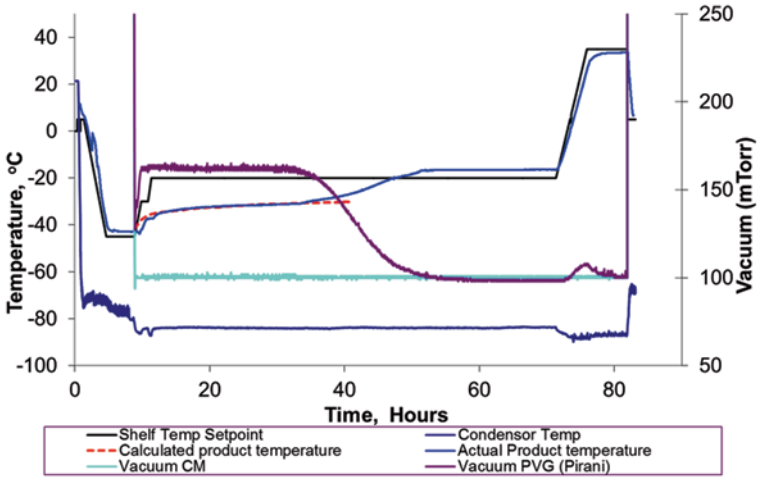

Fig. 5 A lyophilization cycle developed for a model product showing the agreement between the experimental data and the calculated product temperature based on the heat and mass transfer model. Capacitance Manometer (CM), Pirani Vapor Gauge (PVG)

product temperature was estimated to go beyond the collapse temperature (−30 °C), which has the potential to result in poor cake appearance and poor product quality. Therefore, at typical 100 mTorr chamber pressure, the acceptable range of primary drying shelf temperature will be from −25 °C to −20 °C based on this modeling.

Figure 5 gives the comparison of calculated product temperature and the actual thermocouple data during primary drying stage. Good agreement was found between the product temperature measured by thermocouple (blue line) and the predicted product temperature profile (red dashed line). This comparison shows the validity of this K_v and R_p model, which suggests that the developed model allows an accurate prediction of a design space for primary drying at these conditions, in terms of shelf temperature and a set chamber pressure. In addition, the design space was further developed by considering a chamber pressure range along with the shelf temperature to better understand the overall effect on the product temperature profile, relative to collapse. A low limit of 50 mTorr was used as the minimum controllable chamber pressure based on the manufacturing lyo capability, and 200 mTorr was selected as the top pressure limit. A design space considering both shelf temperature and chamber pressure, along with the limitations of the system itself was found to be similar to the one shown in Fig. 3.

Further design of the secondary drying step was conducted, where the shelf temperature was selected with due recognition of the dry state T_g, as measured at the end of primary drying using MDSC. The time was determined by experimental study of the rate of desorption, or residual water content, as a function of time during the secondary drying step. Using a "sample thief," vials were removed for RM analysis by Karl Fisher titration at the end of primary drying, in the middle of the ramp to the secondary drying set point, and after 2, 4, and 6 h of secondary drying