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The use of micro-thermal analysis as a means of in situ characterisation of a pharmaceutical tablet coat

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Abstract

The technique of micro-thermal analysis (MTA) has been applied to a commercial sugar coated ibuprofen tablet in order to identify the ability of the method to differentiate between the coat and the tablet core and to characterise the thermal properties of both components using localised thermal analysis. Thermal conductivity measurements in conjunction with intensity histogram analysis indicated that differentiation across the coat/core interface was possible, with a bimodal distribution of pixel intensities corresponding to thermal conductivity noted. Localised thermal analysis studies indicated that the bulk response was dominated by the incorporated ibuprofen, with a discontinuity seen at ca. 70–80°C, corresponding to the published melting point of the drug. The coat showed a discontinuity at ca. 220°C that may be reasonably ascribed to the melting process. It was also noted that the coat showed a small discontinuity at a temperature corresponding to the melting of ibuprofen. In summary, the technique was shown to be capable of identifying the core/coat interface using thermal conductivity measurements, while localised thermal analysis experiments enable the operator to perform thermal analysis experiments on the individual components in situ.

Keywords: Sugar coat; Ibuprofen; Micro-thermal analysis; Sucrose; Tablet

1. Introduction

Standard thermal analysis techniques, such as differential scanning calorimetry and thermogravimetic analysis, are widely used within the pharmaceutical sciences as a means of characterising the bulk properties of powders and, less commonly, compressed tablets. However, a difficulty associated with such techniques is their inability to characterise distinct entities within multicomponent samples, with the thermal response at any one temperature or time point representing the behaviour of the sample as a whole. A common example is the melting of multicomponent systems, whereby the thermal response of one component may influence that of a second. For example, the melting behaviour of drugs dispersed in carriers with low melting points, such as polyethylene glycol may be significantly affected by the presence of the molten polymer [1]. As pharmaceutical studies are usually performed as a means of gaining information on the structure of the material at room or storage temperature, careful interpretation is clearly required when extrapolating such melting behaviour to the solid state structure at lower temperatures. A further difficulty

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associated with standard thermal techniques is the necessity to present the sample to the instrument in a form whereby thermal conductivity is maximised, usually equating to using small (mg) samples of powdered material. This, represents a serious limitation with respect to the characterisation of whole dosage forms and requires either breakage of the dosage form or analysis of components prior to the final delivery system being assembled. There is, therefore, considerable interest in the development of methodologies whereby whole dosage forms may be characterised.

Recently, the technique of micro-thermal analysis (MTA) has been introduced as a means of characterizing the thermal properties of spatially distinct entities within multicomponent samples [2–4]. MTA combines the principles of atomic force microscopy (AFM) with those of thermal analysis. In essence, the conventional AFM tip is replaced with an ultra-miniature resistive heater. This heater is composed of a Wollaston wire bent to a fine point, with the silver coating etched away to reveal a platinum filament (Fig. 1, [5]). This filament forms a resistive heater, hence, on application of a voltage it is possible to apply a heating signal to highly specific regions of a sample. This may be utilised in two principle modes. Firstly, by suitable calibration the tip can be maintained at a specified temperature. On rastering over the sample surface, the topography is obtained in an identical manner to that found for AFM (albeit at lower resolution due to the large size of the tip). In addition, however, it is possible to measure the thermal conductivity of the sample by assessing the power required to maintain isothermal tip conditions, thereby offering a potential further means of differentiation between components. Thermal conductivity measurements may be obtained in two modes. In the simplest case, the direct current (dc) image is obtained whereby the conductivity is, at least in theory, a simple reflection of the heat loss from the tip into the sample. In fact, the heating programme is usually applied in alternating mode using frequencies in the kHz region in order to improve the signal-to-noise ratio. The dc signal is then calculated from the Fourier transform of the alternating response in a manner analogous to that used for modulated temperature DSC. In addition, it is possible to use an oscillating heating signal whereby the sample may be interrogated to differing depths depending on the frequency used in a manner entirely analogous to that used within the photothermal field. Work is currently ongoing in order to examine the use of alternating current (ac) imaging in terms of amplitude and phase as a means not only of improving contrast but also for the measurement of both thermal conductivity and heat capacity [6–8].

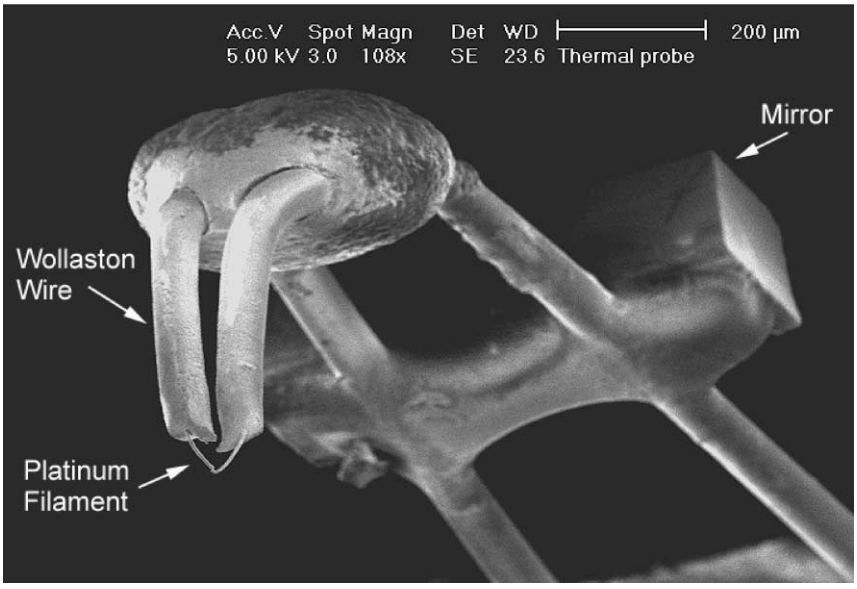


Fig. 1. Scanning electron micrograph of the micro-thermal analysis tip (reproduced from [5]).

The technique may also be used to characterise thermal transitions in highly specific regions of the sample (of the order of a few cubic micrometres), a method known as localised thermal analysis (LTA). The tip is placed on a location on the sample surface and a heating signal applied at a specified rate, with either the temperature (via the voltage) or the probe position measured as a function of temperature. In this manner, the instrument may perform scanning thermal analysis on specific regions of the sample. The heating rates used tend to be high (in the region of 10°C/s) as the response of the tip to the increasing voltage is effectively instantaneous, unlike the case for conventional DSC where the thermal conductivity of the furnace is a limiting factor to the use of very high heating rates. In addition, the high scanning speeds are necessary in order to minimise heat dissemination through the sample. In practice, the resolution using the technique in topographic mode tends to be in the order of 100–1000 nm, which is inferior to conventional AFM due to the relatively bulky tip used, while the minimum scale of scrutiny for the heat ramping studies tends to be of the order of 20 μm.

The ability to characterise distinct regions of a single sample has attracted considerable interest within the polymer sciences [2–4,9,10] and is beginning to attract similar interest within the pharmaceutical arena [11–14], although the technique is still in its infancy within the latter field. In this investigation, we provide a proof of concept study whereby the use of the technique is investigated for the in situ study of a coated tablet system. Both polymeric and sugar coats have been extensively studied within the pharmaceutical field [15–17]. However, it has not been previously possible to examine the thermal behaviour of such coats when on a tablet surface, hence these systems represent a potentially highly interesting application for micro-thermal analysis within the pharmaceutical field. Due to the novelty of this approach, a simple system was chosen, consisting of a sugar-coated tablet. In brief, these coats consist of a number of layers of a solution of sucrose and a gum, such as gelatin or a starch derivative, with drying taking place between each application until a well rounded coat is obtained which is then polished. Sugar coats are invariably thicker than polymer film coats and hence for this application may be expected to be easier to study than the latter. In this manner, the potential strengths and weaknesses of the approach may be identified with a view to applying these findings to a wider range of coated pharmaceutical systems.

2. Materials and methods

The sample used was a commercially available sugar-coated ibuprofen tablet (Sainsburys, UK). In order to expose the interior matrix, the tablet was broken and the surface was filed down using dry ''wet and dry paper''; preliminary studies indicated that a reasonably flat surface was necessary in order for the sample to fall within the z-direction measurement range of the instrument (8–10 μm). Topography and dc thermal images were recorded simultaneously using a 2990 Micro-Thermal Analyzer (TA Instruments, Leatherhead UK). The thermal probe was operated at a tip temperature of 60°C in dc mode with a superimposed modulation amplitude of 5°C and a frequency of 2 kHz (see above). The scan rate used was 50 μm/s over a range of 100 μm × 100 μm. LTA studies were conducted using a scanning rate of 10°C/s. Temperature calibration was performed using a previously established method [13] whereby Nylon 6 (Goodfellows) for the high temperature calibrant, and the recorded onset of thermal feedback at room temperature was used as the other known temperature.

3. Results and discussion

Initial studies were focused on the topography and dc thermal conductivity over the interface between the sugar coat and the bulk tablet in order to establish the most appropriate parameters for distinguishing between the two phases. It should be emphasised that a further reason for the choice of these tablets as models was that the interface was easily located using the optical microscopy facility that accompanies the instrument for the purpose of identifying suitable regions for more detailed analysis.

In the conventional AFM topography image, the border between the two constituents was difficult to discern (Fig. 2). The overriding features in the topography are the grooves caused by the filing procedure used in the exposure of the surface. However, the dc thermal image (averaged from the response to a 2 kHz

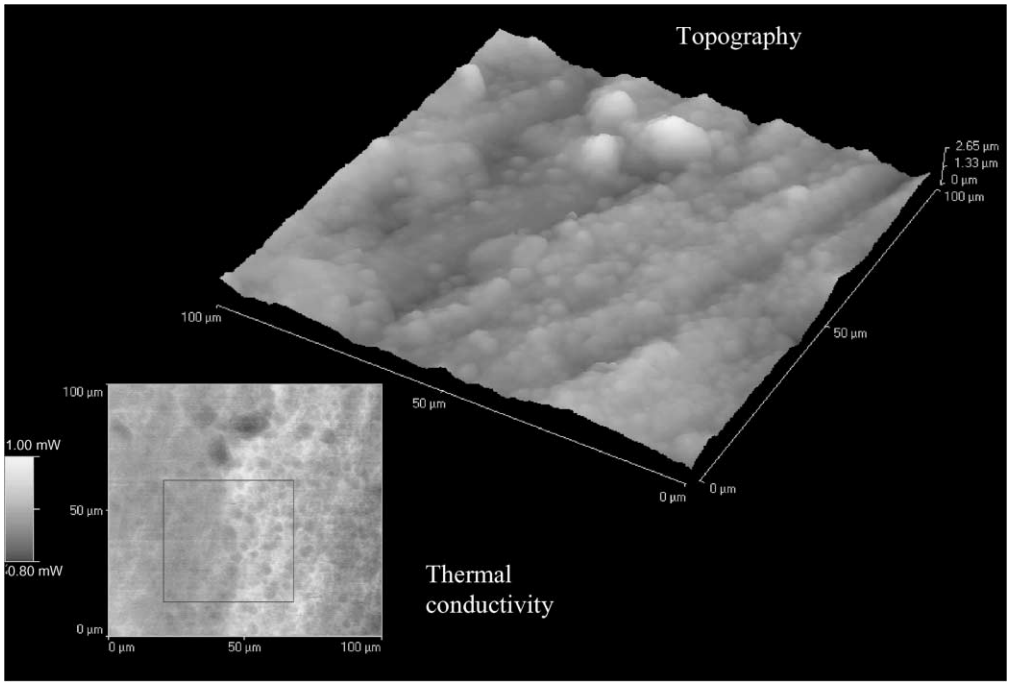


Fig. 2. The 100 µm × 100 µm topographical and thermal conductivity images across the tablet interface. The coating is on the left hand side of the image and the core on the right. Inset into the conductivity image is a 40 µm × 40 µm square, which indicates the area selected for the images shown in Fig. 3(a).

modulated signal) gave a reasonable differentiation across the interface. It should be emphasised that differentiation between components using thermal conductivity has not proved universally successful, with systems such as HPMC-ibuprofen tablets showing no clear distinction between different particles [11]. In theory, the dc power in the probe (P_s^{dc}) required to raise the temperature to the desired value as determined by the thermal conductivity of the sample is given by [18]

$$P_s^{dc} = \frac{3\pi^2}{8}\kappa d(T_s^{dc} - T_0) \quad (1)$$

where κ is the thermal conductivity of the sample, d the diameter of the sample (assuming the sample to be a disk) and T_s^{dc} the temperature at which the sample is to be maintained and T_0 is the reference (effectively ambient) temperature. However, the power in the probe required to raise the temperature and maintain it at the required value is not solely dependent on the thermal conductivity, but is dependent on a number of other factors, the most important of which is the contact area between the probe and the surface. This varies according to the topography of the surface proximal to the probe tip at any point in the scan. Therefore, in practice, the surface topography may have a profound effect on the thermal conductivity signal. This phenomenon is well recognised within the field and essentially results in peaks appearing as low conductivity (dark) areas and troughs as high conductivity (bright) areas. This is because at a peak the effective sample area is relatively low and in a hole or trough it is relatively high. This has proved to be a major difficulty within the field, with the differences in topography dominating the conductivity response. It is, therefore, of interest that in this case the conductivity differences are not a simple reflection of the surface discontinuities. A relatively simple strategy for differentiating between topography-induced contrast and genuine thermal conductivity-based contrast and for simplifying thermal images is described below.

In order to further explore the possibility of differentiating between the phases using thermal conductivity the pixel intensity histogram was obtained. This

data handling approach has been developed recently by Grandy et al. [19] and involves measuring the distribution of conductivity (or topography) pixel intensity for a given image window. Fig. 3a shows the thermal conductivity as before (this time taking a more specific window at the interface). Also shown (inset) are the pixel intensity histograms for the topography and conductivity. It is clear that there is a monomodal height distribution, reflecting the fact that there is no systematic topographic differentiation between phases. The conductivity, however, shows a clear bimodal distribution, adding strength to the argument that the conductivity really is differentiating between the phases and is not a simple reflection of topography. This qualitative approach can be taken a stage further by curve-fitting to the thermal conductivity data set. The results of this are shown in Fig. 3b. It can be seen that two overlapping Gaussian

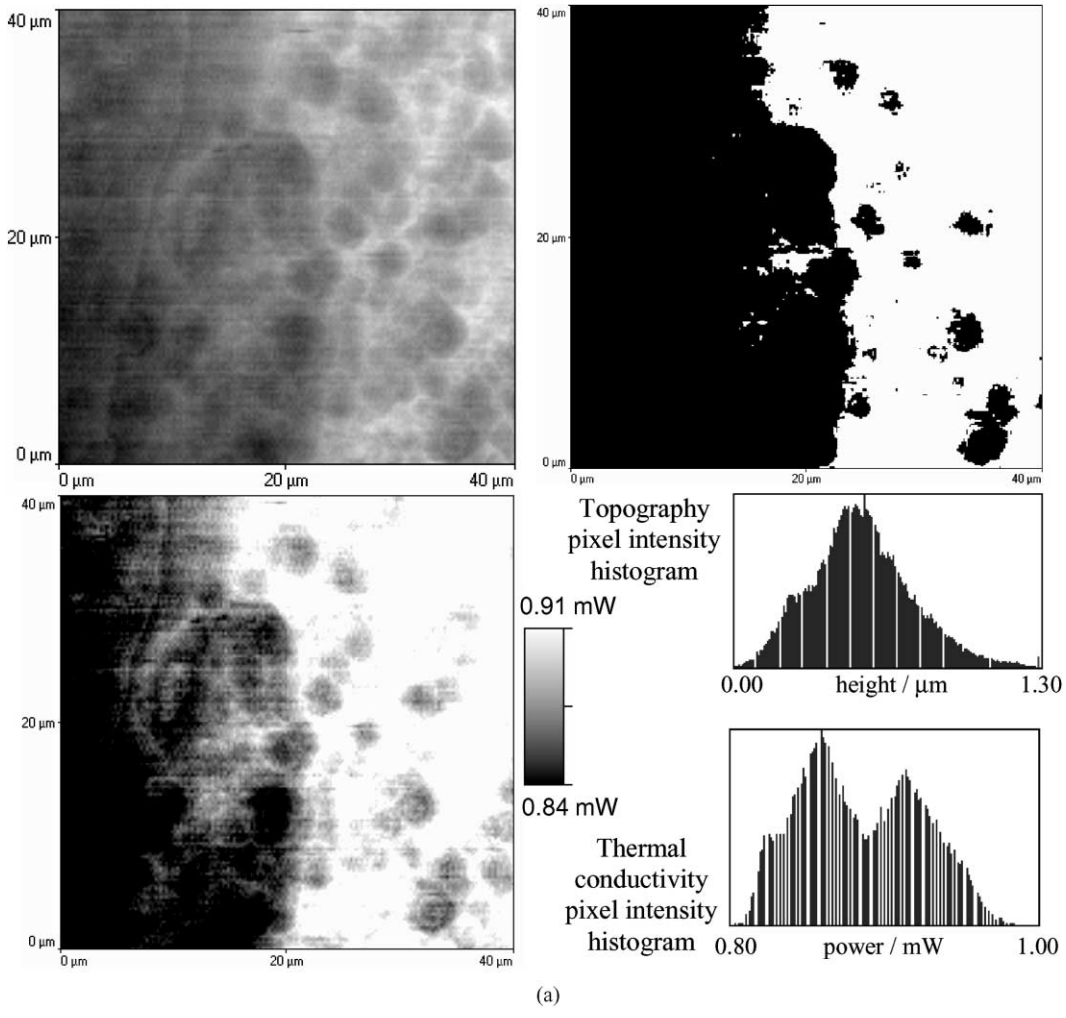
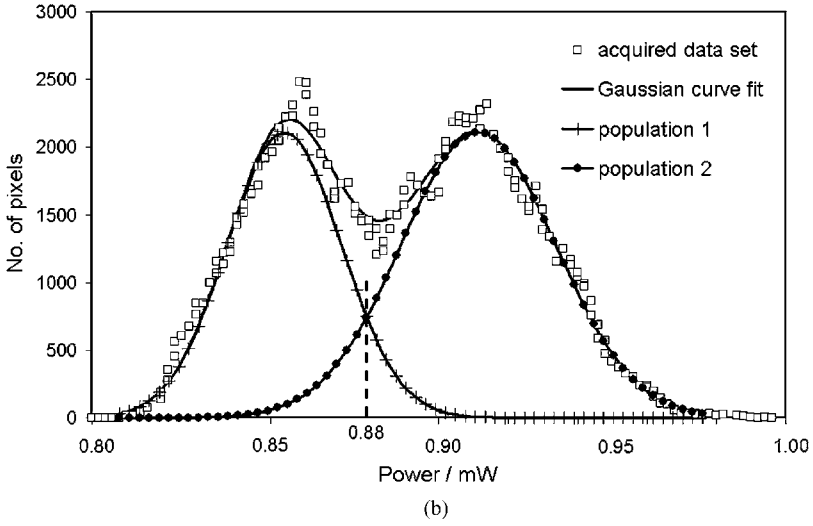


Fig. 3. (a) Top left: 40 µm × 40 µm full greyscale thermal conductivity image and (bottom right) its pixel intensity histogram (*y* axis: arbitrary units; *x*-axis: probe power consumption) and the associated topographic histogram (*y* axis: arbitrary units; *x*-axis: height). Top right: conductivity image shaded black or white according to the imposition of a single intermodal decision boundary at 0.88 mW, derived from the results of Gaussian curve fitting as shown in (b) (black < 0.88 mW < white). At the bottom left is the same conductivity image with all the ''uncertain'' pixels in the overlapping region (0.84–0.91 mW) shown in greyscale (black < 0.84 mW < grey < 0.91 mW < white). (b) Gaussian curve fitting.



(b)

Fig. 3. (*Continued*).

distributions are required to give a reasonable fit to the data. We can now impose an intermodal decision boundary at the power value at which the two populations overlap (0.88 mW). This cut-off value has been applied to the greyscale conductivity image on the left of Fig. 3a to produce the simplified two-colour image on the right. Here, all the pixels which have a value below 0.88 mW are black and all those above it are white. In the region where the two Gaussian distributions overlap, we cannot be sure which phase a particular pixel belongs to, but here we are assigning each pixel in the image to the phase it most probably represents; black for relatively low conductivity and white for relatively high conductivity. In this manner, we have enhanced the differentiation between phases present in a thermal conductivity image. There is apparently a significant amount of the black, low thermal conductivity, phase (the coating) present as islands in the higher thermal conductivity, white, drug phase. This could be a physical result of the sample preparation process or simply a consequence of incorrect assignation of pixels (i.e. they belong to the low-conductivity tail in the conductivity distribution of the drug). Conversely, there is only a small area of the higher conductivity phase present in the coating. This analysis procedure could be taken a stage further by producing an image that was a linear greyscale over the range of overlapping values of conductivity (approximately 0.84–0.91 mW) and, respectively, black and white above and below this range). The black and white regions would then represent areas in which there was 100% certainty as to the identity of the phase at that location and the greyscale pixels would represent the areas of uncertainty. Moreover, the intensity of the greyscale at these "uncertain" locations would be indicative of the probability of a particular pixel belonging to one population or the other. The linear greyscale intensity will, however, only be an approximation of the probability, because the probability distribution itself will not be linear. This process has been carried out to produce the third image in Fig. 3a (bottom left). It can be seen that there is now a somewhat higher concentration (darker grey) of coating in the drug phase and a higher, but still modest, concentration of the (lighter grey) drug phase present in the coating, close to the interface. More sophisticated image processing may be envisaged, based on a more accurate probability distribution, from which it will be possible to estimate the numerical probability of each pixel belonging to one phase or the other.

To further explore the abilities of the technique to characterise the bulk and surface phases, localised thermal analysis was performed on the separate regions identified by the derived thermal image. More specifically, micro-thermomechanical (micro-TMA) experiments were performed on the sample surface, where the displacement of the tip is recorded as a

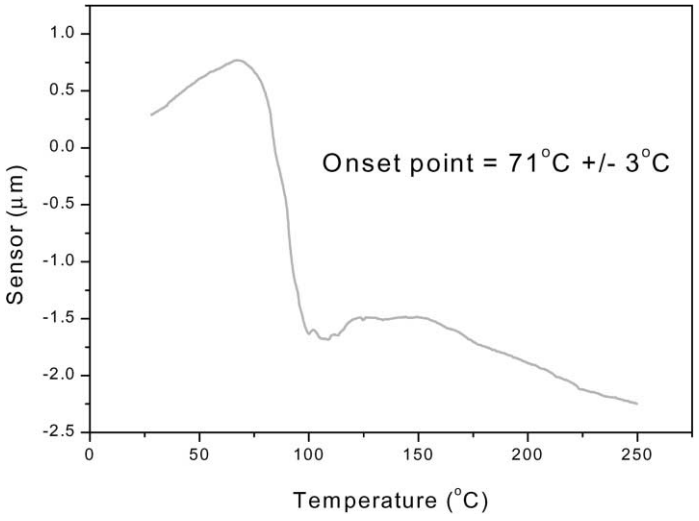


Fig. 4. Localised thermal analysis (micro-TMA) experiments for the tablet core.

function of temperature. The LTA response of the right hand side of the interface, corresponding to bulk tablet core, is shown in Fig. 4. An onset of $71 \pm 3^{\circ}C$ for the melting transition was derived from 10 experiments. This response can be attributed to the melting of ibuprofen (melting point 75–77°C). It is well recognised that MTA is a semi-quantitative technique, hence such imprecisions with respect to published values are not unusual. Typically a tablet formulation will contain the drug, diluents, lubricants and disintegrants, hence, the simplicity of the response over the temperature range studied is in many ways surprising. However, the dose of the drug (200 mg) in relation to the tablet weight (450 mg total) was relatively high, hence the melting of the ibuprofen dominate the LTA response over the temperature range studied, particularly in view of the low melting point of this material.

The result shown in Fig. 5a is a micro-TMA experiment conducted with the thermal probe placed on the left-hand side of the interface shown in Fig. 2, corresponding to the sugar coat. The sensor signal relates to the deflection of the probe in the *z*-direction (the tip will describe an arc) as the tip is heated on the surface of the sample. Using the onset of this displacement gave an observed melting point of $205 \pm 7^{\circ}C$ (the error shows the variance for 10 experiments run at different locations on the left hand side of the interface). This onset temperature lies close to the melting point of sucrose (185–187°C). However, the nature of the coat is in this case unspecified and indeed will itself be multilayered, although the resolution of the instrument is not sufficient at present to differentiate between these layers.

It was noted that a small discontinuity was apparent in the thermal response of the sugar coat (Fig. 5b); this response was found to be present in all the experimental runs and was, therefore, considered to be a real effect. Examination of the derivative of the response (Fig. 5c) indicates that the temperature at which this occurred corresponded well to the melting point of ibuprofen. We believe that this effect is due to contamination of the sugar coat with bulk material during the sanding down of the surface and less traumatic methods for sample preparation, such as the use of glass knives are under investigation. It is also possible (albeit less likely) that the material is a genuine contaminant, possibly generated by partial melting of the ibuprofen during the coating process. We highlight this effect as potential means of identifying small levels of contaminants using the technique. The small discontinuity could not have resulted from contamination of the probe from the previous micro-TMA experiments conducted on the tablet matrix. In between each run, the tip temperature was raised and held at 450°C for a number of seconds in order to pyrolise any contaminating material. This process was conducted after lifting the tip away from the surface and is a standard cleaning routine [2].

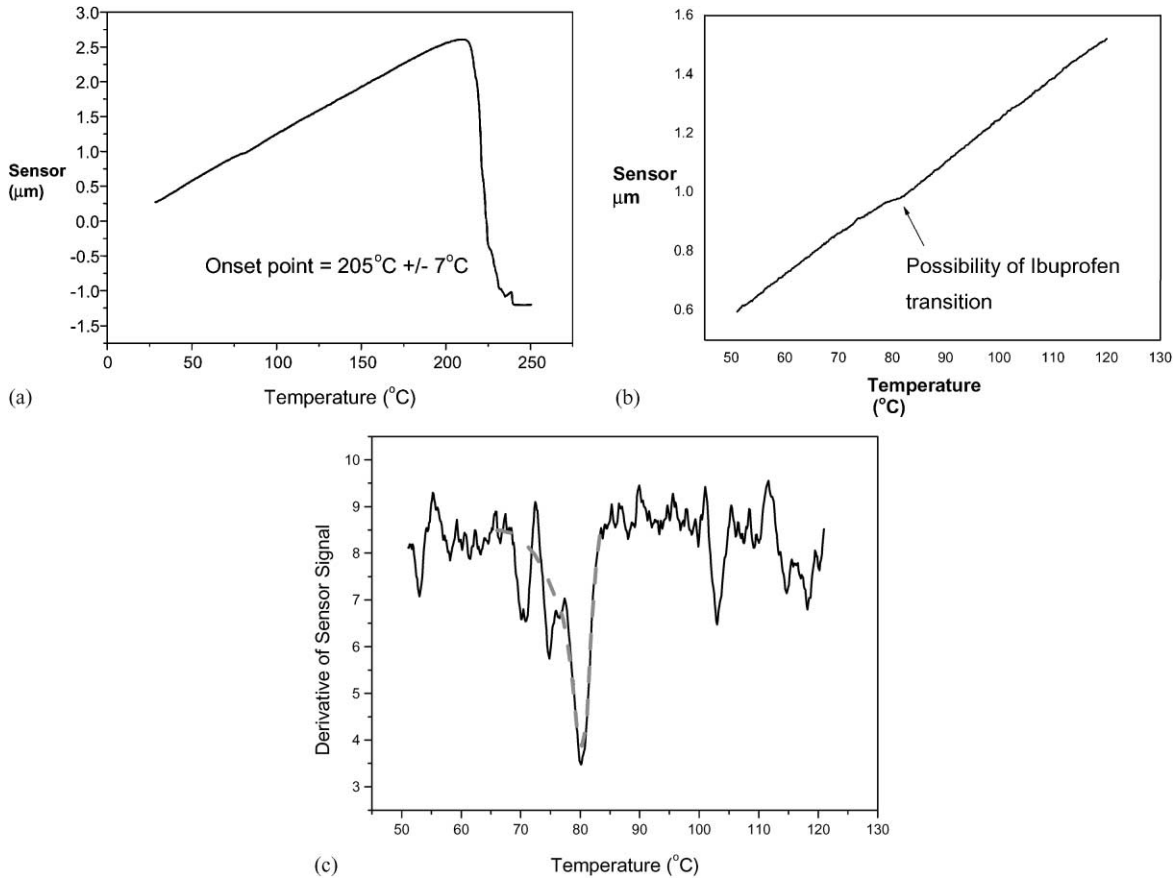


Fig. 5. (a) Localised thermal analysis (micro-TMA) experiments for the sugar coat; (b) detail of same; and (c) derivative signal of same.

4. Conclusion

The study has highlighted the strengths and weaknesses of using micro-thermal analysis as a means of studying sugar coats on tablet surfaces. It is possible to discriminate between the two phases in terms of their thermal conductivity, particularly by using pixel intensity histogram analysis as a means of discriminating between conductivity and topographical effects. Localised thermal analysis again allows discrimination between different phases, with thermal responses seen that corresponded to the melting of the coat and core.

Overall, there do appear to be interesting possibilities for the technique as a means of characterising tablet coats. Clearly, the majority of pharmaceutical systems are polymer film rather than sugar coated. However, the resolution of the technique (down to the micron level and below) may prove to be sufficient to examine these thinner coats in the same manner and to identify events, such as softening and glass transitions and mechanical properties. This will then allow a greater understanding of the behaviour of these films in the practical context of being located on the surface of compressed dosage forms.

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