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Micro-thermal analysis: scanning thermal microscopy and localised thermal analysis

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Abstract

Micro-thermal analysis combines the imaging capabilities of atomic force microscopy with the ability to characterise, with high spatial resolution, the thermal behaviour of materials. The conventional AFM tip is replaced by a miniature heater/thermometer which enables a surface to be visualised according to its response to the input of heat (in addition to measuring its topography). Areas of interest may then be selected and localised thermal analysis (modulated temperature calorimetry and thermomechanical analysis) carried out. Localised dynamic mechanical measurements are also possible. Spatially resolved chemical analysis can be performed using the same basic apparatus by means of pyrolysis gas chromatography-mass spectrometry or high-resolution photothermal infrared spectrometry.

Keywords: Atomic force microscopy; Thermal analysis; Pharmaceuticals

1. Introduction

Thermal methods of analysis are widely used for the characterisation of pharmaceuticals (Hardy, 1992). The most popular thermal method is differential scanning calorimetry (DSC) which measures the heat flow into or out of a sample subjected to a temperature ramp. In this way transition temperatures can be identified and the enthalpies and heat capacity changes associated with them can be determined. In 1992, Reading and co-workers introduced a temperature modulation combined with a deconvolution of the resulting data (Gill et al., 1993; Reading, 1993; Reading et al., 1993, 1994). This new technique is called modulated temperature DSC (MTDSC). MTDSC significantly improves the sensitivity and resolution of the technique towards some transitions while also enabling their 'reversing' or 'non-reversing' character to be probed. Observing and quantifying these effects enables the sample's morphology to be characterised. Initially, MTDSC was restricted to the study of polymers,

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but recently the technique has been applied to the study of foods and pharmaceuticals (e.g. Barnes et al., 1993; Aldén et al., 1995; Wulff and Aldén, 1995; Bell and Tourma, 1996; Coleman and Craig, 1996; Izzard et al., 1996). MTDSC is particularly suited to the study of glass transitions in amorphous drugs (Craig and Royall, 1998; Hill et al., 1998; Royall et al., 1998).

Another popular thermal method is thermomechanical analysis (TMA) where a probe is placed on a specimen with a given force then, as the temperature is increased, changes in sample length (such as accompany softening during melting) are measured (Riga and Neag, 1991). In this way, thermal expansion coefficients and transition temperatures can be determined. When an oscillating load is applied to the specimen, it is possible to monitor the mechanical modulus and damping of the sample as a function of temperature. This technique is known as dynamic mechanical analysis (DMA) (Reading and Haines, 1995). For these techniques the specimen is typically tens of milligrams or even, in the case of TMA and DMA, larger.

However, the results of such measurements represent the sum of all of the constituents in the specimen. The bulk thermal response is often dominated by the higher concentration of the matrix or substrate material. It is difficult to gain detailed characterisation of dilute components, contaminants and less dominant phases without physically altering the sample. In addition, the experiments are often time-consuming—particularly for thermomechanical and dynamic mechanical tests.

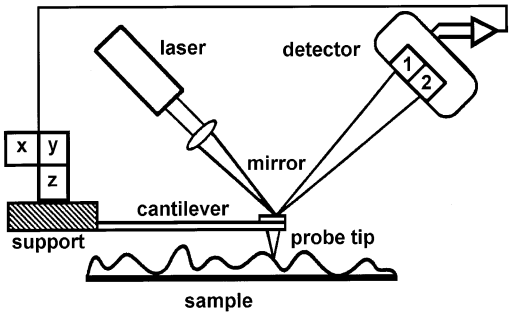

Fig. 1. Atomic force microscope (schematic).

In order to obtain spatially resolved information about a material, the investigator must resort to microscopy. Without employing staining or etching techniques it may be difficult to determine differences in composition across a specimen. Infrared and Raman microspectrometry may be used to investigate chemical composition on a local scale but often the resolution (spatially and structurally) is too poor. Imaging secondary ion mass spectrometry (SIMS) or X-ray photoelectron spectrometry (XPS) can afford similar information but also suffer the same drawbacks in addition to requiring the sample to be in a high vacuum.

The development of the atomic force microscope (AFM) has opened up many new ways of visualising surfaces to very high resolution (Binnig et al., 1986; Wickramasinghe, 1990; Bottomley et al., 1996). A schematic diagram of an AFM is shown in Fig. 1. The instrument consists of a sharp tip mounted on the end of a cantilever which is scanned across the specimen by a pair of piezoelectric elements aligned in the x- and y-axis. As the height of the sample changes the deflection of the tip in contact with the surface is monitored by an optical lever arrangement formed by reflecting a laser beam from the back of the cantilever into a photodetector. The tip is then moved up and down by a feedback loop connected to a z-axis piezo which provides the height of the sample at each x,y position. Besides the topographic information provided by rastering the tip across the sample, other properties can be obtained by measuring the twisting of the cantilever as it is moved across the sample (lateral force microscopy) (Ling and Leggett, 1997). This provides image contrast based on the frictional forces generated from the sample-tip interaction. Other imaging modes, such as force modulation and pulsed force modes can indicate the stiffness of the sample (Rosa-Zeiser et al., 1997).

An advantage of the AFM over the scanning electron microscope is that little sample preparation is required as the sample is not exposed to a high vacuum and electrically insulating materials can be examined. Therefore hydrated, solvent-containing specimens can be imaged. AFM has been used in the biological and pharmaceutical

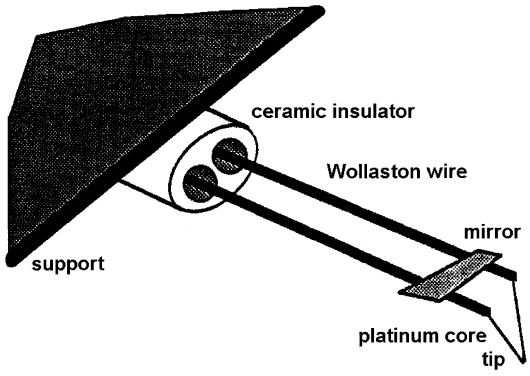

Fig. 2. Thermal probe (schematic).

sciences for the imaging of fibrinogen polymerisation, the budding of a virus of an infected cell and the in vitro degradation of polymer surfaces and nanoparticles (Drake et al., 1989; Häberle et al., 1992; Gref et al., 1994; Shakesheff et al., 1994). The atomic force microscope can obtain images fast enough (about 20 s per image) to allow the observation of in situ processes occurring at interfaces and imaging may be carried out with the sample under a thin film of liquid. AFM and DSC have been used to study solid lipid nanoparticles for the controlled delivery of drugs (zur Mühlen et al., 1996). AFM was used to examine the size and shape of the nanoparticles, whilst DSC was used to study the crystallinity of the occluded drug.

2. Scanning thermal microscopy

We are particularly interested in scanning thermal microscopy (SThM). In this imaging mode, a miniature temperature sensor has replaced the conventional sharp SPM tip (Gmelin et al., 1998). Our studies use the Wollaston wire probe described by Pylkki which consists of a silver wire with a fine platinum core which is bent into a sharp loop and etched to expose the core (Fig. 2) (Dinwiddie et al., 1994; Pylkki et al., 1994). This behaves as a small resistance thermometer as well as a conventional SPM tip. The probe can be heated by passing a current through it, thus the power required to maintain the tip at a constant temperature can be monitored as it is scanned across the specimen. This is used to build up an image based on the contrast in apparent thermal conductivity as well providing the usual topographic information via the optical lever feedback circuit. Fig. 3 shows the topographic and thermal images of the surface of a paracetamol (4-acetamidophenol) tablet used as an 'over the counter' analgesic. The topography illustrates the rough surface of the compact but the thermal image suggests that two thermally dissimilar ma-

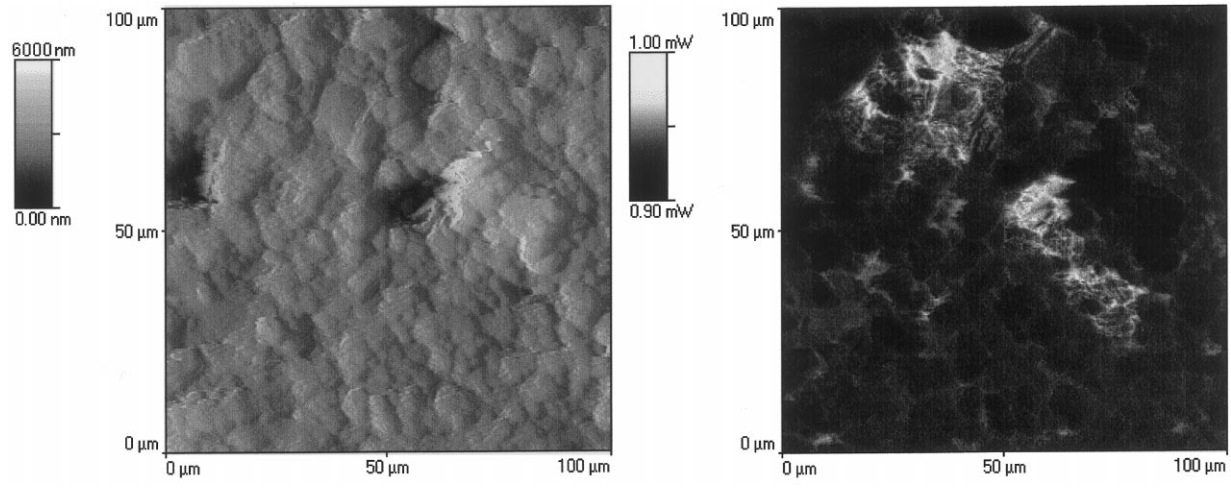

Fig. 3. Topographic (left) and DC thermal (right) images of the surface of a paracetamol tablet.

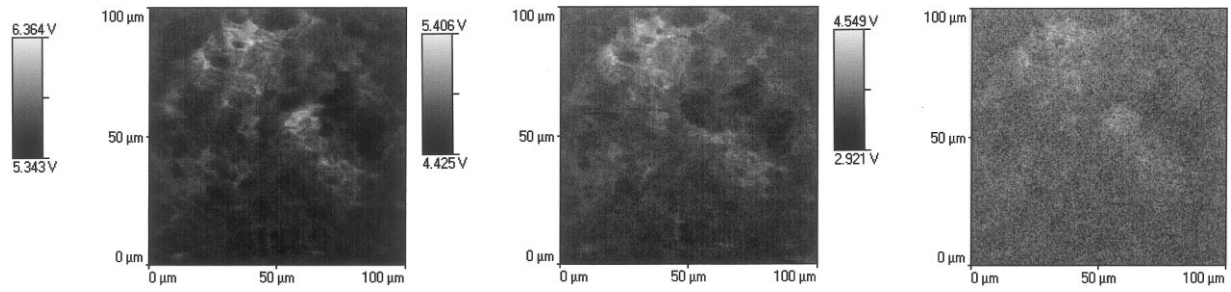

Fig. 4. AC thermal images of the voltage required to modulate the probe temperature with an amplitude of 5°C at 10 kHz (left), 30 kHz (middle) and 100 kHz (right).

terials are present. Although Riuz has made absolute measurements of surface thermal conductivity of semiconductors, this is not routinely possible since the thermal signal is convoluted with the surface roughness of the sample (Riuz et al., 1998). Sharp changes in relief affect the contact area between the probe and the specimen, thus giving rise to changes in the amount of heat that is lost from the tip not arising purely from thermal conductivity differences. For very flat samples, the spatial resolution of thermal properties is of the order of 100 nm and we have successfully used this technique to obtain images of polymer blends of two or more components with different thermal conductivities (Hammiche et al., 1996a). Higher resolution probes based on a combination of an actively heated resistance thermometer and conventional AFM tip technology are under development.

In addition to holding the probe at a constant temperature, it is possible to modulate its temperature. The depth of penetration of the resulting thermal wave is a function of the modulation frequency. Thus we have a means of obtaining depth-specific as well as spatially resolved information about the sample (Balk et al., 1995; Hammiche et al., 1996a). We refer to this as the 'AC thermal image' as opposed to the 'DC thermal image' described earlier. Fig. 4 shows AC thermal images of the same tablet at derived from the voltage required to modulate the probe with an amplitude of 5°C at different frequencies. As the frequency is increased, the second component disappears from view suggesting that it is buried within the lower thermal conductivity matrix. Fig. 5 shows an AC image obtained at 10 kHz based on the phase difference between the applied power and response of the probe.

Thus four images of a sample may be obtained: topography, DC thermal image (related to the apparent thermal conductivity of the surface) and two AC images based on the voltage required to modulate the probe temperature or phase difference between the applied temperature modulation and probe response. The latter images afford depth specific information depending on the modulation conditions, although interpretation of these images is at an early stage.

3. Localised thermal analysis

The design of the probe readily lends itself to thermal analysis (Hammiche et al., 1996b). The tip, when used in conjunction with a reference probe, can be used as an ultra-miniature differential thermal analyser (DTA) cell whereby the difference in electrical energy supplied to the probe in contact with a point on the sample is compared with that of a reference probe as both are scanned in temperature. Furthermore the AC heating technique can be used so that the configuration may be operated as a miniature modulated temperature calorimeter. The term 'DTA' is preferred to 'DSC' since, in a conventional DSC, the instrument is large in comparison to the sample (which can be weighed)—in the SThM, the total sample is large in comparison to the sensor. Although the probe only measures a small area (a few square microns), the sample's mass is unknown therefore

the measurements are currently only qualitative in terms of identifying transition temperatures. This is often sufficient for characterisation purposes, and semi-quantitative information can be obtained by comparing different areas of the same sample. The small scale of the probe means that high heating and cooling rates of the order of tens of degrees per second can be used. Modulation frequencies in the kilohertz region are also typical.

Because the probe is mounted on the microscope stage, its deflection in the z-axis can be monitored during the experiment. This is the microscopic equivalent of TMA. The force-feedback mechanism must be disabled during the experiment otherwise the z-piezo motion would drive the tip through the specimen as it softens. Thus four signals can be measured and displayed: the sensor height position, the differential DC power required to change the probe temperature, and the differential AC power and phase (Fig. 6). Melting of the sample is seen as a step change in the power required to heat the probe, whereas glass transitions are seen as a change in slope of the curve. It is therefore convenient to plot the 'calorimetric' signals as their first-order derivatives with respect to time or temperature so as to resemble a 'macro' DSC experiment (Fig. 7). The localised TMA curve often serves as the primary means of identifying transition temperatures, whereas the accompanying calorimetric response helps to distinguish between melting, crystallisation and glass transition phenomena.

Fig. 8 shows the localised thermal analysis of selected areas of the paracetamol tablet shown in Figs. 3–5. Four locations were examined: two points from the regions of high thermal conductivity in the DC thermal image, and two points from the remaining low thermal conductivity areas. Scans on the latter areas show melting transitions corresponding to the drug whereas no transitions were observed over the temperature range studied for the regions of high thermal conductivity. The high thermal conductivity inclusions (invisible in the conventional topographic image) are probably composed of inert filler such as microcrystalline cellulose or calcium carbonate. Chemical analysis of these areas could be carried out using this apparatus by means of the techniques described in the following section (in addition to their physical characterisation by the localised thermal analysis techniques already described). The localised TMA and DTA measure-

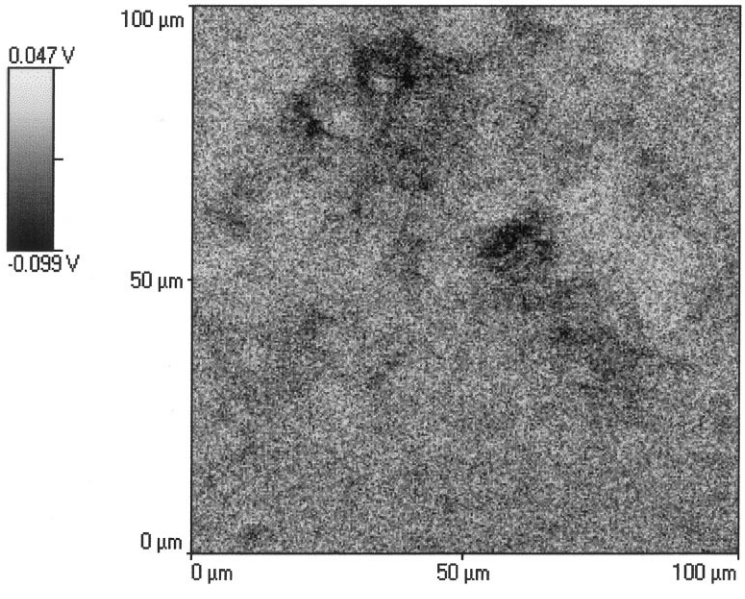

Fig. 5. AC phase image at 10 kHz.

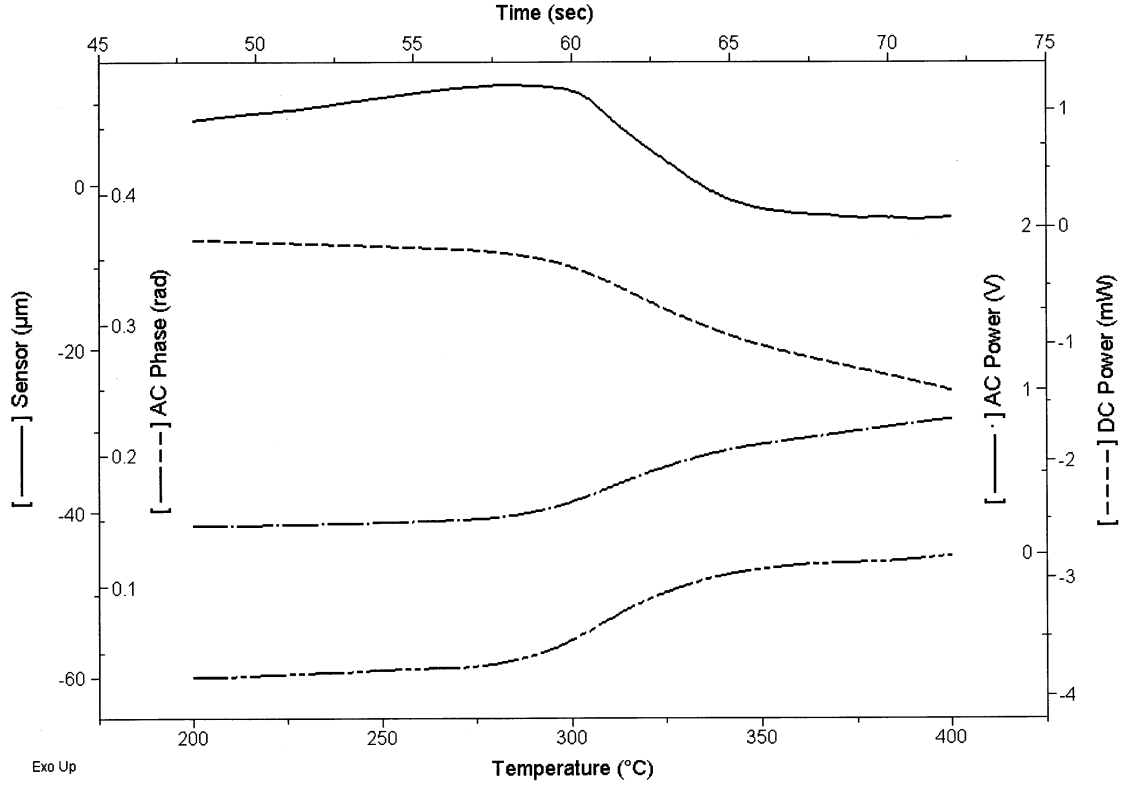

Fig. 6. Typical raw localised thermal analysis data for the melting of a polymer.

ments were carried out at a heating rate of 10°C/s so that the sequence of measurements took only a few minutes. In addition to the ability to perform spatially resolved thermal analysis, the high heating rates that can be employed allow a large number of (small) samples to be examined very quickly. This has obvious advantages in the area of new drug development.

4. Future developments

The examples given above and elsewhere illustrate the imaging capabilities of SThM and the applications of localised DTA and TMA (Lever and Price, 1998; Price et al., 1998, 1999a,b; Reading et al., 1999). Localised dynamic mechanical analysis (DMA) has also been demonstrated, though, at present, this technique is not commercially available (Oulevey et al., 1997; Reading et al., 1998). For this experiment, the sample is vibrated in the z-axis while the temperature of the tip is scanned. Typical results are shown in Fig. 9 for a chip of nylon. Possible alternatives to this configuration include controlling the tip by (for example); modulating the position of the cantilever in the z axis to exert a force normal to the surface (or modulating its position in x and/or y to exert a shear force), applying a modulated magnetic field after rendering the tip susceptible to magnetic attraction or repulsion and modulating the position of the tip using the thermal expansion and contraction of the tip as a modulated temperature programme is applied to it. With the addition of DMA, we have on the micro- the equivalent of all of the more commonly available macro-thermal analysis techniques except dielectric analysis. This may also be possible in future using a probe with two closely spaced electrodes on the tip (Craig, 1995).

An additional imaging mode has recently be demonstrated whereby the thermal expansion of a specimen is detected whilst AC heating is applied to the probe as it is scanned over the surface. The resulting z-axis modulation of the probe arising from thermal expansion and contraction of the surface is detected and used to construct an image based on the thermal expansivity of the sample (Fig. 10). Although Majumdar and colleagues have also described similar measurements (Majumdar, 1998; Majumdar and Varesi, 1998; Varesi and Majumdar, 1998), our approach does not require electrically conductive specimens and employs the same configuration used for thermal conductivity imaging.

Use of thermal imaging with localised thermal analysis has a wide range of applications across a broad range of materials in addition to pharmaceuticals. However, this ability to image and characterise the physics of a system in a spatially resolved way using thermal analysis represents only part of the overall concept; we are also working to extend it to enable chemical analysis using the same basic instrument. In pursuit of this goal, one further capability that has recently been developed, is localised evolved gas analysis with mass spectrometry (MS) and gas chromatography-mass spectrometry (GC-MS). In this experiment, the tip is placed on a point of interest within an image and then rapidly heated to a temperature at which the sample undergoes volatilisation or pyrolysis. The evolved species are captured and analysed by MS or GC-MS. In our current implementation the gases are first trapped in a specially designed tube packed with a suitable sorbent such as Tenax or Carbopak. The tube comes to a fine point which is placed immediately adjacent to the heated tip using a micro-manipulator. As the tip is heated a syringe is used to draw gas through the tube which is then placed in a thermal desorption unit for analysis of the trapped volatiles by GC-MS. Some results from the pyrolysis of a small (10×10 μm square) area of polystyrene are shown in Fig. 11. This particu-

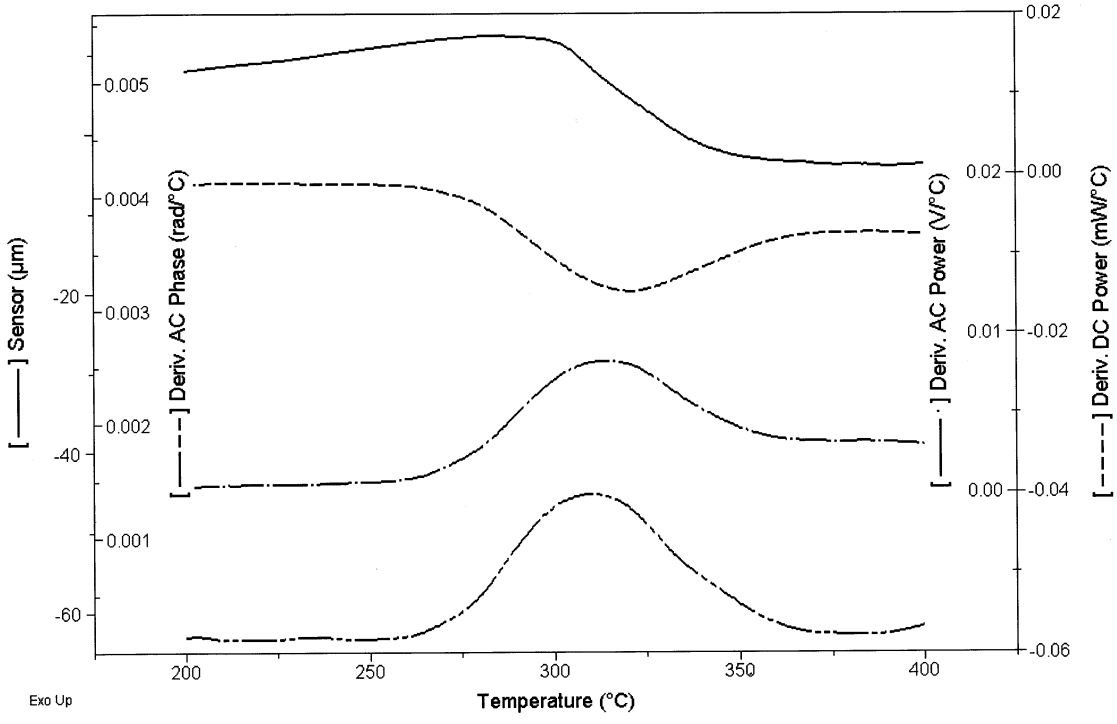

Fig. 7. As Fig. 6 illustrating the use of derivatives for the calorimetric signals.

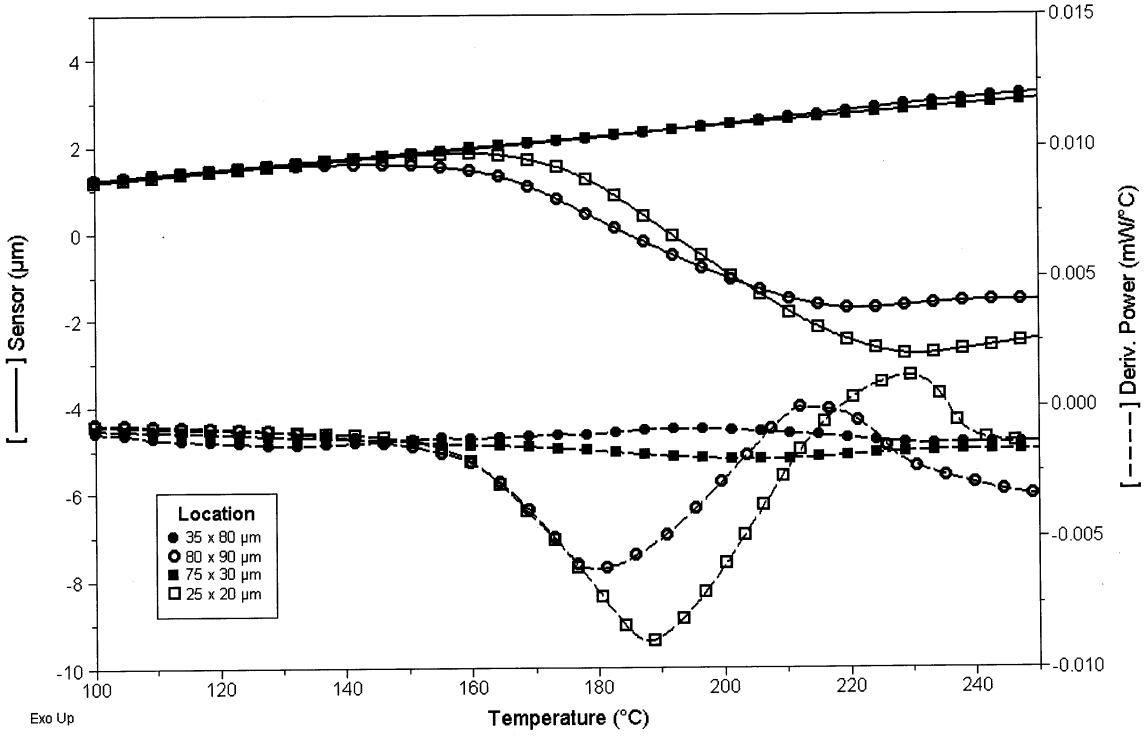

Fig. 8. Localised TMA (solid line) and DTA (broken line) curves for four different points on the images shown in Figs. 3–5.

lar polymer unzips to yield styrene monomer which is trapped and then desorped into the GC-MS.

Also under development is localised infrared spectroscopy. The sample is irradiated with the focused beam from a conventional FTIR spectrometer. When absorption of infrared radiation occurs, the thermal probe detects the local temperature increase. In this way a photothermal IR spectrum can be acquired. Fig. 12 shows the photothermal spectrum of pure paracetamol and the conventional attenuated total reflectance (ATR) spectrum of the same compound. The great advantage of this approach over conventional IR microspectrometry is that the resolution is not limited by the wavelength of the radiation being used. Calculations show that sub-micron resolution should certainly be achievable across the entire mid-IR range (Hammiche et al., 1999).

5. Conclusions

In summary, our goal in developing micro-thermal analysis is to provide a characterisation tool capable of imaging samples in a variety of modes, including those of current AFM technology, with very high resolution. It is also capable of characterising the properties of the sample in a spatially resolved way using thermal analysis. Chemical analysis is then also possible using localised desorption/pyrolysis GC-MS (or just mass spectrometry) and high resolution localised IR spectrometry. All of these capabilities have been demonstrated to work and all have now been combined in a single instrument with the exception of localised IR spectrometry. It is anticipated that this last addition will be achieved in the near future. This new instrument should then prove invaluable in many fields including pharmaceutical science.

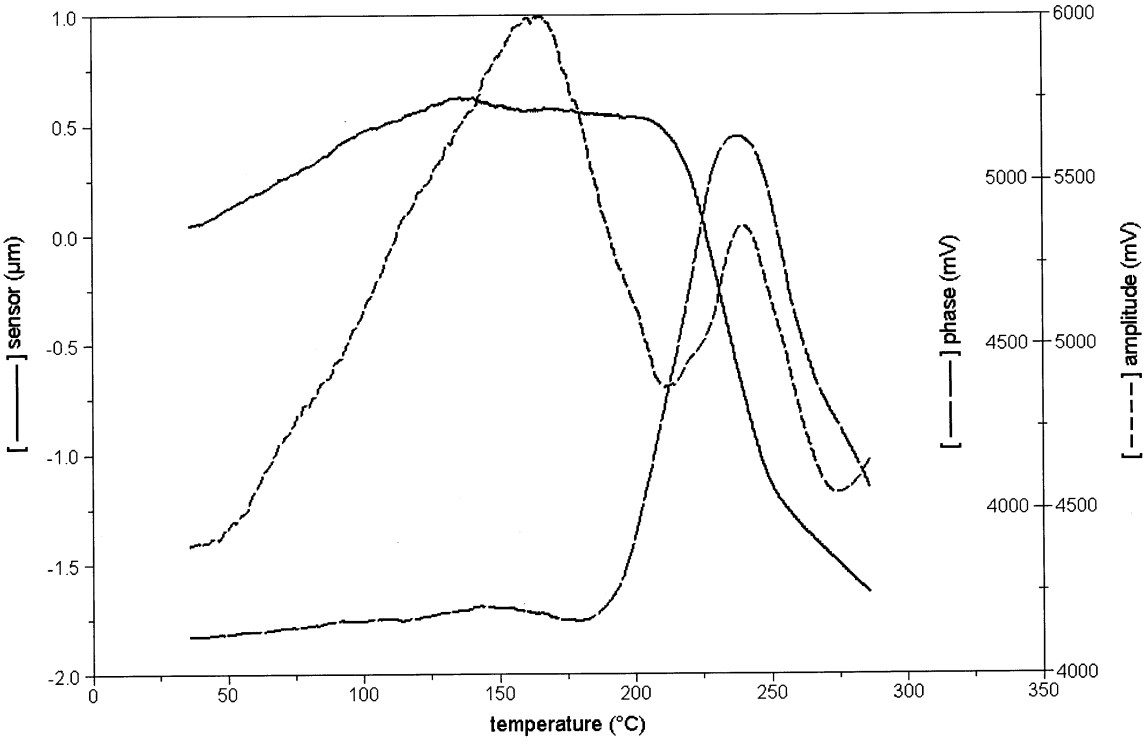

Fig. 9. Localised DMA of nylon showing the glass transition at 140°C and melting at 230°C.

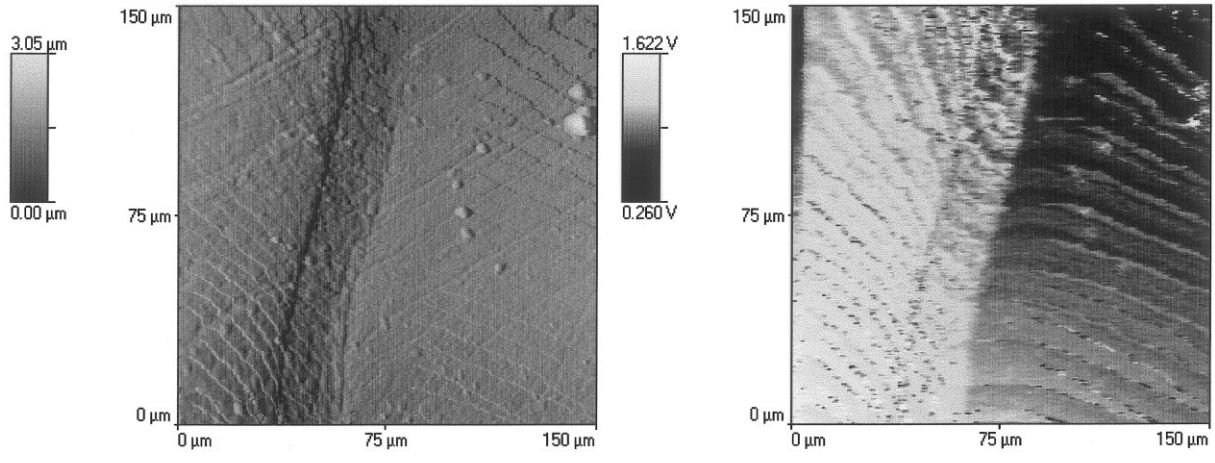

Fig. 10. Topographic (left) and thermal expansion (right) images of a polymer/metal interface. The polymer exhibits a higher thermal expansivity than the metal and shows up bright in thermal expansion image.

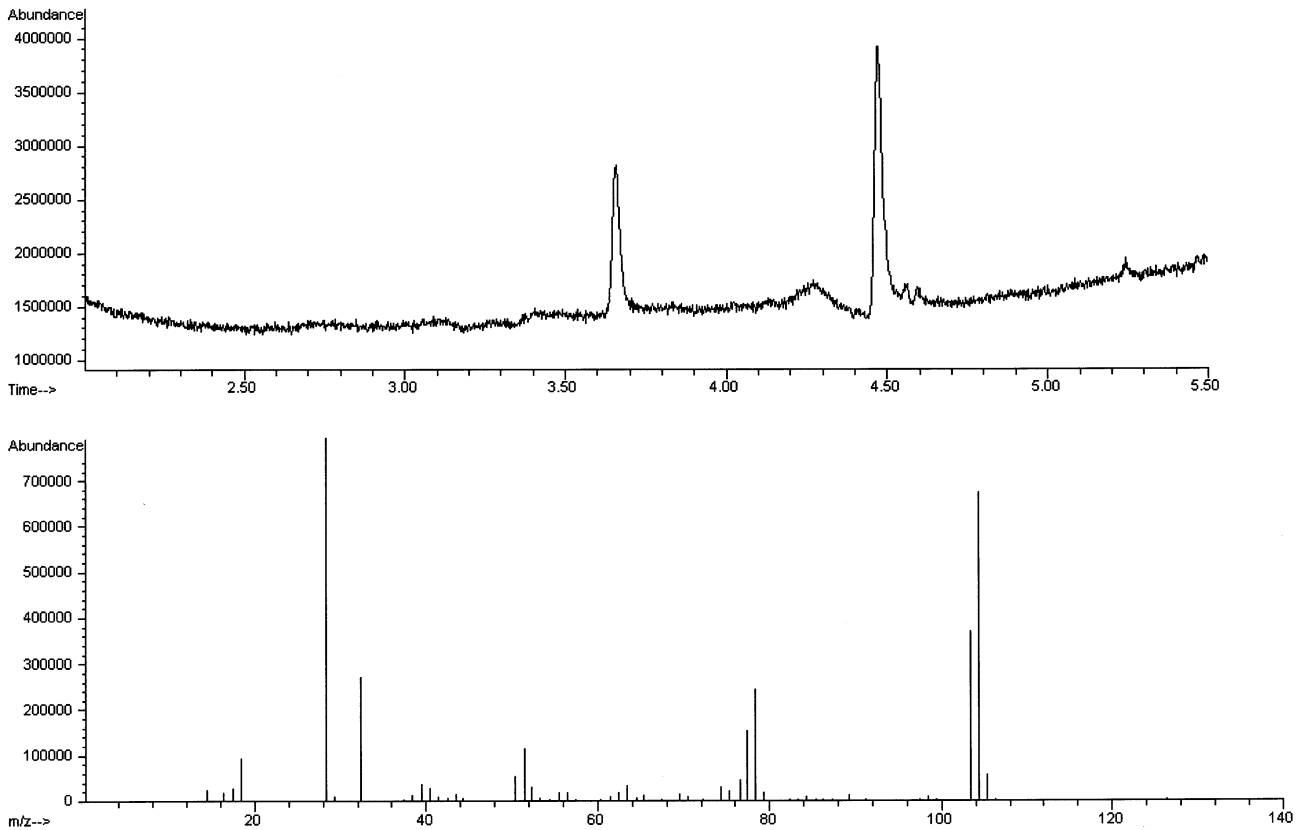

Fig. 11. Total ion chromatogram (top) from the pyrolysis of polystyrene. The peak at retention time 3.66 min is due to bleed from the GC column. The peak at 4.47 min is identified as styrene monomer (mass spectrum shown beneath) arising from the thermal degradation of the polymer.

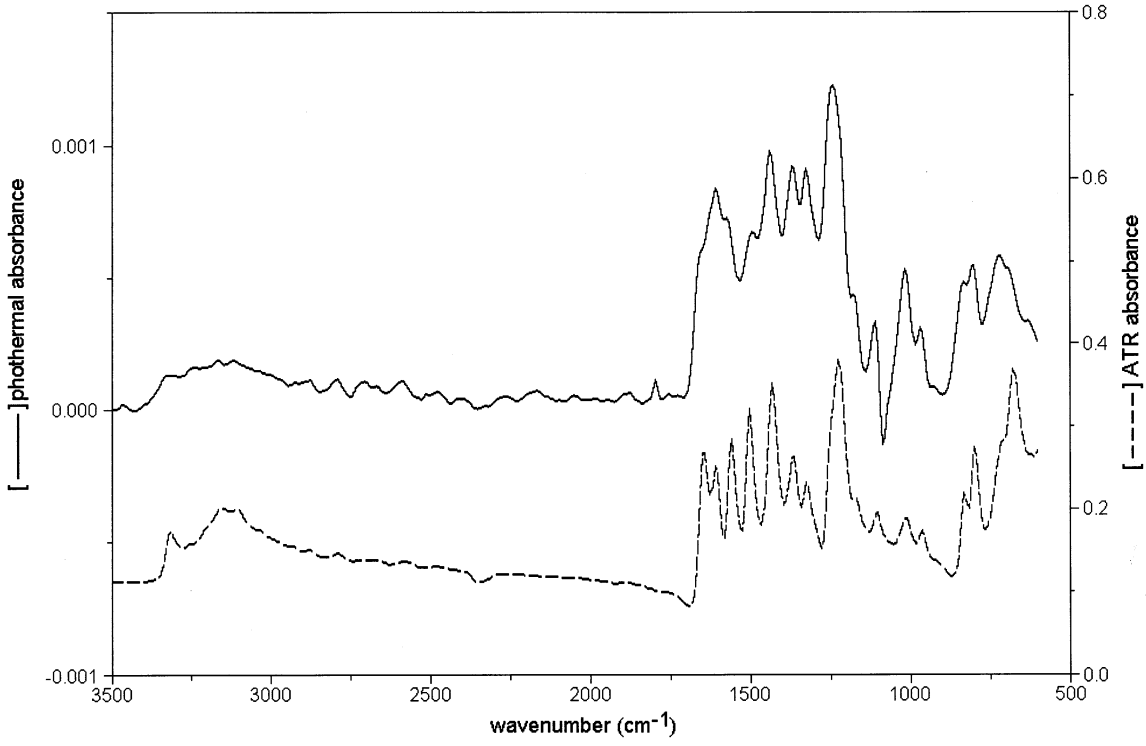

Fig. 12. Photothermal absorption spectrum of paracetamol (solid line) acquired using the thermal probe—the conventional ATR spectrum is shown (broken line) for comparison.

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