sample in the capillary may not freeze with the same degree of supercooling as in a vial.

2. Manometric Temperature Measurement (MTM)

In this technique, the isolation valve connecting the chamber and the condenser is closed very quickly and the chamber pressure is recorded for about 25 s before the valve is reopened. The MTM equation has been used to fit to the recorded pressure rise data as a function of time [51], and the values of dried layer resistance can be obtained as a function of dry layer thickness. It was shown that for 5 % glycine, 5 % mannitol, and 5 % sucrose formulations, the R_p data obtained using MTM method were in good agreement with R_p data calculated with vial thermocouple method when a thermal shield was used in the experiment to remove the influence of a typical radiation. Note that the MTM obtained resistance is no longer accurate once the first row of vial completes primary drying [51, 52]. More details about the MTM application can be found in the PAT chapter.

3. Thermocouple

The product temperature profile alone can normally be used to obtain a useful estimate for the resistance, provided that the temperature can be accurately measured. The product temperature profiles (T_p) during primary drying were recorded and became the input data for the parameter estimation [35]. Based on the steady-state model and least-square minimization algorithm, the sublimation rate and the vapor pressure of ice at the sublimation surface can be calculated from the product temperature, thus the cake resistance can be obtained from Eq. 4. This method has been used for 5 % mannitol, 3 % lactose, and sucrose, and the results obtained using this modeling approach is similar to the values obtained using the MTM method [21].

4. TDLAS

TDLAS can also be applied to the measurement of R_p. TDLAS is designed for measuring the real-time sublimation rate, and the sublimation rate profile obtained can also be used for cake resistance calculation using the steady-state heat and mass transfer equations. In addition, cake resistance can be easily obtained by combining the TDLAS and the temperature probe profile. Using both the product temperature measured in the vial and the average sublimation rate of the entire batch, the resistance and effective pore radius of the dry layer has been estimated during primary drying [21]. This method does not require solution of the complex heat and mass transfer equations, and has been demonstrated with product runs with mannitol, sucrose, lactose, etc. The resistances obtained with three different approaches were compared, and the resistances obtained at the same dry layer thickness are reasonably close for each system [21].

In order to model the primary drying step accurately, it is essential to use a representative cake resistance measurement. The differences in freezing rate and the degree of supercooling play a significant role in determining cake resistance, and thus the cake resistance measured in the small scale dryer cannot be directly used for modeling in large scale production dryer. This value needs to be either mea-