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# Thermal studies on polymorphic structures of ibopamin

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**Abstract**

The crystal polymorphism of ibopamin has been investigated and the measurements suggest that ibopamin exists in two polymorphic forms I and II. The polymorphic monotropic transformation has been verified using differential thermal analysis (DTA) connected with thermomicroscopy (HSM), differential scanning calorimetry (DSC), thermogravimetric analysis (TG) and X-ray powder diffractometry (XRD) equipped with a self-constructed heating device. True densities and specific surface areas of the polymorphs have also been determined. The melting points of forms I and II are $(134.8 \pm 0.4)^{\circ}C$ and $(130.2 \pm 0.5)^{\circ}C$, respectively.

*Keywords:* Ibopamin; Drug; DSC; DTA; HSM; Polymorphism; TG; XRD

## 1. Introduction

Thermal analysis methods such as differential thermal analysis (DTA), differential scanning calorimetry (DSC), thermogravimetry (TG) and hot stage light microscopy (HMS) have found widespread applications in pharmaceutical research in recent years. Extensive work concerning the use of thermomicroscopy in the analysis of pharmaceuticals has been reported by Kuhnert-Brandstätter [1]. Ford and Timmins [2] have directed their attention to the use of thermal analysis in the pharmaceutical research and technology in general. The work of Jacobson and Reier [3] describes the application of DTA to compatibility and stability problems

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between drug excipients and active substances. In fact, thermal analysis has a crucial role in the manufacture of safe pharmaceuticals from raw materials. Thermoanalysis is very useful and time saving for verifying results from other measurement methods, and vice versa. Different thermal analytical methods may also be applied to the study of polymorphism. Optical microscopy is the simplest method for examining differences in crystal forms due to polymorphism as well as the formation of solvates. The hot stage microscope enables the sample to be examined by increasing or decreasing the temperature. By this means, phase changes in the sample may be observed, such as melting, polymorphic transitions, desolvation of a solvate, crystallization and solidification. The purpose of the present paper is to prove the polymorphic behaviour of ibopamin, an organic drug substance.

## 2. Experimental

### *2.1. Material used*

Ibopamin, 4-[2-methylamin(ethyl)]-0-phenylenid-isobutyrate-hydrochloride, is a white crystalline powder. The particle form was determined to be cubic by light microscopy.

### *2.2. Methods*

*Density measurements*

These were carried out using a Micromeritics Autopycnometer 1320. The gas used for measurement was helium.

*Surface area measurements*

Measurements were performed with a Micromeritics FlowSorb 2300 equipment (for application of BET method) and also with the permeameter (for permeametry measurements).

*Differential thermal analysis connected with thermomicroscopy*

An Olympus optical microscope (model BH-2) together with a Mettler FP800 thermosystem with a FP80HT TA microscopy cell was used for the study. The measurements were carried out at atmospheric pressure in air atmosphere. The scanning rate was $1^{\circ}C\ min^{-1}$.

*Differential scanning calorimetric studies*

These were performed with a Perkin Elmer DSC 7 system. The heating rate was mainly $2^{\circ}C\ min^{-1}$ and an atmosphere of nitrogen was used by passing the gas at 25 to 30 ml $min^{-1}$ through the sample cell. Approximately 3 mg (accurately weighed) of ibopamin was used for each analysis.

*Thermogravimetic analyses*

A Perkin Elmer TGA 7 system was used for the investigation. An atmosphere of nitrogen was used by passing the gas at 50 to 60 ml $min^{-1}$ through the oven. The other parameters were the same as those used with the DSC analysis.

*X-ray powder diffraction measurements*

X-ray diffraction measurements were carried out using a Philips PW1830, APD1700 automated diffractometer system with a hot stage assembly under the following conditions: nickel-filtered copper radiation was used for the measurements; tube type, Cu $K\alpha_{1,2}$; wavelength, 1.54060, 1.54439 Å; generator, 50 kV and 40 mA; divergence slit, automatic (irradiated sample length 12.5 mm); receiving slit, 0.1 mm; scatter slit, fixed (4°); detector type, proportional; step size and sample time, 0.010°, 2.00 s, 0.005° $s^{-1}$; peak angle range, 5.000–32.000°. Measured raw data analyzed using the Philips APD1700 software package. The accuracy of the temperature in the hot stage assembly was ±1°C.

## 3. Results and discussion

The measured true density of ibopamin is (1.13 ± 0.02) g $cm^{-3}$.

The specific surface area, obtained by BET and by permeametry, was 0.63 $m^2$ $g^{-1}$ and 0.56 $m^2$ $g^{-1}$, respectively.

The DSC curve of ibopamin (Fig. 1) recorded at a heating rate of 2°C $min^{-1}$ showed two endothermal peaks at 130.7°C and 135.2°C representing forms II and

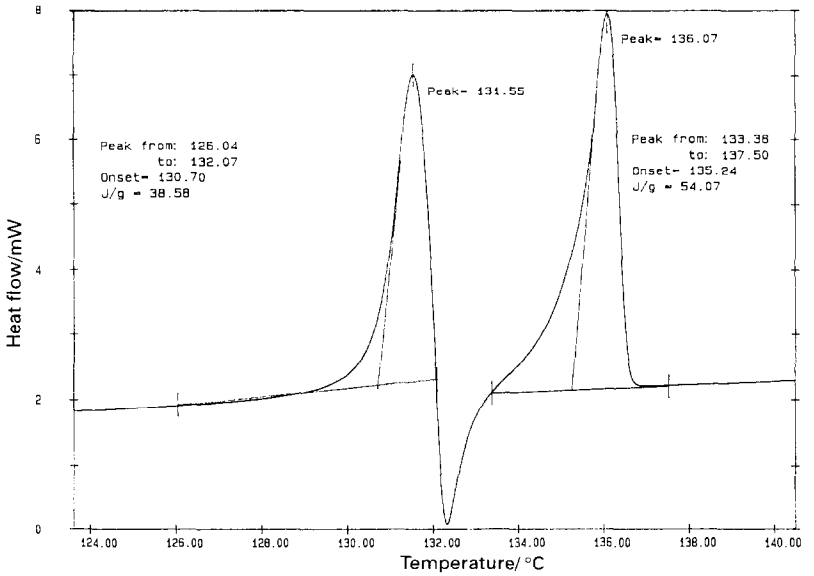



Fig. 1. DSC curve of ibopamin at a heating rate of 2 C $min^{-1}$.

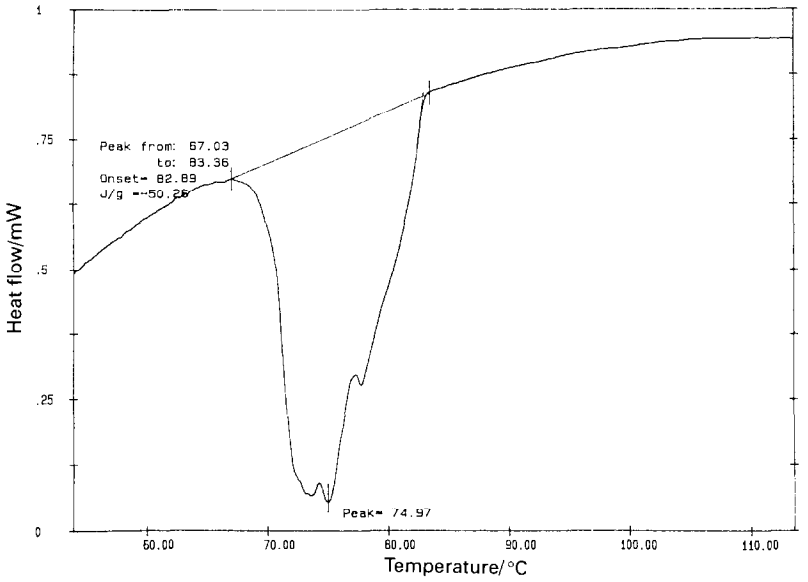



Fig. 2. DSC curve of ibopamin at a cooling rate of $-2$ C $min^{-1}$.

I, respectively. Between the two endotherms there is one exothermal peak at 132.3°C, corresponding to the crystallization of the polymorphic form I. The endothermic enthalpies of forms II and I were also determined by DSC; the values obtained were 38.6 J $g^{-1}$ and 54.1 J $g^{-1}$, respectively. The exothermal enthalpy for recrystallization of form I was $-9.9$ J $g^{-1}$. For organic compounds it is necessary to use lower scanning rates than, perhaps, for many other materials. In this particular case it was apparent that the polymorphic character of ibopamin could be found only if the heating rate was below 10°C $min^{-1}$. After first heating the sample up to 150°C, the same sample was immediately cooled to 50°C at a rate of $-2$°C $min^{-1}$ (Fig. 2) and reheated to 150°C (Fig. 3). The area of exotherm at cooling was $-50.3$ J $g^{-1}$ and the area of the endotherm on reheating was 61.9 J $g^{-1}$.

X-ray powder diffraction patterns of the two polymorphic forms of ibopamin are presented in Figs. 4 and 5 while the $d$ values and relative intensities $I/I_{max}$ expressed as percentages of the strongest line in the pattern are given in Tables 1 and 2.

The DTA traces of ibopamin were recorded and the results are expressed in Fig. 6(a)–(c). The first endotherm at 129.8°C is the melting point of ibopamin II. The exotherm at 131°C shows the crystallization of ibopamin I and the second endotherm at 134.4°C represents the melting point of ibopamin I. On cooling, the recrystallization (Fig. 6(b)) occurred at about 90°C and on reheating (Fig. 6(c)) only one melting point appeared likewise as found above. The same monotropic transformation process with corresponding temperatures is illustrated in the HSM photographs (Fig. 7(a)–(e)).

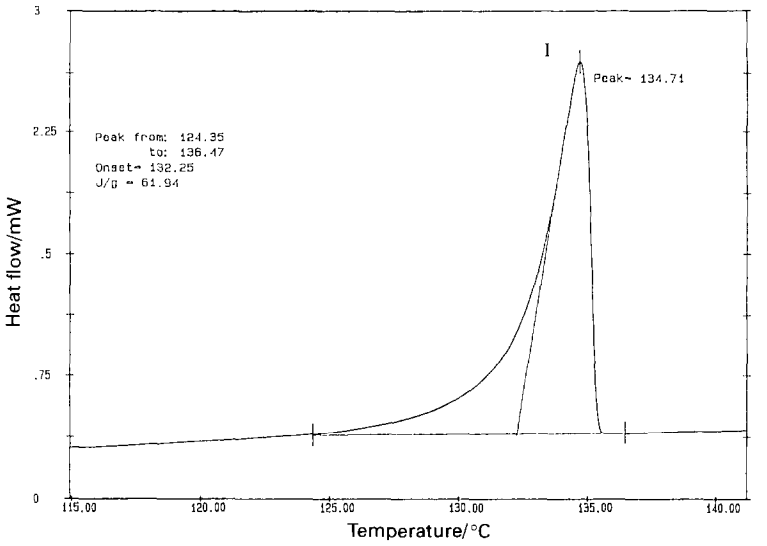



Fig. 3. DSC curve of ibopamin reheated up to 150°C at a rate of 2°C min $^{-1}$.

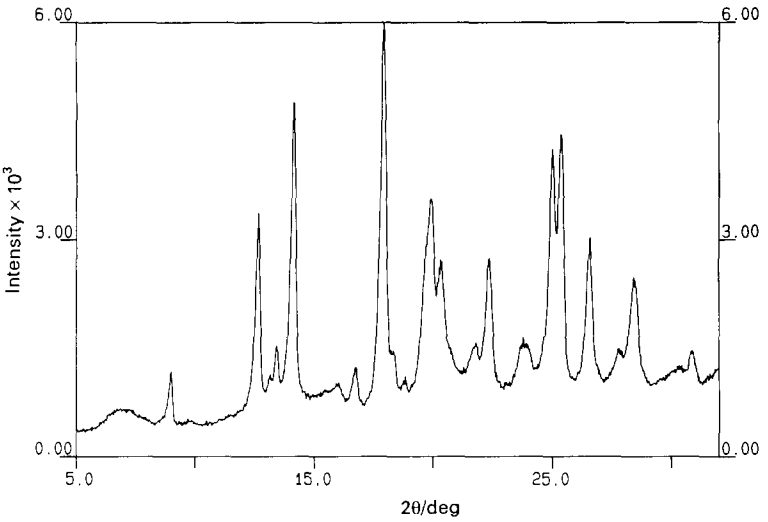



Fig. 4. X-ray powder diffraction pattern of form I of ibopamin.

To exclude the possibility of pseudopolymorphic transformations, the sample was scanned by thermogravimetry. Chemical or other reactions were not found in the temperature range 120–150°C (Fig. 8).

The polymorphic transition from form II to form I was also verified using X-ray powder diffractometry with the hot stage assembly (Fig. 9). The transition could be proved by observing the change in the two characteristic reflections of form II

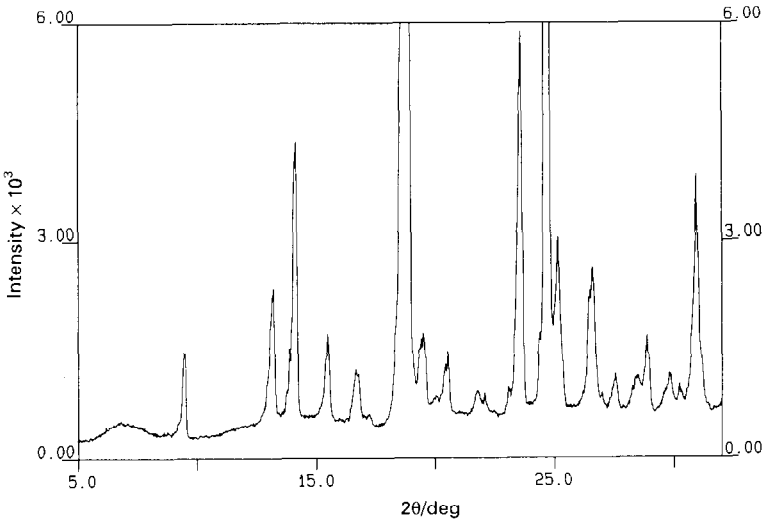



Fig. 5. X-ray powder diffraction pattern of form II of ibopamin.

($2\theta = 9.45°$) and form I ($2\theta = 8.97°$). The X-ray diffraction patterns were determined by raising the temperature in steps of 2°C from 130°C to 138°C and annealing the sample at each temperature for 15 min. It was found that at 130°C

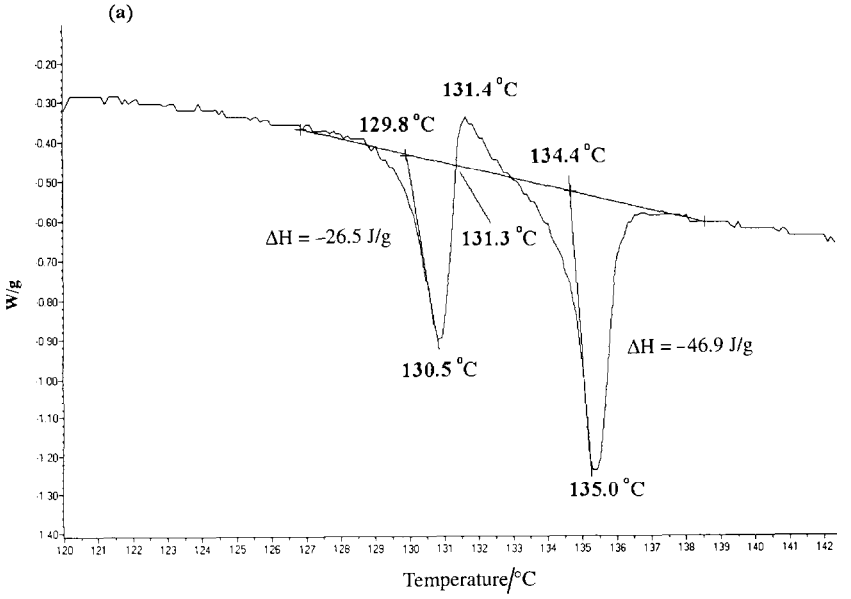
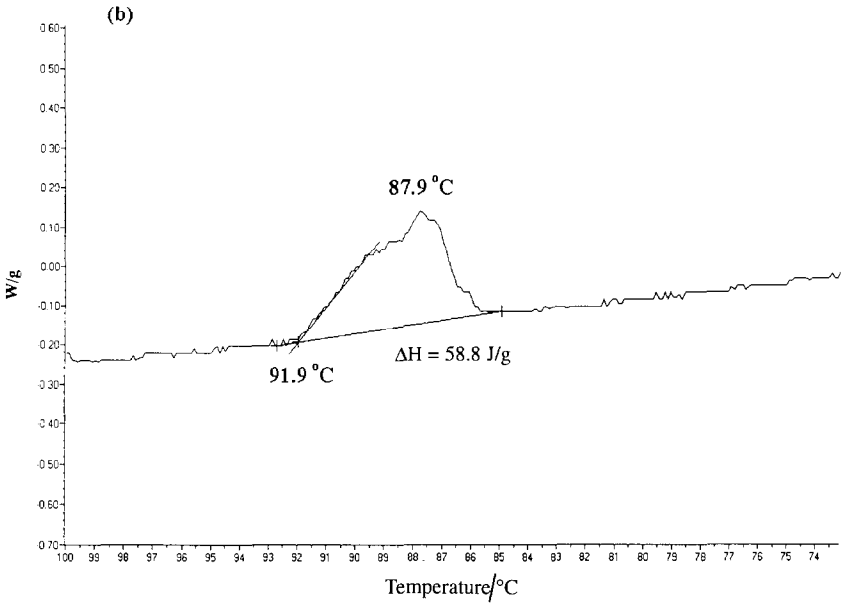



Fig. 6. (a).



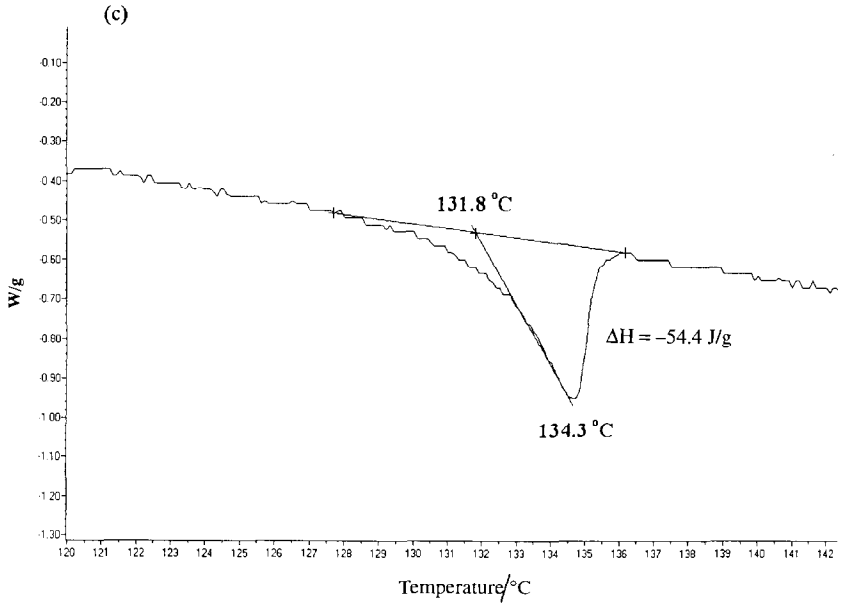
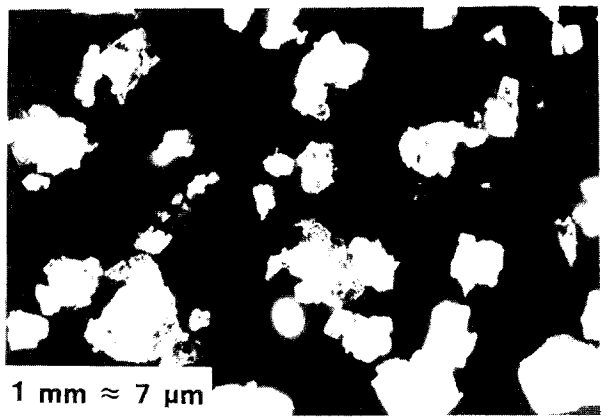
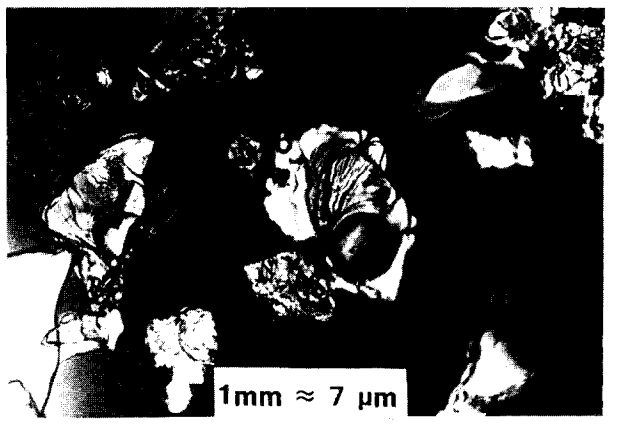
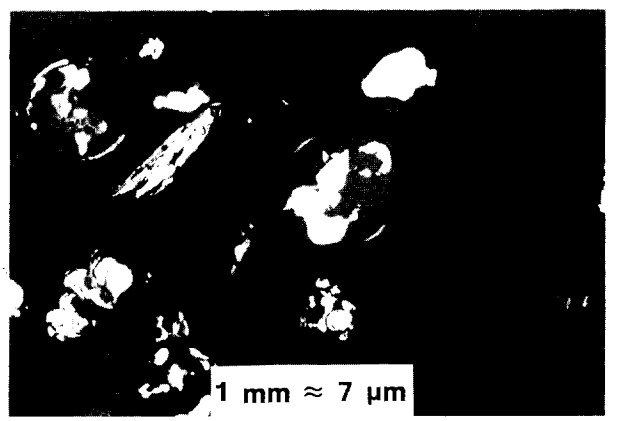




Fig. 6. (a) DTA trace of ibopamin from 120 °C to 145 °C. The first endotherm at 129.8 °C is the melting point of form II. The exotherm at about 131 °C is the crystallization of form I and the second endotherm at 134.4 °C is the melting point of form I. (b) DTA cooling trace of ibopamin from 100 °C to 70 °C. (c) DTA reheating trace of ibopamin form 120 °C to 145 °C.




(c)

Fig. 7. (a) (c).

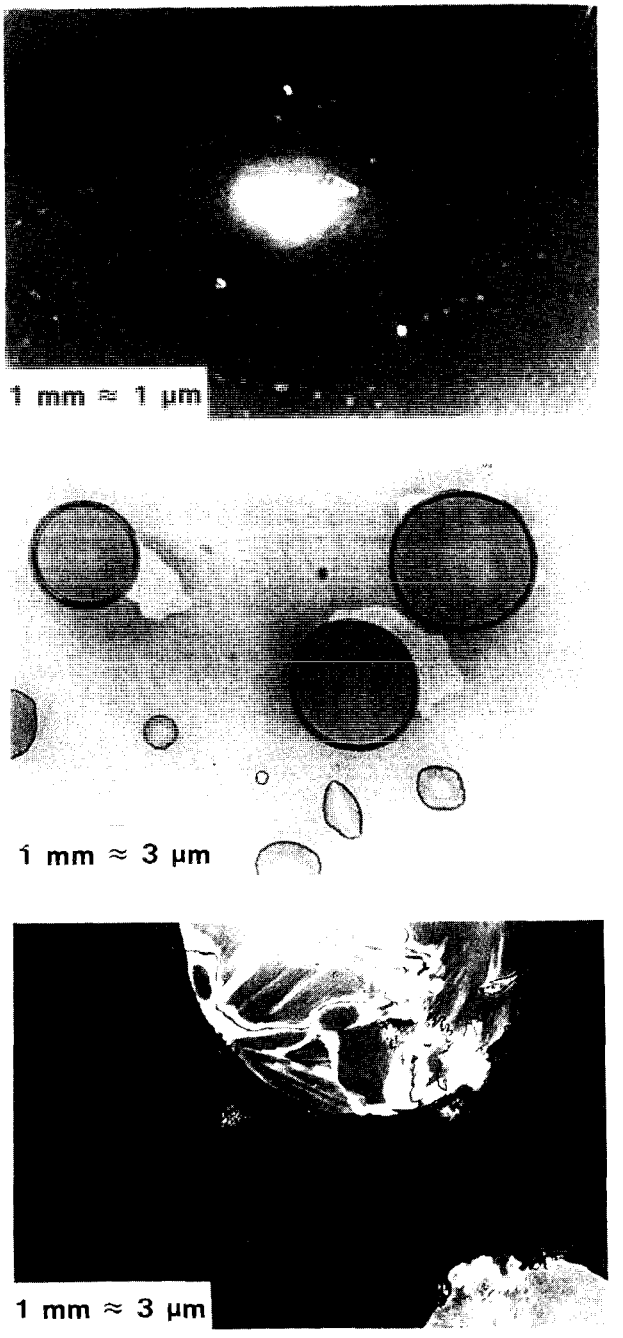



Fig. 7. (a) Particles of ibopamin at room temperature (23 °C), (b) melting has started (130 °C), (c) near melting point (132 °C), (d) recrystallization (133.8 °C), (e) second melting point (134.9 °C) and (f) recrystallization at room temperature (23 °C).

Table 1
X-ray diffraction data for form I of ibopamin

| $2\theta$/deg [a] | $d_{spac}$/Å [b] | $I/I_{max}$ in % [c] |
|---|---|---|
| 8.97 | 9.848 | 13 |
| 12.65 | 6.995 | 54 |
| 13.10 | 6.753 | 10 |
| 13.42 | 6.591 | 19 |
| 14.13 | 6.262 | 83 |
| 15.99 | 5.540 | 4 |
| 16.73 | 5.294 | 8 |
| 17.90 | 4.952 | 100 |
| 18.35 | 4.832 | 13 |
| 18.77 | 4.723 | 6 |
| 19.91 | 4.457 | 52 |
| 20.31 | 4.369 | 35 |
| 21.79 | 4.076 | 9 |
| 22.34 | 3.977 | 30 |
| 23.79 | 3.737 | 15 |
| 24.96 | 3.564 | 61 |
| 25.36 | 3.509 | 63 |
| 26.55 | 3.355 | 36 |
| 27.77 | 3.211 | 8 |
| 28.50 | 3.130 | 24 |
| 30.78 | 2.902 | 8 |

[a] Twice the angle of incidence or reflection.
[b] Interplanar spacing.
[c] Relative intensity (based on maximum intensity of 100; Cu Kα, 50 kV and 40 mA).

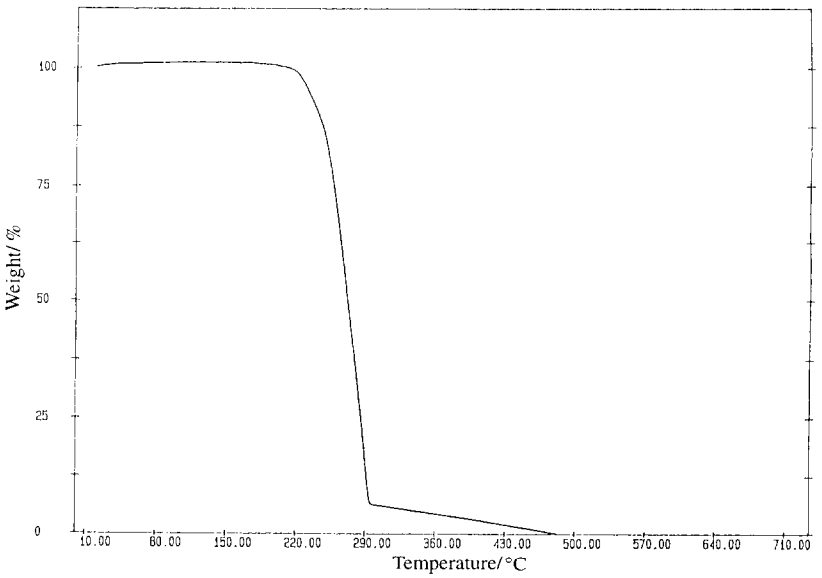



Fig. 8. TG curve of ibopamin.

Table 2
X-ray diffraction data for form II of ibopamin

| $2\theta$/deg [a] | $d_{spac}$/Å [b] | $I/I_{max}$ in % [c] |
|---|---|---|
| 9.45 | 9.354 | 3 |
| 13.16 | 6.721 | 4 |
| 14.15 | 6.256 | 9 |
| 15.45 | 5.731 | 3 |
| 16.67 | 5.313 | 2 |
| 18.85 | 4.704 | 100 |
| 19.52 | 4.545 | 3 |
| 20.47 | 4.336 | 2 |
| 21.71 | 4.090 | 1 |
| 23.58 | 3.770 | 13 |
| 24.68 | 3.604 | 94 |
| 25.10 | 3.545 | 6 |
| 26.54 | 3.357 | 7 |
| 27.50 | 3.241 | 1 |
| 28.39 | 3.142 | 1 |
| 28.84 | 3.094 | 2 |
| 29.77 | 2.998 | 1 |
| 30.20 | 2.957 | 1 |
| 30.90 | 2.892 | 8 |

[a] Twice the angle of incidence or reflection.
[b] Interplanar spacing.
[c] Relative intensity (based on maximum intensity of 100; Cu Kα, 50 kV and 40 mA).

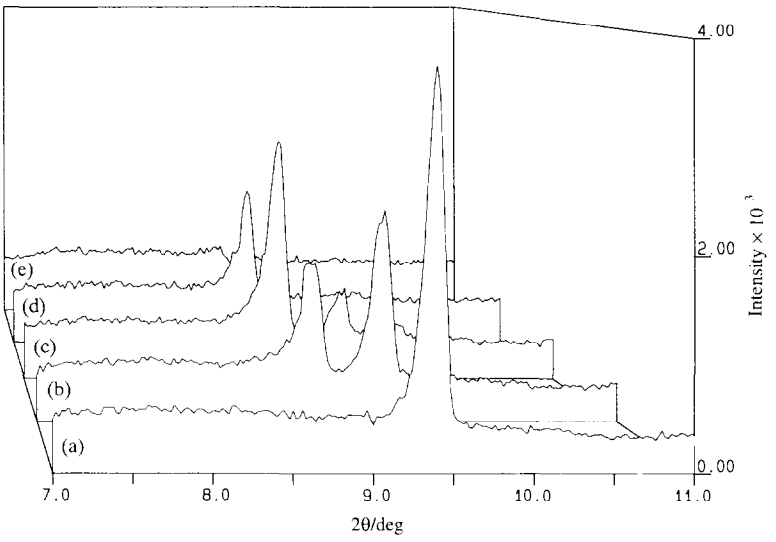



Fig. 9. X-ray powder diffraction patterns of structure transition from form II to form I of ibopamin: curve (a) at 130 °C; curve (b) at 132 °C; curve (c) at 134 °C; curve (d) at 136 °C; and curve (e) above 136 °C.

only the reflection typical for form II appeared, in the temperature range 132–134°C the characteristic reflections of both forms were present. At 136°C the characteristic reflection of form I alone was apparent. Above 136°C, the reflections were absent because the sample had melted.

## 4. Conclusions

Combined thermal studies on the polymorphic changes of ibopamin have been reported. The results obtained show that the combination of different thermal techniques (DSC, XRD with a hot stage assembly, TG, DTA and HSM) are useful when checking the reliability of results.

## Acknowledgements

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