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A study into first and second order thermal transitions of materials using Spectral-DSC

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Abstract Thermal and spectral analysis is conducted routinely to characterise a large range of materials and compounds. However, tests are often conducted independently on separate samples where comparison between essentially the same material can provide conflicting results. Simultaneous thermal and spectral measurements have the advantage of being able to directly compare results using the same sample. A novel design of a simultaneous thermal and spectral technique is described along with application examples that highlight the benefits of this technique. The thermal analysis was conducted using Differential Scanning Calorimetry (DSC) and the in situ spectral analysis was conducted using a Fourier Transform Near Infrared (FT-NIR) spectrometer. Two examples are used to illustrate the versatility and potential advantages of the combined thermal and spectral method. Analysis of the first and second order transitions of polyethylene terephthalate (PET) is presented along with the pharmaceutical polymorphic conversion of carbamazepine from Form III to Form I through an isothermal hold at 160 °C.

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Introduction: simultaneous DSC-FTIR

Previous publications in the area of in situ or simultaneous DSC and FTIR experiments have generally involved the use of a miniature differential thermal analyser positioned under the objective of an infrared spectrometer coupled to a microscope. The simultaneous DSC/FTIR technique first reported by Mirabella [1, 2] relied on transmission infrared microscopy through the specimen compartment of the DSC sample holder using a Mettler microscopy cell. This method requires optically transparent DSC sample pans, usually NaCl or sapphire, and an elaborate optical alignment. Other researchers [3] used two specimens for each DSC-FTIR measurement. Koberstein et al. [3] used one specimen coated on a KBr disk mounted over the sample position of the DSC cell (Mettler FP 80/84), through which the IR beam passed. The second specimen was a bulk sample encased in a standard aluminium pan, placed in the reference position of the DSC cell. The DSC signal was provided by the reference specimen, while the FTIR spectra were recorded simultaneously from the sample specimen using an IBM (model 98) FTIR spectrometer.

A simple but novel way to conduct simultaneous DSC-NIR studies on the cure kinetics of epoxy resins has previously been reported [4]. In this case, the radiation from an external source was collimated and focussed, using lenses, into a DSC cell containing the sample in a glass pan. The reflected light was then focussed into the interferometer and the spectra recorded. Although not using NIR spectroscopy, Strunt and Jayasooriya [5] reported a similar arrangement to the one suggested in the current study for a combined FT-Raman—DSC technique. A low-cost fibre optic probe was employed to couple the FT-Raman spectrometer to a differential scanning calorimeter. The probe efficiency as well as the effect of probe

sampling on the thermograms was investigated prior to examining ammonium nitrate.

Previous attempts to design a combined thermal and spectral technique have been reported in the literature with varying levels of success. In the next section we describe a novel design for a combined DSC/NIR instrument. Advantages offered by the simultaneous DSC-NIR technique are then demonstrated by focusing on two applications of specific polymer transitions and drug polymorphic conversions. Polymorph conversions which are barely visible and sometimes undetectable by DSC are measurable and even quantifiable by near infrared spectroscopy.

Instrumentation: Spectral-DSC

A Mettler Toledo 823e DSC and a Bruker Matrix F- FTIR spectrometer with fibre optic access port were used for the thermal and spectral analysis. The standard DSC lid was modified to accommodate the fibre optic probe, located over the sample specimen within the DSC lid. The design of the lid is shown in Fig. 1.

The glass windows in the DSC lid of the new instrument (Spectral-DSC) were positioned at a 5° angle to avoid light reflection from the top window and subsequently to allow all light delivered through the optical fibre probe to reach the sample. The design of the lid has undergone a number of design iterations to minimise thermal noise and drift, whilst maximising light transition and reflectance.

The custom-made fibre optic probe used in this study had a 2:1 configuration (bifurcated bundle) with one of the arms being connected to the light source and the other to detector port of the FTIR. The distal end of the probe was housed in the DSC lid. The probe was constructed using 50 silica–silica low-OH-PYROCOAT fibres, randomly arranged, from Oxford Electronics, UK. The combined optical fibres were potted in a stainless tube using a high-temperature resistant optical grade adhesive (Epoxy Technology, USA). The bifurcated optical fibre ends were housed and potted in two SMA optical fibre connectors. The three fibre optic bundles were polished using conventional metallographic techniques.

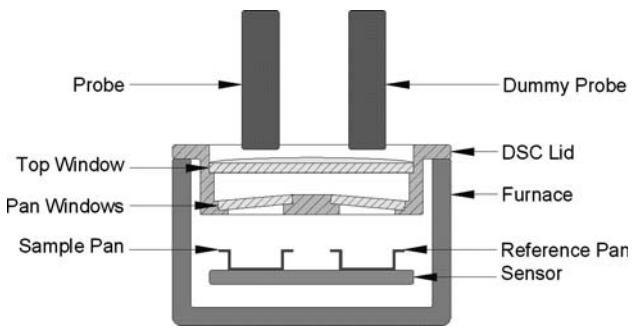

Fig. 1 Schematic diagram of the DSC-NIR system

Material analysis

PET analysis

Polyethylene terephthalate (PET) has captured the global market as the material of choice for the packaging industry. PET is widely used as beverage bottles and in cosmetic and food packaging due to its properties: (i) good design flexibility; (ii) good barrier properties; (iii) lighter than other materials; (iv) as transparent as glass and (v) 100% recyclable. However, in spite of its excellent properties and range of applications, it may be difficult to obtain the exact properties necessary for the product, without a deep understanding of properties such as the degree of crystallinity, glass transition temperature and levels of moisture. PET is a semi-crystalline polymer composed of crystalline and amorphous regions combined to form a variety of microstructures. Most of the studies investigating the structure of PET were carried out using DSC analysis [6–8] with only a few using mid-infrared spectroscopy [9]. No reports of the use of NIR spectroscopy to study PET have been found.

A few attempts to analyse PET by thermal and optical/spectral methods have been described [10, 11]. The system used by Wiedemann [11] involved a hot stage linked to a microscope that was able to record the light intensity of the sample under investigation whilst simultaneously providing images of the heated or cooled sample. Photographs of single crystals of substituted PET (dimethyl 3,6-dichloro-2,5-dihydroxy-terephthalate) at different temperatures before and after the phase transition at 118.9 °C showed a colour change from yellow to white due to the rotation of the molecule. The crystallisation process was also followed at different cooling rates which lead to the formation of single crystals at slow cooling rates and polycrystalline aggregates during rapid cooling. Although interesting and visually very useful, the system described by Wiedemann [11] did not provide any spectral information. In comparison, the system proposed by Compton et al., [10], for investigation of PET recrystallisation, was more attractive. Using the 1,118 and 1,110 cm^{-1} vibrational bands assigned to the trans and gauche conformers of the glycol segment, the authors proved that there is no DSC evidence of recrystallisation of PET at low heating rates in comparison with the large exothermic recrystallisation peak identified at fast heating rates. The mid-IR peaks showed that there is still a raise in peak intensity associated with the recrystallisation independent of the heating rate. The 1,110 cm^{-1} band increased in intensity during the recrystallisation and then decreased to its original level upon melting.

The present study investigates the behaviour of PET further, by monitoring the thermal and spectral behaviour during both first and second order thermal transitions. Glass transition temperature, crystallisation and melting

events are studied using controlled cooled and quenched cooled samples. The system will use near infrared spectroscopy to investigate the spectral changes, in comparison with all previous work carried out in mid infrared region. The use of NIR allows clearer spectral peak identification combined measurements requiring no sample preparation or specialised DSC pans.

Carbamazepine analysis

When developing a new drug, any polymorphs of a new compound represent an area of great interest and investigation for the pharmaceutical industry. The stability of each identified polymorph, along with their processing and bioavailability, are important issues in the development of the new compound. To aid polymorph screening during drug development, a large number of techniques are currently employed: X-ray powder diffraction (XRPD), DSC, TGA, solid-state nuclear magnetic resonance (SSNMR) and vibrational spectroscopy. Although the results of all these methods help the chemist to obtain an overall understanding of the specific compound, in many cases it is very difficult to accurately compare data when it is collected from different samples under different thermal environments and test regimes. The various techniques are carried out independently, often using different substrates. The DSC experiments are generally carried out using aluminium pans, whilst spectroscopic studies use optically transparent materials such as silica, quartz, sodium chloride. The sample masses used in the DSC and FTIR experiments are also significantly different. The former only requires mg of material which can have an influence on the heat transfer efficiency for thermally activated reactions or on the relative temperature profile within the volume of the test specimen. The heating profile employed for a DSC test is extremely accurate, the DSC chamber being designed to accurately control and heat the sample. In comparison, most of the IR tests employed hot cells and heated stages to control the temperature during the IR analysis.

Carbamazepine (CBZ) is a drug used for the treatment of epilepsy and trigeminal neuralgia. It is present in four polymorphic forms, of which three have been extensively characterised in the literature [12, 13]. Figure 2 shows the chemical structure of CBZ. Each form is known to have a specific packing arrangements and crystalline structure. Form III is the most stable form at room temperature and has a monoclinic unit. Form II is present in a trigonal cell, Form IV in a C-centred monoclinic structure and Form I, although not fully determined, is believed to have a triclinic arrangement [14, 15]. This study is focussed on the conversion of Form III to Form I. These two forms are related enantiotropically, where Form III is the most

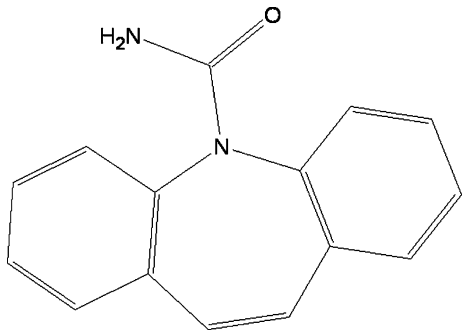

Fig. 2 Chemical structure of carbamazepine

thermodynamically stable form at ambient temperatures and Form I is the more stable form at temperatures above approximately 70 °C. CBZ has been chosen as pharmaceutical compound where combined thermal and spectral analysis will provide greater insights into material behaviour compared to the individual techniques. In spite of the extensive sample preparation required when running mid-IR tests, the literature shows that mid-IR region has been extensively used for identification of the differences between the different polymorphic forms. In comparison, the current study is proposing the use of near infrared spectroscopy, based on an optical fibre probe, as a novel, non-contact, non-destructive technique for polymorph identification in combination with DSC.

Calibration

The DSC was calibrated using indium (m.p. = 156.60 °C). The calibration was carried out using the modified lid with the fibre optic probes in place. Benzoic Acid (m.p. = 122.4 °C) was used as an organic standard to check the calibration of the modified machine. The calibration values obtained using the standard DSC lid were included for comparison purposes (Table 1).

The noise level on the DSC baseline has been evaluated by calculating the minimum-maximum values on a baseline run at 250 °C for 60 min using the modified DSC lid and the standard DSC lid. Noise levels for both types of lid were typically less than 0.002 mW.

Table 1 Calibration using organic reference standard benzoic acid

Organic calibration	Enthalpy of melting (ΔH) (J g^{-1})	Peak onset (°C)
Standard DSC	125.6	122.4
Modified DSC	125.4	122.4

Materials and experimental procedure

PET

The PET material used in this study was provided by Distrupol, known under its commercial name as Melinar Laser Plus. Two types of heat treatment were applied to the PET samples. The first was heated above its melting point at 270 °C and cooled to room temperature at a rate of 10 °C per min. The second was heated to the same temperature but quench cooled in liquid nitrogen. Each PET sample was heated in the range 30–270 °C at 10 °C min^{-1} under a nitrogen flow. Simultaneously, the FTIR was set up to record near infrared spectra over the wavelength range 11,000–4,000 cm^{-1}, at a resolution of 16 cm^{-1} over 64 scans. The sample collection time was 10 s and spectra were recorded continuously throughout the experiment.

Carbamazepine

CBZ Form III was obtained direct from Aldrich and Form I was prepared by heating Form III at 170 °C for 2 h. Once prepared, the crystal forms corresponding to polymorph I and III were checked using XRD (Bruker D5000). Although it is known that CBZ exists in four polymorphic forms, this paper is focussed on the conversion of Form III to Form I.

For the results published in this paper, CBZ Form III was held isothermally for 1 h at 155 °C to allow full conversion to Form I. Simultaneous with the isothermal DSC scan, the spectrometer was set up to record near infrared spectra over the wavelength range 10,000–4,000 cm^{-1}, at a resolution of 16 cm^{-1} over 64 scans. The collection time of each near infrared spectrum was 10 s and spectra were recorded continuously throughout the experiment. In order to confirm the total conversion of CBZ from Form III to Form I, the sample was allowed to cool and then heated in the range 30–210 °C at 10 °C min^{-1} under a nitrogen flow.

Results and discussion

PET

Thermal and spectral techniques are known as two of the most powerful methods used to investigate thermoplastics and their structural changes as a function of temperature. Thermal events such as crystallisation, melting, glass transition temperature, relaxation and aging can all be investigated on the DSC. The DSC can provide analysis of the bulk thermal phase transitions experienced by a polymer, whereas the spectral analysis can provide direct measurements of the structural changes of a polymer to help fully understand the reasons for specific thermal behaviour.

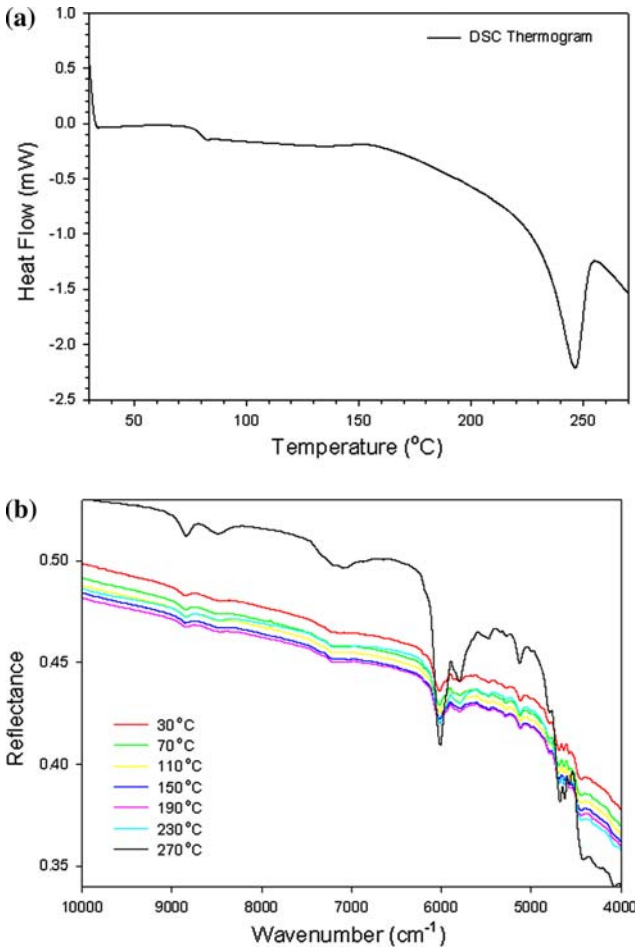

Fig. 3 (**a**) DSC scan (**b**) simultaneous NIR spectra of the controlled cooled PET sample

First and second order thermal transitions such as glass transition and recrystallisation are known to be detectable using thermal analysis methods such as DSC or DMTA [16, 17]. However, depending on the polymer original degree of crystallinity and the type of polymer investigated, these transitions can sometimes pass thermally undetected. The current study shows that by combining the DSC and NIR techniques, weak transitions barely detectable thermally can be confirmed spectrally.

Figure 3a and b presents thermograms of the controlled cooled PET sample and the near infrared spectra recorded during the DSC scan, respectively. Similarly, Fig. 4a and b represents the thermograms of the quench cooled PET sample and the near infrared spectra recorded during the DSC scan, respectively.

Three events can clearly be observed in the heating of the PET samples from 30 °C to 270 °C. In both figures the glass transition, recrystallisation and melting events are evident. The two PET samples differ in the degree of crystallinity due to their heat treatment and thermal history. The quench cooled sample shown in Fig. 4 has a much

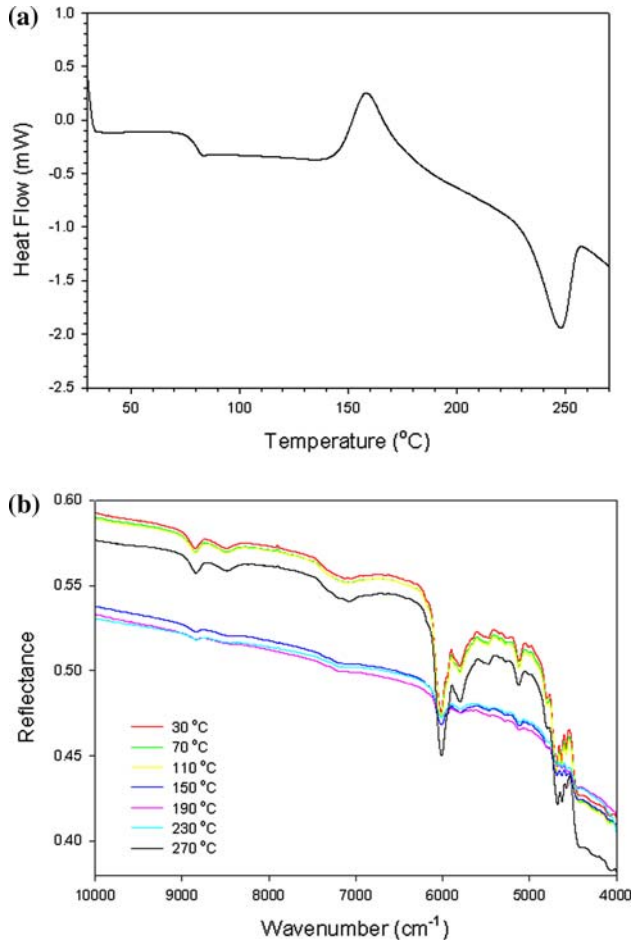

Fig. 4 (**a**) DSC scan (**b**) simultaneous NIR spectra of the quenched cooled PET sample

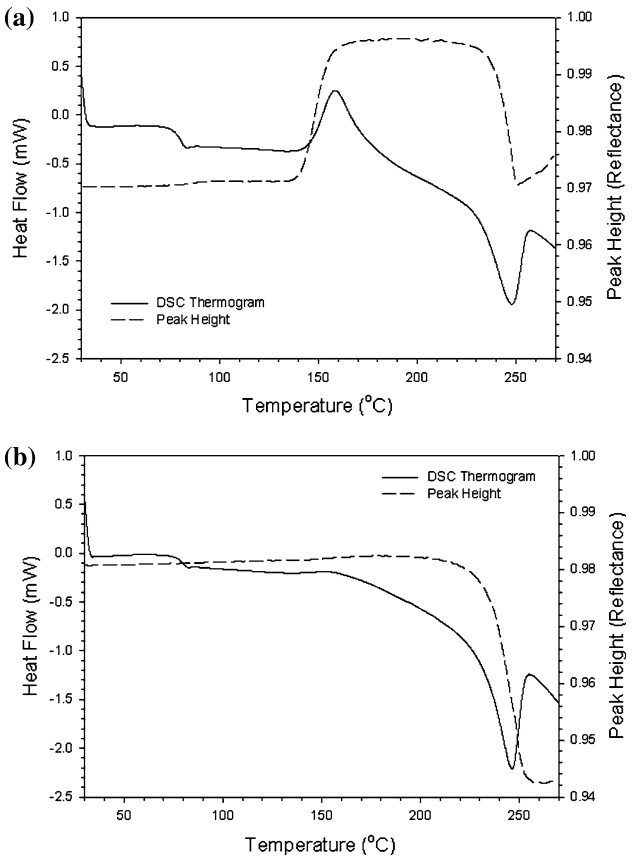

Fig. 5 DSC thermogram and peak height of 6,000 cm^{-1} vibrational band recorded during heating from 30 to 270 °C of (**a**) quench cooled PET and (**b**) controlled cooled PET

lower degree of crystallinity than the controlled cooled which manifests a large cold recrystallisation peak around 155 °C. The samples also differ more subtly in the glass transitions, where a higher change in heat capacity is noticed by the quench cooled sample.

Although PET has been extensively studied in the mid-IR region [9, 18, 19], only few studies tried to carry out the PET peak assignment in the near IR region [20]. Previous mid-infrared studies used the rocking vibration modes of methyl groups [10, 19] or the stretching vibrations of the ether units [19] for quantitative analysis, these peaks being situated in the fingerprint region between 1,000 and 700 cm^{-1}. The overtones or combination bands of these vibrational bands are not detectable in near infrared region. In Figs. 3b and 4b, two prominent, overlapped peaks are noticed in the region 6,300–5,500 cm^{-1}. The band situated at approximately 5,800 cm^{-1} is related to the first overtone of the symmetric and asymmetric CH_2 stretching vibrations and the 6,000 cm^{-1} vibrational peak is associated with the first overtone of the aromatic C–H stretching vibrations. Although not as strong in intensity, the 5,130 cm^{-1} vibrational peak is related to the second overtone of the C=O stretching vibration.

Within the PET chain, the ester groups together with the carbonyl groups create localised positive and negative charges which attract each other and allow the ester groups situated in close vicinity to structure themselves in crystal units. Previous studies [21] concluded that the interactions of polar groups on different chains tend to increase the rotational energy barrier therefore leading to a higher T_g. In comparison, the presence of bulky structures such as the aromatic units is expected to increase the stiffness of the chain and will have an opposite effect during glass transition and recrystallisation, inhibiting the packing of the polymeric chain in crystalline units. In this study, due to molecular effects such as chain stiffness, polarity and chain architecture, the 6,000 cm^{-1} vibrational band is chosen to record the first and second order thermal transition changes. It is expected that the aromatic ring will have strong vibrational activity during glass transition and recrystallisation events.

When comparing the changes in peak height for partially crystalline and amorphous PET in Fig. 5a, b, it can be noticed that both types of samples exhibit significant vibrational changes. During glass transition, materials

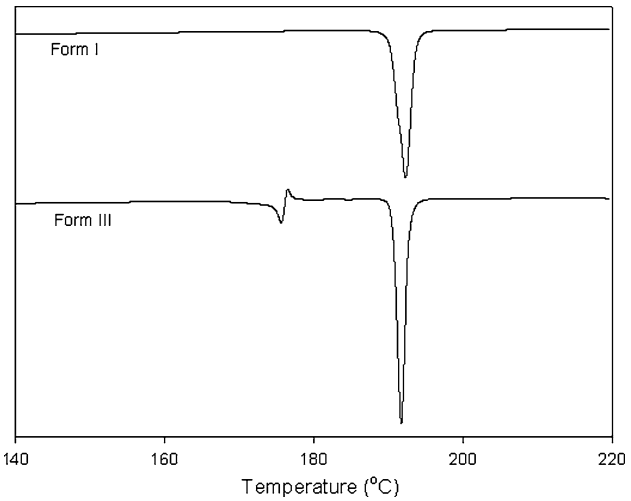

Fig. 6 DSC thermograms of carbamazepine (Form I and III)

change from a glassy, frozen structure to a rubbery like structure that allows small movements and rearrangements of the molecular chains. Being slowly cooled, the controlled cooled PET sample had enough time to initiate crystallisation points and find a more stable solid structure in a lower energy state. In comparison, the quench cooled PET structure was quickly frozen into a highly amorphous form. When the sample temperature is raised to around 150 °C, the molecular chains of quench cooled PET sample are given liberty to move and will react stronger trying to find a more stable arrangement in a lower energy state, as observed by the stronger vibrational effects noticed in amorphous samples than partially crystalline ones.

When comparing these spectral findings with the thermal scans recorded simultaneously from the same samples (Figs. 3a and 4a), it is important to notice that both first and second order transitions, for both polymeric structures, are detectable in near IR region. This shows the advantages offered by the Spectral-DSC when investigating polymeric materials with different degrees of crystallinity.

Carbamazepine

In order to check the polymorphic form of CBZ, both XRD analysis and standard DSC tests were performed. Figure 6 shows thermograms for Form I and Form III of CBZ. The thermogram for Form I shows a single endothermic peak at 192 °C. Form III shows an endothermic peak at 175.7 °C, corresponding to the melting of Form III, followed by an exothermic peak at 176.6 °C, representing the crystallisation of Form I, which later melts at 191.3 °C.

Carbamazepine Form III is an enantiotropic system where conversion to Form I can occur at temperatures above 70 °C. Figure 7a shows the conversion of Form III to Form I by isothermally holding the temperature at 155 °C.

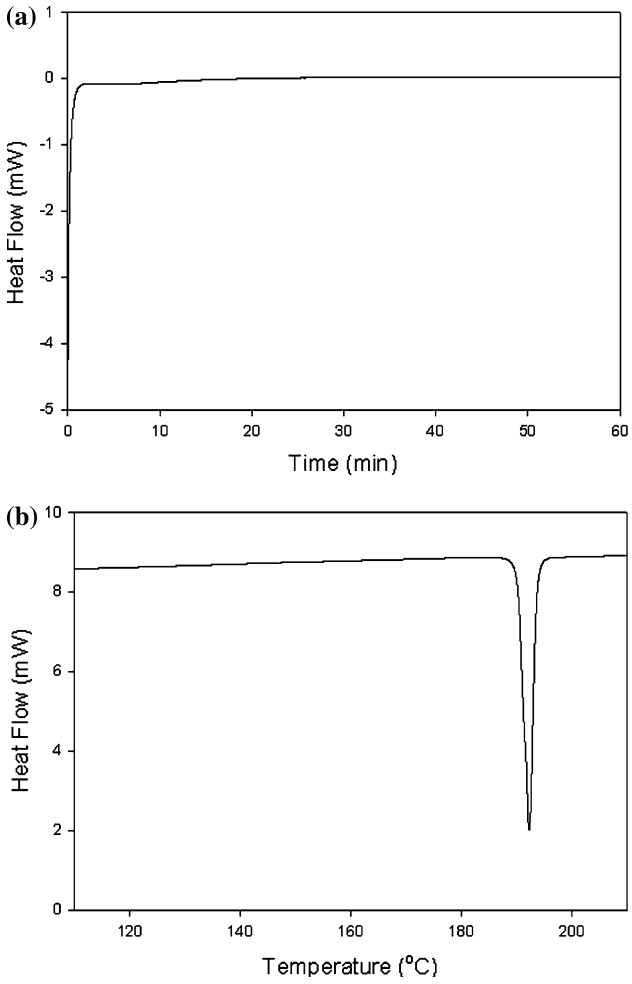

Fig. 7 (**a**) Isothermal conversion of carbamazepine Form III to Form I (**b**) dynamic scan to check for full conversion

The sample was held at this temperature for one hour. Although the conversion to Form I was confirmed by the dynamic scan conducted at the end of the isothermal test (see Fig. 7b), it was impossible to monitor its conversion in real time just by using the DSC. No strong thermal events were noticed during the isothermal conversion.

In contrast, significant spectral changes were detected in the near infrared region when using the combined DSC-NIR method and simultaneously monitoring the isothermal conversion of CBZ from Form III to Form I at 155 °C. Figure 8 shows the spectra recorded during the conversion of carbamazepine Form III to Form I. For clarity, the near infrared spectra were divided into two regions (7,200–5,500 and 5,500–4,400 cm^{-1}) allowing close observation of the major peaks. As it can be readily noticed in Fig. 8, the observed spectral changes were mainly due to peak shifts rather than changes in peak intensities. Although changes in peak intensities have been used in the past to evaluate the kinetic conversion of Form III to Form I [22],

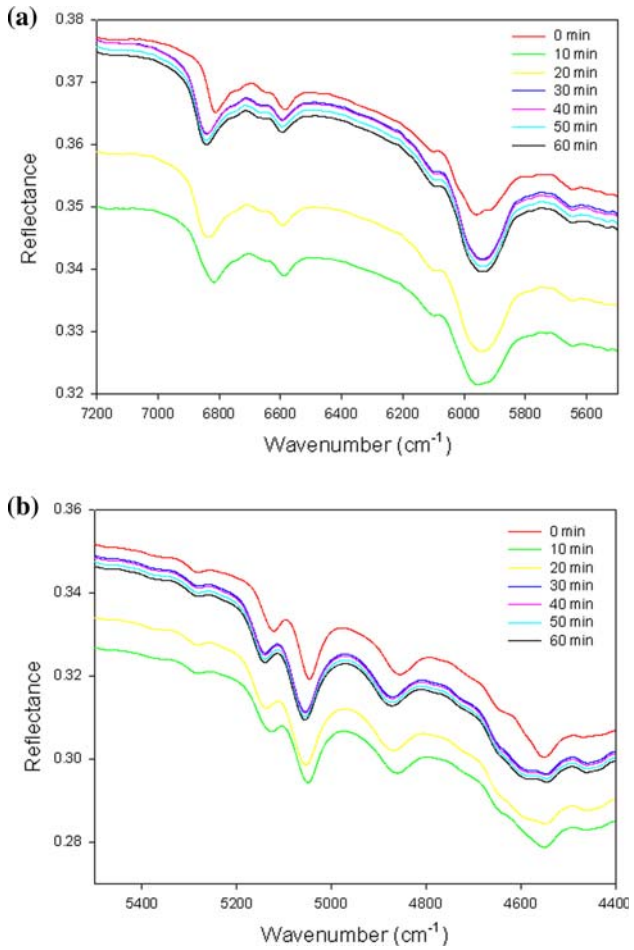

Fig. 8 Near infrared spectra of carbamazepine recorded during conversion from Form III to Form I (**a**) 7,200–5,500 cm^{-1} region and (**b**) 5,500–4,400 cm^{-1} region

the peak position was employed in most cases to identify the CBZ polymorphs [15, 23] and it will be used here to confirm conversion from Form III to Form I.

Near infrared peak assignments of carbamazepine are presented in Table 2.

The 5,060 cm^{-1} and 6,851 cm^{-1} peaks have been used to monitor the peak shifts. The 5,060 cm^{-1} peak corresponding to the 2nd overtone of the C=O stretching vibration whilst the 6,851 cm^{-1} peak is related to the 1st overtone of the $–NH_2$ asymmetric stretching vibration. Figure 9 shows the two peak shifts recorded at 165 °C over 1 h.

The conversion of the polymorphic forms can clearly be distinguished in the spectral analysis. By monitoring the peak position of the 2nd overtone of the C=O stretching vibration, the conversion can be observed to be complete by approximately 30 min. The simultaneous technique clearly provides a powerful tool with which pharmaceutical compounds can be studied, even when no strong thermal events can be observed.

Table 2 Major near infrared peak assignments for carbamazepine Form I and III

Wavenumbers (cm^{-1})		Comments
Form I	Form III	
6851; 6593	6810; 6581	Doublet—first overtone of the $–NH_2$ symmetric and asymmetric stretching vibration located at 3,340 and 3,280 cm^{-1} in mid infrared region
6200–5700	6200–5700	First overtones of the C–H stretching vibrations of aromatic and aliphatic unsaturated vibrations situated between 3,245 and 2,900 cm^{-1} in mid infrared region
5145	5122	Unknown
5060	5048	2nd overtone of the C=O stretching vibration
4883	4866	Unknown—possible combination band of $–NH_2$ stretching and bending vibrations
4800–4500	4800–4500	Strongly overlapped combination bands of C–H aromatic, aliphatic and unsaturated stretching vibrations

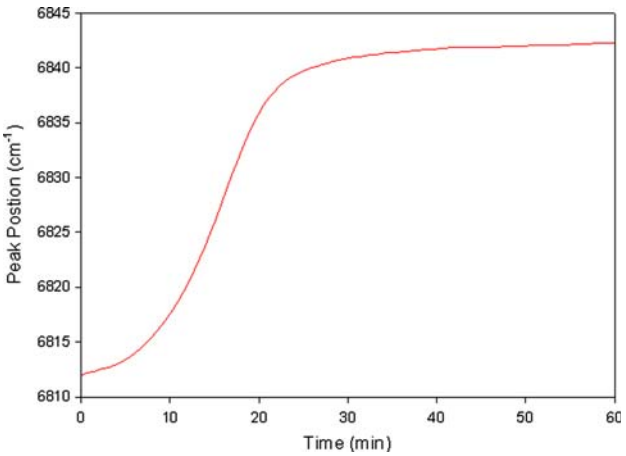

Fig. 9 6,851 cm^{-1} peak shifts corresponding to carbamazepine Form III conversion to Form I

Conclusions

The advantages offered by the new instrument, Spectral-DSC, have been described through examples with direct application in two important industry sectors: (i) packaging sector (PET analysis) and (ii) pharmaceutical industry (CBZ analysis). In both cases, it was shown that the two techniques complement each other, and where the DSC data is limited, the near infrared spectroscopy provides the necessary information. In the pharmaceutical industry, the new system will reduce the number of tests required during drug development stages and will give greater confidence in identifying all polymorphs of specific active ingredients and in

understanding their packing arrangements. In addition, the simultaneous DSC-NIR screening technique will eliminate any errors incurred when using the two techniques separately, such as heating methods, substrates or sample weight.

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