OQ and PQ testing does not provide enough information to evaluate the performance of the freeze-dryer in detail. Further work must be performed to enable a detailed understanding of performance characteristics and limitations, which are critical to cycle development and scale-up. Combining the understanding of performance design and limitations with the developed K_v model enables the development of a design space for primary drying. It is important to design the primary drying step such that the design limitations of the commercial freeze-dryer in question do not prevent execution of the cycle as designed.

Freezing Step

The overall objective of the freezing step is to separate the solvent from the solutes. The solvent in most cases is water, but may also be organic such as ethanol. Another objective of the freezing step is to crystallize any excipients that may be crystallized under conditions during freezing, for example, mannitol or glycine, in order to maximize the collapse temperature, optimize the primary drying step, and improve cake appearance. Although a certain amount of crystallization would occur under normal freezing conditions, the best way to achieve maximum crystallization would be to perform an annealing step, as discussed later.

Freezing is achieved by cooling the product from the loading temperature (after a certain hold time at the end of the loading stage) to a target freezing temperature below the T_g' with a predetermined shelf cooling rate. It was observed that the degree of supercooling can vary by as much as 10 °C throughout the batch, and thus freezing is sometimes referred to as stochastic freezing. The target freezing temperature would normally be ~5 °C below the T_g' and the vials are held at the target temperature for a number of hours. During freezing, as the heat transfer is a result of conduction at high pressure, perhaps with convection, heat transfer is generally good in a vial, and thus the product temperature and shelf temperature should trend closely.

In order to maximize the crystallization of the amorphous excipients, annealing is generally performed before initiation of primary drying. After freezing is complete, the shelf temperature is increased to a temperature above the T_g' and below the eutectic temperature. The vials are held at this annealing temperature for a few hours. This step has several advantages: First, it allows the ice to restructure to an optimum ice crystal size, which is known to increase the rate of primary drying and to decrease the variation in drying time within the batch and between laboratory and manufacturing batches [47]. Second, it enables crystallization of the bulking agent such as mannitol to a high degree. This crystallization event removes the excipient from the amorphous phase and typically results in a higher T_g'.