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USE OF DSC AND TG FOR IDENTIFICATION AND QUANTIFICATION OF THE DOSAGE FORM

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Abstract

Thermal analysis techniques, DSC and TG can advantageously be used in quality control of drug products.

The methods are commonly used in preformulation for the study of polymorphism and for the study of the interactions drug substance-excipients, since these physical interactions can be the basis of the dosage form performance.

For routine control of the drug products, DSC and TG methods which are quick, which require only few mg of the samples and which are automated, are very attractive for routine analysis of drug products. A single scan can give several qualitative and quantitative informations.

DSC offer analytical possibilities only if the drug substance and the excipients do not have physical interactions or limited interactions (e.g. eutectic behaviour). About twenty marketed products have been analyzed by DSC and TG. In most of them identification of drug substance is easy. Several excipients could be identified in a tablet. Quantitations are demonstrated for some drug substances and excipients. DSC purity calculations have been applied to acetyl salicylic acid, paracetamol, cimetidine, pindolol, ibuprofen.

Keywords: dosage form, drug products, DSC, identification, quantitation, TG

Introduction

Thermal analysis techniques, such as differential scanning calorimetry (DSC) and thermogravimetry (TG) are quick techniques and can be applied without treatment of samples. They are commonly used for routine analysis of raw materials [1] and study of polymorphism [2]. In preformulation the techniques are particulary valuable for the construction of phase diagrams [3, 4] and the study of the interactions drug substance excipients. Polymorphism or hydrate formation may be studied by these techniques in granulation, lyophilisates, for development of solid dispersions and even in the dosage form [1–4]. Use of these techniques for identification and quantification of components of the galenical form have been sporadically demonstrated [1–6]. According to R.D. Kirchhoeffer TG is very discriminative for study of potential fraud in the generic drug industry [7]. DSC and TG have been also proposed for analysis of atenolol tablet [8]. The introduction of robotic systems with auto-sampling, data acquisition and data processing make Thermal analysis techniques quite competitive to other routine analytical methods [9].

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Table 1 Results of DSC and TG scans at 20°C min^{-1} of drug products

Product	Onset/ °C	Active ingredient	Onset or melting/°C	Product TG	Comment
Actifed 300mg	53, 100, 145	Paracetamol	169		interaction
		Tripolidine HCl	116–118		
		Pseudo-ephedrine HCl	181–182		
Advil 200mg	72	Ibuprofen	75–77	1.8% at 100°C 63% dec. at 260°C	no lactose, glass transition at 124°C
Antalvic	162	Paracetamol	169	–	no lactose
Aspirin 500 mg	130	Acetylsalicylic acid	135	–	no lactose
Biarison 100 mg	137	Proquazone	141	2.3% /5.4%	lactose·H_2O
DJN 608 60 mg	127	DJN 608	140	–	slight interaction, lactose·H_2O
Doliprane 500 mg	168	Paracetamol	169	2.3%	no lactose
Dihydergot 5 mg	–	Dihydroergotamine	230–235	–	lactose·H_2O
Fortasec 2 mg	–	Loperamide	222	–	lactose·H_2O
Fulcine forte 500 mg	217	Griseofulvine	220	1.9%	no lactose
Haldol 20 mg	150	Haloperidol	150	1.9%	no lactose
Humex (blue pellets)	164	Paracetamol	169	–	blue pellets,no lactose
Paracetamol suppo	168	Paracetamol	169	–	melting after melt of Witepsol
Profenid 50 mg	73/86	Ketoprofen	94	0.4%/3.5%	lactose·H_2O
Sandonorm 1 mg	–	Bopindolol	167	5.73%	pic with dehydration lactose·H_2O
Seloken 100 mg	200	Metoprolol	243–245	2.5%/3.4%	pic with α lactose
Silomat 40 mg	161	Clobutinol	169–170	3.7%	no lactose

Table 1 Continued

Product	Onset/ °C	Active ingredient	Onset or melting/°C	Product TG	Comment
Synedil 120 mg	175	Sulpiride	175–182 (dec.)	–	lactose·H_2O
Tagamet 200 mg	140	Cimetidine	141–143	2.1% at 150°C	–
Totapen 500 mg	125	Ampicilline trihydrate	–	13.0%/15.2%/38.1%	dehydration peak of trihydrate, no lactose and decomposition
Visken 200 mg	165	Pindolol	170	–	no lactose
Zaditen 1 mg	182	Ketotifen	195	–	no lactose
Zaditen MR	–	Ketotifen	195	3.3%	lactose·H_2O, Cetyl palmitate

Experimental

The instruments used are DSC-2 or DSC-7 robotic system of Perkin-Elmer with data station. Thermobalance is the TGA-7 with the DSC-7 Data station.

Tablets are ground and mixed before DSC, TG scans. The content of capsules are introduced without treatment. Most of qualitative experiments are carried out under nitrogen at 20°C min^{-1} heating rate with crimped aluminium pans. If the melting of drug substance is covered by an excipient (e.g. lactose) a lower heating rate is used.

Reanalysis of the curves with high sensitivity allows to study fatty acid derivatives like magnesium stearate, stearic acid, cutina. Lactose monohydrate is characterized by the dehydration peak at about 150°C (TG=5%) and the melting peak of α-lactose at about 220°C. Other excipients like mannitol, saccharose, pluronic, polyethyleneglycol, cetyl palmitate, are characterized by their melting peaks. Calciumhydrogenephosphate dihydrate and calcium sulfate dihydrate are characterized by their strong dehydration peaks and TG values. For the quantitation of single values, the average mass of three capsules and the declared potency were taken into account.

Results and discussion

Table 1 summarizes the experiments carried out with approx. 20 marketed products and dosage forms in development. Comparison was done with the onset of ac-

Table 2 Quantitation of active ingredient or excipients in drug products (n=number of determinations)

Product		Active ingredient	% of theoretical value	
Capsule		Drug substance	98.0 %	(n=10) [3]
Capsule		Mannitol	97.1 %	(n=1)
Capsule	10 mg	Drug substance in	98.2 %	(n=1) [1,2]
	50 mg	development	100.0 %	(n=1)
Doliprane tablet		Paracetamol	101.0 %	(n=1)
Haldol tablet		Haloperidol	94.0 %	(n=10)
Pellet batch 1		Saccharose	100.1 %	(n=1)
Visken tablet		Pindolol	98.0 %	(n=1)

Table 3 Eutectic behaviour between drug substances

Optalidon	°C onset	Tonopan	°C onset
Tablet	95	Tablet	92
Butalbital	139	Butalbital	139
Coffein	239	Coffein	238
Propyphenazon	103	Propyphenazon	103
		Dihydroergotamin	230

Table 4 Purity calculations of drug substance in drug products. Heating rate 2°C min^{-1} except Antalvic (20°C min^{-1})

Drug substance	Active ingredient	Purity
Aspirin	Acetylsalicylic acid	99.3%
Doliprane	Paracetamol	99.4%
Advil	Ibuprofen	98.1%
Visken	Pindolol	98.4%
Tagamet	Cimetidine	99.4%
Antalvic	Paracetamol	98.6%

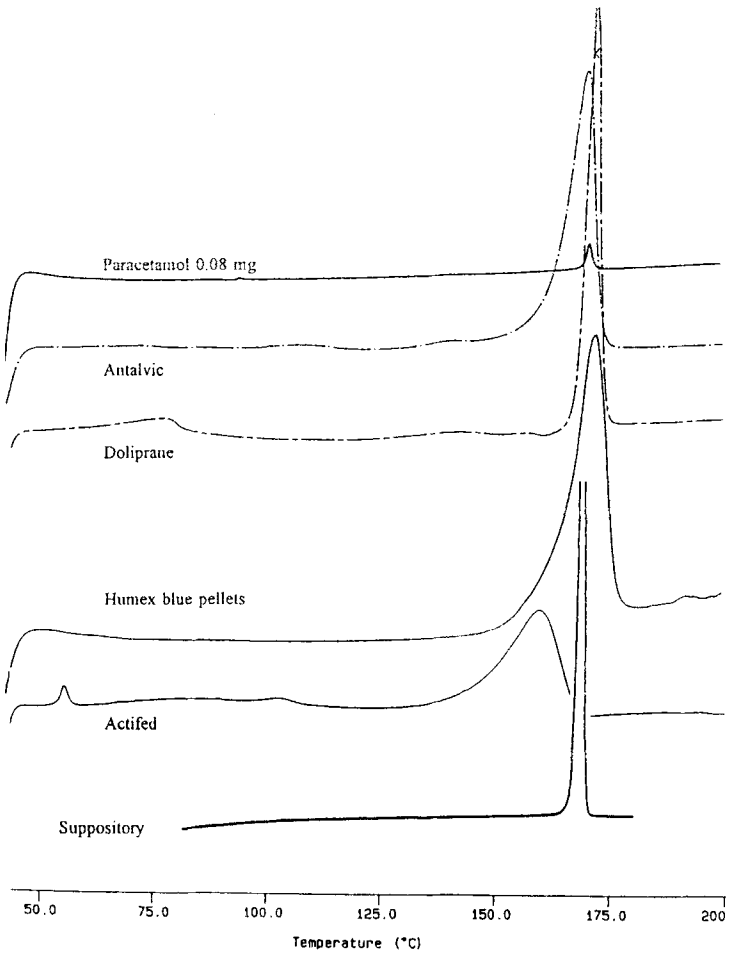

Fig. 1 Comparison of DSC of 4 marketed products and an experimental suppository containing paracetamol at 20°C min^{-1} heating rate

tive ingredient carried out in the same conditions or literature values [10]. Identification is quite easy for highly dosed active ingredients. Generally no interaction with lactose or corn starch occur, therefore quantitative determinations are possible. Table 2 shows some examples in those cases where no or limited interaction occurs between components of the dosage form. The calculations give reliable results. With robotic systems, uniformity of blends and content uniformity are easy to determine [9].

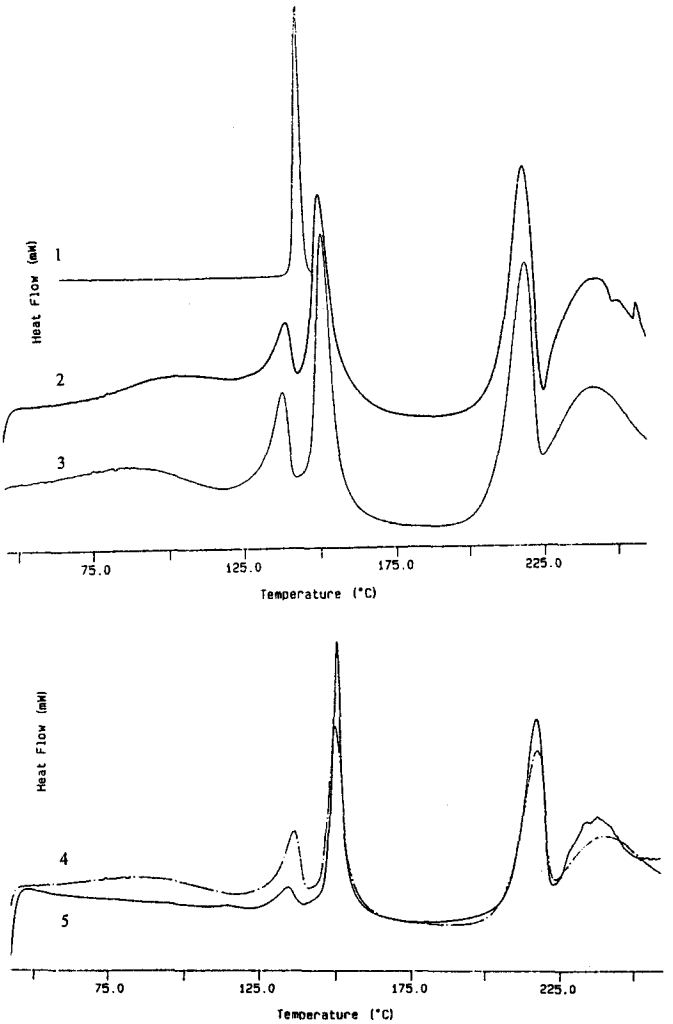

Fig. 2 Comparison of DSC curves of 2 compositions of DJN 608 tablets and DSC curve of the active ingredient. Slight interaction. (1)=DJN 608, (2)=tablet 60 mg formulation 1, (3)=placebo+DJN 608, (4)=formulation 1, (5)=formulation 2

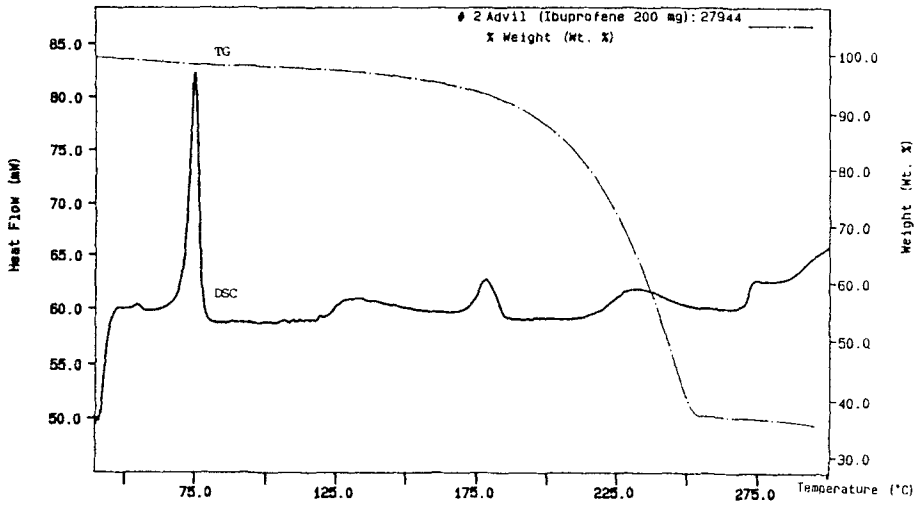

Fig. 3 DSC, TG curves of Advil 200 mg (Ibuprofen)

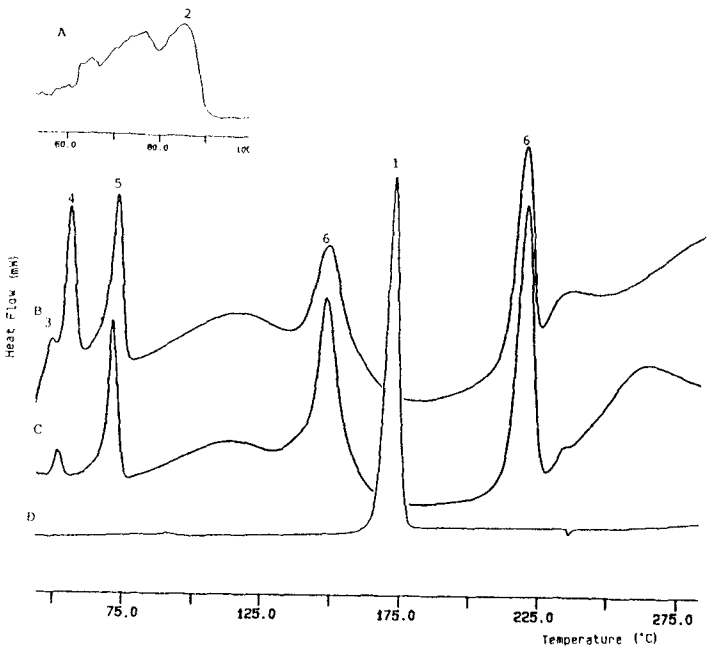

Fig. 4 Comparison of DSC curves of 3 compositions of a new drug substance. The drug substance is not determinable. The excipients are identified. A = formulation 1: (1) mannitol, (2) Cutina; B = formulation 2: (3) poloxamer, (5) glycerol monostearate, (6) lactose monohydrate; C = formulation 3: (3) poloxamer, (4) polyethyleneglycol, (5) glycerol monostearate and (6) lactose monohydrate; D = formulation 1 expanded

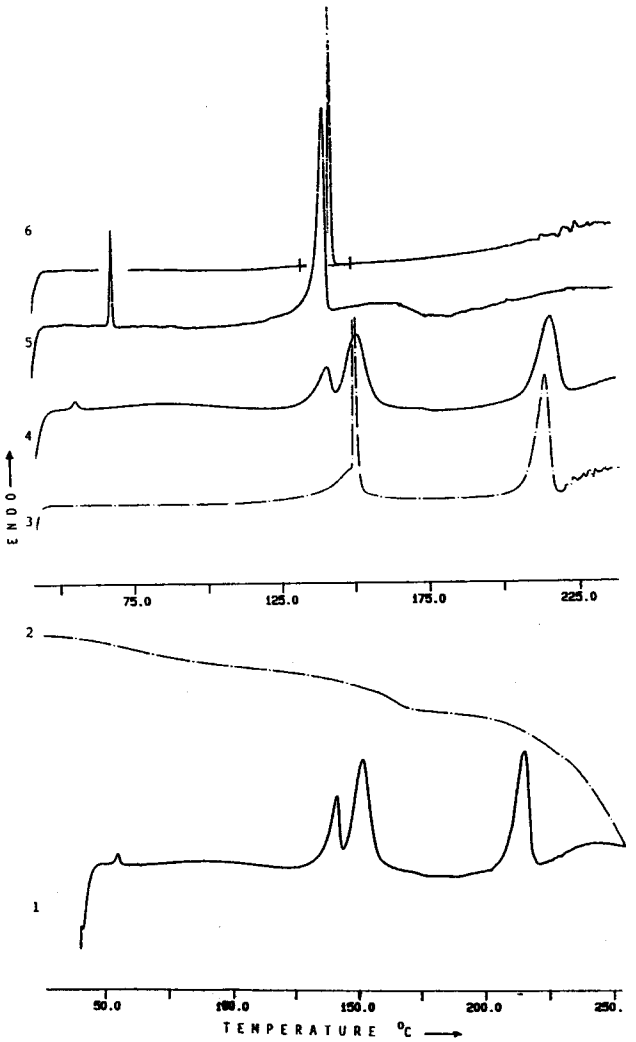

Fig. 5 Biarison tablet: Eutectic behaviour between proquazone and stearic acid. Content of lactose·H_2O via thermogravimetry: theory 2.5%, found 3.0%
1=DSC Biarison tablet, 2=TG Biarison tablet, 3=Lactose+alginic acid,
4=Biarison tablet, 5=Proquazone+10% stearic acid, 6=Proquazone

Figure 1 shows the DSC curves of 4 marketed products and an experimental suppository which contain paracetamol.

Actifed contains paracetamol, trifolidine and pseudo-ephedrin HCl. The interaction does not allow the clear identification of active ingredients.

Theoretically, if no interaction occur between excipients and paracetamol, 0.08 mg of paracetamol could be easily determined.

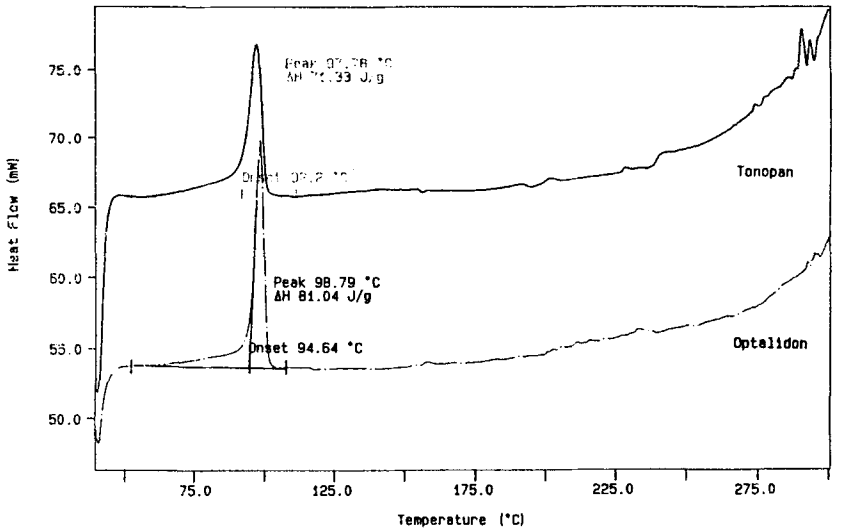

Fig. 6 Eutectic behaviour between components of the tablets. Examples of optalidon and Tonopan

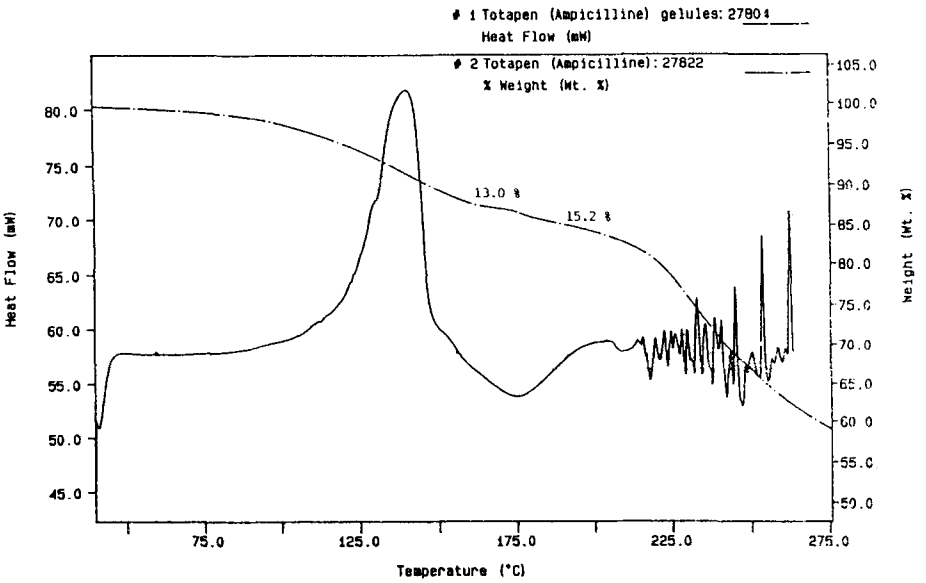

Fig. 7 DSC and TG curves of Totapen (ampicilline trihydrate 500 mg). Theory: 9.3% water, TG found: 13.0%

It is very easy to detect lactose monohydrate or even β-lactose anhydrous in two different placebos. In the product DJN although a slight interaction occurs, the active ingredient is easily identified in two different formulations (Fig. 2).

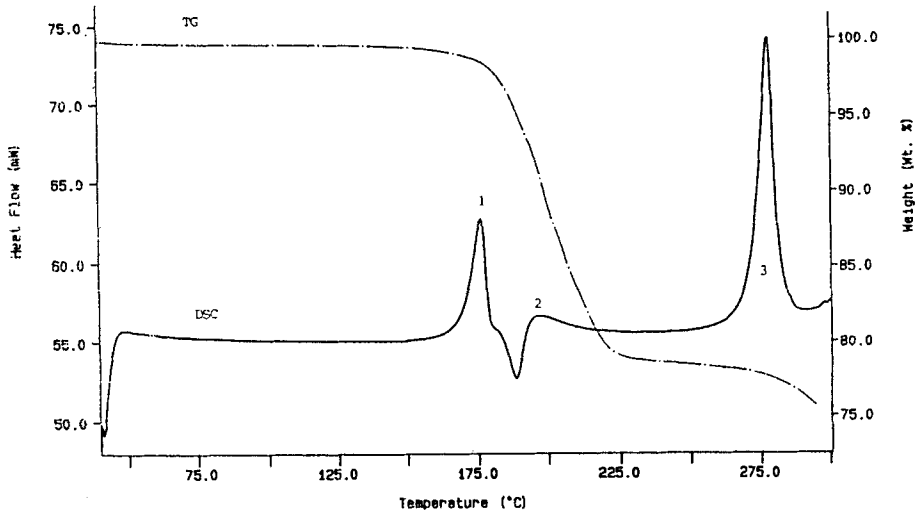

Fig. 8 DSC, TG curves of a malonate salt: (1) melting, decomposition of (2) malonic acid and (3) melting of the base form of the active ingredient. TG: 21.5%, Theory: 21.1% malonic acid

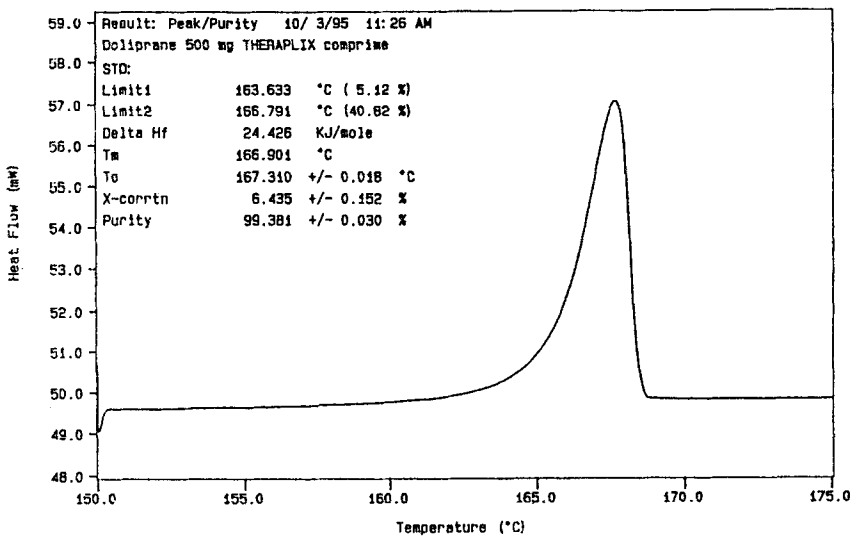

Fig. 9 Example of purity determination of a tablet with high strength: Doliprane

Glass transitions of coating can also serve for identification (Fig. 3).

Figure 4 deals with a drug substance in development. The dosis strength is low, the melting peak is covered by lactose monohydrate, therefore the identification of the active ingredient is not possible. But DSC allows to identify the excipients of

three different formulations, mannitol, poloxamer, polyethyleneglycol, glycerol mono stearate and lactose monohydrate. Cutina could be identified by the study of the expanded scale at low temperature.

Figure 5 shows that proquazone, active ingredient of Biarison has an interaction with stearic acid. Since proquazone is highly dosed, the decreases of the melting point is low and the peak occurs before the dehydration peak of lactose. Other excipients as silicon dioxide, povidone, alginic acid are not identified by DSC, but the dehydration of these excipients occur before the dehydration of lactose monohydrate in the curve of thermogravimetry.

For low dosed products, DSC is limited since an eutectic behaviour with an excipient in higher amount may occur. However the identification of 1 mg Zaditen was possible.

In case of combined products like optalidon and tonopan (Fig. 6 and Table 3), the eutectic interaction between all components make DSC unable for identification. It is interesting to see that the whole product melts at approx. 90°C with active ingredients whose melting points are very high.

Figures 7 and 8 show that TG is very helpful for the identification of drugs: dehydration peak of ampicillin trihydrate (Fig. 7) or melting, decomposition of malonic acid and melting of the base of a malonate salt of a new entity (Fig. 8).

Purity determination is possible [11] as demonstrated in Table 4. Theoretically the true purity should be higher since excipients might be determined as impurity. Example of purity determination is given in Fig. 9 for Doliprane.

Conclusion

DSC and TG techniques with robotic sample devices are very attractive for quick discriminative analysis of drug products, particulary for high dosed products and for identification of excipients. The same scan gives additionally information about polymorphism and pseudo polymorphism of drug substance and excipients.

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