9.1. Use of DSC

Rustichelli et al. (1999) have employed DSC to obtain the phase equilibrium diagrams of the enantiomers of (a) verapamil HCl and (b) gallopamil HCl. In the former case the eutectic composition is at 90% (2S)-(-)-verapamil HCl and in the latter at 70% (2S)-(-)-gallopamil HCl.

Mura et al (1998) have used thermal analysis (DSC) to study compatibility of picotamid with common pharmaceutical excipients (palmitic acid, stearic acid, stearyl alcohol, PEG 20,000, and sorbitol) and showed that the interactions were primarily due to dissolution in the melted excipient.

9.2. Use of Microcalorimetry

Heat conduction microcalorimetry has been used as a method to evaluate stability and excipient stability by a series of researchers. Angerg et al. (1988, 1990, 1993), Hansen et al., (1989), and Wilson et al. (1995) have described the general method and results interpretation. For instance, Angberg et al. studied the oxidation of ascorbic acid in aqueous solution by microacalorimetry, and other researchers have used this method as well. Oliyai and Lindenbaum (1991) studied the decomposition of ampicillin in solution. Tan and Meltzer (1992) studied the solid state stability of 13-*cis*-retinoic acid by means of microcalorimetry and HPLC, and Pikal and Dellerman (1989) studied the kinetics of cephalosporin in the solid and solution states using the same method.

Seltzer et al. (1998) used the method to evaluate stability and excipient compatibility of (S)-(3-(2-4-(S)-(4-(amino-imino-methyl)-phenyl-4-methyl-2,5-dioxo-imidazolidin--1-y1)-acetylamino))-3-phenyl-propionic acid ethyl ester, acetate. The excipients used were potato starch, calcium hydrogen phosphate anhydrous, and colloidal silica.

They consider the reaction A + B→C + D and denote the concentration of C as x, the fraction decomposed at time t. The trace of heat evolved as a function of time is then characterized by

$$\frac{dx}{dt} = -k\{[A_0] - x\}^n \tag{9.26}$$

The amount decomposed is associated with (a usually exothermic) reaction enthalpy, ΔH, where the heat evolved is proportional to x, hence the heat flow is proportional to dx/dt and the proportionality constant is ΔH, so that

$$\phi = \frac{dQ}{dt} = \Delta H \frac{dx}{dt} \tag{9.27}$$

hence

$$\phi = \Delta Hk\left\{[\mathrm{A}_0] - \left(\frac{Q}{\Delta H}\right)\right\} \tag{9.28}$$

For a first-order reaction this becomes

$$\phi = \Delta Hk[\mathrm{A}_0] - kQ \tag{9.29}$$