

MTM limitations include the fact that the product temperature is an average temperature with bias towards the coldest vials and a minimum ice sublimation area is required for accurate results, estimated by a Q value of ≥ 0.23 . For a laboratory freeze dryer with a 50-L chamber, the minimum area would be 150 cm^2 [34]. MTM is only useful for 2/3 of the primary drying step due to the high degree of drying heterogeneity towards the end of primary drying [19].

Benefits of using MTM are clear in that it provides a product temperature profile by noninvasive means, arguably resulting in a more representative profile. This principle could prove to be a powerful PAT tool. It has been observed that MTM is effective at product temperatures as low as -45°C , which covers the majority of freeze-dried formulations. MTM has also been used to measure dry layer resistance (R_p), where it was shown that for 5% glycine, 5% mannitol, and 5% sucrose formulations, R_p data were in good agreement with actual data (vial thermocouple method) when using a thermal shield to remove the influence of atypical radiation [34]. When measuring without a thermal shield, it was noted that the R_p values were consistently lower than actual data.

MTM was also examined as a method to measure the vial heat transfer coefficient (K_v) and sublimation rates in different conditions with and without thermal shields. Using an FTS Dura-Stop/Dura-Top freeze dryer, it was found that K_v was in good agreement with the traditional gravimetric method for 5% sucrose when using a thermal shield such as aluminum foil. Conversely, without the thermal shield, the K_v measurement was consistently higher than for the gravimetric method, which was supported by data generated for multiple concentrations of mannitol, sucrose, and glycine [33].

SMART™ freeze dryer was developed using MTM [32]. The system was designed to enable the scientists to arrive at an optimized cycle in one run, once certain parameters were entered into the software prior to initiating the cycle (maximum allowable temperature, amorphous or crystalline, concentration, fill volume, vial geometry, vial type, number of vials, etc.). In short, the cycle is adjusted in real time (i.e., shelf temperature and chamber pressure), while maintaining the product temperature below the maximum allowable temperature.

Lastly, it has been reported that MTM has applications in the secondary drying step, where it has been shown to be able to predict average moisture content across the batch and the secondary drying endpoint [19, 32]. Residual moisture measured experimentally using Karl Fischer was measured for vials of freeze-dried sucrose (5%) and glycine (5%), where the samples were taken using a sample thief. In another experiment, the residual moisture was predicted by using a series of pressure rise steps (MTM method), where the rate of desorption was estimated using the ideal gas law [19, 32]. Good agreement was found between the residual moisture data generated from both methods.

Overall, MTM is a useful tool for the design and monitoring of the primary drying step, even with a number of limitations that need to be considered. It was also found that MTM was useful in measuring desorption rates and therefore residual moisture during the secondary drying step. However, implementation at commercial scale may be difficult due to the nature and requirements of the tool.