gas onto the surface of a solid, and the BET equation assumes a simple physical adsorption mechanism. The BET experiment is generally performed using inert gases such as nitrogen, argon or krypton, and the experimental temperatures are kept low enough (liquid nitrogen at 77 K) in order to form a sub-monolayer of gas on the sample surface at moderate pressures. The SSA of various freeze-dried 5% mannitol were studied [41]. The SSA of the dried product was found to correlate well with the degree of supercooling and also with the cake resistance of the product, with a higher degree of supercooling resulting in higher SSA and larger resistance. Using this correlation and SSA measurements from both small-scale and large-scale products, one could obtain the cake resistance data from large manufacturing-scale dryer, and further predict scale-up drying differences or modify the freeze-drying process to bring equivalent product temperature profile during scale-up [40].

The formation of crystals in the lyophilized product can be monitored using several techniques, but the "gold standard" is powder X-ray diffractometry (XRD). XRD is an analytical technique used for phase identification of a crystalline material, and it can also provide information on degree of crystallinity in the lyophilized product. Dried sample is loaded into a sample holder, and the scans are generally conducted in the 2θ range between 5° and 60° angle. The identification of the polymorph can be carried out by comparing the diffraction pattern of the sample with reference standard data. Mannitol or glycine is often used as a bulking agent in a protein formulation to obtain a good cake appearance and a robust formulation that resists changes in cake structure during drying, and crystallization of these bulking agents has a large impact on the product appearance and stability. The degree of crystallinity can be estimated by integrating the relative intensities of the crystalline peaks and amorphous halos, and this quantitative analysis can be used to ensure the batch-to-batch consistency and investigate process deviation.

Case Study to Obtain Design Space

Modeling of Primary Drying for a Robust Design Space

A case study is presented to illustrate the use of heat and mass transfer theory modeling in construction of a design space. Primary drying behavior was calculated for a protein product containing sucrose and a bulking agent, filled to 5.3 mL in a 20 cc tubing vial. The protein-active ingredient was of 78 kDa in size, and the collapse temperature was clearly observed at −30 °C with FDM. K_v was measured for the 20 cc vial in a Virtis 35EL laboratory freeze-dryer as per the procedure introduced earlier and is represented by the following equation:

$$K_v = 0.0002 + \frac{0.0025 P_c}{1 + 3.644 P_c}, \tag{6}$$

where P_c is the chamber pressure with the unit of Torr.