

[10]. TDLAS was used to continuously measure the sublimation rate during 5% mannitol run, and the program was able to quickly perform the calculations based on heat and mass transfer equation. It was demonstrated that maximum product temperatures were controlled slightly below the target temperature, and a cascading temperature-ramping cycle is the most efficient cycle design [10].

Unlike thermocouple and other spectroscopic methods mentioned below, TDLAS gives the behavior for the whole batch. Overall, TDLAS shows a great potential to be used as an online monitoring tool for freeze-drying process, especially during manufacturing runs where the application of thermocouples is not possible. However, TDLAS also has some constraints. First, the integration of the technique to freeze dryer is not straightforward. The retrofitting of an old freeze dryer may be quite challenging, and the technique can only be applied to a freeze dryer with a long duct to allow absorption measurement at an angle (typically 45°) to the gas flow velocity vector. Second, the technology requires sophisticated calculations based on the gas concentration and gas flow velocity profile in the duct from the raw data. Therefore, depending on the duct size and configuration, the gas flow dynamics may be quite different between dryers. Spray balls and clean-in-place (CIP) nozzles in vapor duct at large scale may also impact calculations. In order to better understand these factors and facilitate process scale-up, more studies on large-scale manufacturing dryers are required.

Plasma Emission Spectroscopy (LyoTrack)

LyoTrack is a new online device developed to measure the humidity, and thus can be used to determine the endpoint of primary drying for the full batch. LyoTrack relies on inductively coupled plasma/optical emission spectroscopy (ICP/OES). This technology is adapted to the freeze-drying environment to measure water vapor concentration during the drying process [19]. The device is composed of two parts: the ICP plasma generator and the optical spectrometer. The ICP part creates a high power radio frequency wave, and the gas present in the freeze/dryer chamber forms cold plasma. The electrons from the gas atoms and molecules in the chamber are excited to a discrete higher energy state by absorbing this radio-frequency energy. The unstable excited atom will relax to its initial energy level and emit light. The optical spectrometer can thus identify the water vapor in the chamber based on the characteristic wavelengths of the emitted light.

Mayeresse et al. have systematically studied the LyoTrack using different formulations. The results indicate that LyoTrack can be used to determine the endpoint of primary drying with high sensitivity and good reproducibility [16]. The impact of probe location on the signal sensitivity was also studied, and it was found that the LyoTrack was sensitive to gas composition when it was placed in the chamber and in the duct connecting the chamber and the condenser but not in the condenser. The gas composition profile with drying time was similar when two lyophilizers of different scales were used for the same product, suggesting that the device can be used as a characteristic tool in process scale-up.