Recent Advancements in Thermal Analysis

As previously described, freeze-drying is an example of a process where material properties dictate the drying dynamics and these properties and their response to thermal input must be considered when developing lyophilization process parameters. Since the driving force for sublimation is the difference between the temperature-dependent vapor pressure of ice at the product-drying interface and the chamber pressure, the duration of primary drying (i.e., the ice sublimation stage) is very sensitive to product temperature. An increase of 5 °C in product temperature decreases the primary drying time by approximately a factor of two, and since primary drying is normally the longest part of the process, significant time savings can be achieved by running the process at the highest possible temperature consistent with producing high-quality product. However, there is an upper temperature limit above which damage to product quality occurs. For a purely crystalline system, this upper temperature limit is the eutectic temperature, T_{eu}. In most cases, however, the solutes are at least partially amorphous, and it is the viscous flow resulting from being above the glass transition temperature of the freeze-concentrated amorphous solutes, T_g', that causes loss of structure and collapse [27]. The structural deformation classified as collapse normally occurs a few degrees above the T_g', since the system is drying at the same time when viscous flow is taking place, and some time is required for sufficient viscous flow to occur to produce significant structural deformation. The loss of structure is referred to as a "eutectic melt" (crystalline systems) or "collapse" (amorphous systems), and is normally unacceptable in a pharmaceutical product from the viewpoints of the customer, regulatory agencies, and the manufacturer. Collapse frequently results in loss of product elegance, high residual moisture in the final product, possible product degradation, prolonged reconstitution times, and extended secondary drying times, all of which are unacceptable for product quality [27]. Freeze-drying below the collapse temperature, T_c, is typically required to manufacture high-quality pharmaceutical products. Thus, there is a need to accurately determine the product formulation collapse temperature and to design lyophilization processes which maintain the product temperature during primary drying close to, but safely below the collapse temperature. In fact, process QbD is not possible without accurate knowledge of T_c.

In most academic and pharmaceutical industry laboratories, the pharmaceutical product formulation collapse temperature is currently measured using LT-FDM or estimated by determining T_g', the glass transition temperature of the maximally concentrated solute in contact with ice, using differential scanning calorimetry (DSC) [27]. The T_g' is normally 1–3 °C lower than the T_c; however, differences of 5–10 °C have been reported [28]. Using T_g' as an estimate for T_c, typically results in a primary drying temperature that is lower than required and therefore results in significantly longer processing times.

The use of microscopy to monitor the freezing behavior of product solutions and the growth of ice crystals was reported by Luyet in 1960 [29]. The use of a freeze drying microscope to monitor product drying was introduced by MacKenzie