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# Investigation of the polymorphic transformations from glassy nifedipine

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**Abstract**

The polymorphic behaviour of nifedipine was investigated using differential scanning calorimetry (DSC), modulated temperature DSC (MTDSC) and hot stage microscopy (HSM). DSC and MTDSC scans of glassy nifedipine samples revealed the presence of several heating rate-dependent events occurring prior to the main melting endotherm (172 °C) including solid–solid recrystallisation on MTDSC curves. These events were related to the recrystallisation and transformation between different polymorphs of nifedipine. Recrystallisation, solid–solid and solid–liquid–solid transformation processes occurred in glassy nifedipine when heated from 45 °C to its final melting point of 172 °C, including a glass transition at ∼48 °C. It was concluded that there were probably four polymorphic forms of nifedipine. The chemical stability of nifedipine during DSC scanning was established by high performance liquid chromatography (HPLC) with diode array UV detection.
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*Keywords:* Nifedipine; DSC; MTDSC; Polymorphism

## 1. Introduction

There are reports that nifedipine, a calcium-channel blocker, has a number of polymorphs and that the addition of cyclodextrins or polyvinylpyrrolidone affects the occurrence of the metastable forms [1,2]. Eckert and Müller [1] reported the appearance of several events in differential scanning calorimetry (DSC) scans of nifedipine, at a heating rate of 5 °C min$^{-1}$. These events were attributed to the presence of polymorphic Form I (melting peak at 172 °C), Form II (melting at ∼163 °C) and Form III (melting at ∼135 °C). Hirayama et al. [2] produced DSC scans of glassy nifedipine at 10 °C min$^{-1}$, and summarised the thermal transitions as: (i) an endothermic event at 48 °C (glass transition); (ii) an exotherm at 105 °C (crystallisation of form B); (iii) an exotherm at 125 °C (transition of form B to form A); and (iv) an endotherm at 172 °C (melting of form A). 2-Hydroxypropyl-β-cyclodextrin was proposed as an additive that allowed selective preparation of form B of nifedipine [2]. Uekama et al. [3] suggested that the presence of 2-hydroxypropyl-β-cyclodextrin prevented the crystallisation of amorphous nifedipine or form B nifedipine, to the A form of the drug.

Hot stage microscopy (HSM) may be used to evaluate the likelihood of polymorphic transformations in a drug by selective use of controlled heating and

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cooling rates. This may lead to the formation of transient, very unstable polymorphic forms of a drug. In this study, the polymorphic behaviour of nifedipine was investigated using HSM. Additionally, DSC and modulated temperature DSC (MTDSC) were used to confirm the recrystallisation of nifedipine from its glassy melt and to determine whether the modulated technique had potential to evaluate solid–solid transformations. The stability of nifedipine following heating was studied during heating using thermogravimetric analysis (TGA) and high performance liquid chromatography (HPLC).

## 2. Experimental

### 2.1. Materials

Nifedipine BP was used and stored under light-protected conditions to prevent photo-decomposition. HPLC grade acetonitrile and water were obtained from Mallickrodt-Baker (Milton Keynes, UK), and spectrophotometric grade trifluoroacetic acid was supplied by Sigma-Aldrich (Gillingham, UK).

### 2.2. DSC and MTDSC

Aluminium sample pans (40 μl; Part No. 219-0041, Perkin-Elmer, Beaconsfield, UK) were used throughout.

#### 2.2.1. Glass transition of nifedipine

The glass transition of nifedipine was determined by two methods, using a Perkin-Elmer data station with Pyris 1 software. Untreated nifedipine samples were scanned from 20 to 180 °C at 20 °C min$^{-1}$, cooled back to 20 °C at a nominal rate of 200 °C min$^{-1}$ (i.e., an instrument setting but probably in fact a lower rate), held at 20 °C for 5 min before heating to 180 °C at 20 °C min$^{-1}$. The glass transition temperature ($T_g$) was determined from this final DSC heating curve by the half change in specific heat. To determine the $T_g$ from MTDSC data, samples were similarly treated, i.e. heated from 20 to 180 °C at 20 °C min$^{-1}$, cooled to 10 °C at a nominal rate of 200 °C min$^{-1}$ and held for 5 min. The modulated cycle was then applied from 10 °C, using a cycling time of 1 min, heating at 8 °C min$^{-1}$ for 30 s and cooling at 4 °C min$^{-1}$ for 30 s, giving an underlying heating rate of 2 °C min$^{-1}$. Calibrations of heat flow and temperature scale were carried out using zinc (melting point: 419.47 °C), indium (melting point: 156.61 °C; $\Delta H$: 28.45 J g$^{-1}$) and lead (melting point: 327.47 °C).

#### 2.2.2. Recrystallisation studies of glassy nifedipine

Samples of nifedipine (∼3 mg accurately weighed) were placed in aluminium sample pans, sealed and heated to 180 °C using a Perkin-Elmer differential scanning calorimeter DSC7 (Beaconsfield, UK) at 20 °C min$^{-1}$ under an atmosphere of nitrogen. The sample pans were then removed and cooled to room temperature. DSC and MTDSC scans on the cooled samples were carried out from 45 and 60 °C, respectively, using a Perkin-Elmer DSC7 with a TAC7/DX thermal analysis controller, and analysed using MTDSC data analysis software (Perkin-Elmer, Beaconsfield, UK). The glassy nifedipine was scanned at heating rates of 1, 2, 5, 10, 15, 20 and 50 °C min$^{-1}$ for DSC and average heating rates of 0.5, 0.6, 0.625, 0.75, 1 or 2 °C min$^{-1}$ for MTDSC. Both heat/cool and iso/scan modes were applied to the MTDSC scans (Table 1).

### 2.3. HSM

HSM using polarised light was employed to study crystallisation and melting of nifedipine. A central processor FP80 and FP82 hot stage (Mettler-Toledo, Leicester, UK) were used with a BH-2 optical microscope (Olympus, London, UK), equipped with a TK C1381 camera and S-VHS BR-S920E recorder (JVC, London, UK) and a computer. Untreated nifedipine, and samples that had been previously heated to 180 °C at a heating rate of 20 °C min$^{-1}$ and cooled to room temperature to maintain the glassy state, were examined using heating rates of 1, 2, 5, 10 or 20 °C min$^{-1}$.

### 2.4. TGA

A Perkin-Elmer TGA7 thermogravimetric analyser (Beaconsfield, UK) was used to analyse untreated nifedipine samples (∼5 mg, accurately weighed) at heating rates of 1, 2, 5 or 10 °C min$^{-1}$ in an atmosphere of nitrogen.

Table 1
The experimental conditions used for MTDSC scans of nifedipine using iso/scan or heat/cool conditions[a]

| Underlying heating rate (°C min$^{-1}$) | Heat/cool MTDSC | | | | Iso/scan MTDSC | | |
|---|---|---|---|---|---|---|---|
| | Heating | | Cooling | | Heating | | Isothermal period (time, s) |
| | Rate (°C min$^{-1}$) | Time (s) | Rate (°C min$^{-1}$) | Time (s) | Rate (°C min$^{-1}$) | Time (s) | |
| 2 | 8 | 60 | 4 | 60 | | | |
| 1 | 4 | 60 | 2 | 60 | 2 | 60 | 60 |
| | | | | | 2 | 30 | 30 |
| 0.75 | 3 | 30 | 1.5 | 30 | 1.5 | 30 | 30 |
| 0.625 | 2.5 | 24 | 1.25 | 24 | | | |
| 0.6 | | | | | 1.2 | 25 | 25 |
| 0.5 | 2 | 30 | 1 | 30 | 1 | 30 | 30 |

[a] Prior to MTDSC analysis, the samples were heated to 180 °C at 20 °C min$^{-1}$ and rapidly cooled to room temperature.

### 2.5. Evaluation of the thermal stability of nifedipine by HPLC

To assess the stability of nifedipine samples that had been subjected to DSC, pans containing nifedipine, following DSC, were transferred into acetonitrile to produce a solution with a concentration of ∼1 mg ml$^{-1}$. Untreated nifedipine was used for calibration purposes; solutions in acetonitrile were prepared at 0.5, 0.75, 1.0 and 2 mg ml$^{-1}$. A Waters (Watford, UK) HPLC system, comprising a 2690 solvent delivery unit with autosampler and column heater, a 996 diode array UV detector and a Millennium data station were used for the study. The column used was a Symmetry Shield $RP_8$, 150 mm × 3.9 mm, 5 μm particle diameter (Waters Limited, Watford, UK), maintained at 30 °C onto which 5 μl sample volumes were injected. The mobile phase consisted of a water/acetonitrile gradient, modified with 0.1% (v/v) trifluoroacetic acid at a flow rate of 1.0 ml min$^{-1}$. Gradient elution was employed in order to shorten analysis time, to allow screening for a wide range of polarities in possible degradation products, and to avoid artefact peaks from previous injections. Trifluoroacetic acid was added to the mobile phase as an ion-pair reagent to improve retention and prevent tailing of the nifedipine peak. The mobile phase was degassed on-line using a membrane vacuum degasser supplied as an integral part of the HPLC system. Data were acquired over the range 190–350 nm at an optical resolution of 1.2 nm and a sampling rate of 1 spectrum s$^{-1}$. Data extracted at 235 nm were used for quantitation.

## 3. Results and discussion

### 3.1. DSC and HSM

Untreated nifedipine showed a single melting point endotherm with an onset temperature of 172 °C (Fig. 1) and an endothermic change in baseline following melting. TGA suggested that decomposition was an unlikely cause of this phenomenon, since only a very small weight loss (<0.7%) was apparent during heating of the samples, irrespective of heating rate.

HPLC analysis following thermal treatment revealed no apparent impurities in the chromatograms. Both nifedipine standards and melted samples produced a single peak with a mean retention time of 11.5 min. At this retention time, peaks in the chromatograms of melted nifedipine gave UV spectra identical to those produced from injections of nifedipine standards. The UV spectral purity angle was 0.222° for the pre-treated sample, indicating almost perfect homogeneity (100% homogeneity = 0°; 0% homogeneity = 90°). The purity threshold was 1.005. This provides good evidence that the chromatographic peak eluting at the expected retention time for nifedipine consisted of a single chemical entity. It may be thus inferred that nifedipine was chemically stable during DSC analysis. Since there is no decomposition, all heat flow variations may be presumed to stem from structural changes in the sample. Therefore samples were scanned following heating and cooling to assess polymorphic change.

The glass transition of nifedipine was readily apparent in both DSC (Fig. 2) and MTDSC (Fig. 3) curves.

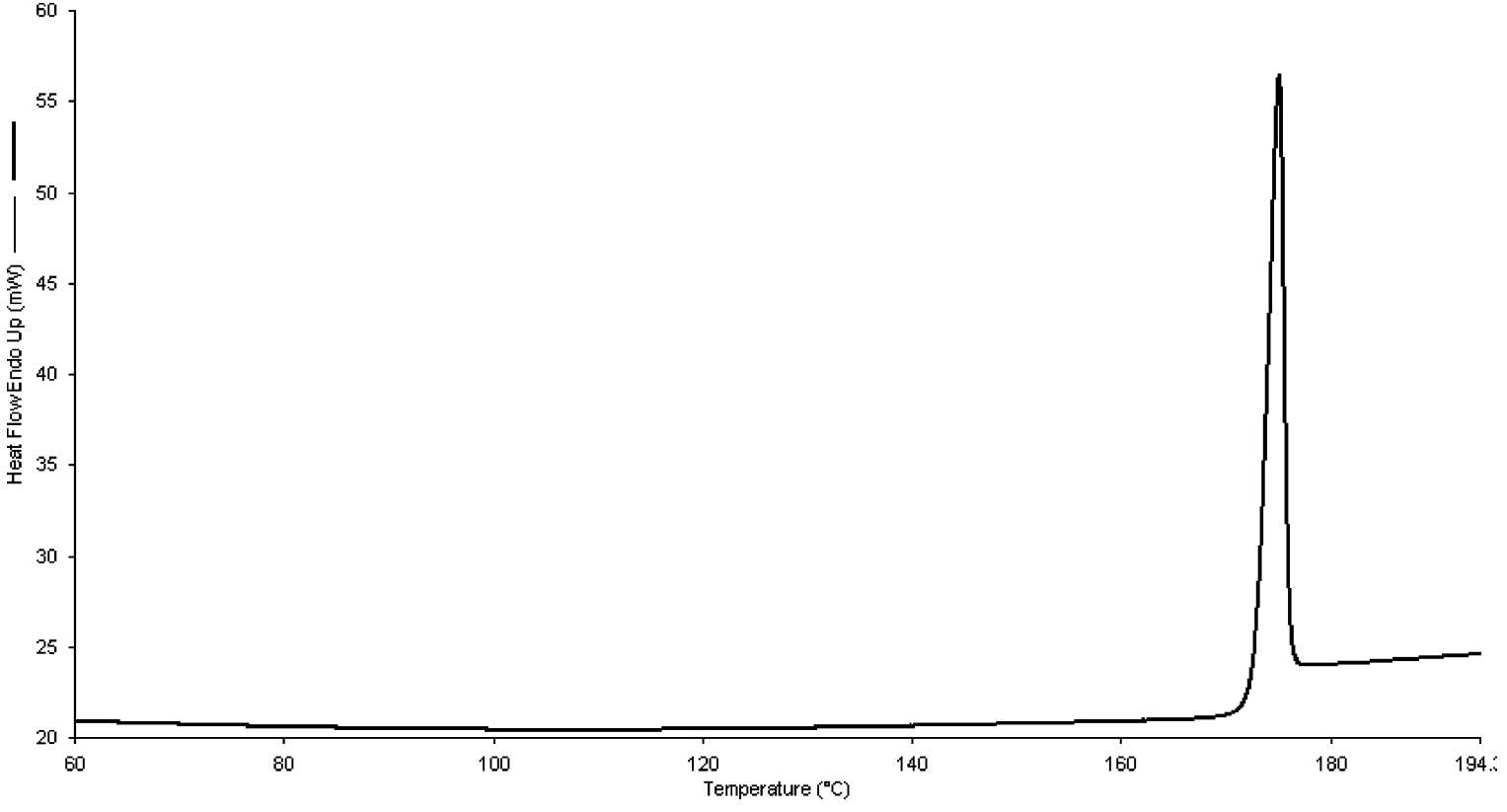



Fig. 1. DSC scan of untreated nifedipine (4.04 mg) obtained at 10 °C $min^{-1}$.

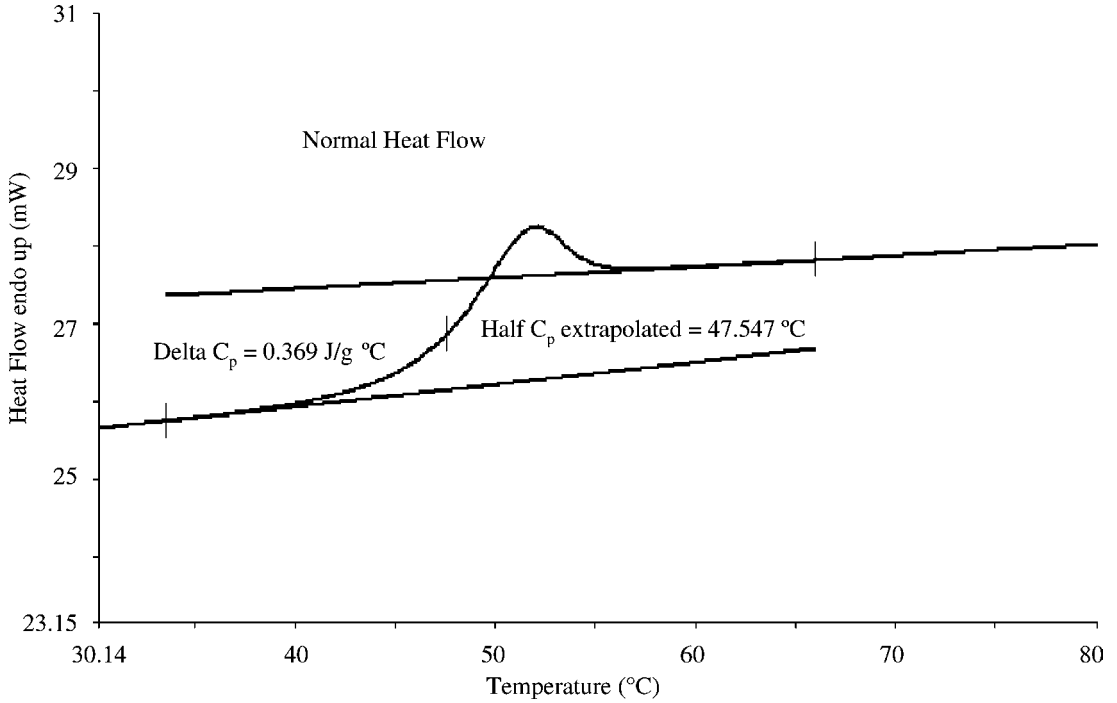



Fig. 2. DSC of a sample of nifedipine (11.480 mg) obtained at 20 °C min$^{-1}$. The sample had previously been heated from 20 to 180 °C at 20 °C min$^{-1}$, immediately cooled to 20 °C at 200 °C min$^{-1}$, and held at 20 °C for 5 min.

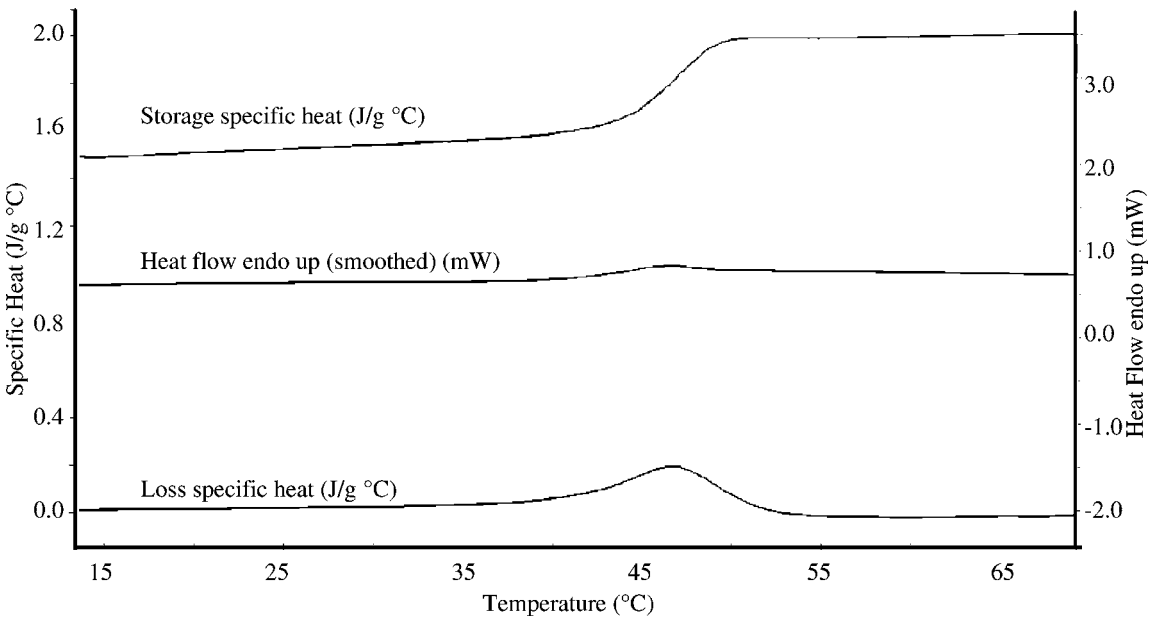



Fig. 3. MTDSC of a sample of nifedipine (11.480 mg) obtained at an underlying heating rate of 2 °C min$^{-1}$, acquired through heating at 4 °C min$^{-1}$ for 30 s and cooling at 2 °C min$^{-1}$ for 30 s. The sample had previously been heated from 20 to 180 °C at 20 °C min$^{-1}$, immediately cooled to 20 °C at 200 °C min$^{-1}$, and held at 20 °C for 5 min.

The DSC curves, showing also a relaxation endotherm, give a typical half $C_p$ extrapolated $T_g$ of 47.5 °C with a $\Delta C_p$ of 0.37 J g$^{-1}$ °C$^{-1}$ (Fig. 2). MTDSC curves gave a typical $T_g$ of 46.5 °C (Fig. 3) derived from the storage specific heat curve. This curve showed a simple step transition: a relaxation event was also apparent on the heat flow curve and an endotherm in the loss specific heat curve.

The $T_g$ values obtained in this study correspond well to the value of 48 °C obtained previously [2]. Resolution of the MTDSC curves showed that the relaxation enthalpy associated with the heat flow curves (Fig. 3) or the DSC curve (Fig. 2) could be removed when the storage specific heat curve was derived. The endotherm was still apparent in the loss specific heat curve (Fig. 3).

Examination of glassy nifedipine by HSM at temperatures >45 °C partly supported earlier data on the thermal analysis of nifedipine [1,2]. Part of this related to the influence of heating rate on the conversions seen for glassy nifedipine. At a heating rate of 1 °C min$^{-1}$ (illustrated as a sequence on the same sample during heating in Fig. 4A–C) crystallisation from the glassy solid occurred in the range 85–105 °C. HSM indicated spherulite growth from a number of nucleation centres with needles of nifedipine developing on top of the spherulites at 100–105 °C (Fig. 4A). In other words, this indicated a liquid–solid transformation with a further possible solid–solid transformation. A further solid–solid transformation of the spherulites and needles to crystals with plate-like habits occurred from ∼109 to 124 °C (Fig. 4B), particularly apparent at ∼112–114 °C. A gradual reduction in intensity and colour of the polarised crystals occurred at ∼125–155 °C concomitant with restructuring. Further minor recrystallisation was apparent at ∼157 °C, with minor melting at 160 °C prior to major melting at 168–171 °C (Fig. 4C). Clearly, this latter melt corresponds to the melting of Form I [1] or Form A nifedipine [2] described previously. Certainly at this low heating rate of 1 °C min$^{-1}$ visual evidence existed for the recrystallisation from the glassy state of spherulites and, almost immediately, of separate needles from the solid structures. Solid–solid transformation to plates occurred at ∼120 °C and gradual further transformations occurred to the stable Form I polymorph. There was no evidence for the melting of a Form III polymorph [2] at 135 °C.

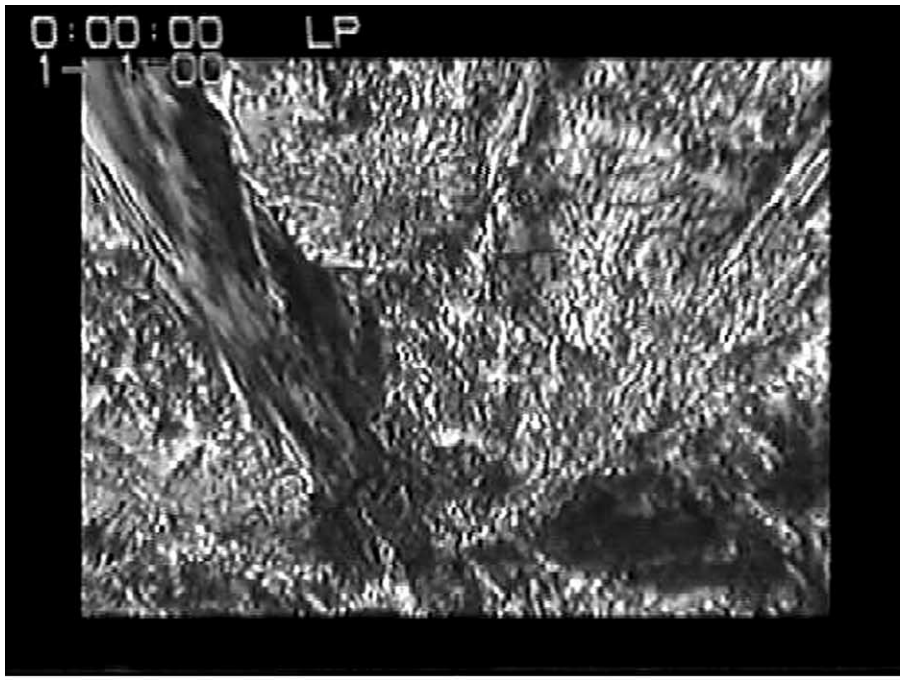
The use of faster scanning rates modified the events that took place. Equivalent transitions occurred at higher temperatures than those seen at 1 °C min$^{-1}$. At 5 °C min$^{-1}$, crystallisation via spherulite formation occurred at ∼113 °C and solid–solid transformation took place in the range 128–146 °C. Further changes were evident at 148 °C and recrystallisation melting occurred at ∼165 °C with final melting at ∼172 °C. This suggests that two polymorphs were present in the sample, the faster rate of 5 °C min$^{-1}$ preventing full conversion of Form II or B [1,2] to the stable polymorph.

At 10 °C min$^{-1}$, crystallisation via spherulite formation occurred at ∼115 °C and solid–solid transformation took place in the range 137–153 °C (Fig. 4D). Further solid–solid changes were evident at 153–161 °C. Melting and some recrystallisation melting occurred at ∼168 °C with final melting at ∼173 °C. At 20 °C min$^{-1}$, crystallisation occurred at 142–153 °C to produce large plate like crystals (Fig. 4E), almost certainly corresponding to the formation of Form II or B [1,2] nifedipine since these crystals melted predominately at ∼168 °C with minor melting at ∼173 °C.

Such observations suggest that, as postulated by Hirayama et al. [2], Form I and Form II polymorphs of nifedipine exist. However, the Form or Forms that originally crystallised from the glass at low heating rates themselves converted to Form II which at the slow heating rates converted to Form I. The HSM data present a more complicated scenario than that proposed by Hirayama et al. [2].

Under the preparative conditions used in this study nifedipine samples, previously melted and cooled, were used to assess polymorphic modifications during re-heating. It is assumed that the samples inside the sealed DSC sample pans took on the same form as those on the microscope slides during HSM heating when transparent, slightly yellow glasses were formed.

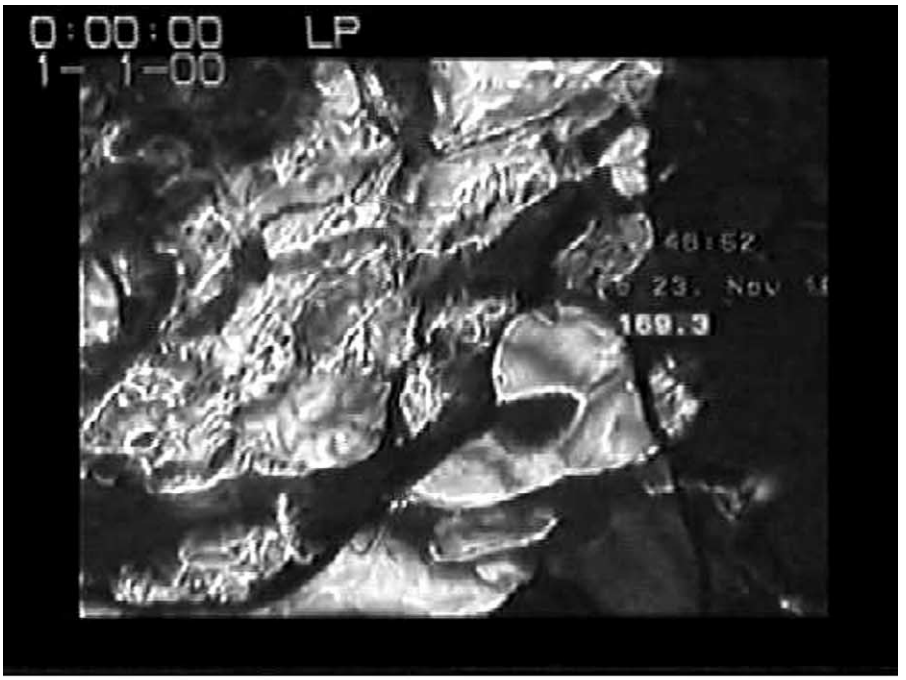
In contrast to untreated samples, DSC of glassy, heat-treated, nifedipine exhibited several exothermic events, which were heating rate-dependent (Fig. 5a and b). At lower heating rates (1 or 2 °C min$^{-1}$), crystallisation started at an onset temperature of ∼80 °C and appeared to be an irregular event (Fig 5b). Another broad but shallow exotherm occurred between 110 and 150 °C, preceded by a small exotherm at



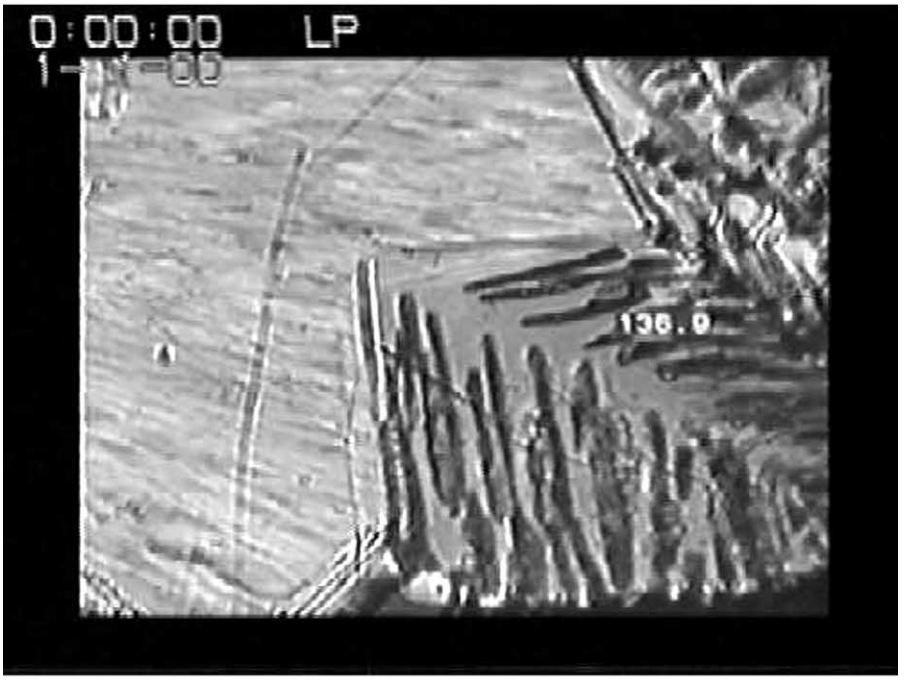

(A)


(B)

Fig. 4. Photomicrographs of the conversions of nifedipine from the glassy state to the crystalline forms. Melt recrystallised nifedpine at: (A) 100 °C heating at 1 °C min$^{-1}$; (B) 106.5 °C heating at 1 °C min$^{-1}$; (C) 169.3 °C heating at 1 °C min$^{-1}$; (D) 136.9 °C heating at 10 °C min$^{-1}$ showing recrystallisation from the melt; (E) 154.9 °C heating at 20 °C min$^{-1}$.




(C)




(D)

Fig. 4. (*Continued*).


(E)

Fig. 4. (*Continued*).

~100–105 °C, and followed by a single melting endotherm at 172 °C. These events broadly corresponded to the HSM data obtained at 1 °C min$^{-1}$ where initial recrystallisation was followed by the development of needle-like structures. A tentative interpretation of this phenomenon could be the formation of the spherulite structures (possibly Form IV) and needle structures (possibly Form III) in the initial exotherm, followed by conversion to Form II in the exotherm at 100–105 °C. This Form II gradually changed to Form I on the broad but shallow exotherm from 110 to 150 °C as exemplified by HSM with development of plate-like structures which gradually changed during heating and finally melted. Complete conversion to Form I was accomplished.

At higher heating rates (5, 10 and 15 °C min$^{-1}$), crystallisation exotherms (Fig 5b) shifted proportionally to higher temperatures, while separation into three or more transitions became apparent and a melting endotherm at 163 °C was observed before the final melting endotherm at 172 °C (Fig. 5a). When crystallisation from the glass was inhibited by faster scanning rates, the third transition was too brief, hindering the transition of Form II to Form I.

At heating rates of 20 and 50 °C min$^{-1}$, the magnitude of the endotherm at 163 °C increased, as an increasing amount of Form II melted and was not converted to Form I. Correspondingly, the endotherm at 172 °C became smaller (e.g. 20 °C min$^{-1}$; Fig. 5a). HSM (Fig. 4E) showed large plate-like crystals that formed only at temperatures in excess of 150 °C. This heating rate dependency and the idea that nifedipine has more than two polymorphic forms were confirmed by HSM. Temperatures of events correlated well for the same heating rate in both DSC and HSM. Polarised light microscopy distinguished between solid–solid transitions and solid–liquid–solid transitions. HSM also showed minor transitions between recrystallisation and melting.

The terminology of Forms I, II and III follow the convention of Eckert and Müller [1], although in no DSC scans or HSM studies could Form III be shown to melt at ~135 °C. Indeed, the data more closely resembled the observations of Hirayama et al. [2]. Put

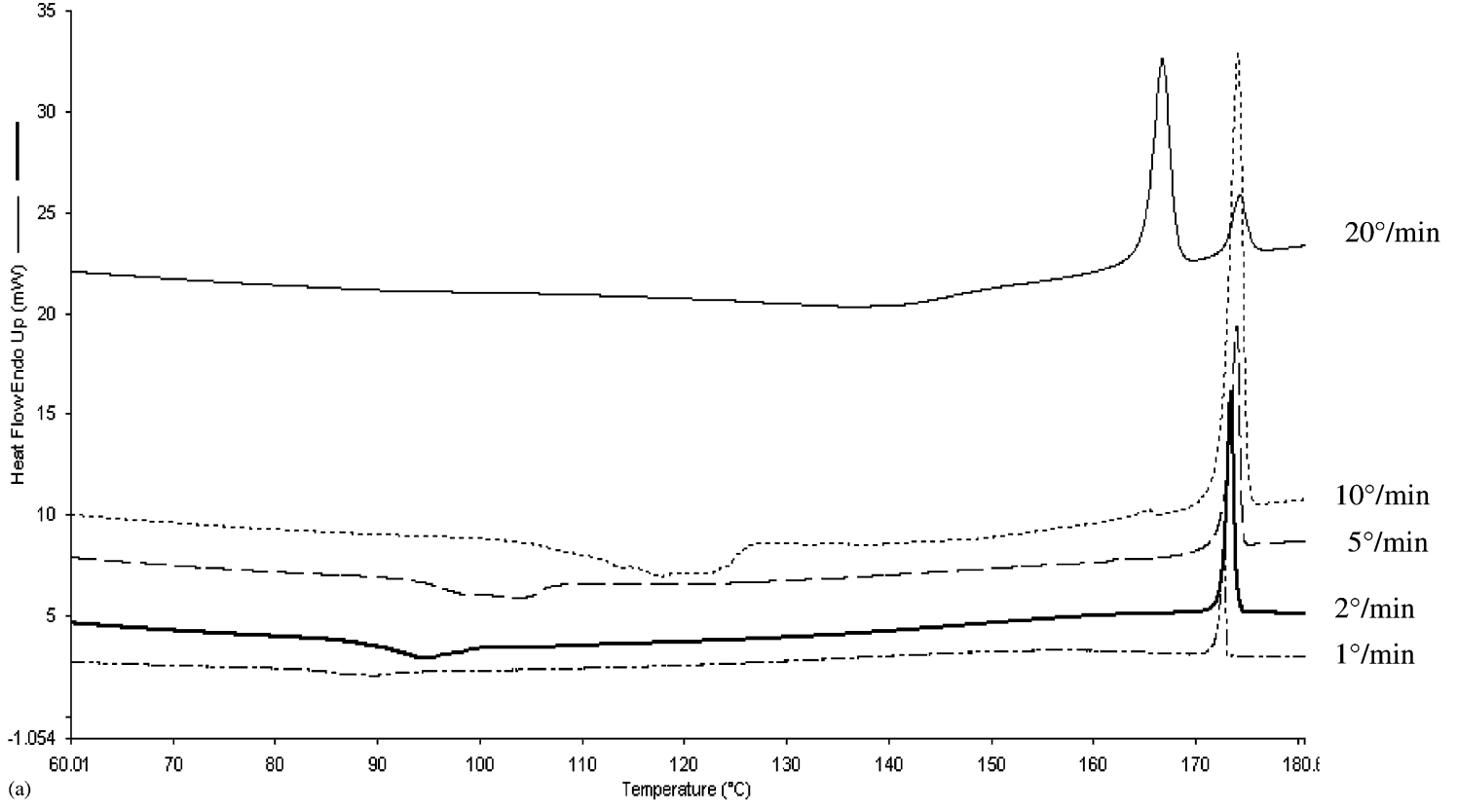



Fig. 5. (a) DSC scans of glassy nifedipine obtained at 1, 2, 5, 10, and 20 °C min$^{-1}$ (reading up). The samples were previously heated to 180 °C at 20 °C min$^{-1}$ and rapidly cooled to room temperature. (b) Expansion of scale of Fig. 6a.

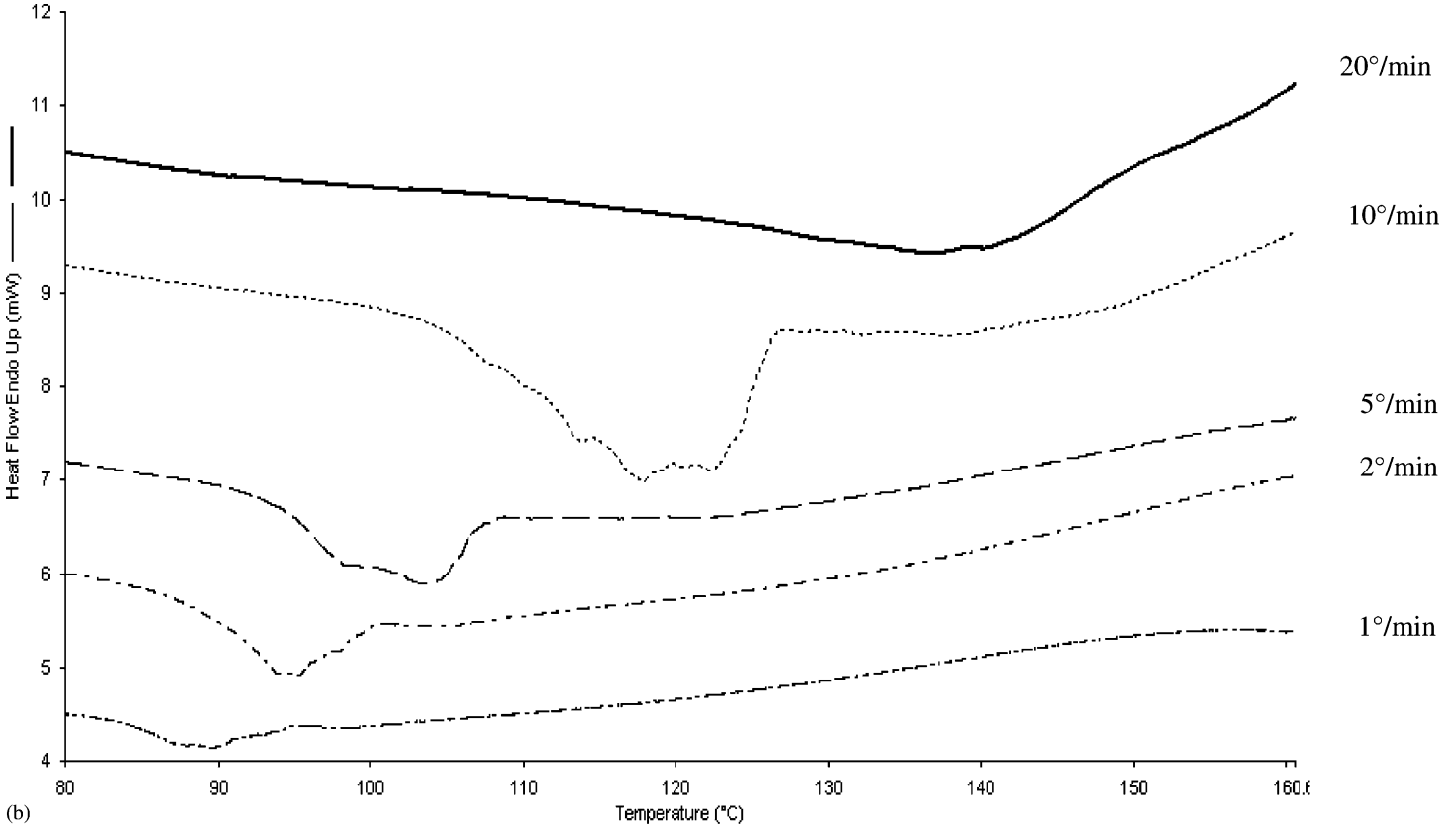



Fig. 5. (*Continued*).

simply, at 1 °C min$^{-1}$ it is likely that Form III and another form, Form IV, recrystallised from the glass and converted to both Form II and Form I as a mixture of polymorphs, which converted to Form I and finally melted. Increasing the heating rates effectively increased the proportion of Form II at its melting point. Thus, at 5 °C min$^{-1}$, Form IV immediately formed and converted to Form III, which converted to both Form I and Form II. As at 1 °C min$^{-1}$, Form II mostly converted to Form I. When the heating rate was increased to 20 °C min$^{-1}$, Form II was present at its melting point in increasing quantities and does not convert under DSC conditions to Form I, although the latter was suggested by HSM data where minor melting occurred at >170 °C.

It must be stressed that this interpretation of HSM and DSC data is not supported at present by infrared or X-ray diffraction data, techniques that might confirm the nature of the solid structures. Undoubtedly, the recrystallisation of nifedipine from its glassy state is more complicated than suggested by earlier studies [1,2]. However, because MTDSC can be used at relatively low heating rates, the technique was used to examine the recrystallisation events observed in HSM and DSC experiments, in an attempt to determine if MTDSC could follow the changes observed in DSC and HSM.

### 3.2. MTDSC

The instrument used in this study used the principles of MTDSC as supplied by Perkin-Elmer for data analysis. Two types of programmes were used to effect modulation. These were heat/hold (iso/scan) and heat/cool repeated temperature change programmes. The averaged heat flow data were used to calculate the heat flow, equivalent to the classical DSC curve. Fourier transformation resulted in the determination of the storage heat capacity ($C'_p$) and the loss heat capacity ($C''_p$) curves derived from the dynamic measurements. Details of the data treatment may be found elsewhere [4,5]. Theoretically, ($C'_p$) is the reversible heat flow and ($C''_p$) gives information on structural and entropy changes.

Two kinds of movement are possible in a sample: (a) the motions of small moieties that are fast and contribute to ($C'_p$) throughout the temperature range; and (b) the motions of co-operative units which have a frequency close to zero at temperatures less than the $T_g$. These latter contribute to ($C'_p$) at temperatures greater than the $T_g$. Clearly, the glass transition is obvious in the modulated processes (Fig. 3). There remains the issue of whether recrystallisation, either liquid to solid or solid to solid is apparent in either the ($C''_p$) or ($C'_p$) curves. He and Craig [6] noted discontinuity in both total and non-reversing signals (non-reversing signals approximate to the loss heat capacity curves used in this study) following the glass transition, but preceding the recrystallisation of glassy indomethacin. This confirmed the difficulty of interpreting heat flow signals during melting events [7].

Fig. 6 shows the curves representative of those found during the heat–iso and heat–cool modulations. It should be realised that the underlying heating process, in either event is slow. The details of those conditions covered are given in Table 1.

With reference to Table 1, four underlying heating rates were used for the iso/scan conditions. The underlying condition of 1 °C min$^{-1}$ using an isothermal and heating period of 60 s gave irregular shaped curves indicative of a failure to control the crystallisation processes. The heat flow gave a sharp exotherm centred at ∼92 °C, a broader exotherm at ∼108 °C and a gradual exotherm between ∼120 and ∼150 °C. Downward peaks occurred in both the loss ($C''_p$) and storage ($C'_p$) curves. Reducing the isothermal and heating periods to 30 s but maintaining the overall heating rate of 1 °C min$^{-1}$ produced smoother curves in which far smaller changes were apparent in the storage and loss curves (Fig. 6a) whilst maintaining the presence of three exotherms in the heat flow curve. Reducing the underlying heating rate to 0.6 or 0.5 °C min$^{-1}$, similar to conventional DSC, lowered the temperatures at which the recrystallisation events occurred and made the broad recrystallisation less obvious.

Similar to the iso/scan conditions, heat/cool data were somewhat erratic at underlying rates of 2 and 1 °C min$^{-1}$, with evidence that uncontrolled recrystallisation caused downward events in both the storage and loss curves. Further reduction in underlying heating rate to 0.625 or 0.5 °C min$^{-1}$, however, produced consistent data (Fig. 6b) which showed three exotherms corresponding to the recrystallisation processes in the heat flow curves, a small “exotherm” in the loss ($C''_p$) curve corresponding to the major liquid–solid recrystallisation (step 1) and a downward

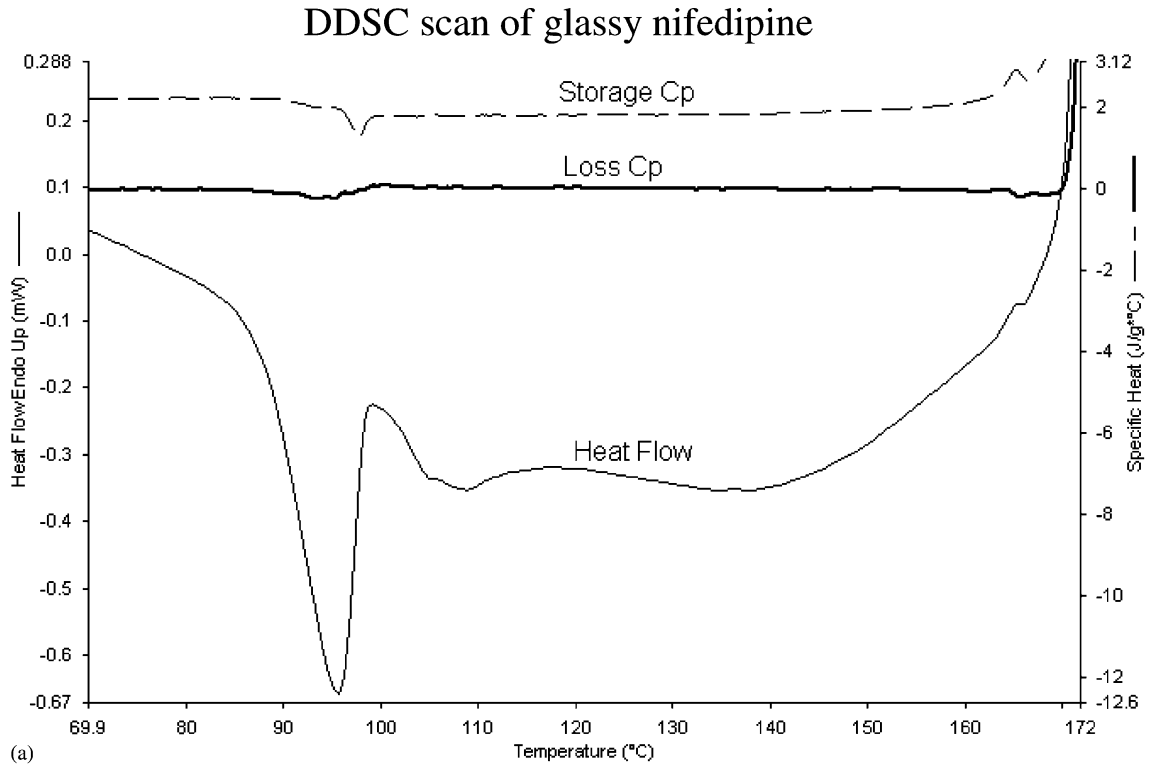
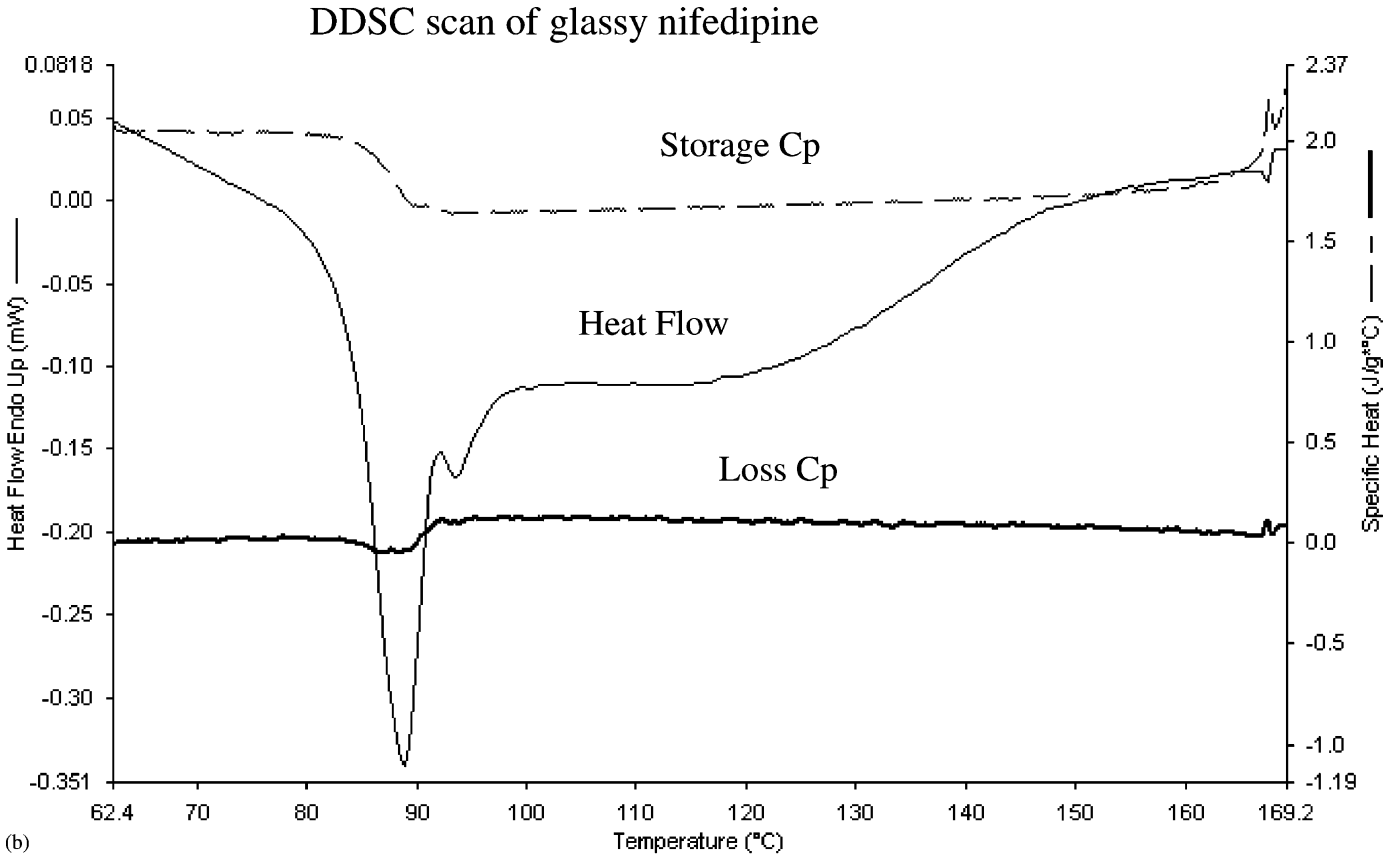



Fig. 6. Typical MTDSC scans of nifedipine using iso/scan or heat/cool conditions. Prior to MTDSC analysis, the samples were heated to 180 °C at 20 °C $min^{-1}$ and rapidly cooled to room temperature. (a) Using isothermal holds of 30 s and raising the temperature for 30 s at 1 °C $min^{-1}$ starting from 60 °C. (b) Alternating heating at 2.5 °C $min^{-1}$ by 1 °C followed by cooling by 0.5 °C at 1.25 °C $min^{-1}$ starting from 60 °C and repeating 230 times.




(b)

Heat/cool: 60°C to 61°C (2,5°C/min) to 60,5°C (1,25°C/min) (230x); average 0.625°C/min

Fig. 6. (*Continued*).

shift in the storage ($C'_p$) curve reflecting a reduction in the specific heat of the material followed by a slight but apparent further drop in specific heat caused by the first solid–solid recrystallisation (step 2). The broad area of recrystallisation, attributable to the production of the Form I polymorph was not, however, detected in either the storage or loss curves.

Glassy nifedipine showed a clearly separated double exotherm between 80 and 110 °C on most scans. At all heating rates used, the heat/cool mode separated both crystallisations better in this temperature range than the iso–heat mode. The storage ($C'_p$) showed a drop in the $C_p$ in the temperature region where the first of the double exotherms was seen. Storage ($C'_p$) measures the change in heat capacity during crystallisation. Since the first crystallisation process is the formation of a metastable crystalline phase out of the glass and the second crystallisation is only a reformation of the crystalline structure, the largest change in heat capacity will correspond to the first. Apparently, therefore, in the storage ($C'_p$) step, the change in heat capacity is measured during crystallisation. Step 1 is the formation of a metastable crystalline phase, and step 2 is a solid–solid transformation. Step 1 will have the largest heat capacity change and is therefore very apparent.

The ($C''_p$) loss curves showed distinct negative peaks and was influenced by the temperature change, which is approximately proportional to the crystallisation rate. The resolution of storage ($C'_p$) was improved by reducing the underlying heating rate (0.5 or 1.0 °C min$^{-1}$). Heat/cool methods seem to be the preferred experimental set-up for cold crystallisation. Cold crystallisation is far from its equilibrium [7]. Therefore there is a small change in the heat flow amplitude that determines ($C'_p$) between 110 and 150 °C.

The trough in ($C''_p$) (Fig. 6b) is not fully understood [7]. Loss in ($C''_p$) occurs due to structural changes, equivalent to an increase in order. The endotherm in ($C''_p$) peak at the $T_g$ (Fig. 3) may be due to a decrease in order. Altogether, this might indicate that, on heating or cooling through a crystallisation event, no temperature cycle induced crystallisation occurs in the heating run or temperature cycle induced melting on the cooling run. The loss ($C''_p$) changes are, however, approximately proportional to the crystallisation rate and thus to the heating rate. Therefore, the peak in loss ($C''_p$) is better seen at the relatively high average heating rate of 1 °C min$^{-1}$. These events are, however, difficult to interpret fully.

## 4. Conclusion

Nifedipine probably displayed four different polymorphs under DSC and MTDSC analysis. These transitions are heating-rate dependent, and HSM data provided visual evidence for the presence of these transitions. There was no decomposition of nifedipine during either the preparation of glassy nifedipine or the actual scanning of it. Modulated techniques registered the glass transition, which was apparent in the heat flow and storage MTDSC curves. Recrystallisation was only partly evident in both the ($C'_p$) and ($C''_p$) curves. ($C''_p$) showed greater sensitivity at faster scanning rates, but explanation of these events is currently unclear.

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