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Pharmaceutical Applications of Micro -Thermal Analysis

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Abstract

Micro-thermal analysis is a recently introduced thermoanalytical technique that combines the principles of scanning probe microscopy (SPM) with thermal analysis via replacement of the probe tip with a thermistor. This allows samples to be spatially scanned in terms of both topography and thermal conductivity, while by placing the probe on a specific region of a sample and heating it is possible to perform localised thermal analysis (LTA) experiments on those regions. In this minireview the principles of the technique are outlined and the current uses within the polymer sciences described. Current pharmaceutical applications are then discussed; these include the identification of components in compressed tablets, the characterisation of drug-loaded polylactic acid microspheres, the analysis of tablet coats and the identification of amorphous and crystalline regions in semicrystalline samples. The current strengths and weaknesses of the technique are outlined, along with a discussion of the future directions in which the approach may be taken.

Keywords: amorphous, atomic force microscopy, indometacin, glass, hydroxypropyl methylcellulose, micro-thermal analysis, tablet coat

Introduction – Basic Principles of Micro-Thermal Analysis

Micro-Thermal Analysis (micro-TA) is the term given to a recently introduced technique that combines the principles of thermal analysis with scanning probe microscopy. The method has attracted considerable interest within the polymer science field and has recently begun to find application within the pharmaceutical sciences. In this short review, we outline the basic principles underpinning the use of the technique and the manner in which the method may be applied, with particular emphasis on current and potential uses within the pharmaceutical arena.

A number of papers have now been published that outline the underlying principles of the technique [1-8] and a major review of the instrumentation and general uses of micro-TA is now available [9], hence only a brief description of these aspects will be given here. Micro-TA represents a development of the family of techniques known as scanning thermal microscopy (SThM) whereby the surface of a sample is examined as a function of temperature. The basis of the analysis is a modification of a typical scanning probe microscope (SPM). In SPM the tip cantilever is attached to a piezoelectric scan head which can control the position of the tip in 3 axes (x,y,z). X-Y piezoelectric actuators are used to scan the tip across the sample surface either in hard contact with the surface (contact mode), intermittent contact with the surface (pulsed force mode) or a constant distance from the surface, interacting with near-surface forces (non-contact mode). The tip is usually scanned across the surface in a raster pattern, while an optical lever (composed of a laser beam reflected from the back of the cantilever onto a 4-zone photodetector) measures the deflection of the cantilever in the z-axis and controls the height of the tip via a force-feedback loop.

The innovation associated with SThM lies in the replacement of the conventional SPM ultra-sharp tip by a thermal probe. This is currently achieved for micro-TA using a Wollaston wire as described by Pylkkinen et al [8]. The Wollaston wire is composed of a length of fine platinum/rhodium alloy wire (3-5 μ m in diameter) coated by a sheath of silver approximately 75 μ m thick. This wire is bent into a V-shape and the silver sheath etched away at the apex to expose the platinum core, forming a pointed tip with a diameter in the region of 1 μ m (Figure 1). A mirror attached to the back of the wire serves as the fulcrum of the optical lever, such that the tip can be controlled in

the same manner as a conventional sharp cantilever tip, albeit with lower spatial resolution due to the increased dimensions of the thermal probe tip. Typically, the resolution is in the region of 100nm-10 μ m. The exposed platinum tip has a much higher resistance than the intact Wollaston wire (approximately 2 Ω) and associated connections. Consequently the application of a current across the assembly results in Joule heating of the tip, thereby providing a means whereby a controlled heating signal may be applied to a highly specific region. Similarly, by incorporating the assembly into a Wheatstone bridge circuit the temperature of the probe may be determined via measurement of the overall resistance of the Wollaston wire, using an identical but remotely located tip as a reference. In this manner the tip may be used both to measure local temperature and to apply localised heat simultaneously.

The ability to both apply and measure heat with high spatial specificity allows the instrument to be used in a number of modes. In the simplest case the instrument can be used passively as a resistive probe to simply measure temperature variations across a sample. More commonly, however, the method is used in active mode whereby a current is applied to the tip in order to apply a heating signal to the sample. It is possible to monitor the power that must be supplied to the sensor probe to maintain constant temperature as the tip is scanned across the sample surface. This in turn allows measurement of the thermal conductivity of the surface, thereby providing an alternative means of surface mapping. However, in all cases it should be borne in mind that the heat transfer conditions are not as fully characterised as in conventional DSC, due to the uncontrolled heat losses/gains from surrounding regions of the sample. In addition, the apparent thermal conductivity may be a reflection of surface topography due to differences in the contact area between the probe and the sample at different positions on the sample surface. For example if the probe is in contact with a “peak” in the sample topography then the contact area will be less than if the probe is in a “valley”. This effect causes an apparent increase in thermal conductivity of valleys compared with peaks and is a non-trivial difficulty that is currently the subject of intense investigation.

A further possibility is the use of a modulated heating signal, both in (quasi)-isothermal mode for surface scanning and in temperature ramping (described below).

Hammiche et al [2] adapted the Wollaston wire-based scanning thermal microscope with the addition of modulation techniques analogous to those used in modulated temperature DSC (MTDSC). In MTDSC a modulation (sine- or square-wave) of controlled frequency and amplitude is applied to the heating program and Fourier analysis used to deconvolute the resultant heat flow data. The theory and uses of MTDSC are already well detailed in the literature and do not warrant re-examination here [10,11]. In the current context, however, the use of a modulated signal presents several potential advantages. In the first instance, by applying a modulated heating program to the sensor the baseline stability may be improved. In addition, the differential modulated power (known as alternating current (AC) power) and phase lag can be measured by the lock-in amplifier (LIA). In μ TA, the differential DC power signal can be considered equivalent to the total heat flow as measured by DSC/MTDSC and the differential AC amplitude is analogous to the complex heat capacity of the sample as measured by MTDSC. The AC phase signal can also be plotted with respect to temperature or time, or displayed as a function of tip location to produce a phase image. In addition, the modulation frequency of the heat flow from the sensor tip affects the depth of penetration of the heating effect. The depth of penetration (λ) of modulated heat supplied to a semi-infinite medium can be estimated as [4]:

Equation 1

$$\lambda = \sqrt{\frac{2D}{\omega}}$$

where ω is the frequency, and thermal diffusivity (D) is defined by

Equation 2

$$D = \kappa / (\rho c_p)$$

where κ is the thermal conductivity of the sample, ρ is the density of the sample, and c_p is the specific heat capacity of the sample. Clearly this represents a possible approach to thermal mapping of materials and an example of this will be given later in the review. However, there are also difficulties associated with the method. It can be

seen from Eqs 1 and 2 that for heterogeneous samples, where the thermal conductivity (κ), density (ρ) and heat capacity (c_p) of the surface may well be variable, the depth of penetration of the heating modulation will not be constant at constant frequency. Several of these parameters will also be subject to degradation by topography-induced sensor power variations. The net effect of this phenomenon is therefore exceedingly difficult to predict; whilst probably increasing contrast in the AC amplitude and AC phase signals, the non-constant depth of modulated signal penetration may result in data not reflective of thermal imaging at an estimated depth.

A further possibility afforded by the method is the application of a scanning heating signal to a sample, thereby allowing thermal analysis to be performed on specific regions. This mode is known as a localised thermal analysis (LTA) and may allow measurement of phase transition temperatures of specific sample regions by measuring the differential DC power, the AC power signals or even the AC phase lag with respect to a reference probe, all of which are related to changes in heat flow to the sample region as a transition is undergone. These signals are often more convenient to interpret as their first order time- or temperature derivatives [7]. In addition to heat flow-related measurements plotted by the control unit for temperature feedback, the instrument may also collect mechanical data related to the sample's response to the thermal program via the force feedback control unit, an approach known as micro-thermomechanical analysis (μ TMA). The information is related to events such as thermal expansion of the sample (resulting in an increasing signal from the z-piezoelectric actuator) or indentation of the probe tip into the sample surface during events such as softening at glass-rubber transitions or melts. These data are sometimes more sensitive than the accompanying heat-flow measurements.

In addition, the effect of tip impingement into the sample surface after a thermal event is visible in subsequent topographical analysis as a crater. The size of the crater may itself be an indication of the local behaviour of the sample and is indicative of the volume of sample that has been affected/investigated by the preceding thermal analysis. Furthermore, any ultra-fine scale effects of scanning with a temperature program in operation may also be visible in subsequent topographical analysis. For example, minute physical/thermal damage to crystalline structure may be visually

detected, indicating thermal effects that may have gone undetected in the heat-flow analysis [4].

A final technical point regards the speed with which scanning thermal analysis can be carried out, compared to macro-scale analysis of similar samples. Because of the very small size of the thermal probe tip, heating rates in the order of 10-20K per second are usual; slower rates would simply result in heat dissemination through wide regions of sample. This allows for very much more rapid experiments and raises the possibility of batch monitoring in an industrial processing situation.

Future technical developments of the instrumentation are already well in hand, and offer the possibility of extending the analytical capabilities of μ TA [9]. Micro-collected evolved gases from a small region of sample pyrolysed by the sensor tip heat may be analysed in remote mass spectrometry (MS) facilities, or using combined gas chromatography and mass spectrometry (GC-MS) [7]. Perhaps further away from the commercial market lies the development of infra-red (IR) absorption spectral analysis at resolution better than diffraction limits. This has been demonstrated experimentally [12] but a suitable commercial IR source remains problematic. The μ TA can also be coupled with a custom designed hot stage, which makes it possible to control the temperature of the bulk sample as well as the sensor tip. Finally, like its parent instrument the SPM, μ TA can be coupled with additional instrumentation to investigate the same sample. For example a μ TA can be positioned above a sample mounted for surface plasmon resonance (SPR) analysis, or placed above a sample on the stage of an inverted light microscope chassis. The light microscope may then be used to perform a range of techniques such as Raman or confocal microscopy from beneath with the addition of co-localised micro thermal analysis from above. Another variation of the technique is to mount a sample on a vibrating heating stage. The observed resultant amplitude and phase of the motion of an ordinary AFM cantilever can then be used to determine the local elastic and visco-elastic properties of the material [5]. This technique has been referred to variously as local DMA (dynamic mechanical analysis), local mechanical spectroscopy, scanning local acceleration microscopy (SLAM) or dynamic mechano-thermal analysis by scanning microscopy (D-MASM).

Applications of Micro-Thermal Analysis

Polymeric Systems

To date, the use of the technique has mainly been confined to the analysis of polymers or composite materials such as polymer blends or polymer:metal composites [12]. This is largely because of the pre-eminence of thermal methods as means of characterising polymers but also because polymeric samples provide excellent test materials for the technique. Indeed, one of the first papers that used micro-TA was concerned with the analysis of the polymer blends of styrene-isoprene-styrene triblock copolymer with polystyrene and polymethylmethacrylate (PMMA) and chlorinated polyethylene (CPE) [6]. These materials are ideally suited to investigation by micro-TA because the different components exhibit high differences in their conductivity, which is a pre-requisite for being able to visualise differences between the phases in a material using isothermal scanning. This is exemplified by Figure 2 in which the domains of polymethylmethacrylate are clearly visible in a chlorinated polyethylene matrix [6].

A further issue of considerable importance within the polymer sciences is the study of the miscibility of polymeric samples. This may be performed using conventional DSC by observing, for example, the convergence or otherwise of the glass transitions of the two components. However, the use of LTA experiments allows such studies to be performed on specific regions of a sample and at interfaces between components, as shown in Figure 3 for acrylonitrile/butadiene/styrene (ABS) and polyamide (PA) blends [2]. The data clearly show the difference in the sensor response for the two materials. The ABS exhibits a well-defined softening event in the region of 405K while the PA melts at 483K. The experiment performed on the interface shows both of these transitions.

Polymers and polymer blends are also especially suitable for the technique because the surfaces of such materials can be manufactured in such a way that they are very flat. This reduces the effect of surface topography on the measured thermal conductivity and so the spatial resolution can be increased to 100 nm [2]. Similarly, comparatively flat surfaces also allow the more accurate use of the AC mode since the effects of topography on the depth of penetration are removed. Figure 4 shows AC

images (equivalent to the complex heat capacity signal from a MTDSC experiment) from a sample that contains a circle of material that has a high thermal diffusivity set in a material of low thermal diffusivity [6]. The surface of the sample has then been covered with a polymer film. The effect of increasing the modulation frequency is to decrease the depth to which the probe can image. Therefore the sample analysed at 30kHz only shows a low thermal conductivity throughout the sample, whilst the same scan at a lower frequency enables greater penetration so that the high conductivity material is now visible below the polymer layer.

Pharmaceutical systems

While the use of micro-TA is still in comparative infancy within the pharmaceutical sciences, a number of studies have now been completed which have identified the basic strengths and weaknesses of the approach within a drug delivery context. In general terms, the key application for the technique is the potential ability to not only discriminate between different materials, or indeed physical forms, within a multicomponent system but also the ability of the method to perform characterisation studies on those individual components *in situ*. Given that effectively all solid state dosage forms are composite materials, the ability to study the individual components in this manner has many potential applications. However, it is essential to be aware of the limitations of the analysis, such as are known at present, hence the difficulties associated with the technique will also be highlighted below.

The initial studies involving the use of the technique were essentially proof of concept investigations, designed to establish the possible utility of the method. These include the study of HPMC-ibuprofen compacts [13], whereby the ability of the technique to discriminate between two chemically different pharmaceutical materials in a model compact was investigated. Tablets were prepared containing HPMC E4M alone, ibuprofen alone and 50:50 mixes of the two materials. Thermal conductivity measurements and LTA studies were performed on the pure materials and mixed systems. The LTA in particular was able to discriminate between the two materials in that the HPMC showed no clear discontinuities from 40°C to 300°C, while the ibuprofen showed a clear movement of the probe at a temperature corresponding well to the melting point of the material. By placing the probe on separate regions of the

tablet surface it was possible to identify the nature of the material by the response to the applied heating signal (Figure 5).

This study did serve to illustrate both strengths and weaknesses of the method. In the first instance, the method is clearly able to detect the melting of a low molecular weight drug and to use this as a means of identifying the location of that drug within a powder compact. This may have important implications not only for characterising the distribution of materials within tablets but also for studying the physical nature of that drug by, for example, identifying polymorphs by their different melting points. However, it should be noted that the thermal conductivity was not able to discriminate between the two materials because of the surface topography dominating the response, as outlined in a previous section. Similarly, it was perhaps surprising that the HPMC did not show any discontinuities. This material is amorphous and shows a glass transition at approximately 180°C; however the transition is extremely small and difficult to detect using DSC [14]. Consequently it was assumed that the absence of any discontinuity (aside from some evidence of degradation at the highest temperatures used) was a function of the fragility of the glass. However, as outlined later in the article, there is an alternative explanation for this observation.

The concept of studying the polymorphic form of drugs using the technique was explored by Sanders et al [15]. These authors studied cimetidine Forms A and B alone and as 50:50 mixes via both thermal conductivity and LTA scans. An interesting feature of this study was that the authors used both sensor position (localised TMA) and derivative power LTA measurements, thereby allowing comparison between the two measuring modes, with good agreement noted between the two. While both polymorphs showed similar melting behaviour, as may be predicted from their melting points (141-143°C, 140-146°C respectively), Polymorph A also showed a response in the power signal at circa 100°C that the authors ascribed to water evaporation.

A further possibility afforded by the technique is the *in situ* study of tablet coats. It has to date proved difficult to study the mechanical and thermal properties of coats when they are actually located on the tablet itself, hence the possibility of being able to do so using micro-TA was considered to be of interest. A commercial sugar coated

ibuprofen tablet, cut to reveal to coated core, was examined in terms of both topography, thermal conductivity and localised thermal analysis [16]. It was noted that while the interface was difficult to discern using topographic imaging, the thermal conductivity showed much clearer discrimination between the two regions. In addition, the data analysis technique of intensity histogram analysis was utilised [17], whereby the intensity distribution of the conductivity pixels is recorded and a decision boundary imposed so as to render pixel intensities greater or less than that value (0.88mW in this case) white or black respectively. The conductivity clearly showed a bimodal distribution of pixel intensity, whereas the topography showed a monomodal distribution (Figure 6), reflecting the differing abilities of the two approaches to discriminate between the coat and the core. By applying the intensity histogram analysis to the conductivity, clearer differentiation of the boundary between the two regions could be obtained. LTA studies were also performed on the two materials, with transitions corresponding to the sugar and ibuprofen seen.

The method may has also been used to examine polysaccharide pellet systems. Pillay and Fassihi [17] used micro-TA to examine the surface properties of calcium-alginate, calcium-pectinate and binary calcium-alginate-pectinate systems. Similarly Royall et al [18] examined the surface properties of polylactic acid (PLA) microspheres loaded with different concentrations of progesterone. A previous study [19] using MTDSC had indicated that at concentrations up to <30%w/w the drug is present as a molecular dispersion through the spheres, as evidenced by plasticization of the glass transition of the PLA (seen at 48°C for the unloaded spheres). However, at 30% w/w a recrystallisation peak is seen at circa 70°C followed by two melting peaks at 112 and 124°C. It was suggested that the drug is at least partially present as a distinct amorphous phase, with this amorphous material recrystallising into two polymorphs of progesterone. At 50%w/w no exotherm was seen but a single melting peak corresponding to the stable polymorph was observed, suggesting that the drug was present as a separate crystalline phase. SEM images indicated changes to the surface morphology of the spheres at concentrations corresponding to the observed MTDSC changes, suggesting that the separate drug phases were located on the sample surface, although this could not be confirmed using the available equipment. A further interesting observation was that a shift in the MTDSC phase angle was noted between

70 and 100°C. The phase angle ϕ represents a combination of sample and instrumental effects and may be given by [21]

Equation 3

$$\phi = \arctan (mC_p^* \omega / K)$$

where m is the sample mass C_p^* is the complex heat capacity, ω is the period and K is an instrument parameter describing the heat transfer characteristics of the system [18]. It was suggested [20] that the shift in phase angle was a function of a change to the physical integrity of the spheres, resulting in a change in K . More specifically, it was suggested that the sample flowing, thus increasing the thermal conductivity between the sample and the pan. This was confirmed using hot stage microscopy, whereby the spheres could be seen to lose their shape over this temperature range.

In order to confirm the presence of drug on the surface of the spheres, LTA studies were performed on samples containing 0, 30 and 50% w/w drug. The results are shown in Figure 7. The 50% systems showed a clear melting discontinuity corresponding to the crystalline progesterone, thereby supporting the hypothesis of a crystalline layer on the sphere surface at this concentration. The data for the 30%w/w systems is less unequivocal, almost certainly due to the low T_g of amorphous progesterone (circa 5°C) leading to the surface layer offering little resistance to the probe over the temperature range under study. However, a key observation was that for the 0% and 30% systems the discontinuity occurred at a temperature much higher than the T_g of PLA (circa 80°C as opposed to 48°C for the T_g as measured using MTDSC). Given the above arguments it was suggested that the micro-TA is not measuring the glass transition as such but rather a softening process, in much the same way as thermomechanical analysis tends to measure the softening rather than the T_g itself. This is in itself not a disadvantage as a knowledge of softening processes is often of great importance in, for example, the study of collapse phenomena for freeze dried products. It is, however, essential to be aware of precisely the process that is being assessed using the technique.

The exploration of the nature of the process under study was furthered by a study into indometacin, whereby micro-TA was utilised to examine amorphous and crystalline regions in a single sample. Royall et al [21] examined compacts of amorphous and crystalline indometacin alone and performed LTA studies on the individual materials. The authors reported a discontinuity in the sensor position that corresponded well to the melting point of the crystalline material but was again considerably higher than the measured T_g for the amorphous system (64°C as opposed to the measured T_g of 42°C). The authors studied the effects of heating rate on the transition, finding little effect when using rates between 2 and 50°C/s. In addition, the size of the crater left after heating was found to be identical in each case (approximately 20µm in diameter; Figure 8). This lack of dependence on heating rate indicated that the discrepancy in discontinuity with T_g was not due to simple superheating of the sample through the glass transition but could again be ascribed to a softening process. Moreover examination of the MTDSC response again showed a shift in the phase lag, which corresponded well to the micro-TA discontinuity. The study also examined sample of amorphous indomethacin that had been stored so as to allow partial recrystallisation to occur. In this particular case the regions of recrystallisation are obvious due to the formation of needle-shaped crystals on the sample surface, thereby rendering the sample well suited to such a proof of concept study. By selecting specific areas on the sample surface it was possible to demonstrate that the technique could distinguish between the different phases in LTA mode (Figure 9).

Conclusions

Micro-TA has a number of potentially important applications within the pharmaceutical sciences. In particular, the ability to perform thermal analysis studies on specific regions of a multicomponent sample allows both identification of the different phases present and characterisation of the nature of those phases. This may be of particular importance for pharmaceutical compacts whereby both mapping of components and identification of the physical form of the drug may be of crucial importance. However, it is also important to be aware of the current limitations of the technique. In particular, the topological dominance of the thermal conductivity remains a problem, although a number of methods including the one outlined above

have been explored. In addition, there are still issues associated with the potential confusion of glass transitions with softening responses, although judicious use of heat flow data in association with sensor position studies may serve to clarify the nature of the transition involved. Finally, the resolution of the instrument is inferior to that of conventional SPM for the reasons given earlier. However, the majority of pharmaceutical dosage forms involve the inclusion of components in the micron size range, for which the technique is adequate. Overall, therefore, the method appears to offer some very exciting possibilities for the characterisation of pharmaceutical dosage forms.

Legends to Figures

Figure 1: Photomicrograph of micro-thermal analysis probe (reproduced with permission from reference 21)

Figure 2: Thermal image of domains of PMMA within a CPE matrix: a) dc-image, b) ac-image, taken at 10 kHz.(reproduced with permission from reference 6)

Figure 3: LTA experiments showing the difference in the sensor response for a ABS/PA blend (reproduced with permission from reference 2)

Figure 4: Two ac-thermal images of a sample with an island of high thermal conductivity material within a matrix of low thermal conductivity material, over both of which there is a polymer coating. Image a) was taken at 1 kHz and b) at 30 kHz.

Figure 5: a) Topographic image of an HPMC/ibuprofen tablet showing three regions (labelled 1-3) on which LTA studies were performed. Thermal conductivity is shown inset b) corresponding LTA responses showing a sharp discontinuity for the position corresponding to an ibuprofen region (reproduced with permission from ref 13)

Figure 6: Thermal conductivity images of an ibuprofen tablet film coat and core, showing the pixel intensity histogram (arbitrary units) for the conductivity and topography. Also shown is the conductivity image shaded black or white according to the imposition of a single intermodal decision boundary (reproduced with permission from ref 16). The core is on the right hand side of the image.

Figure 7: Localised thermal analysis experiments for polylactic acid microspheres containing 0% w/w, 30% w/w and 50% w/w progesterone (reproduced with permission from ref 19)

Figure 8: MTA response for amorphous indometacin, showing a) LTA response at 10°C/s b) topographical image of sample after heating at 10°C/s, * and * (reproduced from ref 22 with permission)

Figure 9: a) Topographical response of partially crystalline indometacin; b) corresponding LTA responses on areas marked numerically on (a) at 10°C/s (reproduced from ref 21 with permission)

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Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

a) b)

Figure 6

Figure 7

Figure 8

Figure 9a

Figure
9b