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A REVIEW OF THE APPLICATIONS OF THERMAL METHODS WITHIN THE PHARMACEUTICAL INDUSTRY

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The aim of this paper is to review current applications for thermal methods within the pharmaceutical industry as well as to present some early work on potential applications for two new thermal methods: Hi-Resolution Thermogravimetric Analysis and Modulated Differential Scanning Calorimetry.

Keywords: Hi-Res TGA, MDSC, pharmaceuticals, review

Introduction

The development of a new ethical pharmaceutical, from the initial synthesis to a licence application, can take between eight to twelve years. Thermal Analysis has many useful applications during this period, ranging from support of the initial fundamental chemical and biological research, through preclinical development to the final stages of licence application.

The purpose of this paper is to review some of the established applications for two thermal analytical techniques: Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TG). New developments in thermal analysis, such as the availability of Hi-Resolution TGA and Modulated DSC have added to the list of potential pharmaceutical applications.

Experimental

Materials used in this study were synthesised by SmithKline Beecham as potential drug candidates. Samples were analysed 'as received'.

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A TA Instruments DSC 2910 Differential Scanning Calorimeter with Modulated-DSC option was used to measure the solvation, phase changes and melting of the drug candidates. The DSC was calibrated for temperature and enthalpy using traceable indium of 99.999% purity under the same experimental conditions used for the samples.

A TA Instruments TGA 2950 Thermogravimetric Analyser with Hi-Res option was used to measure the weight loss profiles of the potential drug candidates. Experimental conditions such as heating rate, atmosphere and Hi-Res index are included in the figures. The TG was calibrated with respect to temperature using traceable indium and lead under the same experimental conditions used for the samples. Experimental methods, calculations and data formating were undertaken using a TA Instruments Thermal Analyst 2200 and associated software. The TGA 2950 was used to weigh all DSC samples to an accuracy of 0.1 μg.

Results and discussion

Characterisation

DSC, along with other analytical techniques such as ^{1}H and ^{13}C NMR., Mass Spectrometry, Elemental Analysis and FTIR are used together to characterise and confirm the structure of any new drug candidate.

DSC is used to determine the melting point, heat of fusion ΔH_f and thermal stability. These values can then be compared with those obtained for future batches manufactured by different processes. synthetic routes or locations.

Thermal stability

Although real time stability data is always required, estimates of both the bulk drug and the formulated product stability are always generated. These are conventional storage tests utilising a variety of temperatures and relative humidity. The data is interpreted using the Arrhenius equation:

$$K = Z e^{-E/RT}$$

where K is the specific rate constant at temperature T
Z is the Arrhenius frequency factor
E is the activation energy
R is the gas constant

Large quantities are stored and periodically assayed (main peak and impurities) by chromatographic techniques and an estimate is made of the time required to reduce the concentration of the drug by 5%.

The variable heating rate method of Ozawa is the most commonly applied method used for DSC stability prediction. The method forms the basis of the ASTM-E698 Thermal Stability Test Method. The method is used if an exothermic decomposition is observed before the sample melts. A series of DSC experiments, at heating rates 2 deg·min^{-1} to 20 deg·min^{-1} are then performed. The method assumed that a constant level of conversion/degradation has taken place at the peak maximum. From a plot of ln. Heating rate (β) *vs.* reciprocal peak temperature, the activation energy (E) and the Arrhenius frequency factor (Z) can be derived, as:

$$E = R \frac{d[-\ln(\beta T^2)]}{d[(1/T)]}$$

and

$$Z = \frac{\beta E e^{-E/RT}}{RT^2}$$

The rate constant at various temperatures can then simply be calculated. The method can be checked by aging a sample at the predicted half-life temperature. Any large deviation from the predicted 50% exotherm of the aged sample can be taken as evidence that the method is not applicable for that particular material. Also, any non-linear log β *vs.* ($1/T$) plot would indicate that competing reactions are occurring during the degradation.

Polymorphism and solid state forms

Polymorphism is the name given to the ability of any compound to exist in more than one crystalline form. This phenomenon is of great importance, as each polymorph may have different physical properties, such as density, hardness, solubility and often the polymorphs have differing stabilities.

However, pharmaceutically, we are interested in all solid state forms, which also include amorphous forms (i.e. glasses) and solvates and hydrates. The reason that this is so important, is that at any given temperature and pressure, one form will be thermodynamically more stable. Therefore less stable forms may convert immediately or under conditions of relatively mild stress – such as grinding.

Figure 1 shows the DSC curve for a mixture of two polymorphic forms. The Form I melts at 145°C whilst Form II, the more stable form, melts at 150°C. These two polymorphic forms are a result of recrystallising the material from different

solvents. Form I has been recrystallised from isopropyl alcohol whilst Form II has been recrystallised from methanol.

The need to use a range of techniques to fully characterise a material is illustrated by the DSC trace in Fig. 2. The material melts sharply at 152°C, but their is a shift in baseline before and after melt. Also, Hot-Stage Microscopy had indicate a 'transition' at around 130°–135°C, but nothing is observed in the DSC curve.

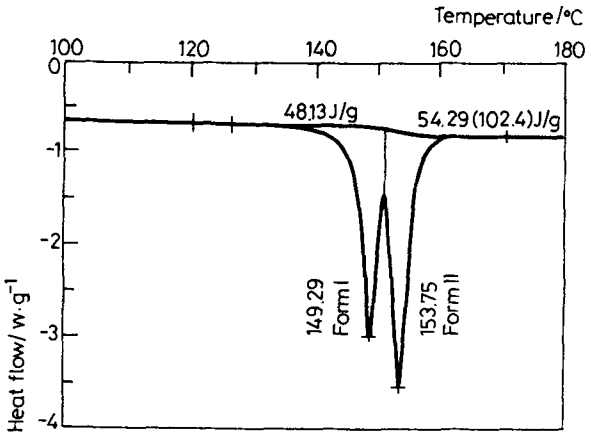

Fig. 1 DSC scan of a drug candidate comprising two polymorphic forms

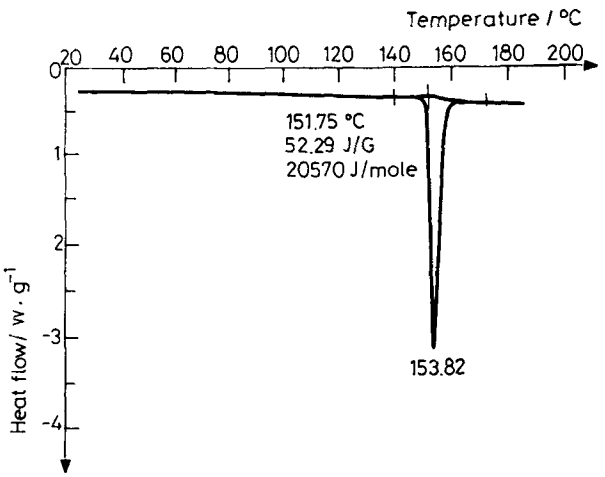

Fig. 2 DSC scan of a potential drug candidate

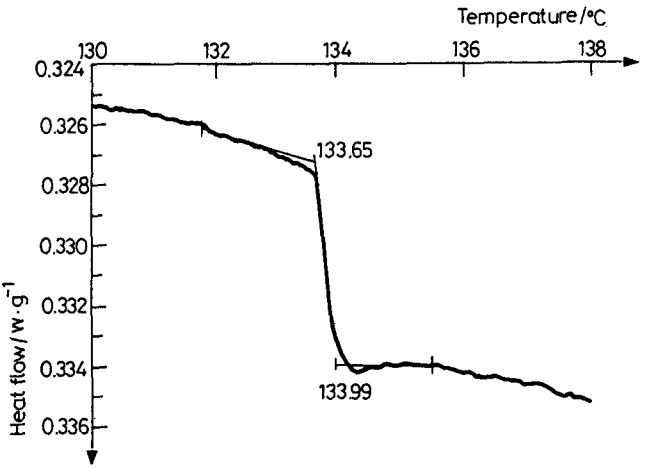

Fig. 3 Expanded area of the potential drug candidate to show a small heat capacity change

Expanding the data between 130° and 138°C (Fig. 3) reveals a small heat capacity change in the sample. Above this temperature the material was found to start loosing weight and this is attributed to the cause of the non-linear DSC baseline.

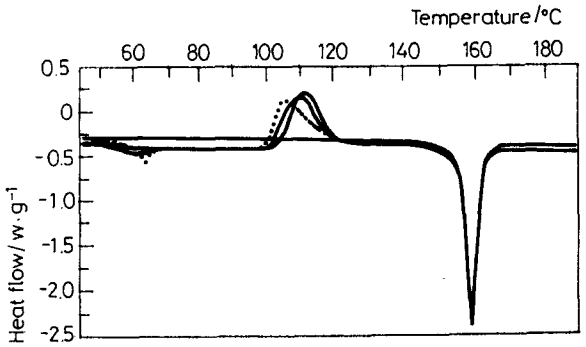

Fig. 4 DSC scan of the potential drug candidate after cooling from the melt at different rates. Drug 'As received' —— ; After quench cooling —— ; After cooling at 5°C/min —— ; After slow cooling -----

If the material is allowed to cool down it forms an amorphous glass at room temperature. The rate of cooling has an effect upon the nature of the glass formed as shown in Fig. 4. When the amorphous material is heated the first transition ob-

served is a glass transition at 55°C followed by crystallisation between 90° and 110°C. Finally, the crystalline material formed melts again at 145°C.

The temperature at which the crystalline material melts after having been heated from the amorphous state is around 7°C lower than that of the 'as received' crystalline material. This may be due to the formation of a lesser stable polymorph when heated from the amorphous state.

Purity

Melting point determinations have long been used as a method of purity assessment of organic materials [1]. The DSC method is based upon the well known Van't Hoff equation:

$$T_s = T_o - \frac{R\,T_o^2\,X_2}{\Delta H_F}\,\frac{1}{F}$$

where T_s is the Sample Temperature (K)

T_o is the Theoretical Melting Point of the 100% pure compound (K)

R is the Gas Constant (1.987 cal·mol^{-1} K^{-1})

X_2 is the Total mole fraction of impurity

ΔH_f is the Heat of fusion of pure compound (cal·mol^{-1})

F is the Fraction of sample melted.

A number of limiting conditions apply to the use of this equation [2], including:

1. The material must not decompose at or near its melting point.
2. The impurities form a eutectic with the main component (i.e. the impurities are soluble in the liquid phase of the pure component).
3. The impurities are not soluble in the main component in the solid phase (i.e. no solid solution are formed).
4. The material is at least 95 mol% pure.

A plot of $1/F$ against temperature can then be used to calculate the slope, from which the mol% purity of the material may be determined. Partly because of the lack of eutectic-point detection, the curve is not a straight line and a correction factor X must be added to each fraction of the curve.

Figure 5 shows the DSC curve and Van't Hoff plot for a typical drug candidate. A small sample size (~1.5 mg) and slow heating rate (1 deg·min^{-1}) is used to minimise thermal gradients within the sample. The melting point of this material has been suppresses by only 0.05°C due to an impurity of 0.08 mol%. A small correction of only 1.76% has been required to linearise the Van't hoff Plot,

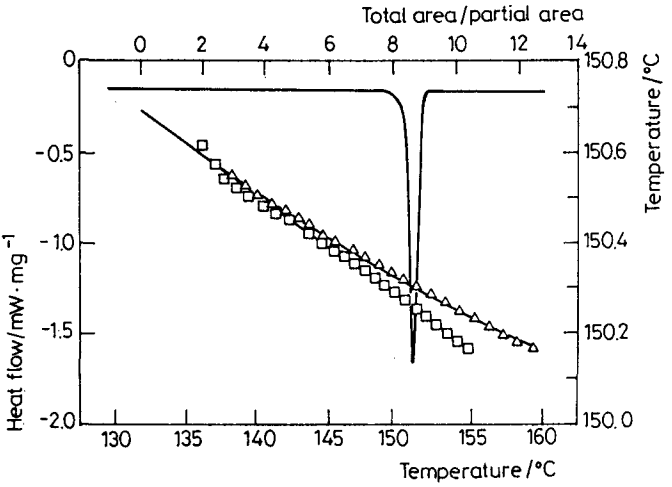

Fig. 5 DSC purity scan and Van't Hoff plot for the potential drug candidate. Purity: 99.92 mole %, melting Pt: 150.7°C, depression: 0.05°C, ΔH: 24.3 kJ/mole, correction: 1.76%, mol. weight: 393.4 g/mole, cell const: 1.094, onset slope: –13.45 mW/°C

if corrections of over 10–15% are required then the sample needs to be reanalysed using either a larger sample size or faster heating rate.

New thermal methods

Modulated DSC

In Modulated DSC a sinusoidal ripple is overlaid onto the conventional linear temperature ramp. If the modulation has low amplitude but high frequency it is possible to obtain a high instantaneous heating rate even though the underlying heating rate is low. The complex signal produced during an MDSC experiment can be deconvoluted using a discrete Fourier Transform. The deconvoluted signal provides information about the reversing and non-reversing nature of each DSC event.

Figure 6 shows some early work on the characterisation of polymorphism by MDSC. It should be stressed that this work was completed on an early version of the MDSC so results may change as the system is further refined.

This material has two polymorphic forms that melt 3°C apart. During the melt of each form there is both a reversing and non-reversing signal. If the material was to recrystallise from the melt there would be a large reversing signal and small non-reversing signal. Conversely, if the material was to cool down to form a glass there would be a large non-reversing signal and small non-reversing sig-

nal. At this early stage in the development of MDSC it is proposed that the ratio of reversing and non-reversing signals for a material may be an indication of the purity of the crystal lattice. The ability of the lattice to change, over a very short time scale, from semi-liquid to semi-solid would depend upon the level of lattice impurity.

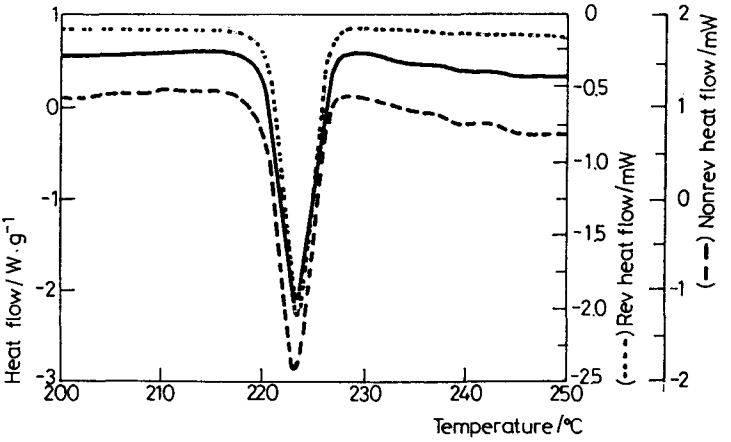

Fig. 6 MDSC scan of a single polymorphic form, Form I

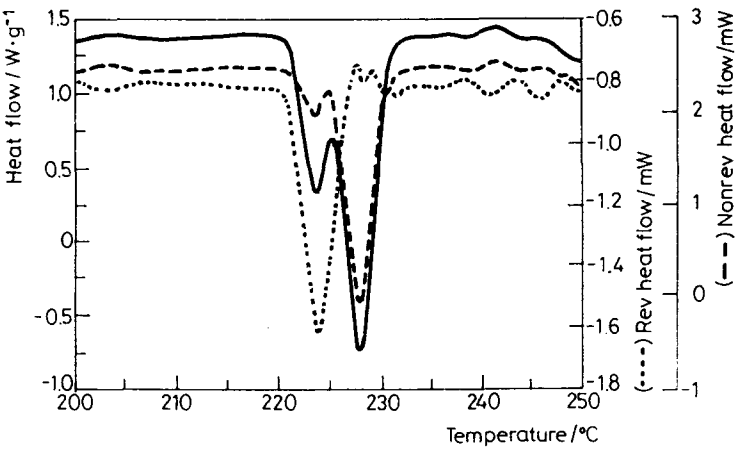

Fig. 7 MDSC scan of a mixture of two polymorphic forms, Form I & Form II

When the two forms are mixed, Fig. 7, the conventional DSC signal shows the melting of the two individual forms. However, the ratio of reversing and non-

reversing signals is very different and the reversing signal for Form II has completely disappeared.

Other work is in progress to evaluate the ratio of reversing and non-reversing signals for a range of materials and to see if there is a correlation with other physical properties.

Hi-Resolution TGA

In Hi-Resolution TGA the heating rate experienced by the sample is a function of the weight loss profile. In simple terms the heating rate is slowed down during a weight loss transition and increased when there is no weight loss transition. This leads to increased resolution, with respect to temperature, of overlapping weight loss events.

The application of this approach to hydrated materials yields improved resolution where the hydrate looses water in more than one step. Loosely bound water will have time to evolve before more strongly bound water. Consequently Free/Bound water is more easily characterised and hydrated water that is held at different points within the lattice can be recognised.

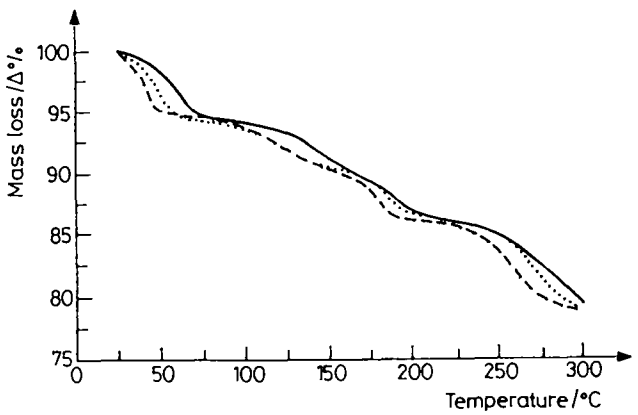

Fig. 8 Comparison of Hi-Res and conventional TG of a hydrated drug candidate. Solid line = conventional TG, Short dash = Hi-Res index 4, Long dash = Hi-Res index 5

Figure 8 shows the weight loss profiles for a hydrated drug candidate run under conventional and Hi-Res TGA. Conventional TG shows 3 weight losses prior to the material degrading at 250°C. However, the amount of weight lost at each step is not stoichiometric. This was initially thought to be due to the material supporting fractional hydration levels.

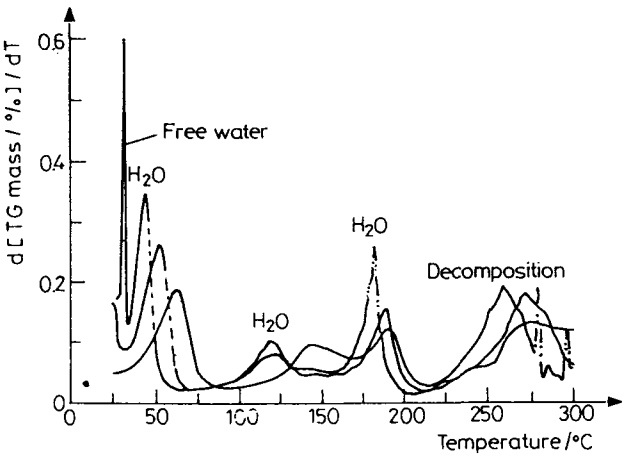

Fig. 9 DTG curves of Hi-Res and conventional TG of a hydrated drug candidate. Conventional DTG —— ; Hi-Res TG index 4 ----; Hi-Res TG index 5 ------

When the sample is analysed by Hi-Res TGA, the first weight loss step is split into two and superior resolution is obtained for the second and third waters. The splitting of the initial weight loss is due to the presence of free water absorbed onto the surface of the material. Conventional TG does not resolve this free water from the first water of hydration. This is more easily shown in Fig. 9 which depicts the first derivative of the conventional and Hi-Res TGA experiments.

Conclusions

The use of new techniques such as Modulated DSC and Hi-Res TGA further enhances the value thermal methods within the pharmaceutical industry.

Modulated DSC provides further solid-state characterisation of organic materials by providing information about the reversing and non-reversing nature of enthalpic transitions. The ratio of reversing to non-reversing behaviour provides may provide information about the nature of polymorphic materials. Also, MDSC may prove useful in providing information about the quality of the organic lattice and crystal purity.

Hi-Resolution TGA provides enhanced resolution of overlapping weight losses and aids in the characterisation of free/bound water, solvation and hydration.

References

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Zusammenfassung — Gegeben wird ein Überblick über aktuelle Anwendungen thermischer Techniken in der Pharmaindustrie sowie eine Darstellung zweier früherer Arbeiten über potentielle Anwendungen zweier neuer thermischer Methoden: Hochauflösende Thermogravimetrische Analyse und Modulierte Differential-Scanning-Kalorimetrie.