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The use of high sensitivity DSC as a means of predicting excipient compatibility

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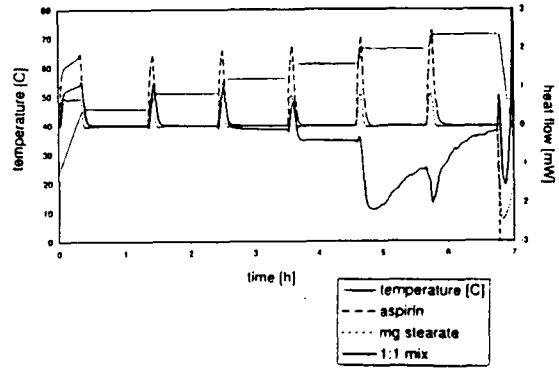
The assessment of excipient compatibility with drug substances is an essential but time-consuming aspect of dosage form development. Conventional DSC has been suggested as a means of predicting such interactions by observing whether changes in the melting behaviour of the two components take place after mixing (e.g. Ford et al 1981). However, changes in melting point may occur for reasons other than chemical incompatibility (Lloyd et al 1997), hence the method is of questionable reliability. In this investigation, we report the use of high sensitivity DSC (HSDSC) run in stepwise isothermal mode as an alternative approach; this equipment allows smaller transitions to be observed than is possible using conventional DSC but also measures energy changes with time at a series of temperatures, hence kinetic events such as degredation may be measured. Consequently, the method may be expected to identify chemical reactivity phenomena in isolation from melting processes. Magnesium stearate and aspirin were used as the model excipient and drug in order to test the above hypothesis on a well-studied system, with stearic acid used as a control.

1:1 mixes of aspirin (75-150μm fraction) and magnesium stearate or stearic acid were prepared using a roller mixer for 5 minutes. Samples of approximately 160mg were scanned at 1°C/min in a Settaram Micro DSC 111 using the temperature programmes stated. Aspirin and salicylic acid contents were assessed using a standard UV assay.

Figure 1 shows the response of the stepwise isothermal runs; with the sample being held for 1 hour at temperatures between 45 °C and 70 °C at 5 °C increments. Evidence for a change in heat flow is seen at 55 °C, while a substantial deviation from the baseline is seen at 65 °C (the peaks represent reequilibration at each temperature). In contrast, no baseline deviation was seen for the stearic acid mixes up to 65 °C, above which the stearic acid melts. Control studies on stearic acid, magnesium stearate and aspirin alone showed no deviation from the baseline up to these temperatures. Chemical assays of aspirin and salicylic acid showed data in good agreement with the above, with no degradation seen for aspirin alone at 66 °C but approximately 40% degradation when mixed with magnesium stearate over the same timescales as the HSDSC experiments.

Figure 1: HSDSC runs of aspirin and magnesium stearate in stepwise isothermal mode



These data indicate that HSDSC may be a potentially highly useful means of rapidly detecting drug-excipient incompatibilities. While more work is clearly required on a range of alternative systems to examine the universality and sensitivity of the method, these early studies indicate that the method may, in the simplest case, be used as a routine screening method, while in the longer term examination of the heat flow profiles at each temperature may allow kinetic analysis to be performed.

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