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APPLICATIONS OF THERMAL ANALYSIS AND COUPLED TECHNIQUES IN PHARMACEUTICAL INDUSTRY

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Abstract

Thermal analysis methods are well-established techniques in research laboratories of pharmaceutical industry. The robustness and sensitivity of instrumentation, the introduction of automation and of reliable software according to the industrial needs widened considerably the areas of applications in the last decade. Calibration of instruments and validation of results follow the state of the art of cGMP as for other analytical techniques. Thermal analysis techniques are especially useful for the study of the behavior of the poly-phasic systems drug substances and excipients and find a unique place for new delivery systems. Since change of temperature and moisture occur by processing and storage, changes of the solid state may have a considerable effect on activity, toxicity and stability of compounds. Current requirements of the International Conference of Harmonisation for the characterization and the quantitation of polymorphism in new entities re-enforce the position of thermal analysis techniques. This challenging task needs the use of complementary methods. Combined techniques and microcalorimetry demonstrate their advantages. This article reviews the current use of thermal analysis and combined techniques in research and development and in production. The advantage of commercially coupled techniques to thermogravimetry is emphasized with some examples.

Keywords: amorphous state, cGMP, DSC-TG, DSC-X-ray diffraction, ICH, ICHQ6, microcalorimetry, pharmaceutical industry, pharmaceutical polymers, phase transitions, phase-diagrams, polymorphism, pseudo-polymorphism, purity analysis, sorption-desorption, TG-FT-IR, TG-MS, thermal analysis coupled techniques, validation of methods

Introduction

Thermal analysis methods applied in pharmaceutical area since the 1970 years in Universities and in research laboratories are now well established techniques. Thermal analysis is a group of techniques in which a property of the sample is measured against time or temperature while the temperature of the sample, in a specified atmosphere is heated or cooled at a fixed rate of temperature change or hold at constant temperature. Considering the number of physical parameters of a substance, which may be measured, the number of techniques derived is very large. Books or review articles dealing with the principle and instrumentation are given in [1–4] and applications of thermal analysis methods for pharmaceuticals focused on industry are given in [5–19].

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The introduction of automation, of reliable hardware and software as well as the increase of sensitivity of the instruments made the method quite more popular. Commercial extremely sensitive calorimeters add new ways of applications. The number of publications dealing with the use of thermal analysis in pharmaceuticals increases considerably in the last decade. Spectroscopic analysis, X-ray diffraction and thermal analysis found common applications and combined techniques or parallel techniques are commonly used for proper interpretations of complex phenomena. Pharmaceutical industry is faced with the new challenges of quicker development and higher performance in term of technology, reliability and up-scale in an international cGMP environment. Commercial instruments follow these needs and the manufacturers now propose coupled techniques.

Methods used in pharmaceutical industry

The applications may be divided roughly in two categories:

– physical changes and measurements, such as melting, crystalline phase changes, changes in liquid and liquid crystalline states, study of polymers, phase diagrams, heat capacity, glass transitions

– and chemical reactions such as decompositions, oxidations.

Manufacturing of pharmaceuticals implies generally two separated steps: manufacturing of the active molecule (drug substance) and manufacturing of the formulation (medicament or dosage form or drug product) which is given to the patient. The formulation itself plays a decisive role in the monitoring of the action in the body, e.g. quick action, long action, site of action. According to the medical needs, the medicament can be applied orally as a tablet, a capsule, a syrup, a solution, or intramuscular or parenterally as injection, as suppository, cream, gel, nasal spray or inhalation. Special delivery systems like depot forms, minipumps, patches allow constant delivery for patients without the needs to be in hospitals. These formulations need auxiliary substances called excipients and adapted technologies for the manufacture of the drug product. For the patient it is mandatory that the product remains identical batch to batch and throughout its shelf life in order to maintain the action at the desired time without unexpected side effects.

This is achieved by the proper choice of the salt form, of the polymorphic form, the control of the drug substance and of the excipients whatever their provenience as well as by the monitoring of the processing and the storage of the drug product.

Single compounds may be characterized through the measurements of heats and temperatures of specific heat, glass transition, melting, boiling, sublimation, decomposition, isomerization or heats of solution, water sorption-desorption. Thermal analysis techniques are the basis for the determination of thermodynamic data of polymorphs, solvates and amorphous forms which may give rise to hurdles in every step of manufacture, storage and transport from raw materials to the medicine distributed to the patient.

For mixtures of several components, the phase diagrams rules have to be considered. If there is no interaction between two compounds in the solid state and miscibility of the liquid state, an eutectic behavior will be observed during heating of the mixture. This behavior is the basis of the purity analysis by DSC and of the study of chiral purifications. If there is no interaction in the solid state and no miscibility in the liquid state, the DSC scan of the mixture of two compounds will be the addition of the two DSC scans. This is the basis of quantitation of components in the drug product. An interaction in the solid state may result from the formation of solid solution with partial or total miscibility, from the formation of complex, or from chemical reaction. Pharmaceuticals may also be studied in aqueous media in order to follow for example protein denaturation, gel formation, liposome formation or in order to design the conditions of lyophilization.

Polymers, packaging materials are widely studied by thermal techniques. Thermal analysis as well as calorimetry finds use in process optimization and in safety.

Table 1 summarizes the main applications of thermal analysis and combined techniques for pharmaceuticals.

Table 1 Main applications of thermal analysis, calorimetry, combined and coupled techniques in pharmaceutical industry

Drug substances and excipients	
Identification, melting, thermodynamic data	Single techniques: DSC, calorimetry, TG, TMA
Polymorphism	
Investigation, choice of the salt form, manufacture, control of crystallization, drying, milling, batch control	DSC, solution calorimetry, microcalorimetry, sub-ambient DSC, TG, variable temperature spectroscopy (IR, NMR, Raman, X-ray), thermomicroscopy, IR-thermomicroscopy, Raman-thermomicroscopy, TG-IR, TG-MS, DSC-X-ray, DTA-TG
Raw materials: storage conditions	DSC, TG, water sorption-desorption isotherms with combined X-ray diffraction, combined with microcalorimetry
Amorphous state	
Temperature T_g of glass transition of single components and influence of moisture, excipients	DSC, MDSC, TG, thermal stimulated current (TSC)
Optimization of formulations: microspheres, lyophilization, coating	DSC, MDSC
Quantitation	DSC, microcalorimetry
Purity	
Raw materials: purification, stability	DSC
Stability	
Thermal decomposition, kinetics	DSC, TG, TG-MS, TG-IR
Compatibility, stability	microcalorimetry

Table 1 Continued

Safety	calorimetry, DSC, TG, DTA-TG, TG-MS, accelerated rate calorimetry (ARC)
Polymers	
Characterization, miscibility, control, stability	DSC, TG, TMA, DMA, TG-MS, TG-IR, MDSC
Drug products	
Physical interactions, phase diagrams	DSC
Process optimization: solid dispersions, solid solutions, microspheres, modified release, lyophilisates	DSC, DSC-spectroscopy, DSC-X-ray, thermomicroscopy, IR Raman, electronmicroscopy
Drug products: control of processes, granulation, mixing, milling, tabletting, spray-drying, kneading, melting, lyophilization	DSC, solution calorimetry, microcalorimetry, sub-ambient DSC, TG, variable temperature spectroscopy (IR, NMR, Raman, X-ray), thermomicroscopy, IR-thermomicroscopy, Raman-thermomicroscopy, TG-IR, TG-MS, DSC-X-ray
Melting point of liquid formulations	Sub-ambient DSC
Identification, quantitation	DSC, TG
Water interaction in gels, creams, polymers	DSC, sub-ambient DSC, DSC-microscopy, DSC-X-ray, DSC-TG, electronmicroscopy
Characterization hydrated phospholipid bilayer	DSC, microcalorimetry
Drug discovery	
Phospholipid-drug interactions	DSC, microcalorimetry, titration calorimetry
Binding thermodynamics, molecular recognition	titration calorimetry

Trends in pharmaceutical industry

Techniques

Every phenomenon where energy change is involved is detectable by DSC (differential scanning calorimetry); therefore DSC is the basic thermal technique used for the industry. Thermogravimetry (TG) (often-called thermogravimetric analysis or TG) is also commonly used since the mass change evaluation allows specific determinations.

In pressure DSC (PDSC), the sample can be submitted to different pressures, which allows to characterize substances at the pressures of processes or to distinguish overlapping peaks observed for example by desolvation [20].

Modulated DSC (MDSC) has been thoroughly examined and discussed. Main advantages are the separation of overlapping events in the DSC scans. The method is generally applied for polymers and dosage forms containing polymers. A review is given by Simon [21].

Microcalorimetry is a growing technique [22, 23] complementary to DSC for the characterization of pharmaceuticals. Larger sample volume and high sensitivity

means that phenomena of very low energy (unmeasurable by DSC) may be studied. The output of the instrument is measured by the rate of heat change (dq/dt) as a function of time with a high sensitivity better than 0.1 μW. Microcalorimetry can be applied to isolated systems in specific atmospheres; or for batch mode where reactants are mixed in the calorimeter. Solution calorimetry can be used in adiabatic or isoperibol modes in microcalorimeters at constant temperature. Calorimeters and reaction calorimeters can be equipped with on line complementary analytical tools.

For the pharmaceutical industry, thermal events, which may occur during processing, should be studied in the industrial conditions; therefore instruments offer the possibility to run experiments under different pressure, different gas atmospheres and different humidities. The water-sorption isotherms which were carried out in the past by weighing samples put in saturated salt atmospheres [24] are now routinely carried out using thermobalances [25] or specific instruments [26]. The measurement of the adsorption or desorption energy can also be measured in calorimeters [27]. Combined and coupled techniques are discussed below.

Calibration and validation

Industry needs differ from academia [28] in terms of speed for obtaining results and in terms of GMP. In GMP area, commercial equipment is used. All manufacturers now offer DSC and TG instruments with automation and sophisticated, robust and sensitive instruments replace manual instruments. The instruments have to be installed, qualified and calibrated (IQ, OQ) and their performance periodically checked by the user (PQ) according to Isonorms and current GMP. Therefore pharmaceutical industry needs certified reference standards, preferably organic substances with known melting points and melting enthalpies additionally to metals [16, 29].

Table 2 gives examples of substances used in our laboratory for the control of the temperature and the energetic output of DSC instruments.

For the control of thermobalances, additionally to certified masses, we use the dehydration of sodium tartrate dihydrate (15.7%) used as standard in Karl Fischer titration, calcium oxalate monohydrate (12.3%) proposed in Pharm. Eur. and coppersulfate pentahydrate (36.1%). The dehydrations cover a temperature range from 50 to 270°C. The standards recommended by ICTA are ferromagnetic standards exhibiting loss of ferromagnetism at their curie point temperature within a magnetic field: nickel (354°C), Permanorm 3 (266°C), Numetal (386°C), Permanorm 5 (459°C), Trafoperm (754°C). The Mettler instrument TGA850 allows using the measurement of the melting points of organic references. It results in very accurate knowledge of the temperature of the sample.

Examples of calibration results are given in reference [16]. Very important for pharmaceutical industry is the confidence of the laboratory, which delivers the reference. Since the heating rate may have an influence on the data, it is recommended to compare the melting point and the melting enthalpy of organic standards, additionally to indium, at different heating rates covering the measurement range. For accurate determinations it is recommended to use standard(s) with a melting in the range of the considered temperature in the sequence of daily analysis.

Table 2 Examples of certified substances used in the laboratory for temperature and for calorimetric controls of DSC

Certified substances	Onset T/°C certificate
Iodobenzene	–31.3
H_2O	0.0
4-Nitrotoluene	51.5
Biphenyl	69.3
Naphthalene	80.2
Benzil	94.7
Acetanilide	114.0
Benzoic acid	122.1
Diphenylacetic acid	146.5
Indium	156.6
Anisic acid	183.1
2-Chloro-anthraquinone	210.0
Tin	231.9
Anthraquinone	284.5
Lead	327.5
Zinc	418.9
Standard substances	**ΔH/J g^{-1}**
Naphthalene (80.2°C)	148.6
Benzil (94.7°C)	112.0
Benzoic acid (80.2°C)	147.2
Biphenyl (69.3°C)	120.4
Diphenylacetic acid (146.5°C)	146.9
Indium (156.6°C)	28.7
Tin (231.9°C)	60.2

Analysis methods have to be validated according to the guideline (ICHQ2, [30]) recommended by the International Conference on Harmonisation (ICH), in terms of repeatability, intermediate precision, accuracy, LOQ, LOD and robustness. The robustness is especially important in thermal analysis since depending upon the sample preparation, the amount analyzed, the heating rate, the gas atmosphere, the sample pan type, overlapping events such as phase changes or decomposition may interact and make the results not meaningful. An example of the study of accuracy is given in Table 3 for a purity analysis by DSC [16]. When impurities are not available, only the comparison of the results with other purity analysis is a way to judge the accuracy of the method. As for all purity analysis, the proper judgment can only be checked with experiments carried out by spiking the sample with impurities and carrying out the analysis. In the example of Table 3,

from the two possible impurities, only one impurity is determined accurately. Discussion about validation of DSC purity method can be found in [31].

Table 3 Example of validation for DSC purity analysis, accuracy

Comparison of DSC and HPLC results				
Batch	97905	97906	98907	98908
DSC sum of impurities/%	0.25	0.18	0.17	0.30
Related substances HPLC sum/%	0.21	0.10	0.20	0.20
DSC purity/%	99.75	99.82	99.73	99.70
HPLC purity	99.79	99.90	99.80	99.80
Comparison of results after spiking known impurities				
Impurity	Purity/% initial	Impurity added/ mole%	Theoretical purity/ %	Purity found/ %
A	99.82%	0.22; 0.23; 0.22	99.60; 99.59; 99.50	99.71; 99.69; 99.64
		0.32; 0.30; 0.32	99.50; 99.52; 99.50	99.45; 99.46; 99.49
		0.50; 0.49; 0.52	99.32; 99.33; 99.30	99.30; 99.30; 99.30
B	99.82%	0.22; 0.22; 0.22	99.60; 99.60; 99.60	99.82; 99.82; 99.82

Table 4 gives an example of validation for the routine determination of loss on drying by thermogravimetry.

Table 4 Example of validation of a TG method for loss on drying assay

Precision	Mettler TGA-850 with autosampler	Perkin Elmer TGA-7 manual
Batch 87902	heating rate 20 K min^{-1}	heating rate 20 K min^{-1}
Relative standard deviation, s_{rel}/%	3.2	2.1
Number of determinations, n	9	7
Absolute standard deviation, s_{abs}/%	0.063	0.040
Mean value/%	1.97	1.93
Individual values/%	2.02, 1.94, 2.03, 2.00, 1.99, 1.98, 1.99, 1.96, 1.82	1.94, 1.90, 1.93, 1.94, 1.86, 1.99, 1.92
Influence of heating rate/K min^{-1}		
5	2.13% (n=1)	
10	2.05% (n=1)	1.99% (n=1)
20	1.97% (n=9)	1.93% (n=7)
Accuracy comparison of methods		
TG at 20 K min^{-1}, n=9	1.97%	
Water Karl Fischer	2.03%	
Solvents GC	not detectable	

Use in production

Thermal analysis techniques are used in production for routine analysis, for follow-up stability studies and for validation of the process.

The important steps of crystallization, and washing of the drug substance have to be understood: Is the solvent a mixture? What are the species which may crystallize or co-crystallize? What are their thermodynamic properties (composition, temperature)? is the process kinetically or thermodynamically driven? According to Sato [32], the polymorphic crystallization is primarily determined by nucleation process in which chemical potential differences and interfacial energy are predominant factors, the polymorphic transformation occurs through four schemes: solid state, solution mediation, melt mediation and interface mediation; therefore, the kinetic of crystallization of the first crystal as well as the crystal growth are multiphasic phenomena to be taken into account. The formation of solvates or hydrates followed by drying into an anhydrous form can be extremely critical for the drying upscale if several hydrates, several anhydrous forms and the amorphous state may occur. Furthermore, the drug substance may undergo transformation during milling. For the dosage form, solvate or hydrate formation may occur during granulation. Excipients may accelerate transformation changes during mixing, tabletting. From our experience these highly critical questions have to be addressed and resolved before the transfer from development to production. Ritonavir discovered by Abbott Laboratories was filed in 1995 and marketed as Norvir. From the discovery until the new drug application, only one crystalline form was known to exist. Two years after the launch of Norvir, some lots of Norvir capsules failed the dissolution specification. A large portion of the drug substance was precipitating out the semi-solid formulation. Investigation carried out at Abbott revealed the fact that a new thermodynamically more stable form had emerged [33].

Thermogravimetry is used for the determination of the loss on drying and the method is validated in terms of precision, accuracy, robustness and limit of quantitation. The technique is very efficient for the validation of drying, milling, and for stability analysis due to the high throughput of the modern instrumentation. DSC purity analysis is commonly used for references and is the best complementary method of impurity testing for registration documents. The method is fast and automatically performed, does not need reference material and may replace other melting point determinations [34]. Details about optimization and validation are given in reference [31]. Figure 1 shows the DSC curves of two batches manufactured differently. The DSC purity analysis is very quick and gives immediately the information needed.

DSC is not recommended for routine quantitative analysis of polymorphs, since kinetic effects may introduce reproducibility problems [35]. Polymorphism problems of excipients such as fatty acid derivatives, sorbitol, mannitol, lactose, magnesium stearate have been discussed [35–37].

Validated routine analysis for polymorphism of drug substance and of excipients generally carried out by spectroscopy (e.g. FT-IR) or by X-ray diffraction is developed based upon polymorphic studies carried out during development.

Amorphous content of raw materials is increasly determined routinely by micro-calorimetry [38].

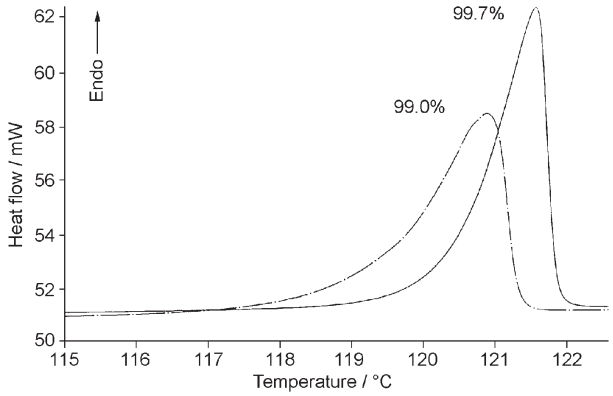

Fig. 1 DSC scans of two batches of different processes

A great number of excipients are polymers. Depending of their nature, they are classical fillers, binders or disintegrating agents for tabletting such as starch or cellulose derivatives, gelifiants for liquid or semi-liquid forms, coating agents like cellulose esters or they can be the driving force of the performance of the drug product. Thermal analysis techniques are also valuable for the routine control of these excipients.

Research and development

Isothermal titration calorimetry [39] is used in drug delivery for the measurement of binding thermodynamics, for the characterization of target compounds and molecular recognition and ligand design.

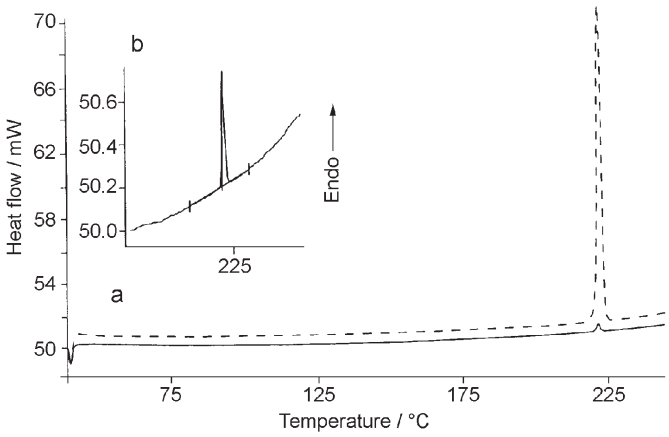

Fig. 2 DSC analysis of an isotopic drug (purity found 99.75%)

In research and early development characterization of material with very small samples is a big advantage. Figure 2 shows the DSC curves of an isotopic material. It was possible to perform analysis down to 0.03 mg (expanded scale Fig. 2b).

The choice of the salt form is very complex since polymorphs, solvates and hydrates as well as different salts have to be considered in the studies permitting the rational selection [40]. Thermal analysis methods are used intensively for such studies. The following case of a drug substance exemplifies the place of sorption-desorption isotherms for the selection of the salt form. The base and the hydrogen-maleate were not hygroscopic, the hydrogentartrate absorbed 6% water and a slight hysteresis in the desorption was observed; the hydrochloride formed a stable hydrate and the hydrogentartrate took water up to 22%.

The most challenging issue in the pharmaceutical industry is the proper study and characterization of polymorphs, and solvates according to the decision tree 4 of the ICH guideline Q6A [41]. Studies including crystallizations, equilibrations, granulating, tabletting have to be conducted in order to detect polymorphs and to characterize them. If properties (solubilities, dissolution, stability, and performance) are different, the impact on the dosage form has to be studied. Depending on the outcome, quantitative validated methods have to be developed and specification set for drug substance or for excipient or/and for the dosage form. Since changes may occur during processing or storage under the influence of mechanic stress, temperature, pressure and moisture, a proper study design has to be set and adequate methods have to be used.

A great number of recent publications deal with the thermodynamic, crystallographic and reaction kinetic of the solid state [42–51]. Many substances exist as polyphasic solids with several crystalline anhydrous and hydrated forms as well as amorphous forms. The current focus of research in the solid-state area is to understand the origin of polymorphism at the molecular level and to predict and prepare at the beginning of development the most stable form [50]. The selection of a metastable form should result from targeted choice, not by chance.

DSC is a fast and sensitive not specific method. Depending on kinetic and crystallographic factors, the solid-solid transitions which should occur during heating or cooling in solid state does not occur and metastable phase diagrams equilibrium curves may be attained [35]. As demonstrated by many examples, the use of several techniques and study design based on the thermodynamic phase rules [52] is mandatory for proper study of solid phases [35, 50, 53, 54] in the pharmaceutical development. Since changing the conditions back to the analysis conditions (temperature, moisture, solvent) gives rises to wrong analysis, experts recognize the advantage of the combined methods or ‘in situ’ methods. Thermomicroscopy [55–58], or hot stage microscopy with videofilms allows studying melting, desolvation, crystallization and solubility experiments. IR thermomicroscopy and Raman thermomicroscopy [59–63] are complementary techniques, which allow having spectroscopic information in parallel. Most spectroscopic instruments have the possibility to adapt heating cells (in situ dynamic analysis). Spectral data (IR [64, 65], Raman [66–69], X-ray diffraction [70–75]) are obtained at temperatures or at humidity levels where thermal events oc-

cur, enabling to avoid artifacts by analyzing samples at room temperature and ambient relative humidity.

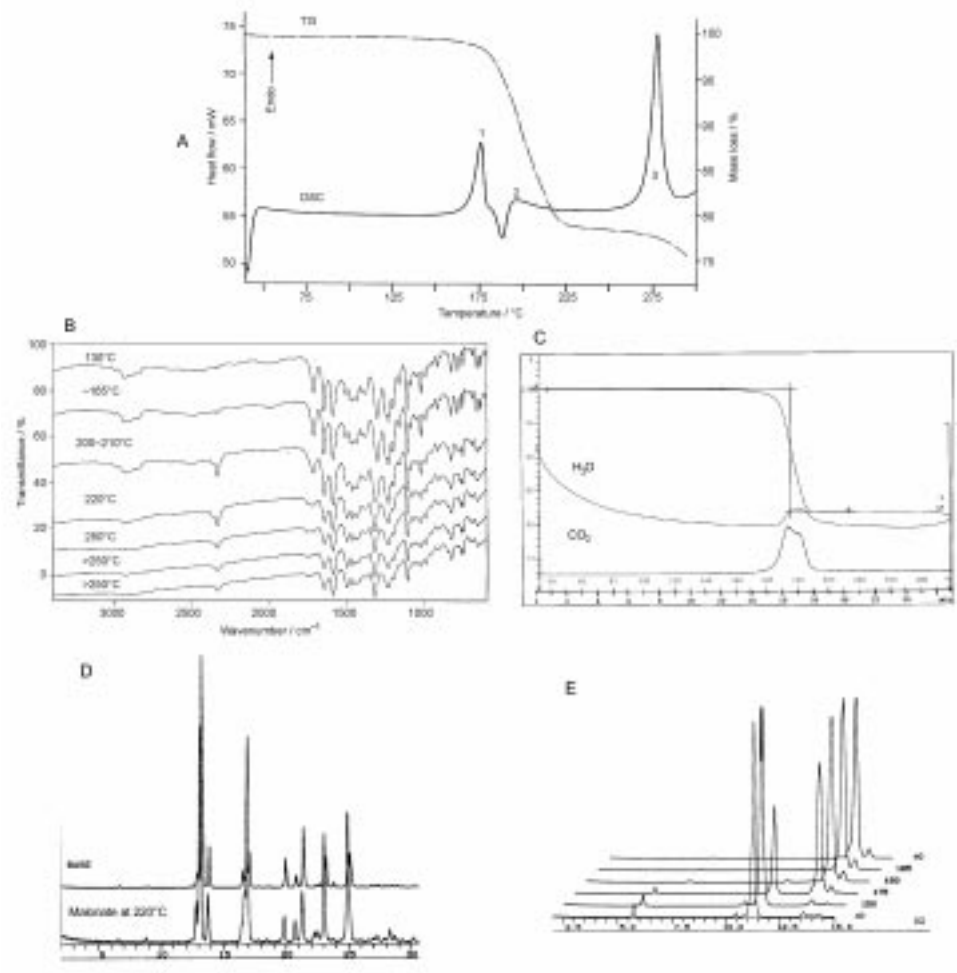

Fig. 3 Interpretation of the DSC curve of a malonate. A – DSC (endotherm) and TG curves; B – FT-IR in the heating cell, bands of the base and of CO_2 appear; C – TG-MS experiment, detection of water and CO_2; D – temperature resolved X-ray diffraction: the X-ray diffraction of the malonate heated until 220°C corresponds to the X-ray diffraction of the base; E – temperature resolved X-ray diffraction scans

All manufacturers of X-ray diffraction now offer resolved temperature X-ray diffraction. We could follow the solid-solid transitions of 6 anhydrous forms of tetracaine hydrochloride as well as the dehydration of the monohydrate by resolved

temperature X-ray diffraction. The first DSC experiments would have concluded to a system with only two forms [74].

The example of the thermal behavior of a malonate, given in Fig. 3, shows the advantage of combined and coupled techniques. The DSC curve (Fig. 3A) is very similar to a dual melting with intermediate crystallization. The TG curve shows a loss of mass with the endo-exotherm 1 and 2. The Fig. 3B shows the thermo-FT-IR experiment in KBr. The IR bands of the malonate change into the IR bands of the base and the band of CO_2 appears. The TG-MS of Fig. 3C shows the formation of water and CO_2 corresponding to the degradation of malonic acid. The temperature resolved X-ray experiment (Fig. 3D and 3E) show the final formation of the base. The malonate decomposes during melting (first endotherm) and the base crystallizes from the melt (exotherm), the final endotherm corresponds to the melting of the base.

Temperature resolved X-ray diffraction offers the unique advantage to obtain diffraction pattern of polymorphs in situ. Today computational calculations allow to day to have the crystal structure of polymorphs. Having the crystal structure, the theoretical X-ray diffractogram can be calculated. The purity of samples can be deduced from their X-ray diffraction pattern and the prediction of the limit of detection of quantitative methods by X-ray diffraction may be obtained.

The coupled X-ray Synchrotron-DSC technique has been developed by Ollivon *et al.* and used for the study of polymorphism of fatty acid derivatives [76, 77].

Variable temperature NMR is also used for polymorphism [78] as for polymers [79].

Thermal analysis methods for characterization of pharmaceutical hydrates are discussed in [80].

Amorphous state is produced by fast crystallization, precipitation, drying, milling, freeze drying or quick cooling from the melt. Amorphous substances are generally hygroscopic, have a better solubility and bioavailability; they have good tabletting properties but are difficult to be milled. Very often they are chemically less stable. They tend to transform into crystalline forms upon storage with possible lost of bioavailability or crystal growth. The transitions are generally fast at temperatures above the glass transition. The temperature of the glass transition is depressed by water [85] and the transformation into a crystalline form occur at lower temperatures. The enthalpy of the exothermic crystallization can be used for the quantitation of amorphous content by DSC [53] or by isothermal microcalorimetry [81–85]. Limits of 0.5–1% can be attained but the method is time consuming. Solution calorimetry is also useful but not very sensitive. MDSC has been also used [86]. The study of the amorphous state is based upon the changes observed in the glass transition. Hancock and Zografi intensively studied the amorphous state of drug substances [87, 88] and used the relaxation energy at the glass transition as well as the dependency of the heating rate for the study of the 'fragility' of the amorphous state [89]. A comparison of all methods for the determination of amorphous content in pharmaceuticals is given in [90].

Figure 4 shows the use of water-sorption desorption isotherm for the study of the micronization of a drug substance. After milling a partial amorphization is

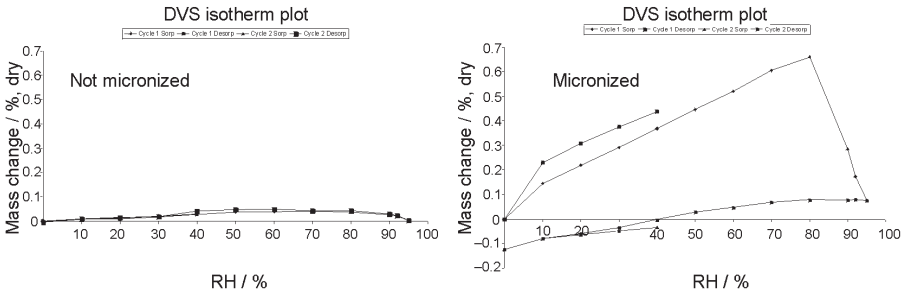

Fig. 4 Water sorption-desorption isotherms of a sample before milling and after milling. Detection of amorphization by the slight hygroscopicity observed for the sample micronized up to approx. 80%. Abrupt decreases due to crystallization

responsible to a slight hygroscopicity up to the relative humidity needed to obtain a spontaneous crystallization.

The chiral crystallization, increasingly replaced by chiral synthesis, remains attractive and DSC curves are the basis for optimization studies [91, 92].

Microcalorimetry can be used efficiently for qualitative comparison of stability and compatibility [93, 94, 53].

Binary phase diagrams are the basis for understanding DSC curves of formulations. Eutectics, solid solutions or compound formation can be observed.

Increasing dissolution rate is one of the challenges of the dosage form development. One approach is the formation of a solid dispersion of a drug with a hydrophilic excipient. The ideal type is the glass solution in which the amorphous substance has a lower thermodynamic barrier to dissolution with a maximally reduced particle size. The intimate presence of hydrophilic excipient can increase wetting and lead to super-saturation in the diffusion layer. A glass solution is formed if drug substance and excipients are miscible. Both being amorphous, the resulting miscible phase has a glass transition which temperature should be higher than the storage temperature even in presence of moisture (which decreases the glass transition). Melt extrusion has advantages over solvent based methods. Complex formation with cyclodextrin derivatives is also a way to improve solubility.

Hydroxypropylcellulose derivatives are commonly used for their swelling properties and the drug substance dissolution is delayed, giving modified release products. Film coating with modified release action is obtained with acrylic polymers and co-polymers. Microspheres for long acting are obtained mainly with polymers and co-polymers of polylactic acid.

For all systems the physical properties of the polymer as it and in the formulation are correlated with the molecular mass, the melting point, the glass transition and the water interaction. DSC allows studying the crystallinity, the glass transition and the energy correlated for the excipient or for blends and formulations. DSC is widely used to study the property of adsorbed water: freezable water or bound water. Thermogravimetry and instruments measuring water sorption and desorption isotherms complete the understanding of polymer-water interactions.

DSC, TG, DMA, TMA, X-ray diffraction and combined techniques are widely used for raw materials [5, 11, 95–98] with microscopy and scanning electron microscopy (SEM).

A recent study of inclusion complexes between beta blockers and cyclodextrin [98] is an example of the current use of combined techniques for preformulation: DSC, X-ray, SEM and solid state NMR were used.

Liposomes are multilayered vesicles consisting of concentric bilayers of phospholipids interdispersed with aqueous phases. In aqueous media, the phospholipids undergo gel, liquid crystalline transitions easy to detect by DSC. The study of the change of these transitions, temperature, peak width and energy allows to characterize the hydrated phospholipid bilayers and to study the liposome formation with drugs [99–101]. MDSC was used for detection of the glass transition of freeze-dried lipo somes [102]. Coupled X-ray diffraction was recently developed for such studies [103].

Thermal analysis is used for the industrial optimization of the freeze drying parameters [104–107].

In all these systems, the solid state of the drug substance has to be checked: is the drug substance, or the excipient amorphous or crystalline in the lyophilisate, in the suppository, in the modified released form with fatty acid derivatives, in the liposome, in the microsphere.

DSC and combined techniques are very helpful in failure investigations as demonstrated in the following example. The drug substance was a hydrochloride salt. The formulation was a hard gelatine capsule filled with a mixture drug substance-lactose monohydrate. Stability screenings were performed with mixtures of drug substance and lactose. During stability studies of this capsule formulation, the formation of needles sticking at the walls of the capsule was observed. Gelatine capsules contain a high amount of water. The needles were identified as the base of the drug substance

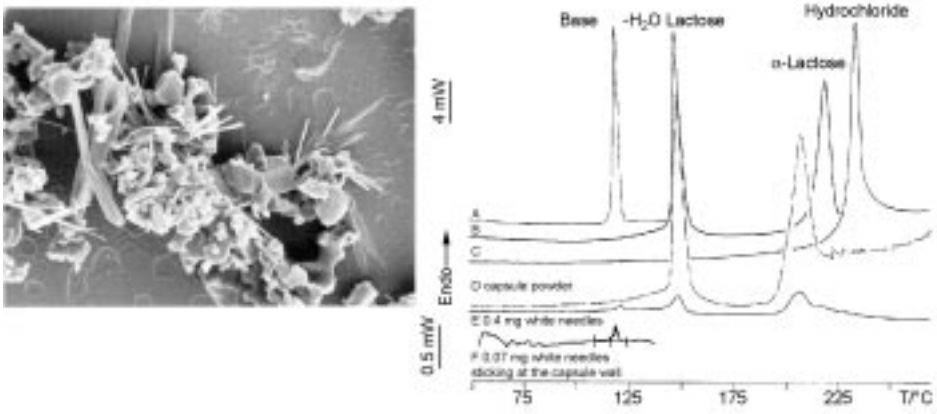

Fig. 5 Scanning electron microscopy (SEM) picture of the capsule powder of a formulation. Needles appear in stability studies. DSC curves of: A – drug as base; B – lactose monohydrate; C – drug as hydrochloride; D – capsule powder; E – white needles with powder; F – white needles of the drug as base

resulting from the dissociation of the hydrochloride in presence of gelatine and water as demonstrated by DSC and FT-IR. The DSC study of this phenomenon is summa-

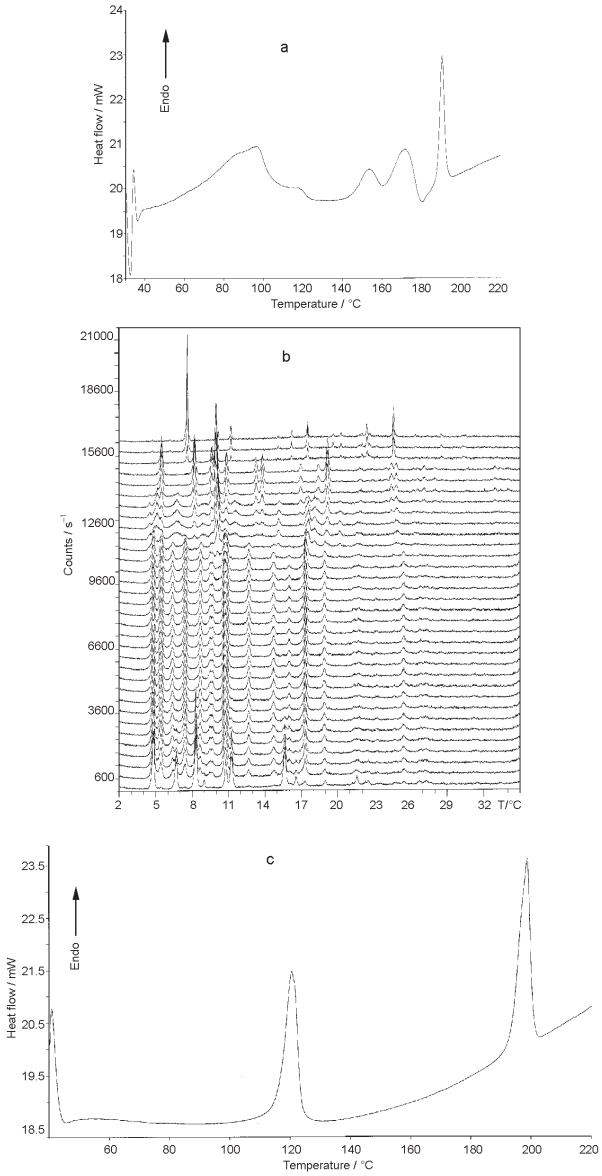

Fig. 6 Study of dehydration of a monohydrate upon heating. 6a – DSC of the monohydrate in a pierced pan 6b – Temperature resolved X-ray diffraction: phases changes correspond to the DSC picture; 6c – DSC of the monohydrate in a tight pan: melting of the monohydrate and melting of the anhydrate

rized by the curves given in Fig. 5. The DSC curves of the drug substance as base (A), of the lactose monohydrate (B), of the drug substance as hydrochloride (C) can be compared with the DSC curves of the capsule powder (D) and with two samples of needles isolated from the wall of the capsule. The hydrochloride of the drug substance has a physical interaction with lactose (displacement of the melting peaks of the drug substance as hydrochloride and of the α-lactose, curve D). The needles are more or less pure drug substance as base and the melting peak of base could be used for quantitation purposes.

Areas where thermal analysis and calorimetry are fully present are the safety studies [107–109].

Place of coupled techniques

Combined or coupled techniques?

Coupled techniques or simultaneous techniques refer to the application of two or more techniques to a sample at the same time, as for example DSC-TG or DTA-TG.

The example of Fig. 6 shows the DSC curve of a monohydrate in a pierced pan (Fig. 6a) and the corresponding temperature resolved X-ray diffraction (Fig. 6b).

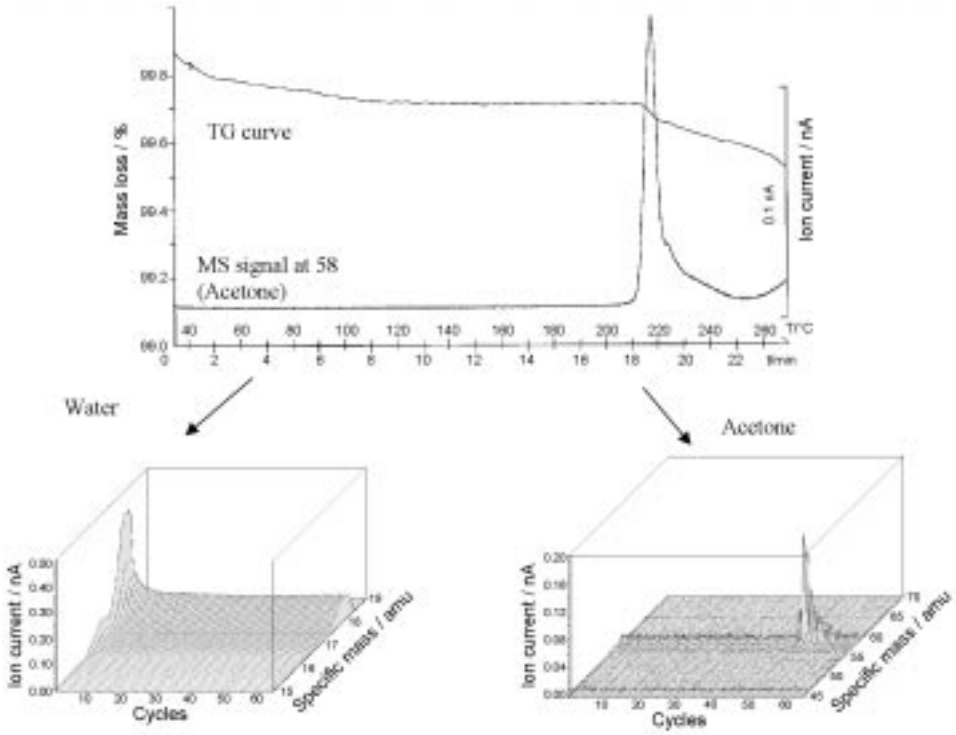

Fig. 7 TG-MS of a drug substance: acetone is encaged and is evolved at the melting

Two metastable anhydrous forms could be identified. The final form is the stable anhydrous form. If the DSC experiment is performed in a very tight pan (Fig. 6c), only two endotherms corresponding to the melting point of the hydrate and to the melting point of the stable anhydrous form are observed. That is, depending on the experimental conditions, different phenomena occurs and methods carried out in parallel cannot always reproduce the same conditions. It is the reason why coupled techniques are very attractive. However, only one instrument is commercially available for DSC-X-ray coupling [110].

Coupling spectroscopic techniques TG-IR [111, 112] or TG-MS [113–118] are now commercially available and found very good applications in pharmaceutical industry.

The gas flow conditions in thermobalances, the design of coupling interfaces, and the features of the gas analyzers are very important. The interface design may be

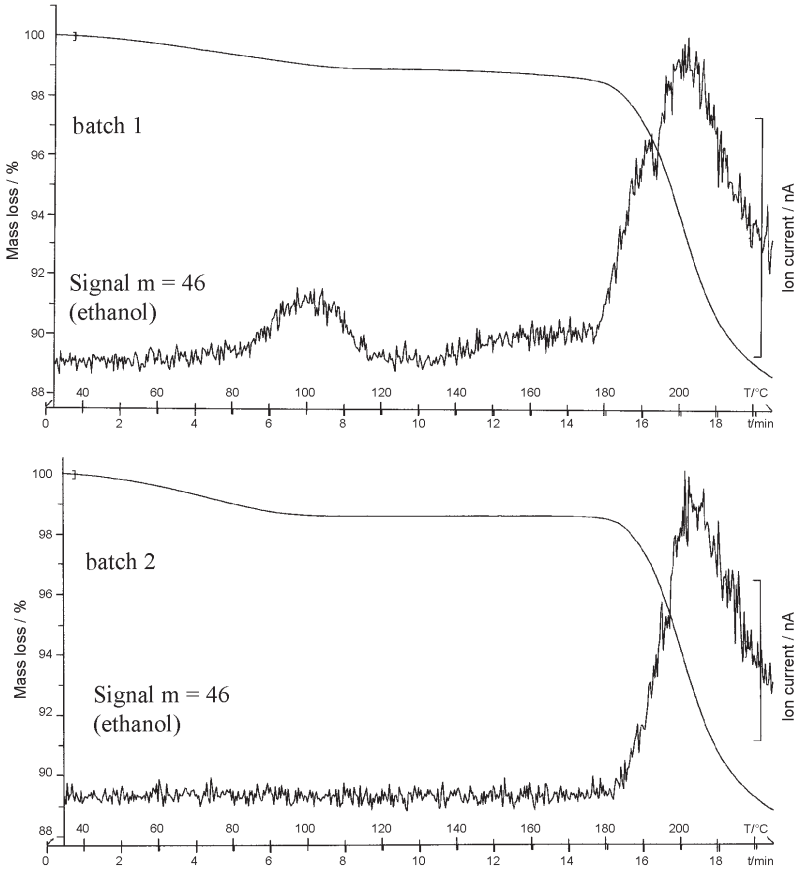

Fig. 8 TG-MS comparison of two batches differently dried. Both batches contain residual water, only batch 1 contains ethanol

critical. The transfer should be rapid and no dilution and no degradation should occur. The mass spectrometer operates in a high vacuum and the molecules may be ionised in various ways. Kaisersberger and Post compared the high sensitivity of the skimmer coupling as compared to the capillary coupling [116]. Quantitative analysis of TG-MS is possible with the pulse TA [118]. Synergism is found by using both TG-FT-IR and TG-MS. We used TG-IR for the detection of the degradation of aspartame [53]. TG-MS is very useful in pharmaceutical development for characterization of hydrates and solvates as demonstrated in references [53, 80], for decomposition and kinetic studies. Following examples show their advantage in quality control during development.

The TG-MS curve of the example given in Fig. 7 shows that the solvent acetone is encaged in the drug and is evolved only during melting. Since decomposition occurs within the melting process, thermogravimetry does not determine residual solvent acetone accurately. The example of Fig. 8 shows two samples of a drug substance dried differently. Both batches contain water. Ethanol is present only in batch 1. The example of Fig. 9 is the detection by TG-MS of residual methylene chloride in a microsphere formulation.

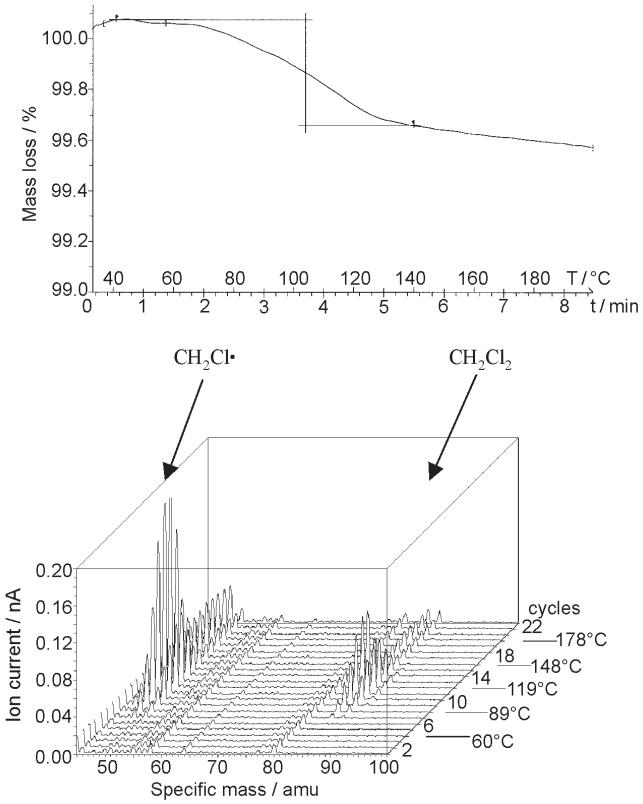

Fig. 9 TG-MS of a microsphere, detection of methylene chloride

Peptides are often lyophilized with acetic acid. TG-MS allows determining TG steps corresponding to water and to acetic acid (Fig. 10).

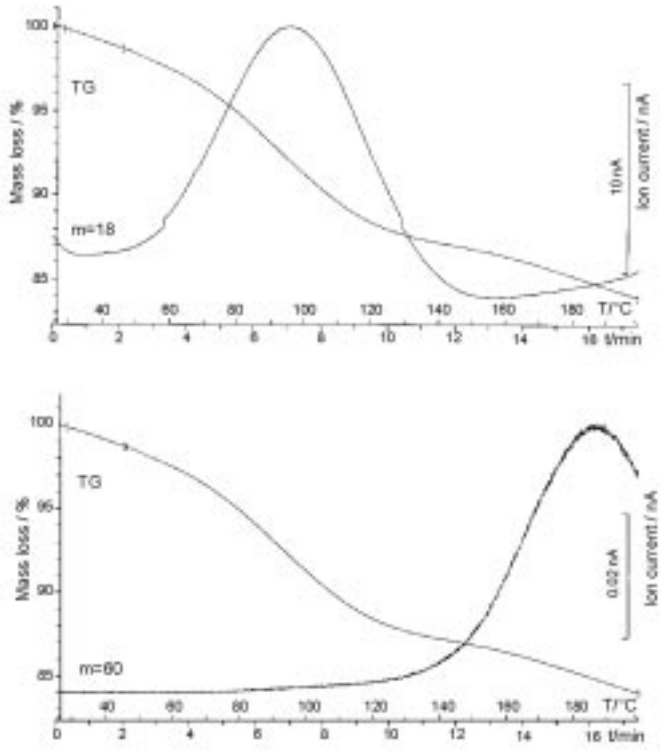

Fig. 10 TG-MS of a peptide, determination of the steps due to the elimination of water (m=18) and of acetic acid (m=60)

Micro-thermal method combines micro-spectroscopic and micro-thermal analysis. It is commercially available to visualize the spatial distribution of phases and components in polymers, pharmaceuticals, foods and electronic materials [119].

Conclusions

Thermal analysis methods find a wide range of current applications in pharmaceutical industry, for the design of the solid state of new molecules, for the control of raw materials, for stability, compatibility studies and for the development of new formulations. A special attention has be given to the validation of different steps of process.

* * *

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