

rani Gauge, capacitance manometer, LyoTrack, manometric temperature measurement (MTM), and TDLAS have been used for the determination of end point of the primary drying stage, and readers can refer to the later PAT chapter for more details. Our view is that the use of the pressure difference between Pirani and differential capacitance manometer is perhaps the best methodology from a perspective of sensitivity, reliability, cost, and preservation of product quality.

Secondary Drying

Once all the ice is removed by sublimation during primary drying, product temperature can be increased to remove the unfrozen water in the product, which is known as desorption drying during the secondary drying stage. A high percentage of RM content in the final product can lower the glass transition temperature (T_g) of the amorphous product below the storage temperature which will lead to collapse and/or perhaps result in crystallization. A high percentage of RM may also have direct effect on chemical stability of the product; normally increased water content, at least above a certain level of $\approx 3\%$, will give an increased rate of chemical degradation. For these reasons, the secondary drying is generally designed to remove most of the unfrozen water to achieve low RM, frequently $< 1\%$ RM content in the final product.

Both the shelf temperature and the shelf temperature ramp rate can affect the finished product quality. The higher shelf temperature ramp rate has been shown to lead to cake shrinkage and therefore, as a general guideline, ramp rate in excess of $0.25^\circ\text{C}/\text{min}$ should be avoided, at least in the first few hours of the ramp from the primary drying temperature to the secondary drying temperature. An increase in shelf temperature leads to an increase in both product temperature and water vapor concentration in the chamber. That is, as product temperature increases sharply with a significant amount of water remaining in the product, there is usually a transient increase in the pressure reading of the Pirani gauge (normally calibrated with Nitrogen). Of course, the increase in product temperature also leads to more rapid drying and decreased RM content. For products that remain amorphous during lyophilization and storage, it is important to keep the shelf temperature during secondary drying below the T_g . Crystalline products carry no real risk of collapse during secondary drying and therefore, higher shelf temperature ramp rates and higher secondary drying shelf temperature may be used. The rate of decrease in moisture content is high during the initial few hours of secondary drying, and typical drying time in excess of 4–6 h is normally not necessary. If at the end of about 6 h the residual water content is still too high, one needs to increase the product temperature. Products having higher solid content ($> 10\%$) may need extra time for secondary drying. It is understood that the secondary drying desorption rate is not a function of chamber pressure in the range typically used for pharmaceutical systems [36].

For secondary drying, dryer limitations of heat or mass transfer are not a factor, shelf temperature and product temperature are almost the same, and chamber pres-