The moisture content of each sample was determined by near-infrared (NIR) content analysis. The NIR used here is provided by a FOSS Model 5000 Rapid Content Analyzer.

All sample preparation for T_g measurement using MDSC took place within a glove box. The relative humidity of the glove box was matched to that of the desiccator each vial had been stored in. This was done to avoid any change in the moisture content of the sample. Approximately 5 to 10 mg of each freeze-dried cake were sealed into a hermetic aluminum DSC sample pan. All DSC work was performed on a TA Instruments 2920 DSC in MDSC mode. Thermogram analysis was carried out with TA Instruments Universal Analysis software. Helium was used as the purging gas. A typical thermogram and testing conditions are given in Figure 13. The scanning rate was 2°C/min, from −40°C to 120°C, modulated at ±0.6°C every 100 seconds. Glass transition values were determined from the reversing heat flow and then corrected to the total heat flow. The relationship of T_g and moisture content for the crystalline matrix formulation is given in Figure 14. It shows if the relationship between T_g and the moisture content of a dry cake is known, an optimum moisture content can be chosen based on the desired storage conditions. Product stability at a higher storage temperature can be achieved by lowering the moisture content of the cake as much as possible. For example, to achieve a product stability at room temperature storage, we have to keep moisture content lower than 2%. In the pharmaceutical industry, it is common practice to use 40°C storage as an accelerated stability test to predict product stability using Arrhenius kinetics. Figure 14 also shows that for this formulation such practice may not be appropriate because it is hardly possible to have T_g above 40°C with a reasonable moisture content. Instead, WLF (Williams-Landel-Ferry) kinetics may better predict the stability as suggested by Franks (1).

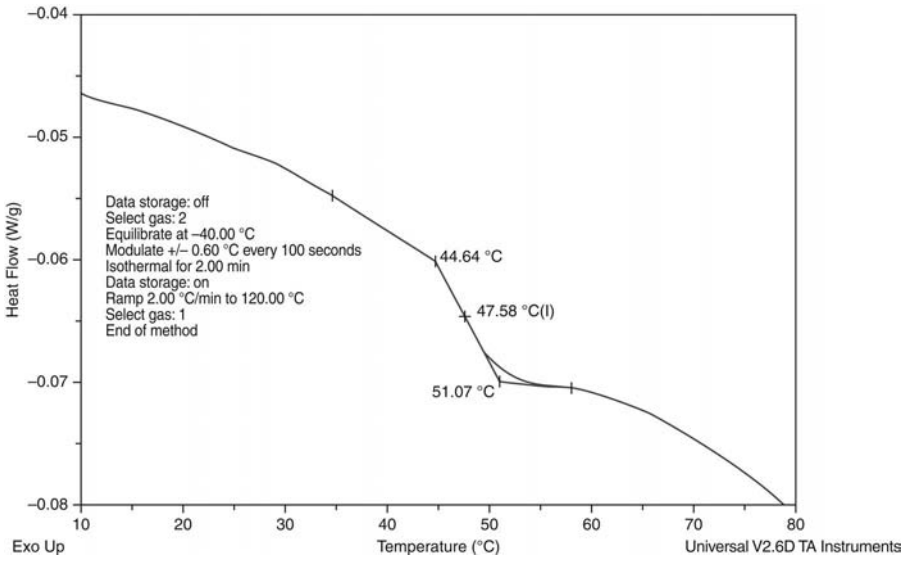

FIGURE 13 A typical thermogram of T_g measurement using MDSC. *Abbreviations*: T_g, glass temperature; MDSC, modulated differential scanning calorimetry.