temperature (T_x), eutectic melting temperature (T_e), glass transition temperature (T_g'), and ice melting temperature (T_{im}). Among these critical temperatures, the glass transition temperature T_g' is one of the most important thermophysical properties of the formulation. For a formulation that forms an amorphous cake after being freeze-dried, the T_g' is also the collapse temperature, which is the most critical factor in ensuring the success of the primary drying. For example, MacKenzie measured the collapse temperature of the formulations with different ratios of sucrose to sodium chloride. He demonstrated that at a certain range of ratios, the lyophilization became impractical as the sodium chloride depressed the collapse temperature to a point below −40°C (13–15). Many other reports are available in determining T_g' by DSC (13,14).

In this chapter, as we have mentioned previously, we focus on the crystalline matrix formulation. The example formulation consists of 2.2% glycine, 1.0% of sucrose, 0.02 M of histidine, 0.03 M of sodium chloride, and 0.0025 M of calcium chloride. The concentration of therapeutic protein is in the range of 50 to 200 μg/mL, which is negligible.

Figure 1 shows a DSC thermogram of warming for the formulation. The sample was frozen to −60°C and then warmed up to 20°C. During the warming, T_g can be observed between −30°C and −35°C. Under these conditions, the highest allowable product temperature during primary drying is about −35°C. In this case, we do not believe that the glycine crystallizes out and, as a result, we must freeze-dry the product below this maximum allowable temperature. The maximum allowable temperature here is also the collapse temperature. In other words, the cake will collapse if the product temperature is higher than this

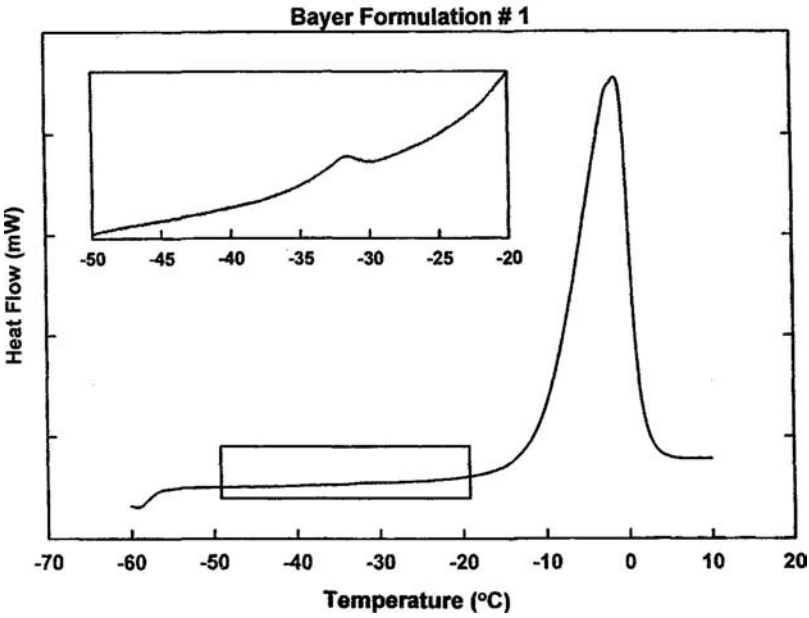

FIGURE 1 A DSC warming thermogram of a crystalline matrix formulation without annealing. *Abbreviation*: DSC, differential scanning calorimetry.