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Letter to the Editor

Comments on Serger et al.'s, (1998, 1999) calorimetric stability studies

Selzer et al. (1998, 1999) have produced two interesting papers describing the application of isothermal microcalorimetry to the study of stability and compatibility testing for solid drug substances. These papers make a significant contribution to the field by providing new theory and application. Given the importance of the work of Selzer et al., it is necessary to raise two points of concern: one in the use of the theory and the other of interpretation of practical data.

Regarding the theory, Selzer et al. (1998, 1999) have presented a very interesting use of the microcalorimetric system to derive activation energies. However, their theoretical development of equations allowing them access to the desired results is flawed and could be misleading. Firstly, they assert, both in their text and in their equations (1), (1a), (2) and (3) (Selzer et al., 1998), that the Ng equation (Ng, 1975) is comprised of concentration terms as would be the case for solution state reactions. In fact the Ng equation is properly cast in terms of fractions of the extent of a solid-state reaction, α, at any time t. Thus the rate constant in the Ng equation has the dimensions s^{-1}. Secondly, they use concentration-based equations in the extension to microcalorimetric data. The extension of these equations into calorimetric terms was previously discussed in correct terms by Willson et al. (1995, 1996). In these publications the reactable material is described by *amount* not concentration. It is required that the term expressed by Selzer et al. (1998, 1999) as $c_0(A)$ is, in reality, expressed as the number of moles of A present, $\mathbf{A}$ ($\Delta_R H$ is a *per mole* quantity). Moreover the dimensions of the rate constant then reflect this requirement. Concentration can be incorporated into Selzer et al.'s type of equation (for example, equation (6)) if it is modified through: $\mathbf{A} = c_0(A)V$, where V is the volume of solution of concentration $c_0(A)$ present in the calorimetric chamber (V must, of course, be in the same dimensions as the concentration) (Beezer, 2000). It is simple then to cast the rate constant in terms related to concentration for purposes of comparison with literature data for solution phase reactions. Selzer et al. (1998) manage to succeed in deriving the desired activation energies because when they use their equation (13) (reproduced here, and see their paper for definition of terms):

$$\ln \Phi_0 = \ln(\Delta_R H c_0^{\nu} C) - (E_A/RT)$$

the errors introduced through the incorrect use of concentration terms are found only in the intercept term of the linear plot of $\ln \Phi_0 \nu T^{-1}$. Thus the activation energies are correctly deduced but the intercept term is in error.

The concern relating to the interpretation of the data rests with the discussion regarding water distribution. Elements of the heat flow processes, sometimes lasting for days, are described by Selzer et al. (1998, 1999) as being due to water distribution microcrystalline cellulose to other materials (e.g. lactose). It is possible that water distribution may occur and also that this distribution may be slow. However, for distribution to occur it would be expected that the transport from one material to another would comprise of an endothermic desorption and an exothermic

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sorption. As desorption and sorption should be almost equal in magnitude (approximately equivalent to the enthalpy of vaporisation/condensation of water) but of opposite sign, the net response would not be expected to be large. Consequently, another physical explanation (as yet unidentified) must exist for the substantial protracted responses. The explanation of the data could be a consequence of water transfer, but is unlikely to simply be a measure of it.

In conclusion, we welcome the contributions from Selzer et al. and hope that the points discussed above will make the work even more valuable.

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