

PHARMACEUTICAL APPLICATIONS OF THERMAL METHODS: THE USE OF DSC AND TG IN THE CHARACTERISATION OF ORGANIC AND INORGANIC HYDRATES

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INTRODUCTION

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 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 H₂O molecules). True hydrates may have their water within the co-ordination sphere of the cation (water of co-ordination) 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°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 organic hydrates may behave.

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°C with a matching endotherm in the DSC at T_e = 98°C. It is not clear from this data if the compound is a hydrate.

Hygroscopicity studies at 20°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 [7]. The initial XRD powder diffractograms showed no difference between the anhydrous or "hydrated" forms, though differences were detected by nujol mull infra red spectra.

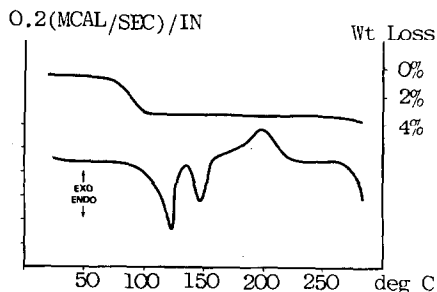


Fig.1. TG & DSC curves of compound.

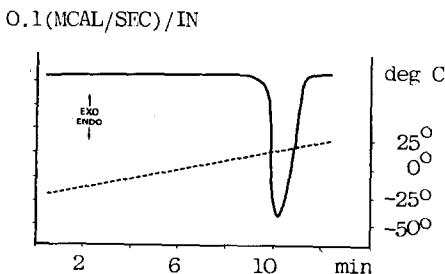


Fig.2A. Cell calibration of water.

Further DSC work was performed using the method for detection of clustered water in polyethylene proposed by K.F. Baker & J. Cattiaux [6]. 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. 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 [6]. Water detected in this way will be truly "free water" and unbound.

Figure 2A shows the DSC curve for water from -50°C to 25°C (as a cell calibration), and figure 2B shows the DSC curves for compound A and compound A plus water.

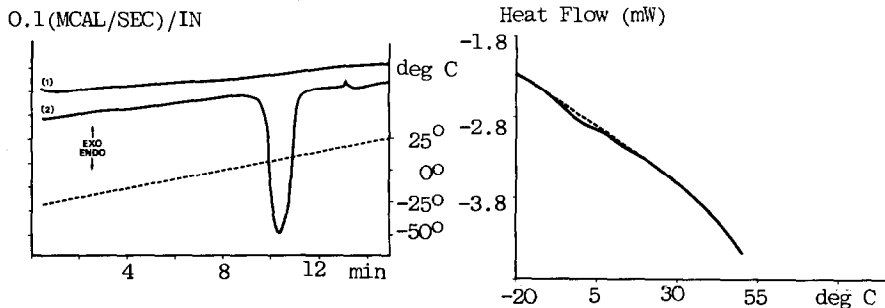


Fig.2B. DSC curves of (1) compound A and (2) compound A + water.

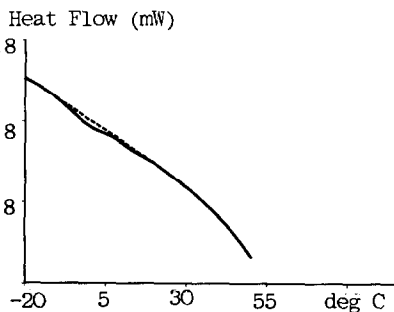
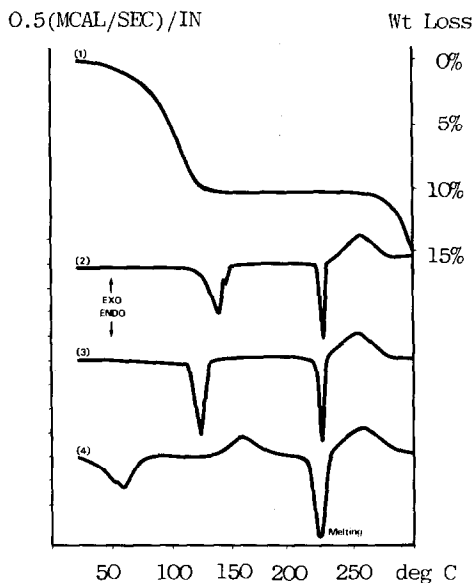


Fig.3. DSC curve of compound B.

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 to the diffraction pattern of the "hydrated" sample. The initial XRD's 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.



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

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

Table 1. Summary of the thermomicroscopy observations for compound C.

Figure 3 shows the DSC curve from -20°C 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 equivalent to 0.1% m/m demonstrating that the 80% of the detected water contamination was adsorbed not clustered.

Figure 4 shows a series of DSC curves for another development compound, (compound C) each with different pan configurations; sealed aluminium pans (2), crimped aluminium pans (3) and open aluminium pans (4). These DSC curves show how the pan type can effect 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.

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° to 130°C . A more stable form crystallises from the melt which itself melts at about 215°C . It is unlikely that the behaviour is an example of incongruent melting of an

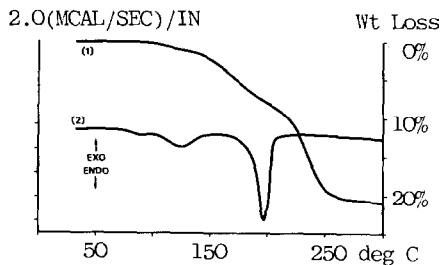


Fig.5A. TG (1) & DSC (2) curves for $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ before compression.

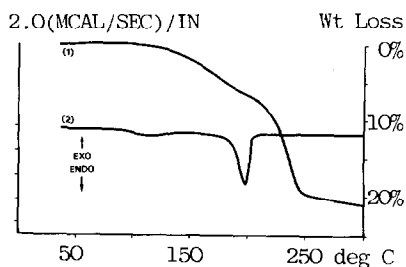


Fig.5B. TG (1) & DSC (2) curves for $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ after compression.

hydrated form of the compound; the weight loss measured by TG is 10.2% (see figure 4(1)) 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 5A & 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 TG are very similar. This might well effect the physical stability of the tablet [8].

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, 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 Jnr. & D.M. Smiths (Eds.), *Aquametry*, 1977, Wiley-Interscience.
- 2 F. Franks (Ed.), *Water, A Comprehensive Treatise Vol.2*, 1973, Plenum Press.
- 3 G.A. Jeffrey, *Water Structure in Organic Hydrates*, *Acc.Chem.Res.* (1969) 2, 344.
- 4 M. Kuhnert-Brandstätter & F. Pröll, *Thermal Analysis of Hydrates of Organic Compounds Part 1*, *Mikrochim Acta* (1983) 2, 463.
- 5 M. Kuhnert-Brandstätter & F. Pröll, *Thermal Analysis of Hydrates of Organic Compounds Part 2*, *Mikrochim Acta* (1983) 3, 287.
- 6 K.F. Baker & J. Cattiaux, *High Sensitivity Determination of Clustered Water in Polythene by DSC*, DuPont Application Brief TA70.
- 7 M. Beal: 8. P.C. Buxton, R.G. Englefield, R.D.Pathak: Unpublished data.