the slope of the regression line, s_b, the standard deviation of the regression, $s_{y/x}$, and the correlation coefficient, r. The activation energies of dehydration were determined from the Arrhenius plots of rate constants from the statistically best-fitting mechanisms.

3. Results and discussion

The water contents of the materials (unfractionated, $9.1 \pm 0.1\%$ w/w; < 500 μm, $9.0 \pm 0.1\%$ w/w; < 150 μm, $8.9 \pm 0.1\%$ w/w; $n = 3$) are consistent with the monohydrate form of theophylline.

3.1. Effects of particle size

Typical isothermal dehydration plots are shown in Fig. 1 for the unfractionated sample. Plots for all the other samples show similar features. In all

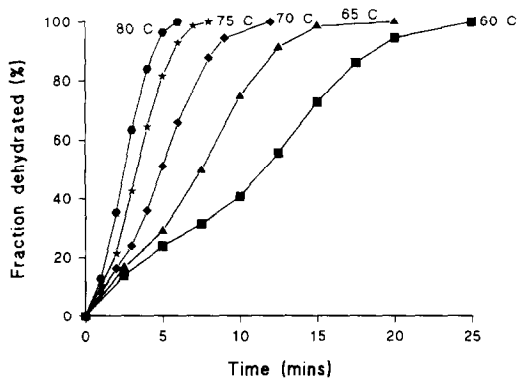

Fig. 1. Representative isothermal dehydration curves of theophylline monohydrate powder (unfractionated, sample weight 17.0 mg).

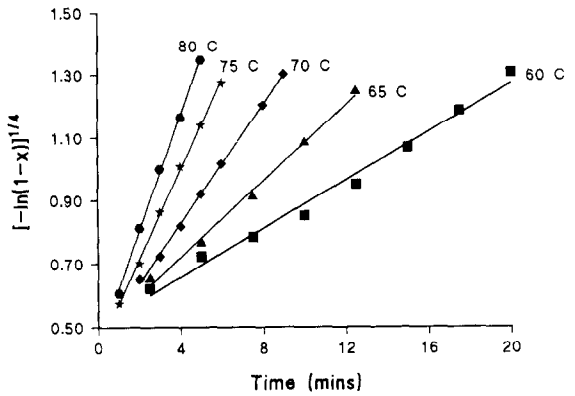

Fig. 2. Representative plot of the best-fitting mechanism for the dehydration of theophylline monohydrate powder (unfractionated, sample weight 17.0 mg).

cases a sigmoidal profile is observed, the dehydration rate increasing with temperature. As expected, at equivalent temperatures, the dehydration rate increases in the order: unfractionated < (< 500 μm) < (< 150 μm) fractions, primarily due to the increased surface area available for dehydration in the smaller particles.

With a constant weight of 17.0 mg, the smallest values for s_b and $s_{y/x}$ in both the unfractionated and the < 500 μm fraction occurred with the Avrami-Erofeev equation ($n = 1/4$) and the two-dimensional phase boundary mechanism (i.e., cylindrical symmetry) for the < 150 μm samples. These mechanisms also had high r values although, as discussed later, greater weighting was given in this study to the other two statistics as indicators of goodness of fit. These results suggest that dehydration in both the unfractionated and the < 500 μm fraction proceeded according to the Avrami-Erofeev equation ($n = 1/4$) while loss of water in the < 150 μm fraction was best described by a two-dimensional phase boundary mechanism (see Table 2). The similarity in the dehydration mechanism of the unfractionated and < 500 μm samples is probably because differences in particle size were smaller.

Fig. 2 is a representative plot of the dehydration according to the best-fitting mechanism, in this case the Avrami-Erofeev model ($n = 1/4$) for the unfractionated sample. The dehydration mechanisms and statistical parameters obtained from similar plots for the other two samples are summarised in Table 2 as well as activation energies of dehydration from the Arrhenius plots (see Fig. 3).

The results in Table 2 suggest a tendency towards lower activation energy with decreasing particle size as reported for the dehydration of sodium citrate dihydrate (Van Dooren, 1982). This could be due to the enhanced dehydration from the greater surface to mass/volume ratio of the smaller particles.

3.2. Effects of sample weight

Representative dehydration curves for the 6.0 mg samples for both the unfractionated and < 150 μm samples are shown in Fig. 4a and b, respectively. In both cases, the time required for complete dehydration was shorter compared to the corresponding curves for the 17.0 mg samples (cf. Fig. 1 and 4a) implying a faster dehydration rate in the smaller weight. The curves in Fig. 4a and b conformed with the Avrami-Erofeev equation ($n = 1/4$) as indicated by their respective s_b and $s_{y/x}$ values (see Table 3). The activation energies of dehydration determined from these mechanisms (70–90 kJ mol^{-1}) are also listed and are consistent with the lower thermal stability of

Table 2
Statistical parameters for best-fitting mechanisms (sample weight = 17.0 mg)

Sample	Mechanism	r	s_b	$s_{y/x}$	E_a (kJ mol^{-1}) [a]
Unfractionated	Avrami-Erofeev ($n = 1/4$)	0.998	0.0027	0.0162	76.3 ± 3.2
< 500 μm	Avrami-Erofeev ($n = 1/4$)	0.999	0.0016	0.0114	75.7 ± 4.9
< 150 μm	two-dimensional phase boundary	0.999	0.0020	0.0124	73.2 ± 6.3

[a] Mean ± S.D., $n = 3$.

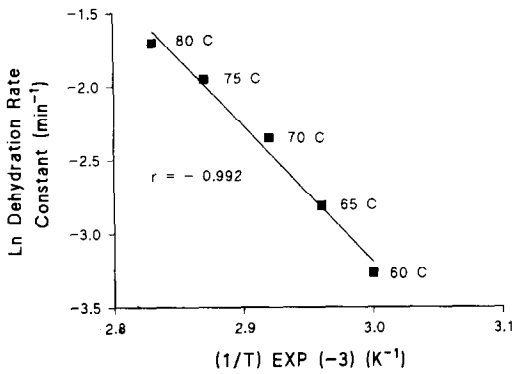

Fig. 3. Representative Arrhenius plot of data from the best-fitting dehydration mechanism (unfractionated, sample weight 17.0 mg).

xanthine hydrates relative to other medicinal hydrates (see Table 4).

The results in Table 3a suggest that a 3-fold variation in the sample weight of the unfractionated sample did not alter the dehydration mechanism of the unfractionated samples. However, corresponding weight variation with the < 150 μm fraction led to an alternative equation giving best fit to experimental data (Table 3b). Thus, the dominant mechanism appears to change from the two-dimensional phase boundary with 17.0 mg to the Avrami-Erofeev ($n = 1/4$) with 6.0 mg, with the effects of sample weight on dehydration dependent on sample particle size.

With both the unfractionated and the < 150 μm fraction, the activation energies of dehydration decreased with increasing sample mass. This inverse relationship between sample weight and activation energy of dehydration has also been observed by other workers and has been attributed to the greater self-cooling effects of larger sample mass on endothermic reactions as well as varying sample geometry (Gallagher and Johnson, 1973; Van Dooren, 1982).

The inter-dependence of particle size and sample weight on dehydration kinetics becomes even more apparent when the combined influence of both factors is considered. For example, with the larger sample weight (i.e., 17.0 mg), dehydration in both the unfractionated and the < 500 μm samples conformed to the Avrami-Erofeev equation ($n = 1/4$) while the < 150 μm samples dehydrated according to a two-dimensional phase boundary model (see Tables 2 and 3). However, with a smaller sample weight (i.e., 6.0 mg), dehydration of both the unfractionated and the < 150 μm samples was best described by the same mechanism, i.e., Avrami-Erofeev ($n = 1/4$). Thus, the difference in dehydration mechanism observed between the unfractionated and the < 150 μm samples with a sample weight of 17.0 mg was no longer evident at the smaller weight.

Such variations in the dehydration kinetics are

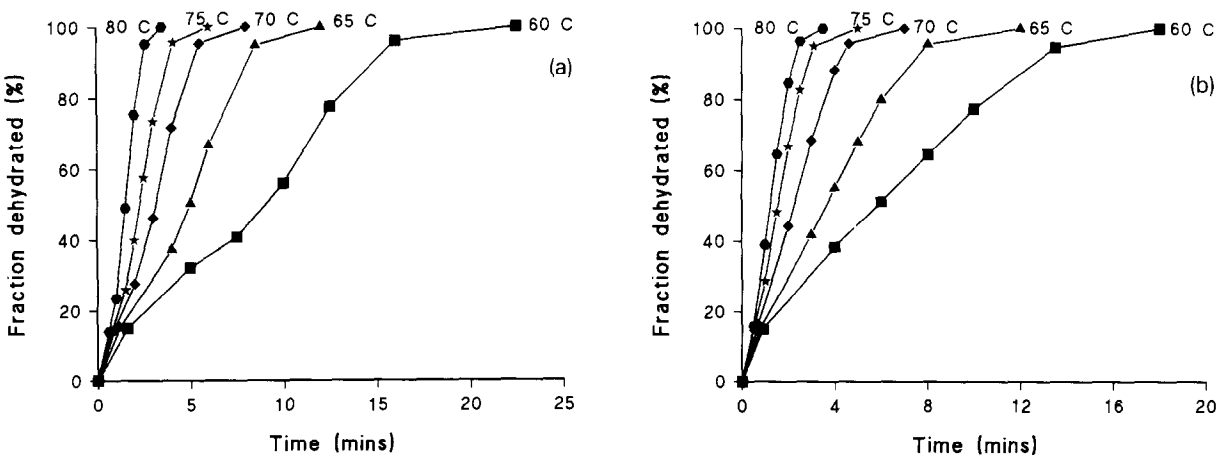

Fig. 4. Representative isothermal dehydration curves of theophylline monohydrate powder (sample weight 6.0 mg). (a) Unfractionated; (b) < 150 μm sieve fraction.

Table 3
Effect of sample weight on the dehydration mechanism and activation energy of theophylline monohydrate

Sample weight (mg)	Dehydration mechanism	r [a]	s_b	$s_{y/x}$	E_a (kJ mol^{-1})
(a) Unfractionated sample					
17.0	Avrami-Erofeev ($n = 1/4$)	0.998	0.0027	0.0162	76.3 ± 3.2
6.0	Avrami-Erofeev ($n = 1/4$)	0.991	0.0067	0.0283	95.4 ± 7.1
(b) < 150 μm sieved fraction					
17.0	two-dimensional phase boundary	0.999	0.0020	0.0124	73.2 ± 6.3
6.0	Avrami-Erofeev ($n = 1/4$)	0.999	0.0033	0.0106	90.0 ± 1.4

[a] Correlation coefficient for best-fitting mechanism, $n = 3$.

due to a number of factors which are consequences of both the particle size and the sample weight used as well as sample particle formation and pre-history, e.g., thermal conductivity, sample geometry, crystal defects, surface characteristics, etc. These are likely to play a greater role the larger the sample mass. The activation energy of dehydration, E_a, under given experimental conditions will be determined by two sets of factors. With a large sample weight, the increased surface area associated with smaller particles will promote dehydration and therefore reduce E_a. On the other hand, with a small sample weight, the accompanying reduction in self-cooling efficiency will tend to increase E_a. The balance between both effects will be determined by the experimental conditions and sample characteristics and could explain the slightly higher E_a for the < 150 μm samples at 6.0 mg compared to the unfractionated samples (see Table 3).

Table 4
Thermally determined dehydration parameters of some medicinal hydrates

Compound	Dehydration temperature (°C) [a]	ΔH_{deh} (kJ mol^{-1}) [b]	E_a (kJ mol^{-1})	Ref. [c]
Mercaptopurine monohydrate [n]	≈ 125	34.6	191.4–263.8	[d]
Erythromycin dihydrate [n]	≈ 120	–	–	[e]
Ampicillin trihydrate	≈ 110	–	–	[f]
Cefixime trihydrate	≈ 110	–	302.9	[g]
Erythromycin monohydrate [n]	≈ 100	–	–	[h]
Sodium prasterone dihydrate	≈ 95	37.7	131.8	[i]
Sulfaguanidine monohydrate	≈ 90	–	167.4	[j]
Theophylline monohydrate	≈ 80	49.6	70–90	[k]
Caffeine (0.8) hydrate	≈ 77	34.5	63.6	[l]
Cephalexin monohydrate	≈ 75	29.8	65.6–72.8	[m]

[a] Peak dehydration temperature; [b] enthalpy of dehydration; [c] references; [d] Niazi (1978); [e] Allen et al. (1978); [f] Takahashi et al. (1984); [g] Kitamura et al. (1989); [h] Allen et al. (1978); [i] Nakagawa et al. (1981, 1982); [j] Sekiguchi et al. (1984); [k] this study; [l] Agbada (1991); [m] Otsuka and Kaneniwa (1983); [n] commercial powder samples; other samples are unfractionated (or intact crystals).

These results indicate that both the dehydration mechanism and activation energy of dehydration are considerably influenced by material properties (e.g., single crystal or powder, sample weight, defects, particle size, etc.) and consequently processing variables during manufacture.

It has been pointed out that dehydration mechanism and hence E_a may be dependent on both the method of heating (i.e., isothermal vs non-isothermal TGA or DSC) and that of deriving the fractional dehydration, x. This dependence is more evident with the non-isothermal or dynamic heating method (Gallagher and Johnson, 1973). It is therefore essential that comparison should relate data acquired from similar experimental designs, using samples with similar characteristics.

Our data show that the dehydration of theophylline monohydrate conforms to either the

Avrami-Erofeev equation ($n = 1/4$) or a two-dimensional phase boundary mechanism depending on the particle size and the sample weight used. It is noteworthy that none of the samples dehydrated according to the one-dimensional phase boundary model expected from the reported anisotropic dehydration of single crystals of theophylline monohydrate (Byrn, 1982). This further supports the view that sample pre-history plays a critical role in dehydration reactions.

Otsuka and Kaneniwa (1988), using an isothermal infrared dehydration apparatus, found that the dehydration mechanism of theophylline monohydrate (sample weight 1 g) was dependent on the nature of the sample (i.e., intact vs ground powder or tablets). The intact powder (< 1.4 mm) was reported to dehydrate according to the Avrami-Erofeev model ($n = 1/2$) as assessed by the correlation coefficient, r, with an activation energy of 84.1 kJ mol^{-1}. This value is in agreement with those determined in this work.

Suzuki et al. (1989) also reported that the dehydration of theophylline monohydrate (sample weight 10 mg, size 150–75 μm) was best described by the Avrami-Erofeev equation ($n = 1/2$) though the statistical parameter on which selection was based was not indicated. They reported an E_a of 120 kJ mol^{-1} which appears to be a high value in view of the stability properties of the xanthine hydrates (Byrn, 1982; Agbada, 1991).

Shefter et al. (1973) employed an X-ray powder diffraction technique and found that theophylline monohydrate dehydrated by zero-order kinetics, with an even higher E_a of 140 kJ mol^{-1}. These studies emphasize the fact that both the mechanism and the activation energy of dehydration could be technique-dependent. Strictly speaking, derived E_a values are directly comparable only if the same mechanism is operative.

The use of the correlation coefficient, r, as the sole determinant of the applicability of a rate equation has been criticised (Davis and Pryor, 1976; Brown and Galwey, 1979) due to its inherent limitations. These include: (a) inability to distinguish between closely related mechanisms; (b) insensitivity to errors in both the fractional conversion, x, and the analysing rate expression; and (c) difficulties in making inferences from similar r values (e.g., $r = 0.999$ and 0.998). Indeed, Brown and Galwey (1979) concluded that r is a most insensitive indicator of the applicability of a rate expression. Our results clearly support this conclusion (Tables 2 and 3). r values of the various mechanisms have been included in Tables 2 and 3 because they are commonly reported and also to emphasize caution in the interpretation of such values.

In this study, the goodness of fit to the kinetic mechanisms was based mainly on two other statistical parameters, the standard deviation of the slope of the regression line, s_b, and the standard deviation of the regression (i.e., the standard deviation of the estimate of y from x), $s_{y/x}$, as suggested by Davis and Pryor (1976). However, a relatively high r value is also desirable as a complementary indicator of correlation between the data and accepted models.

This work has highlighted a number of factors which should be considered when carrying out thermal dehydration experiments. These include: (1) particle size of the powder; (2) sample weight selected to ensure good thermal contact; (3) processing operations used for sample preparation; and (4) caution in the use of correlation coefficient as the sole predictor of goodness of fit to kinetic expressions. This will enable meaningful comparisons of the dehydration/desolvation behaviour of hydrates and other solvates.

3.3. Advantages of outlined approach to the study of dehydration / desolvation

The approach discussed above offers a method for assessing the mechanisms of dehydration/desolvation as well as quantification of the thermal stability of medicinal hydrates in terms of the activation energies of dehydration, analogous to activation energies of other reaction kinetics. In addition, the effects of both sample characteristics (e.g., sample size, particle size) and environmental factors (e.g., humidity, pressure) on dehydration can similarly be quantified. Such information could be particularly relevant for hydrates whose stability is compromised during processing and/or storage.

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