chamber walls will be more significant as the distance between the product compartment and the shelf increases. It should also be noted that proper evaluation of the freezing stage can only be properly assessed for samples under clean conditions since particulate matter can impact the nucleation of ice crystals. Understanding the behavior of the active drug substance itself during freezing is also of critical importance. This is especially crucial for biological products such as proteins. Slower freezing of samples can lead to denaturation of proteins since a longer residence time for the active substance in the freeze-concentrated liquid may favor degradation routes such as aggregation. Annealing has been shown to reduce heterogeneity in ice crystal structure across a batch during freeze-drying in syringes (20). Annealing above the glass transition temperature causes growth of ice crystals, which may decrease product resistance during sublimation of ice in the primary drying phase.

Primary Drying

Primary drying consists of the removal of frozen water (ice) by means of sublimation. Following the freezing phase, the drug product bulk solution is present as a frozen matrix of amorphous and/or crystalline material plus pure ice. During primary drying, the pressure is reduced to a suitable level and the shelf temperature is increased to deliver energy to the system to promote sublimation. Determination of optimum conditions for primary drying is generally the most crucial aspect of lyophilization cycle design. The primary drying phase is also typically the longest step in the lyophilization process. Therefore, optimization of primary drying conditions presents the best opportunity for increased efficiency, reduced cycle time, and decreased process cost. However, during the sublimation process, the product is also most vulnerable to failure. During primary drying it is crucial to stay below the identified critical temperature (i.e., T_g' or T_c) to prevent collapse of the product. It is also important that the sublimation of ice be complete before the end of the primary drying phase. If ice remains when the secondary drying phase begins, the product will likely experience melt-back and result in failure of some or all of the batch.

Dual chamber packages present a unique challenge to primary drying phase development. As noted for the freezing phase, package systems that employ a product chamber separated from the lyophilizer shelf behave differently from traditional vial systems. The radiative heating effects from the chamber walls are much more significant and the ability of the shelf temperature to control these effects is greatly reduced. Therefore, it is often difficult to maintain a uniform product temperature and, thus, uniform drying rate across an entire shelf and/or load of DCCs. One must be cognizant of the fact that product located near the center of the lyophilizer shelves can experience temperatures on the order of 5°C to 15°C lower than their counterparts on the edge of the load near the chamber walls. This product temperature difference will result in significant differences in drying rate. Figure 11 illustrates the higher product temperatures (i.e., higher drying rates) for the perimeter samples as compared to the lower product temperatures (i.e., lower drying rates) for the insulated inside samples. Because of this fact, it is critical when interpreting product temperature data to ensure that both hotter (edge) and colder (center) regions for each shelf within the dryer are identified and evaluated for the impact on the product. One should also note the difference in equilibrium