Therefore, it is normally more efficient to increase secondary drying temperature and/or time to compensate for the impact of smaller surface area on the desorption characteristics of the product post primary drying.

Nucleation Control: Principles and Methodologies

To deal with the stochastic nature of the onset of ice nucleation, a number of homogeneous nucleation methodologies have been examined [16, 27]. One consists of an ice-fog technique, which was found to result in rapid ice nucleation (< 1 min) due to the ice-fog-seeding nucleation within the container [27]. A second technique, which utilizes rapid depressurization within the chamber, has been shown to achieve instantaneous and homogeneous ice nucleation. The ice nucleation temperature chosen is often relatively high (e.g., − 5 °C), which means that larger ice crystals are formed which then reduces the primary drying time. Other methods such as vacuum-induced freezing [17] were also examined. Overall, controlling nucleation during freezing is of critical importance to improve freeze-drying conditions, resulting in a more scalable and reproducible freezing step. If implemented in the cycle design stage, this could provide more confidence in reproducibility of the process and control of product quality in general. In fact, one could argue that, given the availability of controlled ice nucleation at both laboratory and commercial scale [4, 49], it will soon be a part of current good manufacturing practice (cGMP) for freeze-drying to control ice nucleation just as it is cGMP to control primary drying by control of shelf temperature and chamber pressure.

Achieving homogeneous ice crystal size and morphology is very important from a QbD perspective. Without the solid foundation of the freezing step, no matter how well the primary drying step is modeled, there will always be a degree of variability in the performance of both primary and secondary drying, thereby resulting in batch uniformity issue and variation in product quality attributes, which may not be acceptable. Lastly, without the homogeneity of ice crystal formation, scalability will remain a challenge due to the different environments between the laboratory and manufacturing.

Primary Drying

Primary drying is modeled using a series of heat and mass transfer algorithms with the goal of establishing a design space within the freeze-dryer capacity for chamber pressure (P_{ch}) and shelf temperature (T_{sh}) that results in an acceptable product. These two parameters ultimately control the desired product temperature (T_p) during primary drying. Other factors for establishing a design space include the limitations of the freeze-dryer to control chamber pressure and shelf temperature at the desired set points. All these factors make up the design space for primary drying. The set of operating conditions preserving the product quality defines the design space [13].