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USE OF DSC ROBOTIC SYSTEMS IN PHARMACEUTICAL ANALYSIS

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DSC is extremely valuable for analysis of pharmaceuticals. The introduction of robotic systems with data acquisition and processing makes it very competitive to other methods in the field of purity determination or solid state characterization of raw materials. Some applications are also possible to dosage forms. Applications of DSC robotics with statistical results are given.

I. Introduction

Differential scanning calorimetry may be widely used in all fields of pharmaceutical analysis [1–4] for raw materials and dosage forms: identifications, polymorphism and pseudo-polymorphism studies, purity and quantitative analysis.

The introduction of robotic systems with auto-sampling, data acquisition and data processing, makes it quite competitive to other routine analytical methods as melting point determination, spectroscopy or chromatography for routine control as well as for development work.

II. Instrument

Three companies offer robotic systems: Perkin–Elmer (DSC–4 and DSC–7), DuPont and Setaram.

The examples given here have been obtained with the Perkin–Elmer DSC–7 robotic system.

The system is composed of a removable 48 position sample carousel and a pneumatically controlled robotic sampling arm. This automatic loading and unloading system with the DSC sample holder forms an independant unit. Programming and activation are controlled by the Computer PE 7700. When in operation, the robotic arm automatically selects a desired sample from any of the 48

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carousel positions, places it in the DSC sample holder and closes the sample holder enclosure cover.

Several heating/cooling cycles are possible for each sample and are programmed with the computer. Data are aquired according to the given instructions and data processing is possible at any time after the measurement.

The repeatability of the system is demonstrated by the good standard deviations obtained for melting point and melting enthalpy of different samples of pure indium at 3 different heating rates, measured in one run as given in Table 1.

Table 1 Repeatability of the DSC–7 robotic system. Indium at different heating rates

Heating rate, deg·min^{-1}	Melting energy, J g^{-1}	*s*, rel.%	Onset, °C	*s*, rel.%	*n*
10	28.22	0.57	156.83	0.007	6
5	28.55	0.30	156.34	0.003	6
2.5	28.56	0.10	156.29	0.008	6

As expected the calorimetric accuracy is lower at high heating rate. The differences of the onset values are due to the thermal lag of the sample holder and are used for temperature corrections.

III. Rational applications

III.1 Calibration

Calibration of temperature and enthalpies are done very quickly, allowing frequent controls and therefore conforming to pharmaceutical SOPs. Table 2 is an example of a run overnight.

III.2 Raw material characterization

III.2.1 Glass transition

Table 3 demonstrates the reproducibility of glas transition determination of polyvinylpyrrolidone (anhydrous). The DSC scans are given in Fig. 1. The glas transitions of marketed polyvinylpyrrolidone types given in Table 4 can be used for identification.

III.2.2 Melting point determination

DSC allows more accurate melting point determination than classical methods. The onset temperature is defined as melting point.

Table 2 Calibration for temperature and heat

2.1 Temperature. Example at 2 deg·min^{-1} heating rate

Substances	Melting point, °C	Onset found, °C	Deviation, °C
4-Nitrotoluene	52.0	52.9	+0.9
Azobenzene	69.0	69.5	+0.5
Biphenyl	69.2	69.5	+1.1
Naphthalene	80.5	81.4	+0.9
Benzil	95.0	95.3	+0.3
Acetanilide	114.0	115.0	+1.0
Benzoic acid	122.4	123.3	+0.9
Diphenylacetic acid	147.0	147.4	+0.4
Adipic acid	151.4	151.2	+0.2
Indium	156.6	156.6	0.0
Anisic acid	183.0	182.7	−0.3
Salophen	192.0	191.1	−0.9
Tin	232.0	232.0	0.0
Bismuth	271.4	270.5	−0.9
Cadmium	321.1	320.5	−0.6
Lead	327.5	326.6	−0.9
Zinc	419.5	418.9	−0.6

2.2 Calorimetric calibration

Heating rate, deg·min^{-1}	Indium, J g^{-1}	Benzoic acid, J g^{-1}	Naphthalene, J g^{-1}
20	27.9	142.7	145.3
10	27.9	144.3	144.2
5	28.2	144.0	145.0
2.5	28.0	142.2	144.7
Theory	28.5	147.4	148.7

Table 3 Determination of glass transition of polyvinylpyrrolidone (Kollidon K25) Measurements in a second run after quenching at 20 deg min^{-1}

Glass transition	157.1 °C
s, rel.%	0.4%
Maximum	158.2 °C
Minimum	156.4 °C
Delta C_p	24 J g^{-1} C^{-1}
s, rel.%	4%
n	6 values

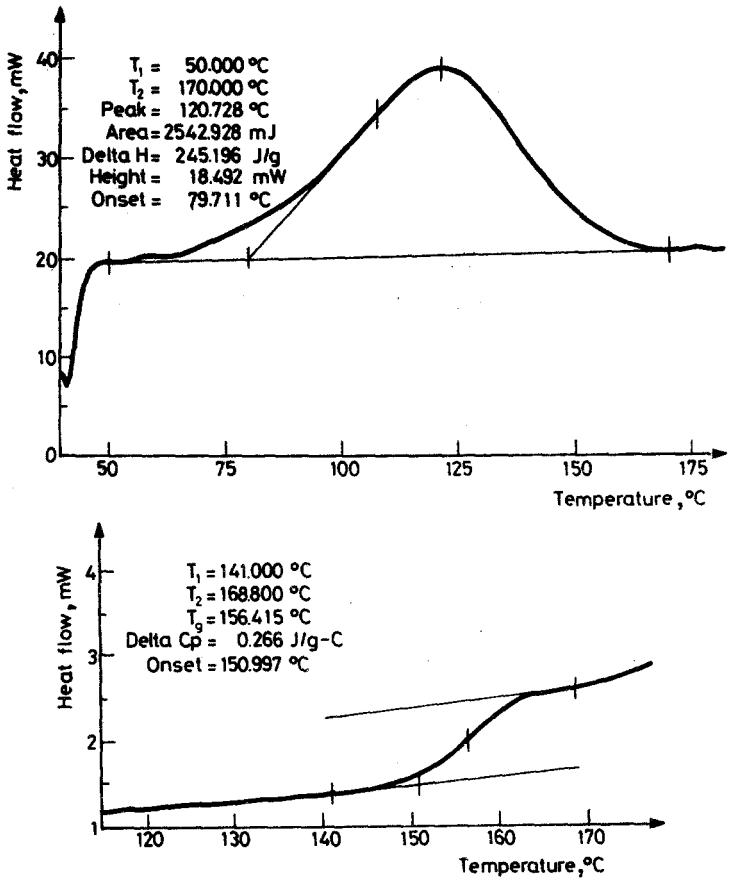

Fig. 1 Glass transition determination of Kollidon 25. DSC scan after first run and quenching

Table 4 Typical glass transition values of different polyvinylpyrrolidone qualities in the anhydrous state

Designation	Glass transition, °C
Kollidon 12	93
Kollidon 17	130
Kollidon 25	156
Kollidon 30	168
Kollidon 90	178
Polyvinylpyrrolidone (crospovidone)	185

Examples of standard deviation obtained with the robotic system are given in Table 5. In the same experiment, purity results and melting energies may be determined. Table 6 demonstrates the rational use of the robot for optimisation. The melting point and the heat of fusion are independent of the heating rate.

Figure 2 shows the use of DSC scans for identification of different polyethylene glycol types by their melting behaviour.

Table 5 Reproducibility of results obtained by the DSC–7 robot of Perkin–Elmer

a) Physostigmine base Heating rate 5 deg/min ΔH = 33 kJ/mol vsp pans			b) Butalbital Heating rate 2.5 deg/min ΔH = 25 kJ/mol vsp pans			vsp pans with holes		
Weight	Onset, °C	Purity	Weight	Onset, °C	Purity	Weight	Onset, °C	Purity
2.197	104.3	99.69	1.583	139.0	99.84	1.551	138.8	99.98
2.196	104.1	99.64	1.561	138.9	99.85	1.565	138.9	99.98
2.109	104.1	99.64	1.578	138.9	99.88	1.553	138.8	99.98
2.109	104.2	99.65	1.540	138.9	99.90	1.544	138.8	99.98
2.188	104.2	99.60	1.527	138.8	99.90	1.578	138.8	99.98
2.222	104.15	99.66	1.537	139.2	99.86	1.512	138.7	99.965
2.186	104.1	99.60	1.519	139.0	99.88			
1.110	104.1	99.70	1.070	139.0	99.88			
3.153	104.0	99.70	2.098	139.0	99.94			
4.241	104.2	99.69	3.069	139.1	99.88			
			4.047	139.4	99.96			
			5.082	139.3	99.96			
x_{10} = 104.15 °C			x_{12} = 139.04 °C			x_6 = 138.79 °C		
s = 0.08			s = 0.18			s = 0.05		
s% = 0.08%			s% = 0.13%			s% = 0.04%		

Table 6 Optimisation of method: influence of heating rate and sample weight with robotic system for a new entity

Heating rate 1.2 deg min^{-1}				2.5 deg min^{-1}				5 deg min^{-1}			
Weight	T_0, °C	Purity	kJ/mol	Weight	T_0, °C	Purity	kJ/mol	Weight	T_0, °C	Purity	kJ/mol
1.041	125.9	99.61	35.4	1.090	126.3	99.41	35.3	1.048	127.1	99.4	35.6
2.084	126.3	99.86	35.2	2.045	126.4	99.53	35.3	2.032	126.8	99.42	35.3
3.105	126.2	99.68	35.3	3.034	126.2	99.57	34.8	3.030	127.1	99.81	35.9
4.007	126.4	99.80	34.5	4.091	126.3	99.54	34.8	4.027	126.8	99.76	36.3
5.073	126.3	99.63	34.2	5.046	126.8	99.77	35.9	5.518	126.5	99.83	34.6

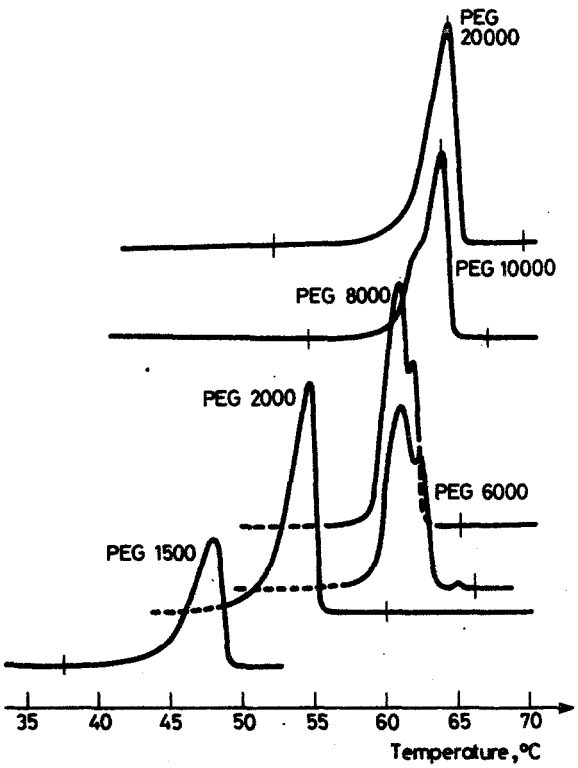

Fig. 2 Identification of different types of polyethylene glycols by means of their melting point. Same run with the robotic system

III.2.3 Hydrate characterization

Dehydration enthalpy and temperature of alpha lactose monohydrate are very characteristic and may be used for identification and quantitation purposes in mixtures.

Table 7 shows the reproducibility of the measurements.

Table 7 Study of lactose monohydrate with DSC–7 robotic system .30 µl pans with holes

Heating rate, deg min^{-1}	Dehydratation				Melting alpha lactose			
	°C	*s* rel.	J g^{-1}	*s* rel.	°C	*s* rel.	J g^{-1}	*s* rel.
20	145.2		113		214.1		108	
5	143.6		106		210.1		80.6	
10 ($n=6$)	143.8	0.22%	106.5	3.4%	210.7	0.1%	102.0	2.1%

III.3 Purity determination

Purity determination is the most attractive application of DSC in pharmaceutical analysis for routine control of drug substances, intermediates and excipients. The robotic system allows easy method optimization as demonstrated in Table 5 and 6: heating rate, sample size, pan type... as well routine determinations since every sample is treated independently.

Table 5 gives examples of accuracy which may be obtained with the robot. As expected the purity results are higher in vsp with holes than with vsp, due to the loss of volatile part.

III.4 Polymorphism studies

III.4.1 Polymorphism screening

Every study of polymorphism first need a screening design. The easiest way is to run the DSC curve after first scanning and quenching.

Other experiments such as crystallisation in different ways or with additives or vibration of excess solid phase in different solvents are also useful. The DSC robot allows quick study of all samples (example Fig. 3). Furthermore information about the purification effect may be deduced as demonstrated in Table 8.

III.4.2 Kinetic studies

The instrument ability of heating/cooling, isothermic cycles allows the study of transition behaviour by heat treatment. Table 9 is a good example of such a study of

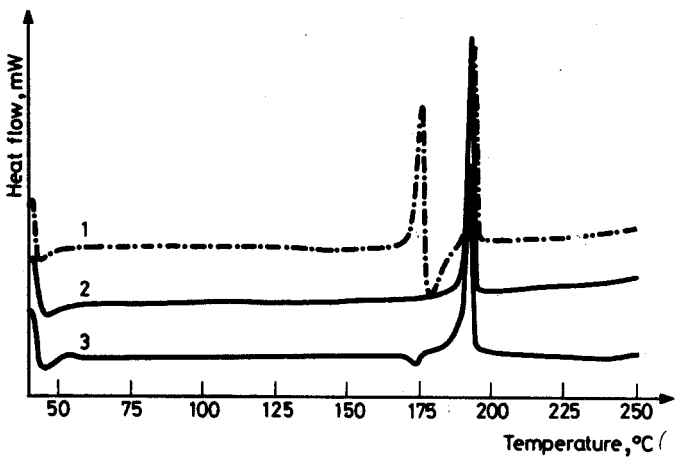

Fig. 3 Polymorphism screening. 1: Sample treated with vibration in isopropanol. 2: Sample before or after treatment at r.t. in hexane or ethylacetate or after DSC run up to 175 °C. 3: Sample treated in hexane at 35 °C

Table 8 Polymorphic study after vibration in different solvents and information on purity in one run

Treatment	Form	Purity, %
Original	I	99.7
Diethylether	I	99.5
Hexane	I	99.5
Acetone	I	99.8
Isopropanol	I	99.75
Ethylacetate	I	99.5
Water	Hydrate	99.65
Ethanol/water	Hydrate	99.6
THF/water	Hydrate + II	99.9

Table 9 Polymorphic kinetic study with DSC robotic system

Isotherm at 105 °C time	Sample 1 (A + amorphous)	Sample 2 (A)
1 hour	47 J g^{-1}	96.5 J g^{-1}
2 hours	64	96.5
3 hours	81	96.5

isothermal treatment at 105° and scanning of the DSC curve in order to measure the melting peak. The melting enthalpy increases with the time of a pretreatment in a batch, while this value remains constant for another batch, demonstrating the presence of amorphous material.

III.4.3 Sample inhomogeneity

The analysis speed of robotic systems allows more experiments, which leads to a great increase in the accuracy of the results. Inhomogeneity of samples may be easily demonstrated. Figure 4 deals with the same samples as in Table 9.

III.4.4 Quantitative determinations

Quantitative determinations of polymorphism are not easy by DSC, due to kinetics in the solid state, with concurrency between solid–solid transitions of small energy and melting, or other crystallisation processes [5, 6].

For the example given in Fig. 5 and Table 10, the polymorphic behaviour of current batches could be observed by means of the solid-solid transition before melting. The reproducibility of the transition is very good.

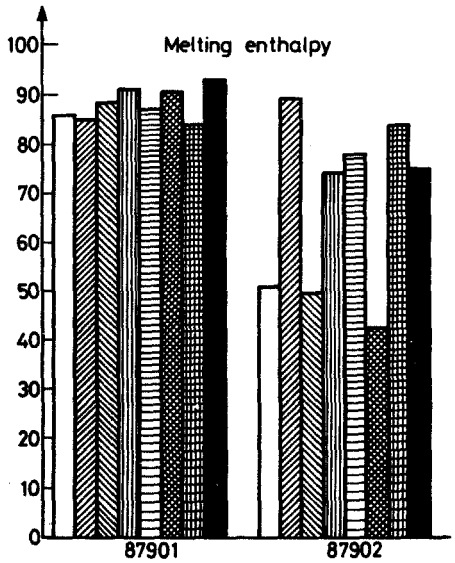

Fig. 4 Crystalline inhomogeneity of the sample 2. Sample 1 is homogeneous. Same example as in Table 9. Sample 1: Heat: 88.2 J g^{-1} *s* rel. 3.7%. Sample 2: Heat: 68 J g^{-1} *s* rel. 26%

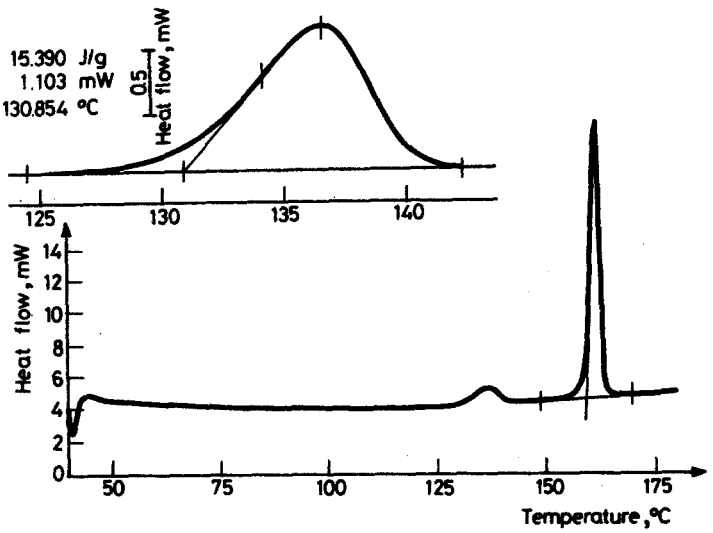

Fig. 5 DSC determination of a solid–solid transition

Table 10 Study of a solid–solid transition before melting point. 10 determinations. Purity 99.9%. Heating rate 10 deg min^{-1}

Transition II →I				Melting of I			
J g^{-1}	*s*, rel.%	onset	*s*, rel.%	J g^{-1}	*s*, rel.%	onset	*s*, rel.%
15.6	6.1	132.0	2.9	105.7	2.9	159.0	0.2

From 5 to 20 deg min^{-1} same heat of transition and of melting of I.

III.4.5 Study of polymorphism after granulation

Figure 6 demonstrates the rational use of robotics for a drug substance exhibiting several crystalline modifications. No change could be observed after granulation.

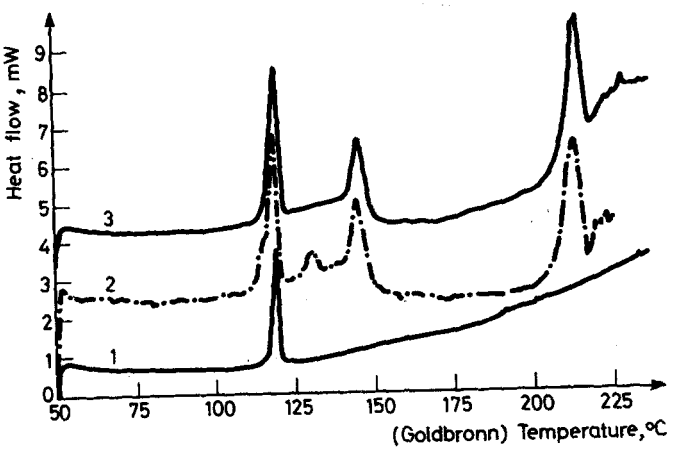

Fig. 6 DSC study of polymorphic behaviour in a granulation process. 1: active ingredient Form B; 2: granulate spiked with 10% Form C (containing traces of Form A); 3: granulate with Form B

III.5 Stability studies

DSC is very helpful both for determining degradation products and for polymorphic transitions [1, 2]. Table 11 demonstrates such a study with a DSC robotic system for the substance described in III.4.5.

Figures 7 and 8 demonstrate the competitivity of DSC robotics with chromatography and melting point, with results of stability samples scanned in the same run.

All results were obtained in one day. The 4 batches are of very reproducible quality and very stable as deduced from the small variations of melting points, melting enthalpies and purity results.

Table 11 Study of stressed samples: influence on polymorphism and purity

Sample	Form	Purity, %
As it	A	98.0
1 month 60 °C	A	97.9
1 month 60 °c+2% water	A+B	98.0
1 month 80 °C	A	98.5
1 month 80 °C+2% water	A+B	97.0
1 month 80 °C under oxygen	A	97.8

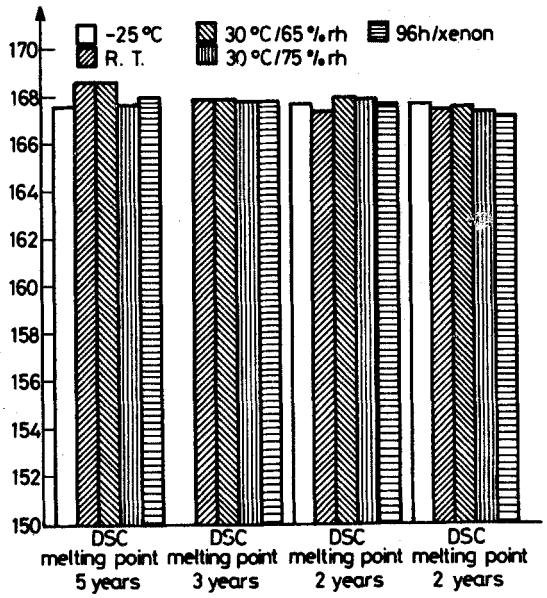

Fig. 7 DSC melting points of 4 different batches of a drug substance after 5 years, 3 years and 2 years storage in different conditions: variation < 1 °C

In the same run a validation of the DSC determination of the degradation product could be made: Purity of the sample as it: 99.8%, purity of the sample spiked with 1% degradation product: 98.8%.

III.6 Quantitative determinations in dosage form

The sensitivity of DSC allows measurements down to 0.063 mg drug substance (Fig. 9).

Therefore if no interaction occurs with excipients (immiscibility in solid and liquid states), quantitation in the dosage form is easy and accurate. Due to the small

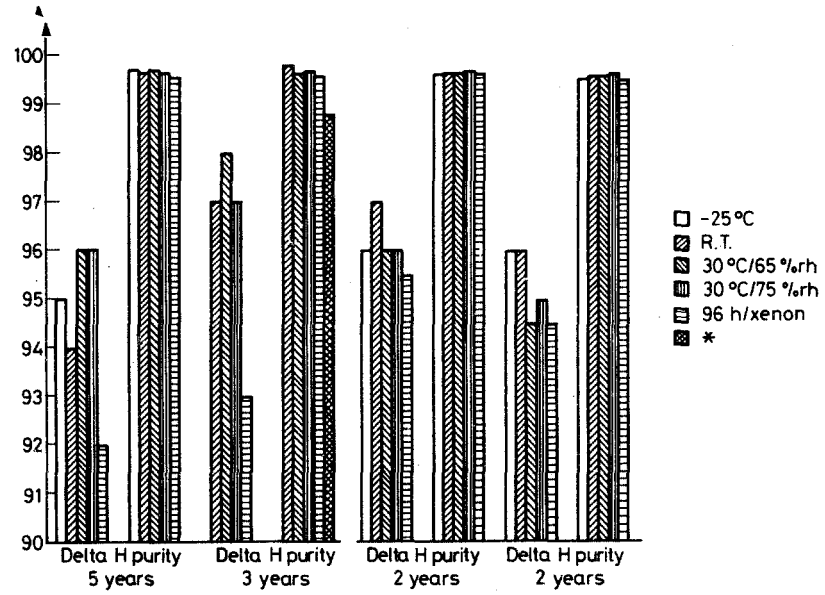

Fig. 8 Melting enthalpies and purity results of 4 different batches after storage in different conditions.
* Purity determination after spiking of 1% degradation product

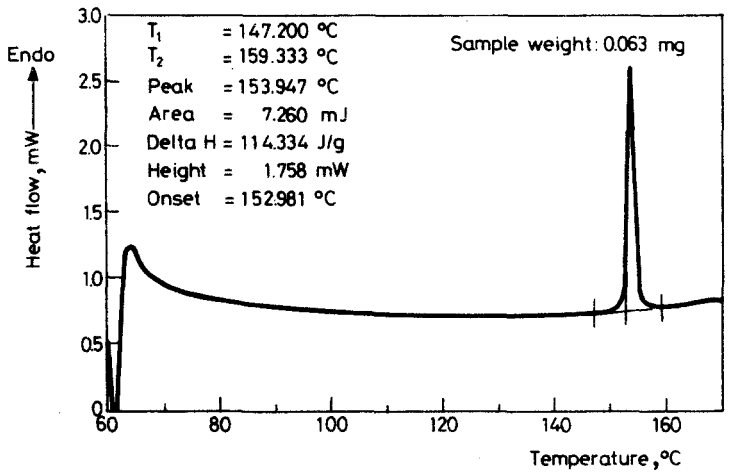

Fig. 9 DSC sensitivity: melting peak of 0.063 mg of a drug substance

Table 12 Quantitation of a drug substance in a capsule with the melting enthalpy at 10 deg min^{-1}. Weight: 5 mg of each capsule

Drug in the capsule, %	Theoretical value
42.2	47.6
46.2	
47.0	
42.8	
46.6	

weight, DSC with the robot would be an attractive method for content uniformity determination. An example of determination with 5 capsules is given in Table 12.

IV. Discussion

We chose examples where the statistical accuracy of the robotic system was demonstrated. The applications are not limited (phase diagrams, interactions, stability in situ, kinetics...). Each experiment may be done with the robotic system, but some prequisite are necessary.

A first run must be done for new substances.

If a volatile part is evolved in decomposition process, it may crystallise under cooling in the sample holder and may stop the mechanical function of the arm. Furthermore the base line may be drastically changed.

The delay time between procedures must be long enough for the system. If the substance undergoes transition at r.t. before measurement, the robotic system is not suitable.

The DSC scan of an Indium sample in a run is highly recommended.

In conclusion DSC robotic systems offers rational measurements, data aquisition and processing allowing accurate rapid analysis in a pharmaceutical laboratory performing routine control.

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Zusammenfassung – Zur Analyse von Arzneimitteln ist DSC außerst wertvoll. Die Einführung von Robotersystemen mit Datenaquisition und -aufarbeitung macht dieses Verfahren auf dem Gebiet der Reinheitsuntersuchung und Feststoffcharakterisierung der Rohmaterialien konkurrenzfähig im. Vergleich zu anderen Methoden. Einige Varianten lassen sich auch auf fertige Präparate anwenden. Es wird die Anwendung von computerisierten DSC-Systemen einschließlich statistischen Ergebnissen gegeben.

Резюме — Дифференциальная сканирующая калориметрия является чрезвычайно полезным методом анализа фармацевтических препаратов. Введение роботных систем со сбором и обработкой информации делает этот метод весьма конкурентно способным по сравнению с другими методами в области определения чистоты фармацевтических препаратов или характеристики исходных сырьевых препаратов в твердом состоянии. Возможно также некоторое использование этого метода для дозировки. Представлено применение роботных ДСК с результатами статистической обработки.