

T_b is the product temperature at the bottom of the vial (K), \hat{Q} is calculated using the relation $\Delta H_s * dm/dt$, where ΔH_s is the heat of ice sublimation (cal/g). L' is the thickness of the dry layer (cm), and K is the thermal conductivity of ice (cal/h.cm.K). L' as a function of time (t) can be represented using [26]:

$$L'(t) = \frac{m_o - m(t)}{p_{ice} \cdot A_p \cdot E} \quad (5)$$

where m_o is the initial mass of water (g) per vial, $m(t)$ is the cumulative mass of sublimed ice up to time t (g), p_{ice} is the density of ice (g/cm³), A_p is internal cross-sectional area of the vial (cm²), and E is the ice volume fraction.

\hat{R}_p as a function of dry layer thickness $L'(t)$, can be represented as [26]:

$$\hat{R}_p = R_o + \frac{A \cdot L'}{1 + B \cdot L'} \quad (6)$$

The parameter R_o , A , and B are constants and can be evaluated from a fit of the Eq. 6 to data using regression analysis.

Selection of the shelf temperature and chamber pressure for the purpose of defining the design space is dependent upon the target product temperature and primary drying time. The approach for generation of the process design space has been discussed by Mockus et al. [7]. In order to construct the design space, shelf and product temperature isotherms are developed using Eqs. 1–6. Multiple shelf temperature isotherms (relationship between chamber pressure and sublimation rate at constant shelf temperature) are generated by using predetermined values K_v (using TDLAS and sublimation tests) and \hat{R}_p (from the first lyophilization run). Here, at a particular shelf temperature and chamber pressure, Eqs. 1–6 are solved iteratively for a product temperature which is then used to calculate the sublimation rate. This approach is repeated for the same shelf temperature but by varying chamber pressure. Ultimately, a series of sublimation rate values as a function of chamber pressure at constant shelf temperature are obtained which can be plotted to generate the shelf temperature isotherm. Product temperature isotherms (relationship between chamber pressure and sublimation rate at constant product temperature) are generated using Eqs. 2–3. Here, at a particular product temperature, P_{ice} is calculated first using Eq. 3 and then at a particular chamber pressure, the sublimation rate is calculated using Eq. 2. This approach yields a series of sublimation rate values as a function of chamber pressure at a constant product temperature, which are then plotted to generate the product temperature isotherm. Using the equipment capability curve and the shelf and product temperature isotherms, the design space for primary drying is generated (Fig. 3).

Figure 3 shows primary drying design space for a hypothetical product. Assuming a target product temperature of -24°C , chamber pressure and shelf temperature conditions of 170 mTorr (A) and $\sim 13^\circ\text{C}$, respectively, would result in the fastest