Calorimetric and spatial characterization of polymorphic transitions in caffeine using quasi-isothermal MTDSC and localized thermomechanical analysis.

Kett, V. (2008). Calorimetric and spatial characterization of polymorphic transitions in caffeine using quasi-isothermal MTDSC and localized thermomechanical analysis. *Journal of Pharmaceutical Sciences*, 97(3), 1285-1300. <https://doi.org/10.1002/jps.21048>

Published in:
Journal of Pharmaceutical Sciences

Document Version:
Early version, also known as pre-print

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

**Calorimetric and Spatial Characterisation of Polymorphic Transitions in Caffeine using
Quasi-Isothermal MTDSC and Localised Thermomechanical Analysis**

**Radhesh Manduva, Vicky L. Kett¹, Mike Reading, Simon R. Banks² and Duncan Q. M.
Craig**

School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich, Norfolk
NR4 7TJ, UK

1. School of Pharmacy, Queen's University Belfast, N.Ireland BT9 7BL, UK
2. Astra Zeneca Research & Development, Charnwood, Loughborough, LE11 5RH, UK.

Correspondence : D.Q.M. Craig (d.craig@uea.ac.uk)

Keywords: atomic force microscopy, caffeine, differential scanning calorimetry,
microthermal analysis, polymorph, tablet

Abstract

The development of two complementary novel approaches (quasi-isothermal modulated temperature DSC and microthermal analysis) for the study of the polymorphic phase transition of a model drug is described, with a view to providing an integrated study of the kinetic, thermodynamic and spatial characteristics of the transformation process. Caffeine was prepared in the Form II and Form I polymorphs and conventional differential scanning calorimetry and hot stage microscopy performed. The Form II to I transition at circa 413K was noted and associated with a change in crystal habit to needle shaped crystals. The heating rate dependence was used to calculate the activation energy as a function of temperature. Quasi-isothermal DSC was used to measure the heat capacity as a function of temperature in a series of (quasi-) isothermal steps, thereby allowing measurement of the transition under conditions of minimal kinetic hindrance. It was also possible to use the measured complex C_p to develop a novel approach to deriving the thermodynamic parameters (ΔH , ΔS and ΔG) associated with the transformation between the two polymorphs. Microthermal analysis in localised thermomechanical analysis mode was able to differentiate between the two polymorphs via a discontinuity associated with the solid state transition which was associated with the change in crystal habit noted during the HSM studies. It was observed that transformation between the polymorphs took place in both directions on compression (i.e. Form II converted to Form I on compression and *vice versa*). It is suggested that these approaches may allow not only a more profound understanding of the mechanistic basis of polymorphic transformation but may also allow spatially resolved analysis of process-induced changes in crystal form.

Introduction

The detection and characterisation of polymorphism continues to be a key consideration for solid state analysis in general and pharmaceutical development in particular. More specifically, there is a need to understand the thermodynamic (equilibrium) relationships between polymorphs, the kinetics of transformation, the specific unit cell structures of the different forms and the factors influencing conversion and generation. To date there has been a considerable body of work produced whereby the solid state structure of polymorphs has been assessed, principally using thermal and spectroscopic techniques (e.g. 1,2), while a number of studies have investigated the free energy relationships between polymorphs (e.g. 3,4) and the kinetics of conversion (e.g. 5,6). In addition, there have been studies whereby the influence of processing on polymorph conversion has been investigated, with particular emphasis on the effect of compaction (e.g. 7,8). Indeed, it is widely recognized by the pharmaceutical industry that polymorph generation during processing (particularly comminution or compression) is a major concern due to performance and regulatory considerations. However, despite this recognition the understanding of the conversion process itself remains poor, particularly both in terms of the link between the thermodynamic and/or kinetic profile of the conversion and the manufacturing procedure in question. The aim of the current study is to introduce two novel approaches for the study of polymorphic conversion for a model drug, caffeine, with a particular view to providing a combined thermodynamic, kinetic and spatial profile of the conversion process, with particular emphasis on studying the effect of compression on the distribution of polymorphs.

Caffeine (1,3,7-trimethyl-2,6-purinedione) is a trimethylated purine derivative and is found in many common drinks as well as being marketed in its own right as a central nervous system stimulant, a smooth muscle relaxant and a component of compound analgesics. Two polymorphic forms have been identified; Form II which is stable at room temperature and Form I which is generated on heating above a transition temperature, reported to be in the region of 140°C (9-12). The forms are believed to be enantiotropic, with the crystal structures described by Edwards et al (13). Two interesting features of the transformation process render it a suitable model compound for the present study. Firstly, the transformation is seen as a well defined endotherm in differential scanning calorimetry (DSC) studies (9), rendering it a suitable for further analysis using scanning thermal techniques. Secondly, the conversion may be induced by compression (14,15), thereby rendering it a suitable model for examining compression-induced transformation.

The two principle techniques employed in this study are DSC, run in conventional, modulated and quasi-isothermal mode, and microthermal analysis (MTA) run in localised thermomechanical analysis (L-TMA) mode whereby thermal events are studied in a spatially resolved manner. Conventional and more recently modulated temperature DSC (MTDSC) are well recognized techniques and the reader is referred to a number of reference sources for more information on their use and operation (e.g. 16,17). Quasi-isothermal MTDSC is a variant on the modulated technique whereby the sample is modulated isothermally at a single underlying temperature for a specified time, after which the temperature is incrementally ramped up or down so as to obtain a profile through a transition consisting of a series of (quasi-) isothermal data sets (18). In this manner the effects of the heating programme are effectively eradicated, hence it becomes possible to obtain fundamental thermodynamic data such as heat capacity through energetic transitions in the absence of kinetic effects. In addition, the true temperature range over which an event occurs can be ascertained as thermal lags associated with the instrument and sample can be negated. The technique has been utilised to study thermal events in polymeric samples (19-21) and recently as a means of studying polymorphic melting processes (22).

A number of publications outlining the principles of micro TA and its related techniques are now available (23-25) and only a brief resumé will be given here. Micro TA represents a development of a technique known as scanning thermal microscopy (SThM) whereby the thermal properties of the surface of a sample are mapped with high spatial resolution. To achieve this, the tip of a conventional scanning probe microscope (SPM) is replaced by a thermal probe. The most widely used probe for micro TA is one based on a Wollaston wire as described by Pylkki et al (26), although much finer probes have very recently become available. The Wollaston wire is composed of a length of fine platinum/rhodium alloy wire (4-5 μm in diameter) coated by a sheath of silver approximately 75 μm 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 contact area in the region of 1 μm^2 . 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 tip, albeit with lower spatial resolution due to the increased dimensions of the thermal probe. 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. With suitable control circuitry 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 an active mode in which a current is passed through the tip in order to apply a heating signal to the sample. By monitoring the power that must be supplied to the sensor probe to maintain constant temperature as the tip is scanned across the sample surface, a measurement of the heat flow into the sample can be made. This is related to the local thermal conductivity of the surface; hence, in isothermal mapping mode the instrument can produce images not only of surface topography but also of thermal conductivity. An alternative approach to isothermal mapping is the application of a scanning heating profile to a sample, thereby allowing thermal analysis to be performed on specific regions of a sample. This mode is known as a localised thermomechanical analysis (L-TMA) and allows measurement of phase transition temperatures of specific sample regions by measuring the differential DC power with respect to the reference probe, the AC power signals or the AC phase lag. Due to the very small size of the thermal probe tip, L-TMA heating rates in the order of 10-20K per second are usual in order to minimise heat dissipation through the sample. The method is becoming increasingly widely recognized in the polymer (27, 28) and pharmaceutical (29) fields as a means of obtaining thermal data on highly specific regions of samples.

Here we describe the combined use of these techniques for the study of polymorphic transitions, with a view to combining the ability of the scanning methods to obtain specific thermodynamic data on the transformation process while also allowing spatial characterisation of the extent of conversion on compression. A key perceived advantage is that, being based on thermal scanning approaches, the two sets of methods have considerable overlap in their analytical approach, hence it is intended that, instead of yielding two valuable but disparate sets of information we instead obtain two profiles that may be interpreted in conjunction.

Materials and Methods

Materials and sample preparation

Caffeine was supplied by Sigma Chemicals, Dorset, UK at >99.6% purity. The two polymorphic forms were prepared as follows. While the as received material could be reasonably assumed to comprise Form II, the sample was annealed at 353K for 12 hours to ensure any residual Form I was converted to the more stable form. The resulting material was confirmed as being Form II by powder XRD and DSC (data not shown). SEM studies indicated that the material was composed of plate-like crystals with small microcrystals attached to the surface, hence reliable size analysis was difficult to perform due to the poor distinction between single particle aggregates and loosely bound agglomerates. However the size of the composite particles was in the region of 50-100 μ m. Form I was prepared using a method based on that suggested by Cesaro and Starec (30) whereby a sample of Form II is heated to above the sublimation temperature (453K) and the resultant vapour collected on an inverted watch glass covering the sample. Samples were used within 12 hours of preparation to minimise reconversion effects. Powder XRD and DSC were again used to confirm the structure of the material (data not shown). SEM studies indicated that Form I was composed of distinct needle-shaped crystals with approximate length 1mm and width axes in the region of 20 μ m. Compacts were prepared in an IR press (200mg samples, 8mm diameter die) using a pressure of 10 tons for 2 minutes.

Thermal analysis

DSC and MTDSC studies were performed using a TA 2920 MDSC (TA Instruments, Leatherhead, UK). Sample sizes of 2-3mg were used throughout in aluminium hermetically sealed pans (Perkin Elmer, MA, USA). For conventional DSC studies, calibration was performed using indium and a purge gas of nitrogen was used with a flow rate of 30mL/min. A range of heating rates between 0.1K/min to 10K/min was used as stated. For MTDSC studies a heating rate of 1K/min was used with a period of 100s and amplitude of +/-1K. Heat capacity calibration was performed using a sapphire disk. Quasi-isothermal (QI-) MTDSC studies were performed using an amplitude of +/-0.75K, a period of 80s, a temperature increment of 0.2K and an isothermal period of 30 minutes. Hot stage microscopy was performed using an Olympus BX 60 heating microscope with a Linkham TP 93 controller, with the sample sandwiched between a slide and cover slip. A heating rate of 1K/minute was used. For all thermal analysis experiments each study was repeated five times.

Microthermal analysis studies

MTA studies were performed using a Micro Thermal Analyser 2990 (TA Instruments, Leatherhead, UK) equipped with a Topometrix Scanning Probe Microscope. The system was calibrated for temperature and displacement using Nylon 6 as calibrant. The instrument was set up to a constant force by applying 10nA current to the Z piezo to keep the probe tip in contact with the surface. For topographic and thermal conductivity images (direct current), the tip was rastered across the sample in contact mode at a 300 μ m/s scan rate with the probe held isothermally at 298K. Localised thermal analysis (LTA) experiments were performed by heating the probe tip in contact with the surface over a temperature range of 323K to 573K at a scanning rate of 10K/s. In order to ascertain the extent to which LTA could differentiate between caffeine polymorphs, compacts of the two forms were prepared as described previously but specific regions of the surface of the tablets were then annealed by the probe at either 353K or 423K for ensuring the generation of the Form II and I polymorphs respectively. For the site specific studies (i.e. compacts were not pre-treated but measured immediately after compression) LTA measurements were performed on over seventy site-specific locations across the whole tablet surface in a circular fashion starting from the outer edges to the middle section of the tablet; these analyses were completed within 5 hours of compression for each compact. The site specific characterisation studies were performed on three different freshly prepared compacts prepared from caffeine Form II and Form I.

Results

Conventional thermal analysis

Hot stage microscopy and differential scanning calorimetry

In the first instance, HSM was used to obtain visual and semi-quantitative information with regard to the transformation between the two polymorphs. Figure 1 depicts the morphological changes for caffeine Form II crystals upon passing through the transition temperature. The images show that from 411K to 419K a continuous change in crystal habit is observed, culminating in the formation of elongated needles at 423K. During the process it was noted that some cloudiness was apparent, almost certainly due to sublimation and condensation between the sample and cover slip. This observation, coupled with the established method of preparing Form I polymorph, suggest that the transformation process occurs via a vapour phase intermediate. On cooling the 'transformed' Form II (i.e. Form I) no

reversion of habit was noted. Similarly, no alterations in crystal habit were noted for freshly prepared Form I caffeine on heating through the same temperature range.

Figure 2a shows the conventional DSC data for freshly prepared caffeine polymorphs at a heating rate of 10K/min (note that the data is shown in terms of heat flow rather than the usually preferred heat capacity due to the latter being considered more specifically in a later section). Upon heating caffeine Form II, two endothermic transitions at onset temperatures 420.0K (+/-1.2K) and 508.4K (+/-0.2K) were observed. The first endothermic transition shows a broad peak with an enthalpy of transition of 2.6 kJ/mole, corresponding to the Form II to Form I transition (9,30). The second endothermic peak may be attributed to the melting transition of Form I. In contrast, the freshly prepared caffeine Form I did not show an intermediate temperature transition but only a melting point at 507.8K (+/-0.3K). Reverse heating to room temperature also showed no intermediate event, implying that the back transformation did not take place within the timescale of the cooling experiment.

In order to establish the involvement or otherwise of a kinetic component to the transformation process, Form II was heated at a range of rates (Figure 2b). Clearly, the onset and peak temperatures are highly dependent on heating rate, as is the transition width. The apparent change in magnitude of the transition is a function of the increased sensitivity of the instrument when run at higher rates; the calculated heats of fusion were extremely similar, indicating no change in the overall energy change associated with the transformation, as may be reasonably expected.

Modulated temperature DSC and quasi-isothermal modulated temperature DSC

Figure 3 depicts the MTDSC heating profile for the caffeine Form II to Form I transition, indicating that the transformation is observed in both the total and non-reversing heat flow curves at 141.4°C (± 0.2) (onset temperature of total heat flow). These two signals represent the equivalent of the conventional DSC and kinetic component of the response respectively according to

$$dQ/dt = C_p \cdot dT/dt + f((t,T)) \quad \text{Eq.1}$$

where dQ/dt is the power output, C_p is the heat capacity, T and t the temperature and time respectively and $f(t,T)$ a kinetic component of the power response that is a function of time and temperature.

One may therefore conclude from the non-reversing signal that the MTDSC data is also indicating that the transformation is at least partially a kinetically hindered process rather than simply reflecting a change in equilibrium energy state. However, the reversing heat flow signal shows a step change at 144.7°C (+/- 0.6), reflecting the change in heat capacity on polymorph transformation which in turn reflects differences in molecular mobility between the two crystal lattices. The melt region itself shows a total and reversing heat flow component (data not shown) but, as the system is not in steady state with respect to the modulated signal, as is usual for melts, these data must be considered artefactual and are not considered further here.

A further method by which the sample heat capacity can be measured is via quasi-isothermal (QI-) MTDSC, whereby the underlying heating rate is effectively 0K/min. This approach is utilised as a means of obtaining underlying heat capacity values independently from overlapping kinetic transitions and involves the measurement of the modulated heat flow signal as a function of time over a series of temperature increments, thereby allowing measurement of the heat capacity over a timescale that is much greater than that of the kinetic event. This is given by (19)

$$mc_p = \frac{A_\Delta}{A} \sqrt{\left(\frac{K}{\omega}\right)^2 + C'^2} = \frac{A_{HF}}{A} x K' \quad \text{Eq.2}$$

where mc_p is the heat capacity for mass m of sample, A_Δ is the maximum amplitude of the temperature difference between sample and reference, A is the temperature amplitude, K is a calibration constant, ω is the frequency of modulation, C' is the heat capacity of empty reference pan and K' is the commonly measured calibration constant that includes C' .

The QI-MTDSC data corresponding to the Form II transition is given in Figure 5, expressed in terms of the reversing heat flow as a function of temperature. The transition can be seen to take place over a more narrow temperature interval (4.1K (± 0.5)) than was the case for the

scanning studies, with a correspondingly lower onset temperature (410.5K (± 0.1)). Both of these observations reflect the reduction of the kinetic component of the transition, although it is noted that the response is still not instantaneous, as would be expected for a true first order reaction. This may reflect the finite time required for the transformation process to take place, despite the prolonged time periods built into the temperature programme. The difference in heat capacity value (ΔC_p) between caffeine polymorphs is measured as 0.057 J/g $^{\circ}$ C (± 0.002), obtained from an average of five experiments.

Thermal conductivity and localised thermal analysis

LTA of compacts of known composition

Before proceeding with any examination of the effects of compaction, it was necessary to ascertain whether the MTA technique could differentiate between the two polymorphs. Figure 5a depicts the L-TMA data for Form II polymorph compacts, annealed so as to ensure physical integrity as described earlier. The sensor showed a steady increase in height associated with sample thermal expansion, commencing at circa 327K, with the melting event seen by probe penetration at 503K (± 7 K). However, a step change was also seen at 421K (± 11 K), corresponding to the temperature of the transition from Form II to Form I observed using DSC. Interestingly, therefore, the data imply that even at heating rates as high as 10K/s the Form II is converting to Form I prior to melting; it was originally hypothesised that the high rates may result in this transition being sufficiently kinetically hindered so as to render measurement of the melting point of Form II possible. Clearly, however, the sample is at least partially converting even at the rates used. The quantitative reproducibility of this transition is relatively poor but the reproducibility of its occurrence was extremely favourable. The suggestion that the discontinuity could be associated with the transition was supported by the analysis of Form I, which showed no such effect (Figure 6b). These data therefore indicated that the different polymorphs could be identified on the basis of the presence or absence of the discontinuity.

Thermal conductivity and L-TMA of melted regions

Having established the possibility of differentiating between polymorphs, it was then necessary to ascertain the likely scale of scrutiny of the analysis and also to investigate whether thermal conductivity could be used as a potential means of differentiation via scanning rather than studying individual point samples. Figure 7 shows the topographic and accompanying thermal images of caffeine Form II compacts taken after an L-TMA study,

with the crater associated with the measurement shown in the centre of the image. Care is required when interpreting both the scale of scrutiny and thermal conductivity measurements. For the scale of scrutiny, the sample will have solidified around the tip after the measurement, necessitating reheating prior to withdrawal. This in turn means that the crater may be larger than the sample that was characterised during the first measurement, hence one may be obtaining a 'worst case' measurement. In this particular case, the data indicate a scale of scrutiny of circa $10 \times 5 \mu\text{m}^2$. Clearly this is larger than one would expect for typical AFM but reflects the relatively large size of the probes used. Secondly, one must consider the possibility of topographic dependence of the thermal conductivity, as the presence of peaks and troughs will alter the relative contact between the tip and surface and hence alter the heat conduction pathway.

Compression induced site specific changes in polymorphic form

Site specific characterisation of caffeine compacts was then performed on tablets whereby no annealing had taken place, thereby allowing assessment of the distribution of polymorphs on the upper tablet surface following the compaction process. By measuring a series of circular areas (and ensuring that the measurements did not fall within the scale of scrutiny of each other) it was possible to map the location of the two polymorphs on both the Form I and Form II tablets. There were some points whereby it was not possible to confidently assign the form to one or other polymorph due to the small size of the discontinuity in relation to baseline noise; it is reasonable to ascribe this effect as representing areas that are at the interface between polymorphic regions. It was interesting to note that interconversion occurred both ways, i.e. Form I was partially converted to Form II and vice versa (Table 1). The extent of conversion for Form I to II and for Form II to I were remarkably similar; in both cases circa 50% of either the middle or outer region was converted to the other polymorph. This indicates that the preponderance for alteration in either direction is approximately the same.

Discussion

The data shown in Figure 1 and 2a describe the well recognized transition between Form II and Form I caffeine. The enantiotropic nature of the transition is supported by consideration of the various indicators, particularly Burger's rules ([31,32], summarised by Lohani and Grant [33]). The justification for these rules may be derived by consideration of the

theoretical thermodynamic phase diagram for enantiotropic and monotropic systems and is described in more detail in the above references. In brief, the observation that the thermal event is endothermic implies firstly enantiotropy and secondly that the thermodynamic transition temperature lies below the observed event (the 'heat of transition rule'). The 'heat of fusion rule' states that the higher melting polymorph has the lower heat of fusion for enantiotropic relationships; as the melting of Form II caffeine has not to our knowledge ever been recorded it is not possible to apply this rule in this case. Similarly the 'entropy of fusion rule' (namely that the higher melting polymorph has a lower entropy of melting) is not applicable here. Interestingly, as well as other test parameters such as density and IR spectra the authors also mention the little used 'heat capacity rule' which states that the higher melting polymorph also has a higher heat capacity at a given temperature. The authors state that use of this method is limited due to the difficulty in accurately measuring small heat capacity changes, an issue which the present paper addresses. Indeed, we show that the heat capacity does indeed increase on conversion from Form II to Form I (see Figure 4).

The kinetic hindrance associated with the transition is clearly indicated by the heating rate dependence of the transition onset and breadth of transition (Figure 2b). Such kinetic hindrance is well recognized for other drug solid-solid transitions; for example Defossement et al (34) have indicated that the solid-solid transition between carbamazepine forms III and I shows a complex heating rate dependence. Perhaps surprisingly, we found the peak maximum to follow the Kissinger equation (35,36) to a reasonable approximation ($r=0.957$). This relationship is given by

$$\frac{d\left[\ln\left(\frac{\Phi}{Tp^2}\right)\right]}{d\left[\frac{1}{Tp}\right]} = -\frac{Ea}{R} \quad (\text{Eq.3})$$

where Φ is the heating rate, Tp is the peak maximum transition temperature and R is the gas constant. The activation energy of the process was calculated as 404.8kJ/mole. It must be remembered that this figure corresponds to the average activation energy over the heating rate range used. It is also possible to perform a range of alternative non-isothermal analyses on the individual data sets using, for example, the isoconversional method of Weese et al (37)

whereby the extent of conversion (α_t) is calculated as a fraction of the heat of transition at temperature t , i.e.

$$\alpha_t = \frac{\Delta H_t}{\Delta H_{tot}} \quad (\text{Eq.4})$$

where H_t the heat of reaction at time t , calculated by integrating the DSC signal up to time t and H_{tot} is the total heat of reaction calculated by integrating the DSC signal over the entire phase transition. The reaction rate can then be written as

$$\frac{d\alpha}{dt} = \left(\frac{d(\Delta H_t)}{dt} \right) \times \left(\frac{1}{\Delta H_{tot}} \right) = \frac{dQ}{dt} \times \left(\frac{1}{\Delta H_{tot}} \right) \quad (\text{Eq.5})$$

where dQ/dt is the heat flow signal. The reaction rate can be written for a simple n^{th} order reaction as

$$\frac{d\alpha}{dt} = k(1-\alpha)^n = Ae^{-\frac{E_a}{RT}} (1-\alpha)^n \quad (\text{Eq.6})$$

where k is the reaction rate constant (s^{-1}) and A is the Arrhenius pre-exponential (s^{-1}). Combining Eqs 5 and 6, the rate constant can be calculated as a function of temperature for a given DSC run by

$$k = \frac{dQ}{dt} \times \left(\frac{1}{\Delta H_{tot}} \right) \times (1-\alpha)^{-n} \quad (\text{Eq.7})$$

from which the activation energy may be found using the Arrhenius equation. The data were fitted over the temperature interval corresponding to the initial region of the transition (assuming $n=1$) and the activation energies calculated as 605.1kJ/mol, 370.9kJ/mol, 255.4kJ/mol, 165.1kJ/mol and 158.8kJ/mol for samples run at 0.1K/min, 1K/min, 2K/min, 5K/min and 10K/min respectively. The analysis has therefore indicated that the apparent E_a values for the caffeine phase transition increase with decreasing heating rate; this in turn implies that the mechanism of transformation changes with heating rate (which given the

suggested complexity of the transformation process is not unlikely) or else that there is a bias in the analytical approach used. Our suggestion is that the proposed solid-vapour-solid transition will be highly dependent on external variables such as the dimensions of the sample container (a view supported by empirical observations) hence the different scanning speeds may result in a range of differences in factors such as the distribution of the drug on the various surfaces involved. The practical implication of this observation is that unfortunately it is likely to prove extremely difficult to develop a generalisable kinetic model for transformation of this drug.

While there is clearly a kinetic component to the transformation process, the event will inevitably be driven by the free energy difference between the two polymorphs as a function of temperature. On that basis it is essential to identify the thermodynamic (equilibrium) as opposed to kinetic transition temperature in order to allow the equilibrium phase relationship between the two forms to be identified. However, identification of this temperature for caffeine (and arguably all enantiotropic drug forms) has proved difficult due to the method dependence of the measurement. This is exemplified by the report of Griesser et al (12) who state that temperatures between 414K and 435K have been cited for caffeine. These authors describe measurement of the sublimation vapour pressure of a range of drugs, including caffeine, arguing that the temperature at which the vapour pressure of the two forms is equal corresponds to the thermodynamic transition temperature; the value they report for caffeine using this method is 409K, significantly lower than other reported values and increasing the range width of cited values to 26K.

In this study we report a novel method of obtaining this temperature whereby we have used QI-MTDSC as a means of measuring the heat capacity as a function of temperature, theoretically eliminating the kinetic component from the transition. The value we obtained using this method was 410.5K which is in reasonably good agreement with that obtained by Griesser et al (12). However, the significant advantage of the QI-MTDSC method is that it also allows the heat capacity to be measured before, after and during the transition. The ability to measure the heat capacity throughout the temperature range under study allows delineation of the enthalpy, entropy and free energy of the process as a function of temperature; this is outlined in Appendix 1. In brief, by fitting the heat capacity data to a non-linear regression model it is possible to derive an empirical expression for heat capacity as a function of temperature which may then be integrated to yield the enthalpy, entropy and

free energy difference between the polymorphs as a function of temperature. In this particular case it was found that the temperature dependent changes are in fact very small compared to the latent heat associated with the transition, which is in itself interesting as the schematic phase diagrams commonly used within the field tend to indicate significant changes in these parameters above and below the transition temperature. Nevertheless the model does represent a new method of quantifying the temperature dependent changes in thermodynamic parameters, based on one simple set of experiments.

It is useful to consider the relationship between these thermodynamic parameters and the process-induced conversion. Several studies have indicated that processes such as compression may induce polymorphic change but to date little work has been conducted with a view to linking fundamental physical properties with the propensity for such change, nor has there been extensive work whereby the spatial distribution of induced changes has been identified. A notable exception with regard to the former is the work of Defossement et al (34) whereby the authors measured the heat flux and volume of expansion of caffeine under a range of pressures and were able to use the Clapeyron equation to quantitatively relate the pressure to the solid-solid solid-liquid transitions. In the present study the emphasis has been placed on using MTA to achieve spatial resolution of the transitions across the tablet surface. Two findings are of particular note. Firstly, differentiation between the polymorphs is possible on the basis of solid-solid transition rather than the melting. This is in many ways counterintuitive as it was originally perceived that the high heating rates might lead to sufficient kinetic hindrance of the transformation so as to allow measurement of the melting point of Form II. In reality the high rates were insufficient to prevent conversion but surprisingly the conversion itself was detected. Examination of Figure 1 indicates that the process involves gross changes in crystal habit and it is conceivable that it is this macroscopic transformation that is being detected. Secondly, and again surprisingly, it was noted that the conversion worked in both directions, with Form I transforming to Form II and *vice versa*. The Clapyron equation may be stated as

$$\ln p = -\frac{\Delta_{sub}H}{RT} + C \quad \text{Eq.8}$$

where p is the pressure, $\Delta_{sub}H$ is the enthalpy of sublimation and C is a constant. Defossement et al (34) noted that at 150MPa the transition temperature of the Form II to Form I conversion was raised to 446K, hence one could reasonably predict that the

conversion of Form 1 to Form 11 would be accelerated at lower temperatures when the pressure is raised but that the Form II to Form I conversion would be impeded. The observation that the transformation may also run in the thermodynamically unfavoured direction implies that an additional process is involved; a likely candidate is the generation of localised heated areas during the compression process.

The LTA studies also indicated that a proportion of the responses gave results which were not entirely unequivocal. This has been previously observed within the field and is the subject of a separate investigation by our group. We also emphasise the very recent introduction of thermal probes that are able to make localised measurements on a nanoscale. This is anticipated to assist the avoidance of material interfaces in measurements made on the microscale during the current investigation.

Conclusions

The study has indicated that the combined use of HSM, conventional DSC and quasi-isothermal MTDSC may allow both the kinetic and thermodynamic profile of polymorphic transitions to be characterised, thereby allowing the equilibrium relationships and the kinetics of transformation to be predicted from a series of simple measurements. Furthermore the transition may be used as a means of differentiating between the polymorphs in a spatially resolved manner, thereby allowing the distribution of transformation to be characterised. For many polymorphs with clearly distinct melting points, such analysis would in many ways be simpler using MTA than the model used in the present case (caffeine), as the LTA studies would simply measure the softening point of the two solids. However the ability to use the more subtle solid phase transition is unexpected and provides a further dimension to the capability of the MTA approach for the study of complex materials. As the probes available for MTA become more refined and measurements are made on a nanoscale the information derivable regarding the transformation will inevitably prove to be more detailed as the scale of scrutiny.

Overall the study has suggested that via a series of relatively simple measurements it is possible to obtain a highly detailed profile of the polymorphic transformation process in terms of the kinetics, the equilibrium thermodynamics, the spatial distribution of the transformation and the dependence of that transformation on the compression profile used. This in turn opens up the possibility of introducing a new sophistication into the

characterisation of complex multicomponent systems such as pharmaceutical compacts as well as a novel means of understanding the fundamental driving forces underpinning polymorphic change.

Acknowledgement

We would like to express our thanks to Mr John Wood, School of Chemical Sciences and Pharmacy UEA, for his invaluable help in developing the thermodynamic model used here.

Appendix 1: Calculation of the temperature dependent changes in enthalpy, entropy and free energy from the data obtained from QI-MTDSC

Integration of the heat capacity as a function of temperature allows the enthalpy and entropy at temperature T_1 to be calculated via

$$H_{T1} = \int_0^{T1} C_p dT + H_0 \quad (\text{Eq.9})$$

$$S_{T1} = \int_0^{T1} \frac{C_p}{T} dT + S_0 \quad (\text{Eq.10})$$

where C_p is the heat capacity (constant pressure) and H_0/S_0 are the enthalpy and entropy at the zero point temperature. We may fit the heat capacity data given in Figure 4 to the form

$$C_p = kT^\alpha \quad (\text{Eq.11})$$

such that

$$\ln C_{p_{FI}} = 1.157 \cdot \ln T - 6.4789 \quad (r^2 = 0.9952) \quad (\text{Eq.12})$$

$$\ln C_{p_{FI}} = 0.7964 \cdot \ln T - 4.2841 \quad (r^2 = 0.9907) \quad (\text{Eq.13})$$

and the differential heat capacity is given by

$$\ln C_{p_{FI-FII}} = -0.3606 \cdot \ln T + 2.1948 \quad (r^2 = 1.0000) \quad (\text{Eq.14})$$

By integrating the above expression between temperature T and the transition temperature 410.5K one obtains

$$\Delta H_{(FI-FII)} = \Delta H_{0(FI-FII)} - 3.23T^{-1.36} + 8.99 \times 10^{-4} \quad (\text{Eq.15})$$

$$\Delta S_{(FI-FII)} = \Delta S_{0(FI-FII)} - 12.21T^{-2.36} + 8.31 \times 10^{-6} \quad (\text{Eq.16})$$

$$\Delta G_{(FI-FII)} = \Delta G_{0(FI-FII)} + 8.98T^{-1.36} - 8.31 \times 10^{-6}T + 8.99 \times 10^{-4} \quad (\text{Eq.17})$$

We may use the transition enthalpy measured in the non-reversing heat flow signal as $\Delta H_{0(FI-FII)}$ while at this temperature $\Delta G_{0(FI-FII)}$ will be zero and hence $\Delta S_{0(FI-FII)}$ will equal $\Delta H_{0(FI-FII)}/T$. It is therefore a simple matter to calculate all three parameters as a function of temperature. Alternatively, and in this case more usefully, we may simply calculate the temperature dependent difference in these parameters as a function of temperature by setting $\Delta H_{0(FI-FII)}$ to zero; this is shown graphically in Figure 8.

References

1. H. G. Brittain, *Polymorphism in Pharmaceutical Solids*, Marcel Dekker, New York, USA **1999**
2. Z. Dong, B.E. Padden, J.S. Salsbury, E.J. Munson, S.A. Schroeder, I. Prakash, D.J.W. Grant, *Pharm.Res.* **2002**, *19*, 330
3. M. Naoki, T. Yoshizawa, N. Fukushima, M. Ogiso, M. Yoshino, *J.Phys.Chem.B*, **1999**, *103*, 6309
4. L. Yu, *J.Pharm.Sci.* **1995** *84*, 966
5. Schmidt, A., Kabaya, S., Appel, M., Khatib, S., Botoshansky, M., Eichen, Y. *J. Am. Chem. Soc.*, **1999**, *121*, 11291
- 6 Yu. L. *J. Am. Chem. Soc.*, **2003**, *125*, 6380
7. Brittain, H. G. (2002) *J. Pharm. Sci.*, **2002**, *91*, 1573
8. Zhang, G. G. Z., Law, D., Schmitt, E. A., Qiu, Y. (2004) *Adv. Drug Delivery Rev.*, **2004**, *56*, 371
9. Bothe, H., Cammenga, H. K. *J. Therm. Anal.*, **1979**, *16*, 267
10. Epple, M., Cammenga, H. K., Sarge, S.M., Diedrich, R. *Thermochim. Acta*, **1995**, *250*, 29
11. Lehto, V. P., Laine, E. *Thermochim. Acta*, **1998**, *317*, 47
12. Griesser, U.J., Szzelagiewicz, M., Hohmeier, U.Ch., Pitt, C., Cianferani, S. *J.Therm.Anal.Calorim.*, **1999**, *57*, 45-60.
13. Edwards, H.G.M., Lawson, E., de Marcel, M., Shields, L, York, P. *J. Chem. Soc., Perkin Trans.*, **1997**, *2*, 1985
14. Pirttimaki, J., Laine, E., Ketolainen, J., Paronen, P. *Int. J. Pharm.*, **1993**, *95*, 93
15. Chan, H. K., Doelker, E. *Drug Dev. Ind. Pharm.*, **1985**, *11*, 315
16. Wunderlich, B., Jin, Y., Boller, A. *Thermochim. Acta*, **1994**, *238*, 277
17. Reading, M. and Hourston, D.J. *Modulated temperature differential scanning calorimetry*. Kluwer Academic Publishers, The Netherlands, **2006**.
18. Chen, W., Dadmun, M., Zhang, G., Boller, A., Wunderlich, B. *Thermochim.Acta*, **1998**, *324*, 87
19. Wunderlich, B., Boller, A., Okazaki, I. Ishikiriya, K. *Thermochim. Acta*, **1997**, *304-305*, 125
20. Scherrenberg, R., Mathot, V., Hemelrijck, A. V. *Thermochim. Acta*, **1999**, *330*, 3
21. Wunderlich, B., Boller, A., Okazaki, I., Ishikiriya, K., Chen, W., Pyda, M., Pak, J., Moon, I., Androsch, R. *Thermochim.Acta*, **1999**, *330*, 21

22. Kawakami, K., Ida, Y. *Thermochim. Acta*, **2005**, 427, 93
23. Hammiche, A., Reading, M., Pollock, H.M., Song, M. and Hourston, D.J. *Rev.Sci.Inst.*, **1996**, 6712, 4268
24. Hammiche A., Price D.M., Dupas E., Mills G., Kulik A., Reading M., Weaver J.M.R., Pollock H.M. *J.Microsc.* **2000**, 199, 180
25. Pollock,H.M. and Hammiche,A. *J.Phys.D: Appl.Phys.* **2001**, 34, R23
26. Pylkki R.J., Moyer P.J., West P.E. *Jpn.J.Appl.Phys I*, **1994**, 33, 3785
27. Oulevey F.B.N., Gremaud G., Kulik A.J., Pollock H.M., Hammiche A., Reading M., Song M., Hourston D.J. *Polymer* **2000**, 41, 3087
28. Grandy, D.B., Hourston, D.J., Price, D.M., Reading, M., Silva, G.G., Song, M., Sykes, P.A. *Macromolecules* **2000**, 33, 9348
29. Royall, P.G., Kett, V.L., Andrews, C.S., Craig, D.Q.M. *J.Phys.Chem.B*, **2001**, 105, 7021
30. Cesaro, A., Starec, G. *J. Phys. Chem.*, **1980**, 84, 1345
31. Burger, A., Ramberger, R. *Mikrochim.Acta*, **1979**, 2, 259
32. Burger, A., Ramberger, R. *Mikrochim.Acta*, **1979**, 2, 273
33. Lohani, S. and Grant, D.J.W. *Thermodynamics of Polymorphs in Polymorphism in the Pharmaceutical industry* Ed Rolf Hilfiker Wiley -VCH Weinheim Germany, **2006**
34. Defossement, G., Randzio, S.L., Legendre, B. *Cryst.Growth Design*, **2004**, 4, 1169
35. Kissinger, H.E. *J.Res.Nat.Bur.Stand.*, **1956**, 57, 217
36. Kissinger, H.E. *Anal.Chem.*, **1957**, 29, 1702
37. Weese, R. K., Maienschein, J. L., Perrino, C. T. *Thermochim. Acta*, **2003**, 401, 1

Initial form of caffeine compact	Total LTA locations = 70		Locations corresponding to Form I LTA sensor responses		Locations corresponding to Form II LTA sensor responses		Unclear sensor responses	
	Outer area	Middle area	Outer Area	Middle area	Outer Area	Middle Area	Outer area	Middle area
Form I	35	35	11 (31%)	14 (40%)	18 (52%)	17 (49%)	6 (17%)	4 (11%)
Form II	30	40	15 (50%)	22 (55%)	9 (30%)	18 (45%)	6 (20%)	0

Table 1. Typical distribution of caffeine polymorphs over the upper surface of freshly prepared caffeine compact prepared from Form I and Form II. Percentages represent % of 70 measurements.

Figure 1: Hot stage microscopy images on heating caffeine Form II through the polymorphic transition temperature

Figure 2a: DSC curves for pure caffeine Form II and Form I polymorphs (y- axis shifted for comparison)

Figure 2b: The influence of heating rate on the DSC response of caffeine Form II, showing the Form II to Form I conversion process (y -axis shifted for comparison)

Figure 3 MTDSC response of freshly prepared caffeine Form II through the polymorphic transition temperature indicating total, reversing and non-reversing heat flow signals with modulation $\pm 1\text{K}$ over 100s period at heating rate 1K/min

Sample : TcaffeineQ @120.001
Size: 2.6470 mg
Method : Anhyd.caffeineQ

DSC

File: Third 0.75°Cover 80s inc 0.2°Ciso 30
Operator : Radhesh
Run Date : 9-Sep-02 16:55
Instrument : 2920 MDSC V 2.6A

Figure 4: QI-MTDSC heat capacity data for caffeine Form II with modulation +/-0.75K over 80s; increment 0.2K; isothermal period 30 minutes

Figure 6a: LTA response of caffeine Form II compacts (annealed to ensure physical integrity); curves reflect repeat measurements on the same compact.

Figure 6b: LTA response of caffeine Form I compacts (annealed to ensure physical integrity); curves reflect repeat measurements on the same compact.

Figure 7: Topographic and thermal conductivity image of caffeine Form II compacts taken at post - LTA measurements a) Topography image with colour mapping for height scaled in the left bar. b) Thermal conductivity image with DC power scaled in the left bar.

Figure 8: Thermodynamic parameters calculated from Equations 15-17 showing the difference in free energy, enthalpy and entropy between caffeine polymorphs I and II (see text for explanation)