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Microcalorimetric investigation of phase transitions: I. Is water desorption from theophylline · HOH a single-step process?

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Abstract

The dehydration of theophylline · HOH has been followed via isothermal calorimetry at 40 and 47°C. The power (P)-time relationship found at 47°C can be fitted as a single Gaussian distribution where the cumulative area up to time t relative to the total area measures fractional dehydration (α). An Avrami-Erofeev plot for solid state nucleation reactions with power 0.25 best linearizes the α vs time relationship yielding a rate constant which corroborates that found by others who used a gravimetric method. At 40°C, endothermic heat flow in the microcalorimeter, temperature difference between sample and reference in differential thermal analysis (DTA), and weight loss in thermogravimetric analysis (TGA), each operated in the isothermal mode indicate that water loss is a multi-step process. Power (P)-time data from the thermal activity monitor at 40°C were deconvoluted into two Gaussian relationships yielding rate constants via Avrami-Erofeev plots for each step with excellent reproducibility. The rate constants for the two steps are about equal at 40°C but there are significant differences in lag times.

Keywords: Microcalorimetry; Solid state reaction kinetics; Dehydration; Theophylline; Isothermal thermogravimetric analysis; Isothermal differential thermal analysis

1. Introduction

Isothermal microcalorimetry through its precise temperature control and great sensitivity in measuring heat flow is proving to have wide application in pharmaceutical and biological sciences. The principles involved and the many systems in which it has been used have been discussed by Buckton and Beezer (1991). These authors indicate that despite the advantages that microcalorimetry offers, it is surprising that compared to DSC comparatively little published work exists to date relating isothermal calorimetry to stability and compatibility studies. This is especially evident in its use to quantify the kinetics of moisture mediated solid state transitions. Although isothermal microcalorimetry has provided

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excellent quantitative data in an assessment of water effects on the degree of disorder in crystalline solids through enthalpy measurements (Sebhatu et al., 1994), its use to measure water mediated solid state kinetics with the possibility of deducing reaction mechanisms is lacking. The study presented here was initiated to explore the validity of analyzing heat flow vs time data for water sorption and desorption reactions using a generalized kinetic theory governing isothermal reactions in solids (Byrn, 1982). Verification of its application required its comparison to the results found by others using a different methodology, in this case isothermal gravimetric analysis. The reaction used as a model was the dehydration of theophylline monohydrate (Lin and Byrn, 1979; Suzuki et al., 1989; Agbada and York, 1994). The dehydration kinetics studied by Suzuki et al. (1989) and Agbada and York (1994) using TGA were conducted at temperatures of 47°C and above where a single-step dehydration apparently occurred. The rate constant found by Suzuki et al. at 47°C was corroborated by the microcalorimetric method reported here. However, when microcalorimetric measurements for theophylline dehydration were made at 40°C, the results disclosed an unexpected multi-step dehydration process. This observation, its substantiation and the method of data analysis are the subject of this paper.

2. Materials and methods

2.1. Materials

Anhydrous crystalline theophylline was purchased from Sigma Chemicals (St. Louis, MO; lot 102H0521) and used as supplied. Theophylline monhydrate was prepared by crystallization from water. The solid monohydrate was sieved (150–250 mm) and stored in a desiccator at room temperature kept at a relative humidity of 58% by equilibrating over a saturated solution of NaBr until the experiment. DSC confirmed the solid phase to be the hydrate (dehydration endotherm at 66°C) and TGA (heated to 150°C, Perkin Elmer, Series 7) showed 8.9% (w/w) weight loss which is stoichiometrically equivalent to a monohydrate.

2.2. Methods

Heat flow (μW) vs time measurements were made in the thermal activity monitor (TAM, Model 2277, ThermoMetric, Jarfalla, Sweden). 1–6 mg of sample was placed in the 4 ml stainless-steel ampoule of ThermoMetric's Model 2277 perfusion/titration accessory. The sample and a reference ampoule containing talc were lowered into the calorimeter in four stages of 7 min each. During the last two 7 min stages a dry nitrogen source was opened. Dry nitrogen was perfused over the surface of the sample at a flow rate of 0.5 or 10 ml/min. The nitrogen tank was connected to the perfusion accessory with an intervening controller that keeps gas flow constant at any rate between 0 and 10 ml/min with a precision of ± 0.01 ml/min; the Matheson Mass Flow Controller, Model 8270-0411 system was used that consists of a flow sensing transducer, a digital readout converter box, a feedback circuit to control flow, and an integral control valve.

Experiments were also conducted using simultaneous DTA/TGA operated in scanning and isothermal modes (Seiko Robotic TG/DTA, Model RTG 220). The scanning experiment was run in duplicate from 25 to 155°C at 5°C/min using a nitrogen flow rate of 40 ml/min and sample sizes of about 7 mg with an empty aluminum pan as reference. The isothermal experiment was run in duplicate using sample sizes of 11.089 and 3.829 mg with empty aluminum pans as reference. The instrument was programmed to scan from 30 to 42°C at 1°C/min and then to hold at 42°C for 180 min. A nitrogen flow rate of 50 ml/min was used.

Data analysis consisted of exporting the power (μW)-time and the area (total heat, μJ)-time relationships from the microcalorimeter as an ASCII file, manipulating the data in a spread sheet (Quattro Pro, Borland, Scotts Valley, CA) and using the fitting programs in Origin (MicroCal, Northampton, MA) to generate best-fit Gaussian relationships and rate constants. In a similar manner scanning and isothermal

TGA/DTA data were exported in ASCII format into Origin and the derivative relationship (d μg/d min) vs time was fitted using two Gaussian relationships.

3. Results and discussion

3.1. Studies at 47°C

Heat flow-time studies for the dehydration of theophylline monohydrate were programmed at 47°C which is the closest the microcalorimeter could be set to conform with the lowest temperature studied by Suzuki et al. (1989), 47.2°C, who used a gravimetric method; the lowest temperature used by Agbada and York (1994) was 60°C where dehydration is complete within 0.5 h. Since the time needed to equilibrate the TAM sample is on the order of 0.5 h, 60°C was judged to be unsuitable for the microcalorimetric method. The power vs time relationship for dehydration using a sample of 1.5 mg is shown in Fig. 1; the experimental raw data is designated by symbols. While the sample contained 9.0% w/w water before the start of the experiment. no water was found to be associated with the solid at the end. Studies were carried out in triplicate using a nitrogen flow rate of both 0.5 ml/min ($\pm$0.01 ml/min) and 10.0 ml/min ($\pm$0.1 ml/min); 10 ml/min was used by

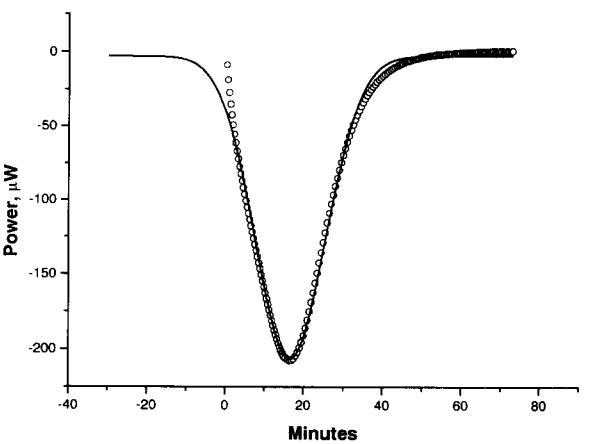

Fig. 1. Power (μW)-time (min) relationship for the dehydration of theophylline monohydrate at 47°C using the thermal activity monitor (TAM). The sample size was 1.5 mg and the nitrogen flow rate was 0.5 ml/min. The sample was temperature equilibrated for a total of 28 min before data were collected. The symbols are the raw data and the solid line is a single Gaussian fit.

Suzuki et al. (1989) in their dehydration study at 47.2°C.

A generalized kinetic behavior for the isothermal decomposition of solids shows that the relationship between fractional completion (α) and time is sigmoidal and several equations have been derived for solid state reactions based on the controlling mechanism of reaction; e.g., nucle-

Table 1
Parameters relevant to the dehydration of theophylline monohydrate at 47°C and a dry nitrogen flush of 0.5 ml/min

	Expt no. and weight used (mg)			Average
	1 (1.2)	2 (1.5)	3 (1.2)	
Kinetic parameters				
Avrami-Erofeev slope [a] (min^{-1}) (SD)	0.0235 (0.0004)	0.0271 (0.0002)	0.0253 (0.0002)	0.0253 (0.0002)
Lag time [b] (min)	0.58	3.65	0.28	1.50
Single Gaussian fit parameters [c]				
Area (A) (mJ)	−4061.7	−4569.8	−4044.2	
Width at half height (W) (min)	18.118	17.905	18.161	
Center (t_o) (min)	14.888	16.585	13.905	
Offset (P_o) (mJ/min)	−8.355	−2.794	−6.145	

[a] Through Eq. 1.
[b] Linear portion of α vs t extrapolated to the x-axis at $\alpha = 0$; $t_L = -$(intercept/slope).
[c] $P = P_o + A/[W(\sqrt{\pi/2})]\{e[-(t - t_o)/W^2]\}$; where P is power (μJ/min).

ation via the Avrami-Erofeev or Prout-Tomkins equation, phase boundaries that advance at constant velocity in one, two or three dimensions, or diffusion via the Jander Equation (Bramford and Tipper, 1980; Byrn, 1982). Recognizing that a sigmoidal α vs time relationship is the fractional segmental integral of a Gaussian relationship, the power-time relationship for dehydration was fitted to such a dependence. Data were baseline corrected by subtracting the power vs time relationship using a sample of anhydrous theophylline in the microcalorimeter and carrying out the experiment under conditions identical to those used for the monohydrate. However, it was found that the correction was so small that it can be neglected under the conditions of these experiments. The solid line in Fig. 1 shows the fit obtained for this data set assuming a single Gaussian relationship between power and time. The least-squares fitted parameters for three separate measurements are given in Table 1 for studies carried out at 0.5 ml/min nitrogen and in Table 2 for those performed at 10 ml/min nitrogen flow. It is not surprising that the Gaussian had to be extrapolated to negative time at 10 ml/min nitrogen, since dehydration undoubtedly was going on at both flow rates during sample equilibration (approx. 30 min before any data were collected). The Gaussian relationship can be analyzed kinetically assuming that the segmental area (μJ) up to time t divided by the total area

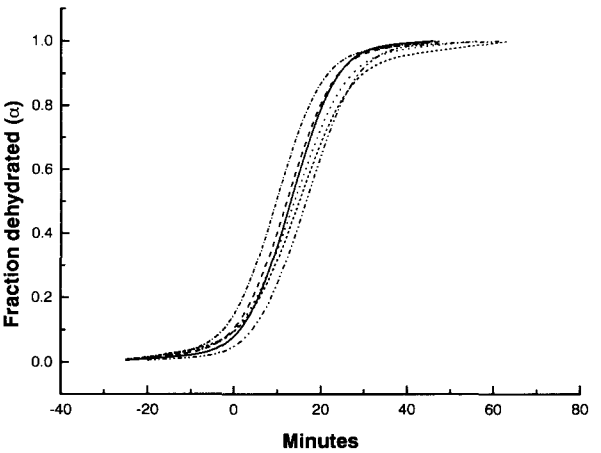

Fig. 2. Relationship between fraction (α) of theophylline monohydrate dehydrated and time (min) at 47°C. The nitrogen flow rate (ml/min), sample weight (mg), and lag time calculated from the linear portion were as follows: (●———●) 10.0, 2.0, −2.73; (— — —) 10.0, 1.3, −1.95; (———) 10.0, 1.8, 0.53; (·····) 0.50, 1.2, 0.58; (------) 0.5, 1.2, 0.28; (●●———●●) 0.50, 1.5, 3.65.

provides a measure of fractional completion (α) of dehydration. Fig. 2 shows the α vs time relationship for six studies carried out at 47°C; three at 0.5 ml/min and three at 10 ml/min nitrogen flow rate. At this temperature nitrogen flow rate was found to have a small but systematic effect on the actual rate of dehydration. Extrapolation of the linear portion of these α vs time curves to $\alpha = 0$ provides a lag time as well as an indication

Table 2
Parameters relevant to the dehydration of theophylline monohydrate at 47°C and a dry nitrogen flush of 10 ml/min

	Expt no. and weight used (mg)			Average
	1 (1.3)	2 (1.8)	3 (2.0)	
Kinetic parameters				
Avrami-Erofeev slope [a] (min^{-1}) (SD)	0.0281 (0.0002)	0.0297 (0.0002)	0.0287 (0.0003)	0.0288 (0.00008)
Lag time[b] (min)	−1.95	0.53	−2.73	−1.37
Single Gaussian fit parameters [c]				
Area (A) (μJ)	−4026.2	−5233.7	−5394.1	
Width at half height (W) (min)	16.530	16.193	15.969	
Center (t_0) (min)	12.198	13.148	9.7554	
Offset (P_0) (μJ/min)	−5.945	−5.548	−9.562	

[a] Through Eq. 1.
[b] Linear portion of α vs t extrapolated to the x-axis at $\alpha = 0$; $t_L = -$(intercept/slope).
[c] $P = P_0 + A/[W(\sqrt{\pi/2})]\{e[-(t-t_0)/W^2]\}$; where P is power (μJ/min).

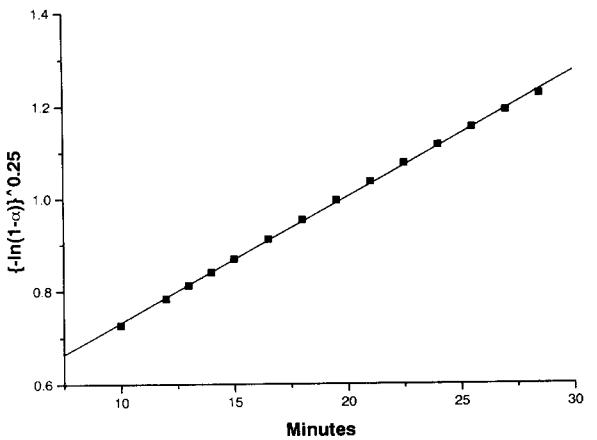

Fig. 3. The 0.25-exponential Avrami-Erofeev plot of the data for the dehydration of 1.5 mg of theophylline monohydrate at 47°C in the TAM (Fig. 1). The slope of the line is 0.0271 with SD 0.0002 min^{-1}.

of the relative reproducibility of the experiment. Lag times are listed in Tables 1 and 2; the lag times at 0.5 ml/min are a little longer than at 10 ml/min, indicating that some dehydration data were probably missed during the equilibration time at the faster nitrogen flow.

When the α vs time data of Fig. 2 were fitted to several equations applicable to solid state reactions (Table 1 in Agbada and York (1994) compiled after Sharp et al. (1966)), an Avrami-Erofeev treatment (Eq. 1) with 0.25 power for a nucleation mechanism was found to best describe the results:

$$[-\ln(1-\alpha)]^{0.25} = kt \qquad (1)$$

where k is a rate constant (t^{-1}). The same best-fit relationship was found by Agbada and York (1994) using a gravimetric method although their study was conducted at a higher temperature. Fig. 3 shows the Avrami-Erofeev fit for the data of Fig. 1; the slope is 0.0271 min^{-1} with standard deviation 0.0002 for 14 data points. Suzuki et al. (1989) reported that a power of 0.5 gave the best fit; these workers restricted the data to $0.2 \leq \alpha \geq 0.9$. Our results, however, indicate that an Avrami-Erofeev relationship with a power of 0.25 fits the entire data set better than a power of 0.5. Table 1 lists the Avrami-Erofeev (power 0.25) slopes and their standard deviations. The reproducibility in k (average = 0.025 min^{-1}) from one trial to another under the same conditions is seen to be $\pm 4\%$.

A strong test of the validity for assuming that a Gaussian relationship exists between power and time and the soundness of extracting kinetic data from it was to compare the microcalorimetric results with those obtained via a gravimetric approach which directly follows weight loss as a function of time albeit with considerable loss in sensitivity in comparison with the microcalorimetric method. Using the microcalorimeter under the same experimental conditions (nitrogen flow 10 ml/min and approximate temperature 47 vs 47.2°C) as those of Suzuki et al. (1989), except for sample size (1–2 mg in microcalorimetric studies), and using their data analysis (i.e., an Avrami-Erofeev equation with 0.5 power), the average rate constant (three trials) was found to be 0.0553 $min^{-1} \pm 2\%$. Interpolation from Fig. 11 in the report by Suzuki et al. (1989) yielded a rate constant of ~ 0.05 min^{-1} showing excellent agreement and more significantly establishes confidence that data treatment via Gaussian estimation of power-time data from the microcalorimeter is reliable.

3.2. Studies at 40°C

During the dehydration of 3–6 mg samples of theophylline monohydrate in the microcalorimeter, a complex heat flow (P) vs time relationship was found. Studies were repeated four times with excellent reproducibility. One such P vs time plot is given in Fig. 4 for a sample size of 3.3 mg; the open circles are the experimental data. It was found that the data could be fitted to two Gaussians with reasonable success; the dashed lines in Fig. 4 depict the individually extracted Gaussians. The solid line in Fig. 4 shows how the sum of the two Gaussian relationships fit the experimental results. A three-Gaussian fit is better but, since the origin of very early heat flows is always uncertain, two-Gaussian fit was used in all subsequent analyses. The two-Gaussian fit parameters estimated for all studies at 40°C are given in Table 3.

The surprising possibility of a two-step dehydration required further testing. Fig. 5 illustrates the power-time relationship for a 4 mg sample of theophylline at 40°C where arrows indicate the water content of the sample remaining as measured by TGA at different times. Samples were obtained by interrupting the experiment at the time indicated in Fig. 5. For example, after about 1 h, 1.8% of the total 9% water initially present was found to be lost. This observation was approximately paralleled by TGA studies which corroborated a two-step water loss with 2.25% water removed in the initial step (Fig. 6A). Moreover, the TGA/DTA measurement (operated isothermally at 42°C and at a nitrogen flow rate of 50 ml/min) shows at least a two-step water loss via TGA with the concomitant DTA measurement indicating that there is a heat event associated with each (Fig. 6B). Interestingly, only one endotherm is observed when DTA was operated in the scanning mode (Fig. 6A).

The two-Gaussian relationships fitted to 40°C microcalorimetric data such as that represented in Fig. 4 can be analyzed individually in a manner identical to that described above for studies performed at 47°C to yield two α-time relationships. Table 3 gives the Gaussian fit parameters and lag times extrapolated from the linear portion of α vs time plots. The lag times for the two individual steps provide a measure of relative reproducibility; shifts in lag time reflect small operator differences in sample introduction and inter-experimental variance in reaching stable heat flow. The inter-experimental difference in lag times is however quite small. As with studies at 47°C, fractional dehydration as a function of time is best linearized by an Avrami-Erofeev relationship with a power of 0.25. Fig. 7 shows such plots for the experimental data from the study represented in Fig. 4. The rate constants derived from the slopes in Fig. 7 are 0.00786 min^{-1} (first Gaussian) and 0.00790 min^{-1} (second Gaussian). The rate con-

Table 3
Parameters relevant to the dehydration of theophylline monohydrate at 40°C and a dry nitrogen flush of 0.5 ml/min

	Expt no. and weight used (mg)				Average
	1 (4.4)	2 (4.6)	3 (5.6)	4 (3.3)	
Kinetic Parameters					
First Gaussian Avrami-Erofeev slope [a] (min^{-1}) (SD)	0.00738	0.00568	0.00885	0.00786	0.00744
	(0.01239)	(0.01204)	(0.01946)	(0.01179)	(0.00132)
Second Gaussian Avrami-Erofeev slope [a] (min^{-1}) (SD)	0.00780	0.00799	0.00638	0.00799	0.00754
	(0.01088)	(0.02097)	(0.01188)	(0.02036)	(0.000779)
First Gaussian lag time [b] (t_L) (min)	−13.89	−12.31	−14.52	−3.99	−11.18
Second Gaussian lag time [c] (t_L) (min)	90.45	79.04	78.46	91.50	84.86
Gaussian fit parameters [c]					
First Gaussian area (A) (μJ)	−6241.6	−8313.0	−5159.0	−5307.3	
Second Gaussian area (A) (μJ)	−15963.0	−11532.0	−19733.0	−10009.0	
First Gaussian width at half height (W) (min)	73.051	84.735	62.913	69.445	
Second Gaussian width at half height (W) (min)	67.189	59.398	79.704	59.141	
First Gaussian center (t_o) (min)	34.828	47.068	25.536	42.818	
Second Gaussian center (t_o) (min)	136.33	120.87	132.4	133.06	
First Gaussian offset (P_o) (μJ/min)	0.9000	−1.2461	0.9846	0.9922	
Second Gaussian offset (P_o) (μJ/min)	1.2839	−1.2461	0.4110	−0.5682	

[a] Through Eq. 1.
[b] Linear portion of α vs t extrapolated to the x-axis at $\alpha = 0$; $t_L = -$(intercept/slope).
[c] $P = P_o + A/[W(\sqrt{\pi/2})]\{e[-(t-t_o)/W^2]\}$; where P is power (μJ/min).

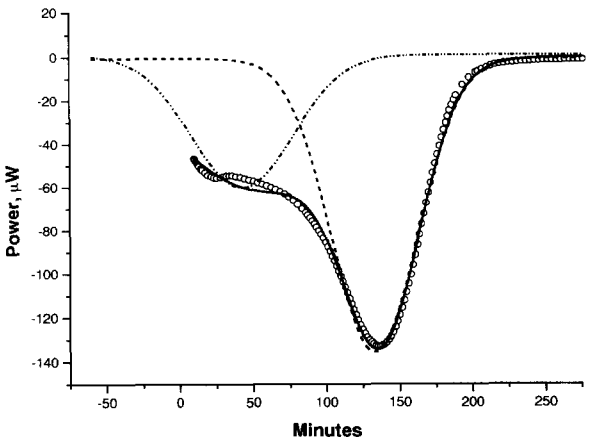

Fig. 4. Power (μW)-time (min) relationship for the dehydration of theophylline monohydrate at 40°C using the thermal activity monitor (TAM). The sample size was 3.3 mg and the nitrogen flow rate was 0.5 ml/min. The sample was temperature equilibrated for a total of 28 min before data were collected. The symbols are the raw data. The raw data are fitted to a two-Gaussian relationship where the individual Gaussians are shown as the stippled lines; first step (●●———●●) and second step (— — —). The solid line shows how the two Gaussians combine to fit the experimental data. The Gaussians have the parameters listed under experiment no. 4 in Table 3.

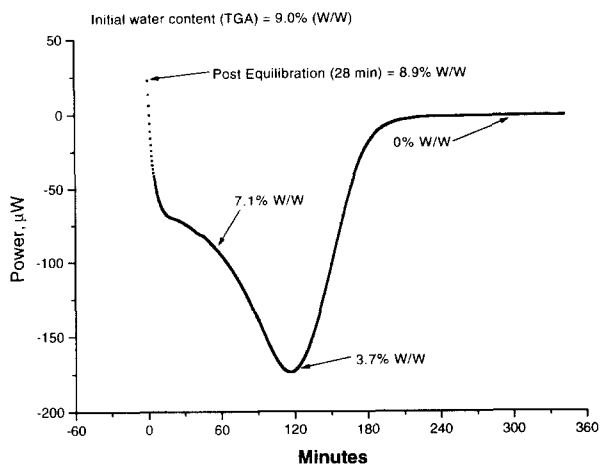

Fig. 5. Power (μW)-time (min) relationship for the dehydration of theophylline monohydrate at 40°C using the thermal activity monitor (TAM). Four separate experiments were run where each was interrupted at the point of the arrows and the amount of water remaining at that time determined via TGA. The times and the amount of water remaining were: immediately after the 28 min equilibration, 9.0% w/w; after ~1 h, 7.1% w/w; after ~2 h, 3.7% w/w; and after 5 h, 0%.

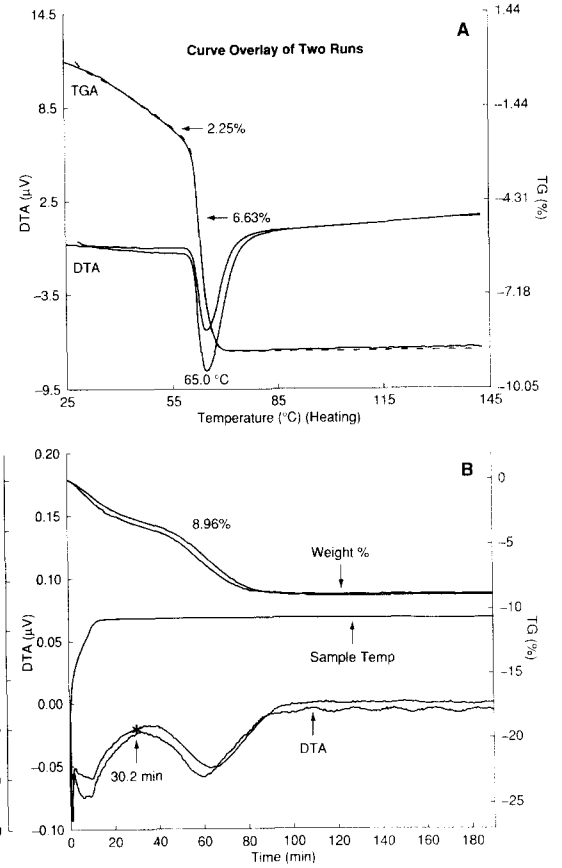

Fig. 6. Simultaneous TGA/DTA determination for several weights of theophylline monohydrate. (A) A scanning experiment overlaying the results of two determinations using a weight of about 7 mg; scan rate, 5°C/min; nitrogen flow rate, 40.0 ml/min; sampling time, 0.5 s. (B) Simultaneous isothermal TGA/DTA determination of the dehydration of theophylline at ~42°C. Two sample sizes were used (11.098 and 3.829 mg) and results normalized to 1 mg for easy comparison. The instrument was ramped from 30 to 40°C at 1°C/min and then held on hold for 180 min. A nitrogen flush of 50.0 ml/min was used. Sampling time was 1.0 s.

stants calculated for the results found in the other three experiments are given in Table 3. The fact that the rate constants for the two steps are very close is a consequence of having selected 40°C for the study; this need not be the case at other temperatures. Temperature effects for the dehydration of theophylline will be the subject of a future communication.

There is independent evidence that theophylline dehydration can occur via more than one process (Lin and Byrn, 1979). The 1,3-dimethylxanthine rings of theophylline stack in the crystal to leave a central core of precise geometry along its long axis (the *c*-axis) where water can reside in a stoichiometric amount (8.9% w/w via TGA) equivalent to a monohydrate. Through hot-stage microscopy at 35°C, Lin and Byrn show that water loss occurs outward from both ends of the crystal parallel to the *c*-axis although some reaction at the side of the crystal (perpendicular to the *c*-axis) can be observed at longer times. Both microcalorimetry and TGA/DTA studies point to the involvement of at least two dehydration steps at 40°C. TGA suggests that about 2.25% of a total 8.88% water is lost during the first phase (Fig. 6A). Using microcalorimetric experimental data, it is possible to calculate the total fraction of water lost as a function of time by measuring segmental areas and dividing by the total area, e.g., as in plots such Fig. 4. The quantity, $1-\alpha$, or fraction of moisture lost then would have the same form as TGA data. Fig. 8 is representative of a plot of $(1-\alpha)$ vs time at 40°C (stippled line) with a similar treatment of microcalorimetric results found at 47°C (solid line) which is added for comparative purposes. The symmetry found at 47°C where a single-step dehydration occurs is markedly diminished at 40°C. The general form of the microcalorimetry derived relationship at 40°C is similar to that of the TGA study of Fig. 6B. A loss of 2.25% corresponds to a fractional loss of 0.25 which should occur at around 70 min which is approximately where the first dehydration step is almost complete while the second step is just starting. 70 min compares well with an approximated 50 min taken for the end of the first dehydration step as seen in the TGA experiment. This is because the isothermal TGA experiment was performed at a slightly higher temperature (42°C) and at a higher nitrogen flow rate. The two-step dehydration at 40°C was more clearly evident when the derivative of the isothermal weight loss-time relationship (Fig. 6B) was plotted as a function of time; Fig. 9A gives the results (symbols, experimental) found for the isothermal TGA study using an 11.089 mg sample. The derivative vs time data (analogous to power-time data in the TAM at 40°C) were deconvoluted into two Gaussians as depicted by the solid lines of Fig. 9A. The deconvoluted data were analyzed in a manner similar to that of the

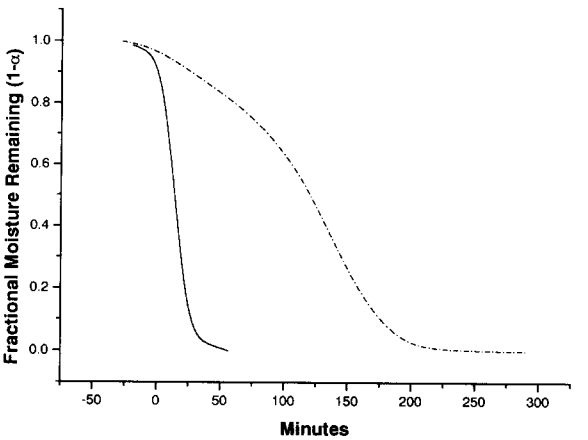

Fig. 8. Total fraction of water remaining $(1-\alpha)$ for the TAM measured dehydration of theophylline at 47°C (———) and 40°C (●———●). Dehydration at 47°C is a one-step process while that at 40°C is a two-step process whose difference is reflected in the symmetry of the sigmoidal relationships. Note the similarity in shape of the 40°C data with that of Fig. 6B where dehydration was followed gravimetrically.

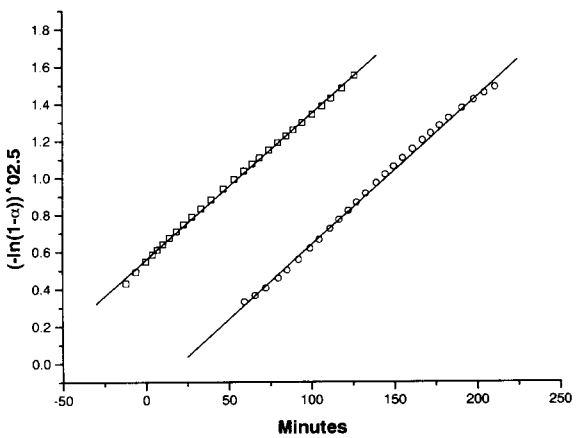

Fig. 7. Linearized plots of the data at 40°C (3.3 mg sample) according to Avrami-Erofeev (Eq. 1). The two steps involved have been separated and treated individually. (□) Refers to the first step whose rate constant is 0.00786 (SD = 0.0118) min^{-1}. (○) Corresponds to the second step with rate constant 0.00799 (SD = 0.0204) min^{-1}.

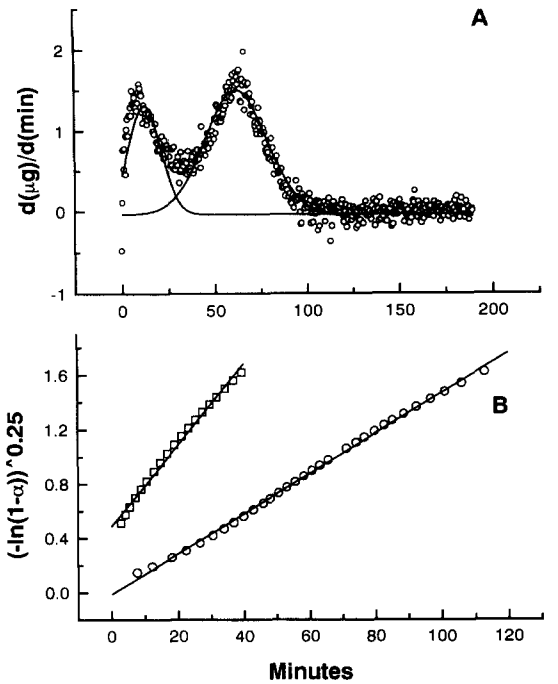

Fig. 9. Using the dehydration data obtained via the isothermal TGA method at 42°C for an 11.098 mg sample, panel A shows the dependence of the first derivative (d μg/d min) of the loss with time (min). The symbols are the experimental derivatives and the solid line is a two-Gaussian fit of the data. Panel B represents Avrami-Erofeev treatment of the fractional completion of water loss (α) as a function of time. Fractional loss is calculated from the segmental area under each Gaussian in panel A. The slope of the first step dependence is 0.0299 (SD = 0.0006) min^{-1} and the slope for the second step is 0.0147 (SD = 0.0001) min^{-1}.

microcalorimetric data to yield fractional loss (α) at selected times. Fig. 9B represents the 0.25 power Avrami-Erofeev plots for such a vs time data. The rate constants and their standard deviations when the sample size was 11.089 mg (Fig. 9B) are 0.0299 (0.0006) min^{-1} for the first Gaussian and 0.0147 (0.0001) min^{-1} for the second Gaussian. When the sample size was 3.829 mg, the rate constants (standard deviations) were 0.0378 (0.0009) min^{-1} for the first Gaussian and 0.0177 (0.0002) min^{-1} for the second Gaussian. The rate constants extracted from the isothermal TGA data are close but not the same as found using microcalorimetry at 40°C (Table 3), perhaps due to a slightly higher temperature and a higher nitrogen flow rate in the TGA study. Flow rate differences may be particularly significant, since different geometries are involved in the two methods. What is most significant is that the TGA approach corroborated the finding that the dehydration of theophylline at temperatures around 40°C involves more than one step and that the gravimetric data can be deconvoluted into two Gaussian relationships yielding fractional loss data that conform to an Avrami-Erofeev (solid state nucleation mechanism) relationship just as was disclosed in the microcalorimetric method.

4. Conclusions

(1) By comparing the results for the dehydration of theophylline monohydrate at 47°C using heat flow-time relationships determined in the isothermal microcalorimeter to results obtained by others using a totally different methodology, it is evident that microcalorimetry can be used reliably to measure rates and thus potentially to deduce mechanisms of dehydration reactions.

(2) A suitable method for analysis of power vs time relationships is to fit the data as a series of Gaussian dependencies (which are usually observed for generalized solid state reactions) and then to determine which of several possible mechanisms would best describe the experimental results by least-squares fitting of relevant equations.

(3) The dehydration of theophylline at 47°C was found to be a single step process conforming with a nucleation mechanism and can be best described by an Avrami-Erofeev equation with power 0.25.

(4) At 40°C the dehydration of theophylline was found to be a two-step process. Each process can be linearized best using an Avrami-Erofeev relationship with power 0.25.

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