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An investigation into the use of stepwise isothermal high sensitivity DSC as a means of detecting drug-excipient incompatibility

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Abstract

The use of stepwise isothermal high sensitivity differential scanning calorimetry (HSDSC) as a novel means of detecting excipient incompatibility is described using aspirin mixes with magnesium stearate and stearic acid as model systems. Aspirin, magnesium stearate and stearic acid alone and as mixes were studied in scanning mode using conventional DSC and were then subjected to a stepwise heating programme using HSDSC, whereby the samples were heated to temperatures between 45 and 70°C and held for 1 h, during which the heat flow to or from the sample was measured. The data indicated that while no thermal events were detected for the individual components or mixes with stearic acid other than melting of stearic acid, 50% w/w mixes of magnesium stearate showed a marked endothermic response at temperatures above 55°C. The data were fitted to an adaptation of an existing kinetic model for the degradation process and a reasonable correlation found. Mixes of the drug with the two excipients were then studied at 60°C over 6 h at concentrations between 1 and 50% w/w. Incompatibilities with magnesium stearate concentrations as low as 1% w/w could be detected using this approach. Compacts of magnesium stearate and aspirin were also studied, with considerably more pronounced thermal events taking place compared to the powder mixes. It is concluded from these studies that while the study has highlighted certain limitations of the approach, stepwise isothermal DSC represents a potentially highly useful means of detecting excipient incompatibilities.

Keywords: Aspirin; Compatibility; Differential scanning calorimetry; Excipient; Magnesium stearate; Stability; Stearic acid

1. Introduction

The difficulties associated with excipient incompatibility are well recognised within the pharmaceutical industry and routinely lead to the

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necessity of performing costly real time and accelerated storage studies. These investigations are often carried out at a period in the development of a drug when there is a paucity of raw material, hence there is also an issue of drug availability if a range of excipients or formulations is to be examined. At present, prediction of incompatibility between a drug and a single excipient is extremely difficult (and prediction for a complete formulation even more so), hence any method of early detection would be of use, even if such a method was only able to screen out the most problematic binary mixes or formulations.

One approach that has been used in this respect is differential scanning calorimetry (DSC), whereby the power differential between a sample and reference is measured as a function of temperature. The use of the method as a means of detecting excipient incompatibilities continues to generate interest (e.g. Venkataram et al., 1995; Mura et al., 1995, 1998; Botha and Lötter, 1989). The premise for this approach is that changes in the melting behaviour of one or other component may be used as an indication of chemical incompatibility. While some industries routinely scan drug-excipient mixes as a means of detecting any such behaviour, the approach is not considered to be fully reliable and its use therefore remains controversial. There are arguably two principal reasons for this unreliability. Firstly, differences in the DSC scans of binary mixes compared to the individual constituents may arise for a number of reasons other than chemical incompatibility. For example, Lloyd et al. (1997) have demonstrated that drug-polyethylene glycol mixes exhibit melting behaviour that does not correspond to that of the individual components due to slow dissolution of the drug in the molten PEG. The second reason is that the seminal work in which this concept was discussed involved a system (magnesium stearate and aspirin) whereby the incompatibility was intrinsically linked to the melting behaviour (Mroso et al., 1982), as will be discussed in more detail below. Consequently, the approach may not be expected to be applicable to all forms of excipient interaction.

The incompatibility between magnesium stearate and aspirin results in the generation of a number of potentially immunogenic products including salicylic acid, salicylsalicylic acid and acetylsalicylsalicylic acid (Bundgaard and DeWeck, 1975; Reepmeyer and Kirchhoefer, 1979; Mroso et al., 1982; Patel et al., 1982) with further decomposition products generated at high temperatures (Taguchi et al., 1981). It was originally believed that the incompatibility took place via the presence of magnesium oxide impurities in the lubricant forming an alkaline environment on hydration, thereby catalysing degradation. However, Mroso et al. (1982) suggested that the main mechanism was a reduction in melting point of the aspirin, thereby generating a liquid layer on the outside of the magnesium stearate particles in which degradation was accelerated, hence the link between changes in melting point and incompatibility for these systems. A number of approaches are available for the modelling of the decomposition of aspirin based on the principle of considering there to be a liquid decomposition layer on the surface of the (spherical) particle which diffuses inwards as the reaction proceeds (Jander, 1927). Nelson et al. (1974) modelled the alkali-induced decomposition of aspirin, while Mroso et al. (1982) studied the specific example of aspirin/magnesium stearate mixed systems. These authors proposed that if the reaction rate is limited by diffusion, an expression may be derived which describes the proportion decomposed in relation to the rate of generation of the liquid layer. In the case of the cylindrical aspirin particles, the expression used was

$$[1-(1-x)^{1/2}]^2 = \frac{2k}{r_0^2}\,t \qquad (1)$$

where x is the fraction of degradation product after time t, k is a constant relating the thickness of the liquid layer y to time via

$$y^2 = 2kt \qquad (2)$$

and r_0 is the initial radius of the cylinder, assuming the length to diameter ratio is such that the end effects are negligible. The authors demonstrated that plots of $[1-(1-x)^{\frac{1}{2}}]^2$ against t showed the predicted linear relationship for a range of magnesium stearate compositions.

In this investigation, we describe the use of high sensitivity DSC (HSDSC), run in stepwise isothermal mode, as a potential alternative approach to studying excipient incompatibilities. HSDSC operates on a similar principle to conventional DSC but displays certain important differences. The technique is $\approx$10–100-fold more sensitive than the conventional method, being able to detect baseline changes below 1 μW, while the sample pan size is considerably greater (approximately 1 ml); both of these considerations result in greater sensitivity to small thermal events. The traditional use for HSDSC lies in the measurement of thermal events in aqueous solutions and suspensions, particularly protein degradation or aggregation reactions and vesicle phase transitions (Chowdry and Cole, 1989; Ladbury and Chowdry, 1998). However, the approach may also be used for solid samples and, as will be demonstrated, can also be used to analyse powder compacts. The method is generally used in scanning mode using a heating rate of 1–2°C/min or lower. However, it is also possible to operate the instrument in isothermal mode in order to monitor kinetic events, hence in this respect the instrument may be used in a similar manner to that of an isothermal microcalorimeter (albeit with lower sensitivity). However, an important advantage of HSDSC is that the temperature may be changed with ease, hence affording the possibility of performing stepwise isothermal runs (which is not practically feasible using microcalorimetry) with a sensitivity greater than DSC. The flexibility associated with the capability of studying the system over a range of temperatures may be of importance not only in terms of deriving kinetic information in order to predict the behaviour over a range of temperatures but may also be of considerable relevance when studying systems whereby reaction mechanisms may change between, for example, real time and accelerated stability storage temperatures.

Given the combination of sensitivity and flexibility associated with HSDSC, it is logical to investigate the use of the technique as a means of detecting excipient incompatibilities. In particular, the use of stepwise studies, whereby the sample is maintained at a single temperature for a given period of time and is then heated or cooled to a different temperature at which the sample is again held, at least partially overcomes the difficulty of detecting signals which correspond to reactions which are extremely slow at low temperatures. It is, however, appreciated that, in common with any accelerated stability study, an assumption is being made that the underlying reaction mechanism remains unchanged at the different temperatures. While there is anecdotal evidence of related approaches being of use from the instrument sales literature, there has not to our knowledge been a study published in the peer reviewed literature, which provides evidence for or against the validity of the method. The objective of the present study is therefore to examine the concept that the technique may be used to detect the aspirin/magnesium stearate incompatibility and, where possible, to identify the strengths and limitations of the approach.

2. Materials and methods

2.1. Materials

Aspirin and magnesium stearate were obtained from Sigma Chemicals, while stearic acid was obtained from Unichema International. In all three cases the 75–150 μm size fractions were used (although it is appreciated that the primary particle size of the magnesium stearate will inevitably be considerably less than the lower sieve limit). Preliminary studies using thermogravimetric analysis gave total water contents of $<1\%$ w/w for the aspirin, 4.64% w/w for the magnesium stearate and $<1\%$ w/w for the stearic acid. Chloroform and acetic acid (99.8%) were obtained from BDH Laboratory Supplies.

2.2. Methodology

Physical mixes containing 1, 10 and 50% w/w magnesium stearate and 50% w/w stearic acid with aspirin were prepared by roller mixing for 5 min. Compacts of diameter 5 mm were prepared via compression of 160 mg of sample using a pressure of 1 ton for 5 min. Conventional DSC studies were performed using a Perkin–Elmer DSC 7, with samples of approximately 5 mg weighed into non-hermetically sealed aluminium pans. A scanning

rate of 10°C/min was used. Approximately 160 mg of sample were loaded into the sample vessel of a Settaram Micro DSC 111. Stepwise studies were conducted by ramping from 25 to 45°C at 10°C/min, followed by holding at 5°C intervals for 1 h up to 70°C. Further isothermal studies were conducted at 60°C for 6 h. All experiments were performed twice, with excellent reproducibility found between runs.

Aspirin degradation was monitored using an adaptation of the method described by Tinker and McBay (1954); while more sophisticated methods are available for degradant determination using, for example, HPLC (Mroso et al., 1982) the objective in this study was to establish whether or not decomposition was taking place or not, hence this simpler method was employed. Pure aspirin and mixes were placed sealed in an oven set at 66°C and samples equivalent to 50 mg aspirin removed at hourly intervals. These samples were made up to 50 ml with chloroform, followed by addition of 1 ml acetic acid. After filtration the sample was assayed photometrically at 278 nm for aspirin. All measurements were taken at least twice, with multiple repeats indicating a coefficient of variation less than 3%.

3. Results and discussion

Fig. 1A and B shows the conventional DSC traces for the excipients and drug alone and the corresponding 50% w/w mixes. As expected, the melting behaviour of the magnesium stearate/aspirin system is altered on mixing the two components (Fig. 1A), with the addition of 50% w/w magnesium stearate resulting in a substantial decrease in the melting peak maximum. This represents the classical behaviour of these systems and correlates well with hot stage microscopy studies which showed the presence of a liquid layer around the aspirin particles on heating in the presence of magnesium stearate (data not shown). The question remains as to why the magnesium stearate should have this melting point lowering effect. Lloyd et al. (1997) have argued that while the fact that non-eutectic binary mixes may have lower melting points than the individual components is well known, the mechanism responsible is less clear. It is recognized that magnesium stearate forms a surface film on the host particles (Miller and York, 1988), hence the intimacy of contact between the two materials may facilitate the melting point lowering process. It is noted that stearic acid also caused changes in the melting behaviour, with decreases in the aspirin melting point seen on adding 50% w/w stearic acid (Fig. 1B).

The effects of stepwise temperature elevation using HSDSC for aspirin alone, magnesium stearate alone and 50% w/w magnesium stearate are shown in Fig. 2A. The temperature is shown by the narrow continuous line and indicates the programme used (5°C increments from 45 to 70°C with steps of 1 h). The peaks in the heat flow curves represent re-equilibration between temperature increments and the time constant of the instrument, while the continuous lines between increments represent the heat flow traces; a baseline heat flow value of zero indicates that there is no difference in energy flux behaviour between the sample and reference vessels. Examination of the curves for the individual components indicates no deviation in heat flow from the baseline, suggesting that no discernible changes are taking place to the samples over the temperature range under study. However, examination of the binary mix clearly shows a marked endothermic deviation from the baseline, indicating that a kinetic thermal event is taking place, particularly at temperatures above 65°C. Fig. 2B shows the equivalent data for the stearic acid systems. No evidence of the extensive deviation from the baseline seen for the magnesium stearate system was observed, although at 65°C a small endothermic heat flow was observed which could correspond to the melting of the stearic acid.

The data shown in Fig. 2A clearly indicate that the stepwise isothermal approach is indicating a temperature and time dependent reaction between the magnesium stearate and aspirin. Working on the assumption that this event is associated with the degradation of the drug, it would be desirable to model the data in terms of the reaction kinetics. However, the stepwise method suffers from the disadvantage familiar to microcalorimetry studies in that drug degradation pathways are almost invariably complex, rendering reliable modelling

difficult to achieve. Nevertheless, it is interesting to speculate that if one re-examines the approach used by Mroso et al. (1982), making x the subject, the expression may be given as

$$x = \left(\frac{2^{3/2}k^{1/2}}{r_0}\right)t^{1/2} - \frac{2kt}{r_0^2} \quad (3)$$

If one now assumes that the enthalpy of reaction is a linear function of degradant concentration, then

$$dH/dt = c \cdot dx/dt \quad (4)$$

where c is a constant of proportionality. Consequently by differentiating Eq. (3) and combining with Eq. (4) one obtains

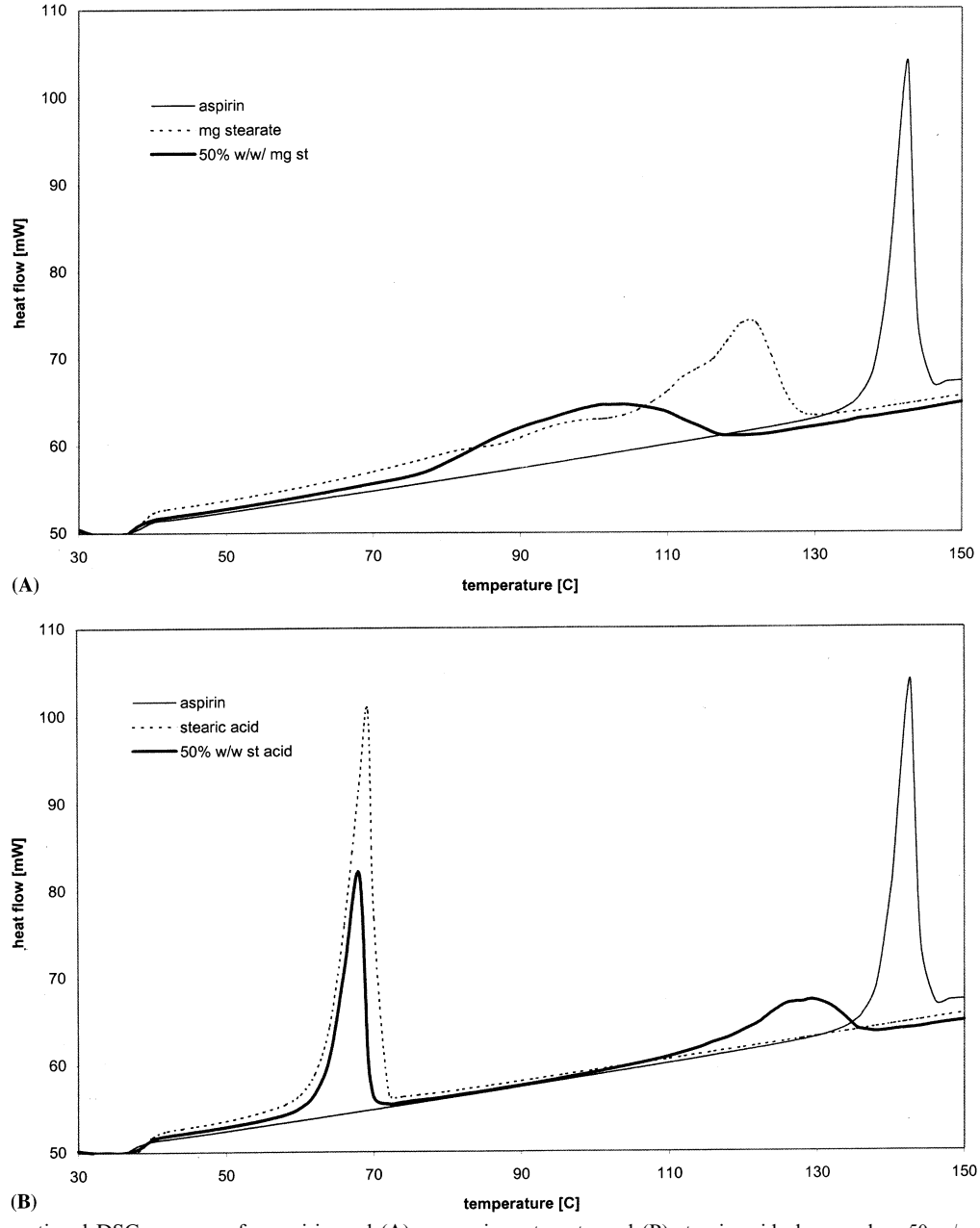

Fig. 1. Conventional DSC responses for aspirin and (A) magnesium stearate and (B) stearic acid alone and as 50 w/w mixes.

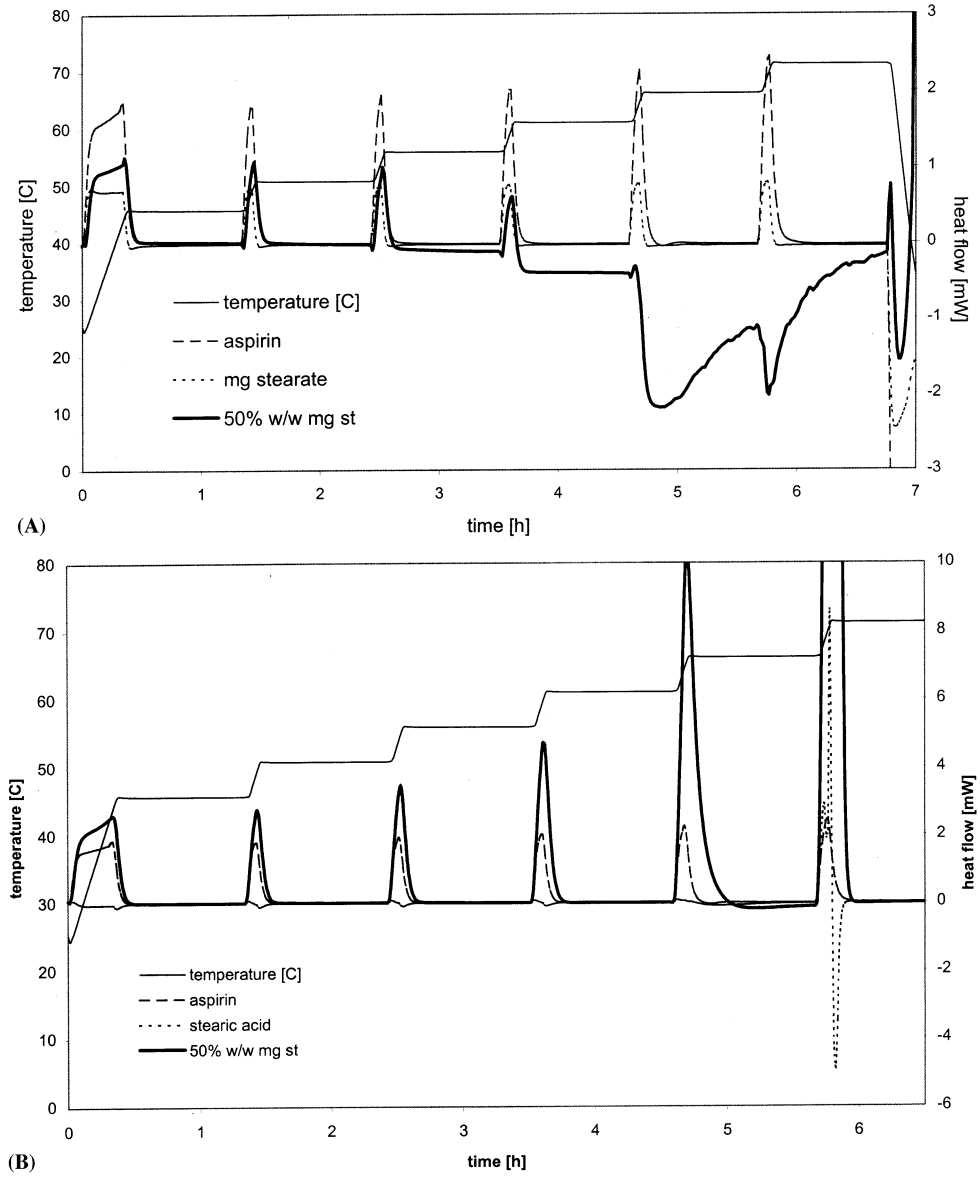

Fig. 2. Stepwise isothermal HSDSC runs using 5°C increments and 1 h holding times for aspirin and (A) magnesium stearate and (B) stearic acid alone and as 50% w/w mixes.

$$\frac{dH}{dt} = \left(\frac{2^{1/2}k^{1/2}}{r_0 t^{1/2}} - \frac{2k}{r_0^2}\right)c \qquad (5)$$

This expression predicts that the observed heat flow will be inversely proportional to the square root of time. Fig. 3 shows the post-equilibration heat flow when dH/dt approaches the baseline for the system taken from the 65 and 70°C inter vals plotted against inverse square root of time, indicating reasonable linearity (although periodicity is noted in both responses). Clearly, this approach is at an early crude stage at present but may represent a useful means of analysis with further development.

The response was then studied at 60°C using a range of magnesium stearate concentrations over a longer period of time in order to investigate the sensitivity of the technique. Fig. 4 shows the response for systems containing 1, 10 and 50% w/w magnesium stearate. While the baseline deviation is greatest for the 50% w/w systems, as expected, it is also clear that the reaction can be

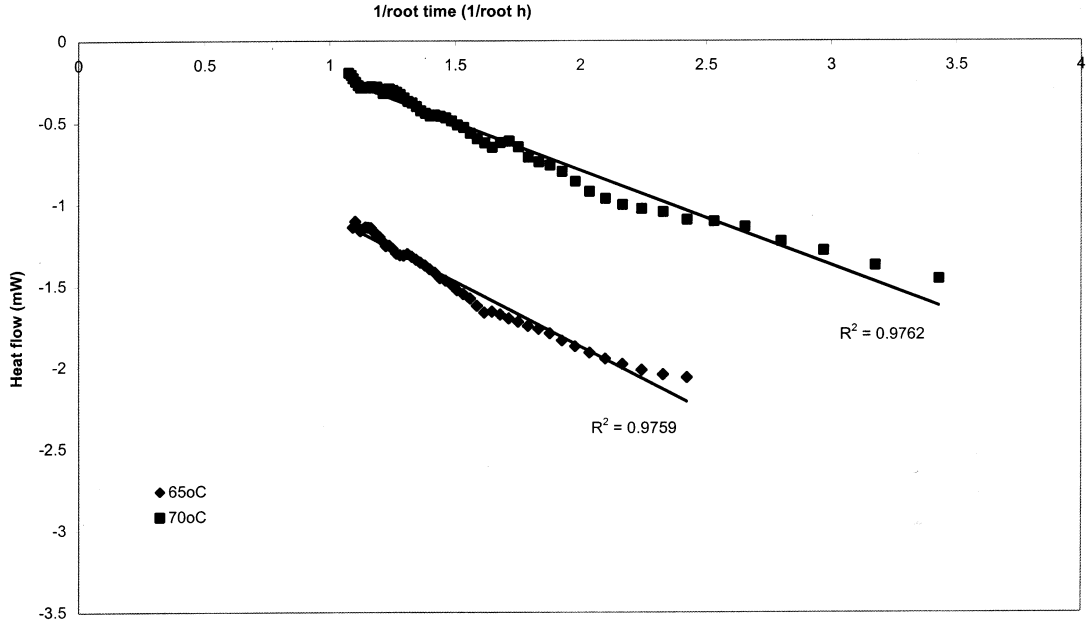

Fig. 3. Plot of heat flow against inverse root time for magnesium stearate and aspirin mixes (50% w/w) taken at 65 and 70°C.

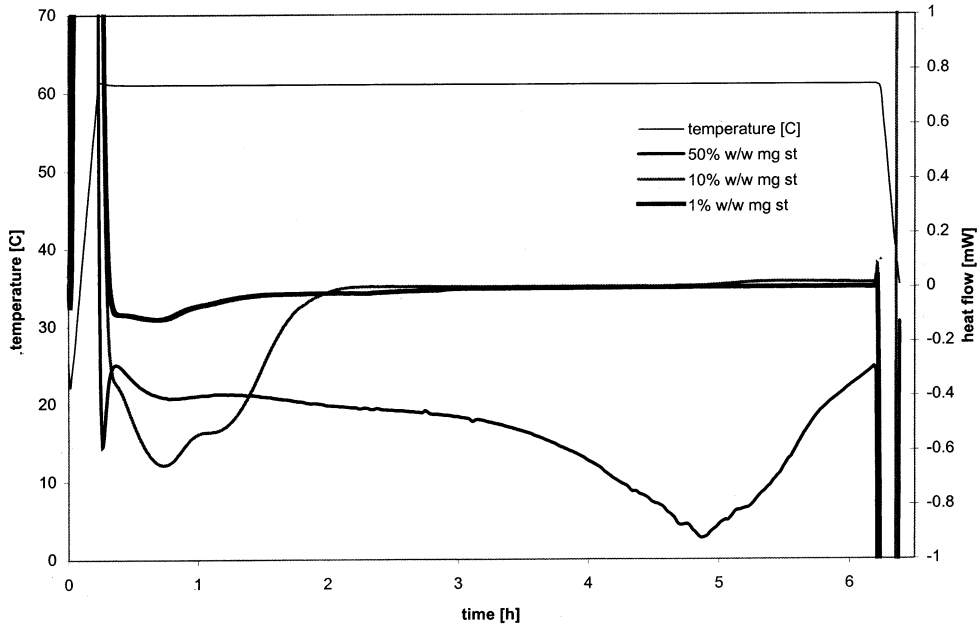

Fig. 4. HSDSC responses for systems containing 1, 10 and 50% w/w magnesium stearate/aspirin mixes held isothermally at 60°C.

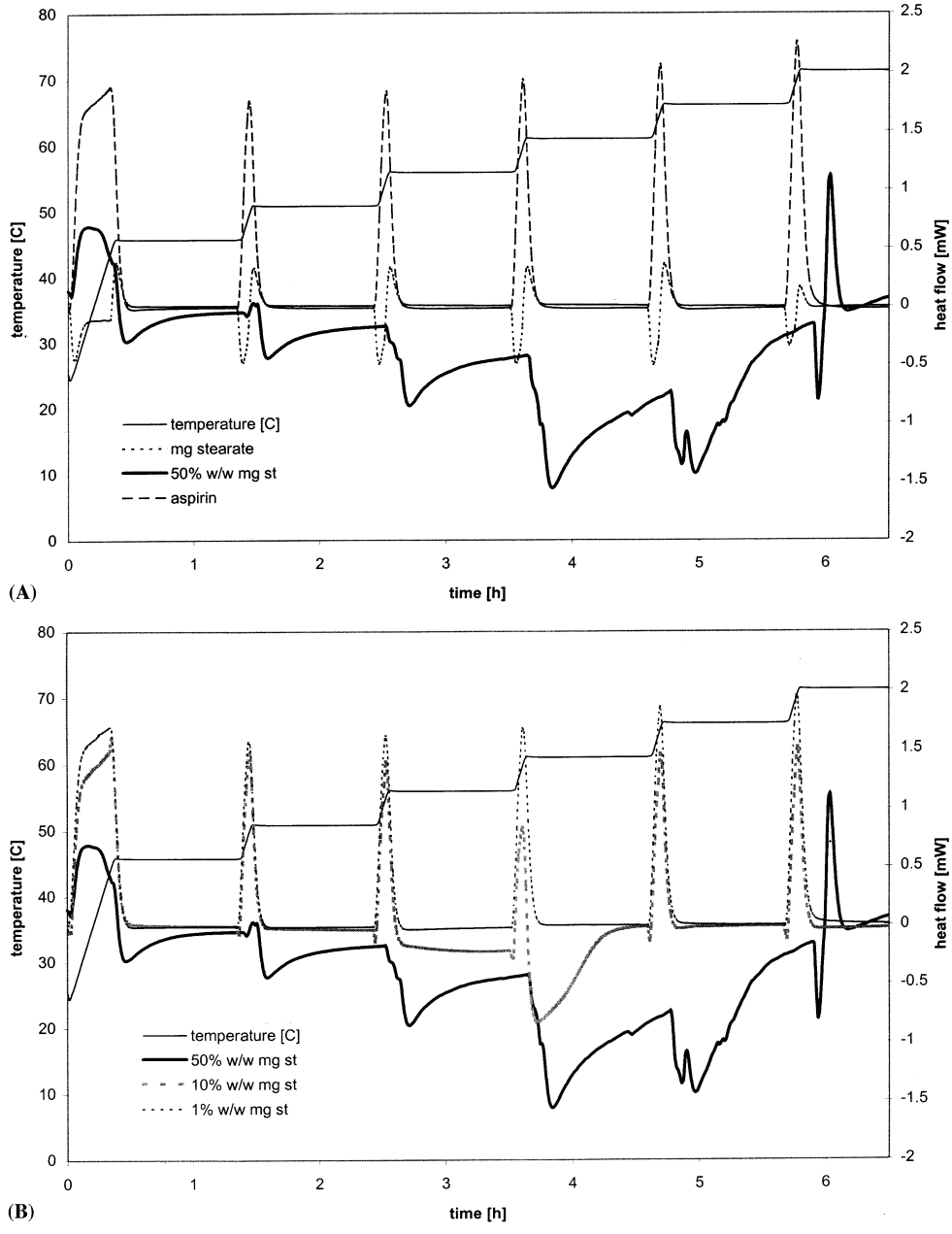

Fig. 5. Stepwise isothermal HSDSC profiles associated with compacts of (A) magnesium stearate, aspirin and 50% w/w mixes (B) 1% w/w, 10% w/w and 50% w/w magnesium stearate aspirin mixes.

detected at the 1% level. The 50% w/w systems showed a steady increase in endothermic response, with an abrupt discontinuity seen after approximately 4.5 h. It is logical to suggest that the initial increase in endothermic heat flow is due to melting, with the time dependence being a function of the thermal conductivity of the sample, while the degradation response predominates after a longer

time period. It is also interesting to note that the energy and timescales of the response are greater for the 50% w/w systems than for the 10 or 1% w/w magnesium stearate systems, despite the fact that there is less aspirin present in the 50% w/w mixes. This may be a reflection of the greater surface coverage of aspirin and the availability of excess excipient, which would allow the reaction to run to nearer completion. The results from the chemical assay indicated that no significant degradation of aspirin alone and 1:1 mixes with stearic acid could be detected over a 6 h period at 66°C, although in mixes with magnesium stearate the aspirin content was 63.2% of the original level.

Fig. 5A and B show the stepwise isothermal profile associated with the compacts containing various concentrations of magnesium stearate. Clearly, the reaction is considerably more marked and is seen at lower temperatures, probably due to the increased degree of contact between the two components and/or the heating effects of the compaction process itself. Fig. 6 shows the isothermal response at 60°C, again showing a markedly different degradation profile compared to that of the powder mixes. These data illustrate firstly that the technique may be used to examine compacts and secondly that compaction appears to have a profound effect on the rate of reaction between the magnesium stearate and the aspirin.

4. Conclusions

The study has indicated that HSDSC may be a useful tool in detecting excipient incompatibility when run in stepwise isothermal mode. Both strengths and weaknesses associated with the approach have been identified. In terms of limitations, it is not yet clear to what extent the approach is generalisable. Aspirin and magnesium stearate mixes are well studied systems which are known to manifest incompatibility associated with changes in thermal behaviour, hence caution is required in assuming that the phenomena observed here may be exhibited by all other systems; more work is clearly required in order to explore this facet of the use of the approach. It has not proved possible to completely distinguish between melting and decomposition processes, even using isothermal studies, although examination of conventional

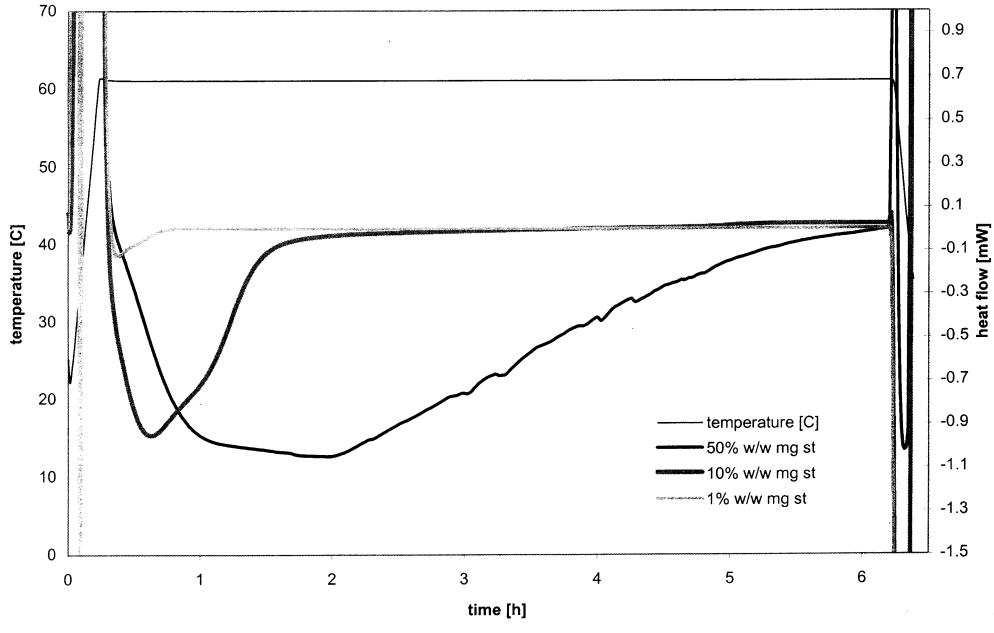

Fig. 6. HSDSC responses for 1% w/w, 10% w/w and 50% w/w magnesium stearate/aspirin compacts held isothermally at 60°C.

DSC traces may be extremely helpful in this respect. Furthermore, the sensitivity limit is not yet clear; some reactions may be accompanied by very limited changes in heat flux, which may not be easily detectable using the method. Similarly, while kinetic analysis remains an interesting possibility, considerably more work is required before this may be performed with confidence. Finally, the approach suffers from the familiar disadvantage of relying on behaviour at elevated temperatures in order to predict room temperature stability.

Even given the perceived limitations outlined above, the study has demonstrated some potentially useful applications of the approach. In particular, the method may be a useful screening technique in order to detect likely candidates for incompatibility, particularly for those reactions which do not involve large heat changes at low temperatures and are thus difficult to detect using microcalorimetry. Consequently, while the absence of baseline deviation may not guarantee compatibility, deviation at an unexpectedly low temperature over a period of time, may be a strong indication of potential problems. Such early warning may save considerable time and cost and indicates that the approach outlined here merits further investigation. The possibility of using powder and compacted systems is also advan-tageous, as clearly the latter may lead to more marked responses which will facilitate detection of incompatibilities. A further possibility, not explored in the present study, is the use of aqueous slurries of the drug and excipient in order to produce a 'worst case scenario' system with respect to moisture effects on the reaction. Overall, therefore, the stepwise isothermal approach may afford a number of advantages over both conventional DSC and isothermal microcalorimetry.

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