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THERMAL BEHAVIOR OF PARACETAMOL-POLYMERIC EXCIPIENTS MIXTURES

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Abstract

The thermal behavior of binary mixtures of paracetamol and a polymeric excipient (microcrystalline cellulose, hydroxypropylmethylcellulose and cross-linked poly(vinylpyrrolidone)) was investigated. The physical mixtures, ranging from 50 to 90% by mass of drug, were submitted to a heating-cooling-heating program in the 35–180°C temperature range. Solid-state analysis was performed by means of differential scanning calorimetry (DSC), hot stage microscopy (HSM), micro-Fourier transformed infrared spectroscopy (MFTIR), and scanning electron microscopy (SEM).

The polymeric excipients were found to address in a reproducible manner the recrystallization of molten paracetamol within the binary mixture into Form II or Form III. The degree of crystallinity of paracetamol in the binary mixtures, evaluated from fusion enthalpies during the first and second heating scans, was influenced by the composition of the mixture, the nature of the excipient and the thermal history. In particular, DSC on mixtures with cross-linked poly(vinylpyrrolidone) and hydroxypropylmethylcellulose with drug contents below 65 and 75%, respectively, evidenced the presence only of amorphous paracetamol after the cooling phase. Microcrystalline cellulose was very effective in directing the recrystallization of molten paracetamol as Form II.

Keywords: DSC, excipient, HSM, MFTIR, paracetamol, polymorphism, SEM

Introduction

Paracetamol, (PCM, N-(4-hydroxyphenyl)acetamide), a popular over-the-counter analgesic, can crystallize in three different polymorphic forms known as Forms I, II and III [1–5]. The relevant chemico-physical properties are summarized in Table 1. Form I, commercially available PCM, is stable at ambient temperature and pressure. However, this polymorph is characterized by poor technological and biopharmaceutical properties in terms of flowability, compactability, wettability and dissolution

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rate. In contrast, the metastable orthorhombic Form II undergoes plastic deformation and is therefore suitable for direct compression [6].

Table 1 Chemico-physical properties of PCM polymorphs

Polymorph	Melting point/ °C	Crystal structure	Methods of preparation	Solubility in water/ mg mL^{-1}; 20°C
I	168–172	monoclinic	recrystallisation	13.12
II	157–159	orthorhombic	recrystallisation/ from the melt	13.28
III	120–130*	n.a.**	from the melt	n.a.**

*Temperature range selected referred to the solid-solid phase transition from Form III to Form II, as described in [8]
**)Not available

The existence of a third crystal form Form III, which is unstable at ambient temperature and pressure, was initially observed by thermoanalytical methods [4, 7] and confirmed with the use of infrared [8] and Raman spectroscopies [9]. However, due to the high physical instability, its crystal structure has not yet been determined.

The advantageous technological and biopharmaceutical properties of Form II have aroused the interest of numerous research groups which have consequently attempted to obtain this polymorph [8, 10, 11]. Preparation of PCM Form II on a laboratory scale has been performed with controversial results by recrystallization from ethanolic and methanolic solutions [1, 2, 10] and from the melt [6, 8], which have proved unsuitable for scaling-up.

Bearing in mind the difficulties in obtaining the metastable polymorph and considering the capacity of several excipients, such as hydroxypropylmethylcellulose and poly(vinylpyrrolidone), to modify the crystal habit of PCM [12–14], our attention focused on the use of polymeric excipients in order to influence the crystallisation of PCM.

We report here about the possibility of preparing the low melting Form II of PCM through fusion and recrystallisation processes from PCM-polymeric excipient binary mixtures. The thermal behaviour of PCM from mixtures with polymeric excipients such as microcrystalline cellulose (Avicel), hydroxypropylmethylcellulose (Methocel) and cross-linked poly(vinylpyrrolidone) (PVP-XL) was investigated. The physical mixtures were subjected to a heating/cooling/heating program. Samples of mixtures were analyzed using thermal methods (DSC and HSM), MFTIR, and SEM.

Experimental

Material

Samples of PCM and of the polymeric excipients were obtained from the manufacturer (PCM: A.C.E.F., Fiorenzuola, Italy; PVP-XL: Kollidon CL, water content 13%

mass/mass, BASF, Ludwigshafen, Germany; Avicel: Avicel PH102®, 180–125 μm, water content 4.8% mass/mass, FMC, Philadelphia, PA; Methocel: Methocel K4M Premium EP®, 180–125 μm, water content 8.3% mass/mass, Colorcon, Orpington, UK) and were used as received.

Methods

Physical mixtures

200 mg of the binary mixture of PCM with each excipient (ranging from 50 to 90% by mass of drug) were prepared by gently mixing in a mortar for 5 min.

Differential scanning calorimetry

Temperature and enthalpy measurements were performed by means of a Mettler DSC 821^e STAR^e system. Samples, 4–5 mg, in pierced aluminum crucibles under a dynamic nitrogen atmosphere (100 mL min^{-1}), were tested for thermal behavior according to the following program: heating from 35 to 180°C, isotherm at 180°C for 5 min, cooling down to 35°C, and reheating up to 180°C.

Scanning rates of 10 K min^{-1} were adopted for all experiments; each analysis was repeated at least three times.

Micro-Fourier transformed infrared spectroscopy

A Jasco MFT-2000 apparatus was used for MFTIR spectroscopy. The spectra were collected at room temperature with a counting time of 90 s per data frame in the 4000–650 cm^{-1} wavenumber range. Samples were prepared by placing particles of the material under investigation on KBr discs (transmittance mode).

When aiming to follow phase transitions evidenced during DSC runs the open aluminum crucible was used as sample holder in the reflectance mode.

In both cases 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.

Hot stage microscopy

A hot stage apparatus (HSF 91, Linkam Scientific Instruments, Tadworth, UK) equipped with a microscope (Labophot II polarising microscope, Nikon, Tokyo, Japan) was used as supplementary source of information. A 3CCD color video camera module (XC-003P Sony, Tokyo, Japan), supported by Image-Pro Plus 4.0 software, allowed the recording of images during temperature scans.

Scanning electron microscopy

Photomicrographs of the single components and their mixtures were carried out using a Jeol 6400 scanning electron microscope: working distance, 14 mm; accelerating voltage,

3–10 kV. Prior to examination, samples were gold sputter-coated to render them electrically conductive.

Results and discussion

Thermal behaviour of single components

In the case of PCM, an endothermic peak at around 167°C, related to the fusion of Form I, was observed by DSC during the first heating cycle, followed by recrystallization during either cooling or reheating. Recrystallization during cooling (~110°C) was followed by fusion at 167°C (Fig. 1, curve (a)), whereas recrystallization at around 83°C during reheating was followed by an endothermic effect at around 157°C due to fusion of Form II (Fig. 1, curve (b)). ΔH_{II}^{f} was not significantly different from the ΔH_{I}^{f}, while ΔH^{c} was in all cases at least 75% of ΔH_{I}^{f}.

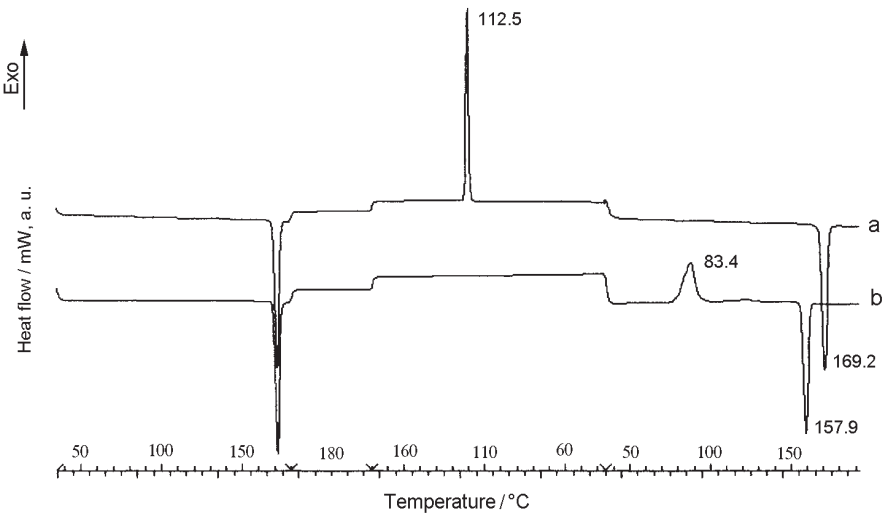

Fig. 1 Thermal behavior of PCM Form I submitted to the heating-cooling-heating program: a – recrystallization as Form I, and b – recrystallization as Form II

Crystallization of amorphous PCM, obtained by fusion, into Form II was also characterized by MFTIR spectroscopy (transmittance mode, Fig. 2). The intensities of absorption bands at 1037 and 1016 cm^{-1} interchange; moreover, the absorption bands at 1037 and 970 cm^{-1} shift to 1033 and 966 cm^{-1}, respectively.

On the other hand, the thermal behaviour of the pure excipients is simply characterized by broad endothermal effects, due to dehydration (water content, 5–15% mass/mass range), in the 35–110°C temperature range (Fig. 3).

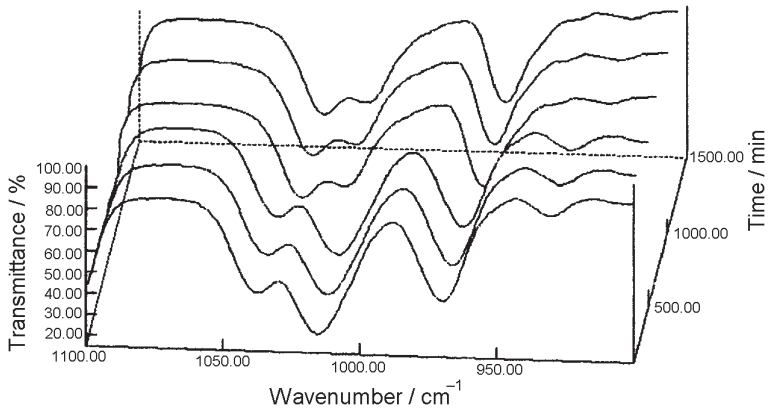

Fig. 2 MFTIR spectra of amorphous PCM recorded at 2.5 min intervals: microscope aperture, 50 μm; transmittance mode

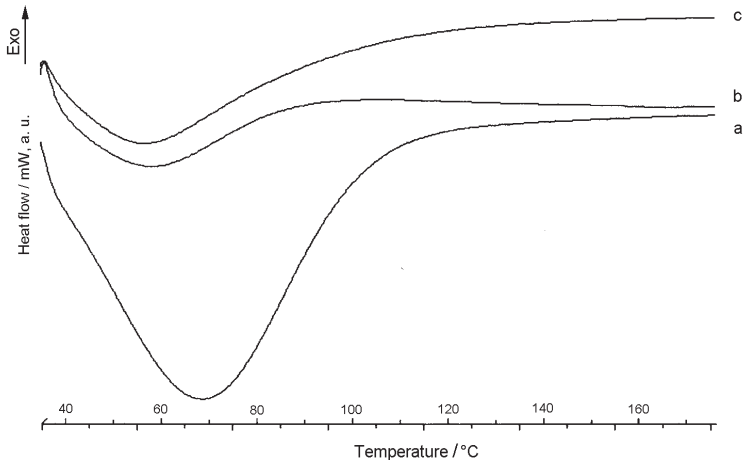

Fig. 3 Thermal behaviors of a – PVP-XL, b – Methocel and c – Avicel

Thermal behaviour of the physical mixtures

PCM/PVP-XL systems

The thermal behavior and the relevant parameters of selected PCM/PVP-XL binary mixtures are reported in Fig. 4 and Table 2, respectively. The increase of PVP-XL contents progressively modifies the overall thermal behavior of PCM. The endothermic event with a peak at ≈170°C, observed during the first heating, is characterized by a broad pre-fusion effect with onset temperatures shifting from 145 down to 127.5°C, as a function of PVP-XL contents. A progressive decrease of the normalized fusion enthalpy (ΔH_1^f) for PCM (first heating run) from –34.1 down to

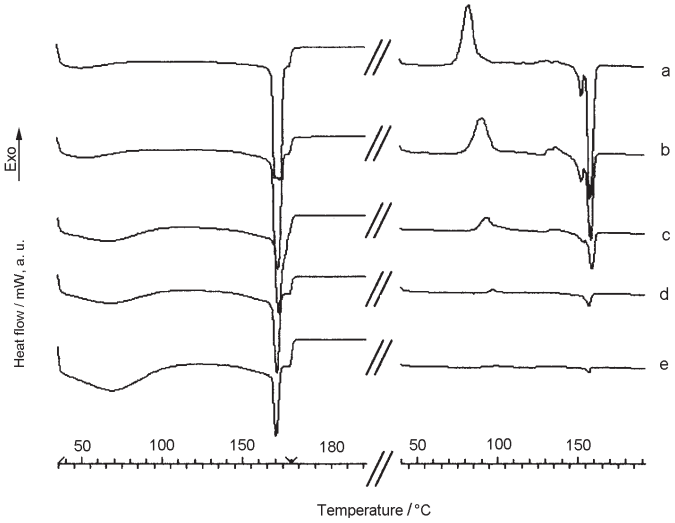

Fig. 4 Thermal behavior of PCM/PVP-XL mixtures, containing a – 90, b – 80, c – 70, d – 65 and e – 60% by mass of drug. Only first and second heating portions are shown

–21.1 kJ mol^{-1} can be observed from data reported in Table 2. This pattern, which is also shown by mixtures with Methocel and Avicel, can be reasonably ascribed to an increasing isolation effect of the crystalline component within the polymeric excipient, which prevents an effective heat transmission within the mass of the binary mixture.

Table 2 Thermal data of PCM/PVP-XL physical mixtures

	First heating			Second heating		
Drug/ %	T_{on}/°C (s.d.)	T_I^f/°C (s. d.)	ΔH_I^f/kJ mol^{-1} (s. d.)	$T_{recryst}$/°C (s.d.)	T_{II}^f/°C (s. d.)	ΔH_{II}^f/kJ mol^{-1} (s. d.)
100	166.9 (0.8)	170.4 (0.9)	–34.1 (0.9)	88.4 (0.1)	158.6 (1.2)	–33.5 (1.7)
90	143.5 (2.8)	171.5 (1.4)	–31.5 (1.9)	84.4 (1.5)	157.5 (0.2)	–26.2 (1.3)
80	140.3 (0.2)	171.0 (0.4)	–27.7 (0.1)	91.0 (0.7)	158.1 (0.1)	–19.6 (0.2)
70	132.8 (7.3)	171.1 (0.1)	–23.5 (0.3)	111.8 (3.4)	157.2 (0.1)	–10.1 (1.7)
60	127.5 (1.5)	170.4 (0.2)	–21.1 (0.6)	–	–	–

No thermal events are visible during the cooling phase, while reheating induces only partially the recrystallization of PCM as Form II. In fact, the degree of crystallinity of PCM (evaluated from the fusion enthalpy of the thermal event at 158°C during the second heating phase, ΔH_{II}^f) decreases as the concentration of PVP-XL increases. The temperature of recrystallization shows a definite trend to shift towards higher values with in-

creasing PVP-XL contents, thus indicating an increasing ability of the polymeric component to stabilize the amorphous state of the drug.

During reheating, the DSC traces of the mixtures containing 90 and 80% of PCM clearly show (Fig. 4) two endothermic peaks (at 153 and 158°C, approximately) within the 145–165°C temperature range. Moreover, all mixtures with compositions down to 65% of PCM exhibit an endo-exo effect of small magnitude in the 110–140°C temperature range, probably due to the presence of small portions of PCM Form III, which has been reported to transform into Form II within the same temperature range [8].

For all mixtures containing 60% (or less) of PCM, the recrystallization of PCM during reheating is no longer evident. This behavior could be due to the formation of drug microcrystalline or amorphous aggregates thoroughly dispersed within the polymeric matrix [15–17], ultimately responsible for the reduction of drug crystallinity.

PCM/Methocel systems

The thermal behavior of PCM-Methocel mixtures is illustrated in Fig. 5, while the relevant thermal parameters are collected in Table 3. The first heating phase is characterized by an endothermic effect at approximately 170°C corresponding to the fusion of Form I of PCM.

Table 3 Thermal data of PCM/Methocel physical mixtures

	First heating			Second heating		
Drug/ %	T_{on}/°C (s.d.)	T_I^f/°C (s. d.)	ΔH_I^f/kJ mol^{-1} (s. d.)	$T_{recryst}$/°C (s.d.)	T_{II}^f/°C (s. d.)	ΔH_{II}^f/kJ mol^{-1} (s. d.)
100	166.9 (0.8)	170.4 (0.9)	–34.1 (0.9)	88.4 (0.1)	158.6 (1.2)	–33.5 (1.7)
90	161.0 (3.8)	169.8 (0.8)	–25.2 (0.9)	103.5 (1.6)	155.2 (0.6)	–21.6 (0.7)
80	158.3 (0.6)	169.4 (0.3)	–23.8 (0.4)	118.0 (2.6)	154.6 (0.2)	–2.9 (0.5)
75	152.4 (1.1)	170.1 (1.3)	–25.1 (0.5)	120.2 (2.7)	155.2 (1.3)	–0.8 (0.7)
70	150.9 (1.4)	169.4 (0.3)	–23.1 (0.2)	118.9 (2.0)	155.5 (1.0)	–0.4 (0.3)
60	146.1 (0.2)	170.1 (0.4)	–21.3 (1.5)	–	–	–

During the second heating, mixtures containing 90% of the drug exhibit an exothermic peak at around 93°C, followed by two close endothermic events at about 139, an exothermic effect at 141 and final endotherm at 156°C. This complex behavior can be interpreted in terms of a preliminary recrystallization of PCM (at 93°C) as a mixture of two polymorphs, Form II and Form III. The latter crystal Form melts at around 139°C, and simultaneously transforms into Form II. This interpretation is corroborated by HSM data, which revealed changes in colour and morphology in the 138–142°C temperature range (Fig. 6, photomicrographs a–c).

As the percentage of Methocel increases, the peak areas associated to these events decrease and the relevant crystallization temperatures shift to higher values, as in the case of PVP-XL containing mixtures.

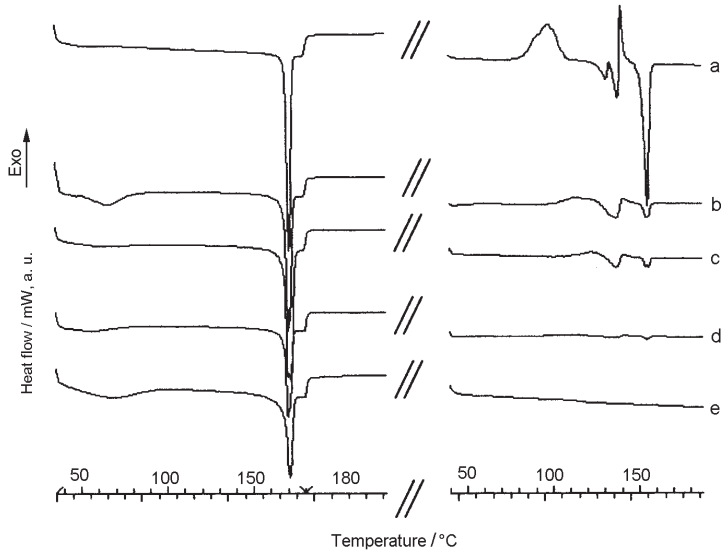

Fig. 5 Thermal behavior of PCM/Methocel mixtures, containing a – 90, b – 80, c – 75, d – 70 and e – 60% by mass of drug. Only first and second heating portions are shown

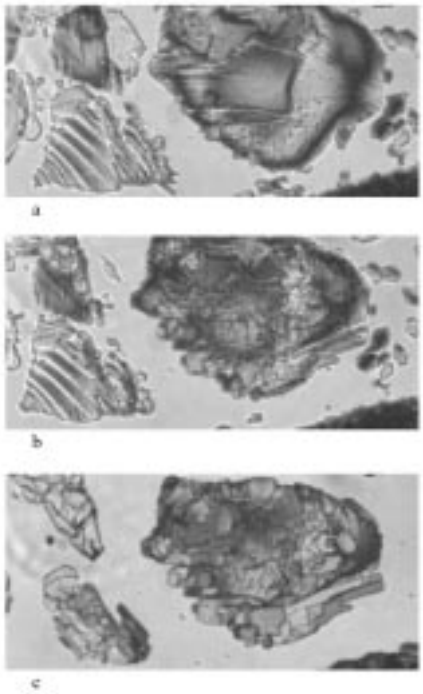

Fig. 6 Photomicrographs of Form III to Form II phase transformation, PCM/Methocel 9:1 mixture, second heating run (HSM): a – 138°C, b – 140°C and c – 142°C

It is important to underline that the pre-fusion effect shown during the first heating run is much smaller than that observed with mixtures containing PVP-XL. Moreover, also Methocel can hinder the recrystallization of the drug during the reheating of mixtures containing maximum 70% by mass of PCM.

MFTIR of PCM/methocel 9:1 mixtures

To gain further confirmation with regard to the solid phases formed during reheating of the PCM/Methocel 9:1 mixture, the exo-endo sequences were exploited to isolate, at room temperature, mixtures containing Form II or III of PCM by slightly modifying the DSC thermal program. To this aim, the reheating phase was stopped at 110 or 141°C to obtain Form III and Form II, respectively. Both samples were then allowed to cool spontaneously down to ambient temperature and analyzed by MFTIR directly inside the open aluminum crucible (reflectance mode), since any attempt to remove solid samples from the pan invariably caused the phase transition of Form III into Form II or Form I. Figure 7 reports the DSC traces of the relevant samples.

Table 4 MFTIR absorption bands (cm^{-1}) of Forms I, II, and III of PCM/Methocel 9:1 mixtures (refer to Fig. 8 for samples preparation)

Form I	Form II	Form III
1901 1876 1851	1888	1887
–	–	1645
–	–	1637
1610	1621	1621
1564	1551	1558
1441	1452	1456
	1425	
1369	1376	1375
–	1280	1280
1259	1240	1248
1242 1227	1220	1225
856	863	864
837	837	836
808	–	–
–	–	743
714	717	711
685	–	691
650	–	–

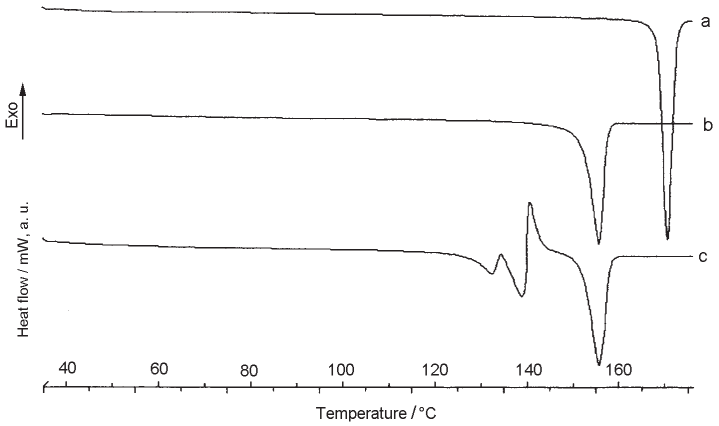

Fig. 7 DSC traces (35–180°C, 10 K min^{-1}) of PCM/Methocel 9:1 mixtures: a – first heating scan, b – third heating scan (the second heating was stopped at 141°C; the pan was then allowed to cool down to ambient temperature spontaneously), and c – third heating scan (the second heating was stopped at 110°C; the pan was then allowed to cool down to ambient temperature spontaneously)

The relevant MFTIR spectra, limited to those regions with the major differences among the crystal phases, i.e. 1950–1800, 1300–1150, and 825–650 cm^{-1}, are reported in Fig. 8, together with the spectrum of the corresponding untreated physical mixture, while the band positions are summarized in Table 4.

Within the 1950–1800 and 1300–1150 cm^{-1} intervals, PCM Form I shows two triplets, compared to the single bands (at approximately 1888 cm^{-1}) and to the doublets at 1240 and 1220 and 1248 and 1225 cm^{-1}, respectively shown by Form II and Form III. Form I can be also identified by the absorption band at 685 cm^{-1}. Furthermore, Form II can be identified by the sharp band at 717 cm^{-1}, while, in the same region, Form III shows a broad band splitted at 743 and 711 cm^{-1}.

Conversion kinetics of Form III into Form II

The conversion kinetics of Form III in Form II in the 9:1 PCM:Methocel mixture was checked by DSC. The samples, prepared as described in the previous section, were kept in the same aluminum pan at room temperature for different periods of time (on a day scale up to 27 days) and then submitted to a heating program from 35 to 180°C. The evaluation of Form III contents variation was performed on the basis of the enthalpy value associated with the endothermic events around 139°C, being aware of the intrinsic uncertainty of such determination due to the overlapping of the exo effect at 141°C. The resulting curve is shown in Fig. 9.

PCM/Avicel systems

The thermal behavior shown by some PCM/Avicel mixtures is reported in Fig. 10, while the relevant parameters are collected in Table 5.

As already described for PVP-XL and Methocel binary mixtures with PCM, Avicel can also address the recrystallization from the melt of the drug as Form II. An increase of the ΔH_{II}^{f} value for the peak at around 158°C is observed, compared to the value relevant to the endothermic peak at approximately 170°C of the first heating run (ΔH_{I}^{f}). This peculiar behavior, different from the corresponding ones demonstrated by PVP-XL and Methocel containing mixtures could be ascribed to two concomitant causes: i) the lack of amorphous residues following the recrystallization, and ii) the segregation of molten PCM after fusion, due to the difference of density. The latter, confirmed by direct observation with HSM and SEM photomicrography, is a further demonstration of poor affinity between the components of the binary mixture.

Table 5 Thermal data of PCM/Avicel physical mixtures

	First heating			Second heating		
Drug/ %	T_{on}/°C (s.d.)	T_{I}^{f}/°C (s. d.)	ΔH_{I}^{f}/kJ mol^{-1} (s. d.)	$T_{recryst}$/°C (s.d.)	T_{II}^{f}/°C (s. d.)	ΔH_{II}^{f}/kJ mol^{-1} (s. d.)
100	166.9 (0.8)	170.4 (0.9)	–34.1 (0.9)	88.4 (0.1)	158.6 (1.2)	–33.5 (1.7)
90	167.6 (0.3)	169.9 (0.3)	–27.1 (0.1)	78.2 (0.5)	157.6 (0.2)	–33.9 (0.6)
80	166.3 (0.9)	170.9 (1.4)	–24.6 (0.3)	80.1 (0.6)	157.8 (0.2)	–30.4 (0.6)
70	166.4 (0.7)	171.0 (0.8)	–24.6 (0.7)	77.9 (0.8)	158.0 (0.4)	–29.9 (0.7)
60	166.8 (0.8)	171.1 (1.6)	–21.3 (0.2)	80.2 (1.0)	158.6 (0.4)	–28.0 (0.4)
50	166.3 (2.2)	172.0 (1.6)	–22.4 (2.4)	77.8 (1.0)	159.2 (1.4)	–27.6 (1.4)

Furthermore an endo-exo effect of small magnitude (within the 0.1–0.3 kJ mol^{-1} range) is present in the 136–148°C temperature interval, probably due to the recrystallization of small amounts of PCM as Form III, fusion and recrystallization as Form II.

PCM/excipient interaction

To quantitatively evaluate the possible interaction between components of the binaries the degree of crystallinity % (DOC) was chosen as a parameter sensitive to the nature of the excipient, to the mixture composition, and to the thermal history of the sample.

DOC was calculated according to the following equation:

$$\mathrm{DOC} = \frac{\Delta H_{\mathrm{mix}}^{\mathrm{f}}}{\Delta H_{\mathrm{PCM}}^{\mathrm{f}}} 100$$

where $\Delta H_{\mathrm{mix}}^{\mathrm{f}}$ and $\Delta H_{\mathrm{PCM}}^{\mathrm{f}}$ are the fusion enthalpies of PCM in the binary mixture and of pure PCM (Form I and Form II), respectively, during first heating at the melting temperature of Form I (DOC1) and during the second heating at the melting temperature of Form II (DOC2). In Figs 11 and 12 DOC1 and DOC2 are plotted *vs.* mixtures composition.

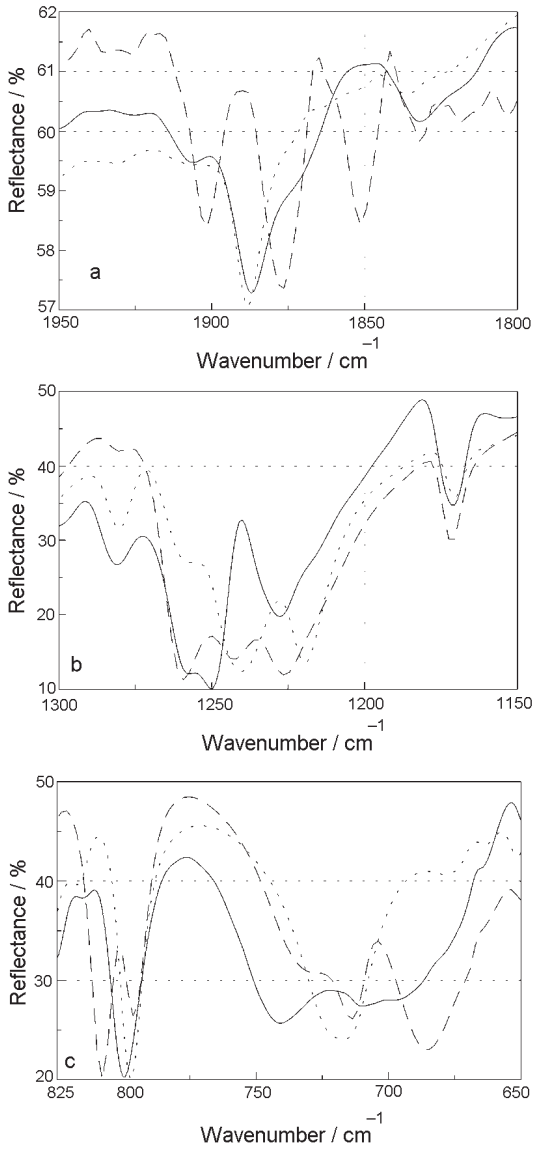

Fig. 8 MFTIR spectra PCM/methocel 9:1 mixtures: a – 1950–1800 cm^{-1} region, b – 1300–1150 cm^{-1} region and c – 850–650 cm^{-1} region. Dashed line: physical mixture as such; dotted line: sample whose second heating was stopped at 141°C; the pan was then allowed to cool down to ambient temperature spontaneously and submitted to MFTIR spectroscopy (reflectance mode); continuous line: sample whose second heating was stopped at 110°C; the pan was then allowed to cool down to ambient temperature spontaneously and submitted to MFTIR spectroscopy (reflectance mode) (Table 4)

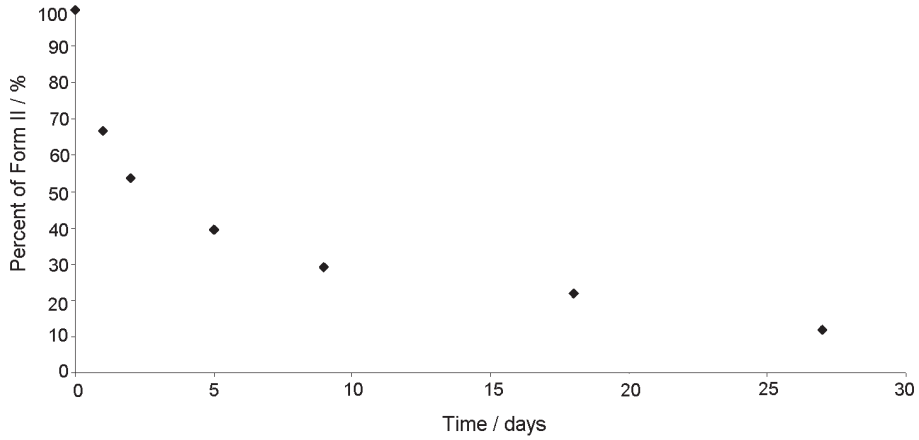

Fig. 9 The conversion kinetics of Form III in Form II (9:1 PCM/Methocel mixture). Each sample pan was stopped at 110°C during the second heating; the pan was then allowed to cool down spontaneously and maintained at ambient temperature on a day time scale

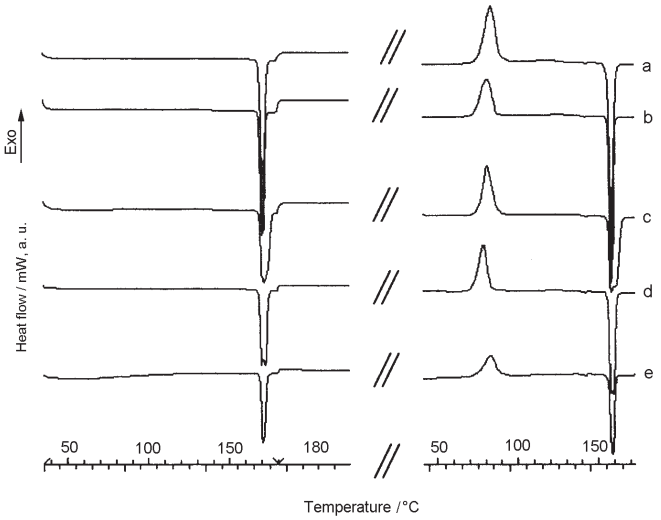

Fig. 10 Thermal behavior of PCM/Avicel mixtures, containing a – 90, b – 80, c – 70, d – 60 and e – 50% by mass of drug. Only first and second heating portions are shown

As far as DOC1 is concerned (Fig. 11) the trend shown by all PCM/excipient mixtures is more or less analogous, leading to a decrease of DOC1 down to approximately 60%. DOC2, evaluated from the thermal effects at approximately 155°C (melting of PCM Form II), allows a substantial differentiation among the interactions between PCM and each of the excipients. DOC2 for the binaries with Avicel at the

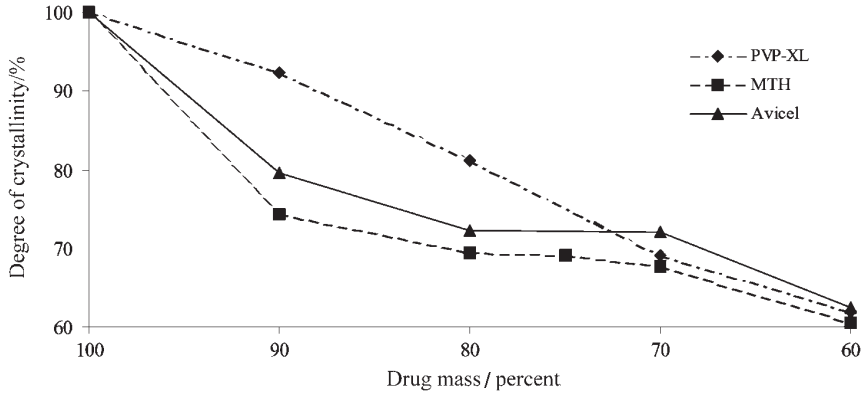

Fig. 11 Degree of crystallinity for PCM/excipient mixtures calculated from melting enthalpies of PCM Form I during first heating scan

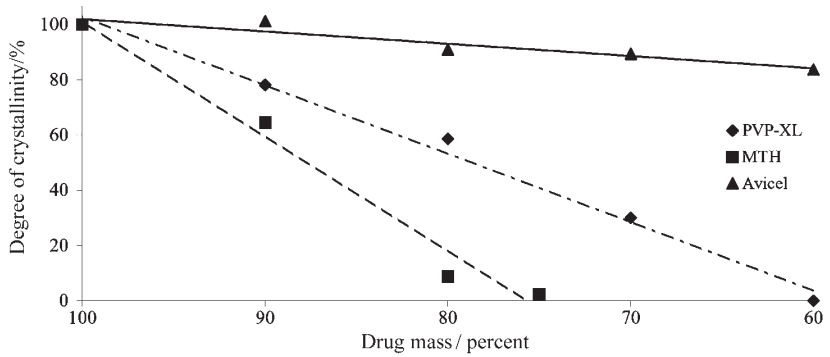

Fig. 12 Degree of crystallinity for PCM/excipient mixtures calculated from melting enthalpies of PCM Form II during second heating scan

end of the thermal program adopted (second heating scan) is >80 with mixtures containing about 60% of PCM. PVP-XL and Methocel cause a much sharper decrease of DOC2, which annihilates for mixtures containing approximately 75 and 60% of PCM, respectively. As an example, SEM photomicrographs of PCM, PVP-XL and their physical mixture 1:1 mass/mass, were taken before and after the thermal treatment, (Fig. 13). While PCM Form I (Fig. 13a) is characterized by the presence of crystals of irregular size and shape and PVP-XL (Fig. 13b) appears as clusters of large porous particles without a definite shape, the physical mixture (Fig. 13c), shows the same features of both components. After heating and subsequent cooling of the physical mixture, only the polymer clusters with a characteristic popcorn-like structure are still visible (Fig. 13d), thus confirming the DSC data on the same mixture (absence of recrystallization and fusion phenomena during the second heating phase, and production of completely amorphous PCM). Analogous results, confirmatory of

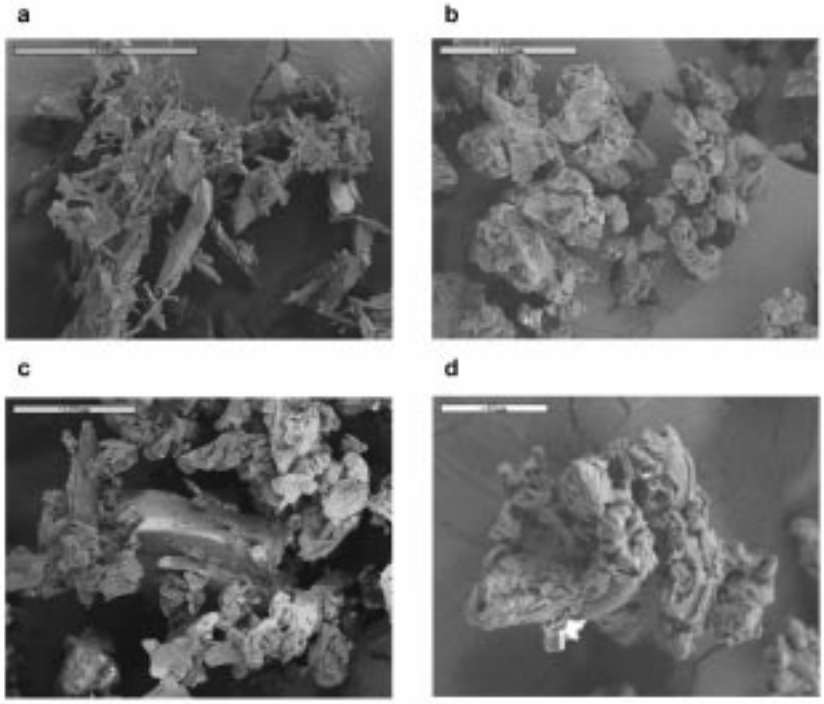

Fig. 13 SEM photomicrographs: a – PCM Form I; b – PVP-XL; c – 1:1 PCM/PVP-XL physical mixture as such; d – 1:1 PCM/PVP-XL physical mixture heated from 35 to 180°C and cooled down to ambient temperature spontaneously

data previously collected by DSC measurements, were obtained with SEM on the other binaries.

Conclusions

Thermal analysis is a first choice analytical method when compatibility among components of pharmaceutical formulations is investigated.

The consideration of excipients generally regarded as 'inert' substances employed to prepare drug products with suitable technological and biopharmaceutical features has been gradually changed to a more adequate concept of physically, chemically and also biopharmaceutically 'active' components. A pertinent exhaustive example of this behavior is represented by cyclodextrins, whose ability to form inclusion complexes, to induce amorphization and, eventually, to increase the solubility in aqueous media and, therefore, the therapeutic efficiency of drugs is well documented.

We have shown that PCM Form II and Form III, as well as amorphous PCM, can be obtained by melting and cooling binary mixtures of PCM and excipients, which are commonly used in pharmaceutical technology and that the composition and the thermal history of the binary mixture also play a definite role in this respect. DSC measurements allowed a fast and reliable screening of the excipients performances to

this respect, while MFTIR and HSM were very useful complements for the thorough characterization of solid phases generated during the thermal process with minimum handling of the products.

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