baseline, suggesting a sudden increase in heat capacity. The operating conditions such as the scanning rate and sample size will depend on the formulation and product properties. For formulations containing crystalline excipients and multiple components or phases, modulated DSC (MDSC) is preferable. MDSC is a development of standard DSC, whereby, a sinusoidal heating modulation is superimposed on the underlying linear heating or cooling signal, thereby facilitating measurement of the experimental glass transition and the heat capacity [45]. The reversing flow signal is determined by multiplying the measured heat capacity by the average heating rate, and it typically clearly reveals the glass transition event.

The critical process design parameter for an amorphous system is the collapse temperature (T_c), which is the temperature above at which the product undergoes structural collapse and loses cake structure [32]. Freeze-drying below T_c is necessary to ensure elegant appearance. Collapse may also lead to higher residual water after secondary drying and can also impact stability in some cases by either negatively impacting or improving stability [25, 46]. FDM is the most common method used for the measurement of collapse temperature. FDM involves monitoring a freeze-drying process at small scale on a temperature-controlled cold stage using a microscope. A small amount of solution is first applied between two glass surfaces and this thin film is then completely frozen. The system is subjected to vacuum to initiate primary drying. The sample temperature is slowly increased at a typical heating rate of 1 °C/min to allow sublimation. As the temperature increases above T_g', viscous flow will result in faster mobility and the structure change of the freeze-dried solid, which ultimately cause the collapse of the dried region. T_c is normally 1–3 °C higher than T_g' measured by DSC; however, differences of 5–10 °C have been reported for high concentration protein system [6].

The thin film used in the traditional FDM freezes differently than product in a vial and drying rates may be quite different than bulk products drying in vials or other commercial containers. Thus, current FDM may not always accurately estimate T_c for freeze-drying in commercial containers. Recently, a new technique based on optical coherence tomography (OCT) was developed to monitor changes in product structure in a vial to estimate T_c during typical freeze-drying. This technique can overcome the limitations associated with FDM, and also provides 3D imaging capability with better resolution to follow the product structure changes. For 5 % sucrose system, the onset of collapse was determined to be −28.9 °C using OCT based on the first-observed gaps in the dried cake, which is about 3 °C higher than measured value using FDM for the same formulation, but with a sucrose-to-BSA formulation, collapse was observed with FDM at about −27 °C, but with OCT no collapse was observed. Moreover, freeze-drying in vials in a laboratory dryer was performed more than 5 °C higher than the FDM collapse temperature with no observable collapse [23]. Therefore, the OCT measurement may provide a more reliable measure of collapse temperature in a commercial container and therefore allow a cycle with a higher shelf temperature to be used to shorten the primary drying stage.