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Solid-state characterization of paracetamol metastable polymorphs formed in binary mixtures with hydroxypropylmethylcellulose

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Abstract

Two metastable polymorphs of paracetamol (forms II and III) were prepared by appropriate thermal methods from binary mixtures containing 10% (w/w) of hydroxypropylmethylcellulose. By controlling the reheating step, it was possible to address the recrystallization of the drug either into form II or III. Moreover, it was observed that form III transforms either into form II or I depending on the preparation method. The physical characterization of the polymorphs was performed by means of micro-Fourier transform infrared spectroscopy (MFTIR) and powder X-ray diffractometry (PXRD), both temperature controlled.

Keywords: Polymorphs of paracetamol; Hydroxypropylmethylcellulose; DSC; Temperature controlled MFTIR; Temperature controlled PXRD

1. Introduction

Two metastable polymorphs (forms II and III) of paracetamol, *N*-(4-hydroxyphenyl)acetamide (PCM), an analgesic and antipyretic drug, have been so far reported in literature [1–6]. Form II, which has been fully characterized [1], possesses better tabletting properties than the stable form I [7], but is difficult to prepare on a large scale [1,4,6–9]. On the other hand, due to its physical instability, very little information is available for form III [2,4].

The investigation of the thermal behavior of the PCM/polymeric excipient binary mixtures (ranging from 50 to 90% (w/w) of drug) has evidenced the possibility of preparing the metastable polymorphs of PCM in the presence of hydroxypropylmethylcellulose (HPMC), a synthetic derivative of cellulose primarily used as a tablet binder, by controlling the mixture composition and the thermal program [10]. The endo–exo events in the 130–140 °C temperature range (differential scanning calorimetry: DSC) have been attributed to the fusion of form III and recrystallization of form II from the melt. In particular, the possibility of a selective preparation of forms II and III from 90/10 (w/w) PCM/HPMC mixtures was envisaged. Moreover, the ability of an

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analogous polymeric excipient to control the drug recrystallization process has been recently described [11].

This paper reports data regarding the preparation and characterization of PCM metastable polymorphs from mixtures containing 10% (w/w) of HPMC. In addition to thermal methods (DSC and hot stage microscopy: HSM), further physical characterization of the solid phases was achieved by means of other peculiar and complementary techniques such as micro-Fourier transform infrared spectroscopy (MFTIR) and powder X-ray diffractometry (PXRD), which were both temperature controlled.

2. Experimental

2.1. Materials

Samples of PCM and HPMC were obtained from the manufacturer (PCM: ACEF, Fiorenzuola, Italy; HPMC: Methocel K4M Premium EP®, 180–125 μm, water content 8.3% (w/w), Colorcon, Orpington, UK) and were used as received.

2.2. Methods

2.2.1. Preparation of 90/10 (w/w) PCM/HPMC binary mixture

The physical mixture was prepared by gently mixing the components in the appropriate amount in a mortar for 5 min.

2.2.2. Differential scanning calorimetry

Temperature and enthalpy measurements were performed by means of a Mettler DSC 821^e STAR^e system (Mettler Toledo, Switzerland). Samples of about 4–5 mg in pierced aluminum crucibles and under a dynamic nitrogen atmosphere (100 ml min^{-1}) were subjected to specific thermal programs. Instrument calibration was performed with standard indium and zinc samples (purity $> 99.99\%$) of known temperatures and enthalpies of melting.

2.2.3. Preparation of metastable polymorphs by DSC

The thermal methods adopted for the preparation of forms II and III were identical in their first heating and cooling steps (heating from 35 to 180 °C, isotherm at 180 °C for 5 min, cooling down to 35 °C), whereas the second heating section was modified as follows.

Form III: heating from 35 to 113 °C, isotherm 2 min; spontaneous cooling to ambient temperature (program 1).

Form II: heating from 35 to 149 °C, isotherm 2 min; spontaneous cooling to ambient temperature (program 2).

A scan rate of 10 K min^{-1} was used.

Samples, obtained via programs 1 and 2, were characterized by submitting them to a final scan from 35 to 180 °C, at different rates (0.1, 1 and 10 K min^{-1}) (program 3).

2.2.4. Hot stage microscopy

A hot stage apparatus (HSF 91, Linkam Scientific Instruments, Tadworth, UK) equipped with a polarising microscope (Labophot II Nikon, Tokyo, Japan) and a color video camera (XC-003P Sony, Tokyo, Japan), supported by Image-Pro® Plus 4.0 software (Media Cybernetics, MD) allowed the recording of images during temperature scans. Samples were placed between two glass cover slides for the visual analysis through the video camera. An aluminum sample holder was used for the temperature controlled MFTIR experiments.

2.2.5. Form III preparation with Köfler apparatus

A hot stage Köfler apparatus (C. Reichert Optische Werke A.G., Wien, Au) with a large heating surface (∼45 cm^2) and accurate temperature control was used to scale-up the preparation of form III from milligrams to grams. The physical mixture was placed between two aluminum sheets and submitted to program 1, and this process ultimately gave rise to a thin crystalline layer (PCM *KA*).

2.2.6. Temperature controlled micro-Fourier transform infrared spectroscopy

A Jasco MFT-2000 apparatus (Tokyo, Japan), supported by Jasco FT software, was used. The spectra were collected in reflectance mode in the 4000–650 cm^{-1} wavenumber range at controlled temperature by means of the HSF 91 apparatus, according to the following program: heating from 35 to 180 °C, scan rate 1 K min^{-1} (counting time 60 s per data frame). Samples obtained from HSM and Köfler apparatus could be analyzed directly in the original sample holder.

The background was previously measured at a microscopic aperture size matching the sample size and set to the shape of a square with sides ranging from 50 to 100 μm. The number of scans was adjusted automatically as a function of sample concentration.

2.2.7. *Temperature controlled powder X-ray diffractometry*

The powder diffraction data were obtained with a Bruker D5005 diffractometer (Karlsruhe, Germany) with a graphite monochromator in the diffracted beam path (Cu Kα radiation: $K\alpha_1 = 1.54056$ Å; $K\alpha_2 = 1.5443$ Å). A system of divergent, receiving and anti-scatter slits of 1°, 1° and 0.2 mm, respectively, was used. The patterns were collected with 40 kV of tube voltage and 35 mA of tube current in the angular range $5 \leq 2\theta \leq 35°$ in a step scan mode (step width 0.03°; counting time 0.3 s per step). A polythermal attachment (TTK450 Anton Paar, Graz, Au) was used to perform suitable thermal cycles between ambient temperature and 180 °C; the experiments were carried out under dynamic nitrogen atmosphere ($5\,\mathrm{l\,h^{-1}}$) to inhibit sample oxidation.

The samples were subjected to different thermal cycles, depending on the method of preparation.

PCM *KA* samples were subjected to the following thermal cycle: heating from 35 to 113 °C (scan rate $10\,\mathrm{K\,min^{-1}}$) and from 113 to 180 °C (scan rate $1\,\mathrm{K\,min^{-1}}$), cooling to 35 °C (scan rate $3\,\mathrm{K\,min^{-1}}$). The diffraction patterns were collected at 35, 113, 118, 123, 127, 135, 150, 155, 165 °C and again at 35 °C, after cooling.

In the case of the 90/10 (w/w) PCM/HPMC physical mixtures, due to the difficulty of an accurate control of the cooling steps below 80 °C, the thermal program 1 was modified as follows: heating from 30 to 180 °C (scan rate $10\,\mathrm{K\,min^{-1}}$), isotherm at 180 °C for 5 min, cooling to 35 °C (scan rate $3\,\mathrm{K\,min^{-1}}$), reheating to 110 °C (scan rate $10\,\mathrm{K\,min^{-1}}$), isotherm at 110 °C for 2 min, cooling from 110 to 80 °C (scan rate $10\,\mathrm{K\,min^{-1}}$) and from 80 to 35 °C (scan rate $3\,\mathrm{K\,min^{-1}}$), reheating from 35 to 110 °C (scan rate $10\,\mathrm{K\,min^{-1}}$) and from 110 to 159 °C (scan rate $1\,\mathrm{K\,min^{-1}}$), cooling to 35 °C (scan rate $10\,\mathrm{K\,min^{-1}}$).

The diffraction patterns were collected: (i) before the thermal treatments at 30 °C; (ii) during the third heating phase at 110, 125, 130, 135, 140, 145, 150, 153, 156, 159 °C; (iii) at 35 °C after the last cooling step.

3. Results and discussion

3.1. *Thermal behavior of the 90/10 (w/w) PCM/HPMC physical mixture*

The physical mixture shows (Fig. 1) an endothermic peak at about 170 °C during the first heating step, corresponding to the fusion of PCM as form I. After the cooling step, the reheating phase is characterized by an exothermic peak around 100 °C, followed by two close endothermic events at about 139 °C, an exothermic effect at 141 °C and a final endothermic effect at 156 °C. Unfortunately, due to the superimposition of the events, the values of enthalpy changes at 139 and 141 °C could not be quantified. Qualitatively, this complex behavior was interpreted in terms of a preliminary recrystallization of PCM (at 100 °C) as form III and traces of form II [10]. Form III melts around 139 °C with subsequent recrystallization of form II.

3.2. *Preparation of metastable polymorphs*

On the basis of the interpretation mentioned above, specific thermal scans were set on for the preparation of the metastable forms III and II. As described in Section 2.2 the second heating stage was interrupted at 113 (program 1, Fig. 2) or at 149 °C (program 2, Fig. 3). Each sample was then cooled to ambient temperature and rescanned to 180 °C to check the solid phase obtained (Fig. 4, curves (a) and (b)).

3.3. *Transition of form III into form II*

In order to investigate the effect of thermal treatment on the transition from forms III to II during DSC analyses, samples of form III were heated at variable scan rates (see Fig. 5). As the scan rate decreases, the entity of the endo–exo effects within the 125–140 °C temperature range diminishes and almost disappears at $0.1\,\mathrm{K\,min^{-1}}$. On the other hand, the endothermic event at around 156 °C splits into two peaks at 153 and

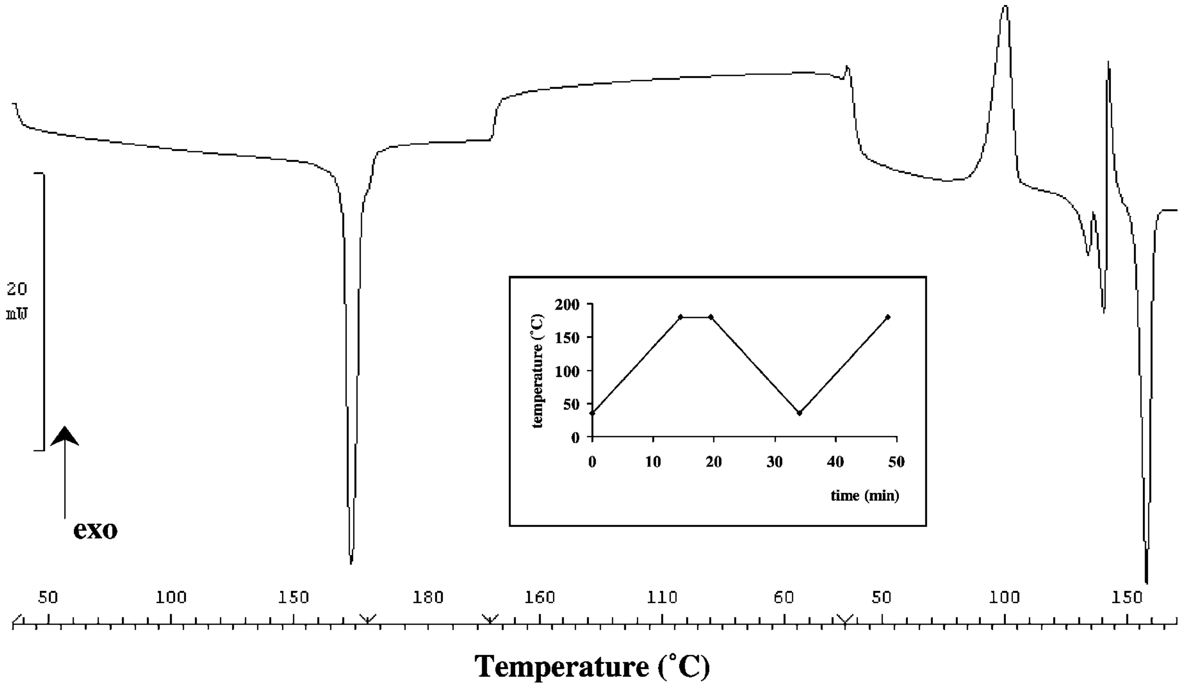

Fig. 1. Thermal behavior (scan rate 10 K min^{-1}) of PCM/HPMC 90/10 mixtures. The heating program is given in the box.

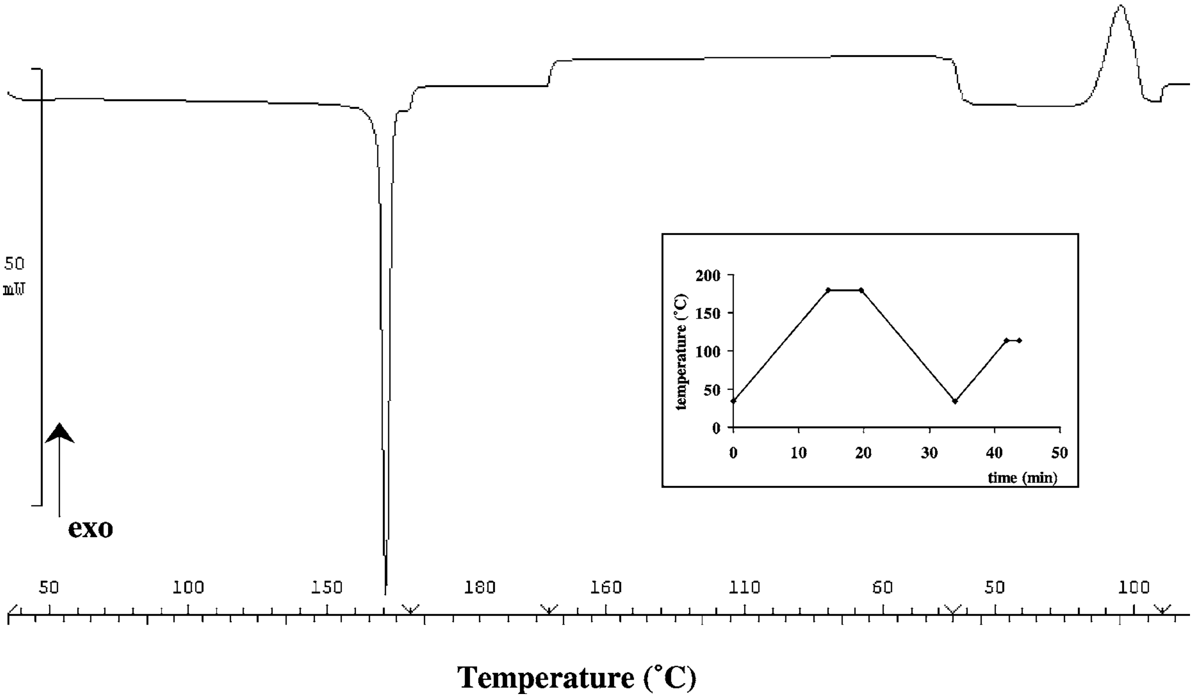

Fig. 2. Thermal behavior (scan rate 10 K min^{-1}) of PCM/HPMC 90/10 mixtures. The heating program is given in the box.

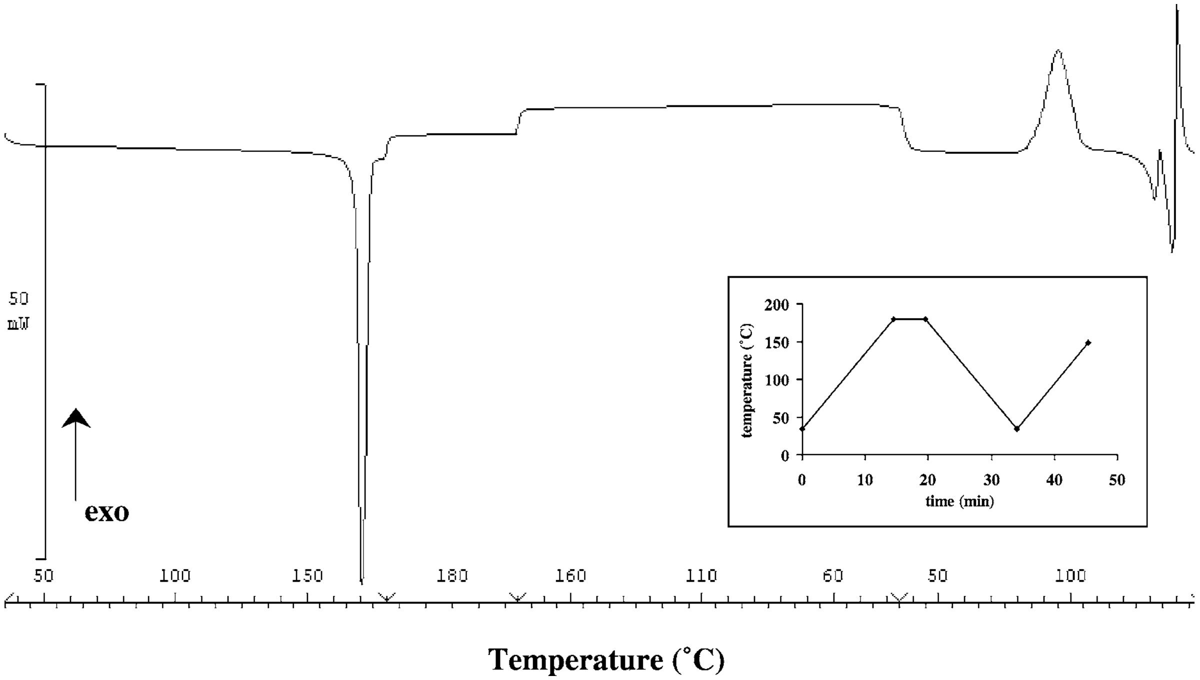

Fig. 3. Thermal behavior (scan rate 10 K min^{-1}) of PCM/HPMC 90/10 mixtures. The heating program is given in the box.

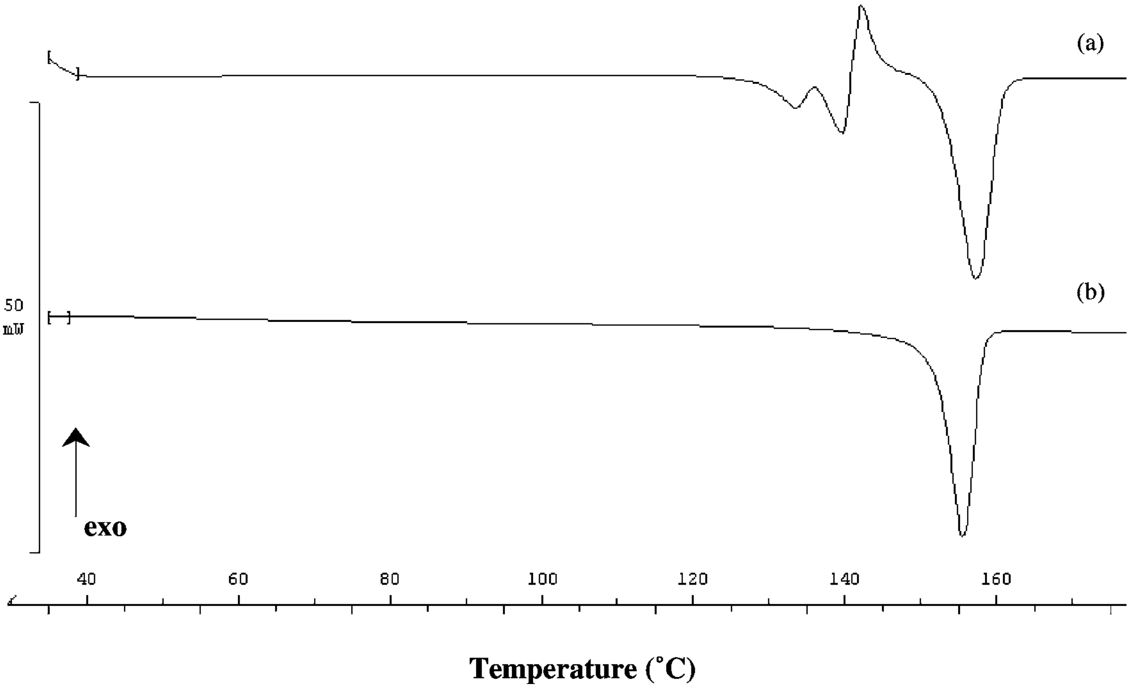

Fig. 4. Thermal behavior of the samples obtained via program 1 (curve (a)) and program 2 (curve (b)): heating from 35 to 180 °C, scan rate 10 K min^{-1}.

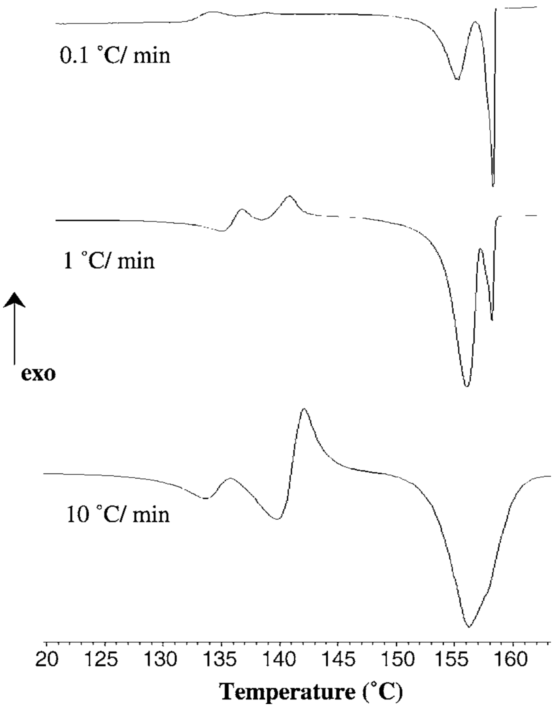

Fig. 5. DSC traces of form III samples (heating from 35 to 180 °C) at three different scan rates.

158 °C, the latter of which is attributed to the melting of form II [1]. At a scan rate of 1 K min^{-1}, the peak at 153 °C has a higher intensity than the one at 158 °C, whereas at a scan rate of 0.1 K min^{-1} the intensities of the two peaks are inverted.

HSM analysis revealed changes in color and thickness of the crystals in the 150–158 °C temperature range.

The samples of form III, obtained with Köfler apparatus (PCM KA) presented different thermal behavior (Fig. 6). The DSC trace shows a broad endothermic event between 100 and 130 °C closely followed by an exothermic peak around 135 °C; finally, two endothermic effects, partially superimposed, are present at 163 and 170 °C, respectively. The final fusion of PCM as form I suggests that samples of form III (PCM KA) probably contain traces of the stable polymorph which induce a transition from forms III to I at about 130 °C, as confirmed by temperature controlled PXRD and micro-FTIR (see the relevant sections).

3.4. Temperature controlled powder X-ray diffractometry

The diffraction patterns of the physical mixture, collected at different temperatures, are shown in Fig. 7. A remarkable change is observed between the two spectra recorded at 30 °C (corresponding to PCM form I) and 110 °C, due to the recrystallization of PCM as form III. During heating, the patterns collected at 125 and 130 °C are very similar even though a remarkable increase in the intensity of the peak at 23.5° is evident. At 135 °C a new series of peaks (14.7, 17.2, 21.5, 27.4, 28.4 and 29.8°), ascribed to form II [9], is observed; their intensities increase as the temperature raises. At 159 °C, the overall decrease of the peak intensities may be due to a partial melting of form II; further recrystallization of this polymorph is observed as the temperature decreases. In fact, comparison of the diffraction pattern collected at 35 °C, with that reported in literature [9], confirms the sole presence of the form II peaks (Fig. 8). Displacement of the peak positions towards lower angles with respect to those reported in literature is due to the misalignment of the sample surface after the melting process. The transformation of form I into form II, passing through the formation of form III, is clearly irreversible.

On the other hand, no significant changes in the diffraction patterns collected in the range of $150 \leq T \leq 158\,°\mathrm{C}$ are observed, though the DSC traces reported in Fig. 5 clearly evidence two endothermic events within the same temperature range whose relative intensities vary as a function of the heating rate. The interpretation of the splitting recorded by DSC is rather complex. The progressive decrease in the intensity of the lower temperature peak together with the increasing intensity of the higher temperature (158 °C) peak, observed by lowering the scanning rate from 10 to 0.1 K min^{-1}, may suggest that some undefined solid-solid heat-induced transformation is taking place.

To verify this hypothesis another sample of form III was submitted to a different thermal DSC cycle: heating from 35 to 125 °C (10 K min^{-1}) and from 125 to 155 °C (1 K min^{-1}), isotherm at 155 °C for 2 min, cooling to 145 °C (1 K min^{-1}) and reheating to 170 °C (1 K min^{-1}). The DSC profile, reported in Fig. 9, shows an endothermic peak at about 154 °C during the first heating scan at 1 K min^{-1}, followed by an

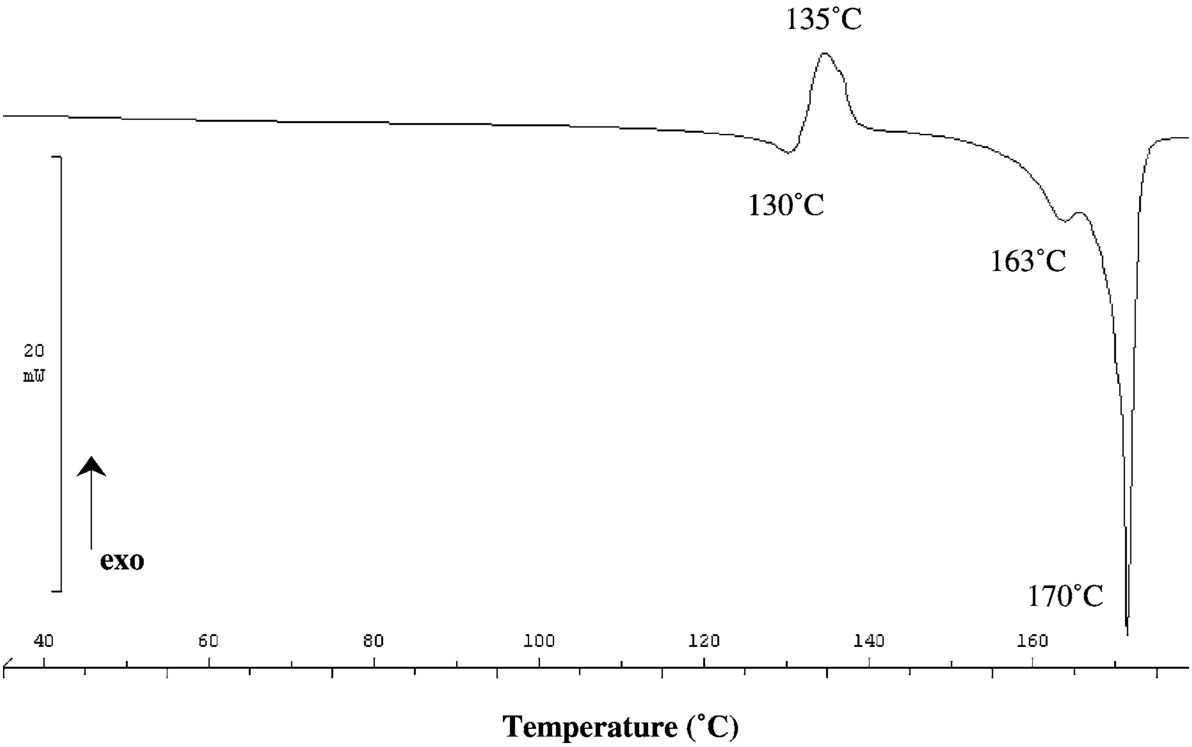

Fig. 6. Thermal behavior of form III, prepared with Köfler apparatus: heating from 35 to 180 °C, scan rate 10 K $\min^{-1}$.

exothermic event at 153 °C during the cooling step and a single endothermic effect at around 157 °C during the last heating step. However, no further indication could be drawn from temperature controlled X-ray diffractometry or HSM. This could be due to several concomitant reasons: (i) large portions of amorphous PCM which fail to recrystallize into form III at 130 °C; (ii) influence of the polymeric excipient in terms of an increase of the viscosity of the molten mass. As a general consideration, this peculiar thermal behavior can be observed only for PCM-excipient mixtures with low HPMC contents (about 10%): when the excipients are present in higher proportions no recrystallization of PCM from the molten mass is detected [10].

The patterns for the PCM *KA* system are shown in Fig. 10. At 35 °C (bottom curve) the peaks observed may be attributed to form III, which changes into form I between 110 and 127 °C and this transition can be observed by following the gradual changes of the patterns collected at 113, 118, 123 and 127 °C. For higher temperatures, form I remains stable up to 165 °C and is the only form observed after cooling. Therefore, starting from form III, obtained via Köfler treatment, only form I is obtained. This may be due to the presence of form I nuclei in the starting material as seen in the initial pattern at 35 °C (Figs. 10 and 11). On the contrary, form III, obtained by thermal treatment of the physical mixture, is free from form I traces, as shown by the comparison of the patterns in Fig. 11 (curve b).

These results agree with the DSC findings, previously discussed. As for the physical mixture, the diffraction profiles show an initial formation of form II at 135 °C and a remarkable increase in intensity of the reflections at 140 °C. This behavior is in agreement with the endo–exo events, observed in DSC in the 139–141 °C temperature range, attributed to the fusion of form III and the subsequent transformation into form II. Moreover, form II melts at about 158 °C (Fig. 5) and the pattern at 159 °C (Fig. 7) shows an overall decrease in intensity, due to a partial fusion process.

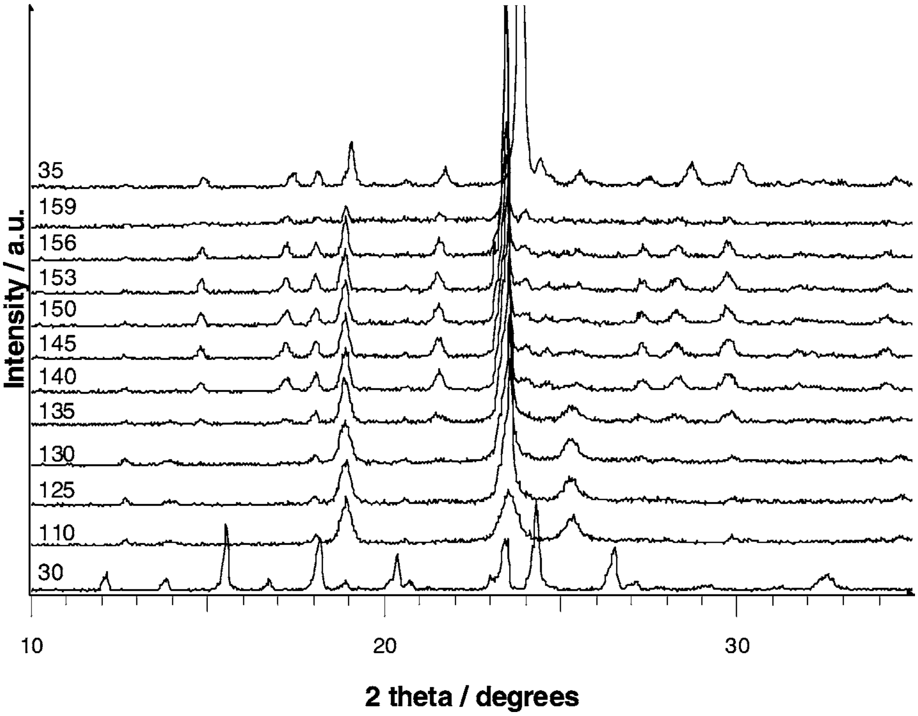

Fig. 7. X-ray diffraction patterns for the physical mixture collected at the indicated temperatures (°C).

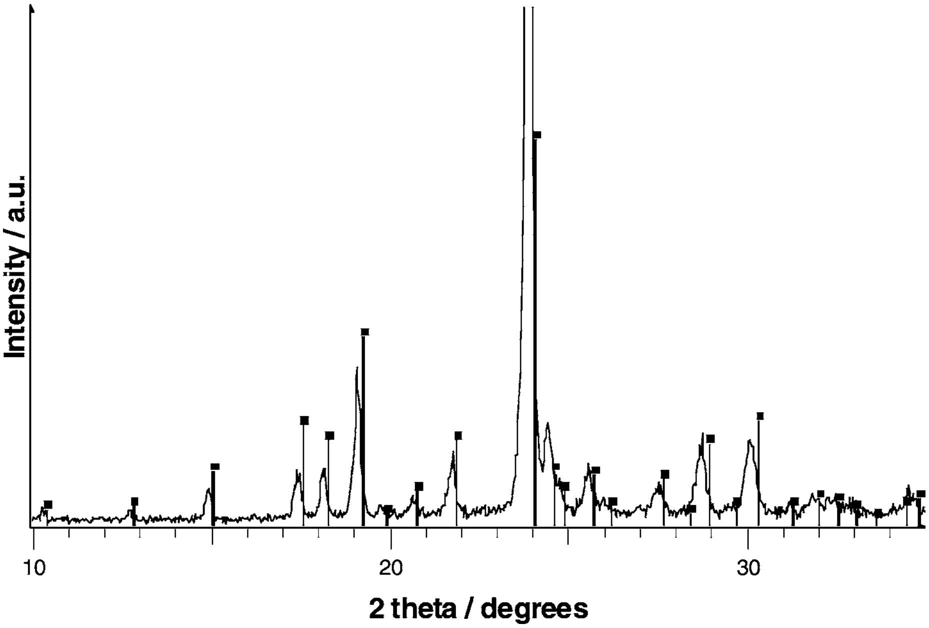

Fig. 8. X-ray diffraction pattern of the physical mixture at 35 °C after thermal treatment compared with the peak positions (vertical bars) of form II reported in [7].

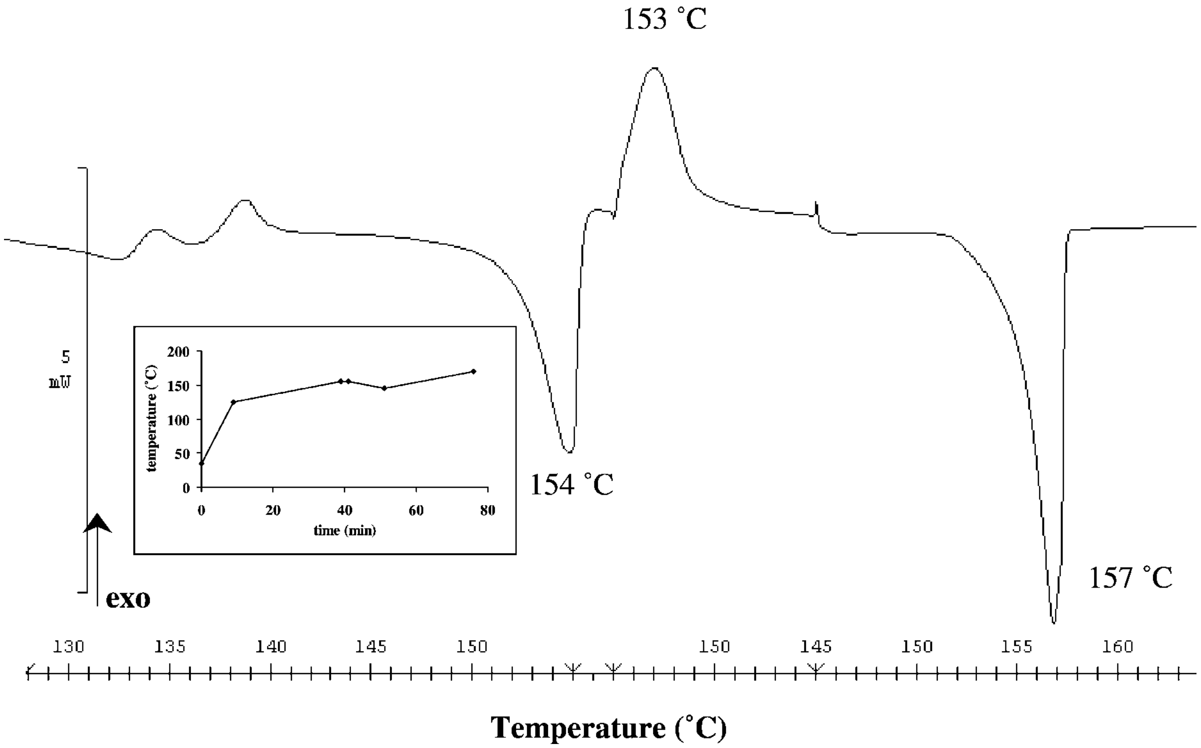

Fig. 9. DSC trace of form III submitted to the thermal program according to the box.

In the case of PCM KA, the transformation at about 127 °C of form III into form I and not into form II, is supported by the endothermic peak at about 130 °C (Fig. 6) followed by the two endothermic effects at 163 and 170 °C (melting point of form I).

3.5. Temperature controlled MFTIR spectroscopy

The transition of form III to either form II or to form I was also checked by temperature controlled MFTIR, observing the changes, during heating, of the characteristic absorption bands for each crystalline modification. The IR spectra of form III, obtained in situ by the hot stage apparatus following the same thermal program outlined in Fig. 2, show significant changes at around 140–142 °C (Figs. 12 and 13).

While the relative intensities of the transmission bands remain fairly constant up to approximately 135 °C, above this temperature all MFTIR spectra are characterized by badly defined peaks reaching a minimum of resolution at 147 °C. The intensity of the bands at 1507 and 1560 cm^{-1}, corresponding to the stretching vibrations of aromatic function (C=C) and amidic group (C=N), respectively, progressively becomes smaller. The peak at 1420 cm^{-1} disappears between 139 and 141 °C and this behavior could be attributed to the formation of different intermolecular interactions, depending on the crystalline structure. The band at 1560 cm^{-1} disappears within 140–142 °C and a new peak at 1571 cm^{-1} appears in the 143–145 °C temperature range; furthermore, a peak at 1473 cm^{-1} is not present at 145 °C. Moreover, in the 139–145 °C temperature range, a transformation in band shape is observed for the band of form III at 710 cm^{-1}, which changes into a broad band, characteristic of form II.

In the case of form III (PCM KA), the relative intensities of the peaks decrease significantly on heating from 60 to 141 °C. Above this temperature, the characteristic bands of form I in the 1900–1850 and 1530–1500 cm^{-1} regions appear, indicating that the transition of forms III to I is taking place.

The modifications observed in the spectra collected in the 137–147 °C temperature range could be ascribed

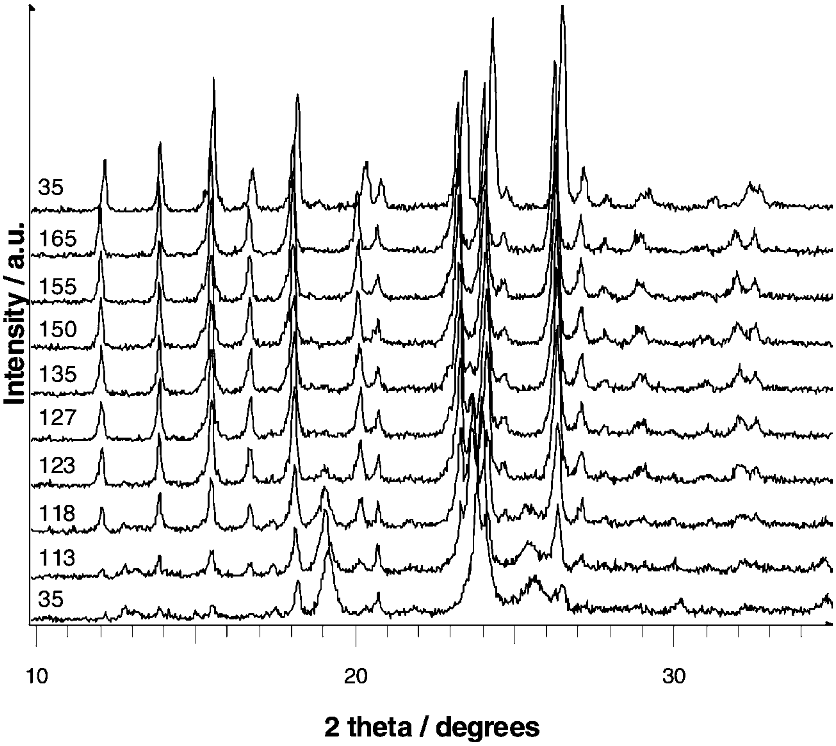

Fig. 10. X-ray diffraction patterns of the sample formed by Köfler apparatus collected at the indicated temperatures (°C).

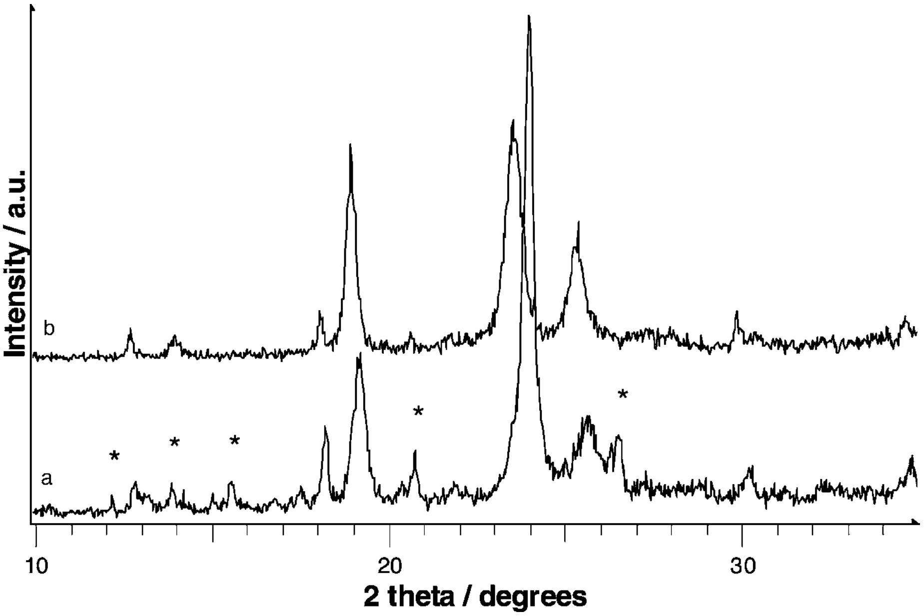

Fig. 11. X-ray diffraction pattern of the sample formed by Köfler apparatus at 35 °C (form III) (a), compared with that obtained for the physical mixture after the thermal treatment described in the text (b). The stars indicate the peak positions of form I.

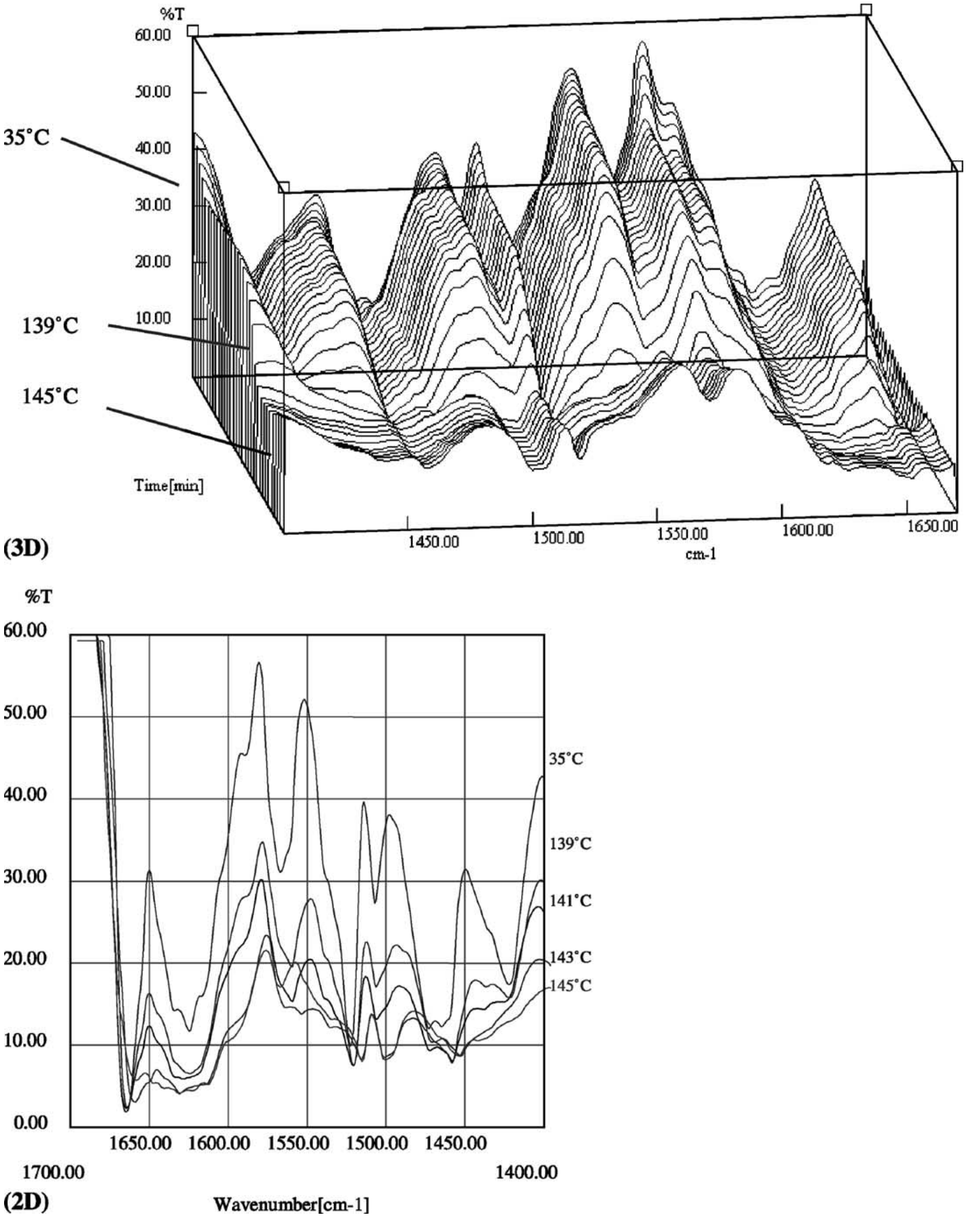

Fig. 12. Temperature controlled MFTIR spectra of PCM/HPMC 90/10 mixtures, recorded at 1 min intervals, in the 1700–1400 cm^{-1} region: microscope aperture, 50 μm; transmittance mode.

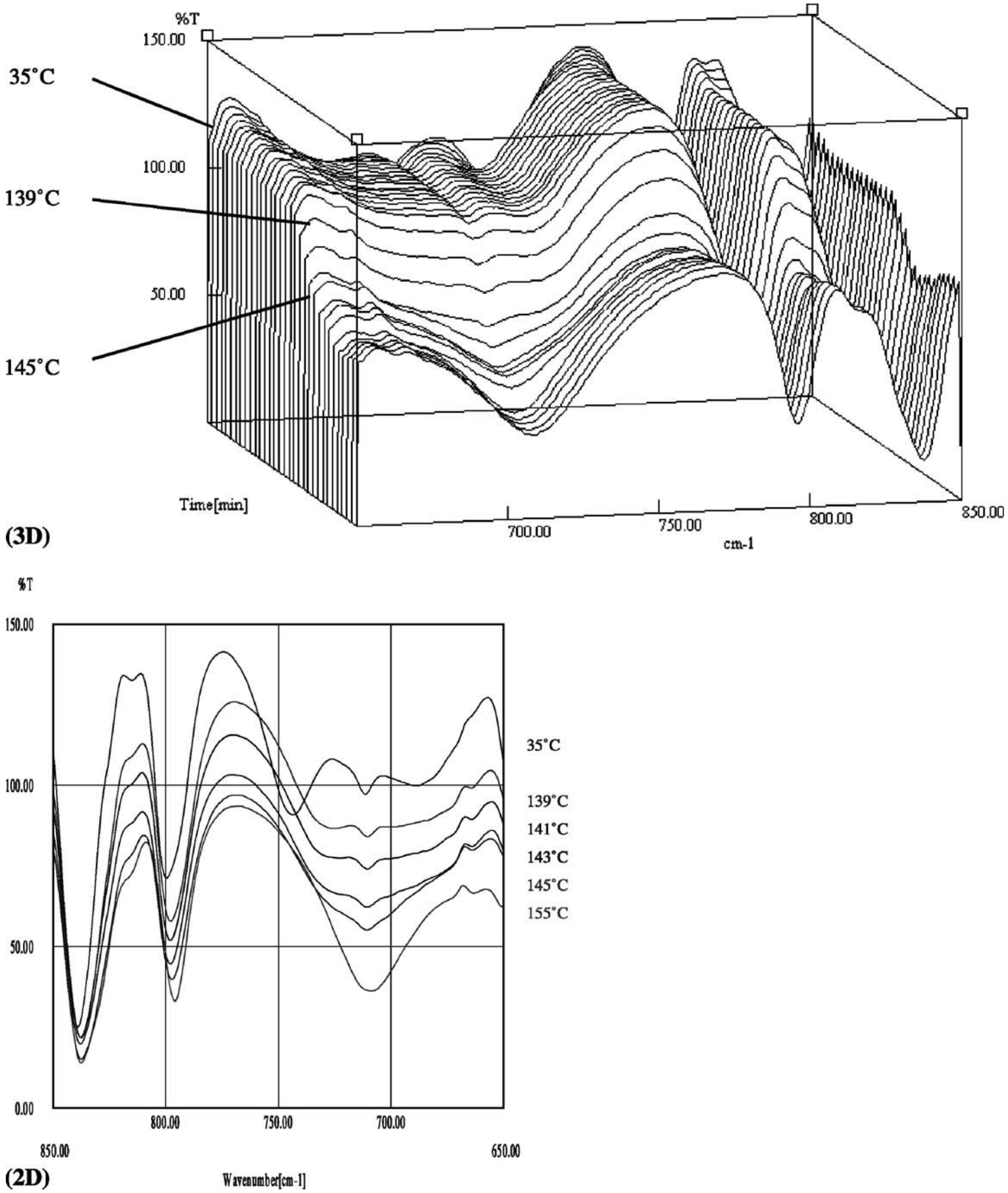

Fig. 13. Temperature controlled MFTIR spectra of PCM/HPMC 90/10 mixtures, recorded at 1 min intervals, in the 850–650 cm^{-1} region: microscope aperture, 50 μm; transmittance mode.

to the fusion of form III at 140 °C, followed by complete recrystallization of the melt as form I at 144 °C.

4. Conclusions

Hydroxypropylmethylcellulose is widely used in oral and topical pharmaceutical formulations [12]. In oral products, HPMC is primarily used as a tablet binder, in film-coating, and as an extended-release tablet matrix. Concentrations of between 2 and 5% (w/w) may be used as a binder in either wet- or dry-granulation process.

This study shows that metastable polymorphs (forms II and III) of paracetamol can be prepared by suitable thermal treatments from mixtures of PCM form I and HPMC. The characterization of the polymorphs by thermal, diffractometric and spectroscopic analyses highlighted the stability ranges and the relationships between the different crystalline modifications of PCM. Metastable form III can transform into form II or I depending on the preparation method. In fact, form III, produced by melting PCM form I in a physical mixture with 10 wt.% of HPMC, converts progressively into form II above 130 °C. On the other hand, on scaling up the preparation of form III, as a crystalline layer, from milligrams to grams via an alternative method, this polymorph changes into form I on heating, presumably due to the presence of nuclei of the high melting polymorph.

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