sured directly in a large scale production dryer or corrected using a correction factor based upon measured or estimated differences in degree of supercooling. In addition, the potential impact of drying temperature on resistance needs to be considered. The effect of drying temperature on resistance was found to be quite dramatic for potassium chloride or a dobutamine hydrochloride–mannitol (weight ratio of 1.12:1) system, and a large increase in shelf temperature resulted in a transition to a type-IV curve with a significant reduction in resistance [34]. At higher temperature close to the eutectic temperature for these crystalline systems, hydrodynamic surface flow of adsorbed water may account for the observed behavior [34]. However, with systems exceed a T_g', changes in pore structure do occur as a result of what is sometimes termed "microcollapse," with the net result of reducing resistance. For example, mass transfer resistances of an antibody (rhuMAb HER2) formulated in trehalose as well as protein-free formulations containing trehalose and sucrose were investigated. Mass transfer resistance of all three formulations was found to decrease significantly with increases in shelf temperature for each system. For 4.5 % sucrose formulation, about a sixfold decrease in the cake resistance was noticed at a dryer thickness of 1 cm when the shelf temperature increased from −30 to −20 °C [24]. The microscopic determination of cake structure supported the view that the decreased resistance at elevated temperature may be the result of small-scale product collapse. Thus, when planning to run near or above a T_g' or eutectic temperature, it would be prudent to evaluate the impact of product temperature on the resistance parameters, at least the impact of temperature on the parameter, A2, which was done previously [34].

Primary Drying Design Space Modeling: Designing Robustness Upfront

The goal of this section is to provide a scientific approach for building a design space for evaluating the impact of CPP (shelf temperature, chamber pressure, and primary drying time) on the quality attributes (RM content, reconstitution time, and product physicochemical stability) of the product. A robust and optimized cycle can be designed through the use of mathematical modeling, and a design space can be obtained in which the cycle can produce consistent product quality [42].

In terms of QbD, the emphasis for developing the primary drying step is on using heat and mass transfer simulations along with risk assessment. Mathematical modeling of primary drying has been previously presented [13, 19, 31, 42] and enabled development of a design space as a function of two primary control variables shelf temperature (T_{shelf}) and chamber pressure (P_{chamber}) with product temperature and primary drying time being the output.

Once K_v and cake resistance have been determined, the cycle performance can be modeled and optimized. Using the K_v ratio established, cycle performance can be predicted for both edge and center vials over a range of conditions, resulting in a design space similar to the one shown in Fig. 3. Such a plot allows the user to express the T_{product} as a function of the independent variables, T_{shelf}, and P_{chamber}. This modeling allows the user to choose cycle conditions such that the primary dry-