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Review Paper

Primary Drying End point Determination in Lyophilization: a Review

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Abstract:
The main objective of optimization of the lyophilization cycle is the reduction of the primary drying time which is longest phase of the lyophilization.Determination of the end point in primary drying helps to optimize process time as well as process cost.
This paper is focused on the methods like Product Temperature Measurement vs Shelf temperature determination, Capacitance Manometer vs Pirani Convergence Test, Dew Point Determination via Moisture Sensor, Tunable Diode Laser Absorption Spectroscopy, Barometric Pressure Rise Test and LYOTRACK (Gas Plasma Spectroscopy) used to determine the end of primary drying in lyophilization.
Keywords*: Lyophilization, Manometer, Gas Plasma Spectroscopy, Tunable Diode Laser Absorption Spectroscopy, Barometric Pressure Rise Test.*

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I. Introduction:

Freeze drying, or lyophilization as it is referred to in the Pharmaceutical and Diagnostic Industries, is a dehydration technique, which enables liquid or slurry products, which have previously been frozen to be dried under a vacuum (1).

In pharmaceutical industries it is widely used methods for the manufacturing of products which are unstable in solution state(2,3).

There is always need to give stability to the most of the biopharmaceuticals which not sufficiently stable for long times in the aqueous solution. Lyophilization technique provides low temperature cacuum drying resulting in removal of solvent contributing long term stability (4.5).

The freeze-drying (also known as lyophilization) of pharmaceutical products is consists of three major steps involving the freezing of the product, the sublimation of ice (primary drying) and the desorption of water (secondary drying) from the product(6,7).

Freezing is an efficient dessication step where most of the solvent, typically water, is separated from the solutes to form ice. As freezing progresses, the solute phase becomes highly concentrated and is termed the "freeze concentrate" by the end of freezing.Primary drying, or ice sublimation begins whenever the chamber pressure is reduced and the shelf temperature is raised to supply the heat removed by ice sublimation. During primary drying the chamber pressure (vacuum) is well below the vapor pressure of ice and ice is transferred from the product to the condenser by sublimation and crystallization on to the cold coils/plates (<-50°C) in the condenser

Secondary drying is the stage where the water is desorbed from the freeze concentrate, usually at elevated temperature and low pressure. Some secondary drying occurs at the very beginning of primary drying as ice is removed from a region, but the bulk of secondary drying occurs after primary drying is over and the product temperature has increased (8,9,10,11,12). Freeze drying is a complex process which consist of certain aspects that enfluence on the freeze-drying operation.Freezing temperature and time , Drying temperature and time and Vaccum applied these are the key aspects which play an important role in the optimization of the process (13,14,15).

The main objective of optimization of the lyophilization cycle is the reduction of the primary drying time which is longest phase of the lyophilization.

Determination of the end point in primary drying helps to optimize process time as well as process cost.The focus of this research was to describe the various methods that have been used for determination of the end point of drying is an expensive process with relatively long processing times. Of the

three steps in freeze-drying, primary drying is the longest step, and hence, optimization of this step is the focus in the subject of current interest.

There are number of methods currently being used by pharmaceutical industries for the determnation of end point of the process. In this paper we have discussed following methods for the determiation of end of primary drying.

1. Product Temperature Measurement vs Shelf temperature determination
2. Capacitance Manometer vs Pirani Convergence Test
3. Dew Point via Moisture Sensor
4. Barometric Pressure Rise Test
5. Tunable Diode Laser Absorption Spectroscopy
6. LYOTRACK (Gas Plasma Spectroscopy)

Product Temperature Measurement vs Shelf temperature

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. The end point of primary drying can also be determined from the product thermocouple response, assuming the vials containing the thermocouples are representative of the batch as a whole.The determination of the end of primary drying form the product thermocouple response when the product temperature reaches the shelf temperature set point is one of the commonly used methods (16). There is always difference between the degree of supercooling between thermocouple and non-thermocouple containing Vials it gives understanding that the vials which contains the thermocouple are not representative of the whole batch vials (17). Due to the side radiation effects from the walls and door of the chamber where thermocouple containg vials are kept the thermocouple vials nucleate at higher temerature with low product resistance resulting in faster drying. And the actual time for drying is more than the expected (18).

Capacitance Manometer vs Pirani Convergence Test

The pressue results fluctuations of pirani vacuum guage is mainly the result of gas composition.The presence of the water vapour yield in the high value of Pirani vacuum sensors reading.If the pirani guage is the only vacuum sensor on the system it will give the high pressure readings and if the system is on only capacitance manometer it will produce the pressure readings Irrespetive to the water content of the environment.If the freeze dryer is is equipped with both sensors it can be utilized for the determination of the end of primary drying in lyophilization.In the characterization of the pirani and the capacitance manometer against each other in a dry, empty and refrigerated system with nothing on the shelf The difference in their pressure readings will be relatively small (mT to 10's of mT) when the system is working properly.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.In the presence of high water vapour content in the environment the pirani sensor will gives the high pressure reading than the capacitance manometer indicating that the sublimation is still going on. As the sublimation decreases it means as the water vapour concentration in the chamber is less resulting the pirani and capacitance manometers will approach the ΔP that was established in a dry, empty and refrigerated system. Finally this ΔP value indicates that the end of primary drying (19).

Dew Point via Moisture Sensor

The Dew point is temperature at which ice has an equilibrium vapor pressure equal to the measured partial pressure of water. A moisture sensor can 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 (20).The Dew point determination is based on the changes in the capacitance of the film of the aluminium oxide due to the adsorption of water at a given partial pressure.This capacitance can be translated into voltage output which is "calibrated" to read the frost point/dew point or the partial pressure of water (21).

Similar to the Pirani, thepoint where "dew point" starts dropping indicates that the sublimation is "essentially" complete, i.e. gas composition is changing from mostly water vapor to nitrogen (Fig. 1).

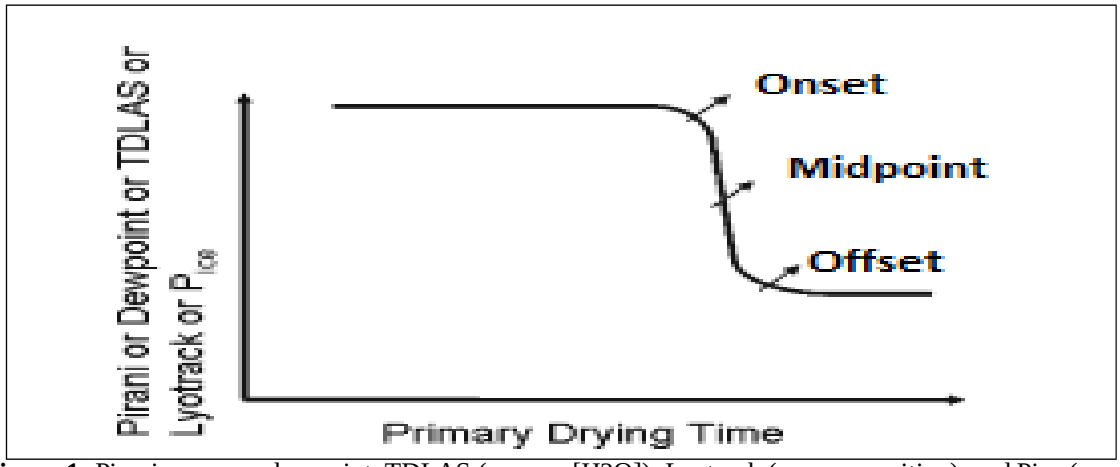

Figure 1: Pirani pressure, dew point, TDLAS (process [H2O]), Lyotrack (gas composition), and Pice (vapor pressure of ice from pressure rise test) profile during primary drying

Barometric Pressure Rise Test

It is one of the routinely used method of the determination of the end of primary drying.For the sublimation to occurs the pressure difference (ΔP) between the chamber and the consenser is the key driving force.When the isolation valve is closed between the chamber and condenser the pressure inside the chamber will increase due to the sublimation of the ice. The test gives pressure rise in the system over a period of time.This pressure rise creates a baseline for conditions when the isolation valve is closed. During the product cycle run , when 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. indicating that there is still sublimation occurring (22,23,24,25).

The Pressure Rise Test (PRT) method that was originally proposed by Neumann (26). The test suggested that during primary drying the rise in the pressure is due to the saturation pressure over the sublimation surface. The PRT Estimate the various measures of the process such as product temperature, residual moisture, heat and mass transfer coefficients.

The accuracy of the test is mainly depends upon the processing condition (27).The various studies have been conducted to evaluate the pressure rise test (28-32). An advancement to the pressure rise test the mesurement of the manometric temperature measurement enable to evaluate the mechanisms which contributes the preesure rise in the chamber : (i) direct sublimation of ice through the dried product layer at a constant temperature, (ii) an increase in the temperature at the sublimation interface due to equilibration of the temperature gradient across the frozen layer, (iii) an increase in the ice temperature due to continued heating of the frozen matrix during the measurement (33). The only requirement for the mesurement for the manometric temperature measurement is the availability of the valve between the chamber and condenser which plays rapidly as pressure rise test.The various factors which plays important role in the measurement of the pressure rise test / manometric temperature measurement are dimensions of the chamber , load, product temperature and the progerssion of the primary drying process. In the investigation of the PRT/MTM , pressure increase is larger and faster with increase in a batch size, decrease in the size of the chamber and with increase in product temperature during primary drying. To obtain the reliable results these factors to be taken for the consideration (27).

Tunable Diode Laser Absorption Spectroscopy

TDLAS is the specialized system have sensitivity for the flow of water vapours utilized for the determination of the end of primary drying process.It is a near-IR-based optical method for determining the mass flow rate of water vapor When placed between the chamber and condenser. TDLAS has placed position in the design and optimization of the lyophilization cycle. It measures water vapor concentration (molecules/cm3) in the connecting duct . The basic principle of TDLAS is measuring absorption of radiation by water vapor to monitor the trace concentration of water vapor in real time.The TDLAS system is composed of two laser beams one is directed with the flow and other is against the vapour flow. A laser beam is passed through a gas mixture containing a quantity of the target gas, and the beam's wavelength is tuned to one of the target gas's absorption lines to accurately measure the absorption of that beam from which one can deduce the average concentration of target gas molecules integrated over the beam's path length (34-35). This system measures the heat transfer coefficient (Kv), resistance of the dry product to flow of water vapour and the sublimation rate which are precisely taking consideration in the optimization of the cycle (36). This system can be used for both lab scale Lyophilizer and production scale Lyophilizer.

The application of the TDLAS for the Production lyophilizer is still under developoment.The study showed that the quantitative difference between TDLAS and gravimetric measurement for the lab scale lyophilizer is about 6% and that for Production scale lyophilizer is 25%.The main reason for this unsetted results are due to the measurement of the gas velocity used in calculating the water vapor mass flow rate. Another main concern to use TDLAS as measuremnt technology of mass flow is the presence of any physical structures in the flow which will represents asymmetric results (37).

LYOTRACK (GAS PLASMA SPECTROSCOPY)

Alcatel Vacuum Technology, France manufactured a device called Lyotrack which is the current addition to the online monitoring devices for freeze-drying process. Lyotrack is based on optical emission spectroscopy and measures water vapor concentration during the drying process. It consists of a plasma generator and an optical spectrometer. The plasma generator creates a radio frequency wave (440 MHz) whose energy is transmitted to the gases present inside the plasma tube via the radio frequency antenna. The gas inside the plasma tube becomes a plasma, which is composed of atoms and molecules (excited or not), ions, electrons, and photons. The excited atom is not stable and upon de-excitation will return instantaneously to its initial energy level. In this phase, it will emit light. The wavelengths of the emitted light are the characteristic signatures for the identification of the atom or molecule. The point where water vapor concentration starts sharply decreasing (i.e., onset) indicates that the gas composition is changing, and hence sublimation is "essentially" complete (34,38,39,40).

Mayeresse et al. (41) have studied and suggested that Lyotrack can be used to determine the end point of primary drying with good reproducibility and sensitivity.

II. Conclusion:

Freeze-drying is an expensive process with relatively long processing times. Of the three steps in freeze-drying, primary drying is the longest step, and hence, optimization of this step is the focus in the subject of current interest. The focus of this review was to describe the various methods that have been used for determination of the end point of primary drying,

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