Solid-State Chemistry of Drugs

SECOND EDITION

Stephen R. Byrn
Ralph R. Pfeiffer
Joseph G. Stowell

SSCI, Inc. • West Lafayette, Indiana
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Thermal Methods of Analysis

Thermal analysis generally refers to any method involving heating the sample and measuring the change in some physical property. The most important thermal methods for the study of solid-state chemistry are **thermogravimetric analysis** (TGA), **differential scanning calorimetry** (DSC), and thermal microscopy (discussed in Section 4.4). Thermogravimetric analysis measures the change in the mass of sample as the temperature is changed. Differential scanning calorimetry involves measuring the difference between the temperature of the sample and a reference compound as the temperature of the system is changed, thus providing information on the enthalpy change of various solid-state processes. Thermal methods of analysis are important analytical tools for characterizing pharmaceutical solids. The use of TGA and DSC in conjunction with thermal microscopy (Section 4.4) can elucidate many behaviors of solids.

5.1 THERMOGRAVIMETRIC ANALYSIS (TGA)

Basically, a thermogravimetric instrument consists of a microbalance connected to a sample compartment situated in a small oven with computer-controlled temperature programming. A dry nitrogen atmosphere is most commonly used, however, other gases can be employed (the compostion and flow dynamics of the gas are important perameters.) This method measures the change in mass with temperature and is often used to study the loss of solvent of crystallization or other solid → solid + gas reactions. A typical TGA trace is shown in Figure 5.1. In studies of solid-state chemistry, TGA is usually performed in one of three modes:

1. **Isothermal mode**—the temperature is kept constant.
2. **Quasi-isothermal mode**—the sample is heated to a constant mass through a series of increasing temperatures.
3. **Dynamic mode**—the temperature is raised at a known rate, typically linear.

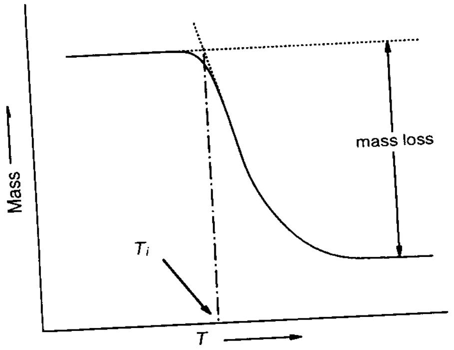

Figure 5.1 A typical TGA trace for a single-state mass loss with T_i (the transition temperature) marked. The temperature corresponding to the point at which tangents to the original baseline and to the slope of the tracing represents the transition temperature T_i.

The last approach uses high heating rates in temperature regions where no weight changes are occurring and slow rates in regions where weight changes do occur, thus avoiding transition temperature overshoot and blurring of peaks from overlapping transitions.

There are a number of factors or conditions that affect TGA curves including the heating rate, atmosphere, geometry of the sample holder (pan), particle size of the sample, nature of the reaction, treatment of the sample, thermal conductivity of the sample, and sample weight. The effect of the heating rate has been extensively studied (Wendlandt, 1974). In general, as the heating rate is increased, the apparent starting temperature of the thermal event (T_i) increases. However, this condition can sometimes be corrected by decreasing the sample size.

The atmosphere can have a dramatic effect on the TGA curve. For example, an atmosphere already containing the product gas can increase T_i or stop the reaction completely. In addition, the atmosphere can change the course of the reaction, particularly if the atmospheric gas reacts with either the products or the reactant. Knowledge of how the substance responds to changes in relative humidity (RH) is essential to proper handling of the sample before the scan is started. For these reasons, it is a prudent practice to use an atmosphere of dry nitrogen when performing a study.

Although dependent on the reaction mechanism, the particle size of the sample has a predictable effect on the TGA curve in general. The smaller the particle size, the faster the reaction and the lower the value of T_i. This is because the smaller particle sizes allow more rapid escape of the product gas. Obviously, the nature of the reaction affects T_i which will be lower for more facile reactions.

In addition, the treatment of the sample, and in particular the extent of compression of the sample, will obviously affect the T_i. For example, increased compression will increase T_i since the product gas will have less opportunity to escape.

Finally, the thermal conductivity of the sample will influence T_i. Anomalous effects may be obtained if the temperature of the sample is not uniform because of poor thermal conductivity.

The rates of reactions of the type shown in Equation 5.1 can be determined using

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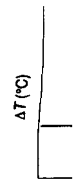

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TGA. Obviously, isothermal TGA traces can be used to determine the rate of the reaction and the rate law governing the reaction by simply plotting weight loss versus time. These plots can then be analyzed as described in Chapter 3. Dynamic TGA has also been used to determine the rates of such gas-evolving reactions. However, in general, the kinetic data thus obtained should be substantiated by other data. Isothermal thermogravimetric analysis has been used extensively in our laboratory to study the desolvation of crystal solvates (Chapter 16).

$$A_{\text{solid}} \longrightarrow B_{\text{solid}} + C_{\text{gas}} \qquad (5.1)$$

5.2 DIFFERENTIAL SCANNING CALORIMETRY (DSC)

Differential scanning calorimetry (DSC) is a method which measures the difference in energy (heat flux or heat flow) between a reference (R) and a sample (S). A typical DSC sample compartment is shown in Figure 5.2.

The result of a DSC analysis is a thermogram, a plot of $\Delta T = T_s - T_r$ (temperature

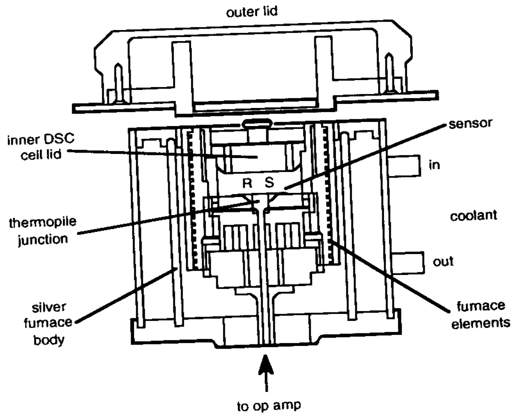

Figure 5.2 Cross section of a Cahn® DSC 4000 cell. The sample pan (S) and the reference pan (R) are positioned in the sensor (Cahn Instruments, 1996).

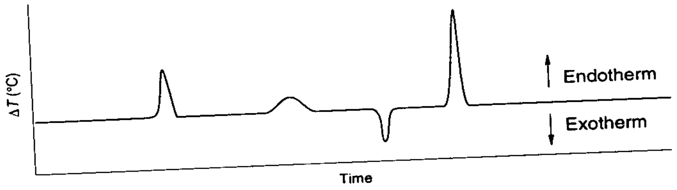

Figure 5.3 A hypothetical DSC thermogram showing the changes that might occur upon heating a sample.

difference) versus T. Figure 5.3 shows an idealized DSC trace. The endotherms represent processes in which heat is absorbed, such as solvent loss, phase transitions, or melting. The exotherms represent processes such as crystallization or chemical reactions where heat is evolved. In addition, the area under a peak is proportional to the heat change involved. Thus this method, with proper calibration, can be used to determine the enthalpies (ΔH)) of the various processes. The method can also be used as an accurate measure of the melting point and purity of the sample. In fact, the change of melting point is related to the mole fraction of impurities as given by Equation 5.2:

$$T_s = T_0 - \frac{T_0^2 R X_i}{F \Delta H_f} \qquad (5.2)$$

where T_s is the sample temperature, T_0 is the melting point of the pure compound, R is the gas constant, X_i is the mole fraction of the impurity, F is the fraction of the solid melted, and ΔH_f is the enthalpy of fusion of the pure compound. According to the equation, a plot of T_s versus $1/F$ should give a straight line whose slope is proportional to X_i (Brittain *et al.*, 1991). However, the equation appears to fail when purity is less than 97%. Application of this equation is illustrated by the DSC thermograms shown in Figure 5.4.

There are a number of factors other than purity that can affect the DSC curve including heating rate, atmosphere, sample holder, particle size, and sample packing. In general, a greater heating rate will cause a shift of the peaks to higher temperatures. A decreased heating rate also usually causes endotherms and exotherms to become sharper. The shape of the sample holder and whether it is open, totally sealed, or contains a pin prick to vent gases can also affect a DSC curve. When a DSC experiment is performed in a closed pan, the resulting atmosphere within the sample holder can greatly affect the resulting DSC curve. Obviously, a tightly sealed sample holder would not allow vapor to escape, thereby changing the behavior or mechanism of a

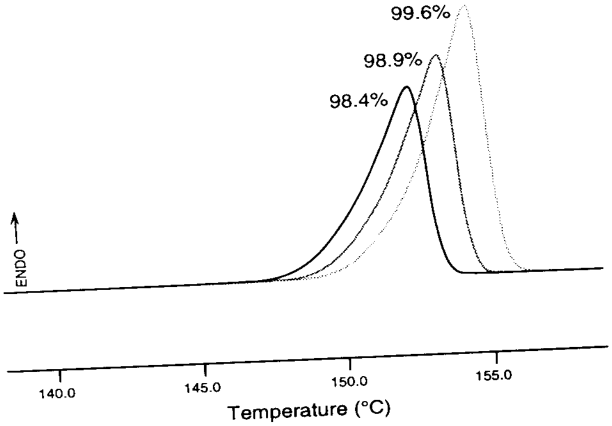

Figure 5.4 DSC thermograms of three ethoxycarbonyl-3-phenylpropyl-L-alanine samples of varying purity from different manufacturers (Giron, 1990).

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