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Assessment of nicotinamide polymorphs by differential scanning calorimetry

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Abstract

The thermal behaviour of nicotinamide was investigated by differential scanning calorimetry (DSC). Nicotinamide was heated to 140°C, cooled and subsequently re-heated using DSC. Nicotinamide displayed four polymorphs. The melting points of Forms I, II, III and IV were 126–128, 112–117, 107–111 and 101–103°C, respectively. Untreated nicotinamide composed only of Form I. When molten and subsequently cooled, a mixture of polymorphs recrystallised. When the molten liquid was cooled to temperatures <80°C, the main product was Form I. In these scans, conversion from the metastable forms to the stable one without accompanying melting was observed at low re-heating rates. At higher rates, the melting of the metastable form became more obvious and it occurred concomitantly with recrystallisation of the stable form. When molten samples were cooled to 80 or 85°C and held isothermally, Form II was predominantly formed and the formation of Form I could not be detected. Form II was converted to Form I by cooling to 30°C. Form I was the stable form; others were metastable.

Keywords: Nicotinamide; Polymorphs; DSC; Scanning rate dependence; Isothermal hold

1. Introduction

Solid dispersions are extensively investigated for improving the dissolution properties of poorly water-soluble drugs [1–3]. These are prepared with drugs and carriers by intermediate action of heat [4–6], solvent or a combination of heat and solvent [7,8]. The heating method should result in no inherent toxicity from residual solvent. However, the heating method may require careful control of heating and cooling conditions because of the potential problems of polymorphic modifications.

Nicotinamide, viz. pyridine-3-carboxyamide, is one of the components of vitamin B. It was reported that the solubilities of nifedipine [9,10], indomethacin [11] or halofantrine [12] are increased by forming solid dispersions with nicotinamide. In spite of these potential utilities of nicotinamide, the thermal properties of this compound have not been fully investigated. Fused nicotinamide shows a different differential scanning calorimetry (DSC) scan to the scan of the untreated material [13]. The polymorphic modifications of nicotinamide and their interconversion have not been explained in detail. In the present paper, the relationships between nicotinamide polymorphs and the heating and cooling conditions are reported.

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2. Materials and methods

2.1. Materials

Reagent grade nicotinamide was purchased from BDH Laboratories (Poole, England) and used without further purification.

2.2. DSC analysis

The DSC scans were carried out using a Perkin-Elmer DSC7 calorimeter. The calorimeter was calibrated for temperature against the melting points of indium and zinc (156.60 and 419.47°C, respectively) and for enthalpies against the heat of fusion of indium ($\Delta H_f = 28.45$ J g^{-1}).

Samples (normally 2–5 mg) were placed in aluminum pans and aluminum lids were crimped in position. Each sample was initially held at 50°C for 1 min prior to analysis. These samples were heated to 140°C, maintained at this temperature for 0.5 min, cooled to 30, 50, 70, 80, 85 or 90°C, held isothermally at these temperatures for periods varying from 0 to 20 min and subsequently re-heated to 140°C. The heating, cooling and re-heating scans were carried out under the rates specified in the discussion.

2.3. Thermogravimetic analysis

Thermogravimetic (TG) analysis of nicotinamide was determined using a Perkin-Elmer TGA7 thermogravimetric analyser equipped with a Perkin-Elmer TAC7 controller. The apparatus was calibrated against the magnetic transition temperatures of nickel and iron (354 and 780°C, respectively) and weight against a 100-mg Class M calibration standard (Part No. 0990-8397, Perkin-Elmer).

The initial weights of samples analysed were 4.5–7.7 mg. Samples were heated from 30 to 140°C at a rate of 1.0 or 10.0°C min^{-1}.

2.4. Hot stage microscopic observation

Untreated nicotinamide was placed on a glass microscope slide and covered by a glass cover slip. The thermal behaviour of the sample was observed using hot stage microscopy. The hot stage, the microscope and the central processor of the system used were a Mettler FP82, an Olympus BH-2 and a Mettler FP80, respectively. Samples were heated from 50 to 140°C, cooled to ambient temperature by removing the slide out of the stage and subsequently heating to 140°C again. The heating and re-heating rates were in the range 1–20°C min^{-1}. Accuracy of the hot stage was routinely checked against the melting of indomethacin B.P. and ibuprofen B.P.

2.5. Stability of nicotinamide during heating

The stability of nicotinamide during heating was checked by high performance liquid chromatography (HPLC). Nicotinamide samples were placed in uncovered aluminum pans and heated in the DSC7 calorimeter. Samples were held at 50°C for 1 min, heated to and maintained at 140°C for 0.5 min, and subsequently cooled to 30°C. Heating and cooling rates were 20°C min^{-1}. Following heat treatment, samples were also maintained at 80°C for 20 min during the cooling procedure. Samples were dissolved in methanol and the quantity of nicotinamide remaining determined by HPLC using a Model 2690 Separation Module (Waters Limited, Watford, UK) with a Waters 996 photodiode array detector. The data system used was a Millenium 32. The injection volume was 3 μl and the column used was a Symmetry Shield^{TM} RP_8 (3.9 × 150 mm, 5 μm d.p., Waters Limited, Watford, UK) at a temperature of 30°C. A gradient elution profile was used, comprising initially 1 v/v% aqueous acetonitrile, containing 0.1 v/v% trifluoroacetic acid. This composition was maintained for 2 min, and then the proportion of acetonitrile increased linearly over 8 min to 70 v/v%. This ratio was maintained for 2.90 min and subsequently decreased linearly over 0.1 min to the starting composition. The column was allowed to equibrate for 5 min prior to the next injection. Nicotinamide was determined by UV detection at 260 nm.

3. Results and discussion

3.1. Thermal behaviour of the untreated nicotinamide

Untreated nicotinamide was heated to 140°C at 1–30°C min^{-1} using DSC. Each scan (represented

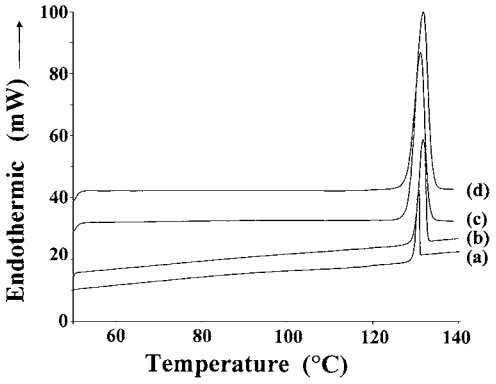

Fig. 1. DSC heating scans of untreated nicotinamide. Heating rate: (a) 1°C min^{-1}, (b) 5°C min^{-1}, (c) 10°C min^{-1}, (d) 20°C min^{-1}.

by Fig. 1) exhibited one sharp peak with onset temperature of 126–128°C and melting enthalpies of ~209 J g^{-1} (Table 1). The fact that no other events were apparent indicated that the untreated nicotinamide contained one crystal form. Slight baseline displacements were observed between the baselines prior to the onset and following the offset temperatures of the melting peaks. This suggests that slight decomposition of nicotinamide might have occurred on melting. However, the weight loss after heating to 140°C at rates of 1 and 10°C min^{-1}, determined by TG, were in the ranges 0.31–0.34 w/w% and <0.02 w/w% ($n = 2$), respectively. Neither significant reduction in peak areas nor new peaks originating from decomposition of nicotinamide with heating were detected by HPLC. Therefore, nicotinamide was considered to be stable under the DSC conditions employed.

The thermal behaviour of nicotinamide during heating to 140°C was observed using hot stage microscopy. Crystals melted in the range 124–130°C. No changes were observed at lower temperatures. These observations confirm that nicotinamide was originally composed of one crystal form.

3.2. Characterisation of nicotinamide polymorphs

Heating, cooling and re-heating of nicotinamide were carried out at various rates. Several patterns of endothermic peaks due to melting of the samples were

Table 1
Characterisation of nicotinamide crystal forms

Heating rate (°C min^{-1})	1	5	10	20	30	Mean	S.D.[a]	n
Form I (untreated)								
Onset temperature (°C)	125.9–128.3	127.8–128.2	126.5–128.4	128.0–128.3	127.9–128.4	128.1	0.9	20
Peak temperature (°C)	130.7–132.5	130.8–133.1	131.2–133.5	130.2–134.6	131.0–133.8	131.5	1.5	20
ΔH (J g^{-1})	207.5–218.8	208.8–219.2	204.3–205.2	182.8–228.3	197.7–221.9	208.9	9.6	20
Form I (from recrystallised material)								
Onset temperature (°C)	127.7–128.4	128.1–129.6	124.8–128.8	127.9–130.1	127.5–128.5	128.0	0.9	32
Peak temperature (°C)	128.8–129.3	129.5–133.6	130.1–130.7	131.1–135.6	131.5–134.5	131.3	1.7	33
ΔH (J g−^{1})	182.7–242.7	208.8–261.7	189.3–210.2	208.6–228.3	191.7–191.9	208.6	22.0	13
Form II								
Onset temperature (°C)	113.3–116.9	112.2–115.4	112.6–115.4	113.5–116.2	111.6–116.1	114.5	1.4	26
Peak temperature (°C)	113.7–117.2	113.1–117.5	113.3–117.7	114.7–120.2	114.9–120.9	115.9	1.9	48
ΔH (J g^{-1})	156.1–160.2	153.8–171.3	146.7–164.6	150.3–180.5	167.6–180.5	161.6	9.7	12
Form III								
Onset temperature (°C)	107.6	108.2		109.1–110.6	106.9–110.7	108.9	1.1	12
Peak temperature (°C)	108.9	109.1		110.0–113.6	109.1–113.5	111.5	1.5	15
ΔH (J g^{-1})	148.6				167.3	158.0	13.2	2
Form IV[b]								
Onset temperature (°C)	103.1	101.1–102.0		102.0		102.1	0.7	4
Peak temperature (°C)	104.2	103.9		102.2–105.2		103.9	0.9	6

[a] Standard deviation.
[b] ΔH of Form IV was not determined.

observed in the re-heating scans, depending on the operating conditions of DSC. These peaks were classified into four types, i.e. Forms I, II, III and IV, defined by the temperatures when the onset of melting and the peak temperature occurred. The DSC characteristics of the four polymorphic forms of nicotinamide are shown in Table 1. The peak maxima of the endotherms of Forms I, II, III and IV were 131.5 ± 1.5, 115.9 ± 1.9, 111.5 ± 1.5 and 103.9 ± 0.9°C, respectively.

Onset temperatures are defined as the temperatures where the baselines intersected the extrapolated tangents at the midpoints of the peaks [14]. Although this analysis slightly overestimates the onset temperature, it diminishes the personal bias of judgement of the onset. Because sample weight, filling state and the heating rate affect the onset and peak temperatures [15], these conditions were carefully controlled. The peak temperature has somewhat larger variance compared with the onset temperature (Table 1). This is due to the fact that onset temperature reflects the temperature when the threshold of the energy for melting was supplied to the sample, while peak temperature is influenced by the dynamical equilibrium between supplied heat and the content of the solid portion which is gradually converted to the molten liquid in the sample [16]. On the contrary, the reproducibility of the onset temperature was such that the standard deviation was <1.4°C. Consequently in this study, the peaks were characterised by onset temperatures unless multiple peaks overlapped each other.

ΔH denotes the enthalpy change caused by melting of the sample per unit weight. The value of the Form I was significantly larger than that of the Form II ($P < 0.001$) or Form III ($P < 0.05$; *t*-test). It suggests that Form I is the stable form, the other forms are metastable and that these polymorphs are monotropic according to Burger's rule [17]. The ΔH values of the Form IV could not be calculated, because the peaks originating from the melting of Form IV could not be solely obtained and other peaks always appeared during re-heating.

3.3. Effect of cooling rates on the nicotinamide polymorphs

The DSC cooling and re-heating scans of nicotinamide are shown in Fig. 2. The initial heating rate and cooling rate were 20 and 5°C min^{-1}, respectively. The samples were heated to 140°C, held at 140°C for 0.5 min, cooled to 30°C and held for 0.5 min prior to subsequent re-heating. Fig. 2a shows a typical cooling scan under these heating and cooling conditions. A large split exothermic peak, due to the recrystallisation of nicotinamide, is observed at 68–60°C (Fig. 2a). Also several small exothermic peaks existed at lower temperatures. These complex aspects of the cooling scans were not reproducible. However, a large split exothermic peak in the range 85–60°C and several subsequent smaller peaks were observed in each scan. The enthalpy of the main recrystallisation peak was -129.8 ± 16.1 J g^{-1} ($n = 8$).

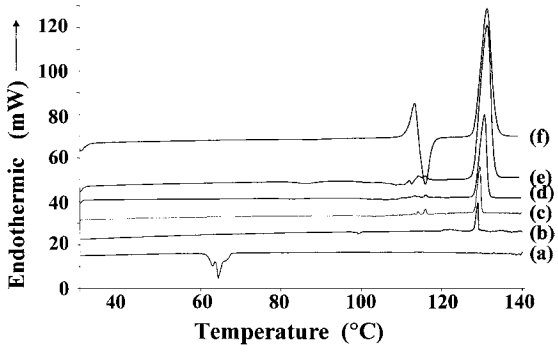

Fig. 2. DSC cooling and re-heating scans of nicotinamide. Initial heating rate: 20°C min^{-1}, cooling rate: (a) 5°C min^{-1}. Re-heating curves: (b) 1°C min^{-1}, (c) 5°C min^{-1}, (d) 10°C min^{-1}, (e) 20°C min^{-1}, (f) 30°C min^{-1}.

Fig. 2b–f are typical re-heating scans. The main peak is due to the melting of the Form I in each scan. Form I was thus considered as the main product of these heating and cooling operations. However, other endothermic peaks were obtained. It suggests that other forms, possibly Forms II, III and IV, were also produced under these conditions. Although the relative size between the endotherm of Form I and those of the other forms varied in each experimental run, the melting endotherm of Form I was always apparent. The variations in their relative size were probably due to the unpredictable nucleation process mentioned by Bottom [18], and He and Craig [19]. Exothermic peaks were observed in these scans (Fig. 2b, c, e and f). It suggests that recrystallisation occurred on re-heating as well as during cooling. Conversion from one solid form to another without accompanying melting was observed at the slow scanning rates of

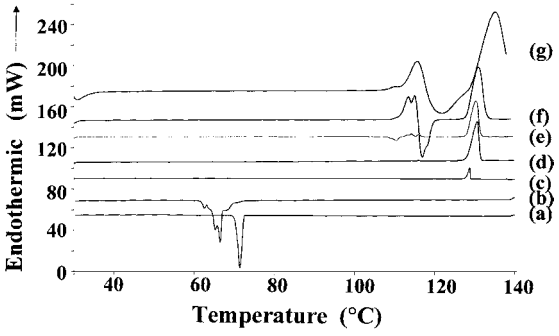

Fig. 3. DSC cooling and re-heating scans of nicotinamide. Initial heating rate: 20°C min^{-1}, cooling rate: (a) and (b) 10°C min^{-1}. Re-heating curves: (c) 1°C min^{-1}, (d) 5°C min^{-1}, (e) 10°C min^{-1}, (f) 20°C min^{-1}, (g) 50°C min^{-1}.

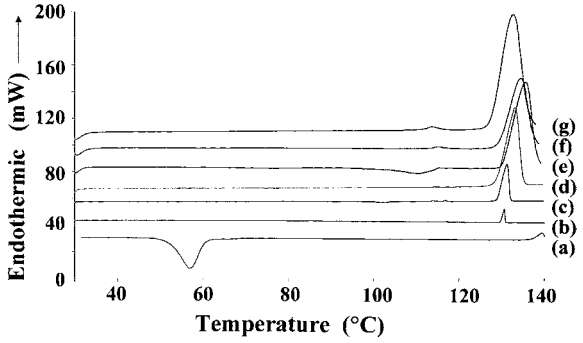

Fig. 4. DSC cooling and re-heating scans of nicotinamide. Initial heating rate: 20°C min^{-1}, cooling rate: (a) 30°C min^{-1}. Re-heating curves (b) 1°C min^{-1}, (c) 5°C min^{-1}, (d) 10°C min^{-1}, (e) 20°C min^{-1}, (f) 30°C min^{-1}, (g) 50°C min^{-1}.

1, 5 and 20°C min^{-1}. At the rate of 30°C min^{-1} (Fig. 2e), conversion from Form III to Form I occurred via melting of Form III and subsequent recrystallisation of Form I. This phenomenon is caused by insufficient heat supply due to the rapid heating. Melting of Form III occurred before the solid–solid conversion.

Fig. 3 shows typical DSC scans at a cooling rate of 10°C min^{-1} and subsequent re-heating. The cooling scans were not reproducible and showed either sharp peaks such as Fig. 3a or large split peaks as Fig. 3b. No relationship between sample weight and the peak aspects could be recognised. The enthalpy change was -132.3 ± 20.2 J g^{-1} ($n = 14$). Large endotherms due to the melting of Form I were observed in the re-heating scans (Fig. 3c–g). Other endothermic peaks also existed. A solid → liquid → solid conversion from Form III to Form I became more obvious with increase in the re-heating rate. This could be due to the fact that gradual recrystallisation at the lower temperature was suppressed because of the rapid supply of heat during the faster re-heating procedures. Consequently, recrystallisation of Form I occurred concomitantly with melting of Forms III and IV.

Fig. 4 shows typical DSC cooling and re-heating scans from samples examined following cooling rate at 30°C min^{-1}. The cooling scan exhibited only one sharp exotherm (Fig. 4a). The re-heating scans exhibited sharp endothermic peaks caused by melting of Form I and small endotherms originating from Form III. Similar results were obtained at an approximate cooling rate of 250°C min^{-1} (data not shown). Although a precise cooling rate of 250°C min^{-1} was not controllable, this rate was the fastest attainable with the DSC instrument used.

Nicotinamide, following fusion at 140°C and subsequent cooling, was re-heated and examined using a hot stage microscope. Recrystallisation was observed in the range 64–105°C although the temperature was not reproducible. This result suggests that the conversion of Form III to Form I occurred during re-heating and supported the DSC data that some conversion of the solid state occurred before melting took place.

From Figs. 2–4, Form I appeared to be the main product of cooling to 30°C and subsequent re-heating. Form III frequently existed. Forms II and IV might be formed under these conditions. The endotherm that originates from Form III became smaller and that from Form I became more predominant with increase in the cooling rate. The data suggest that Form I, which was preferentially formed by rapid cooling, is the stable form and other forms are metastable.

3.4. Recrystallisation of nicotinamide under isothermal conditions

Nicotinamide samples were heated to 140°C at 20°C min^{-1}, cooled to 80°C at 10°C min^{-1}, held at 80°C for 10 min and subsequently re-heated. The DSC isothermal scan at 80°C exhibited either only one sharp peak (Fig. 5a) or a complex one (Fig. 5b). Although recrystallisation occurred and ended mostly during the isothermal step (Fig. 5a and b), it occasionally started during the cooling step (Fig. 5c) or ended during re-heating (Fig. 5d).

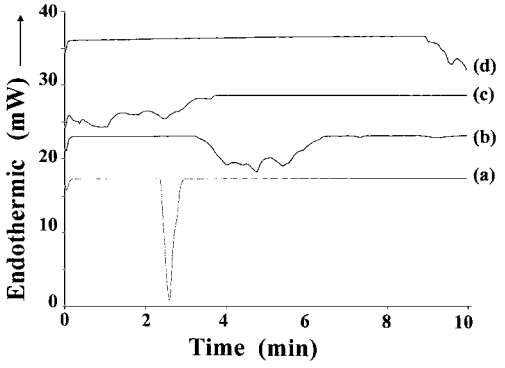

Fig. 5. Typical DSC isothermal scans of nicotinamide at 80°C. Initial heating rate: 20°C min^{-1}, cooling rate: 10°C min^{-1}, holding temperature: 80°C. (a) and (b) Recrystallisation occurred and ended during the holding time. (c) Recrystallisation was initiated during the cooling step and ended during the isothermal one. (d) Recrystallisation was initiated during the isothermal stage and ended during the re-heating one.

Fig. 6a–f shows the re-heating scans of samples, when recrystallisation started and ended during the isothermal step at 80°C. No scan exhibited the peak originating from Form I. At the low re-heating rate of 1°C min^{-1}, a sharp peak due to the melting of either Form III (Fig. 6a) or Form II (Fig. 6b) appeared. At faster rates, two peaks originating from Forms II and III are observed. The former endotherm was larger than the latter. A small exothermic peak was observed at 86°C in Fig. 6a. Such peaks were not observed in Fig. 6b–f. It is considered that Form II was the main product of these scanning conditions. The small

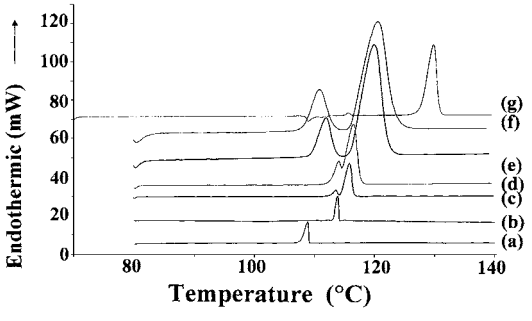

Fig. 6. DSC re-heating scans of nicotinamide after holding at 80 or 70°C. Initial heating rate: 20°C min^{-1}, cooling rate: 10°C min^{-1}. Holding temperature: (a)–(f) 80°C, (g) 70°C. Re-heating curves: (a) and (b) 1°C min^{-1}, (c) 5°C min^{-1}, (d) 10°C min^{-1}, (e) 20°C min^{-1}, (f) 30°C min^{-1}, (g) 10°C min^{-1}.

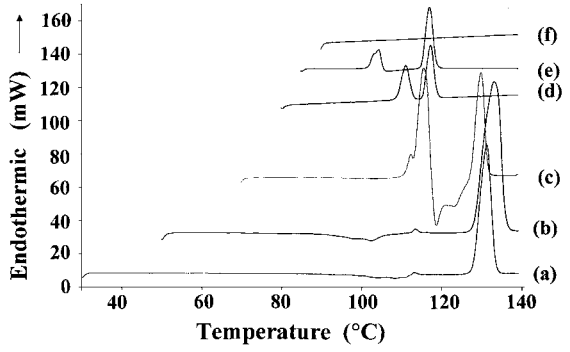

Fig. 7. Effect of holding temperature on the DSC re-heating scans of nicotinamide. Initial heating rate: 100°C min^{-1}, cooling rate: 100°C min^{-1}, re-heating rate: 20°C min^{-1}. Holding temperature: (a) 30°C, (b) 50°C, (c) 70°C, (d) 80°C, (e) 85°C, (f) 90°C.

exothermic peak in Fig. 6a was presumably due to the conversion of Form II to Form III. On the contrary, Form I was the main product when nicotinamide was cooled to 70°C and subsequently held at this temperature (Fig. 6g).

The effect of the holding temperature on the recrystallisation of nicotinamide is shown in Fig. 7. The re-heating rate was 20°C min^{-1}. In order to initiate and terminate the recrystallisation during the isothermal procedure, the cooling rate and holding time were 100°C min^{-1} and 20 min, respectively, rather than the conditions of Fig. 6. Consequently, the recrystallisation commenced and ended during the holding step, except at the holding temperature of 90°C. When nicotinamide was cooled to lower than 80°C, Form I was predominantly formed, while Form II was the main product under the holding temperature of 80 or 85°C. When the cooling was stopped at 90°C, neither melting nor recrystallisation occurred in the isothermal and re-heating scans.

3.5. Recrystallisation of nicotinamide during re-heating

Nicotinamide was cooled to 80°C and immediately heated without isothermal holding it at 80°C. When the re-heating rate was low (1 or 5°C min^{-1}), recrystallisation occurred at a lower temperature in the re-heating scan (Fig. 8a and b). The main product of these scans was Form II. Neither recrystallisation nor melting occurred in the re-heating scan at the faster rates

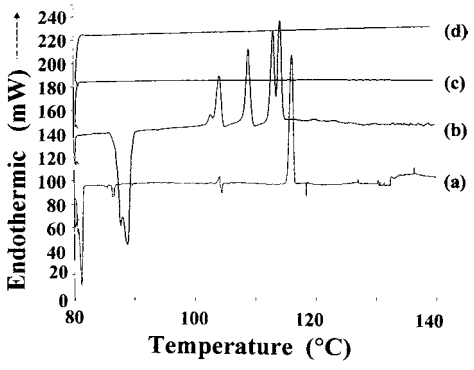

Fig. 8. Recrystallisataion of nicotinamide during re-heating procedure. Initial heating rate: 20°C min^{-1}, cooling rate: 10°C min^{-1}. Re-heating curves: (a) 1°C min^{-1}, (b) 5°C min^{-1}, (c) 10°C min^{-1}, (d) 20°C min^{-1}.

(10 or 20°C min^{-1}, Fig. 8c and d). This is due to the fact that nicotinamide was insufficiently cooled and subsequently re-heated before the solidification occurred at the larger re-heating rate.

3.6. Solid to solid conversion of nicotinamide

Nicotinamide was heated to 140°C, cooled to 80°C, held at 80°C for 20 min, cooled to 30°C and subsequently re-heated. The DSC cooling and re-heating scans are shown in Fig. 9. The product after cooling to 80°C and subsequent holding at the temperature is considered to be Form II, as described above. However, when it was cooled to 30°C, Form II was converted to

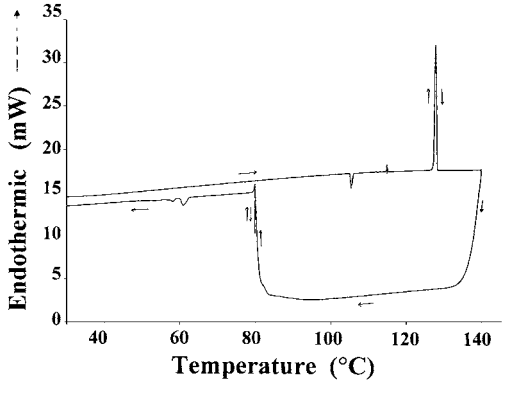

Fig. 9. DSC cooling and re-heating scans of nicotinamide obtained by heating to 140°C at 100°C min^{-1}, followed by cooling to 80°C at 100°C min^{-1}, holding at 80°C for 20 min, cooling to 30°C at 10°C min^{-1} and heating to 140°C at 1°C min^{-1}.

Form I. The exothermic peaks were observed at ca. 61 and 105°C in the further cooling and re-heating scans, respectively. These peaks are considered to be caused by the conversion from Form II to Form I without accompanying melting. The peak due to the melting of Form II is also detectable in the re-heating scan.

The original nicotinamide powder was heated to 80°C, held for 20 min and subsequently heated to 140°C. The heating curve exhibited only one small peak originating from Form I (data not shown). The conversion from Form I to Form II did not occur in these procedures. These results denote that Form I is a stable form and Form II is a metastable one. It was confirmed by these results as well as the ΔH data in Table 1 that the solid–solid polymorphic change from Form II to Form I is monotropic.

The X-ray diffraction patterns of nicotinamide investigated at ambient temperature have been reported earlier [20]. No significant change in the X-ray diffraction pattern of nicotinamide was obtained by heating to 140°C nor by subsequent cooling and holding at 80°C. This was due to a lack of significant decomposition and that Form II crystals were converted to Form I by cooling to ambient temperature.

This clarified the facts that nicotinamide displays polymorphic changes and that cooling conditions affects its polymorphs significantly. Fused nicotinamide shows a different DSC scan to the scan of the untreated material due to the co-existence of the polymorphs [13]. Consequently, precise control of cooling is necessary for the preparation of solid dispersions with nicotinamide.

4. Conclusion

Nicotinamide has at least four polymorphs. Form I is the stable form. When nicotinamide is melted and subsequently cooled to temperatures <80°C, Form I preferentially recrystallises. When cooling is stopped at the higher temperature (80 or 85°C), Form II predominantly forms.

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