[30, 31]. Within the past 10–15 years, advanced commercial instrumentation has been introduced to provide scientists with a robust tool for routinely performing FDM and determining product formulation collapse temperature of thin-film product samples. LT-FDM is a scattering-limited light transmission measurement that is performed using a vacuum cold stage and a high-resolution imaging microscope which typically includes an option to record movies of the images. A thin film (10–100 μm) of solution (1–2 μl) is frozen between microscope coverslips and is subjected to vacuum. The temperature is raised, typically at a ramp rate of ~1 °C/min, and stabilized at a new temperature set point to initiate sublimation. Light transmission images are acquired to monitor the progression of the sublimation front through the frozen, thin-film sample. The process of raising the temperature, stabilization, and imaging is repeated and correlated to thermocouple (TC)-based product temperature measurements until visual changes are observed that are indicative of viscous flow and product collapse. Collapse is indicated by the consolidation and growth in size of dried product pores. Polarized light microscopy is often used to enhance the imaging and the visualization of collapse.

The use of thin-film samples in LT-FDM has a number of limitations for the measurement methodology. Although LT-FDM provides useful information regarding collapse on thin samples, it does not provide information regarding product formulation micro collapse or the onset of collapse in 3D samples, representative of commercial freeze-drying in vials or other container systems. T_c in a product vial may be quite different than in a thin film due to differences in ice nucleation causing differences in dry layer resistance, pressure gradients in the dry layer, and the heat transfer and drying rates [27]. Collapse is a dynamic event which is dependent on viscous flow of the product; therefore, if drying occurs before significant viscous flow occurs, the cake will not collapse even if the temperature is above the glass transition temperature of the solute phase, T_g'. LT-FDM of a thin film may not be representative of these dynamic processes. Both theoretical and experimental evidence suggests that freeze-drying in a vial is sufficiently different than in a 2D sample such that T_c for a product in a vial may be several degrees (or more) higher than measured using conventional LT-FDM, particularly for protein formulations [27]. This will result in the use of lower primary drying shelf temperatures and thus lower than required product temperatures. The reduction in primary drying temperatures will lead to longer drying times and un-optimized lyophilization processes.

Optical Coherence Tomography-Based FDM

Recently, a new collapse temperature determination approach was demonstrated based upon the application of OCT interrogation of a product formulation contained within a standard 10-ml pharmaceutical vial undergoing drying in a single-vial freeze-dryer [11, 12]. OCT is the optical analog of ultrasound [32, 33] providing cross-sectional imaging enabled by the measurement of the magnitude and echo time delay of backscattered light using a Michelson interferometer. The OCT-based