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EXCIPIENT COMPATIBILITY ASSESSMENT BY ISOTHERMAL MICROCALORIMETRY

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The application of isothermal microcalorimetry to excipient compatibility screening can potentially provide substantial advantages over more traditional techniques. The purpose of this study was to develop and evaluate an isothermal microcalorimetric method for predicting drug-excipient compatibility.

Drug excipient mixtures were prepared by mix/milling components in a vibratory ball mill. Individual component and mixture particle size distribution were assessed by Malvem analysis. Samples were calorimetrically examined using a Thennometric 2277 TAM microcalorimeter at 50 °C under fixed relative humidity. Data were collected over a 15 hour period after 1-4 days equilibration time. A theoretical heat flow for no interaction was calculated from the heat flow of the individual mixture components and compared to the actual heat flow for the mixture. A weighted compatibility factor was then calculated from the calorimetric data as a means of assessing mixture compatibility. Results were compared to similar samples examined by HPLC analysis after longer term storage.

Data are presented for a new drug (NCE) currently under development for oral administration, 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 an acceptable 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 analysis after much longer storage.

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.