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Solid-state study of polymorphic drugs: carbamazepine☆

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Abstract

Polymorphs of a compound have solid crystalline phases with different internal crystal lattices; in pharmaceuticals, differences due to polymorphism and pseudopolymorphism can affect bioavailability and effective clinical use. The aim of this work was to obtain the different polymorphic modifications of the anticonvulsant drug, carbamazepine, and to characterise them by means of typical structure-sensitive analytical techniques, such as FT-IR spectroscopy, XRPD and DSC. Further investigations were also performed by Hot Stage FT-IR thermomicroscopy, which permitted the visible and spectroscopic characterisation of the polymorphic forms during heating. Our results confirm the existence of three different polymorphic forms for anhydrous carbamazepine: Form III, the commercial one, Form I, obtained by heating Form III and Form II, crystallised from ethanolic solution. Substantial differences were detected among the polymorphs with regard to solid-state properties. Moreover, Hot Stage FT-IR thermomicroscopy proved its analytical potential to characterise the drug's polymorphism.

Keywords: Carbamazepine; Polymorphism; Solid state characterisation; Hot Stage FT-IR thermomicroscopy; X-Ray powder diffraction; Differential scanning calorimetry

1. Introduction

Polymorphism is the crystallisation of the same compound in more than one distinct crystal architecture and is associated with different crystal packing arrangements; this phenomenon is very common in pharmaceuticals. Because they have different crystal structures, polymorphs have different chemical and physical properties; they have different melting points, different chemical reactivity, different dissolution rates and different bioavailability. Polymorphs can be interconverted by phase transformations or a solvent-mediated process; phase transformations can also be induced by heat or mechanical stress [1].

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Any defining characteristic that might affect the stability or availability of the drug substance in a solid dosage form should be monitored and controlled; tablet dosage forms have to fulfil several requirements before they are considered acceptable by the Official Pharmacopoeia. The Food and Drug Administration (FDA) requires analytical procedures for the detection of polymorphic, hydrated, or amorphous forms in the drug substances. A full evaluation of possible variations in crystallography that might be encountered is now essential for the development of a new drug compound; therefore the physical characterisation of solids has become an extremely important area in pharmaceutics and has been the subject of many studies involving different analytical methods [2].

Carbamazepine (CBZ) is a well-established drug used in the treatment of epilepsy and trigeminal neuralgia [3,4]. This drug has been investigated by several authors with respect to polymorphism and the physical stability of various solid phases; however, the numerous results reported in the literature seem to be heterogeneous with regard to the number of the modifications and their exact characterisation [5–18]. Two modifications have been identified for anhydrous carbamazepine; nevertheless, certain analytical results suggest the existence of additional forms and the formation of mixed crystals.

With regard to carbamazepine dihydrate, several studies have also indicated the existence of more than one solid form, although recent litera-

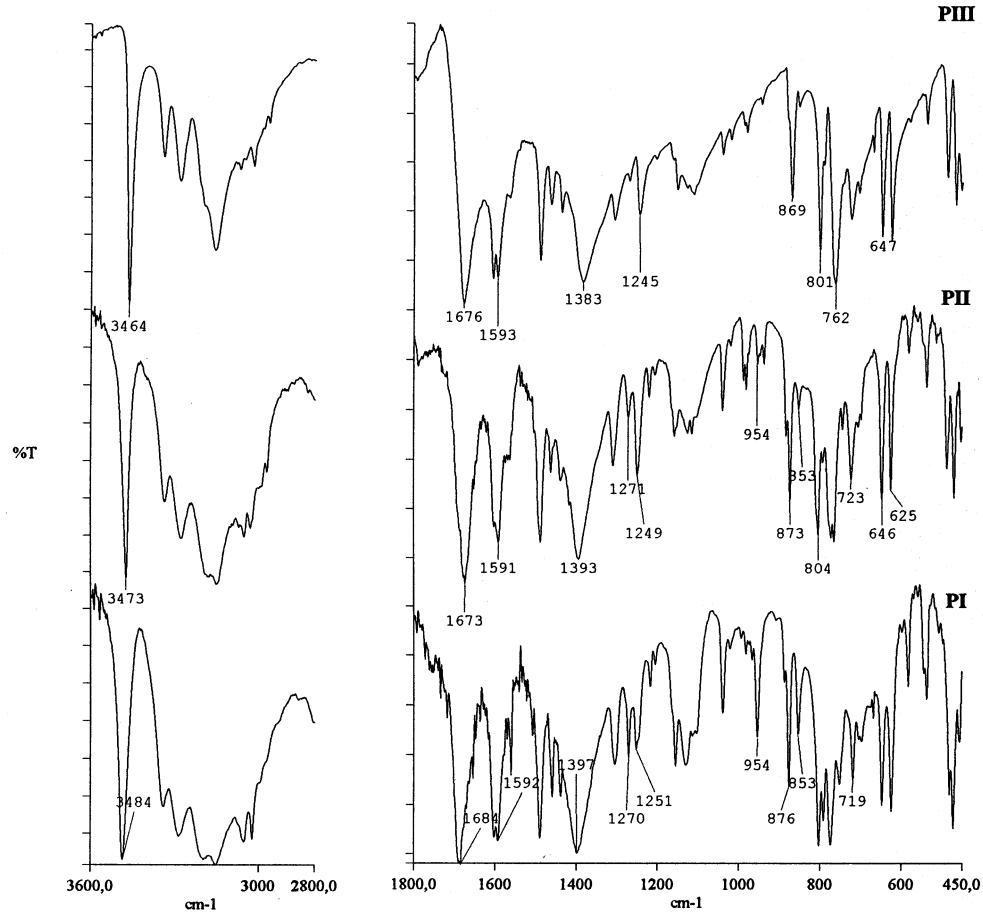

Fig. 1. FT-IR spectra of anhydrous CBZ polymorphs: Polymorph III (PIII), Polymorph II (PII) and Polymorph I (PI).

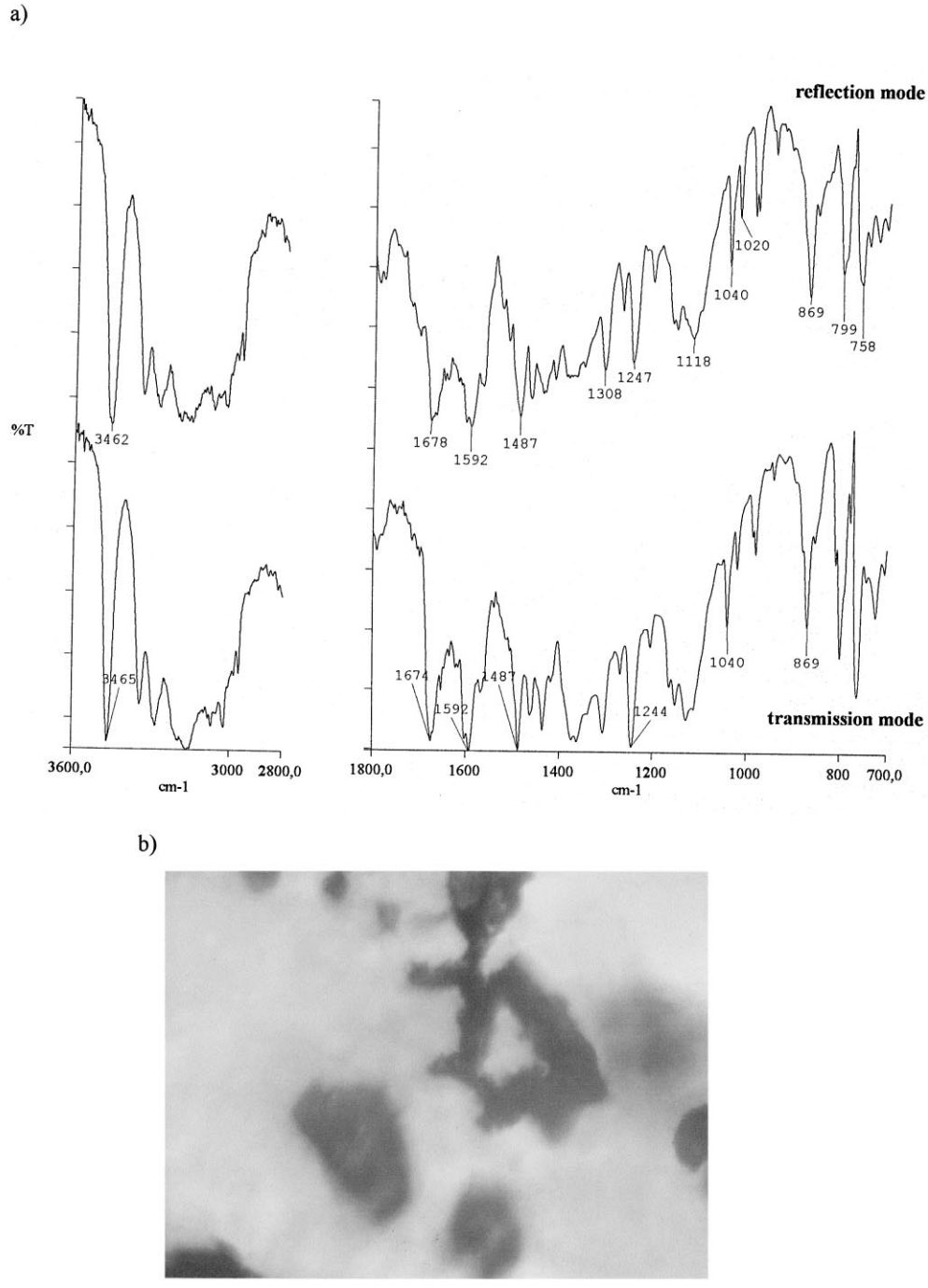

Fig. 2. Hot stage FT-IR thermomicroscopy: (a) FT-IR spectra at room temperature of commercial CBZ in reflection mode and in transmission mode; (b) visible image of commercial CBZ at room temperature.

ture contains no evidence supporting the existence of true polymorphs for this form [10–12,15,19–21].

Differential scanning calorimetry (DSC) is a widely applied technique in drug polymorphism studies, but it does not in itself provide sufficient evidence of the existence of polymorphism; it is essential that other techniques be applied to analyze this phenomenon correctly.

The aim of this report is the physical characterisation of the different polymorphic forms of anhydrous carbamazepine by ordinary solid-state

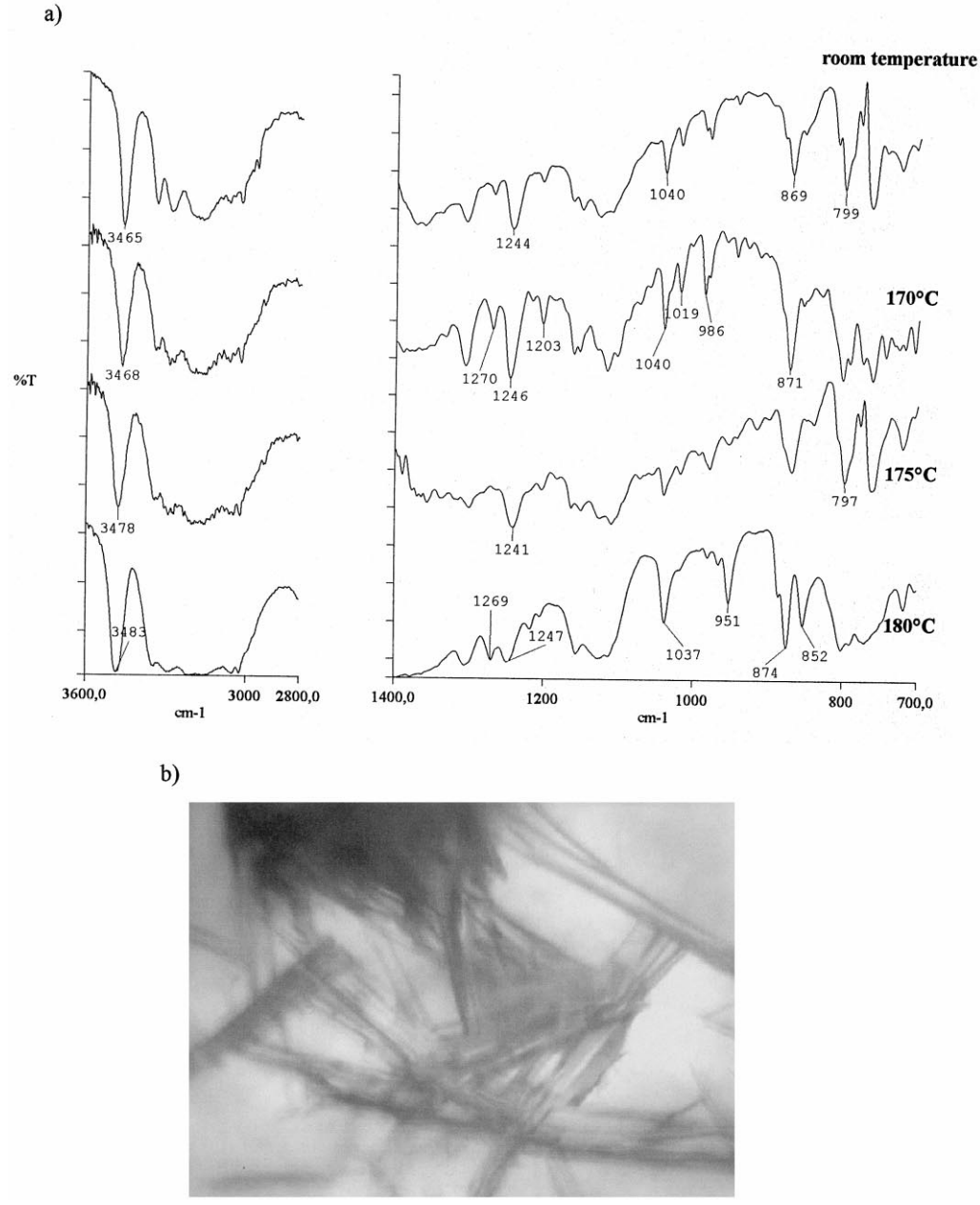

Fig. 3. Hot stage FT-IR thermomicroscopy: (a) FT-IR spectra of commercial CBZ converting into Polymorph I during heating (20°C min^{-1}); (b) visible image of CBZ after melting and resolidification.

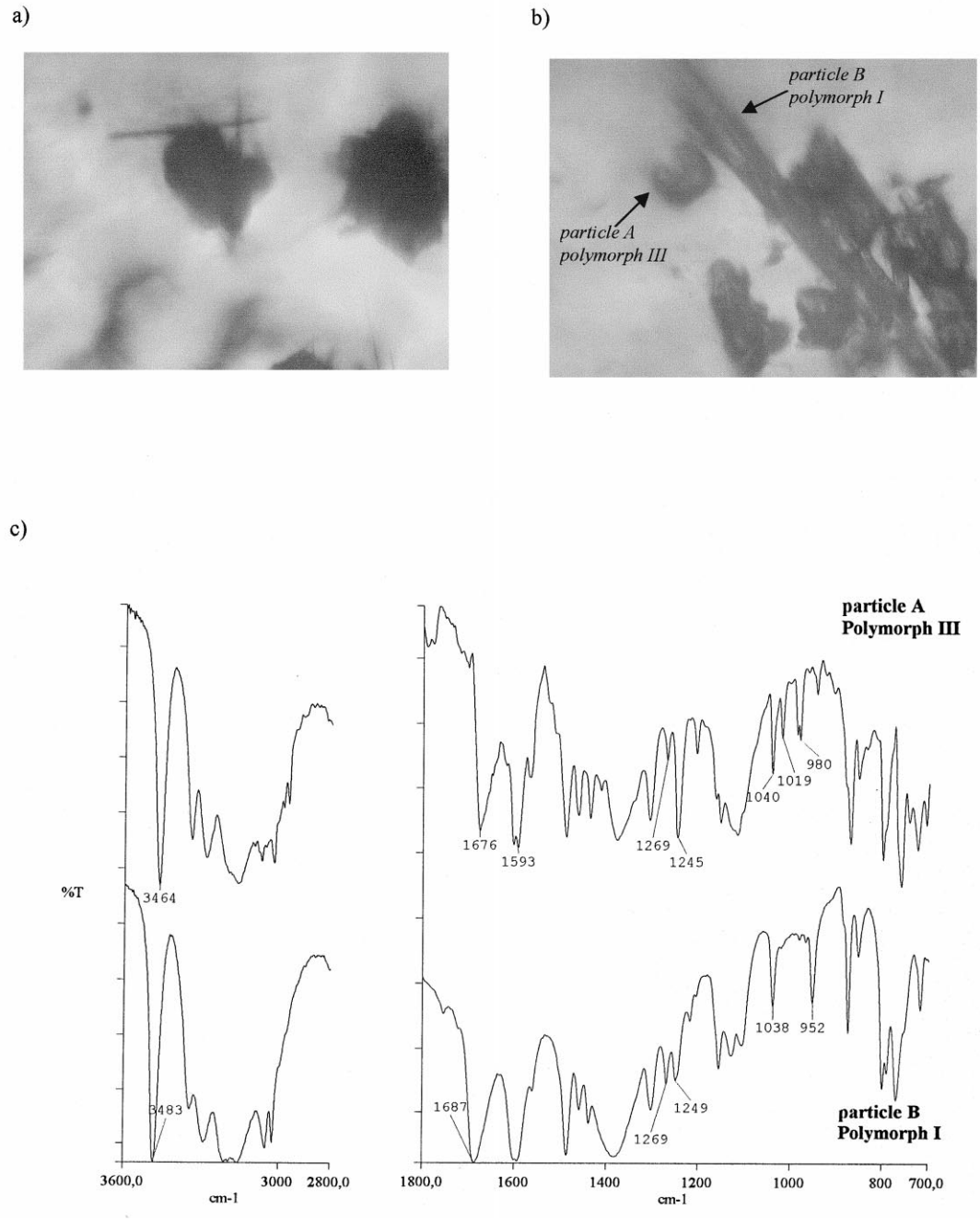

Fig. 4. Hot stage FT-IR thermomicroscopy: (a) visible image above 120°C of Polymorph III converting into Polymorph I (heating rate: 2°C min^{-1}); (b) visible image at 165°C of crystals belonging to Polymorph III and Polymorph I (heating rate: 2°C min^{-1}); (c) FT-IR spectra at 165°C of crystals belonging to Polymorph III and Polymorph I (heating rate: 2°C min^{-1}).

techniques such as Fourier transform infrared spectroscopy (FT-IR), diffuse reflectance IR Fourier transform (DRIFT) spectroscopy, X-ray powder diffraction (XRPD), polarised light hot stage microscopy (HSM) and differential scanning calorimetry (DSC).

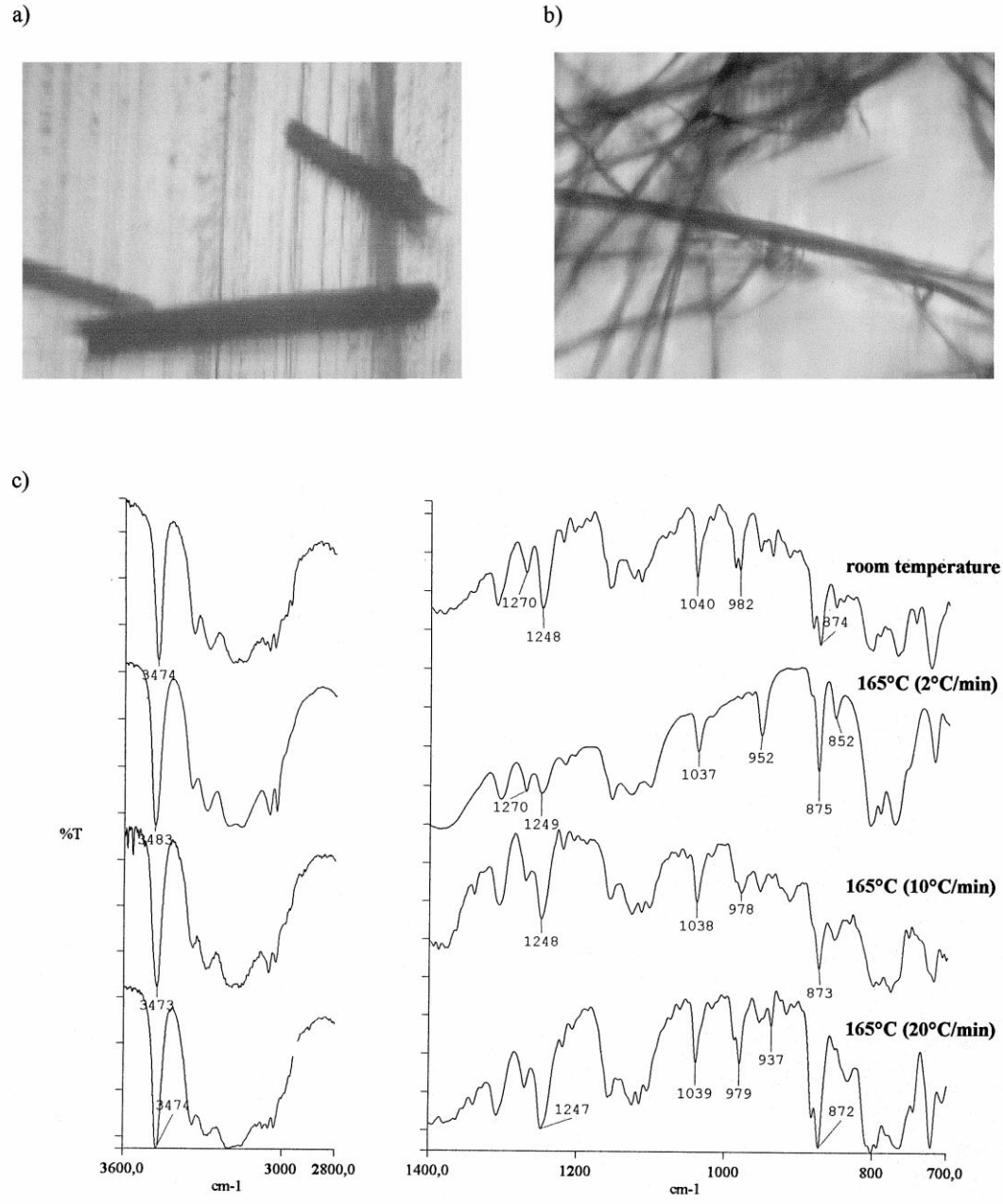

Fig. 5. Hot stage FT-IR thermomicroscopy: (a) visible image of CBZ Polymorph II at room temperature; (b) visible image at 165°C of Polymorph II converting into Polymorph I (heating rate: 2°C min^{-1}); (c) FT-IR spectra of Polymorph II at room temperature and heated up to 165°C with different heating rate: 2, 10 and 20°C min^{-1}.

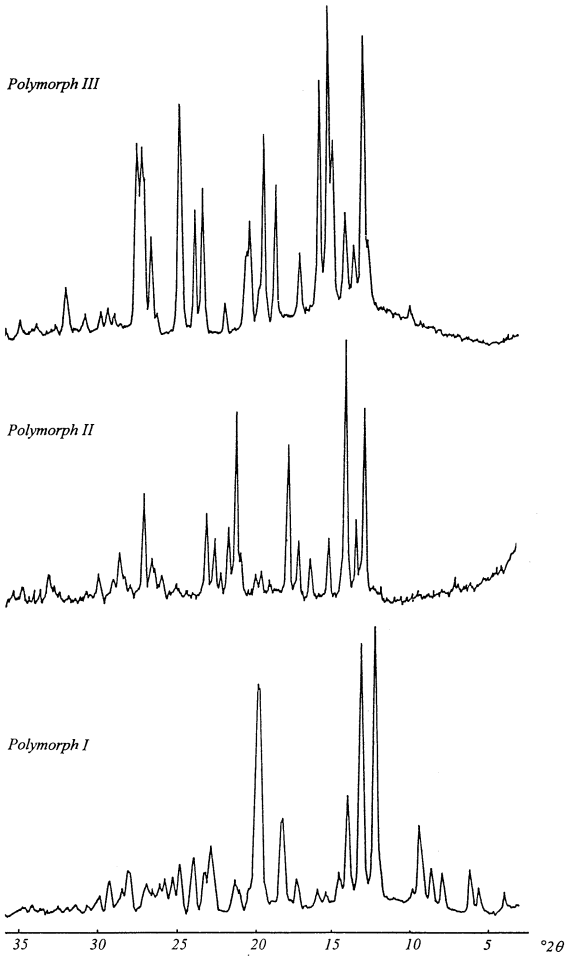

Fig. 6. X-Ray powder diffraction patterns of anhydrous CBZ polymorphs.

Also, the forms were characterised by FT-IR thermomicroscopy, a new method for investigating polymorphism that affords visual confirmation of the events suggested by the DSC curves. FT-IR microspectroscopy is one of the most potent techniques available to the modern chemist, allowing samples measuring 10 μm or less to be visualised and characterised, thanks to permanently aligned optics for IR and visible; this innovative system links visible images, typical of hot stage microscopy, with FT-IR data to provide new methods of data collection that are both simple and effective [22].

The analysis of the IR spectra recorded on-line during heating gives a series of information which is distinctive of the phases involved during thermoanalysis; the interpretation of this information enables the existence of polymorphism and the transition mode to be assessed and a spectroscopic characterisation of the polymorphic forms to be arrived at.

In this report we describe the preparation and characterisation of the principal forms of anhydrous CBZ. The data obtained demonstrate the power of solid-state techniques in determining the polymorphic composition of production batches, as required by the authorities for approval.

2. Experimental

2.1. Materials

The basic materials were anhydrous commercial carbamazepine (CBZ) and carbamazepine USP grade obtained from Sigma; they were stored in airtight containers [23–26] at 4°C. The solvents used were of analytical grade (Baker).

2.2. Fourier transform infrared spectroscopy (FT-IR)

Spectra were recorded on a Perkin Elmer Mod. 1600 FT-IR spectrophotometer, equipped with a deuterium triglycine sulfate (DTGS) detector. Setting parameters: resolution 4 cm^{-1}; apodization weak. The data region was 4000–450 cm^{-1} and the number of scans per spectrum 32. Spectra were obtained in the transmission mode in KBr pellets. The samples were also ground gently with KBr and analysed directly in the DRIFT mode (Diffuse Reflectance IR Fourier Transform), thus mechanically avoiding polymorphic transitions possibly induced by extended grinding.

2.3. Hot stage FT-IR thermomicroscopy

Analyses were performed with an FT-IR microscope i-Series 2000 equipped with a mercury cadmium telluride (MCT) detector and Infrared Microspectroscopy Automated Graphical Envi-

ronment (IMAGE) software (Perkin Elmer) to control a motorised microscope stage. Setting parameters: resolution 4 cm^{-1}; apodization weak; data region 4000–700 cm^{-1}.

Programmed sample heating was performed with a Micro-Press-H™ (Watlow) sample compression hot stage for infrared microscopes, equipped with heater and thermocouple for high temperature operation, up to 200°C. Also included was a Proportional-Integral-Derivative (PID) microprocessor-based temperature controller for accurate temperature control to ± 1°C.

A few crystals of the analyte were placed on the support in the hot stage sample compartment of the microscope and the area of interest was selected by a variable aperture mask. Spectra were acquired in transmission between two thin KBr pellets both at room temperature and during programmed heating. Alternatively, spectra were recorded in reflection mode using an aluminum covered inert support; in this case, the crystals were covered with a thin KBr disk to avoid

Table 1
Principal X-ray powder diffraction values for anhydrous CBZ polymorphs

Polymorph III			Polymorph II			Polymorph I		
d (Å)	2°θ	I/I_0 (%)	d (Å)	2°θ	I/I_0 (%)	d (Å)	2°θ	I/I_0 (%)
8.79	10.05	5	7.49	11.80	7	22.35	3.95	7
6.99	12.65	23	6.88	12.85	75	15.91	5.55	9
6.83	12.95	90	6.60	13.40	33	14.48	6.10	16
6.52	13.55	21	6.32	14.00	100	11.18	7.90	13
6.26	14.10	81	5.86	15.10	24	10.21	8.65	15
5.94	14.90	55	5.43	16.30	17	9.40	9.40	30
5.82	15.20	100	5.18	17.10	23	9.02	9.80	7
5.60	15.80	76	4.98	17.80	62	7.22	12.25	100
5.20	17.05	21	4.67	19.00	9	6.75	13.10	94
4.77	18.06	45	4.55	19.50	12	6.34	13.95	40
4.57	19.40	63	4.46	19.90	10	6.10	14.50	12
4.36	20.35	35	4.25	20.90	18	5.75	15.40	5
4.33	20.50	26	4.19	21.20	73	5.55	15.95	7
4.13	21.50	9	4.09	21.70	29	5.29	16.75	2
3.81	23.35	47	4.00	22.20	11	5.12	17.30	11
3.73	23.85	41	3.95	22.50	23	4.84	18.30	34
3.57	24.90	77	3.85	23.10	34	4.48	19.80	81
3.39	26.25	8	3.56	25.00	7	4.46	19.90	83
3.34	26.65	32	3.42	26.00	11	4.33	20.50	9
3.29	27.10	51	3.37	26.40	13	4.20	21.10	7
3.27	27.20	61	3.36	26.50	17	4.15	21.40	12
3.24	27.50	62	3.29	27.10	41	3.90	22.80	25
3.08	28.95	6	3.14	28.40	10	3.82	23.25	15
3.04	29.35	8	3.12	28.60	18	3.71	23.95	21
2.97	29.85	7	3.09	28.90	9	3.58	24.85	18
2.89	30.85	6	2.98	29.90	11	3.52	25.30	14
2.79	32.00	16	2.74	32.70	7	3.45	25.80	13
2.74	32.65	4	2.71	33.00	12	3.40	26.20	11
2.57	34.90	7	2.66	33.60	6	3.35	26.60	9
2.43	36.90	5	2.64	33.90	5	3.31	26.90	10
2.38	37.70	4	2.58	34.70	7	3.30	27.00	11
2.25	40.05	5				3.18	28.10	10
2.01	40.85	7				3.13	28.50	9
						3.05	29.95	11
						2.98	30.00	6
						2.91	30.70	3

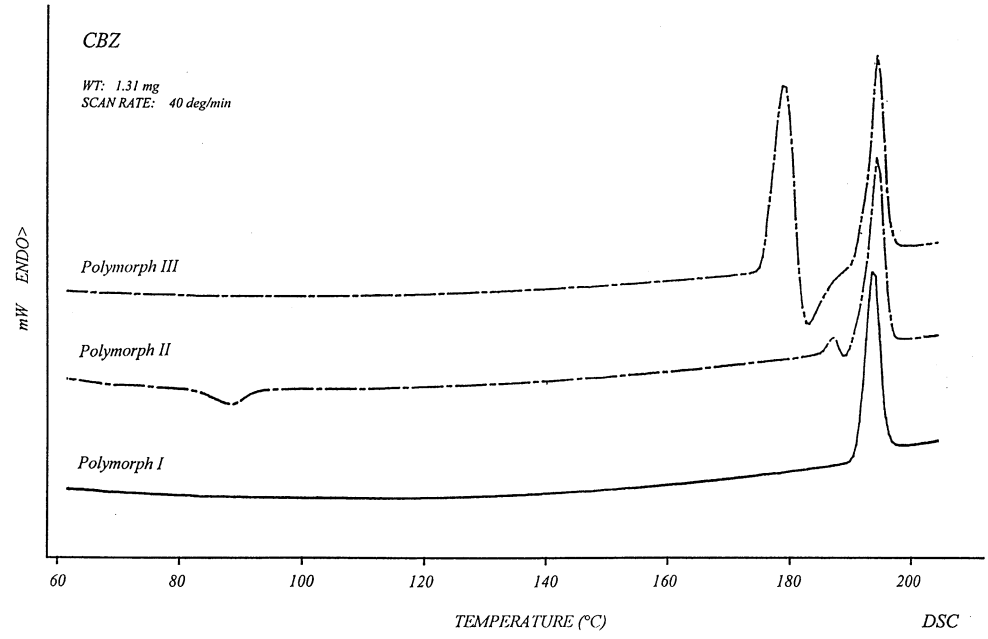

Fig. 7. DSC traces for anhydrous CBZ polymorphs.

sample loss due to sublimation [14] during programmed heating.

Melting points and physical changes in the crystals were examined over the temperature range 40–200°C with a different heating program (2–20°C min^{-1}).

2.4. X-Ray powder diffraction (XRPD)

The main characteristics and setting parameters of the diffractometer were: Ni filtered Cu Kα radiation ($\lambda = 1.5418$ Å); high voltage 40 kV; tube current 20 mA; time constant 4 s; angular speed 1° (2°θ) per min; 1, −0.1, −1° slits, angular range $3 < 2°\theta < 40°$.

2.5. Differential scanning calorimetry (DSC)

The thermal behavior of the samples was studied with a Perkin Elmer DSC-4 instrument under dry nitrogen purge (20 ml min^{-1}) over a temperature range of 40–210°C at different heating rates.

The instrument was calibrated with indium (99.99% pure), having a melting point of 156.6°C and a heat of fusion of 28.45 J g^{-1} (at 40°C min^{-1}).

The Perkin Elmer TADS software (Thermal Analysis Data Station) was used to calculate extrapolated onset temperature, peak temperature and enthalpy value for each thermal event.

2.6. Hot stage microscopy (HSM)

Heating behaviors were examined with a Kofler hot stage microscope (Reichert Thermovar). The samples were placed on the hot stage at room temperature and heated at a rate of 10°C min^{-1}.

2.7. Preparation of the samples

2.7.1. Polymorph III (nomenclature as Krahn and Mielck [12] and Behme and Brooke [14])

According to Kala [11], the monoclinic form can be obtained by cooling boiled acetone solutions of commercial CBZ. Alternatively, it can be crystallised from boiling solutions of commercial CBZ in methanol [12] or other solvents with high dielectric constants [13] by cooling slowly.

Our attempt to crystallise polymorph III from boiling solvents always produced polymorph I, even though this polymorph should be obtained

only by rapid cooling. We therefore used commercial CBZ and CBZ USP grade as Form III without further purification.

2.7.2. Polymorph II (nomenclature as Krahn and Mielck [12])

Krahn obtained this form from freshly pre-

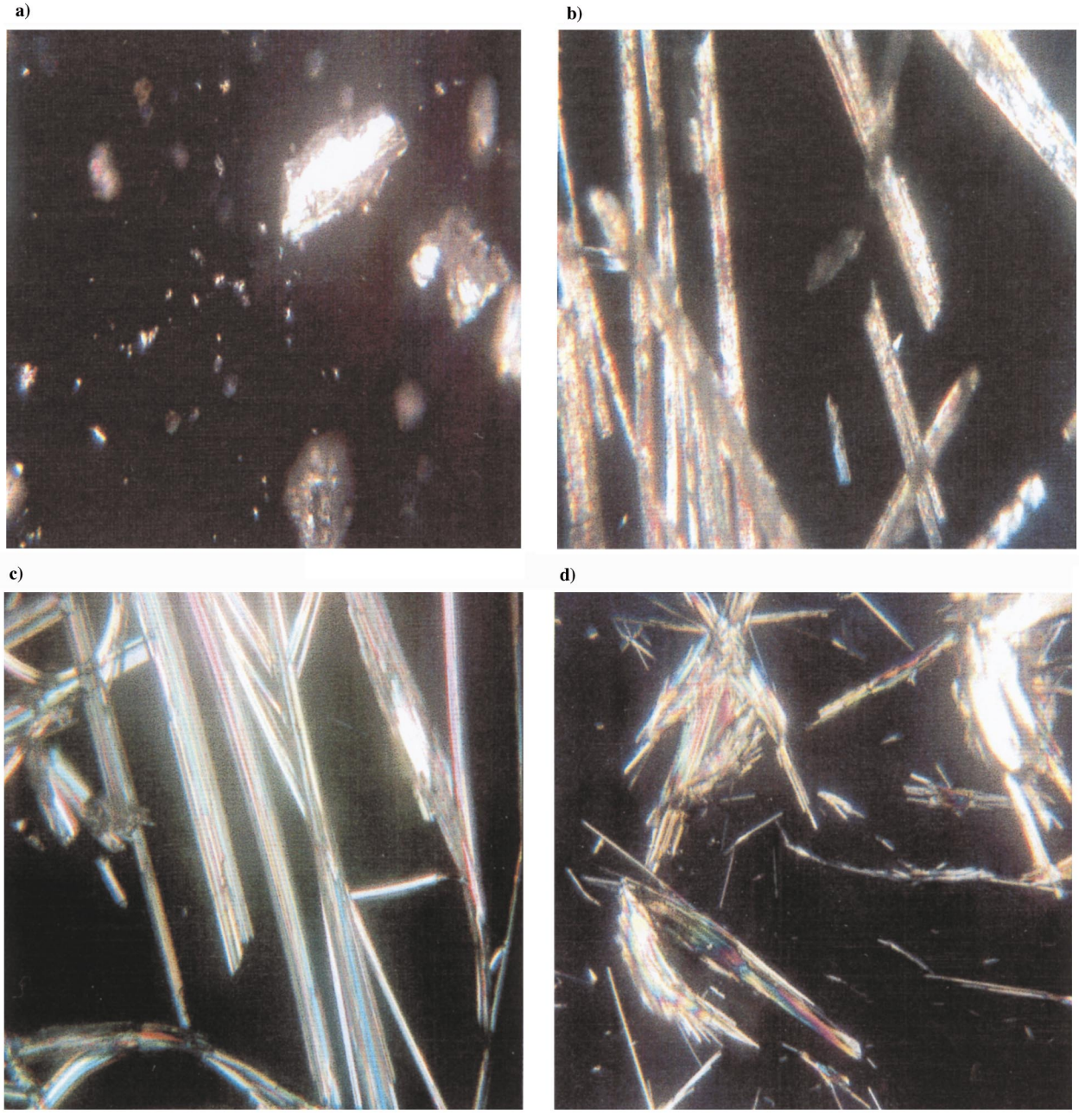

Fig. 8. Kofler hot stage microscopy: (a) polarised light image at room temperature of CBZ Polymorph III; (b) polarised light image at room temperature of CBZ Polymorph II; (c) polarised light image at room temperature of CBZ Polymorph I; (d) polarised light image at room temperature of CBZ Polymorph III melted and recrystallised.

pared CBZ dihydrate by dehydrating at 20°C in a vacuum desiccator over P_2O_5.

We crystallised polymorph II from an ethanolic solution of commercial CBZ by adding iced water and cooling immediately in an ice bath. The needles obtained after 1 h were filtered and dried for 24 h in a vacuum desiccator over activated silica gel.

2.7.3. Polymorph I (nomenclature as Krahn and Mielck [12] and Behme and Brooke [14])

Lowes [13] obtained the trigonal form upon crystallisation from solvents with low dielectric constants, irrespective of cooling rate. According to the literature, polymorph I could also be obtained by heating Form III in an oven at 140°C for 9 h [11], at 140°C for 4 h [14], or at 170°C for 2 h [21].

Our experiments proved that heating commercial CBZ at 170°C for 1 h, or at 150°C for 1 h 45 min, caused its complete transformation into polymorph I.

3. Results and discussion

3.1. Fourier transform infrared spectroscopy (FT-IR)

The FT-IR spectra of commercial CBZ and CBZ USP grade, recorded in KBr pellets, corresponded with those previously reported for polymorph III (i.e. β-monoclinic modification crystals with habit prisms) by Kala, Krahn, Lowes and coworkers [11–13] and for polymorph I by Matsuda et al. [16].

FT-IR analyses were also performed in diffuse reflectance (DRIFT) to avoid transitions that might take place at high temperature and pressure during compression of a pellet. In fact, the possibility of minimal sample preparation and the sensitivity to polymorphism make DRIFT spectrometry an ideal candidate for studies of crystal forms of pharmaceutical compounds. The mixing with KBr was done gently to ensure that polymorphism was not influenced. No differences were found between the spectra recorded in transmission with KBr pellets and those recorded by the DRIFT technique, confirming that no change in crystal modification resulted from extended grinding and compression, as previously reported [20,27].

The FT-IR spectra of both commercial CBZ and CBZ USP grade exhibited no distinctive changes even after vigorous grinding in a mortar; no polymorphic transitions due to the increase in internal energy would therefore appear to have occurred.

Another point of caution is sample heating, which can take place even with a laser wavelength. In the present study, heating effects were studied by comparing spectra obtained with stepwise rotation of the sample; any heating effects were below the limit of detection.

Bands characteristic of polymorph III (Fig. 1) were found at 3464 cm^{-1} (–NH valence vibration), 1676 cm^{-1} (–CO–R vibration), 1605 and 1593 cm^{-1} (range of –C=C– and –C=O vibration and –NH deformation), 1383 and 1019 cm^{-1}. The band at 1271 cm^{-1} (–C≡N bond) is less intense than that at 1245 cm^{-1} and the band at 850 cm^{-1} is weak.

Fig. 1 also shows the FT-IR spectrum of polymorph II; characteristic signals were found at 3473, as reported previously by Krahn [12], 1673 and 1393 cm^{-1}; the band at 1271 cm^{-1} is less intense than the band at 1249 cm^{-1}, as occurred in polymorph III, and the bands at 954 and 853 cm^{-1} are weak.

Substantial differences could be detected between polymorph III and polymorph I, in both band position and intensity (Fig. 1). There was a general shift of band position to higher wave numbers; in particular, the bands present in Form III at 3464, 1676 and 1383 cm^{-1} were located in Form I at 3484, 1684 and 1397 cm^{-1}. Since the –NH band was located at a lower wave number in polymorph III, the presence of intermolecular hydrogen bonds should be more marked in this polymorph than in the others. The intensities of the bands at 1270 and 1251 cm^{-1} were different in Form III and similar in Form I. The bands at 954 and 853 cm^{-1}, lacking or weakly present in Form III, were evident in Form I.

These data correspond with those previously reported for polymorph I (α-trigonal modification crystals with habit needles) by Kala, Krahn, Lowes and coworkers [11–13] and for the polymorph III by Matsuda et al. [16].

After identification and characterisation of different polymorphs, FT-IR spectroscopy was performed to assess the purity of commercial CBZ, as reported by Borka et al. [15]. For this purpose we heated a commercial CBZ sample at 170°C for 2 min on the sample stage of a hot stage microscope, to cause a partial transformation Form III → Form I. The corresponding FT-IR spectrum showed the coexistence of both polymorphs: the NH– band was split (3468 and 3464 cm^{-1}), the band at 1676 and 1390 cm^{-1} lay between the corresponding values in Form III and Form I.

3.2. Hot stage FT-IR thermomicroscopy

Typical spectra of commercial CBZ or CBZ USP grade, recorded at room temperature in reflection and in transmission mode, are shown in Fig. 2a together with the corresponding visible image (Fig. 2b).

This form was heated at 20°C min^{-1} up to 200°C to characterise the transition Form III → Form I by dynamic FT-IR microspectroscopy. To increase the data acquisition speed, only five scans per spectrum were programmed (recording rate: one spectrum every 5°C).

All spectra recorded up to 170°C were similar to the spectrum at room temperature (Fig. 3a), because no phase modifications occurred (–NH valence vibration: 3465 cm^{-1}). This band shifted to 3478 cm^{-1} at 175°C and then to 3483 cm^{-1} at 180°C; this change was associated with the transition Form III → Form I. The bands at 951 and 852 cm^{-1}, characteristic of Form I, were also evident at 180°C. The spectrum at 175°C showed noisy bands probably due to the intermediate formation of a melt phase during transition. Over 195°C, Form I melted and, after recrystallisation, the IR spectrum was identical to the one recorded at 180°C (polymorph I itself). Fig. 3b shows a representative visible image of CBZ after melting and resolidification.

We tried to obtain new polymorphic forms by cooling melted CBZ with different cooling rate; but no evident differences were found in the corresponding FT-IR spectra.

When CBZ polymorph III was heated up to 165°C at a slow rate (2°C min^{-1}), hair-like structures grew on the crystal surfaces at temperatures above 120°C (Fig. 4a), as reported in previous HSM investigations [13]. At 165°C, it was possible to recognize typical crystals of both Form III and Form I (Fig. 4b); the simultaneous presence of the two polymorphic forms was confirmed by recording the FT-IR spectra on the corresponding particles, as shown in Fig. 4c. After 45 min at 165°C all crystals appeared as very thin needles and their FT-IR spectra were in agreement with those recorded for polymorph I.

Fig. 5a shows the characteristic needles of polymorph II at room temperature. This sample was subjected to different heating programs: 2, 10 and 20°C min^{-1}. Slow heating caused the growth of hair-like structures on the crystals at temperatures above 120°C, while at 165°C most crystals converted into Form I, as confirmed by the corresponding visible image and FT-IR spectrum, the band at 3474 cm^{-1} being shifted to 3483 cm^{-1} (Fig. 5b,c). On the other hand, samples heated at 10 and 20°C min^{-1} displayed no modifications up to the melting point, as occurred for polymorph III. At 185°C, after melting and resolidification, all recorded spectra were consistent with that of polymorph I, regardless of heating rate.

3.3. X-Ray powder diffraction

X-Ray powder diffractometry (XRPD) is a powerful technique for the identification of crystalline solid phases. Every crystalline solid phase has a unique XRPD pattern, which can form the basis for its identification.

Commercial CBZ showed a pattern identical to CBZ USP reference standard (Fig. 6) and the data obtained (Table 1) were in agreement with those published for polymorph III by Lowes et al. [13]. Characteristic high-intensity diffraction peaks were detected at: $2°\theta = 14.9$, 15.2, 15.8, 27.2, 27.5, and 32.0°.

Polymorph II displayed an X-ray pattern with characteristic peaks at $2°\theta = 17.8$, 21.2 and 33°, distinguishing itself from the known Forms III and I (Fig. 6, Table 1).

X-Ray powder diffractogram (Fig. 6) and principal diffraction values for polymorph I (Table 1) were in agreement to those published for Form I by Kala, Krahn and coworkers [11,12]; typical signals were recorded at $2°\theta = 6.1$, 9.4, 12.25, 19.80, 19.90, and 22.80°.

Mixtures of Forms III and I, obtained by heating commercial CBZ at 170°C for 2 min on the hot stage, showed relative signal intensities in their X-ray diffractograms that were proportional to the corresponding amounts of III and I.

3.4. Differential scanning calorimetry

DSC curves at 40°C min^{-1} of commercial CBZ or CBZ USP grade (Fig. 7) showed two endotherms of fusion. The first peak corresponded to the melting of Form III (175.92°C), followed by exothermic crystallisation as polymorph I (181.66°C), which subsequently melted (192.1°C). The DSC traces, as well as the melting point value, depended on the analytical heating rate, and it was possible to observe very different curves owing to differences in the rate of transformation Form III → Form I.

A decrease in scan rate caused a decrease in the first peak area; a heating rate of 5°C min^{-1} caused the solid–solid transition into Form I around 155°C and the corresponding heat of transition was estimated to average 8.37 J g^{-1}. In this case, the DSC curve showed only the melting of the higher melting form (190.78°C), as occurred during analysis of polymorph I itself, at a heating rate of 40°C min^{-1} (Fig. 7).

Our findings were in agreement with the literature [12]; no differences were found between uncrushed and crushed CBZ.

The DSC curve of polymorph II (Fig. 7), recorded at 40°C min^{-1}, differed from those of Form III and Form I, showing an exotherm at 80.37°C, due to the presence of amorphous sample crystallizing during DSC scan, and two endotherms at 183.15 and 189.59°C.

The mixture of Forms III and I, obtained by HSM, presented a DSC curve similar to commercial CBZ but with a reduction in the first endotherm, confirming the partial transformation into trigonal CBZ.

Fig. 8 shows the polarised light images recorded with Hot Stage Kofler microscopy for CBZ polymorphs and for CBZ melted and recrystallised.

4. Conclusions

FT-IR spectroscopy, X-ray diffraction on powder and DSC calorimetry enabled us to identify and characterise the different polymorphs of carbamazepine; the results permit us to assert that CBZ exists in at least three anhydrous forms.

In the IR spectrum of polymorph I (higher melting form) the first band occurs at a higher frequency than that of the corresponding band of polymorph III; according to the 'infra-red rule', this would be evidence of enantiotropism between Forms III and I, as previously suggested by Kala et al. [11]. This was confirmed by the existence of an endothermal solid–solid transition, whose enthalpy was measured directly by DSC.

Again, according to the 'infra-red rule' Forms III and II are also enantiotropic pairs, and therefore the most stable form at room temperature has the highest lattice energy, as is evident from the heat of fusion [28]. The crystal modification II also transformed above 140°C into Form I and this should be further evidence of enantiotropic transformation. These findings are consistent with the thermodynamic rules of Burger [29] for enantiotropic systems.

This paper also reports a hot stage FT-IR thermomicroscopic method that is eminently suitable for analysing non-homogeneous samples, since it allows FT-IR spectra and visible images to be recorded on single crystals. Being able to heat the sample stage enabled us to record FT-IR spectra at different temperatures during heating and cooling, which meant that all the polymorphic transitions occurring in the sample could be completely studied.

The inconsistency found in the British and European Pharmacopoeia [24,25] is worthy of note:

both quote the FT-IR spectrum of Form III and the melting point of Form I as reference standard without stating that the operative heating rate markedly influences the thermal analysis. In fact, only slow heating rates lead to a sharp endotherm (melting of Form I); otherwise, an extensive melting process is observed due to the melting of Form III and the recrystallisation and melting of Form I.

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