MTM, TDLAS, and plasma emission spectroscopy (Lyotrack) can be used to detect the primary drying point.

3. Moisture content

Since the freeze-drying process is essentially a water removal process, it is of great importance to constantly monitor residual moisture. NIR-based technology has been developed for this purpose, and can be used to provide a complete inspection of all the vials from the same batch. In addition, TDLAS has been developed to monitor the sublimation rate, which can also be used to track the amount of water removed and monitor the moisture content.

4. Changes in molecular structure

Recently, spectroscopic methods such as Raman and NIR were developed for monitoring of water–ice phase transition and mannitol polymorphism transition. In addition, protein conformational changes and the protein–excipient interactions during the freeze-drying process can also be studied. These techniques can give more insights into protein conformational stability and the lyoprotectant–protein hydrogen bonding interaction in real-time during the dehydration process.

This chapter intends to provide a comprehensive review of latest PAT tools for freeze-drying, with emphasis on suitability for a large-scale manufacturing process where PAT implementation and sterility concerns become critical. First, each of the latest process monitoring devices is reviewed in terms of the major applications and limitations. Second, all these techniques are summarized based on their capabilities, practical advantages, and scalability to a large-scale freeze dryer. Finally, the current most commonly used PAT tools are discussed, and future implementation of promising PAT tools is presented.

Process Analytical Technology

Product Temperature Probe

It is well understood that product temperature is the critical parameter of interest for an effective freeze-drying process [15]. In general, during the primary drying stage, the product temperature should be maintained below the maximal allowable critical temperature [19]. Frequently, thermocouples are used to monitor this parameter during the freeze-drying cycle at the laboratory or pilot scale. At a large scale, thermocouples or RTDs may also be used, the latter of which is preferred due to its mechanical robustness and effective sterilization. Lastly, thermocouples are used to determine the endpoint of primary drying [18–20].

During the primary drying stage, there is a difference between the shelf and product temperature, which is due to the heat absorbed by the sublimation process. The endpoint is the point at which the product temperature equilibrates with the shelf temperature. In the example shown in Fig. 1, the product temperature remains quite