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Thermophysical characterization studies of pharmaceutical hydrates [1]

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Abstract

The use of both differential scanning calorimetry and thermogravimetry to study the solid state dehydration of hydrated pharmaceutical compounds, and the subsequent behavior of the anhydrous drug is discussed. Three compounds, each with differing thermal behavior serve as examples. Emphasis is placed on applying current solid state reaction kinetics theory to analyze non-isothermal data and ascribe possible mechanisms for the various physicochemical transformations and physical transitions monitored.

Solvent removal from a final product can effect partial or total dehydration. It is necessary to ascertain the dehydration temperature limits, and, of equal importance to examine the ability of the compound to rehydrate. The dehydration/rehydration behavior of a drug candidate is described as a practical demonstration of the utility of thermal analysis in pharmaceutical process development.

INTRODUCTION

Many active pharmaceutical compounds and those under development exist as hydrates. Thermoanalytical and microcalorimetric procedures are often employed to assess drug compound stability. Is the monitored exothermicity a true measure of the potential instability of a drug hydrate? How does the possible endothermic dehydration affect such stability assessments? As pointed out by Townsend [1] materials are stabilized to a certain extent by preceding endothermic events. Process development of new potential pharmaceutical candidates very often involves solvent drying of final products. Dependent on the difficulties encountered in such operations, partial or total dehydration of hydrated compounds can occur. Does the anhydrous material readily rehydrate? If not, what are the optimal conditions? Such considerations necessitate a detailed knowledge

[1] Dedicated to Hans Georg Wiedemann.

of the dehydration characteristics of the drug hydrate and, to a certain extent, information regarding the nature and subsequent behavior of the anhydrous compound.

Thermal analysis provides a more than adequate means for answering such questions. Brancone and Ferrari [2] early demonstrated the potential of using DTA in analyzing for the presence of solvent in a drug. Kuhnert-Brandstatter and Proll [3] have utilized DSC, TG and EGA to augment hot stage microscopy studies of drug desolvation behavior. In the last two decades there has been a paucity of thermoanalytical investigations aimed at elucidating the mechanisms of drug dehydration using solid state reaction kinetics theory. Otsuka and Kameniwa [4] measured the energetics of the step-wise dehydration of cephalexin dihydrates. Niazi [5] employed DSC to measure the dehydration enthalpy of mercaptopurine. The character of the heat flow curves indicates some complexity in the removal of water. The magnitude of the few examples of dehydration activation energies are typical for diffusion-controlled reactions. In certain cases, e.g. erythromycin, several hydrates are indicated, but dehydration and rehydration are relatively easy, indicative of a loose association of water with the host molecule [6].

As pointed out by Marti [7], DSC and TG are the thermoanalytical procedures most used to characterize drug behavior in the solid state. He also pointed out the complications generated by the presence of hydrates or solvates in an active substance. Further problems may result if the active drug can exist in both the crystalline and amorphous states. This paper will describe how DSC and TG have been utilized to study a number of pharmaceutical hydrates which exemplify the presence of such complications. Information on three active drugs, two monohydrates and a trihydrate will be presented. Proprietary considerations dictate that these pharmaceutical compounds not be identified. Information relating to the stepwise dehydration and rehydration of a drug candidate under development will also be discussed.

EXPERIMENTAL

DSC and TG measurements were made with the Mettler TA-3000 system employing open aluminum and alumina crucibles, respectively. Loosely distributed samples, in the 3–10 mg range, were used in a flowing nitrogen atmosphere according to instrument specifications. Except for a case of multiple curve comparison, all DSC data are presented as weight-normalized heat flow ($W\,g^{-1}$). A mW relative scale is employed for the exception. TG data is presented as a percentage of the initial sample weight.

RESULTS AND DISCUSSION

Drug A

The endothermic dehydration of this monohydrated compound proceeds stoichiometrically (4.23% theoretical weight loss) in the 70–110°C range, as shown in Fig. 1, with a $53.3 \pm 0.4\ \text{kJ mol}^{-1}$ enthalpy. The anhydrous salt produced is an opaque amorphous solid which recrystallizes exothermically in the 110–130°C range before melting at 172.4°C. There is no thermogravimetric evidence for a multi-step dehydration but characteristic changes in the endothermic profile at different heating rates point to a multiple reaction process. Figure 2 shows a comparison of dynamic scan DSC records at a series of low to medium rates. The strong heating rate dependence of both chemical and physical processes is clearly indicative of different reaction kinetics control.

Table 1 summarizes the enthalpic data and *n*th order Arrhenius analyses for the kinetics of both the dehydration and subsequent recrystallization, using the Mettler TA72 software. The reaction order, $n = 2/3$, is consistent with the contracting volume (R3) mechanism for the dehydration. The large magnitude activation energies and pre-exponential factors, together with an order close to unity is typical for a random nucleation (A2 or A3)

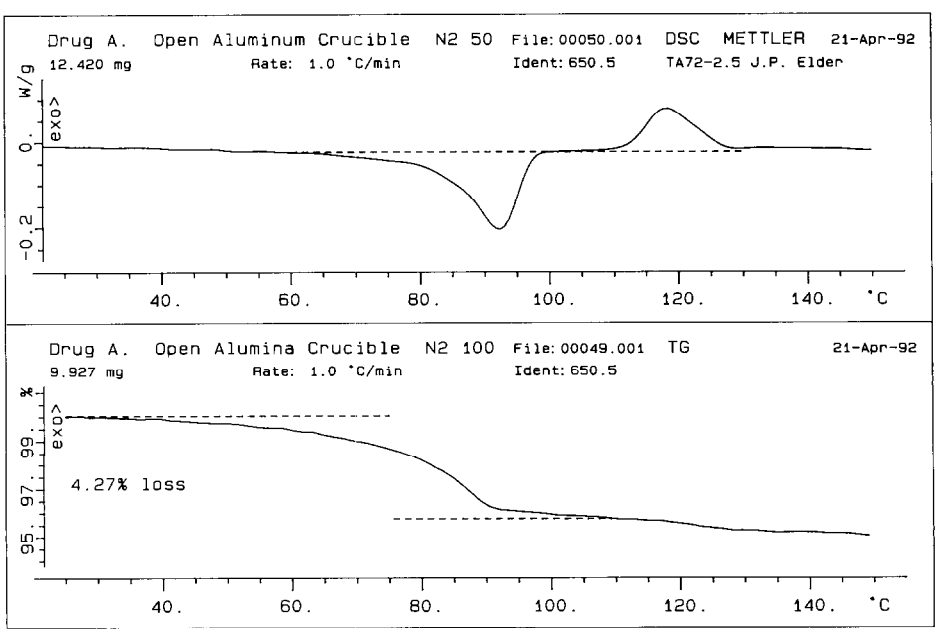

Fig. 1. DSC/TG profiles at $1°\text{C min}^{-1}$ for Drug A.

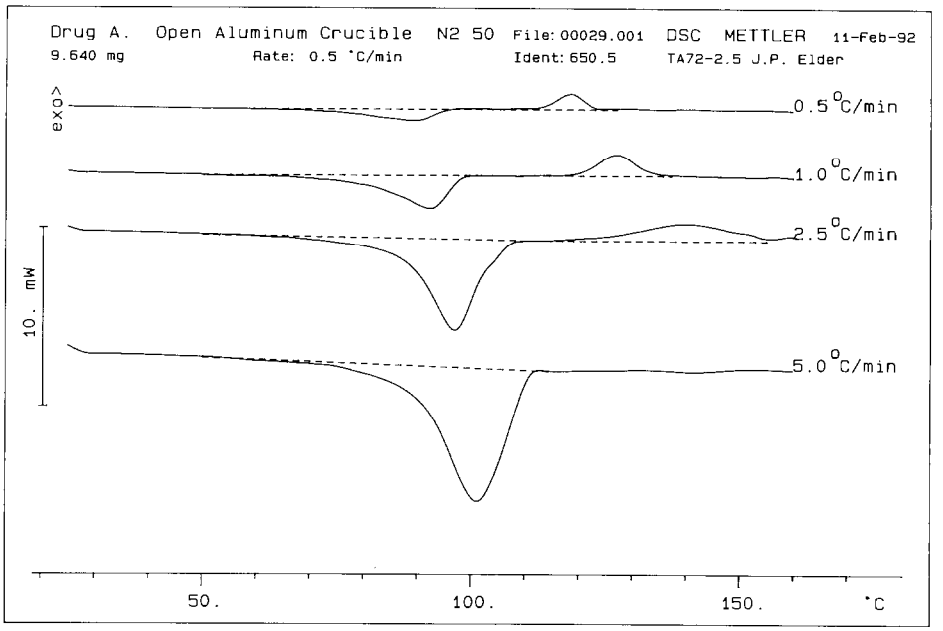

Fig. 2. Comparison of DSC profiles at 0.5, 1, 2.5 and 5°C min^{-1} for Drug A.

mechanism for the recrystallization, when analyzed, by use of the Arrhenius equation [8, 9]. However, more realistic and correct values are obtained by employing peak analysis. Using the generalized Kissinger equation [8], one obtains the values given in Table 2. The Kissinger and

TABLE 1

Enthalpy and Arrhenius parameters (DSC data) for Drug A

β/°C min^{-1}	ΔH/J g^{-1}	T_{max}/°C	α_{max} [a]	E/kJ mol^{-1}	ln A/A s^{-1}	n
A. Dehydration						
0.75	126.4	90.9	0.758	184.4 ± 3.4	54.83 ± 1.12	0.66 ± 0.02
1.00	124.9	92.1	0.720	191.3 ± 7.2	57.22 ± 2.39	0.69 ± 0.07
1.50	125.1	94.2	0.706	205.2 ± 8.9	61.80 ± 2.95	0.66 ± 0.17
2.50	124.1	96.9	0.675	206.5 ± 15.0	62.05 ± 4.96	0.66 ± 0.30
5.00	125.7	100.3	0.620	200.8 ± 6.7	60.17 ± 2.19	0.66 ± 0.20
	$125.2_4 \pm 0.8_6$					
B. Recrystallization						
0.25	54.8	110.8	0.605	927.2 ± 2.2	284.66 ± 0.69	1.04 ± 0.02
0.50	56.2	118.9	0.625	688.3 ± 2.2	205.84 ± 0.67	1.15 ± 0.07
0.75	54.8	123.6	0.590	623.0 ± 1.1	187.75 ± 0.32	1.21 ± 0.00
1.00	55.6	127.3	0.550	506.2 ± 3.2	147.01 ± 0.95	1.47 ± 0.02
	$55.3_5 \pm 0.6_8$					

[a] Dimensionless extent of reaction at T_{max} (DSC peak).

TABLE 2

Kissinger analysis reaction kinetics parameters

Compound	Process	Heating rate range/ °C min^{-1}	Model [8, 9]	n Range	E/kJ mol^{-1}	A/s^{-1}
Drug A	Dehydration	0.75–5.0	Fn	0.46–0.77	219.8	8.88×10^{28}
Drug A	Dehydration	0.75–5.0	R3		221.3	4.81×10^{28}
Drug A	Dehydration	0.75–5.0	D4		189.1	3.17×10^{23}
Drug A	Recrystallization	0.25–1.00	Fn	1.10 ± 0.18	101.0	1.90×10^{10}
Drug A	Recrystallization	0.25–1.00	A3		102.4	3.16×10^{10}
Drug A	Recrystallization	0.25–1.00	A2		102.4	3.11×10^{10}
Drug B	Dehydration	1.0–10.0	Fn	0.59 ± 0.12	65.2	1.51×10^{7}
Drug B	Dehydration	12.5–20.0	Fn	0.58 ± 0.10	92.1	1.57×10^{11}
Drug B	Dehydration	1.0–10.0	R2		64.9	6.82×10^{6}
Drug B	Dehydration	1.0–10.0	R3		64.8	4.44×10^{6}
Drug B	Dehydration	12.5–20.0	D4		101.4	3.34×10^{11}

Arrhenius nth order analytical values for the dehydration are comparable, as they should be. However, for the recrystallization, the Kissinger-derived parameters are more realistic. Furthermore, the nth order, A2 and A3 model values are comparable, as is correct.

Drug B

Like the previous compound, Drug B is a monohydrate, which dehydrates endothermically (55.8 ± 1.7 kJ mol^{-1}) in the 25–130°C region with a 4.8% stoichiometric weight loss. The anhydrous compound is also an amorphous solid, which recrystallizes exothermically (9.0 ± 0.4 kJ mol^{-1}) at 157.1°C at a 10°C min^{-1} heating rate. Under these scan conditions, melting proceeds with decomposition at 177.1°C (31.2 ± 0.6 kJ mol^{-1}). The subsequent behavior of the anhydrous melt is interesting, solidifying to a vitreous solid which recrystallizes to a polymorphic form, but will not be pursued further. With regard to the initially formed anhydrous compound, three phenomena occur which tend to distort and obscure its thermal characterization, particularly when monitored at lower heating rates. In the endotherm characterizing the dehydration, a minor distortion at about 95°C is observed prior or subsequent to the major DSC peak, dependent upon the heating rate, as shown in the upper half of Figs. 3–5. This is attributed to a concurrent reversible solid state transition in a functional group adduct in the drug. This, however, has no effect on the dynamic TG characteristics of the dehydration, which as in the case of Drug A (lower half of Fig. 1) shows an undistorted single step weight loss profile. Such a transition has been shown to occur reversibly on heating and cooling the adduct in its

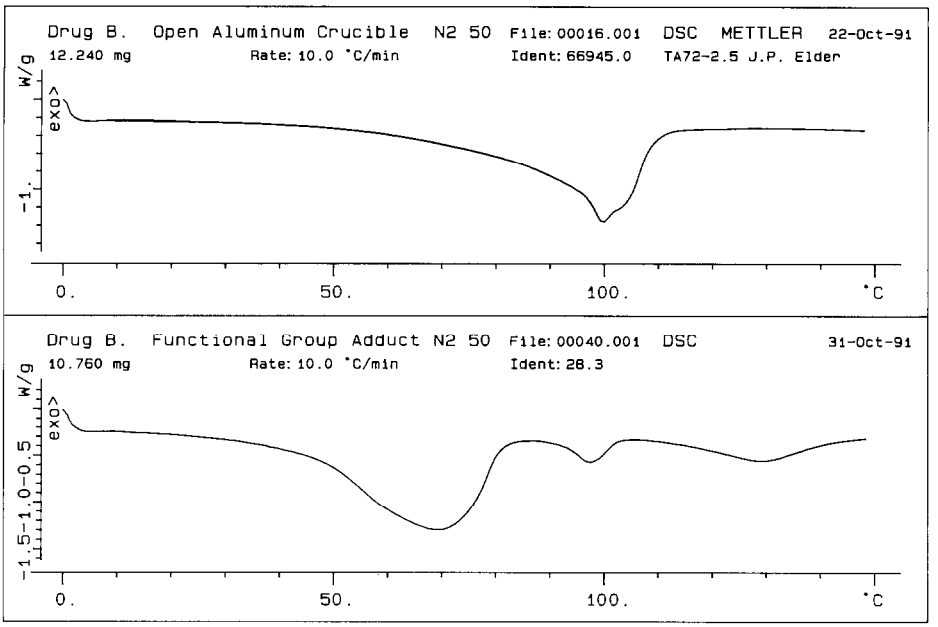

Fig. 3. DSC profiles at 10°C min^{-1} for Drug B/adduct compound hydrate.

hydrated form. The characteristic endothermic/exothermic DSC signals occur at 95°C irrespective of the heating rate used. Figures 3–5 show, for comparison, the 0–150°C endothermic signal profiles of Drug B and the hydrated adduct compound at 10, 5 and 2.5°C min^{-1}, respectively. As is seen, the position of the drug endothermic distortion is almost exactly in line with the adduct solid state transition endotherm. Since this distortion appears not to have any effect on the position of the dehydration DSC peak, it is possible to use peak analysis to postulate the dehydration mechanism, and evaluate the reaction kinetics parameters. The results of this analysis are given in Table 2. *n*th Order analysis showed a discontinuity in the linear Kissinger plot ($\ln \beta/T_{max}^2 - 1/T_{max}$) over the 1–20°C min^{-1} range, in the interval between 10 and 12.5°C min^{-1}. For heating rates of 10°C min^{-1} or less, the process appears to be controlled by a material shrinkage mechanism, but one cannot differentiate between the R2 and R3 models [8]. At the higher heating rates, dehydration is diffusion controlled, the Gintsling–Brounshtein [10, 11] D4 mechanism yielding the best fit.

Non-isothermal measurements of the crystallization of the amorphous dehydrated drug necessitate operating at much lower scan rates than 10°C min^{-1} since, under these heating conditions, the crystallization exotherm and subsequent fusion endotherm are not resolved. At low heating rates, as verified by isothermal TG, there are small weight losses

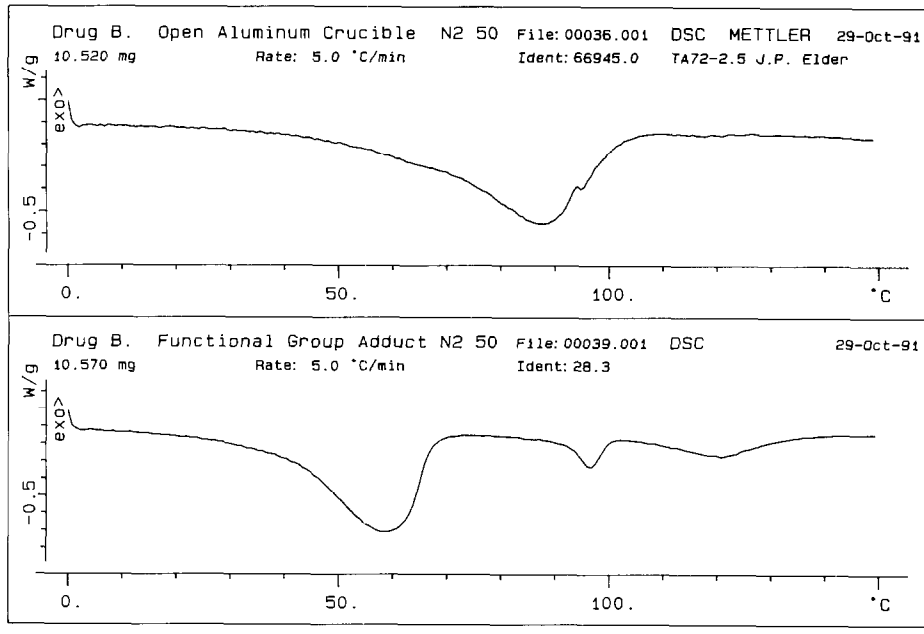

Fig. 4. DSC profiles at 5°C min^{-1} for Drug B/adduct compound hydrate.

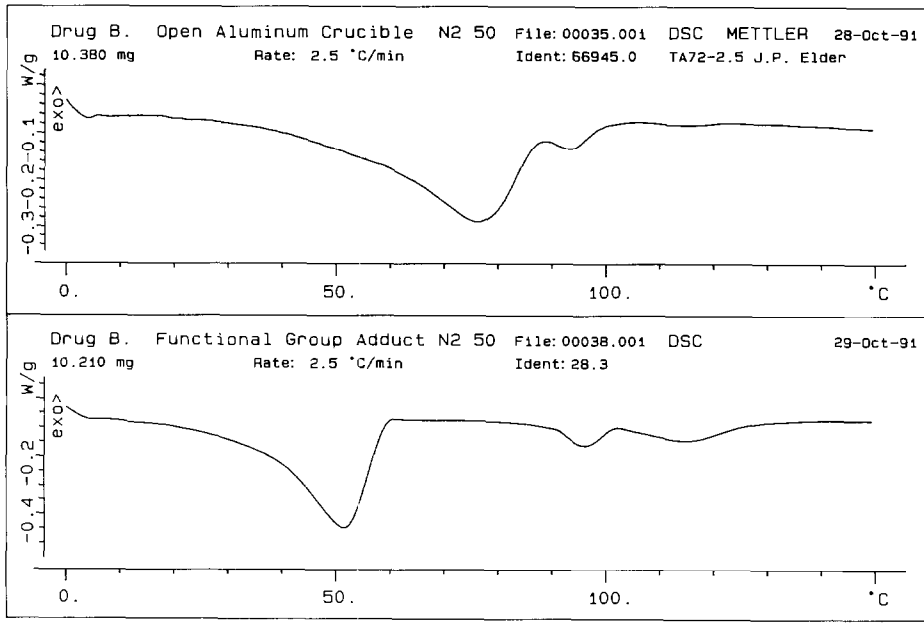

Fig. 5. DSC profiles at 2.5°C min^{-1} for Drug B/adduct compound hydrate.

due to solid state sublimation. Long term stress at temperatures close to melting indicate that thermal degradation does occur.

Drug C

This trihydrated crystalline salt dehydrates stoichiometrically (16.6% weight loss) in the 25–150°C region producing a crystalline anhydrous salt. The characteristic thermal data at a 10°C min^{-1} heating rate is shown in Fig. 6. Although the TG profile shows a single stage process, there is an approximate 0.9% weight loss between 25 and 80°C prior to the major dehydration. Measurements at lower heating rates confirm this. Thus, at 1°C min^{-1} the 25–80°C loss (shown in Fig. 7) is 1.77%. Although there is no concurrent DSC evidence, the DTG signal does confirm the low magnitude first stage. Since, it is too large to be ascribed to loss of residual organic solvent in the pure sample used, assayed at less than 0.01%, and the total weight loss agrees with the stoichiometric loss of three water molecules, it is construed to be a two-stage process. It is interesting to compare the DSC profiles at two heating rates. A shoulder is evident on the leading and trailing legs of the dehydration endotherm of 10 and 1°C min^{-1}, respectively. Although a non-isothermal kinetics study was not carried out, it is hypothesized that the moving shoulder is indicative of multiple reactions proceeding at different rates at various reaction interfaces in the crystalline solid.

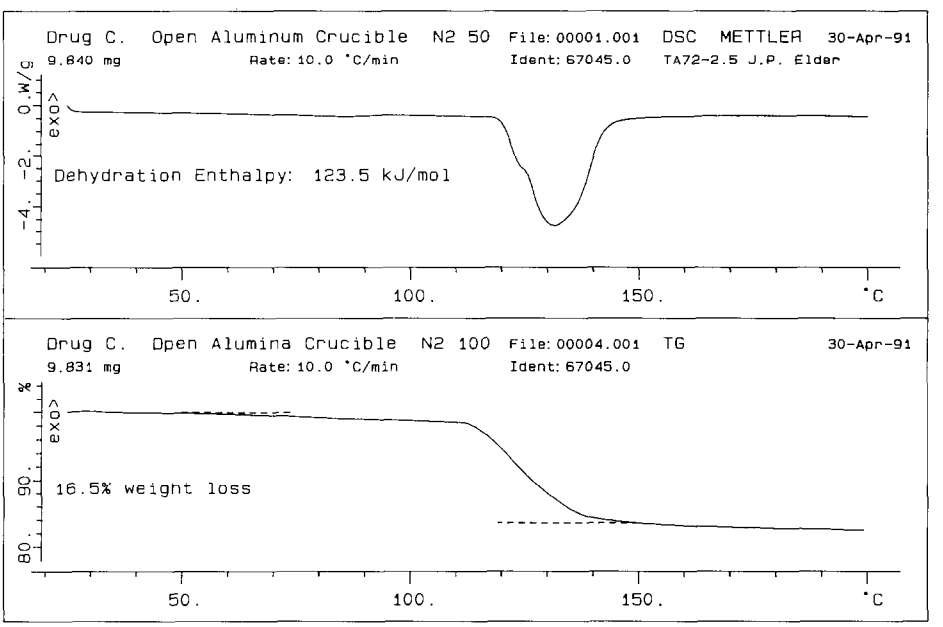

Fig. 6. DSC/TG profiles at 10°C min^{-1} for Drug C.

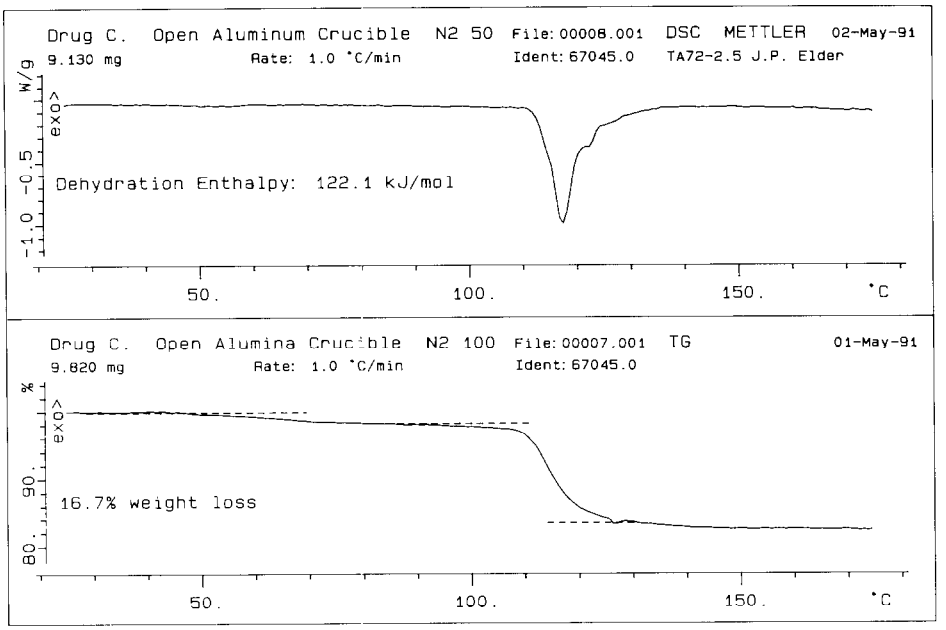

Fig. 7. DSC/TG profiles at 1°C min^{-1} for Drug C.

Candidate drug D

Process solvent drying optimization of this candidate compound necessitated investigating both its dehydration and rehydration. Ostensibly a trihydrate, the Karl Fischer value indicates it is closer to a 3.5 hydrate. Figure 8 shows the DSC and TG profiles of the total dehydration of this solvent-free compound in a flowing dry nitrogen atmosphere. As can be seen, there are two merging, unresolved endotherms in the 5–60°C region, followed by a third distinct endotherm between 60 and 110°C. The TG record indicates that, even at room temperature, a weight loss process is on-going. However, between 25 and 110°C, it is clear that two distinct dehydrations are occurring namely: trihydrate to monohydrate, and monohydrate to anhydrous compound. The ratio of both the weight losses and enthalpy changes are 2:1. Furthermore, the actual weight losses are close to theoretical (3.44%) for each water molecule, with a dehydration enthalpy of 1.5 kJ $(mol\ H_2O)^{-1}$.

Figure 9 shows the isothermal weight gain profile as the anhydrous compound rehydrates in a flowing ambient air atmosphere. The 12% increase agrees well with the original sample KF value. The time profile is logarithmic. The rehydration follows nth order kinetics with $n = 0.43$. These facts indicate that diffusion of water vapor through the compound is rate-controlling (Gintsling–Brounshtein [10, 11] D4 model) rather than phase boundary movement (R2 model [8]). Figure 10 shows the DSC

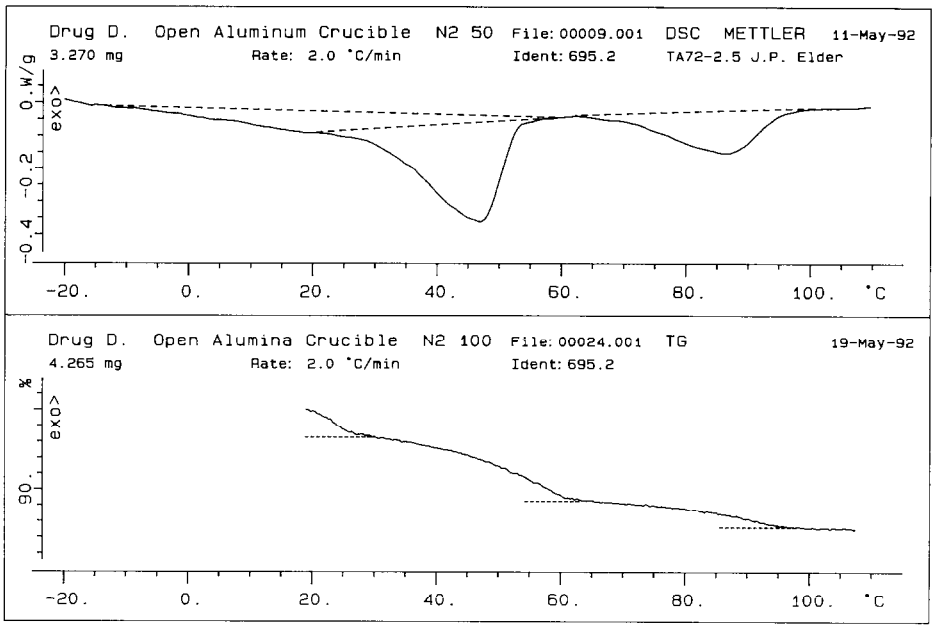

Fig. 8. DSC/TG profiles at 2°C min^{-1} for candidate Drug D.

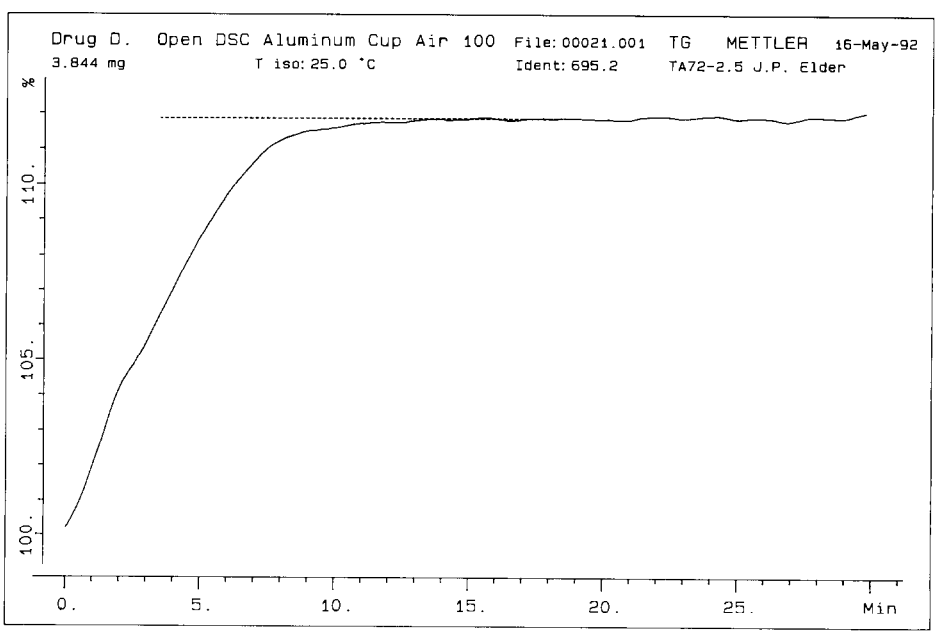

Fig. 9. TG profile at 25°C for candidate Drug D rehydration.

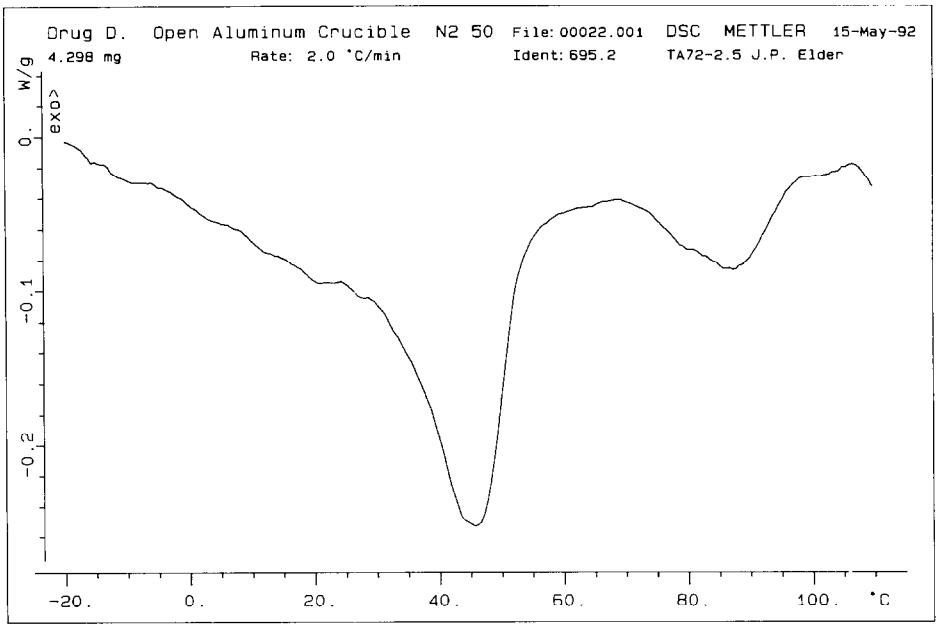

Fig. 10. DSC profile at 2°C min^{-1} for candidate drug D (rehydrated).

profile characterizing the dehydration of this rehydrated sample, and compares well with that shown in Fig. 8. Thus, rehydration proceeds continuously to the 3.5 hydrate stage. The endothermic region between 5 and 25°C is attributed not to loss of any residual organic solvent, assayed at less than 0.2%, but rather to loss of loosely bound water shared between two compound molecules, perhaps by hydrogen bonding.

CONCLUSION

The utility of employing both DSC and TG in studying these several pharmaceutical hydrates has proved highly successful. The non-isothermal approach at extreme but reasonable linear heating rates should be used, as exemplified by the investigation of Drug A. Thus, in this study, if a single measurement at 10°C min^{-1} had been used, recrystallization of the glassy anhydrous compound would have been missed, and the subsequent low intensity melt endotherm would have indicated an extremely low fusion enthalpy. Likewise, measurements at very low heating rates have their problems, e.g. sublimative loss and onset of thermal degradation, confirmed by isothermal studies. Following identification of each DSC signal and the concurrent TG step, one is advised to examine the state of the residual sample in the open crucible, and any region above the crucible for signs of condensed sublimate.

Distortions in a DSC record can deleteriously affect the Arrhenius

analysis of single heating rate data aimed at elucidating reaction kinetics, as exemplified by the Drug B study. Peak analysis, using the generalized Kissinger equation, obviates this potential problem.

Since during development, many drug intermediates exist as solvates, it may be necessary in support of process R&D, to study solvation and desolvation. By saturating the normal purge gas with the appropriate solvent, one can monitor solvation by isothermal TG, as described for the rehydration of the drug candidate (vide supra) and following the desolvation by non-isothermal means.

It must be emphasized that the work described should be construed only as a general treatment of the main features of the drugs' dehydration and related phenomena. Other studies, utilizing thermoanalytical techniques, supported by NMR and hot-stage XRPD, which have been carried out by outer groups in the organization [12], stress the extremely complex behavior of drug solvates, dependent among other things upon sample pretreatment and heating conditions.

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