

spectroscopy, can give useful information about the quality of the final product, these technologies do not directly provide real-time process information. Here, we mainly focus on the online monitoring devices used in the freeze-drying process.

QbD design of a robust freeze-drying process relies on the thorough understanding of the impact of the formulation and process parameters on product quality. The critical formulation factors include the properties and amount of the drug and each excipient used and their interactions [31]. The CPPs include, but are not limited to drying shelf temperature, chamber pressure, freezing/heating ramp rate, etc. Process optimization depends on understanding each freeze-drying stage, monitoring CPPs and controlling them whenever necessary.

Due to the extreme conditions used in the freeze-drying process (low temperature, high vacuum, and high temperature for sterilization), only limited PAT devices are compatible with the harsh environment. During the early development history in freeze-drying, there was not much understanding about the required technology and visual inspection was mainly used to guide process development. The Pirani gauge was later employed to monitor or control the pressure during the drying process, and it is still being explored for regular use in good manufacturing practice (GMP) environment. Also the thermocouple was implemented to monitor product temperature, which has greatly accelerated the development of lyophilization field. Lately, more advanced tools such as manometric temperature measurement (MTM), tunable diode laser adsorption spectroscopy (TDLAS), and near-infrared (NIR) are being developed to monitor the product temperature, moisture level, and sublimation rate during lyophilization. These new technologies have a great potential in monitoring and controlling the freeze-drying process.

Based on their design applications, PAT tools for lyophilization can be categorized to the following four types:

1. Product temperature monitoring

The product needs to be fully frozen and should be dried below a critical temperature (collapse temperature for amorphous system or melt temperature for crystalline system) to ensure an elegant cake appearance. In addition, the product quality is heavily influenced by the thermal history which the product has experienced during the sample preparation process [35]. Therefore, it is critical to monitor and control the product temperature during the freeze-drying process. Both wired product temperature probes such as thermocouples and resistance temperature detectors (RTDs), and wireless probes such as the temperature remote interrogation system (TEMPRIS) have been developed for this purpose.

2. Primary drying endpoint

The endpoint of primary drying is the point at which sublimation rate is low enough to suggest that primary drying is almost complete. At the end of primary drying, the cake structure should be retained without any collapse, and it should not melt back even after exposure to ambient temperature [23]. This structural retention indicates that most frozen water has been removed by sublimation and the cycle can be progressed into secondary drying to further remove the “bound” water. Pirani gauge,