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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-