Technical Note

Some Common Methods Used to Detect the End of Primary Drying

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The process of freeze drying (also known as lyophilization) consists of three major steps, including; freezing, primary drying and secondary drying. The primary drying phase is typically the longest and most complex part of the process. Therefore, methods to automatically determine the end of primary drying can speed help to optimize process time. In some instances multiple methods may also be employed by the operator if desired.

Product Temperature Set-Point End of Primary Drying
Frozen product will have a lower temperature than the temperature controlled shelf while sublimation is occurring. It can be assumed that when the product temperature approaches the shelf temperature or a temperature well above 0C that there is no ice left in the product and therefore the product has reached the end of primary drying.

A typical software program can use this method as follows: The user enters an 'end of primary drying' product temperature. When the product temperature average reaches the defined set-point in the primary drying recipe, the program will automatically advance from the recipe to a predefined finishing routine and then to secondary drying. The finishing routine can be used to ensure that all vials have completed primary drying before entering secondary drying. If the finishing routine is not programmed, then the recipe jumps automatically to secondary drying. This feature is particularly useful for use with small lots of product.

Capacitance Manometer vs Pirani Convergence Test (Capacitance manometer and Pirani are required)
The Pirani vacuum gauge is built in such a way that the gas composition will alter its pressure reading. Pirani vacuum sensors read erroneously high in the presence of water vapor. This means that if a pirani sensor is the only vacuum sensor on the system it will indicate an erroneously high pressure reading and the transfer of that information to a dryer with a capacitance manometer will, in most likelihood, not work as smoothly as possible. A capacitance manometer is designed in such a way that it indicates the absolute vacuum and is not affected by water vapor in the system. If a freeze dryer is equipped with both sensors on the tray dryer the sensors can be utilized to indicate the end of primary drying. The first step would be to characterize the pirani and the capacitance manometer against each other in a dry, empty and refrigerated system. The freeze dryer is turned on, as per the manufacturer's operator manual, with nothing on the shelf. The shelf temperature can be left at room temperature or set for a lower temperature, the condenser is activated to be fully on and the system vacuum pump is activated. The freeze dryer is allowed a period of time to become stable in this condition and the pirani and capacitance manometers are read. The difference in their pressure readings in a dry, empty and refrigerated freeze dryer will be relatively small (mT to 10's of mT) when the system is working properly. These two gauges should NOT be calibrated against each other. There may always be slight differences in their readings do to their difference in design. The difference in pressure (ΔP) between these two gauges, when dry, empty and refrigerated, indicates how close they come together when there is little to no water vapor in the gas mix over the product.

The intent of primary drying is to maximize the sublimation rate within the product. As such the gases in the chamber have a high water vapor content. Subsequently the pirani sensor will read higher than the capacitance manometer. As freeze drying progresses and the amount of ice converting to vapor through the sublimation process will decrease as the product becomes lyophilized from top through the bottom of the product. Eventually the pirani and capacitance manometers will approach the ΔP that was established in a dry, empty and refrigerated system. Approaching this ΔP value indicates that the end of primary drying has occurred.

In most freeze dryers this process has been built into the software. The operator must determine the ΔP for the two sensors as indicated above. The user enters an pressure differential that would indicate end of primary drying into the software program. During the primary drying process, when the differential is met, the software program jumps to a finishing sequence and then secondary drying.

Dew Point via Moisture Sensor (Moisture sensor is required)
A moisture sensor may be mounted in a freeze dryer and is used to respond to the residual moisture content of the product. Moisture sensors measure in dew point (deg C). Moisture sensors can determine the presence of liquid or ice in amounts of less than 1%; therefore, a sharp decrease in the dew point at the end of primary drying indicates that the composition of water in the drying chamber has shifted from solid ice to vapor. The user first must determine the acceptable system dew point that represents a dry product.

A typical software program can use this method as follows: The user enters a dew point (deg C) and when the product reaches this point, the program jumps to a finishing sequence and then to secondary drying. Moisture Sensors measure the humidity level in the freeze dryer and can determine and indicate the end point of the primary drying cycle.

Barometric Pressure Rise (Isolation valve is required)
The barometric pressure rise approach is best used with a system that has been characterized in a dry, empty and refrigerated state. Similar to the approach used for characterizing the capacitance manometer and pirani convergence approach the freeze dryer is run, the isolation valve is closed and the pressure rise in the system over a period of time (typically minutes) is determined. This pressure rise creates a baseline for conditions when the isolation valve is closed. During a product run, when the freeze drying chamber is isolated from the condenser and vacuum pump (via the isolation valve) the sublimation of ice to vapor will force the pressure in the system to rise. With ice in the chamber the pressure will rise faster than the rate that was determined when characterizing the system dry, empty and refrigerated, thus indicating that there is still sublimation occurring. The slower the pressure rise, the less ice present. A typical acceptable pressure rise to determine the end of primary drying is less 6mT in 30 seconds with 3 or more readings in an hour.

A typical software program can use this method as well. The user enters the test time, the acceptable pressure rise and how often to repeat the test during the primary drying recipe. The program will advance to a finishing sequence and then secondary drying when the pre-set pressure rise rate is reached.

Tunable Diode Laser Absorption Spectroscopy
This technique, also referred to as TDLAS is a specialized system typically attached in a particular configuration to the port of a freeze dryer between the tray chamber and the condenser. The TDLAS will monitor mass flow between these two areas with a sensitivity to water vapor flow and can indicate when the end of primary drying has occurred.

AccuFlux Heat Flow Monitoring

Heat flow measurements into the product container from a shelf provide information with regard to the status of sublimation. As sublimation continues it removes energy (heat) as the vapor molecules leave the product. When sublimation starts to decrease the concomitant heat flow into the product will start to decrease and heat flow will approach very low numbers. Additional information on Heat Flow as a freeze drying monitoring device can be found at Tech Note *AccuFlux - Heat Flux Sensors Used in Monitoring the Freeze Drying Process.*