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The development of microthermal analysis and photothermal microspectroscopy as novel approaches to drug–excipient compatibility studies

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Abstract

The use of microthermal analysis as a novel means of assessing chemical incompatibility between drugs and excipients is assessed using magnesium stearate and acetylsalicylic acid as a model system. Localised thermomechanical analysis (L-TMA), localised differential thermal analysis (L-DTA), nanosampling, thermally assisted particle manipulation (TAPM) and photothermal microspectrometry (PTMS) are developed as a means of allowing extremely small quantities of drug and excipient to be heated in close proximity to each other. Differential scanning calorimetry (DSC), hot stage microscopy (HSM) and temperature controlled attenuated total internal reflection (ATR) FTIR were used as supportive techniques. L-TMA and macroscopic TMA of magnesium stearate indicated that the endothermic DSC peak normally associated with melting does not correspond to significant liquefaction. An optimised method for detecting the interaction at a particulate level of scrutiny was developed whereby the drug is placed on the excipient surface via TAPM and the construct heated, allowing the interaction to be detected in both the L-TMA and L-DTA signal. PTMS allowed spectra to be obtained on nanogram-sized samples and also allowed the interaction to be detected. The study has therefore demonstrated the potential for using TAPM with PTMS for studying interactions at an individual particle level.

Keywords: Atomic force microscopy; Microthermal analysis; Drug–excipient compatibility; Acetylsalicylic acid; Magnesium stearate

1. Introduction

The difficulties associated with drug–excipient chemical incompatibility are well recognised within the pharmaceutical industry. More specifically, in order to predict long terms stability it is necessary to perform real time and accelerated storage studies. These involve preparation of samples, storage under real or stressed conditions and chromatographic analysis at set times using a suitable stability-indicating method. The above procedures are costly and time-consuming. Furthermore, in the early stages of drug development there is often a paucity of raw material, hence there is an issue of drug availability for the appropriate testing. It is therefore desirable to develop approaches whereby potential chemical incompatibilities may be detected quickly and reliably, using small amounts of material. Furthermore, there is growing interest within the industry in developing high throughput techniques for rapid screening of a large number of drug–excipient combinations, again indicating the need for rapid methods that use small amounts of sample.

Thermal methods such as differential scanning calorimetry (DSC) have been extensively explored as a means of predicting drug–excipient compatibility (Giron, 1986; Wesolowski, 1992), whereby the binary systems are heated and the melting behaviour and accompanying thermal events monitored. The principle of the technique is that changes in the thermal profile of the drug and/or excipient may be used as an indication of chemical incompatibility, with the appearance, shift or disappearance of characteristic endothermic/exothermic peaks or a change in the relevant enthalpy values indicating a possible interaction. A number of systems have been studied in this manner, the classic example being magnesium stearate and acetylsalicylic acid (aspirin). The chemical incompatibility between the two materials results in the generation of a number of potentially immunogenic products, such as salicylic

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acid, salicylsalicylic acid and acetylsalicylsalicylic acid (Reepmeyer and Kirchhoefer, 1979; Mroso et al., 1982). Several theories have been proposed in order to explain the mechanism of this chemical incompatibility. Acetylsalicylic acid is a moisture-sensitive drug (Mitrevej and Hollenbeck, 1983), hence its degradation is often associated with the presence of water (Kornblum and Zoglio, 1967) and/or alkaline pH (Nelson et al., 1974). Kornblum and Zoglio (1967) found that the rate of acetylsalicylic acid decomposition in suspensions with lubricants such as magnesium stearate was associated with the high solubility of the magnesium salt of acetylsalicylic acid, which formed a buffer with solvated acetylsalicylic acid, creating a pH environment that was detrimental to the stability of the compound. The presence of MgO impurities in magnesium stearate was also suggested to catalyse degradation by creating an alkaline pH environment (Jaminet and Louis, 1968). However, the relationship between pH and decomposition is controversial, with other authors claiming that pH does not play a significant part in the solid state decomposition (Mroso et al., 1982). The same authors proposed that the main mechanism of incompatibility was the reduction of acetylsalicylic acid's melting point, which would generate a liquid layer on the surface of magnesium stearate particles, thereby accelerating decomposition. The presence of liquid films around decomposing acetylsalicylic acid particles was demonstrated by microscopic examination. Similarly, Miller and York (1988) described the formation of a magnesium stearate surface film around acetylsalicylic acid particles, suggesting that the intimate contact between the two materials may facilitate the lowering of the acetylsalicylic acid melting point.

In general terms, the strengths and weaknesses of using DSC for drug–excipient compatibility are well recognised. The method does not give specific chemical information and will therefore not be able to provide definitive proof of degradation. Furthermore, as one is invariably interested in monitoring solid state reactions, the process will occur at point contacts between the two materials, hence even if a sizeable mass of sample is being heated the 'quantity' of reactive sites will inevitably be small, resulting in issues with both sensitivity and efficiency of sample usage at a stage of development when the available quantity of drug may well be very limited. Indeed, it is the sensitivity and hence reliability issue that has led to the method having fallen into limited use within the industry at the present time.

On the positive side, the thermal approach, if suitably refined, could prove to be an invaluable method of identifying potential incompatibilities in a rapid and reliable manner, i.e. it could be used to screen out potentially incompatible systems, thereby saving considerable time and cost. In addition, the premise by which the thermal approaches have been used is undoubtedly sound; the presence of a chemical instability between two materials must involve some form of heat change. It is therefore reasonable to suggest that this heat change may be monitored, either as a peak in a temperature scanning experiment or a heat exchange process in an isothermal one, the issue being whether either such thermal event is actually detectable in practice. Nevertheless, if one manages the expectations of what thermal analysis could yield then, if the issues of sensitivity and drug–excipient contact could be resolved, the method might still prove to be highly effective screening approach, particularly if it could be adapted to a high throughput approach whereby 'dangerous' combinations could be identified at an early stage.

In this study, we propose the use of microthermal analysis with thermally assisted nanosampling as a novel approach to studying drug–excipient compatibility. The principles of microthermal analysis have been described elsewhere (Murray et al., 1998; Price et al., 1998, 1999) hence only a brief description will be given here. The method is a derivative of atomic force microscopy whereby the probe is replaced with a miniaturised thermistor, allowing the temperature of the tip to be both controlled and measured. The classical measuring mode is localised thermomechanical analysis (L-TMA), whereby the position of the tip is measured as a function of temperature. As the material undergoes a transition such as melting the probe penetrates into the sample, thereby allowing the temperature at which the mechanical properties of the material immediately under the tip to be assessed. A further, less widely used approach is localised differential thermal analysis (L-DTA) whereby the temperature difference between the probe tip and a remote reference is measured as a function of temperature, thereby allowing the detection of thermal transitions via a differential temperature signal in a manner analogous to conventional differential thermal analysis (DTA).

Recently, we have developed a number of derivatives of microthermal analysis to allow a greater range of manipulation or measurements modes to be available to the operator (Reading et al., 2002; Harding et al., 2007). It is helpful to the present discussion to describe three approaches in particular. Firstly, nanosampling whereby the tip is introduced to a sample surface, heated so as soften that surface and become partially covered with material and then removed. Typically the tip retains some of the sample in the nanogram to picogram range. Secondly, thermally assisted particle manipulation involves the tip being used to pick up a particle by placing the tip on the particle then heating it to soften the material so it sticks to the tip. Finally, photothermal IR involves the application of an IR beam to a sample in close proximity to the tip and the measurement of the temperature fluctuations as a function of frequency (via Fourier transformation). This then enables the spectra of samples on or close to the tip to be obtained.

By employing either of the first two techniques, the tip (with the nanosample or particle) can be placed on a surface and then subjected to a heating program, hence interactions between the material on the tip and surface on which the tip is placed can theoretically be studied. Given this background it is logical to suggest that the ability to both manipulate small quantities of material and to measure thermal properties at high heating rates renders the microthermal technique a potential method of high throughput screening for drug–excipient compatibility. However, we suggest that a further, potentially very significant advantage is that by using such small quantities on a tip surface the proportion of that sample that will be in contact or very close proximity to the sample will be much higher than is the case for a normal powder mix, hence the sensitivity per unit quantity of material will be similarly enhanced. On this basis we describe here a proof of concept study whereby we use the example of magnesium stea-

rate and acetylsalicylic acid as a means of demonstrating whether a very small mass of drug in contact with an excipient surface can result in the detection of a recognised incompatibility.

2. Materials and methods

Acetylsalicylic acid (BUFA B.V. Uitgeest, Holland) and magnesium stearate (Acros Organics, New Jersey, USA) were used as received. Compacts of pure materials were produced using a 13 mm evacuable IR sample press (Specac, UK) using a pressure of 5 T for 1 min. Magnesium stearate–acetylsalicylic acid mixtures (50:50, w/w) were prepared by mixing manually for 5 min using a spatula. Bulk magnesium stearate was kept in a sealed container under ambient conditions prior to use; mixed or prepared samples were used immediately.

Differential scanning calorimetry experiments were performed using a TA Instruments 2920 Differential Scanning Calorimeter. Samples were placed in crimped aluminium pans and heated at 10 °C/min. Thermogravimetric analysis (TGA) was performed using a TA Instruments 2950 Thermogravimetric Analyzer. Samples were heated from ambient temperature to 300 °C at 10 °C/min. Thermomechanical analysis (TMA) studies were performed with a TA Instruments 2940 Thermomechanical Analyzer using a penetration probe and a heating rate of 3 °C/min. As the microthermal analysis also involves thermomechanical measurements, albeit at a very small scale, the conventional TMA experiments are referred to as macroscopic TMA for clarity. Hot stage microscopy (HSM) studies were carried out using a Leica DMLS Microscope with a Mettler Toledo FP82HT hot stage and a FP90 central processor. Samples were heated to 200 °C using a 10 °C/min heating rate.

Microthermal analysis was performed as indicated in each section using a TA Instruments (New Castle, DE, USA) 2990 μTA Microthermal Analyzer with a Thermomicroscopes Explorer AFM head and a Wollaston wire thermal probe (Veeco, CA, USA). Samples were fixed to the magnetic stub using double-sided tape and mounted onto an X–Y translating microscope stage. The instrument was calibrated for temperature and displacement according to the manufacturer's recommendations. Poly(ethylene terephtalate) (PET) was used as a calibrant; the room temperature 'kick-in point' was used as the other known temperature point for a two point calibration. The temperature program is started below ambient (so the electrical power supplied to the probe is initially zero) then, as the program temperature rises to room temperature, the control system begins to supply power and this can be seen on the thermal signal (giving rise to the so-called 'kick-in point').

In this work, LTA was performed using a net 'force' of 10 ± 1 nA. and a heating rate of 20 °C/s. Specific spring constants are not available for these tips, although they are in the region of 5–10 N/m, and hence an equivalent current measurement is used. All LTA experiments were repeated five times. L-TMA and L-DTA signals are collected simultaneously during LTA. Heat flow related measurements are taken by temperature feedback control unit, whereas the force feedback control unit is used to collect mechanical data. Baseline subtraction was used in all the measurements for which results are presented. This is achieved automatically by carrying out a run with the probe held in air over the same temperature range and at the same heating rate as the subsequent experiment. An important point to note is that, at any point, a "clean probe" function can be used that heats the probe to 700 °C or higher so the probe can always be restored to a pristine condition whenever required.

The IR spectra of the bulk materials were collected using an FTIR spectrometer (IFS66/S model, Bruker Optics limited, Coventry, UK). A Golden Gate™ heated diamond ATR top-plate was connected with a 3000 Series™ high stability temperature controller with RS232 control (Specac Ltd., Kent, UK). The IR spectra of the physical mixture in bulk were acquired before and after an additional thermal treatment (90 °C for 15 min) on the sample. The thermal treatment of the physical mixture was performed on the ATR sample stage. Photothermal microspectroscopy (PTMS) analysis was implemented by integrating, using a dedicated optical interface, Thermomicroscopes Explorer AFM equipped with a Wollaston wire thermal probe and the FTIR spectrometer. The magnesium stearate and acetylsalicylic acid particles were picked up by the Wollaston probe and the individual IR spectra of the particles were taken and compared with the ATR-FTIR spectra of the corresponding bulk materials. The IR spectra of the physical mixture particles on the tip were acquired on the tip at room temperature then the tip was heated 90 °C and held for 15 min. The spectra of the heated mixture particles were then acquired at room temperature and compared with the results of the particle without heating and the ATR-FTIR results of the bulk materials.

3. Results

3.1. Thermal behaviour of pure components

The melting point of acetylsalicylic acid, determined by DSC, was 139.6 °C (±0.2 °C) (data not shown) with decomposition seen as a broad peak at circa 170 °C. The localised thermomechanical analysis (L-TMA) response of the pure acetylsalicylic acid compact is shown in Fig. 1. Here the tip is seen to rise marginally due to thermal expansion of the sample followed by a rapid onset penetration, corresponding to the melting of the material

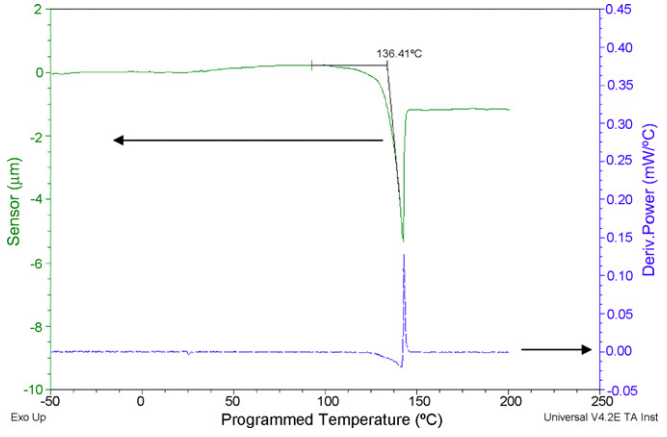

Fig. 1. Localised thermomechanical analysis (L-TMA) of an acetylsalycilic acid compact (heating rate 20 °C/s).

immediately underneath the probe. The melting point was identified as 136 °C (±0.9 °C), which is in reasonable agreement with conventional thermal studies. The derivative of the power signal shows an endothermic followed by an exothermic trend. This may be interpreted as being due to the signal being a function of both the heat absorption during melting and the change in contact between the tip and sample. As the probe penetrates during melting, there is increased thermal coupling between the probe and the sample as the contact area increases, while as melting proceeds the probe breaks free of the sample and so the thermal coupling decreases, leading to what appears as an exothermic peak (note that these changes in coupling appear as peaks due to the use of the derivative signal).

A DSC study of magnesium stearate powder performed in open aluminium pans revealed a complex profile containing four endothermic and one exothermic peak (Fig. 2). The thermal profile is difficult to interpret due to the complex chemical constitution of magnesium stearate, the commercial material containing a mixture of long chained aliphatic acids with a variable water and polymorphic content. Similar profiles have been observed previously (Ertel and Carstensen, 1988; Wada and Matsubara, 1992; Ketolainen et al., 1995; Bruni et al., 2002; Koivisto et al., 2004; Bracconi et al., 2005), with most authors arguing that the low temperature endotherms are associated with dehydration events, followed by fusion (melting) at higher temperatures. TGA studies revealed two weight loss peaks in the derivative weight signal at circa 82 and 100 °C; these are also clearly seen in the derivative signal shown in Fig. 2. These were in good agreement with the first two endothermic peaks seen in the DSC heat flow signal, indicating that the origin of the peaks was indeed dehydration of material. The loss of crystalline water was considered to be responsible for the weight loss, most probably converting dihydrate form of magnesium stearate to the anhydrous form via the monohydrate as an intermediate product, although the poor chemical specificity of the commercial material renders precise explanation difficult. In general, magnesium stearate has been reported to contain 0–3 molecules of water per base molecule (Rajala and Laine, 1995), depending on the commercial batch used and the storage conditions. DSC endotherms that were not accompanied by any measurable TGA weight loss could be assigned to melting of magnesium stearate and its impurities or polymorphic forms (Mura et al., 1998; Bruni et al., 2002; Marini et al., 2003). The main fusion peak, seen at circa 118 °C, is believed to correspond to melting of magnesium stearate. The right shoulder of the main peak at circa 125 °C may stem from the melting of palmitate or higher-melting stearate polymorphs. The exothermic peak at approximately 157 °C is believed to originate from the chemical transformation of inorganic impurities, these being principally magnesium salts residues (Bracconi et al., 2005).

Preliminary studies indicated that the DSC responses of the scrapings from the compacts matched those of the powder outlined above. L-TMA studies on compacts, however, revealed a single transition at 153.0 °C (±1.8 °C) (Fig. 3a). This result was not in accordance with the previously obtained DSC results which suggested that melting takes place at considerably lower temperatures. Further investigations were carried out by visual observation of the melting process using HSM. At approximately 120 °C, the material took the form of a transparent, viscous mass. It was only after the temperature of approximately 150 °C was reached that the material became more fluid. It is suggested that the transition at circa 120 °C could not be

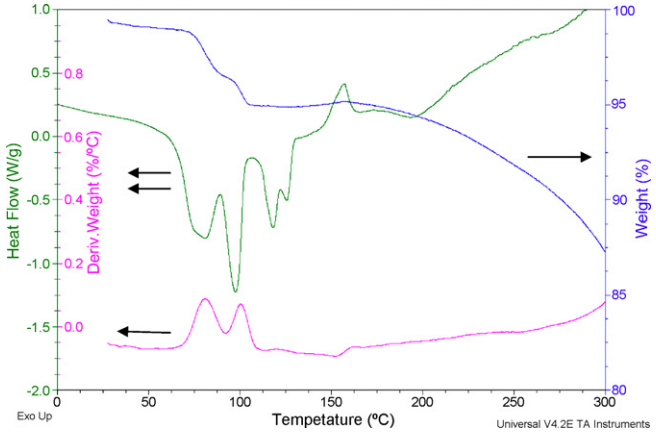

Fig. 2. Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA, raw data and derivative signal shown) of magnesium stearate as received. All studies were run at 10 °C/min. The arrows indicate the scale, with the double arrow indicating the heat flow (DSC) data.

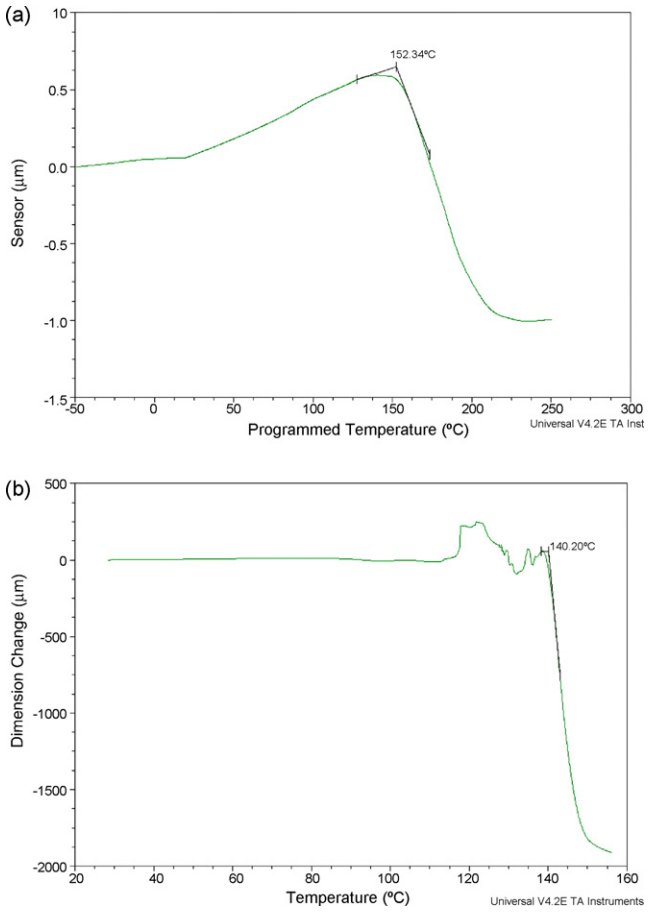

Fig. 3. (a) Localised thermomechanical (L-TMA; 20 °C/s) and (b) macroscopic thermomechanical analysis (TMA; 3 °C/min) study of a magnesium stearate compact.

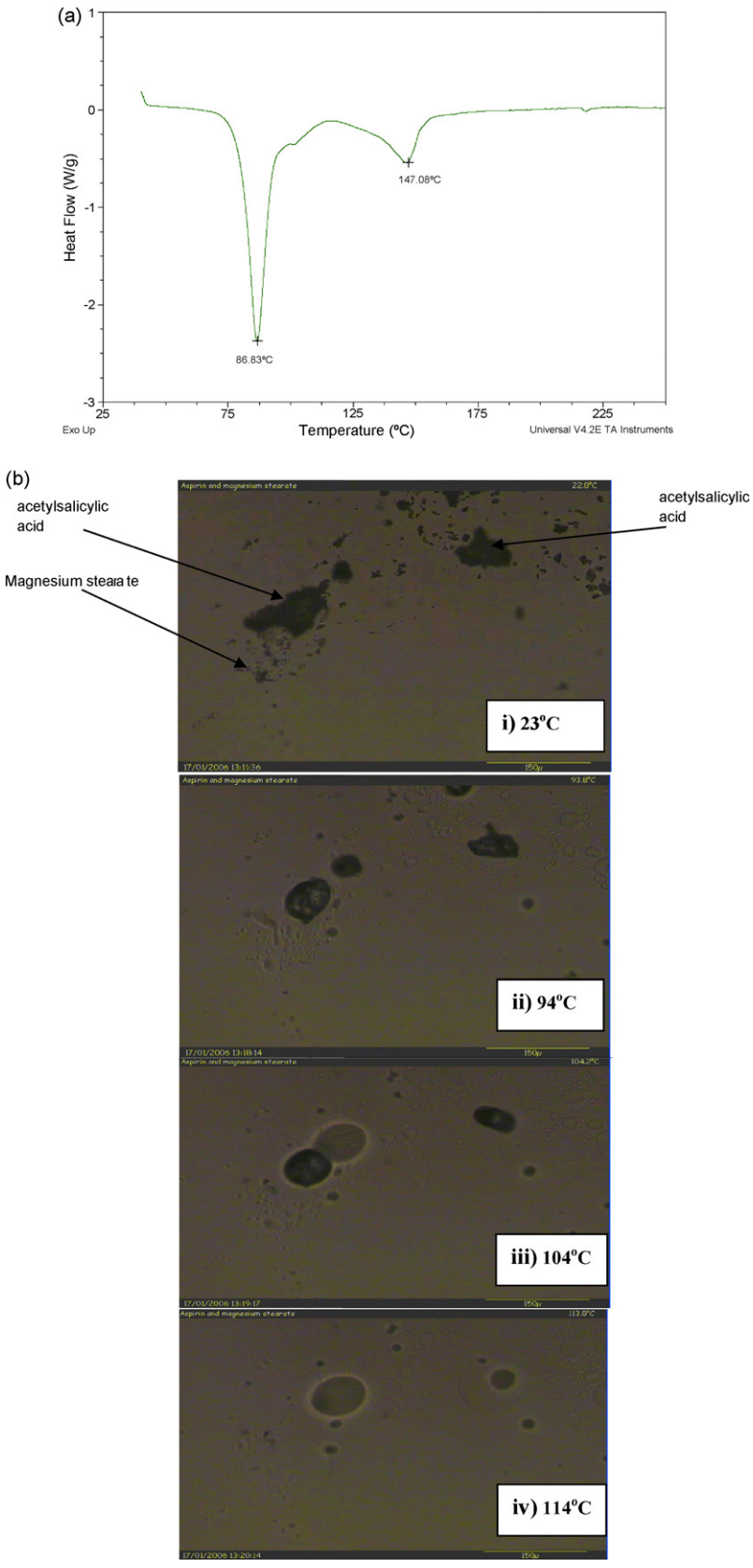

Fig. 4. (a) DSC of magnesium stearate–acetylsalicylic acid (50:50, w/w) physical mix at 10 °C/min and (b) HSM results for magnesium stearate–acetylsalicylic acid physical mix (50:50, w/w) at (i) 23 °C; (ii) 94 °C; (iii) 104 °C and (iv) 114 °C. Mixes were 50/50 composition and a heating rate of 10 °C/min was used.

detected via L-TMA because of the limited change in the mechanical and viscoelastic properties of the sample, indicating that the transition is not a simple solid to liquid transition but rather a partial melting which results in the formation of a semisolid material. Macroscopic TMA, performed on magnesium stearate compacts (Fig. 3b) showed a significant probe penetration at approximately 140 °C; noise was consistently noted in the region immediately prior to the probe penetration, suggesting a degree of mechanical perturbation. While this penetration temperature does not correspond precisely to the L-TMA studies, both investigations (and the HSM studies) indicate that the material undergoes a mechanical change well above the melting point of the material as suggested by DSC.

3.2. Thermal behaviour of physical mixes of magnesium stearate and acetylsalicylic acid

The melting behaviour of the magnesium stearate–acetylsalicylic acid physical mixture was altered on mixing the two components resulting in a substantial decrease in the melting peak maximum. The DSC thermogram showed two endothermic peaks in the heat flow signal: a main peak at circa 87 °C, followed by a broader peak at approximately 147 °C (Fig. 4a). This behaviour has been noted previously (Miller and York, 1988; Wissing et al., 2000), although the mechanism responsible for the melting point lowering effect is less clear.

The equivalent HSM study (Fig. 4b) showed larger particles of acetylsalicylic acid surrounded by fine particles of magnesium stearate. On heating, a liquid layer was formed around the acetylsalicylic acid particles at approximately 90 °C, with particles dissolving slowly into the liquid layer. Similar findings were reported previously by Miller and York (1988) and Mroso et al. (1982). The intimate contact between the two materials was suggested to have facilitated the interaction.

3.3. Investigation using nanosampling

The chemical incompatibility between magnesium stearate and acetylsalicylic acid was studied using the nanosampling technique, as described by Harding et al. (2007). The technique is based on the principle of contaminating a thermal probe with a minuscule amount of a lower melting material using LTA. This probe is then used to perform thermal analysis on a higher melting material. In summary, we found that no change was detected regardless of which material was used as the nanosample and which as the surface. It was also found that PTMS detected no material on the tip after thermal analysis of the two materials. It was concluded that no material adhered to the tip. This could have been remedied by changing the chemistry or geometry of the tip but this was not pursued here. Instead, particle manipulation techniques were used as an alternative approach.

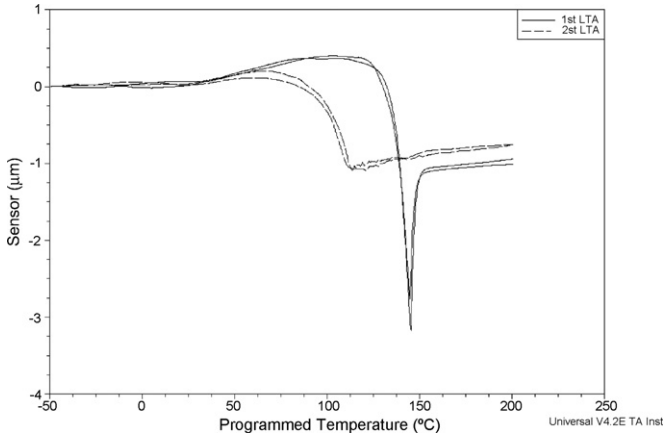

Fig. 5. L-TMA profiles of an acetylsalicylic acid tablet showing L-TMA data at the same location on first and second scan using a maximum temperature 200 °C (20 °C/s).

3.4. Thermal interaction studies using thermally assisted particle manipulation

A larger amount of contaminant could be deposited on a tip using a particle manipulation technique whereby the heated tip is used to 'pick up' a particle at a temperature whereby the particle is softened and adhesion increased, as described previously (Harding et al., 2007). However, when using elevated temperatures to assist in 'sticking' the particle to the tip, care must be taken to ensure that the particle is not chemically changed by decomposition (a particular danger when dealing with acetylsalicylic acid due to its thermolability). This decomposition is illustrated in Fig. 5, whereby an acetylsalicylic acid compact was subject to localised thermal signal rising to a temperature of 200 °C. After cooling the tip, a second experiment was then performed in the same location. The result was a lower melting temperature on the second run due to the introduction of impurities from decomposition induced by the first heating. However, this decomposition did not occur (i.e. the two scans were superimposable) when the maximum temperature used was 140 °C, hence this was chosen as the temperature for attaching the particle. To this end, acetylsalicylic acid particles were sprinkled over a glass slide and attached to a Wollaston wire held isothermally at 140 °C. As soon as the particles were attached, the temperature of the probe was reduced to 25 °C. This was performed so as to minimise the decomposition of acetylsalicylic acid while also anchoring the particle to the tip.

The particle-loaded probe was then used to perform L-TMA on a magnesium stearate compact at 5 °C/s (Fig. 6). The thermal profiles obtained differed significantly from the profiles shown in Fig. 3a, with the probe penetration onset at approximately 70 °C. These results suggest that the magnesium stearate–acetylsalicylic acid interaction could be detected using the particle manipulation technique. The same experiment carried out with an acetylsalicylic acid particle on an acetylsalicylic acid compact gave the same onset of penetration temperature as the compact alone and so the considerable change in the thermal behaviour must be due to an interaction between the particle and the magnesium stearate compact.

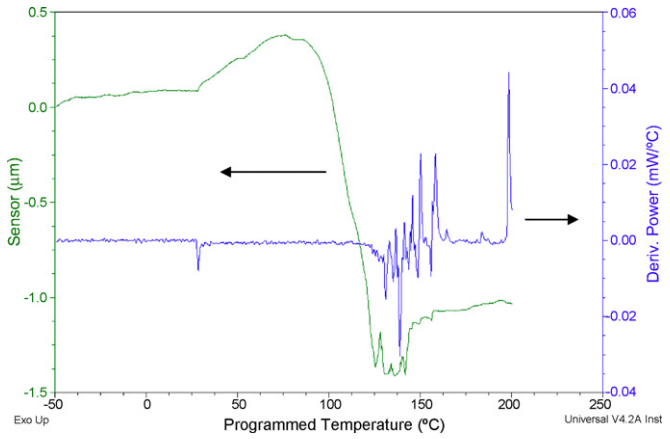

Fig. 6. L-TMA (5 °C/s) of a magnesium stearate compact performed with a tip on which a salicylic acid particle has been attached at 25 °C. L-DTA signal also shown (note that the peak at 35 °C corresponds to the kick-in temperature).

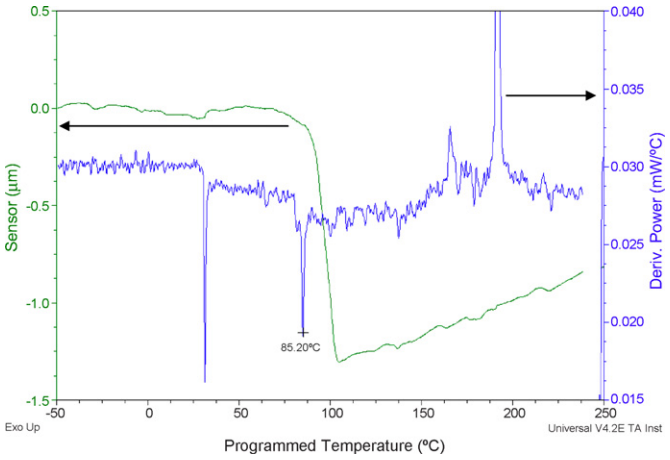

Fig. 7. L-TMA and L-DTA profiles (5 °C/s) of acetylsalicylic acid deposited on a magnesium stearate compact.

3.5. Thermal interaction studies using non-thermal particle manipulation

It was noted that the L-TMA results in Fig. 6 resemble the profiles of decomposed acetylsalicylic acid, as shown in Fig. 5. While this is entirely consistent with the detection of the drug–excipient compatibility, there was a possibility, although considered unlikely, that the particles of acetylsalicylic acid decomposed on manipulation; in other words the response seen was that of a previously decomposed aspirin particle rather than the interaction with magnesium stearate. In order to investigate this possibility, a series of 'blank' experiments was performed. The heating step used to achieve particle attachment to the tip was omitted from the particle manipulation protocol, thus eliminating the possibility of thermal decomposition. Acetylsalicylic acid particles were attached to a probe at room temperature via electrostatic and van der Waals forces via simple contact between the probe and the particle. This method proved considerably more difficult than the one involving heating; particles did not attach to the tip readily and several attempts needed to be made in order to ensure particles were secured firmly thus perseverance were required. However it was noted that picking up particles without the use of heat is now a possibility. The tip with acetylsalicylic acid particles was then used to perform L-TMA on a magnesium stearate compact. The results showed a very similar profile to the previous experiment, thereby invalidating the decomposition theory as no opportunity for prior thermal decomposition had been presented.

3.6. Localised differential thermal analysis and a modified thermally assisted particle manipulation method

In a further development of this experiment, particles of acetylsalicylic acid were attached to a probe at 25 °C. The probe was brought lightly into contact with the surface of a magnesium stearate compact and briefly heated to 140 °C to deposit the drug particles on the magnesium stearate surface (confirmed by subsequent imaging). In other words, instead of attaching the particle to the tip the particle was deposited on the surface and the construct then interrogated by a clean tip. The probe was positioned on the deposited particles and L-TMA/L-DTA performed at 5 °C/s. The results showed the interaction in both L-DTA and L-TMA signals (Fig. 7). Interestingly, a clear transition is seen in the L-DTA signal at the onset of the L-TMA transition.

3.7. Combining tip-controlled thermal processing and PTMS

Particles of acetylsalicylic acid and magnesium stearate were picked up (at room temperature) and spectra were taken and compared with ATR spectra; these data are shown in Fig. 8a. Essentially the same peaks are seen by both techniques but the relative heights are different due to the different physical principles of the two methods. However, it is worth emphasising that, if one assumes an individual particle of, for example, aspirin, has a diameter in the region of 10 µm the spectra obtained from the PTMS is obtained on sample sizes in the nanogram region.

The probe was then inserted into a 50/50 physical mixture and a small (unspecified) number of particles were picked up. The PTMS spectra confirmed that this sample was a composite of both materials. The tip was then heated to 90 °C for 15 min. In parallel with this, temperature controlled (conventional) ATR-FTIR was performed under an identical thermal cycle for comparison. It was observed that the spectra changed in a similar way using both techniques; in Fig. 8b the region of the spectrum of the mixture that exhibited the most marked change is highlighted. The ATR spectra is shown in Fig. 8b (Spectrum C; before heating) and (Spectrum D; after heating) and compared with the PTMS equivalents in (Spectrums E and F; before and after heating, respectively). In both cases several peaks are seen to diminish while others increase in a broadly similar way. Given the chemical complexity of the interaction, it is not appropriate to attempt to interpret the spectra specifically at this stage. What is however clear is that changes can be seen as a consequence of the interaction between the two components and this can be followed using PTMS on extremely small quantities of material.

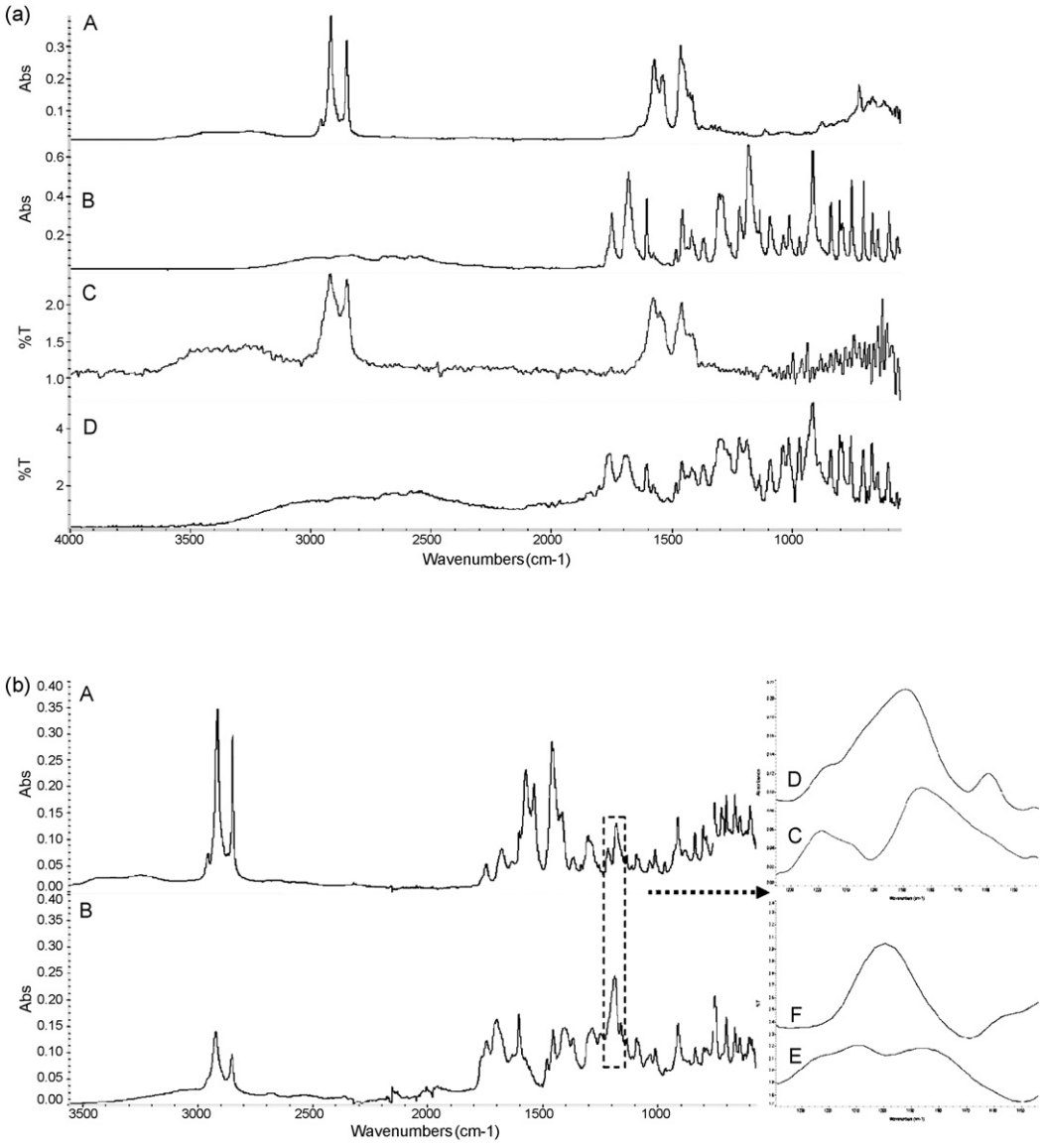

Fig. 8. (a) Full ATR-FTIR spectra of (A) magnesium stearate and (B) acetylsalicylic acid; full PTMS spectra of (C) magnesium stearate particles on the tip and (D) acetylsalicylic acid particles on the tip. (b) Full ATR-FTIR spectra of (A) the magnesium stearate–acetylsalicylic acid (50:50, w/w) physical mix and (B) the mix after 15 mins thermal treatment at 90 °C; (C and D) are the ATR-FTIR results of highlighted region (1240–1140 cm^{-1}) of the mix before and after the thermal treatment, respectively; the partial PTMS spectra at the same region (1240–1140 cm^{-1}) of (E) the mix particles on the tip without thermal treatment, and (F) after 15 mins of holding the tip temperature at 90 °C.

4. Discussion

The study has addressed three issues regarding the development of novel thermally based excipient compatibility studies. Firstly, a number of interesting observations have been made regarding the use of conventional thermal techniques. More specifically, the observation that the thermomechanical behaviour did not correspond to the putative melting point of the magnesium stearate is of interest and implies that while at least partial melting takes place at the designated endotherm, the liquefaction process is more complex which may in turn imply the generation of either a very viscous molten material or a structured material.

The second set of observations relate to the use of probe techniques to detect the interaction. We report here on approaches that both have and have not worked in order to aid development of the method. The nanosampling technique was not successful in this case as no material was collected on the tip. It is not yet clear which materials may be successfully nanosampled and what factors determine the amount and extent of sample capture. The fact that we have identified materials for which the technique in its current basic form does not result in effective sampling is a useful comparator for future refinements, while the use of PTMS to identify whether any material has been sampled or not is demonstrated. We also describe three approaches for introducing the drug and excipient to each other on a microscale. Firstly, we use the established technique of thermally assisted particle manipulation, whereby the heated tip partially melts a particle to allow adhesion which may then be placed in contact

with the excipient surface; we describe the problem of thermal degradation associated with this technique. The next manipulation technique is to pick up the particle at room temperature via simple electrostatic/short range force adhesion. This method is more time-consuming and cumbersome but clearly avoids the problem of heating. Thirdly, we describe a technique whereby rather than touching the excipient surface with an attached particle, that particle is 'melted off' the tip and allowed to form a construct on the excipient surface. Using L-TMA, it was possible to detect the interaction via a reduction in the penetration temperature using all three methods. However, it was noted that the clearest L-DTA signal came using the third (construct) approach. We suggest that this is due to the contact between the tip and sample remaining largely unaltered with this approach. However, it is clear that overall there are a number of possible related approaches whereby excipient compatibility can be detected at the level of a single particle.

The final issue addressed by the study is the use of PTMS as a novel means of detecting degradation spectroscopically. We outline a simple but effective technique whereby we are able to pick up a mixed sample and then detect changes in the spectra after heating. While we are not in a position to specifically interpret the spectra at this stage, the fact that such interactions may be detected on such a small sample is, we suggest, highly significant.

5. Conclusions

The study has demonstrated that it is possible to detect thermally induced drug–excipient incompatibility at the level of single particles. More specifically we can use measurement of changes in probe penetration, differential thermal analysis or photothermal microspectroscopy to detect and possibly chemically characterise such incompatibilities. The fact that it is possible to detect such changes on extremely small samples may have advantages in terms of drug conservation for developmental compounds and enhanced sensitivity due to intimate contact between the two materials. With further development, it is also conceivable that the approach could be used for high throughput screening. We therefore suggest that the microthermal techniques may provide a novel and innovative set of methods for detecting excipient incompatibilities with drugs.

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