Characterization of Drug-Excipient Compatibility

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Microcalorimetry offers a simple and rapid approach for identifying excipients compatible with an active pharmaceutical ingredient (API). In a typical compatibility experiment, a solution, suspension or solid mixture of the API and excipient is placed in the calorimeter and the thermal activity at a constant temperature is monitored. The rate of heat production is proportional to the rate of chemical and/or physical processes taking place in the sample. The rate of heat produced by the API and excipient are measured individually, and the sum of the heat rates from the individual components is compared with the heat rate from the mixture. If the heat rate from the mixture is significantly different from the sum of the heat rates from the individual components, the excipient is incompatible with the API.

The following example serves to illustrate how microcalorimetry can be used to quickly screen excipients during the formulation process. In Figure a, 100 mg of the API (which contains a primary amine) was mixed with an equal weight of lactose and 20% water. The sample was placed in one compartment of a TAM, lactose alone with 20% water was placed in a second sample chamber, and the API with 20% water was placed in a third. The red curve shows the sum of the heat output of the lactose sample alone and the API sample alone. The blue curve shows the heat output from the API/lactose blend. The large exothermic process occurring in the blend clearly shows that a reaction (in this case, the Maillard con-

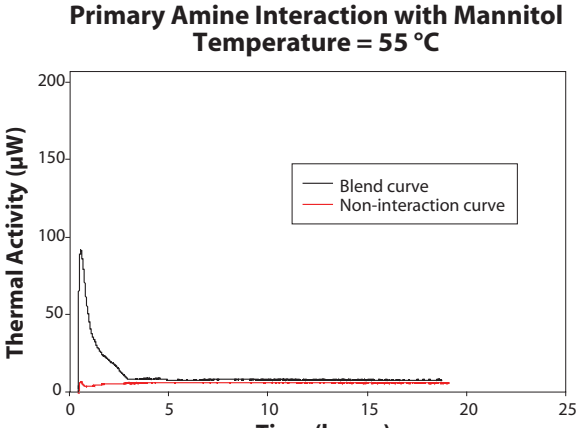

Figure b. Lack of interaction of an API containing a primary amine with mannitol.

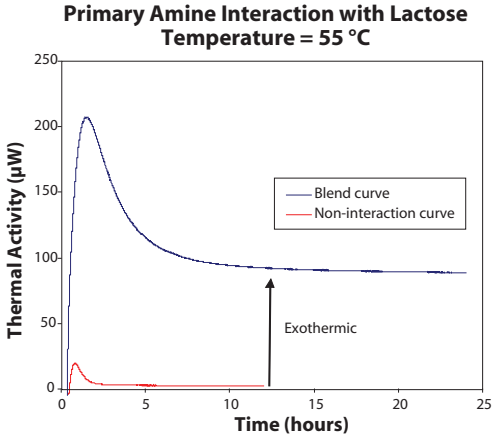

Figure a. Interaction of an API containing a primary amine with lactose.

densation reaction) is occurring, and thus lactose is not compatible as an excipient with this API.

Figure b shows the same API, now mixed with mannitol. The API/mannitol blend is very similar to the sum of the curves for the individual components, suggesting that mannitol is a much more promising excipient than lactose for formulating this API. The mannitol results, requiring just hours to obtain, would typically be followed up by more traditional, detailed excipient compatibility analyses such as HPLC. In contrast, since the calorimetry results strongly indicate that lactose is not an appropriate excipient for this drug, further studies with lactose would be unnecessary.