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An investigation into the use of micro-thermal analysis for the solid state characterisation of an HPMC tablet formulation

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Abstract

The use of micro-thermal analysis (μTA™) as a novel means of differentiating between components in a model tablet formulation is described. This technique involves a modification of atomic force microscopy (AFM) such that the standard AFM tip is replaced with a Wollaston wire, thereby allowing the probe to act as a thermistor and temperature probe. Consequently it is possible to map not only the topology but also the thermal conductivity of the sample. Furthermore, it is possible to apply a heating signal to the material and thereby to perform thermal analysis on highly localised regions of the sample. Compacts were prepared comprising ibuprofen, HPMC E4M prem and 1:1 mixes of the two components and analysed using a μTA™ micro-thermal analyser. The surface topology and conductivity images of the three systems are reported. In addition, the ability of the technique to perform thermal analysis on highly specific regions of the sample is described. The method was able to differentiate between the components of the sample on the basis of micro-thermomechanical experiments. The implications of the use of the technique for the study of pharmaceutical tablets is discussed.

Keywords: Atomic force microscopy; Micro-thermal analysis; Hydroxypropyl methylcellulose; Ibuprofen

1. Introduction

The solid state characterisation of individual components within compressed tablet formulations remains a persistent challenge in dosage form development. In particular it has proved difficult to identify separate phases and to map their spatial distribution within a compressed system. Such information may be of considerable use in understanding a range of processing and product performance characteristics such as the physical state of tablet components post compression, drug release profiles and storage instability.

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In this investigation we examine the use of micro-thermal analysis (μTA™) as a novel means of identifying components in a binary tablet system. This technique is a recently introduced thermoanalytical method which combines the principles of atomic force microscopy (AFM) with those of thermal analysis. The innovation of the μTA™ system lies with the modification of the probe. The tip of the conventional AFM probe is replaced by a Wollaston wire arrangement, this being a 5 μm diameter platinum filament coated with silver. The wire is bent to a fine point and the silver etched away to reveal the platinum filament Hammiche et al., 1996; Lever and Price, 1998. It is possible to obtain topological information using this probe in the same manner as standard contact mode AFM, albeit at present with lower resolution. However, during operation the thermal probe forms part of an electrical bridge circuit, allowing the tip to record the resistance of the platinum filament. Consequently, it is possible to apply a voltage to the Wollaston wire such that isothermal conditions are maintained in the sample area immediately adjacent to the probe. In a typical experiment the tip is rastered over the test surface following the normal AFM contact mode to build up a topological image. Simultaneously, the power required to maintain the probe tip at constant temperature as it passes over the surface is recorded. This signal is a function of the surface thermal conductivity which is therefore mapped alongside the topology. The temperature of the probe may also be modulated in a sinusoidal manner around a particular value in a similar fashion as modulated temperature differential scanning calorimetry (MTDSC) McPhillips et al., 1999; Price et al., 1998. As with MTDSC, the response to the temperature modulation may be examined in terms of the phase and amplitude for the output sinusoidal signal to give the AC phase thermal image and the AC amplitude thermal image, respectively Reading, 1993.

The sample preparation for this simultaneous topography measurement and thermal imaging is relatively straightforward. No specialised coating procedures are required and the solid material may simply be placed on the dedicated stage. Alternatively the whole microscope may be placed on the surface of the material under study. The maximum scan range is a 100 μm by a 100 μm square, while the resolution is, at present, usually in the region of 1 μm. Clearly, this resolution is far inferior to that expected for conventional AFM, this being a result of the size of the probes available. However, higher resolutions have been described and the design of new probes is expected to improve this figure still further. The maximum dynamic range in the Z-axis is 10 μm Reading et al., 1998. Despite this value being higher than found for conventional AFM, the sample must be relatively smooth with no surface features including sudden steps of more than 10 μm, again as a result of the larger probe size used.

Once the topographic and the thermal images are recorded it is possible to investigate different domains. These may be identified in the DC image by areas of contrasting thermal conductivity. For example, Reading et al., 1998 have successfully identified different domains in pre-formed phase separated polymethylmethacrylate–polycarbonate blends. This approach depends on the thermal conductivity between components being sufficiently high so as to allow differentiation.

Localised thermal analysis experiments are possible on these domains by locating the probe at a specific point on the sample and applying a temperature ramp. The heating rates are high (up to 25°C/s) due to the size of the heating element being large with respect to the volume of sample under scrutiny. This volume will depend on the heat transfer of the sample and the temperature program but is typically in the order of 10 μm^3 Reading, 1993. For the present work we report micro-thermomechanical (micro-TMA) experiments on the surface of the compacts. In this mode the displacement of the tip is recorded as a function of temperature. When the sample begins to melt or soften the applied load causes the downward deflection of the cantilever. The output from such an experiment is the displacement or sensor signal in μm against temperature. Secondly, thermal events may be identified by changes in heat flow in a manner analogous to conventional DSC. However, an important difference is that in this case a modulated rather than linear signal is applied, hence the approach has

been termed micro-modulated differential thermal analysis (Micro-MDTA). An oscillating signal is used for three reasons. Firstly, the modulation improves the signal-to-noise ratio for the same reasons as those described for MTDSC McPhillips et al., 1999. Secondly, using a temperature modulation focuses the thermal signal to the close vicinity of the probe. This is further aided by the use of fast heating rates which are typically two orders of magnitude greater than those used in conventional thermal methods, thereby reducing extensive thermal diffusivity in relation to the timescale of the experiment. Thirdly, the use of a modulated signal is intrinsic to the use of the technique in thermal scanning mode as the instrument measures the power required to maintain constant modulation, which is expressed as a derivative against temperature.

Given that the use of the technique is in its infancy, there are only a limited number of publications available in the peer reviewed literature thus far, these being exclusively concerned with polymeric systems Royall et al., 1998; Reading, 1993; Lever and Price, 1998. However, these studies have indicated that the technique may identify different components within complex systems on a microscopic basis either by differences in thermal conductivity or responses to localised temperature ramping signals. It is therefore logical to suggest that the technique may be capable of identifying and mapping different components within a compressed tablet formulation, based on similar principles. In this study, we examine the ability of the technique to identify the components of a model binary formulation containing ibuprofen and HPMC E4M Prem grade. This

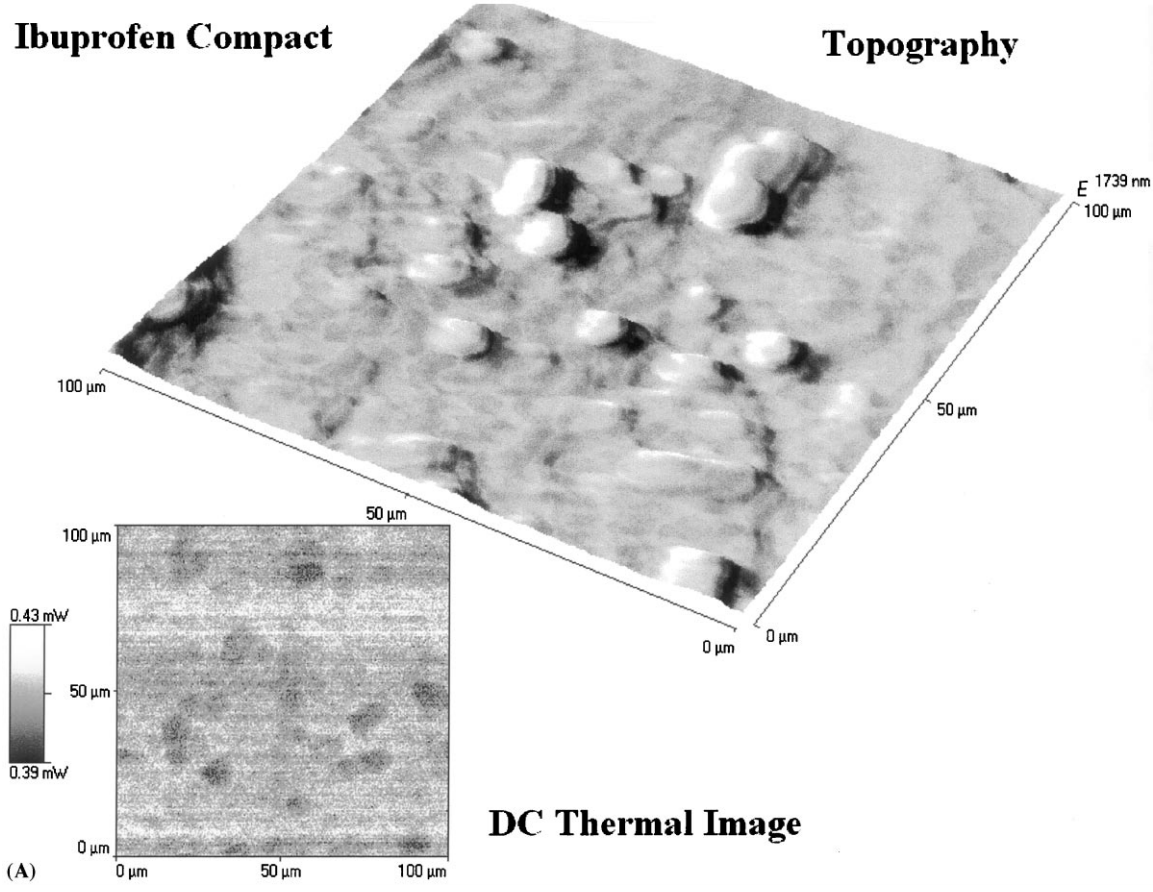

Fig. 1. Micro-thermal analysis images of (a) ibuprofen and (b) HPMC alone, showing topography and thermal conductivity.

approach has been adopted in order develop our understanding of the strengths and weaknesses of the approach in the context of pharmaceutical systems.

2. Materials and methods

2.1. Preparation of compacts

Compacts of ibuprofen (Sigma, 99.9% purity) were prepared in an infrared sample press. Four hundred milligrams of the sample were weighed and the powder poured into an 8 mm die. A circular steel rod of the same dimensions as the die bore was inserted into the assembly. A pressure of 2 tons was applied for 1 min and the resulting compacts removed and used immediately. Compacts of HPMC (E4M Prem, Dow Chemical Company) and 1:1 mixes of the two components were prepared in the same manner.

2.2. Micro-thermal analysis studies

A TA Instruments μTA 2990 Micro-Thermal Analyzer was used throughout the study. The system was calibrated for temperature and displacement (in X, Y, and Z axis) according to the manufacturers standard procedure Reading et al., 1998. Tablet samples were mounted onto metal sample studs and located on an $X-Y$ stage to aid sample alignment. Standard topography and thermal conductivity images were obtained in contact mode at 400 μm/s scan rate with the probe held

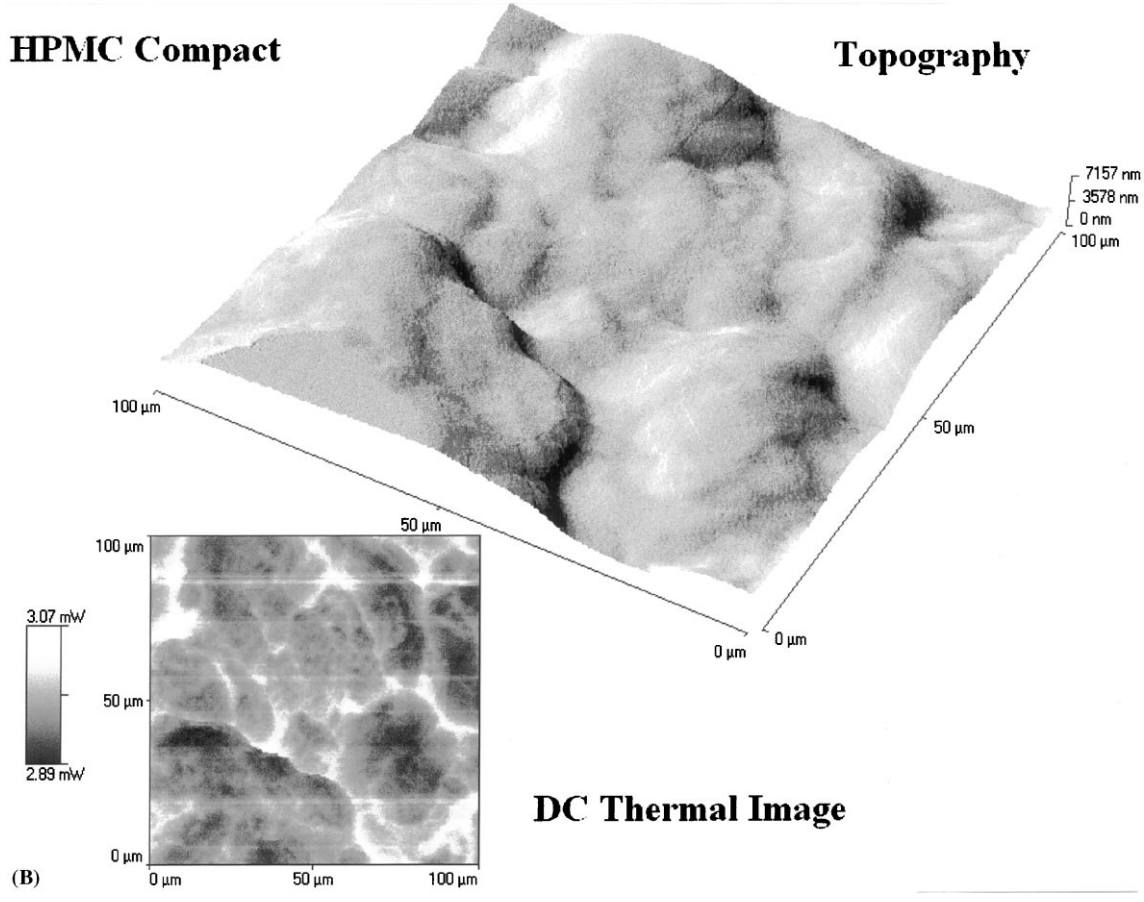

Fig. 1. (*Continued*)

isothermally at 40°C. Images have been optimised using standard AFM image analysis principles Reading et al., 1998. Local thermal analysis data were obtained at 10°C/s between room temperature and 400°C with a modulation frequency of 5 kHz and a modulation amplitude of 5°C.

3. Results and discussion

3.1. Ibuprofen and HPMC alone

Fig. 1a and b shows the topography and thermal conductivity images of ibuprofen and HPMC alone. Probe shape and size is a significant factor determining the spatial resolution with which an AFM probe is able to image the surface topography of a sample. The thermal conductivity represents a novel method of imaging pharmaceutical samples but suffers from two drawbacks which have been discussed in more detail by Royall et al., 1998. In brief, there is not yet a suitable calibration method available for surface thermal conductivity, hence the technique is currently semi-quantitative (but may be highly effective as a means of phase differentiation Lever and Price, 1998). Secondly, comparison of the topographical and thermal conductivity images indicates that the latter is influenced by the former. This is due to changes in heat flow resulting from changes in topography; when a probe is in a trough it is primarily surrounded by the sample, while when the probe is on a peak it is primarily surrounded by air. Consequently, the measured thermal conductivity increases and decreases, respectively, even when a single phase is present. It is therefore highly instructive to compare the topographic and conductivity images, as these allow changes in the conductivity as a result of topology to be identified. This appears to be the case for these samples, with both materials showing a largely smooth and uniform surface in terms of both topography and conductivity. Areas of differing conductivity may be related to physical surface imperfections.

Fig. 2a and b show the localised thermal analysis data for ibuprofen and HPMC, with repeat

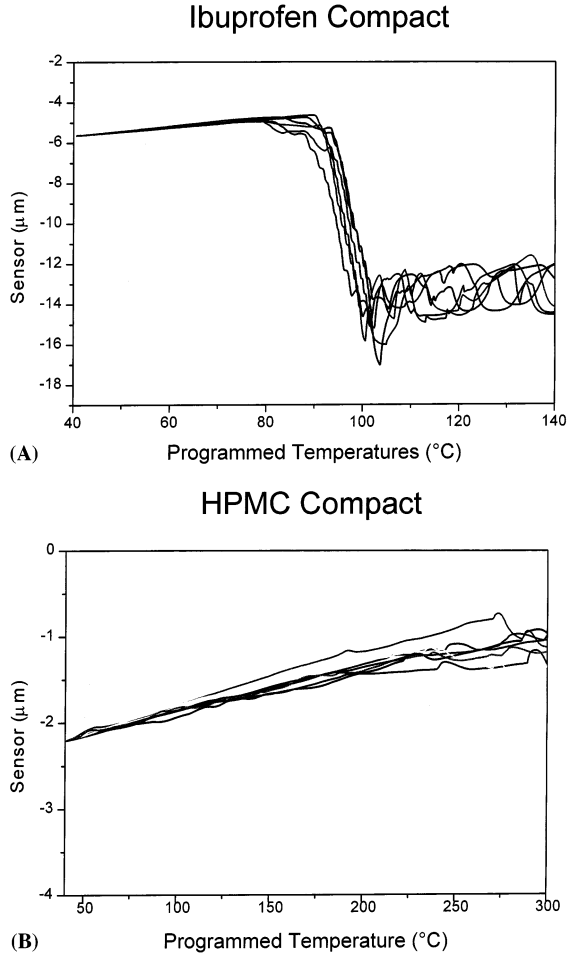

Fig. 2. Localised thermal analysis for compacts of (a) ibuprofen and (b) HPMC.

studies over different areas of the tablet surface shown. The ibuprofen compact shows the melting of the ibuprofen in contact with the probe, seen by a discontinuity in the sensor signal. The sensor signal relates to the deflection of the probe in the z-plane as the tip is heated on the surface of the sample. Using the onset of this displacement gave an observed melting point of 85 ± 3°C, which is in satisfactory agreement with the results obtained using conventional DSC. The HPMC, however, shows no clear discontinuity, although there does appear to be some softening at higher temperatures. A recent study by TA Instruments, 1999 has highlighted the difficulties associated with measuring the *Tg* for this material due to the

polymer showing only a small change in heat capacity.

It should be emphasised that the nature of processes such as melting or glass transition measurements needs to be considered in the context of such a narrow spatial resolution. Conventional DSC involves the use of a small sample inserted into a large furnace which yields a specimen average response. The apparatus used here involves the application of a small localised heater to a sample which is, in relative terms, infinitely large. Consequently, the 'melting' of a sample using micro-TA may not necessarily be directly comparable to that seen using conventional thermal techniques. This also raises issues of calibration which have not yet been fully resolved. A significant difference between micro-TA and 'macro-TA' studies is that with the former the sample weight is unknown and so quantitative calorimetric measurements are not possible. Subsequent topographical imaging following localised thermal analysis gives an indication of the volume of material that has undergone the thermal event Reading, 1993. While the technique is currently semi-quantitative in this respect it does provide a means to producing response signatures of the various phases present. Given all of the above, the apparatus is best considered as a means of obtaining highly localised relative transition temperatures.

Fig. 3 shows the topographic and thermal conductivity images of the ibuprofen-HPMC mixes. It did not prove possible to differentiate between these two components on the basis of thermal conductivity, with the differences again being directly related to the topography. However, by selecting areas of the compact surface it is possible to perform localised thermal analysis. This is

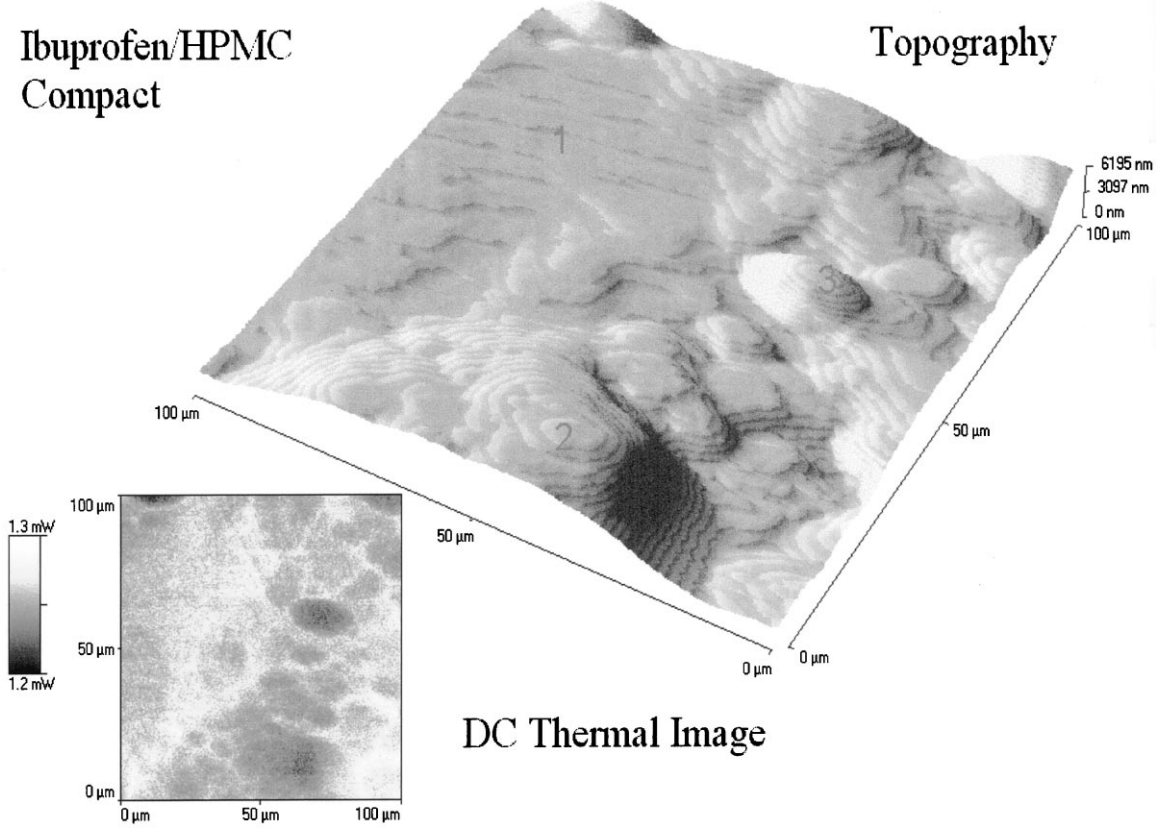

Fig. 3. Topographic and thermal conductivity image of ibuprofen–HPMC compacts.

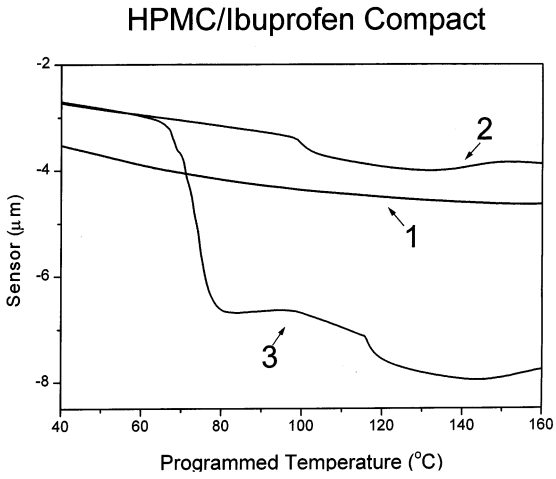

Fig. 4. Local thermal analysis for the areas highlighted in Fig. 3.

shown in Fig. 4 for the three areas highlighted on Fig. 3. It can be clearly seen that the areas correspond to different components of the compact, with the sharp melting point of the ibuprofen being seen in clear contrast to the largely featureless responses of the HPMC areas.

4. Conclusions

The study has highlighted some of the strengths and weaknesses of the μTA approach with reference to the study of pharmaceutical compacts. The technique has been shown to be capable of resolving the constituents of the tablets on the basis of their response to a heating signal. Not only does this facilitate spatial resolution but also opens up the possibility of physical characterisation of these components within a product. The highlighted disadvantages include the semi-quantitative nature of the technique, the limitations of resolution and the difficulties in differentiating between material with similar thermal conductivities. However, given the early stage of development of the technique, many of these problems are likely to be resolved in the foreseeable future. As a proof of concept study, these early results may be considered to be highly encouraging.

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