

End of Primary Drying Methods

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The process of freeze drying / 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 the process.

The purpose of primary drying is to remove all the 'unbound' interstitial water from the product. To optimize the primary drying phase of freeze drying one of several techniques can be used.

1. Product Temperature End of Primary Drying Setpoint

Frozen product will always have a lower temperature than the temperature controlled shelf. 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 (Tpe). When the product temperature average reaches (Tpe) the defined setpoint in the primary drying recipe, the program will automatically advance from the recipe to a predefined (3 step) 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.

2. Capacitance Manometer Differential Test (Capacitance manometer is required)

The Pirani vacuum gauge measures relative vacuum and responds to the vapor present in the freeze dryer. The capacitance manometer indicates the absolute vacuum and is not affected by vapor pressure. When the two gauges read within a predetermined reading the primary drying process can be considered complete.

A typical software program can use this method as follows: In a clean and dry system the user identifies the differential between the two gauges. The user enters an pressure differential that would indicate end of primary drying. During the primary drying process, when the differential is met, the program jumps to a finishing sequence and then secondary drying.

3. Dew Point via Moisture Sensor (Moisture sensor is required)

A moisture sensor may be 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.

4. Barometric Pressure Rise (Isolation valve is required)

Barometric pressure rise occurs when water vapor escapes from ice during sublimation. When the freeze drying chamber is isolated from the condenser and vacuum pump, the vapor pressure will force the vacuum to rise. With ice in the chamber the pressure will rise faster than without ice present, thus indicating that the product has not reached the end of drying. 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 in 3 or more readings in an hour.

A typical software program can use this method as follows: 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.

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