importance (FDA, The Gold Sheet, 1985). The following is an expanded list of these methodologies available for evaluation:

- Melting point (HSM)
- IRS
- XRPD
- Thermal analytical techniques (e.g., DSC, differential thermal analysis [DTA], TGA, and the like)
- Solid-state Raman spectroscopy
- Crystalline index of refraction
- Phase solubility analysis
- Solution pH profile determination
- Solution calorimetry
- Comparative intrinsic dissolution rates
- Cross-polarization/magic angle spinning (CP/MAS) solid-state NMR
- Hygroscopicity measurement (particularly for salts)

6.9.1 Thermal Analysis

There are a number of interrelated thermal analytical techniques that can be used to characterize the salts and the polymorphs of candidate drugs. The melting point of a salt can be manipulated to produce compounds with desirable physicochemical properties for specific formulation types. Of the thermal methods available for investigating polymorphism and related phenomena, DSC, TGA, and HSM are the most widely used methods.

6.9.2 Differential Scanning Calorimetry

Differential scanning calorimetry is one of the most frequently used methods to study solid-state properties. The flux-type DSC involves heating the sample and reference samples at a constant rate by using thermocouples, to determine how much heat is flowing into each sample and thus finding the differences between the two. Examples of such DSC instrumentation are those provided by Mettler and duPont. The power compensation DSC (e.g., PerkinElmer), an exothermic or endothermic event, occurs when a sample is heated, and the power added or subtracted to one or both furnaces to compensate for the energy change occurring in the sample is measured. Thus, the system is maintained in a thermally neutral position at all times, and the amount of power required to maintain the system at equilibrium is directly proportional to the energy changes occurring in the sample. In both types of DSC measurements, only a few milligrams of the compound suffice. The sample can be heated in an open pan or in hermetically sealed chambers, where there may or may not be vents to release moisture or solvents; the compound may be subjected to pyrolysis in the testing phase.

Although the instrumentation available in the recent years has become very sophisticated, making such analysis possible with great consistency, the interpretation of the results is highly dependent on a keen understanding of the factors that affect the results. For example, such subtle factors as the type of pan, the heating rate used, the