addition to simply evaluating the collapse temperature of a material, provide a brief description of some of the more widely used thermal methods, and discuss some of the issues with data interpretation in the light of the relevance of the information to formulation and lyo-cycle development.

Freeze-Drying Microscopy

Cryomicroscopy and FDM have been employed as methods of evaluating the freezing and lyophilization behavior of simple solutions and formulations since the middle of the 20th century, ever since eminent researchers such as Rey and Mackenzie showed how this information could be useful in-process development (21,22). There are now commercially available systems that enable temperatures to be controlled to within a fraction of a degree and pressure to be controlled and monitored throughout the analytical process. Digital cameras have further allowed images to be captured and saved in galleries that enable retrospective analysis of information to allow the collapse event to be pinpointed to within a fraction of a degree, as well as the ability to compile images into video format. We define the onset of the collapse event (the lower temperature limit giving first visible signs of viscous flow) as $T_{c\ (onset)}$ and the endpoint of the event (upper temperature limit where no observable drying structure remains) as $T_{c\ (endpoint)}$. Others have defined these events as T_{oc} and T_{fc}, respectively (23).

Operationally, with modern FDM designs, pressure control is rendered insignificant by virtue of the fact that the sample is in good thermal contact with the drying block and is in the format of a thin layer sandwiched between two cover slips, as depicted in Figure 1. Employing such a format means that heat input to the sample by convection is minimized; however, the pressure in the sample chamber should be lower than the vapor pressure of ice at the corresponding sample temperature. Additionally, the use of a relatively thin sample minimizes the effect of sublimation cooling on the sample, which would otherwise render it at a lower temperature than the temperature-controlled block.

FDM provides the ability to determine a number of events occurring in a material as it is frozen and subsequently dehydrated under vacuum, including nucleation temperature (although this is somewhat of a misnomer, given the random nature of ice crystal formation), eutectic melting, collapse, microcollapse (in certain instances), the effect of annealing a sample on ice crystal structure

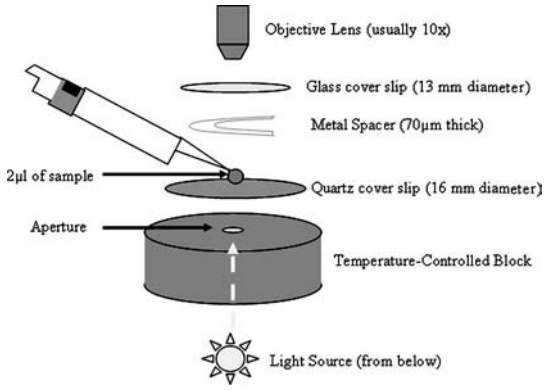

FIGURE 1 Sample format employed for freeze-drying microscopy analysis using Lyostat2 (Biopharma Technology Limited, Winchester, U.K.).