



FIGURE 2 A DSC warming thermogram of a crystalline matrix formulation after annealing. *Abbreviation:* DSC, differential scanning calorimetry.

maximum allowable temperature during sublimation. Generally speaking, the lower the allowable product temperature, the less efficient the freeze-drying cycle. It may even become impractical for large-scale production if the highest allowable temperature approaches -40°C .

For the crystalline matrix-type formulation, however, adding an annealing step in freezing may make a significant difference in the freeze-drying process. Figure 2 shows a DSC thermogram of the same formulation described above, but it has been annealed during freezing. As before, the sample was first frozen to -60°C . Then the sample temperature was slowly increased to -20°C and held for one hour at this temperature. We call this step annealing or heat treatment. After holding at -20°C for one hour, the sample was again slowly frozen down to -60°C to a fully frozen state. The sample was then warmed to 20°C . The thermogram shown in Figure 2 is from the last warming. As a result of the annealing, as shown in the thermogram, the thermal event observed between -30°C and -35°C disappeared. Instead, there is a new thermal event, like a shoulder, which occurred at a temperature above -10°C . We believe the new thermal event is the eutectic melting of the glycine. It appears like a shoulder on the thermogram because the peak of glycine melting was quickly integrated into the peak of the ice melting. This also indicates that annealing has made glycine crystallize out as evidenced by the eutectic melting of glycine during the warming. The complete crystallization of the crystalline component makes the thermal transition shift to -10°C . In other words, it is evident that annealing will allow primary drying to occur at a much higher product temperature because, for the crystalline matrix formulation, the eutectic melting temperature, T_{er} , is the collapse temperature, T_c . This is a clear advantage of the crystalline matrix-type formulation. However, care must be taken to prevent protein