

The principle involves fitting the MTM equation (Eq. 1) to the pressure rise data, generated from opening and closing the isolation valve, by nonlinear regression analysis [33].

$$P(t) = P_{\text{ice}} - (P_{\text{ice}} - P_0) \exp \left[ - \left( \frac{3.461 N A_p T_s}{V (\widehat{R}_p + \widehat{R}_s)} \right) t \right] + 0.0465 P_{\text{ice}} \Delta T \left[ 1 - 0.811 \exp \left( - \frac{0.114}{L_{\text{ice}}} t \right) \right] + X_t \quad (1)$$

where  $P_{\text{ice}}$  is the vapor pressure of ice (Torr) at the sublimation interface;  $P_0$  is the chamber pressure (Torr);  $N$  is the total number of filled vials;  $A_p$  is the inner cross-sectional area of the vial ( $\text{cm}^2$ );  $T_s$  is the shelf temperature (K);  $V$  is the chamber volume (L);  $\widehat{R}_p + \widehat{R}_s$  is the total area normalized product and stopper resistance (determined by the fit);  $L_{\text{ice}}$  is the ice thickness (cm);  $\Delta T$  is the temperature difference between ice sublimation interface and bottom of vials; and  $X$  is a constant (Torr/second).

Fitting Eq. 1 to the pressure rise data yields a vapor pressure of ice,  $P_{\text{ice}}$ , and the  $\widehat{R}_p + \widehat{R}_s$  total resistance of product and stoppers. The MTM product temperature can be calculated from the vapor pressure of ice ( $P_{\text{ice}}$ ) by Eq. 2.

$$\ln(P_{\text{ice}}) = \frac{-6144.96}{T_p} + 24.01849 \quad (2)$$

where  $T_p$  is the product temperature (K) and  $P_{\text{ice}}$  is the MTM fitted vapor pressure of ice.

When considering the application of MTM to collect product temperature data during the primary drying stage of the cycle, it should be noted that the product temperature is measured from pressure rise data, calculated using a CM and applying Eq. 1. As the pressure rise measurement is a function of the full chamber over a time period of 25 s, it does not discriminate between vials at specific locations within the freeze dryer. The calculated product temperature using the MTM equation is therefore an average of the entire batch [24].

Studies were performed to understand the comparability between product temperature measurement using thermocouples and MTM [34]. Sample of 5% sucrose was used with a target product temperature of  $-40^\circ\text{C}$ , which is well below the sucrose collapse temperature of  $-32^\circ\text{C}$ . It was found that the temperature gradient was negligible during the drying step, the comparative thermocouple and MTM measurements were in good agreement. A second experiment using 5% glycine suggested that the average product temperature was heavily skewed towards the coldest vials (interior or center vials as opposed to edge vials). Interior vials form the majority of vials when considering the overall array on a given shelf. As the edge vials display higher temperatures due to the influence of radiative heat transfer, this should be taken into account from thermocouple placement.