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Excipient compatibility as assessed by isothermal microcalorimetry

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Pharmaceutical development has always been faced with the challenge of rapidly developing formulations exhibiting long-term stability and bioavailability without the benefit of supporting long term data at normal storage conditions. Drug-excipient compatibility assessments are therefore carried out over shorter time intervals (typically weeks to months) at elevated temperatures in order to predict long term stability at ambient conditions. Traditionally, analyses of stressed samples are most often performed by HPLC in which the decrease in the parent peak and/or increases in degradation peaks are monitored. Ideally, these analyses should be validated for every excipient and degradant encountered. This is generally time consuming and often not very practical at the early stages of development. Expeditious excipient compatibility screening is a formidable challenge confronting every major pharmaceutical company. Because of the fast, highly competitive pace of development processes today, more traditional screening techniques are often inadequate in terms of timeliness and reliability. The application of microcalorimetry to excipient compatibility screening can potentially provide substantial payback by providing by more timely and reliable data.

The purpose of this work was to develop and evaluate an isothermal calorimetric method for predicting drug-excipient compatibility. In order to ensure thorough and intimate mixing of the drug and excipient, mixtures were prepared by mix/milling components in a vibratory ball mill (1:1 binary mixtures). Individual component and mixture particle size reduction and distribution were assessed by Malvern analysis. Samples were calorimetrically examined in glass crimp-top vials using a Thermometric 2277 TAM microcalorimeter at 50C under fixed relative humidity. Data were collected over a 15 hour time interval after 1 to 4 days equilibration time. A theoretical heat flow for no interaction is calculated from the heat flow of the individual mixture components and compared to the actual heat flow for the mixture. A weighted compatibility factor is then calculated from the calorimetry data as a means of assessing mixture compatibility. Results are compared to similar samples examined by HPLC analysis after longer term storage.

As an example of this technique, data are presented for a new drug (NCE) currently under development, with a range of excipients. A basic premise for the microcalorimetric analyses is that milling the mixture components individually results in approximately the same particle size distribution as milling mixture components together. From the limited number of components analysed, the authors are satisfied that this is a fair, but not perfect assumption in this approach to excipient compatibility screening. The NCE-excipient samples showed very good reproducibility in signal output and calculated compatibility factors. In general, the calorimetric data compared well to HPLC analyses of similar samples after longer term storage. With mixtures containing a hygroscopic excipient, the no interaction heat flow calculated by this technique may not be appropriately compared to the actual mixture (*e.g.* NCE-sodium starch glycolate, mannitol-sodium starch glycolate).

In conclusion, a useful method for screening drug-excipient compatibility by microcalorimetry was developed. In a relatively short time-frame, this technique can provide the formulator with meaningful data by which sensible decisions can be made with respect to the choice of excipients to use. However, the reliability of this method for mixtures containing hygroscopic components is currently unresolved.