FDA Initiatives Impact Lyophilisation Process Development and Optimisation

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Freeze drying or lyophilisation is a frequently used method to manufacture protein-based parenteral drugs. Two FDA initiatives – Process Analytical Technology and Quality by Design – are being applied to better understand the lyophilisation process and to optimise its cycles

Keywords

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Process Analytical Technology (PAT)
Tunable diode laser absorption spectrometry (TDLAS)

We are currently seeing an increasing number of successful biologically based drugs. In any given year, two dozen new drug candidates reach 'to watch' status, from which pharmaceutically active monoclonal antibodies (mAbs) typically achieve a significantly higher approval rate (approximately 21 per cent) compared to new chemical entities at five per cent (1).

Most mAb-based drugs and other biologically based molecules – proteins, for instance – generally require lyophilisation to improve stability and long-term storage. The traditional approach to developing a manufacturing process for lyophilised products was largely based on trial and error. Controllable process variables (such as shelf temperature and chamber pressure) were manipulated to find conditions that would produce a product with acceptable characteristics (cake appearance, shelf-life stability, moisture, potency, and reconstitution times, for example). However, there were several problems with this approach.

The cycles were often very conservative to ensure that they were not at risk of failure. Given the capital and operating costs of lyophilisation, this had a negative impact on the manufacturing costs and throughput for a lyophilised drug. While there may be tolerances built into the cycle, the traditional approach neither determined how close the cycle was to optimum, nor how close it was to failure. The traditional approach also did not encourage improvements in development or manufacturing processes once fixed, due to the regulatory burden involved in filing deviations with the Food and Drug Administration (FDA).

QBD and PAT Initiatives

In an effort to reduce the regulatory burden and encourage manufacturers to adopt new development and manufacturing technologies, the FDA released two significant documents relating to Quality by Design (QBD) and Process Analytical Technology (PAT) (2,3). The focus of each is based on the concept that quality should not be inspected solely at the end of production, but must be designed into the entire manufacturing process.

PAT encourages and supports innovation and efficiency in the development, manufacturing and quality assurance of pharmaceutical products. It is closely aligned with the FDA's philosophical QBD approach, which encourages manufacturers to use the latest scientific and technical tools to develop lyophiliation cycles. As stated in the PAT guidelines, the goal of PAT is to enhance understanding and control the manufacturing process, which is consistent with the current QBD system. PAT represents a set of 'tools' that include:

- Multivariate tools for design, data acquisition and analysis
- Process analysers
- Process control tools
- Continuous improvement and knowledge management systems

PAT Toolbox for Lyophilisation

In lyophilisation, PAT tools are developed around measuring and controlling critical product and process parameters (4). Two key parameters include product temperature (Tp) and moisture level, which indicates that drying is almost complete. It is critical during a freeze-drying cycle that Tp does not exceed its critical temperature, as measured by differential scanning calorimetry or collapse temperature, as determined by freeze-dry microscopy. However, Tp cannot be controlled directly, but is established by the interaction of the two controllable process parameters: shelf temperature and chamber pressure. The process parameters directly influence the Tp and therefore affect product quality.

The PAT 'toolbox' for lyophilisation includes both single vial monitoring and batch monitoring methods. Single vial methods for monitoring product temperature include thermocouples, resistance thermal detectors (RTDs) and TEMPRIS wireless sensors. Single vial methods for determining mass flow (sublimation rates) and product drying end-points include microbalances and near-infrared (NIR) or Raman spectroscopy. Batch methods for monitoring the lyophilisation process include:

Primary drying end-point determination for 10 per cent sucrose: controlled versus uncontrolled nucleation

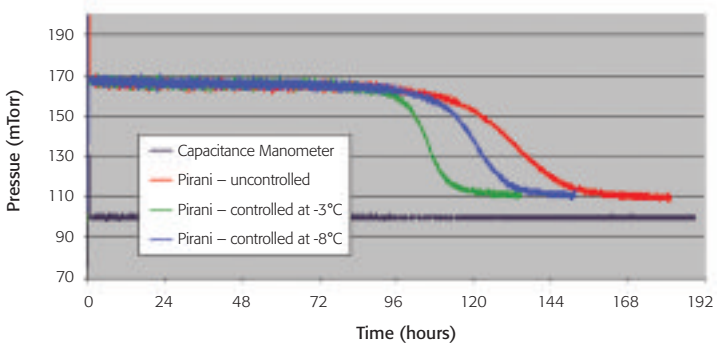


Figure 1: The end of primary drying where the Pirani gauge converges with the Capacitance Manometer (5)

- Comparative pressure measurements, which can determine the end of primary drying by monitoring both the Pirani gauge and the Capacitance Manometer
- Manometric Temperature Measurement (MTM) or SMART™ freeze drying, which can dynamically alter shelf temperature and chamber pressure to maintain a given target temperature
- Tunable diode laser absorption spectroscopy (TDLAS) which can measure mass flow and determine sublimation rate and batch average product temperature

While other methods are commonly used, particularly thermocouples and RTDs, we will focus on the three batch methods above, as these are considered to be some of the most powerful techniques being used to control, monitor and understand the lyophilisation process.

Comparative Pressure Measurements

Also referred to as Pirani/CM convergence technique, comparative pressure measurements for the determination of the end of drying rely on the presence in the freeze dryer of two different pressure measurement instruments: the Capacitance Manometer and the Pirani gauge. The Capacitance Manometer pressure measurement is independent of the gas present, and always reads the true pressure. The Pirani reading is dependent on the type of gas present. It is calibrated for nitrogen. However, as long as there is water vapour present in the system – indicating that sublimation is still taking place – the Pirani reads an elevated pressure.

As primary drying comes to an end, the gas in the dryer is mainly nitrogen, and the Pirani and Capacitance Manometer will read the same pressure. The Pirani reading has 'converged' with the Capacitance Manometer reading (see Figure 1) (5). At this point, the freeze dryer can either be manually stepped into secondary drying, or advance automatically if it has Pirani/CM convergence programmed into the software.

MTM or SMART Freeze Drying

SMART is a technology which allows cycle optimisation in the first laboratory experiment (6). Based on key information inputs – such as critical temperature, number of vials, fill volume, vial size, amorphous or eutectic formulation – SMART will do the following:

- Select a freezing protocol
- Choose a target temperature
- Select an optimum chamber pressure
- Dynamically adjust shelf temperature to maximise heat while keeping the Tp a safe distance below critical

SMART is based on the MTM equation (7). During primary drying, a valve between the chamber and condenser is periodically closed for short periods of time. During these periods of time, pressure rise measurements are taken and inserted into the MTM equation to get pressure over ice and product resistance (Rp) values. Using heat and mass transfer equations, a number of other parameters are calculated, including the product temperature at the ice surface interface. The shelf temperature adjustment is made to keep this below the target temperature (see Figure 2). A number of critical process and product parameters may be calculated during a SMART run, including sublimation rate.

TDLAS Techniques

TDLAS is an NIR spectroscopic method to determine trace concentrations of gases. In a lyophiliser, the TDLAS is mounted in a duct between the chamber and the condenser. TDLAS can determine the concentration of water vapour and gas flow velocity, and from this establish mass flow during the freeze-drying cycle (see Figure 3). It is commonly used as a method to determine sublimation rate and can be used to predict the end point of primary drying, batch average Tp and Rp, and key critical product parameters. In the example of determination of design space shown in Figure 4, TDLAS was used to pinpoint sublimation rate. TDLAS

Figure 2: SMART freeze-drying cycle obtained from SMART Freeze Dryer. SMART freeze drying shows dynamic control (three changes) to shelf temperature during primary drying while maintaining the product temperature (Tmtm) below the critical temperature. After the three quick changes, SMART maintains the shelf temperature at approximately 5°C through the remainder of primary drying (4)

Example: Freeze-drying cycle obtained from SMART Freeze-Dryer:
25mg/mL bovine serum albumin (BSA) plus 75mg/mL sucrose, partial load (112), 20mL tubing vials, 5mL fill volume. Chamber pressure: 94 mTorr. Collapse temperature: -20°C

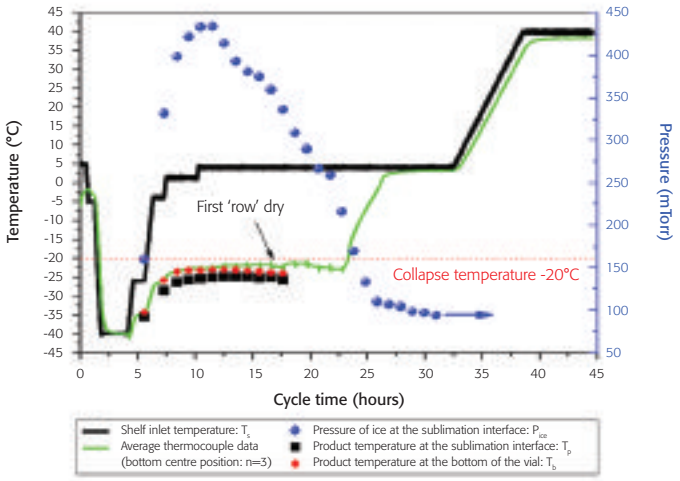


Figure 3: TDLAS graph showing mass flow rate (6)

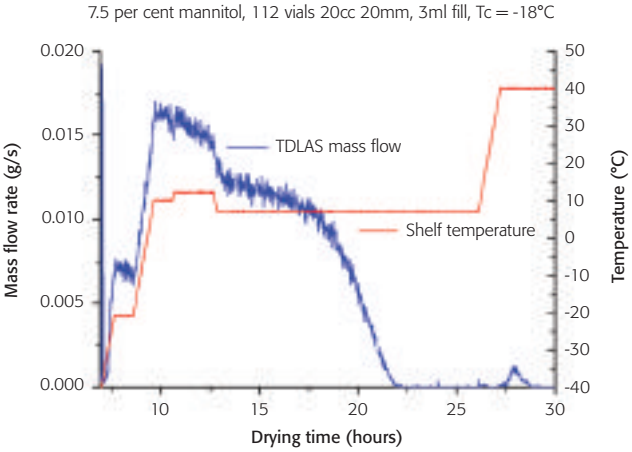
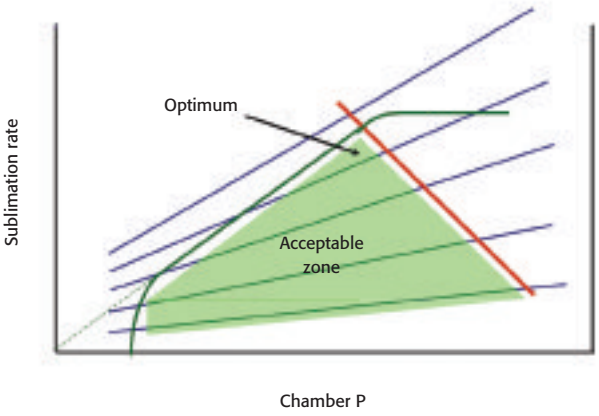


Figure 4: Hypothetical design space for a lyophilised product – the optimum cycle follows from the design space concept (8)



is of particular interest because it can be installed on production freeze dryers.

QBD in Freeze Drying

The key elements of QBD are as follows (8):

- Assurance of product quality via the design of robust formulations and processes
- Scientific understanding of how formulation and processing affect product performance
- Ability to effect continuous improvement
- Reduced regulatory burden

Determination of Design Space

As previously described, traditionally lyophilisation cycle development was conducted through trial and error to determine conditions that produced an acceptable product. In QBD, optimal process conditions are established based on a thorough knowledge of the process. This leads to the development of a 'design space' for the process and product. Not only can this lead to determination of the edges of failure, it can cause the optimal cycle conditions. Figure 4 shows a design space determined for a hypothetical lyophilised biopharmaceutical. In this example, sublimation rate is set as a function of chamber pressure. The light blue lines represent shelf temperature isotherms. The red line is the critical temperature of the formulation above which the product is deemed to fail. The dark green line represents the performance limits of the dryer. Sublimation rates beyond this line will result in choked flow and loss of pressure control. The optimum control point is the warmest temperature within the acceptable range. This leads to the highest sublimation rate and the shortest primary drying cycle. Once a design space is determined, the product should be acceptable under the FDA's QBD definition as long as the conditions remain in the acceptable zone, even if there is an anomaly in the process.

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