

rectly controlled using shelf temperature and chamber pressure and is dependent on formulation, primary container, and the corresponding apparent heat transfer coefficient. Primary drying, however, can have significant economic impact as it is the longest step in drying. In general, it is recommended that a conservative cycle is obtained by maintaining product temperature several degrees ($\sim 2\text{--}5^\circ\text{C}$) below collapse temperature which in turn is a few degrees below glass transition temperature [48]. Operating at higher (scorch) temperature, however, may result in uniform distribution of bound water and temperature and a balance between cycle time and product safety must be established [49]. It must be noted that high viscosity of the formulation matrix in the frozen state can severely limit the reaction kinetics (Stokes–Einstein relationship) and it might be feasible to obtain a quality dried product with drying temperature above T_g' [50]. In certain cases, crystalline bulking agents such as glycine and mannitol ($T_{eu} \sim -3^\circ\text{C}$) might be added to increase the collapse temperature of the product and to achieve faster primary drying. In general, approximately 5°C increase in shelf temperature increases the product temperature by approximately 1°C and every 1°C change in product temperature may expedite the primary drying by approximately 13% [16, 42]. However, in such cases, an annealing step must be added to ensure complete crystallinity and the ratio of crystalline to amorphous excipient must be $>67\%$. Amorphous bulking agents such as sucrose and trehalose are also added to the low concentration solids ($<1\%$) containing products to prevent “blowout” [10]. Radiative heat from the freeze-dryer walls and door can induce heterogeneity through edge effects. Additionally, ultra-low pressure may further add to inter-batch heterogeneity and even cause product contamination (pump oil, stopper components, etc.) [51, 52]. Thus, it is recommended that optimal chamber pressure that allows for fastest sublimation and homogenous heat transfer must be chosen. End of primary drying can be monitored using multiple methods such as convergence of shelf temperature and thermocouple, convergence of pirani and capacitance measurement, tunable diode laser adsorption spectroscopy (TDLAS), mass spectrometry, dew-point sensor and/or MTM/pressure rise method [10, 41]. If a thermocouple is used to monitor end of primary drying, an additional 20% soak time must be allowed for nonthermocouple vials to finish primary drying.

Stage 3: Secondary Drying

Post completion of primary drying, the shelf temperature is ramped slowly (approximately $0.1\text{--}0.5^\circ\text{C}/\text{min}$) to avoid product collapse while removing water by desorption during this stage. It is recommended that secondary drying must be carried out for a shorter period of time at higher temperature as the desorption rate of water decreases substantially with time. Furthermore, shorter secondary drying results in faster cabinet turnaround during manufacturing. It must be noted that the rate of desorption is dependent on product-specific surface area (i.e., freezing and formulation specific), shelf temperature, and container heat transfer coefficient. In our experience, lower moisture is not always better for stability and an optimal