Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 252 (2003) 235–240
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Further investigations into the use of high sensitivity differential scanning calorimetry as a means of predicting drug–excipient interactions

Frances M. McDaid [a], Susan A. Barker [a,*], Shaun Fitzpatrick [b], Catherine R. Petts [b], Duncan Q.M. Craig [a]

[a] *The School of Pharmacy, The Queen's University of Belfast, Medical Biology Centre, 97 Lisburn Road, Belfast, Northern Ireland BT9 7BL, UK*
[b] *Merck Sharp and Dohme Research Laboratories, Hertford Road, Hoddesdon, Herts EN11 9BU, UK*

Received 7 July 2002; received in revised form 27 November 2002; accepted 28 November 2002

Abstract

The early prediction of drug–excipient incompatibility is vital in the pharmaceutical industry to avoid costly material wastage and time delays. We report here on the use of high sensitivity differential scanning calorimetry (HSDSC) to examine the compatibility between an experimental drug (Drug A) and common pharmaceutical excipients. Short-term HSDSC experiments (up to 25 h) indicated that Drug A was stable in the presence of moisture and was compatible with both lactose monohydrate and magnesium stearate in the dry state, but showed degradation in the presence of magnesium stearate and water in combination. These results agreed with conventional stability studies, in which extensive degradation was observed in the Drug A–magnesium stearate system after storage at 40 °C/75% RH for 4 weeks but not under other conditions. These results indicate that HSDSC may be used to examine the compatibility of experimental drugs with conventional excipients and, in particular, illustrate the importance of incorporating humidity as an experimental variable in order to fully establish the stability profile of the material under test.

Keywords: Differential scanning calorimetry; High sensitivity differential scanning calorimetry; Excipient compatibility; Stability

1. Introduction

The early prediction of excipient incompatibility with drugs has remained a persistent difficulty within the pharmaceutical industry. In particular, the low availability of drug and the time constraints associated with the early stages of formulation development have made such predictability particularly desirable. However, there is a paucity of reliable methods by which early screening can be achieved and in practice most companies rely on real-time methods, albeit under accelerated storage conditions such as elevated humidity and temperature. Nevertheless, the development of approaches whereby even gross incompatibilities could be detected in a matter of hours rather than weeks would be of considerable benefit. There have been several studies utilising thermal methods, either involving temperature ramping programmes (Venkataram et al., 1995; Mura et al., 1995, 1998; Botha and Lötter, 1989) or isothermal microcalorimetry (Schmitt

* Corresponding author. Tel.: +44-2890-272251; fax: +44-2890-247794.
E-mail address: s.barker@qub.ac.uk (S.A. Barker).

0378-5173/02/$ – see front matter © 2002 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0378-5173(02)00651-8

et al., 2001). Both approaches have strengths and weaknesses. Ramping methods lack the sensitivity of microcalorimetry, while the latter is not easily utilised at elevated temperatures, hence if the incompatibility is energetically weak at room temperature the response may not be detected.

We recently reported a method whereby the technique of high sensitivity DSC (HSDSC) could be used as a means of detecting the interaction between a model drug and an excipient (Wissing et al., 2000). In particular, we explored the use of step-wise temperature programming whereby a mixture of the two materials could be examined isothermally for a given period of time, followed by heating to a higher temperature whereupon the sample was again held isothermally. In this manner we argued that the temperature flexibility of DSC could be combined with the isothermal sensitivity of microcalorimetry. Any change in the system studied, e.g. chemical degradation, dissolution, temperature re-equilibration, etc. can be seen on the HSDSC trace as a deviation of the heat flow from its baseline value. Temperature re-equilibration peaks are sharp peaks seen at the start of each isothermal period, whereas heat flow deviations due to chemical changes are seen as broad peaks with a somewhat 'rough' outline during the isothermal period.

In our earlier work (Wissing et al., 2000), we also proposed a model whereby the heat flow so measured (dH/dt) could be related to the rate of degradation via

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

where k is a constant relating the thickness of the reactant layer on a cylindrical tablet with radius r_0 at time t and c is a constant relating the heat flow to the concentration of degradant. However, an acknowledged limitation of our approach was that we chose aspirin and magnesium stearate as a model system. This represents a well-known incompatibility that is also energetically profound. Previous studies have indicated that the reaction occurs via a reduction in melting point of the aspirin, thereby generating a liquid layer in which degradation is accelerated (Mroso et al., 1982). Given the phase change involved in this reaction, its detection using thermal methods will almost certainly be simpler than for a system whereby degradation may take place on a molecular basis without the involvement of macroscopic changes.

In this investigation, we examine the use of related HSDSC approaches with a more realistic system, in order to examine whether the method may be of use in practical situations. An experimental drug (Drug A) was utilised, with spray-dried lactose monohydrate and magnesium stearate as model excipients. In-house studies had indicated that there was a long-term stability issue with the latter, particularly at elevated humidities, but no evidence of incompatibility was found with the former. The objective of the study was therefore to examine the applicability of the HSDSC method as used for the aspirin–magnesium stearate system and to explore ways in which the approach may be modified in the light of findings to study a wider range of more energetically discrete incompatibilities.

2. Materials and methods

2.1. Materials

Drug A (low molecular weight, aqueous solubility >300 mg/ml, melting point 147.8 °C) was used as received from the suppliers (Merck Sharp and Dohme Research Laboratories, Hoddesdon, UK). Thermogravimetric analysis indicated that the material had negligible water levels on receipt. Magnesium stearate was supplied by Mallinckrodt (St Louis, MO, USA) while spray-dried lactose monohydrate (Fast Flo) was supplied by K & K Greeff Ltd. (Croydon, UK).

2.2. Conventional stability studies

For the conventional stability studies, binary compacts were prepared by mixing 5% (w/w) drug and 95% (w/w) excipient (magnesium stearate or lactose monohydrate) in a mortar and pestle and then compressing 100 mg of the powder mix between 6.5 mm diameter punches at a force of 1 ton. The binary compacts were then stored for up to 6 weeks under the following conditions: 5 °C/50% RH, 40 °C/20% RH and 40 °C/75% RH. Samples were then assayed for intact drug and degradant levels using a proprietary HPLC method.

2.3. HSDSC studies

A previously-calibrated Settaram Micro DSC III was used for all HSDSC studies. In all studies, a heating rate of 1 °C/min was used.

For the 'dry' HSDSC studies, both powder samples and compacts were studied. Powder samples of Drug A, magnesium stearate and lactose monohydrate were used as received. Binary compacts were prepared by mixing 50% (w/w) drug and 50% (w/w) excipient (magnesium stearate or lactose monohydrate) on a roller mixer and then compressing 75 mg of the powder mix between 5 mm diameter punches at a pressure of 1 ton. (Smaller compacts were required for the HSDSC studies than for the conventional stability studies, due to the small volume of the HSDSC cell.) The samples were loaded into the sample cell and subjected to the following heating/holding programme: 45–70 °C, with 1 h holding times every 5 °C.

Table 1
Degradant levels observed in binary compacts of Drug A and magnesium stearate or lactose (5% (w/w) drug/95% (w/w) excipient), stored under various conditions

Storage condition	Excipient	
	Magnesium stearate (%)	Lactose (%)
5 °C/50% RH (6 weeks)	<0.1	<0.1
40 °C/20% RH (6 weeks)	<0.1	<0.1
40 °C/75% RH (4 weeks)	5.8	0.3

For the 'wet' HSDSC studies, slurries were prepared by mixing the individual ingredients and 50:50% (w/w) drug/excipient mixes with water in a weight ratio of 2:1 water to solid. The 'wet' samples were used immediately after preparation and subjected to the following heating/holding programme: 30–90 °C, with 2 h holding times every 5 °C. Finally, 'wet' samples

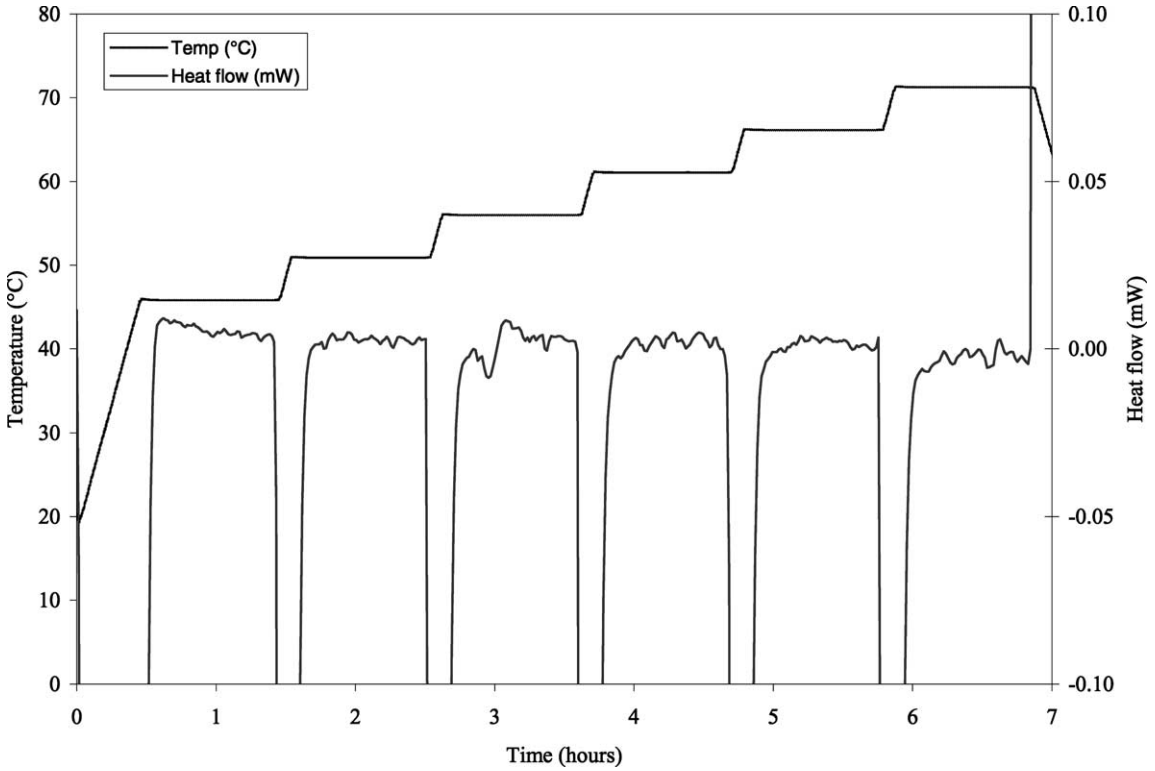

Fig. 1. HSDSC profiles for dry compacts of Drug A and magnesium stearate (50:50%; w/w) held for 1 h every 5 °C, total sample size circa 75 mg).

were held at 20 °C for 2 h after preparation, heated to 70 °C and held there for 2 h.

All experiments were performed at least twice, with excellent reproducibility found between runs.

3. Results and discussion

The results from the conventional stability study are given in Table 1. While there was no evidence for extensive degradation under low humidity conditions, degradation was seen for the samples stored at 75% RH, with considerably more extensive drug degradation being seen in the presence of magnesium stearate than lactose monohydrate.

Initial HSDSC studies focused on utilising a similar approach to that used for the aspirin–magnesium stearate system (Wissing et al., 2000). In this method, the sample was heated at 5 °C increments between 45 and 70 °C, with a view to establishing whether a discontinuity in the heat flow could be detected for the Drug A–magnesium stearate system but not for the drug alone, the excipients alone or the drug–lactose monohydrate system. Both powder mixes and binary compacts were studied under a series of different conditions, but no discontinuity corresponding to degradation was observed in any sample, even with holding times of 10 h at each temperature. This is illustrated in Fig. 1 for holding times of 1 h. Clearly, the greater subtlety of the incompatibility for this real-life system compared to the considerably more energetic aspirin–magnesium stearate system has resulted in the conventional 'dry' step-wise approach being inappropriate. However, it should be emphasised that the Drug A–magnesium stearate incompatibility was seen in the conventional stability studies only at elevated humidities. It was therefore decided that the experimental conditions used for the HSDSC studies should incorporate humidity as a design factor.

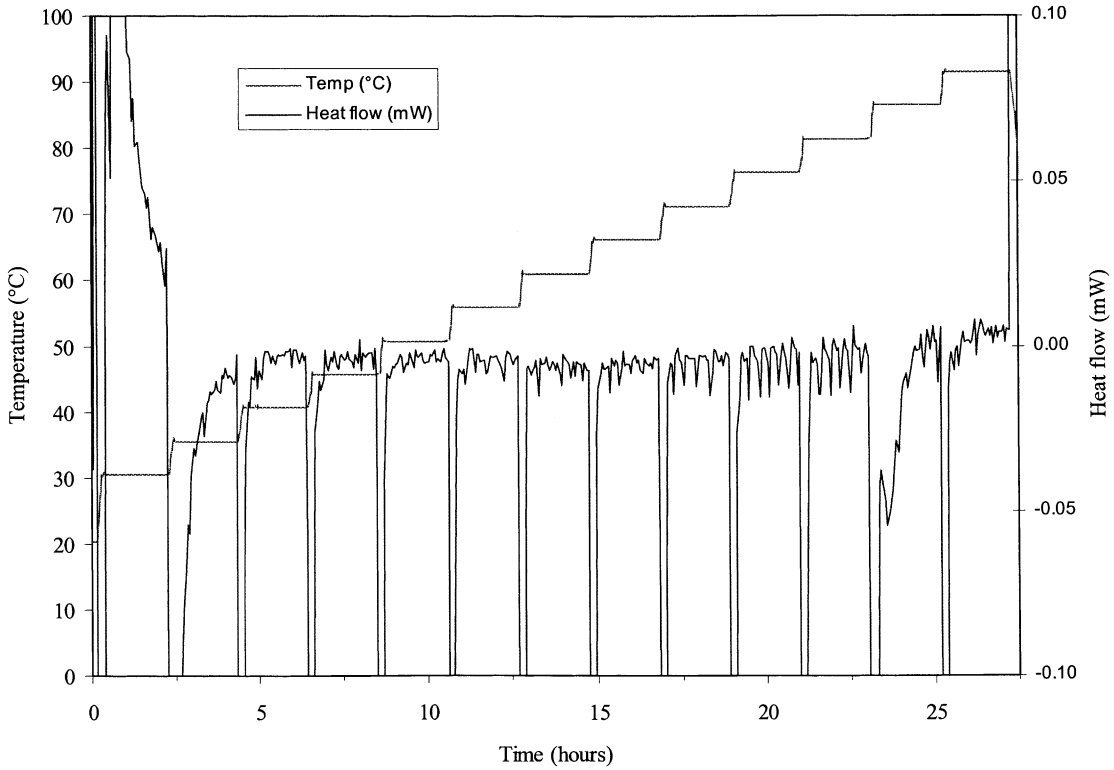

Fig. 2. HSDSC profiles for Drug A–magnesium stearate–water slurries (16.7:16.7:66.6% (w/w), total sample size 120 mg), showing thermal events at 35 and 85 °C (held for 2 h every 5 °C).

To this effect, slurries of the powder samples (drug alone, excipients alone and the 50:50% (w/w) drug:excipient mixtures) were prepared using a water-to-powder ratio of 2:1. The materials were then subjected to the following heating programme: 30–90 °C, with 2 h holding times every 5 °C. In this case, discontinuities in the heat flow were clearly seen for the Drug A–magnesium stearate system at 35 and 85 °C (Fig. 2), but not for any other 'wet' system. It was suggested that the low temperature discontinuities may be due to drug dissolution in the aqueous phase of the slurry. In order to test this hypothesis, the system was held at 20 °C for 2 h prior to the experiment in order to allow sufficient time for the drug to dissolve. The deviation from the baseline at low temperatures was found to be considerably reduced under these circumstances, hence lending support to the hypothesis that this event represents a dissolution process.

Having established that the use of an aqueous slurry may lead to a more discernible degradation behaviour, the experimental conditions were then optimised so as to maximise the differentiation between the various systems. It was found that in this case, heating the system to 70 °C and holding isothermally allowed the discontinuity to be observed rapidly and reproducibly. This is shown in Fig. 3, whereby the response of the drug–water slurry, the magnesium stearate–water slurry and the drug–magnesium stearate–water slurry are compared. Clearly, the last of these shows a heat flow response over and above the temperature re-equilibration. Equivalent studies using lactose monohydrate did not show this response, reflecting the lower degradation seen for Drug A with this excipient, even at high humidities.

Overall, therefore, the HSDSC approach does appear to be able to rapidly detect incompatibilities that are only seen at long time periods at elevated humidities. In particular, the use of aqueous slurries as a means of simulating a long-term humid environment appears to have some merit for those responses

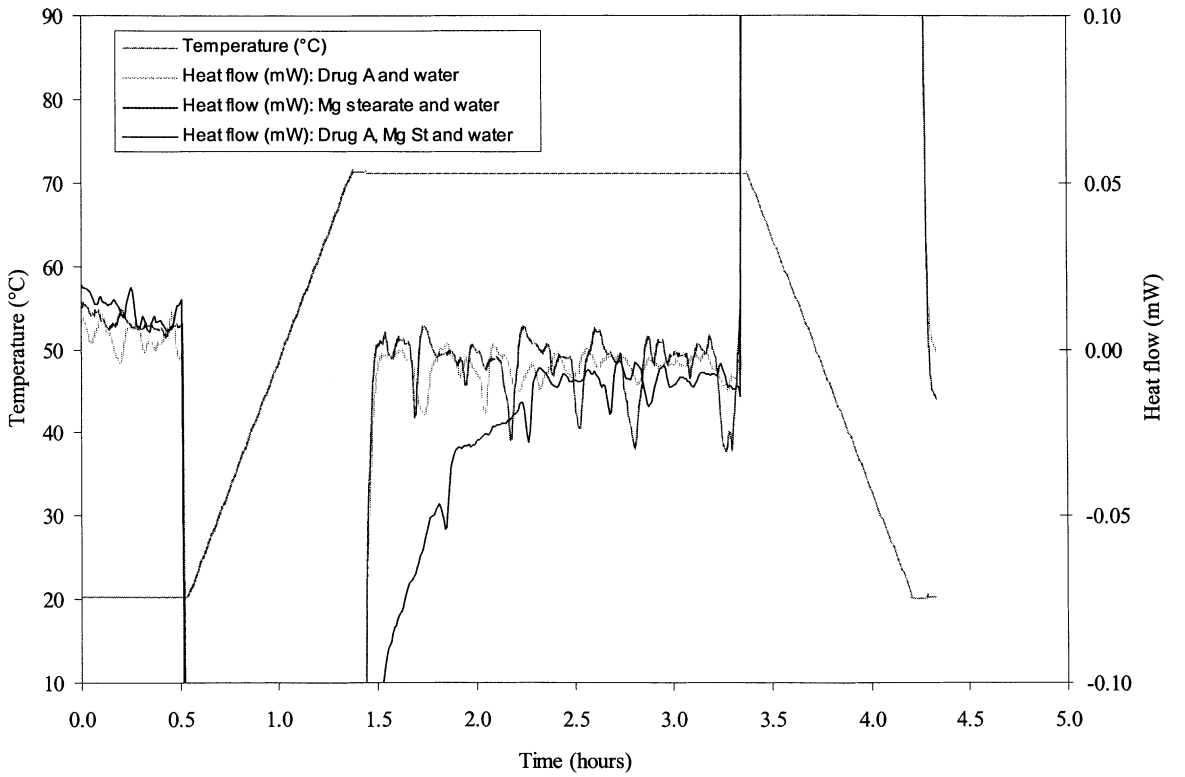

Fig. 3. HSDSC profiles for slurries of Drug A–water, magnesium stearate–water; Drug A–magnesium stearate–water (67% solid:33% (w/w) water, total sample size 120 mg) (held for 2 h at 70 °C).

whereby the incompatibility is exacerbated by the presence of moisture. That said, we wish to highlight some of the assumptions and limitations of the approach in its current state of development. In the first instance, the use of slurries will improve the contact between the sample and container, hence there may be a contribution to the increased sensitivity from this source (although the absence of a response for lactose mixes would indicate that this effect is small). Secondly, we are cautious not to make direct comparisons between the slurry data and the chemical assay, as the latter was performed in the solid state in the presence of humidity rather than liquid water. Such studies could be mimicked either way, i.e. either by performing the assay on the slurries or including isolated salt solutions in the HSDSC cell, hence the potential is there for more sophisticated analysis. However, we believe that the study has indicated that while the method requires further refinement, as a proof of concept the study does suggest that HSDSC may be used as a rapid and simple means of screening for excipient incompatibility in real-life systems.

References

Botha, S.A., Lötter, A.P., 1989. Compatibility study between ketoprofen and tablet excipients using differential scanning calorimetry. Drug Dev. Ind. Pharm. 15, 415–426.

Mroso, P.V., Po, A.L.W., Irwin, W.J., 1982. Solid state stability of aspirin in the presence of excipients—kinetic interpretation, modeling and prediction. J. Pharm. Sci. 71, 1096–1101.

Mura, P., Manderioli, A., Bramanti, G., Furlanetto, S., Pinzauti, S., 1995. Utilization of differential scanning calorimetry as a screening technique to determine the compatibility of ketoprofen with excipients. Int. J. Pharm. 119, 71–79.

Mura, P., Faucci, M.T., Manderioli, A., Furlanetto, S., Pinzauti, S., 1998. Thermal analysis as a screening technique in preformulation studies of picotamide solid dosage forms. Drug Dev. Ind. Pharm. 24, 747–756.

Schmitt, E.A., Peck, K., Sun, Y., Geoffroy, J.M., 2001. Rapid, practical and predictive excipient compatibility screening using isothermal microcalorimetry. Thermochim. Acta 380, 175–183.

Venkataram, S., Khohlokwane, M., Wallis, S.H., 1995. Differential scanning calorimetry as a quick scanning technique for solid state stability studies. Drug Dev. Ind. Pharm. 21, 847–855.

Wissing, S., Craig, D.Q.M., Barker, S.A., Moore, W.D., 2000. An investigation into the use of stepwise isothermal high sensitivity DSC as a means of detecting drug–excipient incompatibility. Int. J. Pharm. 199, 141–150.