

CHARACTERISATION OF ORGANIC AND INORGANIC HYDRATES AND SOLVATES BY THERMAL METHODS

D.E. BROWN and M.J. HARDY *

Beecham Pharmaceuticals, Biosciences Research Centre, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (Gt. Britain)

(Received 15 February 1985)

ABSTRACT

The presence of water or solvents in organic or inorganic materials requires that the “mixture” should be characterised as to whether the solvent is bound or free. Thermal methods have proven valuable in this process, although it is common for inconclusive results to be obtained by these methods alone. An additional approach is to measure clustered water by the technique of K.F. Baker, J. Cattiaux. This technique has been applied to some organic and inorganic hydrates and solvates.

Thermal analysis data are presented and conclusions drawn on the nature of the water or solvent content.

INTRODUCTION

The development of novel pharmaceutical compounds requires that a great deal of information is required about their physical properties. Solubility (in a range of solvents and aqueous pH ranges), hygroscopicity, impurity profile, water/solvent content, particle size and shape, and thermal properties are just some of the main parameters that are monitored; not only on single batches, as batch-to-batch variations in any of the above parameters is often critical. Where there are observed differences in the crystal morphology of two batches of the same compound, this can indicate either polymorphic or hydration–solvation state changes between the two batches and it must be further investigated. This discussion is only concerned with the characterisation of water or solvent present in a compound by the use of thermal methods of analysis.

A hydrate may be defined as a particular form of a solid compound which has water associated with it. This definition is very general; it will cover both stoichiometric and non-stoichiometric water–compound ratios. It will also

* Author to whom enquiries should be directed.

cover water present in any of the following ways: physically adsorbed, chemisorbed, zeolites, clathrates, pseudohydrates (a hydrate where the water is present as $-OH$ and $-H$ groups, as hydroxyl or as hydroxonium ions), or true hydrates (the water is present as H_2O molecules). True hydrates may have their water within the coordination sphere of the cation (water of coordination) or hydrogen bonded to an anion or within the lattice (lattice water) [1,2]. Organic hydrate structure is discussed in detail by Jeffrey [3].

Thermal methods have been frequently used in the characterisation of both organic and inorganic crystalline hydrates [1,4]. The usual procedure is to run both DSC and TG curves over a suitable temperature range (usually ambient to $300^\circ C$ is sufficient) and compare any endotherms or exotherms in the DSC to the TG curve. Hot stage microscopy can also be useful in the identification of the peaks on the DSC curve. In this way the material's behaviour can be monitored; Kuhnert-Brandstätter and Pröll [4,5] describe many ways in which organic hydrates may behave.

EXPERIMENTAL

DSC and TG curves were all generated on a DuPont 990 system with 910 DSC cell and 951 thermobalance, except Fig. 3, which was generated on a DuPont 1090B system (courtesy of Mr. J. Leckenby, DuPont (UK) Ltd.). The hot stage microscopy was carried out on a Stanton-Redcroft transmitted light hot stage plus Universal temperature programmer.

RESULTS AND DISCUSSION

Figure 1 shows typical DSC and TG curves for a potential organic hydrate, compound A. The TG curve shows a broad dehydration occurring over the range 70 to $100^\circ C$ with a matching endotherm in the DSC curve at $T_e = 98^\circ C$. It is not clear from these data whether or not the compound is a hydrate.

Hygroscopicity studies at $20^\circ C$ showed that anhydrous material stabilised over air with 33% RH to about 3.5% (m/m) water and that "wet" material (53% (m/m) water added) stabilised over air with 43% RH to about 3.5% (m/m) water [6]. The initial XRD powder diffractograms showed no difference between the anhydrous or "hydrated" forms, though differences were detected by nujol mull infrared spectra.

Further DSC work was performed using the method for detection of clustered water in polyethylene proposed by Baker and Cattiaux [7]. The method is based on the measurement of the enthalpy of melting of frozen water after the sample has been cooled to a sufficiently low temperature for the water to freeze. This method will only detect the clustered water present.

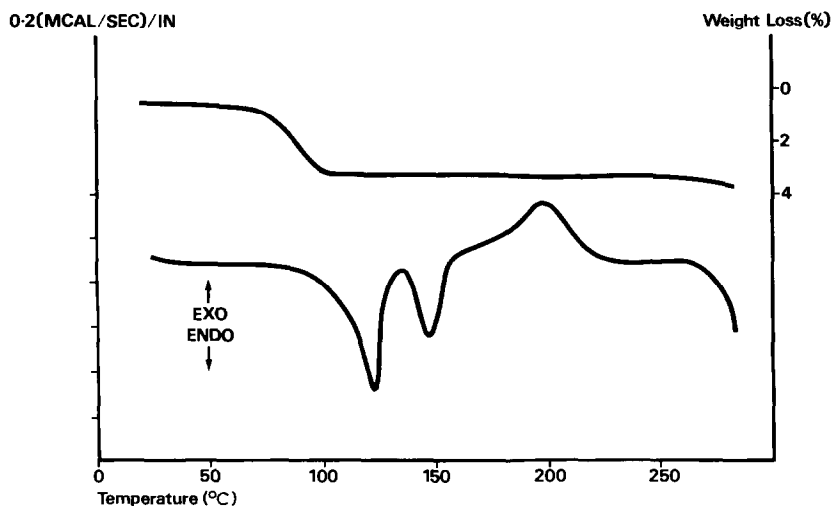


Fig. 1. TG and DSC curves of compound A.

The freely adsorbed water forms a monolayer on the surface of the material and so does not have sufficient near neighbours to form the ice lattice on cooling [7]. Water detected in this way will be truly “free water” and unbound.

Figure 2A shows the DSC curve for water from -50 to 25°C (as a cell calibration), and Fig. 2B shows the DSC curves for compound A and compound A plus water. The DSC curve for compound A alone (Fig. 2B, trace 1) shows no melting endotherm for water. This demonstrates that no clustered water is detected. An estimate of the limit of detection can be obtained from the trace of compound A plus water (Fig. 2B, trace 2). An area of 1 cm^2 was taken as the arbitrary limit which, in this case, equates to a mass of water of about $20\text{ }\mu\text{g}$. For a sample mass of 10 mg this gives a limit of detection of $< 0.2\%$ (m/m).

This clearly shows the water to be non-clustered and therefore either adsorbed to the surface or truly hydrated. Repeating the XRD work with freshly prepared anhydrous material did show differences in the diffraction pattern of the “hydrated” sample. The initial XRD work did not show differences since the anhydrous sample had rehydrated on storage.

The “clustered water” method is also of use when very low moisture contents are required for drug stability. Figure 3 shows the DSC curve from -20 to 55°C of another development drug (sample B) which had a very low water content (0.5% (m/m)) by a coulometric Karl-Fischer titration). The DSC technique gave an enthalpy of 0.41 J g^{-1} equivalent to 0.1% (m/m) demonstrating that 80% of the detected water contamination was adsorbed not clustered. This type of determination could be of value for moisture-sensitive materials.

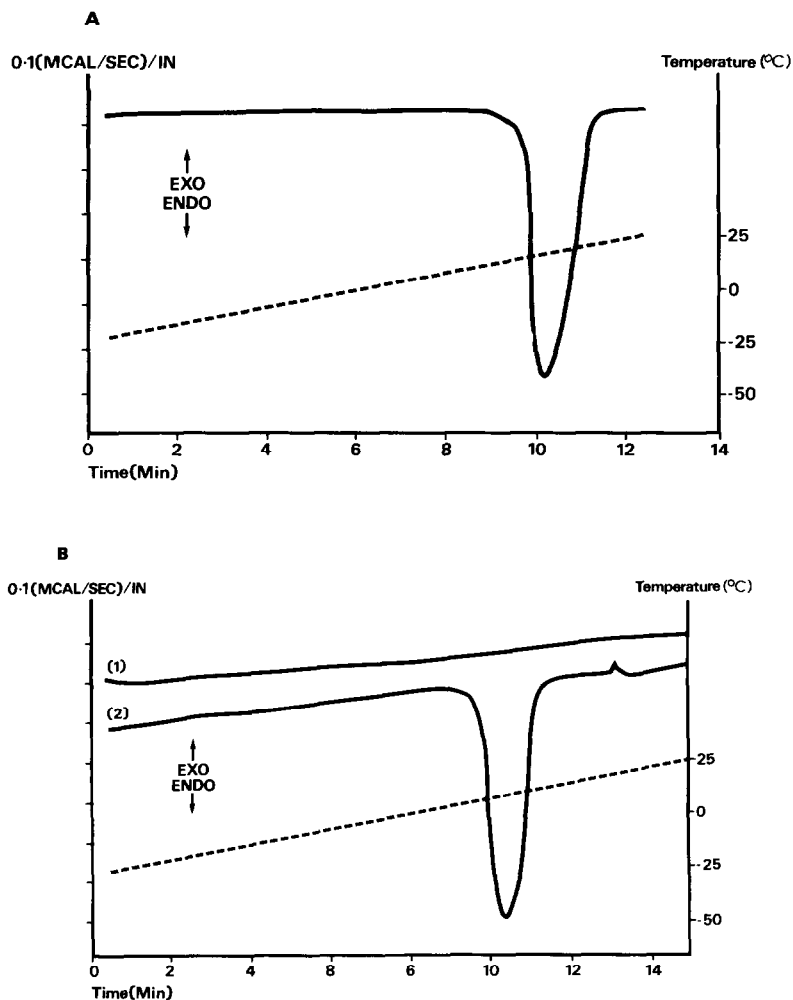


Fig. 2. (A) Cell calibration for water. (B) DSC curves for (1) compound A and (2) compound A plus water.

Figure 4 shows a series of DSC curves for another development compound (compound C), each with different pan configurations: sealed aluminium pans, trace (2), crimped aluminium pans, trace (3) and open aluminium pans, trace (4). These DSC curves show how the pan type can affect dehydration endotherms. It is interesting to note that the open-pan DSC curve shows extra peaks. In order to characterise these extra peaks, hot stage microscopy was performed (see Table 1).

The effects seen in the crimped and sealed pans will be due to the increased internal pan pressure. This delays the moisture loss and masks the melting/recrystallisation transitions; the initial melting is very broad and is not clearly seen on the open-pan DSC curve. Figure 5 shows the compound

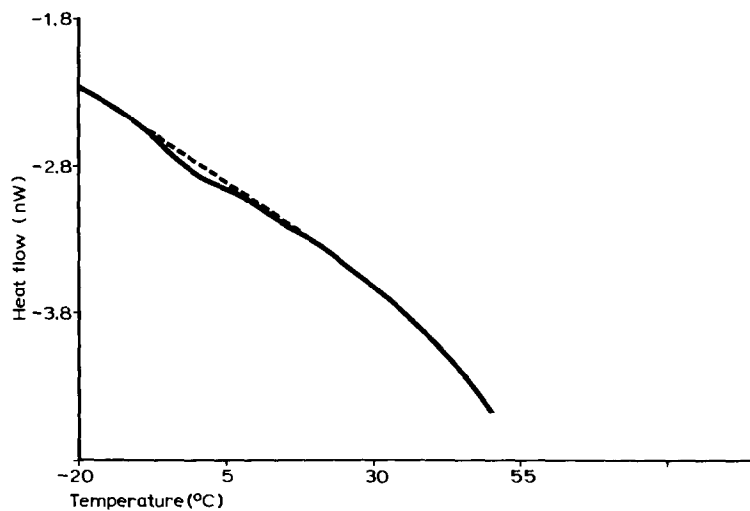


Fig. 3. DSC curve of compound B.

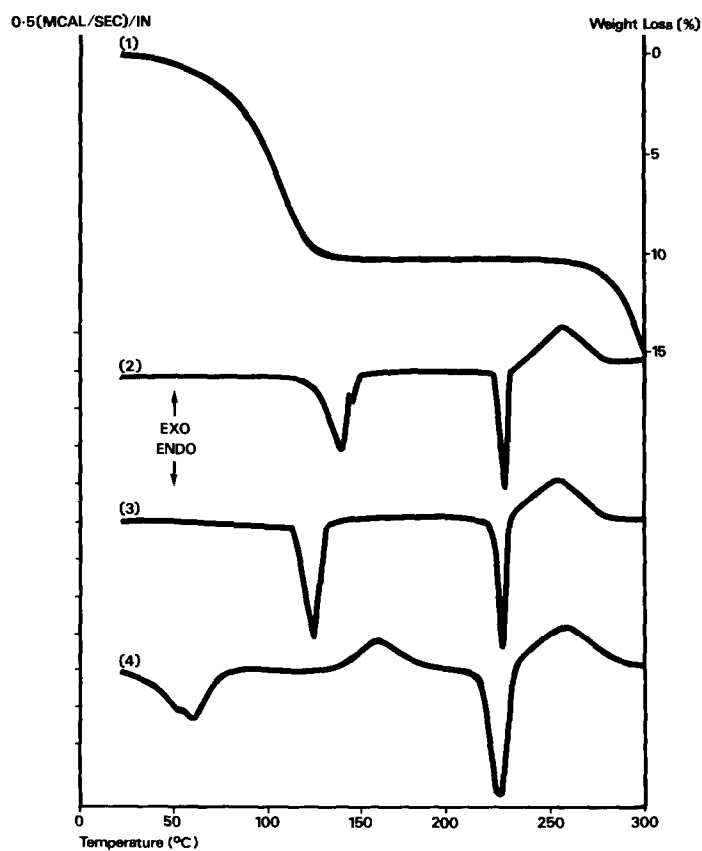


Fig. 4. TG and DSC curves for compound C: (1) TG curve: DSC curves: (2) sealed pan, (3) crimped pan and (4) open pan.

TABLE 1

Summary of thermomicroscopy observations for compound C

Temperature range (°C)	Observation
112–130	Sample melts
140–170	Sample recrystallises
220	Sample melts with decomposition
240–260	Sample undergoes further decomposition

C and compound C plus water traces over the temperature range -50 to 20°C , demonstrating the lack of clustered water.

The thermal analysis of this sample suggests that the material exists in a trihydrate form (theory, 10.6% (m/m) water) which will readily dehydrate to give a metastable anhydrous form which melts in the range 112 – 130°C . A more stable form crystallises from the melt which itself melts at about 215°C . It is unlikely that this behaviour is an example of incongruent melting of a hydrated form of the compound; the weight loss measured by TG is 10.2% (see Fig. 4, curve 4) whilst the initial moisture level, as determined by a coulometric Karl–Fischer titration, was 10.6% (m/m). Further work (powder XRD, IR, NMR) is underway to confirm this behaviour.

Excipient hydrates are also important as they are often the major component in solid dosage forms. Figures 6A and B show the DSC and TG curves of calcium phosphate dihydrate before and after compression; the curves generated after compression were on samples of ground tablets. The DSC results clearly show that the pressure treatment has altered the way the moisture is bound in the excipient, although the total moisture contents, by

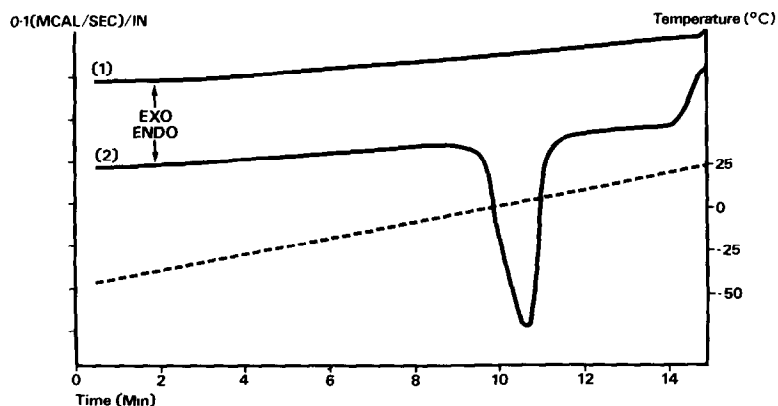


Fig. 5. DSC curves of (1) sample C and (2) sample C plus water.

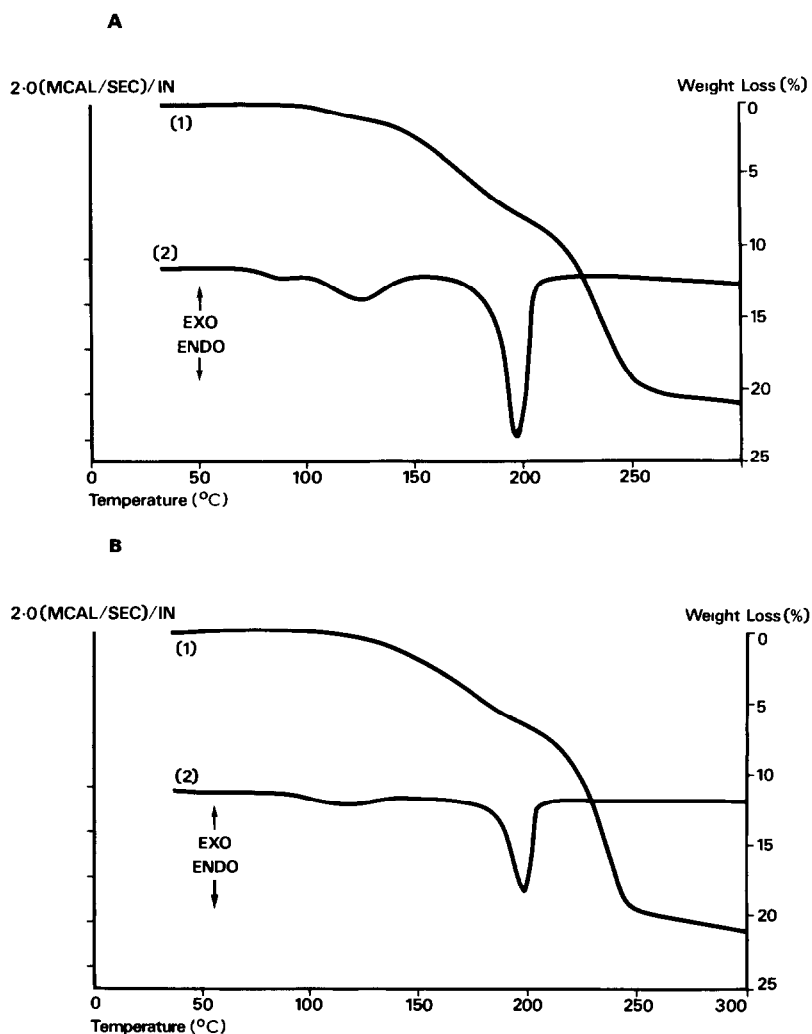


Fig. 6A. TG (1) and DSC (2) curves for $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ before compression. B. TG (1) and DSC (2) curves for $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ after compression.

TG (Figs. 6A and B), are very similar. This might well affect the physical stability of the tablet [8].

The methods are also applicable to solvates. Sample D was identified as a 3:1 ratio of drug to 2-methylpropan-2-ol. Figure 7 shows the DSC curves from -25 to 50°C for the "solvate" (trace 1) and 2-methylpropan-2-ol trace (2). The "solvate" trace (1) shows no melting endotherm for the 2-methylpropan-2-ol (from trace 2, $T_e = 18^{\circ}\text{C}$) showing that the solvent is bound (not clustered) or absorbed to the sample. The minor endotherms detected at T_e 7°C (trace 1) and $T_e - 7^{\circ}\text{C}$ (trace 2) have not been identified.

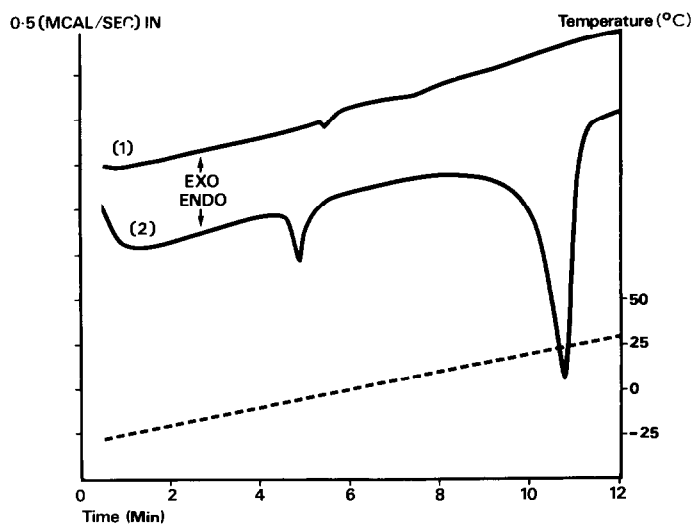


Fig. 7. DSC curves of (1) sample D and (2) sample D plus 2-methylpropan-2-ol.

CONCLUSION

Thermal analysis techniques are very valuable in the characterisation of hydrates and solvates. DSC and TG can often discriminate between free and bound water, although adsorbed water, zeolite-type water and clathrate-type water systems are not easily separated from “true hydrates”.

The thermal analysis data should be used along with data from other techniques, such as IR and XRD, in order to form a definitive characterisation.

REFERENCES

- 1 J. Mitchell, Jr. and D.M. Smiths (Eds.), *Aquametry*, Wiley-Interscience, New York, 1977.
- 2 F. Franks (Ed.), *Water, A Comprehensive Treatise*, Vol. 2, Plenum Press, New York, 1973.
- 3 G.A. Jeffrey, *Acc. Chem. Res.*, 2 (1969) 344.
- 4 M. Kuhnert-Brandstätter and F. Pröll, *Mikrochim. Acta*, 2 (1983) 463.
- 5 M. Kuhnert-Brandstätter and F. Pröll, *Mikrochim. Acta*, 3 (1983) 287.
- 6 M. Beal, unpublished data.
- 7 K.F. Baker and J. Cattiaux, High sensitivity determination of clustered water in polythene by DSC, DuPont Application Brief TA70.
- 8 P.C. Buxton, R.G. Englefield and R.D. Pathak, unpublished data.