Spotlight

Cooling & Freezing Technologies

*Lyophilisation is a proven method for greatly increasing the shelf life and stability for a large variety of products, which are unstable in their native state. The growing prevalence of protein-based therapeutics is driving the increasing need for improved methods of freeze-drying process development. In order to streamline the drug development approval process, cycles must now be justified for each specific product. The goal is to have the most efficient cycle possible designed around the formulations unique thermal properties. Smart™ Freeze-Dryer technology delivers the cycle optimisation technology to the formulation scientist so that the most efficient cycle can be derived in as little as one freeze-drying run.*

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# Removing the Trial and Error From Developing Lyophilisation Cycles

## FREEZE DRYING PROCESS DEVELOPMENT CHALLENGES

Major challenges in lyophilisation are development of an optimised lyophilisation cycle and the scale-up of the lyophilisation cycle from a laboratory to a pilot or production scale unit. Understanding the characteristics of the product and the lyophiliser performance is a crucial prerequisite to successful freeze-drying. Many products that are candidates for freeze drying, such as protein based therapeutics, are in short supply and can be very expensive to produce. Lyophilisation is a time and energy intensive process that can take days and weeks to complete. Shortening the lyophilisation cycle development process to produce an optimised lyophilisation cycle, can increase efficiency, accelerate development time and thus reduce time to market and save valuable product. Transfer of an optimised lyophilisation cycle from the development stage to production scale should provide the most efficient drying cycle, thus furthering the return on investment.

The lyophilisation process consists of first freezing the product to a temperature at which all formulation components form a rigid solid. This is followed by primary drying, in which up to 95% of the frozen water or ice is removed. During primary drying, controlled temperature shelves are utilised to provide the energy for sublimation of the ice. In-turn the pressure in the chamber must also be controlled in a way that heat can be added to the product to facilitate sublimation of the water, without causing melting or instability of the already dried product matrix. The sublimated water vapor from the product, travels into the product chamber and is transferred to the condenser due to the pressure differential between the product chamber and the condenser. The water vapour is then frozen onto the coils or plates in the condenser, thus helping the condenser to remain in a low pressure condition relative to the product chamber [1]. Any remaining water not removed during primary drying is removed during a secondary, desorption drying step.

Critical parameters in developing a lyophilisation cycle and to successful freeze-drying include knowing the collapse temperature of the formulation, the stability of the active pharmaceutical ingredient, and the properties of the excipients [2]. In addition to properties of the formulation, shelf temperature, chamber pressure, system geometry and the product container all play major roles in lyophilisation cycle development. Many lyophilisation processes are developed in a 'trial-and-error' manner that often results in unoptimised lyophilisation cycles that may not transfer well from the laboratory to production scale-up.

## ACCELERATING LYOPHILISATION CYCLE DEVELOPMENT

FTS SMART Freeze-Dryer™ Technology from SP Industries is a breakthrough development tool for accelerating and streamlining the development of lyophilisation cycles. Developed through a partnership between the University of Connecticut and Purdue University and partially funded through the Centre for Pharmaceutical Processing Research (CPPR), SMART Freeze-Dryer Technology run on an FTS LyoStar II System (Figure 1) provides both experienced and new lyophilisation scientists a means of developing optimised lyophilisation cycles with a reduction in average cycle development time of up to 78%, based on independent testing results. SMART Freeze Dryer Technology reduces the average cycle development process to one or two runs, rather than the conventional series of six to eight runs, not only reducing development time, but also reducing materials costs by one-third or more. This leaves the development scientist more time for studying other factors contributing to an optimised lyophilisation cycle such as excipient choices and parameter extremes and their subsequent effect on the freeze dried product.


*Figure 1. FTS LyoStar II running SMART Freeze Dryer™ Technology.*

The principle behind SMART Freeze-Dyer Technology is the use of the manometric temperature measurement (MTM) technology. MTM delivers an accurate calculation of the product temperature at the sublimation interface without having to place thermocouples or other temperature sensors in the product vials. Measurement of the product temperature at the sublimation interface is critical for determining the correct parameters for preventing product collapse or 'melt back' during primary drying.

The conventional method for measuring product temperature during a freeze drying cycle is by placing a few selected temperature sensors in vials. Note that placing sensors in the vials may affect the freezing and drying behavior of the samples by inducing ice nucleation or acting as a thermal pathway. These issues make placing a thermocouple in a vial, a less than ideal representation of what is actually occurring in the majority of vials present in the product chamber. In addition, temperature sensors or thermocouples placed in vials are located toward the bottom of the vial, not at the sublimation interface, and therefore do not give as accurate a measurement of product temperature at the sublimation-ice interface [1]. Thermocouples are sometimes difficult to repeatedly place in the same position and have their own inherent inaccuracies across their temperature range.

With the MTM technique, an isolation valve is placed between the product drying chamber and the freeze dryer condenser. Input parameters prior to running a SMART lyophilisation cycle include the number of product vials, the fill volume of the vials, whether the product is amorphous or crystalline, and the collapse temperature or eutectic point of the product. During execution of the lyophilisation cycle using SMART the isolation valve is rapidly and automatically closed and the rise in pressure is measured for 25 seconds at regular intervals during primary drying. The raw data is accumulated and used in the MTM equation to calculate the product temperature at the ice surface interface, the dried layer resistance, the ice thickness, and the heat flow and mass transfer.

SMART applies this information to automatically adjust the shelf and vacuum set-points of the lyophiliser during freeze drying, thus achieving and maintaining the product temperature precisely at the target temperature throughout the lyophilisation cycle.

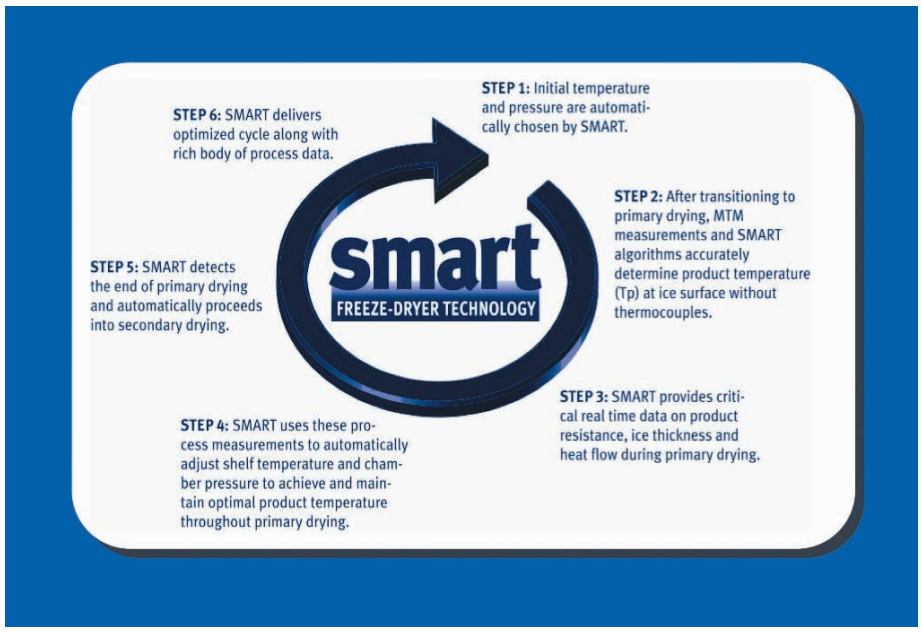


*Figure 2. The SMART Freeze-Dryer Technology Process.*

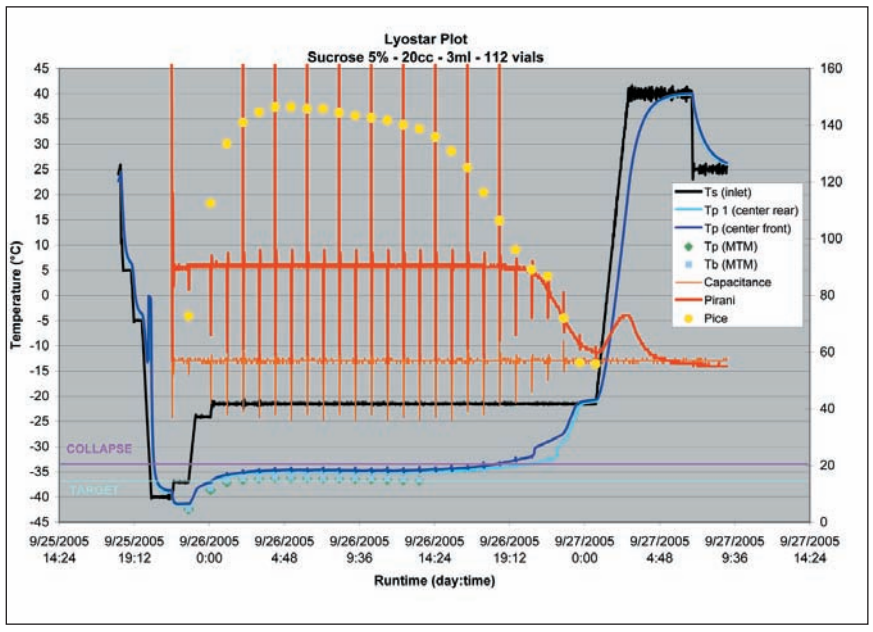


*Figure 3. A graphical representation of an actual Smart cycle showing how tightly controlled the product temperature is 3° below its collapse temperature throughout primary drying.*

In practice, in order to get good MTM data, a minimum product surface area of greater than 300 square centimeters or three quarters of a sample tray is required. Other requirements include that the lyophilisation system be relatively leak free, the sample be in an aqueous solvent, the recommended solids content be between three and 15% and the optimal vial fill is ideally no more than one-third the volume of the selected product container.

## CRITICAL PARAMETERS IN CYCLE DEVELOPMENT

One of the critical parameters for successful cycle development using SMART Freeze Dryer Technology is the critical temperature at which the product needs to be maintained throughout the primary drying phase. This critical temperature is determined from either the glass transition temperature of the product (Tg') or the collapse temperature (Tc) [3]. These values are most commonly determined by Differential Scanning Calorimetry (DSC) or Freeze-Dry Microscopy. The precision of the input parameters for set up of a SMART lyophilisation cycle will determine the quality of the MTM fit and therefore the resultant lyophilisation process design.

*Figure 2* summarises the steps in SMART Freeze Dryer Technology operation. Based on user input, an initial temperature and pressure are automatically chosen by the SMART Freeze Dryer software. After transitioning to primary drying, MTM measurements begin and are fed into the SMART algorithms to determine the product temperature at the sublimation surface. The SMART software provides real time data on the product resistance, ice thickness, and heat transfer flow during primary drying (*Figure 3*). Using these process measurements, SMART automatically adjusts the shelf temperature and drying chamber pressure to maintain the optimal product temperature throughout primary drying. SMART detects the end of primary drying and automatically proceeds into secondary drying. At the end of the process, SMART delivers an optimised lyophilisation cycle along with all the process data.

*Figure 4* gives results from two case studies of process development savings that were achieved by applying SMART Freeze Dryer Technology. Both laboratories reported breaking even on their investment in new technology in less than three months. Primary savings were achieved through SMART's ability to deliver an optimised lyophilisation cycle after just a few experimental runs. The average cycle development time was reduced by 62 days or 78%. Development savings, primarily in labour and active ingredient material costs, averaged $40,029. With an average of eight development programs per year, the average annual savings is $320,232.

## CONCLUSIONS

SMART Technology has proven benefits in field use. Even the most experienced Lyophilisation scientists have achieved gains in cycle efficiency using Smart. The calculated data of dried layer resistance, ice thickness, heat flow and mass transfer and product temperature at the ice surface has proven extremely valuable in providing a never before available window into what is happening in the product while it is in the freeze-dryer.

In response to user feedback, the original Smart Technology has been enhanced to also offer Smart data collection on pre-existing recipes. This additional feature delivers the capability for the scientist to perform robustness testing, show equivalence or trouble shoot existing cycles while generating additional invaluable data from which to make informed decisions.

This tremendous improvement over the legacy method of trial and error cycle design is clear. Smart Technology delivers the capability to safely and quickly auto-optimise freeze-drying cycles based the specific requirements of each unique formulation. Thus, Smart Freeze-Dryer is truly the break-through method of choice for today's Lyophilisation scientists.

## REFERENCES

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| Case #1 Detail | Traditional Approach | SMART Approach | Savings |
|---|---|---|---|
| Number of Experimental Runs Performed | 10 | 2 | 8 |
| Estimated Development Time (days) | 95 | 19 | 76 |
| Analytical (DSC) Costs | $1,000 | $1,000 | $0 |
| Labor Costs | $36,060 | $2,412 | $33,648 |
| Material Costs | $93,750 | $75,000 | $18,750 |
| Total Costs per Development Program | $130,810 | $78,412 | $52,398 |
| Development Programs per Year | 8 | 8 | -- |
| **Total Annual Cycle Development Costs** | **$1,046,480** | **$627,296** | **$419,184** |

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*Figure 4. SMART Freeze-Dryer Technology Delivers Robust ROI - Case Study Details.*