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THERMAL ANALYSIS OF PHARMACEUTICAL COMPOUNDS. V. THE USE OF DIFFERENTIAL SCANNING CALORIMETRY IN THE ANALYSIS OF CERTAIN PHARMACEUTICALS

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ABSTRACT

Differential scanning calorimetric (DSC) analysis was carried out for some interesting pharmaceutical compounds which have different thermal characteristics. The compounds investigated were phenacetin, cholesterol myristate, sulphathiazole, sulphadiazine, sulphadimethyloxazole, sulphamerazine and sulphadimidine. The DSC scans of the compounds were thoroughly studied and the pronounced features for each are given, including their behaviour on fusion. It is confirmed that some of the examined pharmaceuticals, such as sulphathiazole, sulphadiazine and sulphadimethyloxazole, exist in polymorphic forms. The information obtained is useful in interpreting the results of the examination of the compounds by thermogravimetry (TG), derivative thermogravimetry (DTG), differential thermal analysis (DTA) and their melting point determinations using the Kofler microscope. The heat of reaction is calculated for all the reactions of the compounds studied.

The possibility of purity determination of the examined compounds by a thermoanalytical method was studied. The DSC method was found to be suitable for the purity determination of sulphamerazine and sulphadimidine in addition to phenacetin for which the method is known to be applicable. The remaining compounds, on the other hand, do not exhibit the required characteristics for the determination of purity by the DSC method. DSC was also found to contribute to stability studies, where sulphathiazole was found to be the least stable among the examined sulphonamides.

INTRODUCTION

In recent years, thermal analysis techniques have found widespread application in research, development and quality control laboratories [1]. Differential scanning calorimetry (DSC) is the most widely used thermal analysis technique by which the fundamental thermal properties can be measured [2].

The estimation of the purity of pharmaceutical compounds is one of the most important aspects of a drug profile. Many of the techniques used are time consuming and require large amounts of sample. The analytical methods currently used to determine the purity of organic compounds include

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such techniques as phase solubility analysis, chromatographic and spectroscopic methods [3,4].

A thermoanalytical method which makes use of DSC has been used successfully in recent years for the determination of absolute purity. The method is based on the van't Hoff equation and the working conditions and some applications have been studied [5–10]. The method is rapid, accurate and precise, but it is not universally applicable to all materials [5].

The calorimetric purity method is accepted by the U.S. Pharmacopeia/National Formulary [11] as a reference test method and is in preparation as a standard ASTM test [12].

The present work is a continuation of the series of studies of the thermal analysis of pharmaceutical compounds [13–16] and records a DSC study of some interesting pharmaceuticals. The use of DSC for the calculation of the heats of transition and purity, where possible, of these pharmaceuticals is also achieved.

The samples used for the present study include phenacetin (as a model material for which the purity determination was previously done by the calorimetric method [17]), cholesterol myristate (undergoing liquid–liquid transition) and some sulphonamides (sulphathiazole, sulphadiazine, sulphadimethyloxazole, sulphamerazine and sulphadimidine).

Of the commercial sulphonamides, about 65% are polymorphic [18]. The study of polymorphism is particularly interesting since unstable forms frequently crystallize from solvents and some of them occur as commercial products not in the highest melting modification but in an unstable or metastable form [19].

A comparison is also made of the melting point determination of the examined sulphonamides by DSC, DTA and the Kofler microscope.

EXPERIMENTAL

Materials and apparatus

Pharmaceutical compounds

(1) Phenacetin ($C_{10}H_{13}NO_2$), M.W. 179.22; Merck.

(2) Cholesterol myristate ($C_{41}H_{72}O_2$), M.W. 579.03; Merck.

(3) Sulphathiazole ($C_9H_9O_2N_3S_2$); M.W. 255.32; El Nasr Pharmaceutical Chemicals Co.

(4) Sulphadiazine ($C_{10}H_{10}O_2N_4S$), M.W. 250.28; El Nasr Pharmaceutical Chemicals Co.

(5) Sulphadimethyloxazole ($C_{11}H_{13}N_3O_2S$), M.W. 267.3; Nordmark-Werke Gmbh, Hamburg.

(6) Sulphamerazine ($C_{11}H_{12}O_2N_4S$), M.W. 264.37; El Nasr Pharmaceutical Chemicals Co.

(7) Sulphadimidine ($C_{12}H_{14}O_2N_4S$), M.W. 278.34; El Nasr Pharmaceutical Chemicals Co.

Standard materials

(1) Indium
(2) Tin

Apparatus

(1) DuPont 990 Thermal Analyzer programmer/recorder used with 910 Differential Scanning Calorimeter (DSC) system.
(2) DuPont 1090 Thermal Analysis/data system used with 910 DSC system.
(3) The Paulik–Paulik–Erdey Derivatograph, Type No. 3465; MOM, Hungary.
(4) Kofler microscope; Reichert, Austria.
(5) Planimeter; MOM, Hungary.

Procedures and calculations

The whole study was carried out using the 910 DSC system with the aid of the 990 thermal analyzer programmer/recorder or the 1090 microcomputer-controlled thermal analysis data system. As an example, the conditions for the model sample, phenacetin, using the 990 thermal analyzer programming recorder was as follows.

DSC scan

Accurately weighed (2–5 mg) of the sample were placed in the DSC pan and the cover fitted using the sample encapsulating press. An empty pan and lid treated in the same way was used as reference. The scan was made under the following conditions:

atmosphere: nitrogen at 50 ml min^{-1}
heating rate: 10°C min^{-1}
shift (cm): 0
starting temperature: room temperature
limit temperature: 300°C
Program rate: return to start
sensitivity: 5 mV cm^{-1}

Generally, a scan was first made to 500°C and then another scan was run to the lowest interesting temperature.

Calculation of the heat of reaction, ΔH

The following procedure was perfectly general, but the temperature range and program rate varied depending on the particular system being studied.

For phenacetin:
sample size: 3.4 mg
sensitivity DSC Y: 0.5 mV cm^{-1}
sensitivity TY′: 20 mV cm^{-1}
temperature program rate: 10°C min^{-1}
zero shift: 0
time base: 0.5 min cm^{-1}
starting temperature: 96°C
final temperature: 160°C
mode: return to start

The DSC scan obtained and the peak area were used to calculate ΔH by substitution in

$$\Delta H = \frac{A}{m}(60\ BE\ \Delta qs)$$

where A = the peak area in cm^2, m = the sample mass in mg, B = the time base setting in min cm^{-1}, E = the cell calibration coefficient at the temperature of the experiment in mW mV^{-1} (dimensionless), Δqs = the Y axis range setting in mV cm^{-1} (mcal s^{-1} in^{-1}), and ΔH = the heat of fusion in J g^{-1}.

The determination of the cell calibration coefficient (E) was carried out using indium, the heat of fusion of which is accurately known, as a standard.

Determination of purity

Purity determination was based on the van't Hoff equation modified to

$$T_s = T_0 - \left(\frac{RT_0^2X^2}{\Delta H_f}\right)\frac{1}{F}$$

where ΔH_f = heat of fusion of the pure major component (cal $mole^{-1}$), R = the gas constant (1.987 cal mole K^{-1}), T_s = the sample temperature (K), T_0 = the melting point of the pure major compound (K), X_2 = the mole fraction impurity, and F = the fraction of sample melted at T_s.

A plot of T_s vs. $1/F$ will be a line of slope $-RT_0^2X^2/\Delta H_f$.

ΔH_f may be obtained directly from the DSC scan or from the literature and the mole fraction impurity calculated. The purity was calculated by subtracting the impurity level, expressed in percent, from 100. Typical control parameters were:

sample weight: 1–5 mg
atmosphere: nitrogen (50 ml min^{-1})
heating rate: 1°C min^{-1}
time base: 0.5 min cm^{-1}
sensitivity: selected to maximize area
range: 0.5 mV cm^{-1}
zero shift: 0
program mode: return to start

starting temperature: 8° below melting point
limit temperature: 15°C above melting point
reference: empty pan and lid.

The same investigations (DSC studies, heats of reaction and determination of purity) were made using the 1090 thermal analysis data system.

The 1090/910 DSC system is a microcomputer-controlled analyzer that collects, processes, stores and reports data in the form desired for optimum display or analysis by playing back in the autoscale mode.

Absolute purity was quickly and easily determined with the 1090 Thermal Analyzer. Automatic calibration, data analysis results and the completed final report (including the thermal curves) were presented on one single sheet of paper [17].

RESULTS AND DISCUSSION

DSC scans for indium and tin, as reference materials used for calibration, are shown in Fig. 1. Detailed information for both, e.g. melting temperatures and heat of fusion, are shown in Figs. 2 and 3, respectively. For indium, the starting fusion temperature is 157.1°C and the peak temperature is 158.8°C. For tin, the temperature of the start of fusion is 231.5°C, that of the peak is 233.2°C and its heat of fusion is found to be 62.2 J g^{-1}. A thorough examination of these reference materials is needed for the calculation of heat of fusion and determination of purity of the samples studied.

The DSC scan of phenacetin is shown in Fig. 4. For calculation of its heat of fusion, the cell calibration coefficient was determined using indium and was found to be 0.193. Another DSC of phenacetin was carried out on time

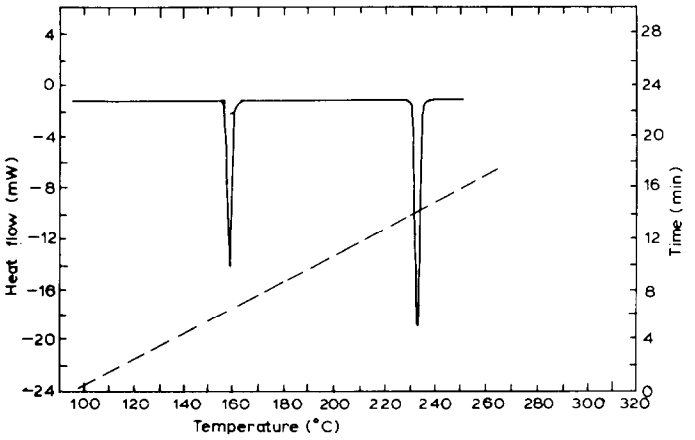

Fig. 1. Calibration DSC scans for indium (4.95 mg) and tin (4.41 mg). Heating rate, 10°C min^{-1}; ————, heat flows; - - - - - - time.

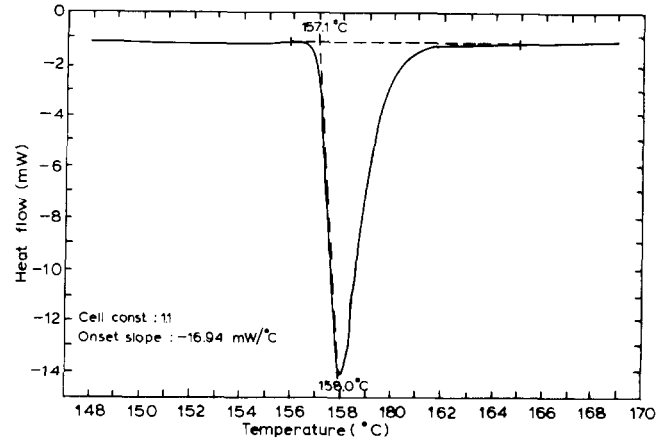

Fig. 2. Calibration DSC scan for indium (4.95 mg). Heating rate, 10°C min^{-1}; cell constant, 1.100; onset of slope -16.94 mW $°C^{-1}$.

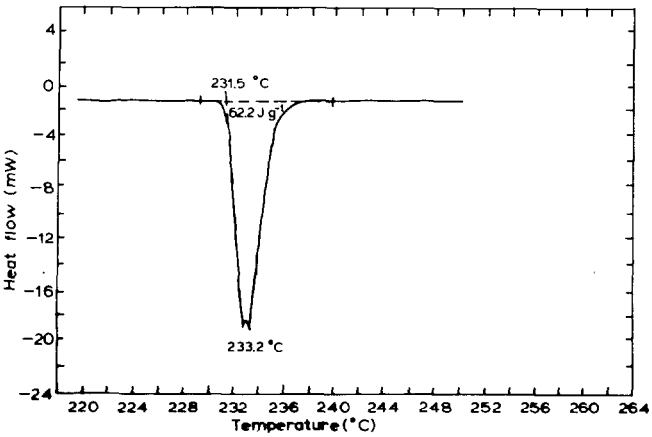

Fig. 3. Calibration DSC scan for tin (4.41 mg). Heating rate, 10°C min^{-1}.

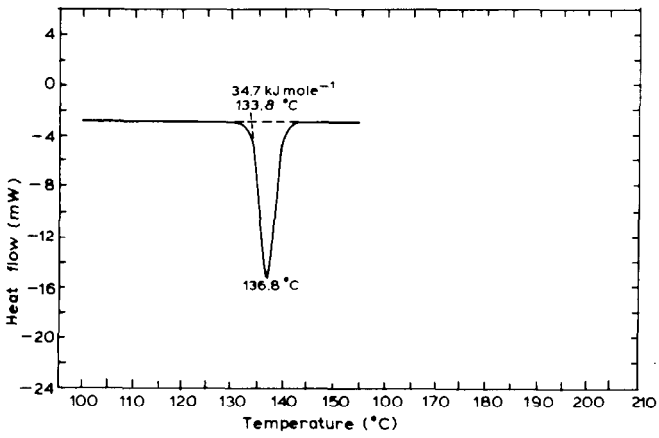

Fig. 4. DSC scan of phenacetin.

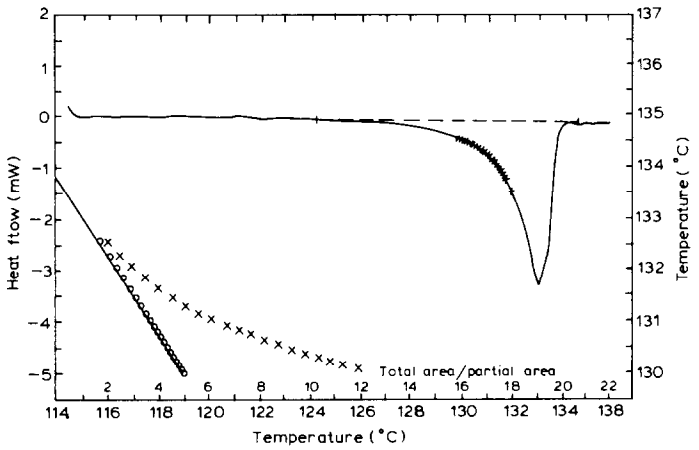

Fig. 5. DSC scan of 98 mole% phenacetin (1.96 mg). Heating rate, 1°C min^{-1}; program, dynamic purity. Found: purity, 97.80 mole%; ΔH 40.6 kJ $mole^{-1}$; melting point, 133.9°C; depression, 0.75°C; correction, 14.27%; M.W. 179.2; cell constant, 1.100; onset of slope, -16.94 mW $°C^{-1}$.

base and its heat of fusion, calculated according to the previously mentioned method, was found to be 34.7 kJ $mole^{-1}$.

The purity of the examined phenacetin sample as determined manually by the given procedure was found to be 99.8 mole%. The purity of another sample, stated to contain 98 mole % of phenacetin, was determined by the microprocesser analyzer and was found to be 97.8 mole% phenacetin. The results are given in Fig. 5.

Differential scanning calorimetric study of cholesteryl myristate, Fig. 6, reveals three endothermic transformations. The first reaction is considerably

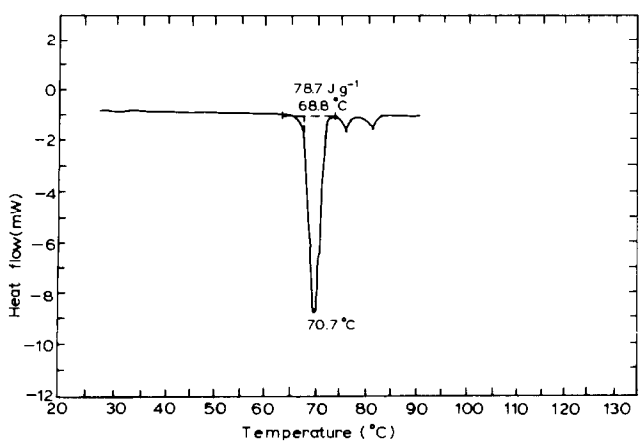

Fig. 6. DSC scan of cholesterol myristate (3.35 mg). Heating rate, 5°C min^{-1}.

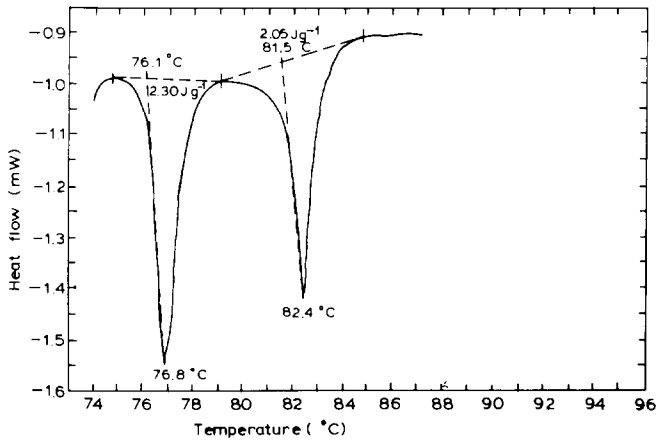

Fig. 7. DSC scan of cholesterol myristate (3.35 mg). Heating rate, 5°C min^{-1}; program, interactive DSC V1.1.

larger than the other two. The starting and peak temperatures are 68.8 and 70.7, 76.1 and 76.9, 81.5 and 82.4°C, respectively, for the three reactions. The heat of the first reaction was calculated by carrying out a scan on a time base and was found to be 78.7 J g^{-1}. The other two transformations were too small to calculate their heats of reaction manually. The use of the microcomputer analyzer enabled their determination to be carried out and they were found to be 2.3 and 2.05 J g^{-1} for the second and third transformations, respectively (Fig. 7).

Cholesterol myristate is an example of a substance undergoing liquid–liquid transition [20,21]. The first peak is the melting of the solid and the formation of the smectic liquid crystal phase. The second transition is the

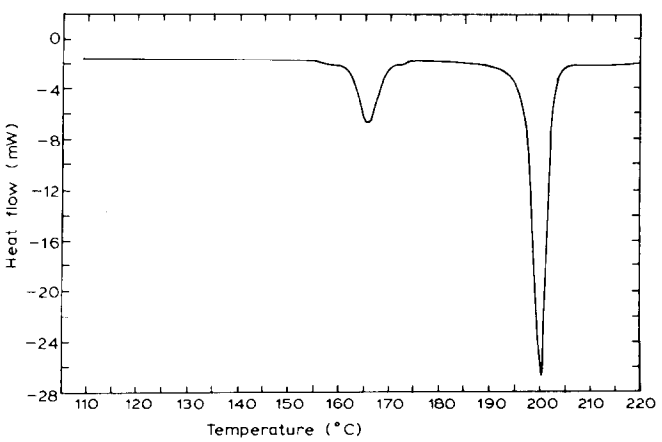

Fig. 8. DSC scan of sulphathiazole (5.11 mg). Heating rate, 10°C min^{-1}; program, extended playback V1.1.

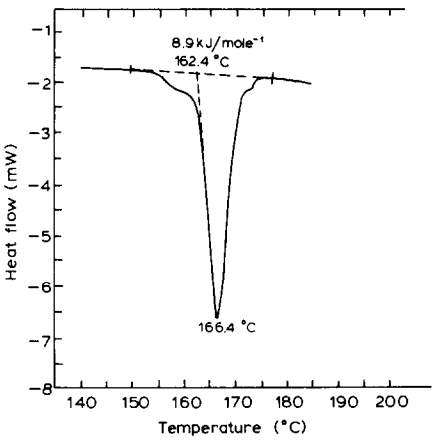

Fig. 9. DSC scan of sulphathiazole (5.11 mg). Heating rate, 10°C min^{-1}; program, interactive DSC V1.1. First reaction.

change from the smectic to the cholesteric phase, while the third peak represents transformation to the isotropic liquid. From the quantitative calculation of the heat of reaction (ΔH), the low energy liquid crystal transitions are observed for the second and third reactions (2.3 and 2.05 J g^{-1}, respectively) in contrast to the high figure of the first reaction (78.7 J g^{-1}). The purity of cholesterol myristate cannot be determined by the differential scanning calorimetric method since it undergoes liquid–liquid transition.

The differential scanning calorimetric behaviour of some sulphonamides, an important analytical group, many of its members undergoing polymorphism, is interesting in this concept.

Figure 8 illustrates the DSC scan of sulphathiazole. It shows two endo-

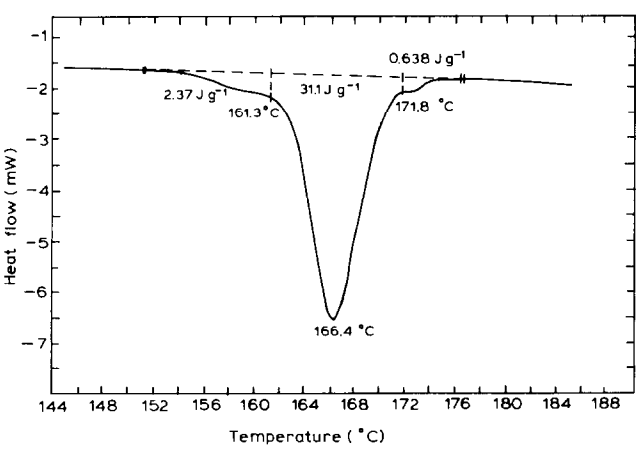

Fig. 10. DSC scan of sulphathiazole (first reaction).

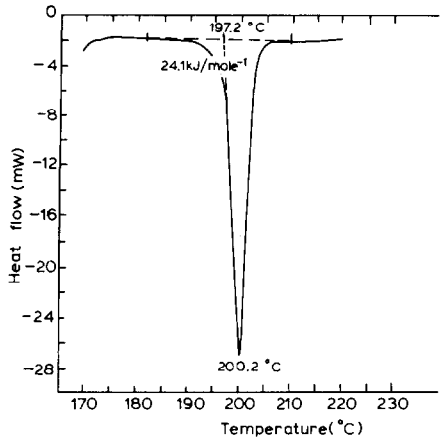

Fig. 11. DSC scan of sulphathiazole (5.11 mg). Heating rate, 10°C min^{-1}; program, interactive DSC V1.1. Second reaction.

thermic reactions with peak temperatures at 166.4 and 200.2°C, respectively. The first peak appears to be formed of three stages the main of which is the middle stage. Quantitative calculations of the heat of reaction (ΔH) give 8.93 kJ $mole^{-1}$ for the first reaction (Fig. 9) [2.37, 31.1 and 0.638 J g^{-1} for the three constituent stages, respectively (Fig. 10)] and 24.1 KJ $mole^{-1}$ for the second reaction (Fig. 11).

In order to verify the nature of the corresponding reactions, a sulphathiazole sample was treated at a slower heating rate where the peaks were resolved, indicating solid–solid transitions and not decomposition reactions. Also, the sample was heated to the end of the first peak (about 180°C), cooled and the DSC scan recorded on heating again to the end of the second peak (about 220°C). It was observed that the first peak disappeared and was

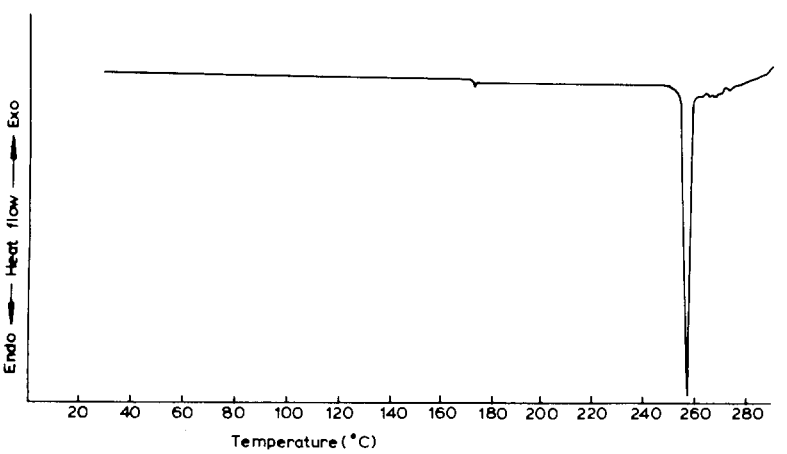

Fig. 12. DSC scan of sulphadiazine (2 mg).

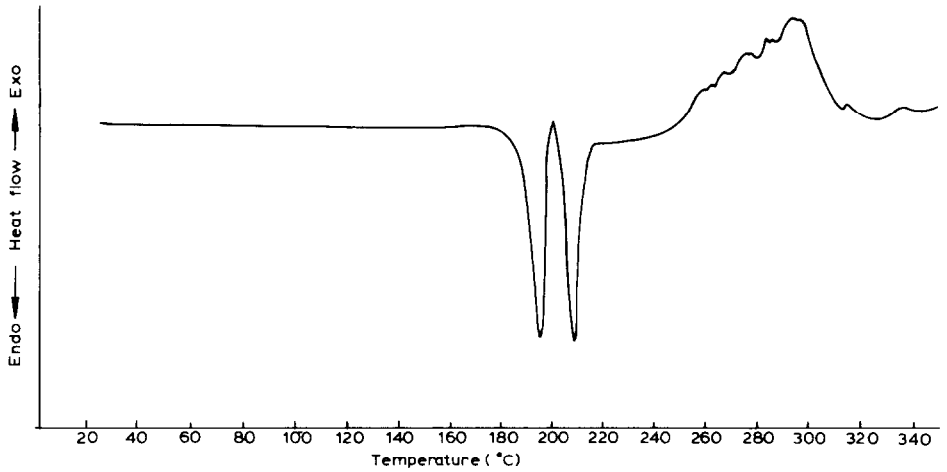

Fig. 13. DSC scan of sulphadimethyloxazole (6 mg).

added to the second peak. This indicates a multiple phase system which, on heating, irreversibly changes and does not recover on cooling since it is transformed into one phase. Thus more than one crystal form is present.

This result is in accordance with the author's observation in a previous work on sulphathiazole, sulphadiazine, sulphamerazine and sulphadimidine [15], in which the compounds were examined by thermogravimetry (TG), derivative thermogravimetry (DTG) and differential thermal analysis (DTA). Their melting points were determined by the Kofler microscope and compared with those stated in the literature. The melting point of sulphathiazole was found in the literature to be 200–203°C, but when it was determined by the Kofler microscope it was found to be 171–173°C. On examining the thermoanalytical curves of sulphathiazole, the DTA curve showed two endothermic peaks at 172 and 208°C, which were not accompanied by weight loss. The first peak was in accordance with the melting point as determined by the Kofler microscope, while the second was in agreement

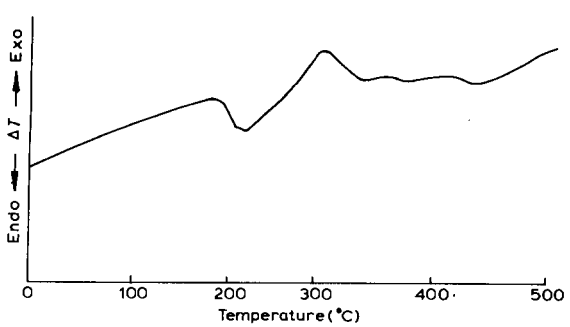

Fig. 14. DTA curve of sulphadimethyloxazole (100 mg).

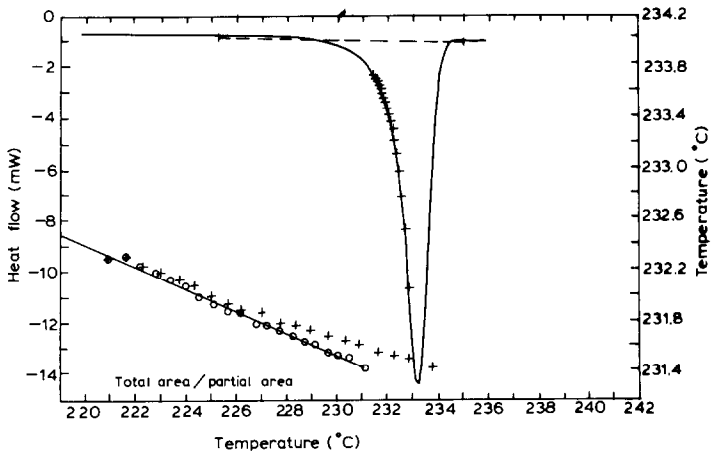

Fig. 15. DSC scan of a very pure sample of sulphamerazine (3.6 mg). Heating rate, 2 deg min^{-1}; program, dynamic purity V1.1. Found: purity, 99.81 mole%; ΔH, 45.8 kJ $mole^{-1}$; melting point, 232.5°C; depression, 0.09°C; correction, 1.67%; M.W. 264.3; cell constant, 1.100; onset of slope, -16.94 mW $°C^{-1}$.

with the melting point of sulphathiazole as stated in the literature [22,23]. This was attributed to polymorphism and the presence of more than one crystal form.

The purity of sulphathiazole cannot be determined by the DSC method for two reasons. One is the presence of more than one crystal form and the other is that the melting (second) peak is immediately followed by an exothermic decomposition peak. DTG, TG and DTA studies also revealed

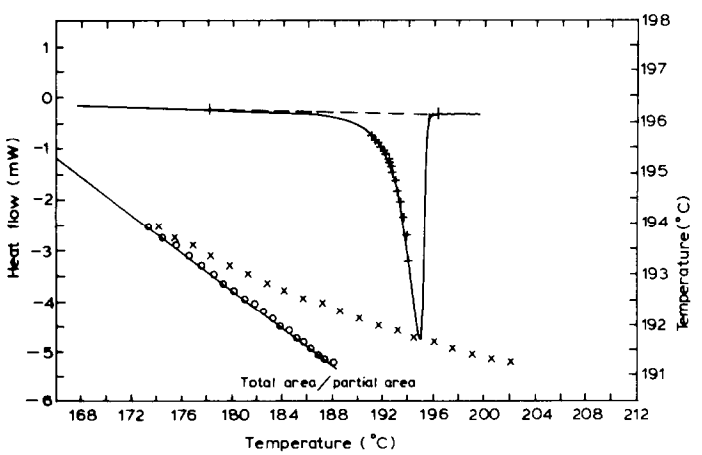

Fig. 16. DSC scan of a pure sample of sulphadimidine (4.5 mg). Heating rate 1°C min^{-1}; program, dynamic purity V1.1. Found: purity, 98.16 mole%; ΔH, 44.8 kJ $mole^{-1}$; melting point, 195.4°C; depression, 0.75°C; correction, 8.73%; M.W. 278.3; cell constant; 1.100; onset of slope, -16.94 mW $°C^{-1}$.

an exothermic decomposition reaction having a peak temperature at about 256°C [15].

On examining sulphadiazine by DSC (Fig. 12), an endothermic reaction was observed with starting and peak temperatures at 248 and 257°C, respectively, which was followed immediately by an exothermic reaction. It was observed that, before the endothermic reaction, there was a difference in base line corresponding to a difference in specific heat. This was attributed to a solid–solid transformation characteristic of a phase change from one crystalline form to another. This is emphasized by the work previously carried out by the author on sulphadiazine [15], in which the endothermic peak at 252°C, corresponding to the melting of the compound (as determined by the Kofler microscope and stated in the literature), was preceded by another one at 200°C. This latter peak was not accompanied by weight loss, as was concluded from its TG and DTG curves, and was attributed to crystal transformation. The heat of reaction was calculated in the previously stated manner and found to be 43.3 kJ $mole^{-1}$.

The purity of sulphadiazine cannot be determined by the DSC method due to the presence of more than one crystal form and to the fact that melting is immediately followed by an exothermic decomposition peak. The previous study (DTG, TG and DTA) revealed that melting is immediately followed by an exothermic decomposition reaction having a peak temperature at 305°C [15].

In the analysis of sulphadimethyloxazole by DSC (Fig. 13), two endothermic reactions occurred. The starting temperatures were 170 and 201°C, while the peak temperatures were 195 and 208°C for the two reactions, respectively. The first reaction may be due to crystal transformation and the

TABLE 1

Differential scanning calorimetric reactions of sulphonamides

Sample	First reaction			Second reaction			Purity by DSC method (mole %)
	Temp. (°C)		Heat of reaction (kJ $mole^{-1}$)	Temp. (°C)		Heat of reaction (kJ $mole^{-1}$)	
	Start	Peak		start	Peak		
Sulphathiazole	15.3	166.4	8.93	185	200.2	24.1	
Sulphadiazine	248.0	257.0	43.30				
Sulphadimethyl-oxazole	170.0	195.0	17.28	201	208	11.6	
Sulphamerazine	229.2	233.2	45.80				99.81
Sulphadimidine	180.0	195.4	44.80				98.16

second to melting of the compound. The results are clarified by carrying out a DTA examination using the derivatograph (Fig. 14). The endothermic reaction corresponding to melting of sulphadimethyloxazole with a peak temperature of 220°C includes a small inflection at about 210°C due to crystal transformation. The melting point of sulphadimethyloxazole was also determined by the Kofler microscope and found to be 179–181°C.

Quantitative calculations of the heat of reaction (ΔH) were performed and found to be 17.28 kJ mole^{-1} for the first reaction and 11.6 kJ mole^{-1} for the second reaction.

The purity of sulphadimethyloxazole cannot be determined by the DSC method since, in addition to the presence of polymorphic forms, the second reaction is followed immediately by an exothermic decomposition reaction.

For sulphamerazine, the DSC examination (Fig. 15) shows an endothermic reaction with a very sharp peak in the interesting temperature range. The reaction starts at 229.2°C and has peak temperature at 233.2°C.

The sample seems to be suitable for purity determination by the DSC method, since no reactions were apparent before or immediately after melting. It is found to be very pure (99.81 mole%) and a purity determination according to the official method [22] gave a figure of 99.65%. The quantitative determination of the heat of reaction was also performed and found to be 45.8 kJ mole^{-1}.

Examination of sulphadimidine by DSC (Fig. 16), showed an endothermic reaction in the interesting temperature range with starting and peak temperatures at about 180 and 195.4°C, respectively. The reaction peak was very sharp and suitable for the determination of the purity of the compound by the DSC method. The purity was determined and found to be 98.16 mole%. The heat of reaction was also calculated and found to be 44.8 kJ mole^{-1}.

Table 1 summarizes the reactions of the examined sulphonamides, including their starting temperatures, peak temperatures and heats of reaction. The

TABLE 2

Melting point determination of sulphonamides

Sulphonamide	Melting temperature (°C)			
	Literature	Kofler microscope	DTA	DSC
Sulphathiazole	200–203	171–173	172, 208	200.2
Sulphadiazine	252–256	247–250	252	257.0
Sulphadimethyl-oxazole	200–204	179–181	220	208.0
Sulphamerazine	235–239	241–243	244	233.2
Sulphadimidine	196–199	198–200	203	195.4

results of purity determinations by the calorimetric method, when applicable, are also presented.

A correlation is found between the stability of sulphonamides, the starting temperature and heat of the first reaction. It is found that sulphathiazole (whose first reaction has the lowest starting temperature, peak temperature and heat of reaction) is the least stable. This is in accordance with the previous results obtained by DTA, TG and DTG techniques. Sulphadimethyloxazole is more stable than sulphathiazole, but it is less stable than the other examined sulphonamides.

Table 2 presents the melting points of the sulphonamides obtained by using the different thermal techniques (DTA, Kofler microscope and DSC). The results are compared with the data given in the literature [19,22,23]. A considerable correlation is observed, but in most cases, the DSC method seems to be the best.

As a conclusion, DSC has a contribution to make in the analysis of pharmaceuticals. It seems to be useful in their characterization since it offers the ability of measuring melting points, transition temperatures and heats associated with them. Also, it may give an idea of the stability of the compounds. In addition, other behavioural manifestations such as polymorphism are also determined, as in the case of sulphathiazole, sulphadiazine and sulphadimethyloxazole. Further, the purity of some pharmaceutical compounds (such as sulphamerazine and sulphadimidine) is successfully determined by the calorimetric method.

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