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Applications of thermal analysis in the pharmaceutical industry*

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Abstract: Thermal analysis includes all methods measuring some parameter during the heating of a sample. Differential scanning calorimetry (or differential thermal analysis) where the parameter is heat flow into and out of the sample and thermogravimetry where the parameter is the weight change of the sample are of great value for the pharmaceutical industry.

Characterisation of drug substance, excipients, and packaging material: identification, purity, polymorphism, solvation, stability, . . ., may be routinely done. Further examples demonstrating the use of these methods for the development of the dosage form are given: choice of the salt form, phase-diagrams, drug substance–excipient interactions, physical changes on processing or during storage, and even analysis of the dosage form.

Keywords: *Differential thermal analysis; differential scanning calorimetry; thermogravimetry; purity; polymorphism; solvation; stability; raw materials; excipients; dosage form.*

Introduction

Thermal analysis includes all methods which measure some parameter and its dependence on temperature while heating a sample. The two techniques mainly used in pharmaceutical analysis are:

Differential scanning calorimetry or differential thermal analysis where the parameter is heat flow into and out of the sample, and thermogravimetry where the parameter is the weight change of the sample.

Differential thermal analysis has been developed by Le Chatelier as early as 1887. The pharmaceutical industry became interested in the method only in the years 1960–1970 with the appearance on the market of the first quantitative differential scanning calorimeter [1].

An explosion of interest in the technology followed, due to the wide range of applications in pharmacy. The technique is even described in the USP. But the interest for its routine use decreased because at that time neither software nor comfortable hardware were available. A purity analysis with a planimeter and regression calculation

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without a computer is a tedious process requiring at least 2–3 h, not át all adequate for quality control.

Now, due to technological improvement and better understanding, thermal analysis is rapidly becoming a powerful tool in the arsenal of techniques that is currently available to the analytical chemist.

In the near future, the general use of robotics will make the methodology as essential in every laboratory [2].

Principles and Experimental Factors

Principle of differential scanning calorimetry (DSC)

Two ovens are linearly heated. One oven contains the sample in a closed pan, the other one contains an empty pan as a balance, called a reference pan. Two methods of measurements are generally used. If the sample pan and the reference pan are heated linearly, they will initially be at the same temperature. If a change such as melting occurs in the sample, energy is used by the sample because the process is endothermic. Because of the necessary energy of melting the temperature remains constant in the sample pan. Thus, a difference of temperature occurs between the sample pan and reference pan.

In the first method called "heat flux DSC" the instrument measures this temperature difference. Through calibration this temperature difference is transformed into heat flow dq/dt.

In the second method, which is called DSC, two individual heaters are used in order to monitor the individual heating rates. A control system regulates the temperature difference between sample and reference. If any difference is detected the individual heatings will be corrected such that the temperature is kept the same in both pans. That is, when an endothermic or exothermic process occurs, the instrument delivers the compensation energy which must be given in order to maintain equal temperature in both pans.

In the first case temperature is the primary measurement, in the second case energy. Each instrument needs calibration and can deliver the same information: heat flow as a function of the time (or temperature). For first order transitions, like melting or crystallisation, the integration of the curve gives the energy involved in the transition. For second order transitions, the signal gives changes of the specific heat, for example for glass transitions in polymers.

Thermogravimetry (TG)

Here too, a sample pan and a reference pan are used, one pan for each side of a balance. The sample pan is enclosed, without contact, in an oven. This oven is linearly heated. The balance is cooled in order to maintain a constant temperature in the weighing mechanism.

The TG signal is the change of the weight versus the time or the programmed temperature. The derivative curve DTG is very often used in order to make the different steps more evident.

Experimental factors

One characteristic of these methods is that curves made with different instruments cannot be compared like fingerprints. Corrections must be calibrated or calculated depending on the instrument used. Great care must be given to the temperature. The

temperature plotted on the abscissa is in some instruments the programmed temperature, not the real temperature in the sample. The actual temperature depends on the instrument and the heating rate. Modern instruments with a computer allow one to obtain the actual temperature of the sample directly.

Great efforts have been made in the last years in order to "validate" the different instruments not only in comparing both measurements' principles and results [3–9], but also in determining the influential parameters: heating or cooling rate, particle size, weight, resolution, atmosphere, etc. [10–15].

The problem of finding generally accepted standard materials for temperature or heat is not resolved (transition points or melting points [16–19]). Less work has been done for TG, due to the difficulty in finding standards. Magnetic transitions and dropping weight of metals are the most recent proposal [20, 21].

Some thermodynamic basics

All transitions or reactions where energy changes are involved may be measured by DSC. All transitions where a weight change is involved are detected by TG. For use in the pharmaceutical area we must consider:

For a single product. Specific heat, glass transition, melting, boiling, sublimation, decomposition, isomeration.

For mixtures. (a) Hydrates or solvates, or volatile compounds in the formulation: loss of water or a volatile compound (quantitation) before or during the melting; (b) mixtures of solid compounds:

(b.1) no interaction in the solid state
miscibility in the melt: eutectic behaviour, purity determination;
If the compounds are not miscible in the liquid state: analysis of the compounds in the dosage forms. The DSC curve of the mixture is the addition of the DSC curves of each compound;

(b.2) interaction in the solid state
solid solution, amorphous state, complex formation or compounds, chemical reactions.

Applications of Thermal Analysis for Raw Materials, Excipients, Packaging Materials

The applications of thermal analysis in the pharmaceutical industry are growing, especially for analytical purposes [22–28]. A recent overview article has been published by H. Wollmann and V. Braunn which mentions literature on approximately 500 compounds [29].

Identification purposes and determination of thermodynamic parameters

Through two parameters: heat and temperature, or weight and temperature, the typical DSC or TG curves of single products allow their identification.

The melting DSC behaviour of polymers is used for identification of packaging material, the glass transition of amorphous cellulose derivatives used in film coating, of polyvinylpyrrolidone and of biodegradable drug carriers [30–32] have been studied. Discrimination between several types of polyvinylpyrrolidone is demonstrated in Fig. 1.

Figure 2 deals with the behaviour of a drug carrier, L-polylactic acid. After the first

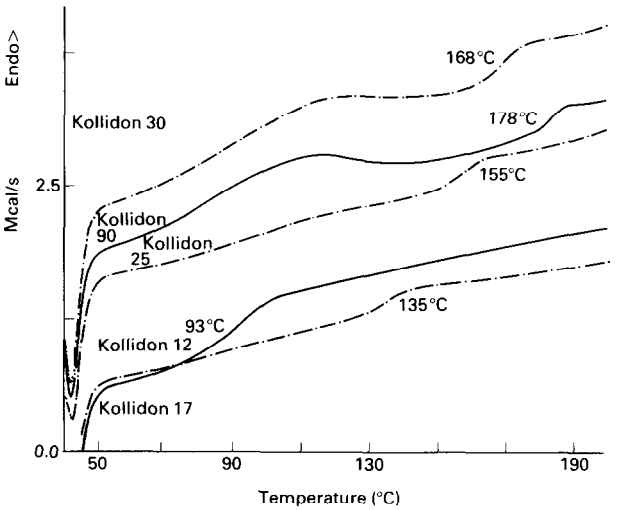

Figure 1
Differentiating identification of polyvinylpyrrolidone (Kollidon) by means of glass transitions.

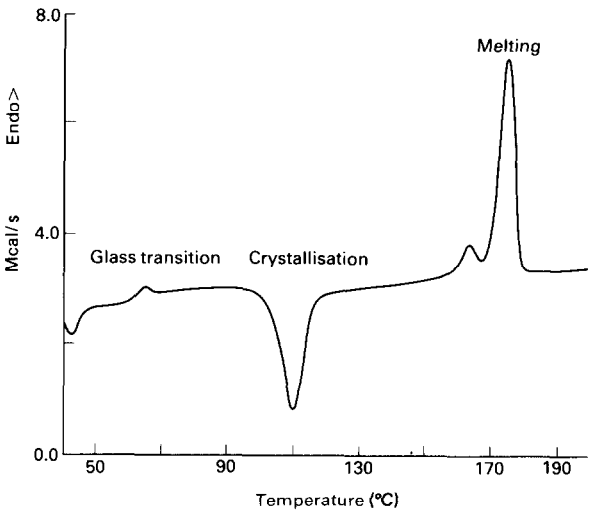

Figure 2
DSC second run of quenched L-polylactic acid: glass transition, crystallisation and melting. The first run shows only melting behaviour.

run, the melting of the crystalline sample, the second run of the quenched (amorphous) sample shows the glass transition, crystallisation and further melting.

Most inorganic hydrates used as excipients may be quickly identified through typical dehydration and melting DSC curves. If TG curves are carried out in parallel, the identification is quite selective for compounds like lactose dihydrate and anhydrous (α and β), calcium sulphate dihydrate or hemihydrate, sodium phosphate dibasic, anhydrous, heptahydrate, sodium phosphate monobasic, monohydrate, sodium phosphate tribasic, sodium carbonate, etc.

Study of polymorphism

The existence of different crystalline modifications (and amorphous states), of a single compound is called polymorphism. The crystalline modifications melt in the same liquid phase, but all thermodynamic parameters in the solid state are different: melting, sublimation, kinetics, stability, solubilities and — what is extremely important for the dosage form — different dissolution rates and bioavailabilities [33–30].

Three types of DSC-curves may be obtained.

(a) Solid–solid transition before melting. The energies of these transitions are generally small. The transition is reversible (enantiotropy) or irreversible (monotropy), Fig. 3 for the case of penicillamine.

(b) Melting of the crystalline form and recrystallisation to a second form from the melt which has a higher melting point, i.e. substances with two melting points. Depending on the heating rate, processes a and b may overlap leading to misunderstanding and difficulties in interpretation when identifying mixtures (e.g. mannitol in Fig. 4).

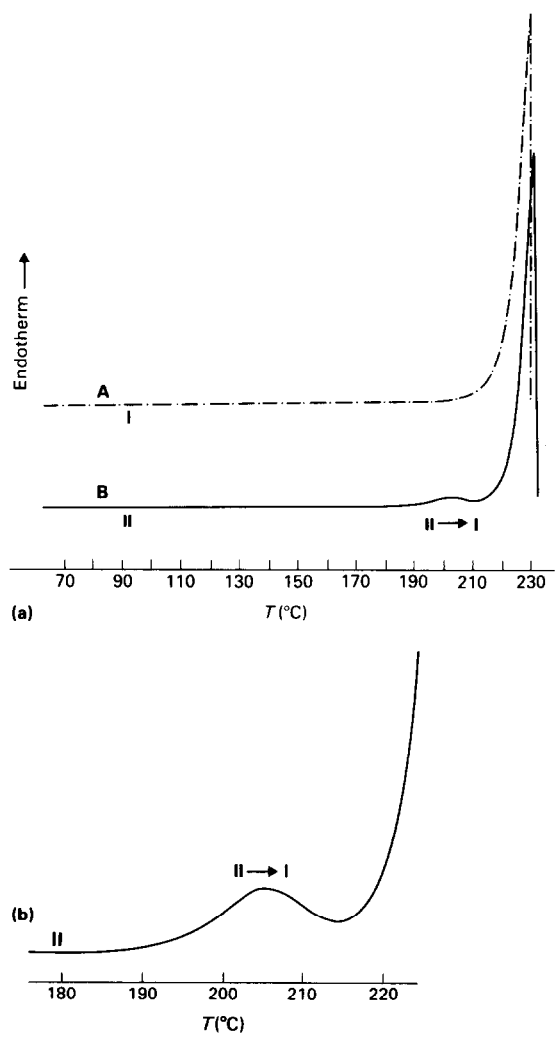

Figure 3
Solid–solid transition. Example of Penicillamine (20°C min^{-1}): (a) range 20; (b) range 2.

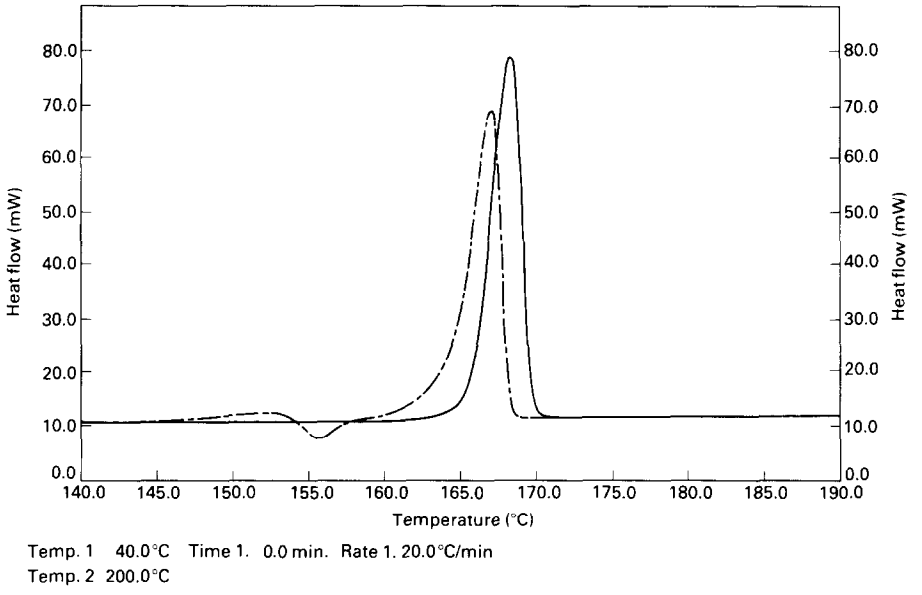

Figure 4
Two melting points. Example of two batches of mannitol.

(c) Each crystalline form melts without any transition to the other form, neither in the solid state nor in the liquid state. The melting points may differ by only 1°C or have a difference as great as 50°C or more. The melting energies may be very different. This case is the most favourable case for quantitation of polymorphism as shown in Fig. 5. Here we can detect less than 5% of form II in form I [40].

Not only active ingredients, but also quite a lot of usual excipients (dyestuff, waxes, sugars, glycerides, propylgallate, aspartame, etc.) are problematic in that they undergo polymorphism. Recently it has been published [41] that different forms of sorbitol give formulation problems, the γ stable form being most suitable. We include now DSC and TG in the quality control of sorbitol (Fig. 6). Furthermore the purity may be determined.

For mixtures of amorphous and crystalline forms, without crystallisation of the amorphous in crystalline state during heating, the crystallinity may be calculated from the melting endotherm.

Hydrates and solvates — pseudopolymorphism

Hydrates and solvates give rise to the same problems as polymorphs because of their different properties in the solid state.

TG combined with DSC allows the best understanding of these species, especially differentiation between polymorphism and pseudopolymorphism. For a great number of substances, crystallisation in different solvents gives solvates which on drying may give anhydrous forms with different properties, especially solubilities or hygroscopicity. Figure 7 deals with a very hygroscopic salt. It had been decided to crystallise it as a stable dihydrate from an isopropanol–water mixture. Depending on the crystallisation conditions, an undesirable solvate was obtained as detected by means of DSC/TG. Water/ethanol mixtures are very often chosen for recrystallisation since they are not toxic. Unfortunately, undesirable mixtures of solvate/hydrate may result as demon-

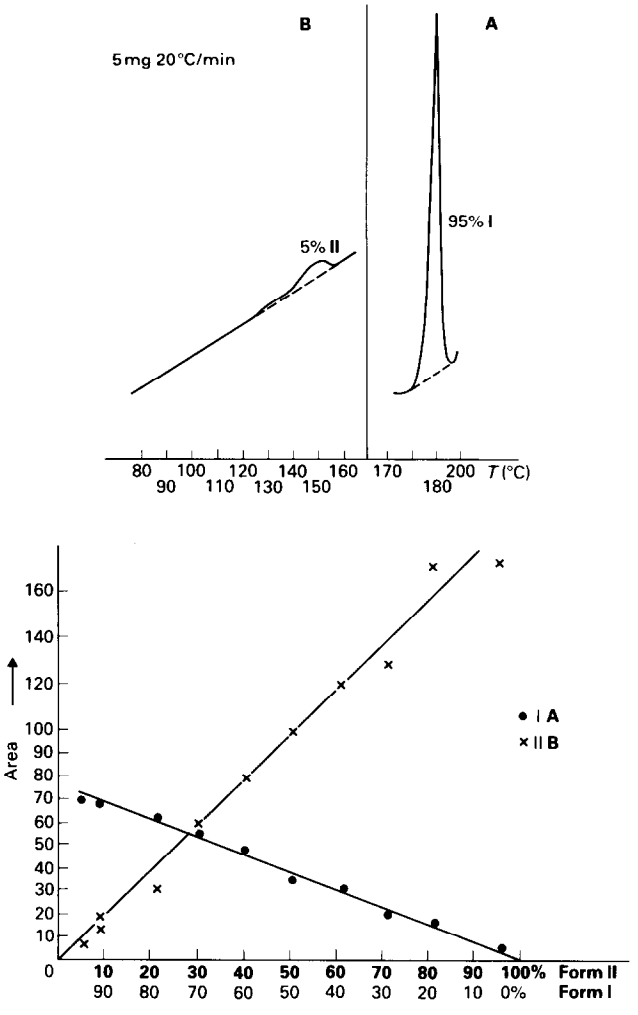

Figure 5
Determination of crystalline modification II in modification I. Scale A: 41.9 mJ s^{-1} and scale B: 4.2 mJ s^{-1}.

strated in Fig. 8. According to Nyqrist [46], the hydrate form of a new chemical entity is dominating 3:1. We suggest the use of thermal analysis for studying different salts of a new drug substance: the polymorphism behaviour and different steps of hydration are quickly identified, allowing the best choice of the salt at a very early stage of development [29] (Fig. 9).

Entrapped solvent

Solvent is very often entrapped in crystals and escapes only during melting or dissolving. A TG-result is more quickly obtained than a GC analysis of the sample.

TG for determination of volatile compounds

TG uses only 1 mg or less, which is a big advantage for potent substances such as peptides. In addition, classical loss-on-drying conditions (in vacuum or at 105°C) may not

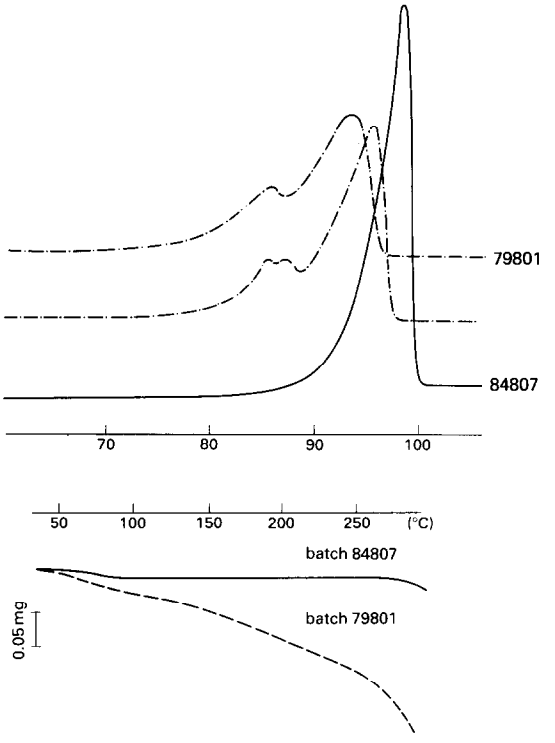

Figure 6
Sorbitol. DSC and TG curves of different batches. Only the γ Form is accepted (batch 84807). The old quality has a different stability behaviour (TG).

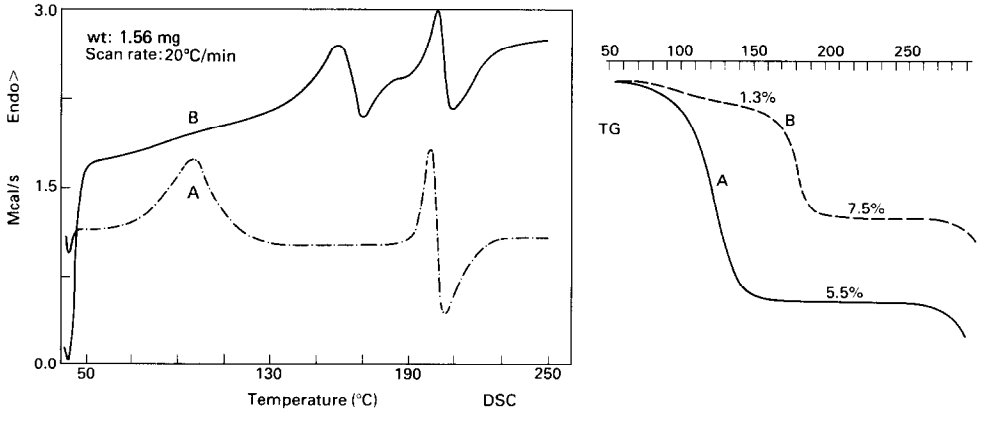

Figure 7
Quick differentiation between a solvate (B) and the desired dihydrate (A). I: DSC curves; II: TG curves.

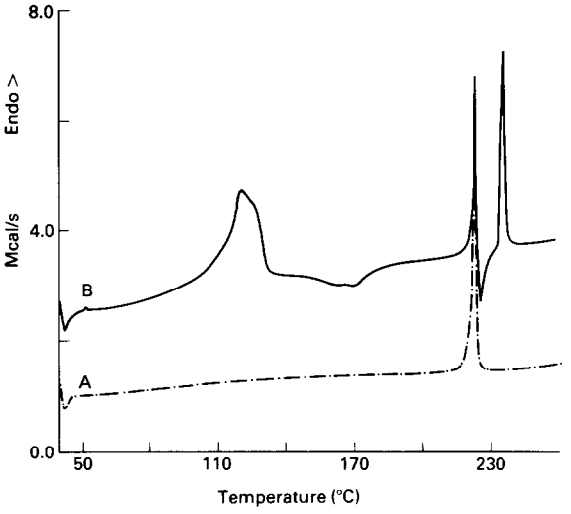

Figure 8
DSC curve of a solvate–hydrate mixture after equilibration in water/ethanol. Melting then exothermic crystallisations and 2 meltings of anhydrous forms. A: usual anhydrous form; B: solvate–hydrate mixture.

Choice of the salt of the drug substance = DSC/TG

	hmo	hml	hfu	hta
DSC Curve	1 form	mixture	1 form	mixture
92% r.h. DSC	no change	change	no change	hydrate
TG	0%	0.22%	0%	6%
Polymorphism				
Isopropanol	no change	change	no change	change
Ethanol/water	no change	-	no change	-

Conclusion: From these studies hml and hta are rejected.
hmo and hfu have equivalent stability behaviour
hmo being more soluble has been chosen for further development.

Figure 9
Choice of the salt of the drug substance = DSC/TG.

be possible for a substance due to sublimation or decomposition: this can be solved by TG, where no decrease in the curve occurs before melting. We use TG routinely for a loss-on-drying assay, not only for a drug substance and excipients but also for all our reference standards.

Purity determination

The eutectic behaviour between the drug substance (or excipient) and its impurities is the basis for the purity determination by DSC. Figure 10 shows the phase diagram of a eutectic: melting curves as a function of the concentration of the 2 components in the mixture. The corresponding DSC curve is given in Fig. 10: an endotherm is observed at the eutectic temperature, then the melting of crystal A occurs. Impurities affect DSC the curve by depressing the melting point and broadening the melting curve. The amount of impurities may be calculated from the melting point depression $\Delta T = T_0 - T_m$. The van't Hoff law for diluted solutions is

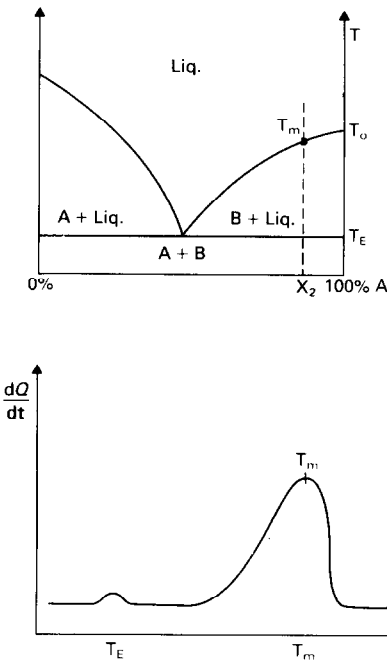

Figure 10
Two components phase diagram showing eutectic behaviour and DSC curve corresponding to the mixture x_2.

$$x = \frac{-\Delta T \cdot \Delta H_f}{RT_o^2},$$

where x is the mole fraction of impurities, ΔT the melting depression, ΔH_f the molar enthalpy of fusion of the pure raw material, T_o the melting point of pure material and R the gas constant (1.987 kal. $mol^{-1}k^{-1}$ of 8.314 $Jmol^{-1}K^{-1}$).

The DSC procedure does not directly measure ΔT, but can be used to calculate it from the melting curve with no need for the pure material. At the eutectic point, all of B is in the liquid phase. During the melting of A after the eutectic the concentration of B varies in the liquid phase. This causes the broadening of the DSC curve.

The melting curve is divided into small portions. The melted fraction F_i is calculated for each point and the curve T_i as a function of $1/F_i$ is plotted, where T_i is the temperature at fraction F_i.

From the relation $T_i = T_o - \Delta T\ (1/F_i)$ the slope ΔT and the ordinate T_o can be calculated. In part because of the lack of the detection of a eutectic, the curve is not a straight line, and a correction factor K must be added to each fraction of the curve. This is best done with a calculator.

Characteristics of this determination follow:

Impurities which have an eutectic behaviour are measured;

The sum of impurities must be <2%;

The result is expressed in mole % without knowledge of impurities;

Pure material is not needed;

Small amounts of material are used (1–2 mg or less);

If decomposition occurs during melting it can give erroneous results;

The purity results are obtained after less than 1/2 h;

For discussion about advantages, limits and calculations see [43–45]. Figure 11 deals with several batches of β-Hydroxypropyltheophylline from different manufacturers: the TLC purity method of quality control could not detect any difference.

DSC allows us to recognize and differentiate polymorphism and purity problems. The quality control used for a raw material was an HPLC assay. A sample had a melting point below the requirements, but all other parameters complied. DSC curves showed a new, quite different situation. The sample was a low melting crystalline modification with 98% purity but surprising new information appeared: the reference batch was very impure and furthermore a mixture of 2 crystalline modifications.

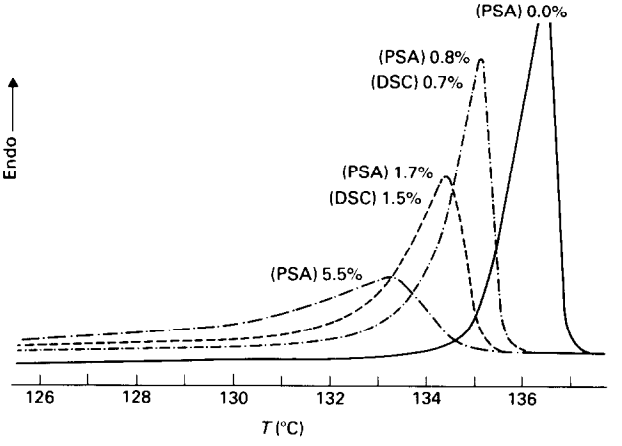

Figure 11
β-hydroxypropyltheophylline: DSC curves of several lots of different manufacturers. Same purity by TLC.

Figure 12 shows the great value of DSC for stability screening [10, 22, 23]. Degradation products may have quite different behaviour in TLC or HPLC, leading to falsely optimistic conclusions. In this example the TLC or HPLC purity method were not able to detect the instability of the compound due to quite different properties of the degradation products (for combined use of TLC and DSC in stress experiments see [46]).

DSC helps to very quickly choose the right purification conditions [26, 27]. One further advantage: the DSC curve with a given instrument is a fingerprint, and we can detect cross contamination or batch mixups. It is very efficient for reanalysis of the control stock. Furthermore, due to the small weight, any inhomogenity of a sample can easily be detected [10, 26]. DSC will surely replace the melting point determination in the pharmacopoeia for both a drug substance and excipients.

Determination of enantiomeric purity

The phase diagram of antipodes is only in 5% of all cases an eutectic. 90% of the time the 2 antipodes give a racemic compound. Once the phase diagram type is known, quantitation is possible using the Schröder von Laar equation (eutectic) or Prigogine–Defay equation (racemate) [47–49].

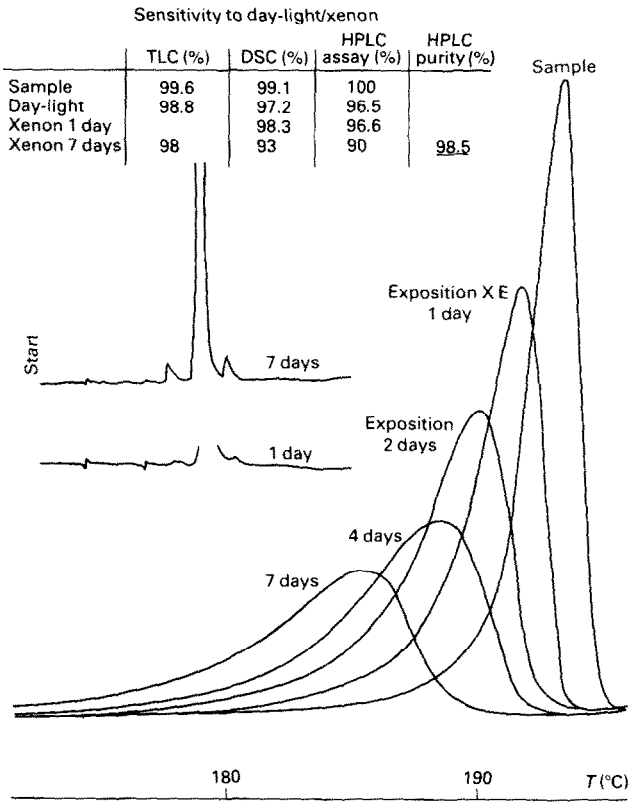

Figure 12
Advantage of DSC in stability: DSC screening of stressed samples. Comparison of DSC results with HPLC assay.

Decomposition and oxidation

Oxidation and decomposition are studied to determine the safety of the manufacturing process. In some cases oxidation behaviour is the best characteristic for the choice of excipient [50], quality control of vegetable oils or polymers.

Use of DSC and TG for Galenical Form

Help for preformulation

Choice of the best salt is the prerequisite for development of a dosage form.

Use of DSC for prediction of compatibilities has been suggested, but only in a few cases is prediction of chemical interaction possible [51–54]. Nevertheless, the DSC curves of mixtures help one understand the physical interaction between a drug substance and excipients.

Eutectic behaviour does not mean incompatibility. But it may explain difficulties with a given composition during processing.

We studied the problem of a composition which gave difficulties during tabletting. The reason was that the excipients and drug substance had an eutectic behaviour with a

strong depression of the melting point. Although it contained high melting drug substance (caffeine), the tablet melted totally at 60°C.

Figure 13 shows how DSC helps compatibility studies after storage. The initial DSC curve of the mixture of drug substance with excipients shows in some cases no interactions and in other cases interactions. After storage we can see degradation only

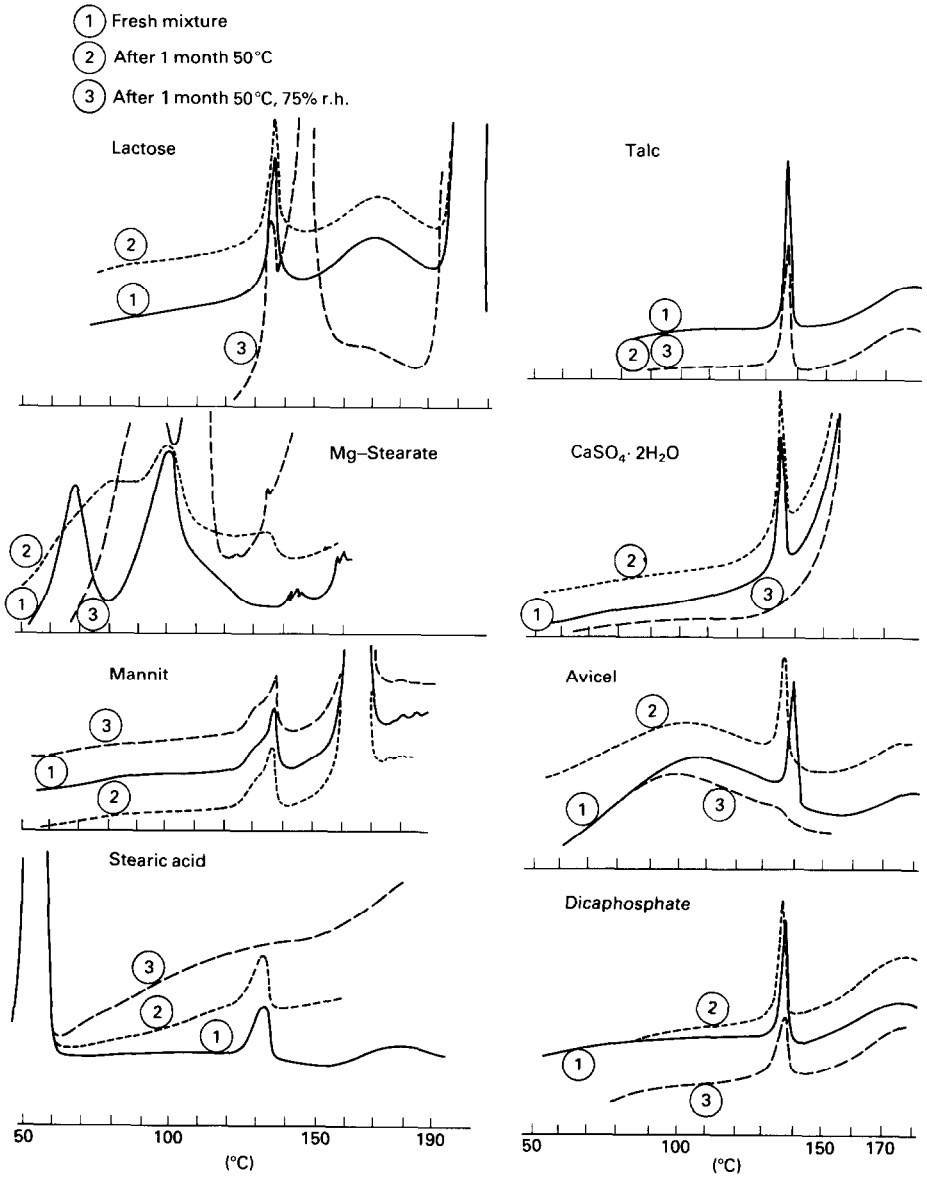

Figure 13
DSC curves of mixtures of 10% drug substance with excipients. The initial DSC curves suggest an incompatibility only with mannitol and magnesium stearate. The DSC curves after storage at 50°C and 75% r.h. allow differentiation of the excipients: degradation with stearic acid, calcium sulphate dihydrate and avicel.

with some excipients, especially in the presence of water. No correlation with the initial DSC interaction could be clearly observed.

The phase diagram is the basis for the galenical development of controlled release systems and the study of their stability [59–61] (solid dispersions, solid solution). Here DSC plays a dominant role.

Control of processing

Polymorphism and pseudopolymorphism may occur during processing: tabletting, spray drying, granulation, suspensions [58, 59].

Physical changes during storage of the dosage form [60]

In some ideal cases, the polymorphism behaviour of the drug substance can be studied in the solid state. DSC is quite useful as a support for the development of suppositories. Fatty suppository masses are complex mixtures with different crystalline modifications and undergo slow transition into the higher melting form during storage, as demonstrated in Fig. 14. If the melting point of the mass increases to above 37°C, this may lead to products which become ineffective on storage. The initial choice of the suppository mass is easily made with DSC. The checking of manufacturing reproducibility is also very efficient [24]. Furthermore the identity and uniform distribution of the drug substance may be determined.

Other physical changes of excipients may be detected with DSC. For example, anhydrous lactose may turn to the monohydrate. The crystallisation of excipients in tablets has been followed with DSC [6].

Figure 15 deals with 2 modifications of a drug substance for which only an amorphous state was known at the beginning of development. Crystalline modification A was obtained only after many crystallisation studies. In this case, a liquid galenical form had been developed. A quite new, stable, very insoluble modification appeared after storage. Therefore, the solubility of this new undesirable modification had to be determined in order to obtain a suitable formulation.

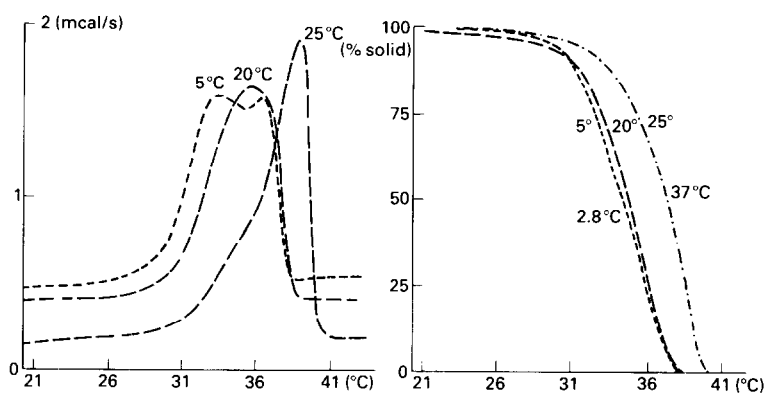

Figure 14
DSC curves and plot % solid of compressed suppositories of paracetamol after 18 months storage (2.5°C/min^{-1}).

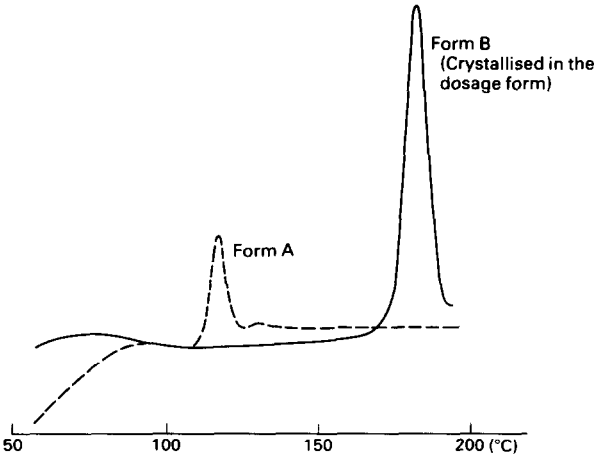

Figure 15
DSC curves of 2 modifications. Form B appeared in the liquid dosage form.

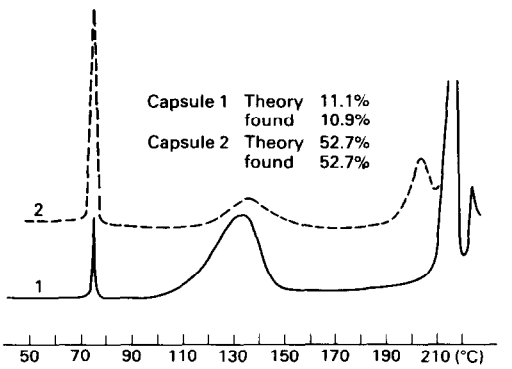

Figure 16
Identification and quantitation of the drug substance in a capsule suspected to be wrong (DSC curve).

Analysis of the dosage form

Identification of excipients, and even their quantitation in an unknown matrix with excipients such as lactose, mannitol and saccharose is possible, if no interaction is observed.

Quantitative analysis of a drug substance in the dosage form by means of DSC or TG has been suggested [62, 63]. This is possible for mixtures without any physical interaction. An example is given in Fig. 16. A mix-up was suspected. DSC could confirm the identity, the right crystalline modification and the correct dosage.

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