at a shelf temperature of 35 °C. Final moisture of approximately 0.5 % was obtained in the drug product.

Figure 5 represents the final cycle developed for this product. The length of primary drying stage was intentionally increased by approximately 25 % to accommodate for any potential scale-up differences. The impact of variation in K_v due to both position effects and nonuniformity among vials and the impact of variation in R_p due to ice nucleation variation were also considered using the modeling approach, and an extra safety factor in primary drying length was included to ensure the completion of the primary drying step for the worst case scenario. The cycle was further verified experimentally, and the resulting product showed acceptable product quality attributes along with a good product temperature profile, suggesting the suitability of the lyo process. To complete the development and scale-up of this lyophilization cycle, the model was adjusted with the K_v data obtained from the commercial scale lyo scale-up. The operating ranges were then adjusted to maintain the original product temperature profile as determined in the laboratory. Therefore, comparability in the product temperature profile was targeted as opposed to comparability in the shelf temperature and pressure parameters as in the traditional approach.

Expand the Design Space Using a Scale-Down Model

The above modeling approach, which is based on the results of steady-state heat and mass transfer theory, is very useful for cycle development. It allows the prediction of product temperature at different drying conditions, and has been widely used for primary drying robustness studies and design space construction. The process design space as illustrated above is based on process limitations imposed by the product and equipment capability. However, this modeling approach also has some limitations. First, the product temperature limitation for an amorphous system is mainly based on the collapse temperature (T_c) measured by FDM, and the obtained maximum product temperature may not be the "failure point." It has been reported that collapse may not be detrimental to the in-process or long-term stability of freeze-dried proteins [46, 53], and it is possible to perform primary drying at temperatures above the T_c for some formulations such as high concentration protein formulations or formulations containing both crystalline and amorphous components [6]. Systems such as these may be dried at much higher temperature, well above the T_c, without macroscopic product collapse or loss of any perceptible measure of product quality. Secondly, it is generally assumed that the cake resistance measured at a low product temperature can be used to predict primary drying performance at a higher temperature. This assumption could generate large error in sublimation rate calculations for a system where cake resistance is highly dependent on the drying temperature. As discussed earlier, when the shelf temperature was increased from −30 ºC to −20 ºC, the product temperature in a 4.5 % sucrose-based formulation increased above T_c, which resulted in a sixfold decrease in cake resistance [24].