Ice Nucleation, Supercooling, and Annealing

Ice nucleation is a stochastic event and the temperature at which ice nucleates in a vial is usually different between the laboratory-scale and commercial-scale dryers. Further, the nucleation temperature is variable from vial to vial within the same batch. The uncontrolled nature of ice nucleation presents complications during the transfer of a lyophilization cycle between laboratory and manufacturing and potentially also between established manufacturing environments. Ice nucleation occurs well below the equilibrium freezing temperature under normal atmospheric pressure conditions. The degree of supercooling is the difference between the thermodynamic (equilibrium) freezing point and the temperature at which ice crystals actually first form in the sample.

Variations in the degree of supercooling reflects the random nature of nucleation and depends on product properties and conditions [32]. Convention wisdom states that a low particulate "class 100" environment leads to a higher degree of supercooling and conversely, a high particulate laboratory environment leads to a lower degree of supercooling. However, while plausible, direct experimental confirmation of this interpretation is limited. Higher degree of supercooling will result in the formation of smaller ice crystals, and smaller pores will be left during sublimation in the dry layer which increases the mass transfer resistance to the flow of water vapor. On the other hand, lower degree of supercooling will lead to lower resistance to the flow of water vapor through the dried layer. Primary drying time is longer for a product with higher cake resistance even using the same conditions of shelf temperature and chamber pressure. Therefore, primary drying time is longer for a cycle running on a commercial freeze-dryer than for a cycle at laboratory scale. This duration difference between laboratory and commercial scale makes it challenging to estimate the end point of primary drying in manufacturing based on typical laboratory data. The traditional approach is to add few hours, or perhaps ≈ 20 % of the laboratory primary drying time, to the duration of primary drying in the manufacturing process. However, this is not an ideal approach and may lead to product defects if the secondary drying is initiated before the end of primary drying. Alternately, using a much longer (arbitrary) duration of primary drying in manufacturing likely will waste time without any positive impact on product quality. Using a PAT tool such as a Pirani gauge is an ideal solution to establish the end point of primary drying [29], and this methodology can be used in dryers of nearly all sizes and designs.

Ice nucleation plays an important role in the secondary drying process, as residual moisture (RM) is a function of specific surface area (SSA) of the lyophilized cake [36]. Large ice crystals result in lower resistance to vapor flow during sublimation but also a lower SSA [48]. This, in turn, results in a reduced efficiency during secondary drying, as the rate of secondary drying is roughly proportional to the SSA [36]. Therefore, a larger SSA (smaller ice crystals) is optimum for an efficient secondary drying process. However, the impact of having smaller ice crystals is generally more severe on primary drying because it is the longest step in the cycle.