a tunable diode laser absorption spectroscopy (TDLAS), and a computer program was used to perform the heat and mass transfer computations with the nonlinear least-squares algorithm. It can be seen that the order of vial heat transfer rate is: Schott-10TS > Schott-20T > Schott-10T > Wheaton-5T > FV-50T > Wheaton-50 at typical chamber pressures [20].

Lyophilization Development and Scale-Up

Due to the significant amount of publications on quantitative analyses of lyophilization in the past two decades, the QbD approach presented in this chapter focuses on the use of a mathematical model based on heat and mass transfer. Estimation of K_v and R_p is essential to the application of this model to obtain a design space [13]. The key element here is to estimate the K_v for a given vial as a function of pressure and to evaluate the R_p of the formulation for an ice nucleation temperature and product temperature range during primary drying that are characteristic of the process one intends to run. This is normally accomplished by running a conservative cycle of the formulation in question, and assuring that drying is performed below the critical product temperature, where R_p is essentially independent of product temperature. Further details are provided in this chapter in relation to the QbD concept and it applications to different stages of lyophilization process.

Liquid Characterization

For a rational development of a stable formulation, complete characterization of the protein solution is necessary. In addition to the structural characterization of protein native structure using conventional spectroscopic methods such as circular dichroism (CD), florescence, or Fourier transform infrared spectroscopy (FTIR), thermal analysis of the frozen state using differential scanning calorimetry (DSC) and freeze-drying microscopy (FDM) is very important to obtain the maximum allowable product temperature to be used in the primary drying process.

During the initial freezing stage, water will be converted into ice and the solute will be concentrated. Unless a critical low temperature is reached, the protein system still exhibits high “mobility” on an experimental timescale and degradation can still occur. This critical temperature during freezing step is called T_g', which is referred as the glass temperature of the maximally concentrated freeze-concentrate [32]. The freezing temperature should be below T_g' to ensure the whole system is completely frozen.

DSC is commonly used to measure the T_g' for a system. The protein solution is first completely frozen (to about $-60\,^{\circ}\mathrm{C}$), and then the temperature is scanned linearly to about $0\,^{\circ}\mathrm{C}$. T_g' is the temperature at which there is a sharp change in the