

# APPLICATION NOTE

## PROCESS ANALYTICAL TECHNOLOGY EMPLOYED IN THE FREEZE DRYING PROCESS TO DETERMINE THE END OF PRIMARY DRYING AND CYCLE OPTIMISATION



### Introduction

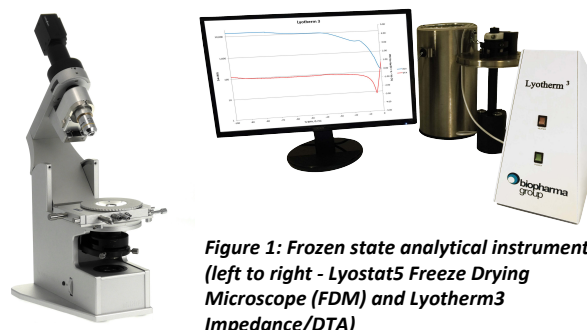
Process Analytical Technologies (PAT) are analytical methods that can help to monitor a process in real time, enabling measurement of its effectiveness and assess how well the process achieves its end goal. They are employed in the manufacturing of various drug forms including solid dose, liquid dose, semi-solids, and freeze drying (lyophilisation). Freeze drying is a low temperature process in which a solvent, typically water, is removed from a frozen material by sublimation under vacuum, leaving the freeze concentrated material behind, which is then referred to as a freeze dried cake or lyophile. Freeze drying is employed to preserve and extend the shelf life of heat-labile drugs which when in solution degrade too rapidly, to stabilise bio-pharmaceutical molecules or to make the material more convenient for transport at ambient conditions rather than be refrigerated.

### Critical Temperature Determination

One of the most important parameters for designing the freeze drying process for a product is the critical temperature of the starting formulation. Primary drying carried out above critical temperatures usually leads to loss of cake structure, loss of activity and poor stability. These critical temperatures can be defined as:

- The frozen state glass transition ( $T_g'$ ), measured as a thermal event resulting from an amorphous solute changing from a brittle solid to a more rubbery material as its temperature is raised; at this point, molecular mobility increases, as does the chance of API degrading.
- Collapse temperature ( $T_c$ ) – this occurs at or above the frozen state glass transition; as the amorphous material is warmed further, molecular mobility increases and viscosity decreases such that the material can no longer support its own weight during sublimation and physically collapses through viscous flow.
- Eutectic melt ( $T_{eu}$ ) - crystalline materials may form eutectic solids through annealing the amorphous form of that material, or spontaneously upon cooling. Upon warming, the eutectic solid (consisting of solute + ice) becomes a eutectic liquid, which may be characterised by an endothermic change in the material.

During freeze drying, if the product temperature during primary drying is below its eutectic melt (crystalline material), or above its frozen state glass transition but below its collapse temperature (amorphous material), it should produce a dried cake with good structure and good activity. There are several analytical techniques (Figure 1) that can be employed to define the critical temperatures and understand the behaviour of the material in the frozen state.



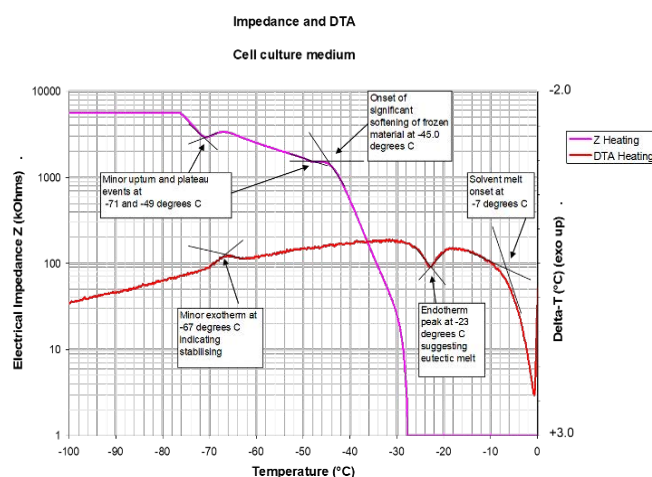
**Figure 1: Frozen state analytical instruments (left to right - Lyostat5 Freeze Drying Microscope (FDM) and Lyotherm3 Impedance/DTA)**

The Lyostat5 freeze drying microscope (FDM) offers real-time observations of the behaviour upon heating during freeze drying which allows determination of the temperature at which the material undergoes collapse (Figure 2), or eutectic melting.



**Figure 2: Images of sucrose under vacuum & upon heating from FDM**

Lyotherm analysis (Figure 3) is used to detect frozen state transitions by measuring the temperature differential using Differential Thermal Analysis (DTA) against a reference, usually pure water. This is also combined with electrical impedance analysis ( $Z_{sin\phi}$ ) which is measured at the same time and indicates changes in molecular mobility. Lyotherm can indicate changes in molecular mobility such as softening events which may not be associated with a measurable change in heat flow. Lyotherm is a complementary instrument to the FDM and can be employed to confirm the observations made during the FDM analysis or even to provide evidence as to which particular formulation components may be responsible for the observed structural changes.



**Figure 3: Example Lyotherm Analysis Trace (annotated with transitions)**

## Monitoring Primary Drying with PAT

If the product exceeds its critical temperature during primary drying this may have a detrimental effect on the final product quality, not just due to poor appearance as shown by the left vial in Figure 4, but also because this is usually associated with loss of activity, high residual moisture levels and an increase in reconstitution time. Not all products if collapsed during primary drying will have poor activity, but the majority typically will.

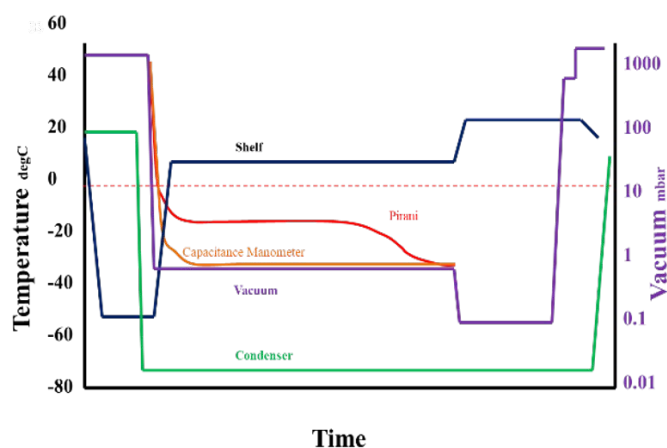


**Figure 4: Freeze Dried Cakes with Collapsed (L) and Good (R) Structure**

Once the critical temperature of the product has been determined for primary drying, the process parameters of the freeze drying cycle can be selected. Primary drying can be aided by several PATs to measure temperature of the product and determine when primary drying is complete.

The main PAT used to monitor the product during the freeze drying cycle is the use of temperature probes, placed directly in the solution prior to freezing and monitor the product temperature throughout the entire process. This allows determination of whether the product temperature exceeds its critical temperature during the cycle, while the cooling effect of the ice sublimation can be used to determine the end of primary drying. As the vacuum is applied, sublimation cooling occurs. By using the cooling effect of the ice being removed by sublimation, the shelf temperature can be increased to supply more heat to the chamber and accelerate the sublimation rate while still maintaining the product temperature below its critical temperature.

Because the rate of sublimation and temperature differ across a shelf, yet probes are each limited to monitoring one individual point or vial in a batch, they should be placed in the centre and edge of the shelf to give an idea of the range of the temperatures the product is experiencing. During freeze drying, the vacuum is typically controlled by reference to a capacitance manometer (CM); if a Pirani Vacuum Gauge (PVG) is also used in parallel with the CM, then in a more humid environment the PVG will give a higher reading relative to the CM and thus can indicate that sublimation is taking place. Additionally, once sublimation ceases, the PVG reading should fall to match the CM gauge reading (Figure 5); this allows the end point of primary drying to be determined.



**Figure 5: Example Freeze Drying Trace showing typical CM and Pirani readings during a cycle**

Cycle development - is typically done by trial-and-error. The conditions of the shelf temperature and chamber pressure are altered to ensure that the cycle is optimised and is as short as possible while maintaining the product quality by not exceeding the critical temperatures. Technology developed by SP scientific in the LyoStar freeze dryers (Figure 6) eliminates the requirement for the trial-and-error approach. The technology employs a method called Manometer Temperature Measurement (MTM), which is able to calculate the average product temperature across a batch during the primary drying by monitoring a series of parameters during the cycle and using a complex algorithm that also takes into account user-inputted critical parameters such as batch size, critical temperature etc. The SMART technology will then produce a safe freeze drying cycle from the outset, which can then be further optimized in subsequent runs.



**Figure 6: LyoStar3**

## Conclusion

Many process analytical technologies can be employed to monitor the product temperature and determine the rate and end point of primary drying. The importance of identifying the critical temperatures is paramount in developing an efficient and cost-effective cycle. Determining the product temperature during primary drying can be achieved with a range of techniques and comparing against the formulation's critical temperature, which should be established for all products prior to freeze drying, using the Lyostat5 FDM and Lyotherm3 to identify these temperatures. Monitoring and maintaining the product temperature below these critical temperatures is important to ensure that high quality product is produced. By adjusting the cycle parameters within these defined boundaries, an optimised cycle for the product can be created which will also save time during manufacturing, critically impacting on cost production and competitiveness in the market.