

'Smart' Freeze-Drying

By removing the 'trial-and-error' element from developing lyophilisation processes, a new technology enables users to optimise lyophilisation cycles and ensure the smooth transfer from laboratory- to production-scale.

By Debra Sesholtz and Leslie Mather at SP Industries

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Lyophilisation is the process of drying a product in a frozen state under vacuum to increase product stability, minimise the effects of oxidation and degradation, and increase the shelf-life of the product. The process has found application for preserving products including biologicals, bacterial cultures, water-damaged documents, tissue preparations, food and therapeutic products such as vaccines, drugs, antibodies and proteins. The continuing discovery and development of protein-based therapeutics is driving an increasing need for improvements in freeze-drying process development.

PROCESS DEVELOPMENT CHALLENGES

Major challenges in lyophilisation are the development of an optimised lyophilisation cycle, and 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 are crucial for 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 further increasing 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 vapour 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; it 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 thus 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 non-optimised lyophilisation cycles that may not transfer well from the laboratory to production scale-up.

ACCELERATING LYOPHILISATION CYCLE DEVELOPMENT

At SP Industries, we have commercialised a technology (FTS SMART Freeze-Dryer™ Technology) for accelerating and streamlining the development of lyophilisation cycles. Created through a partnership between the University of Connecticut and Purdue University, and partially funded through the Center for Pharmaceutical Processing Research (CPPR), the technology, run on an FTS LyoStar II System (see Figure 1, page 88), provides both experienced and new



Figure 1: An FTS LyoStar II running SMART Freeze Dryer™ Technology

lyophilisation scientists with a means of developing optimised lyophilisation cycles with a reduction in average cycle development-time of up to 78%, based on independent testing results. The technology reduces the average cycle development process to one or two runs, rather than the conventional series of six to eight runs – thereby not only reducing development time, but also reducing materials costs by one-third or more. This leaves the development scientist with 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.

The principle behind the technology is the use of manometric temperature measurement (MTM). This 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 to place a few selected temperature sensors in vials. Note, however, that this may affect the freezing and drying behaviour of the samples by inducing ice nucleation or acting as a thermal pathway. These issues make placing a thermocouple in a vial a poor representation for 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 towards the bottom of the vial – not at the sublimation interface – and therefore do not give an 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, 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.

This information is then applied 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.

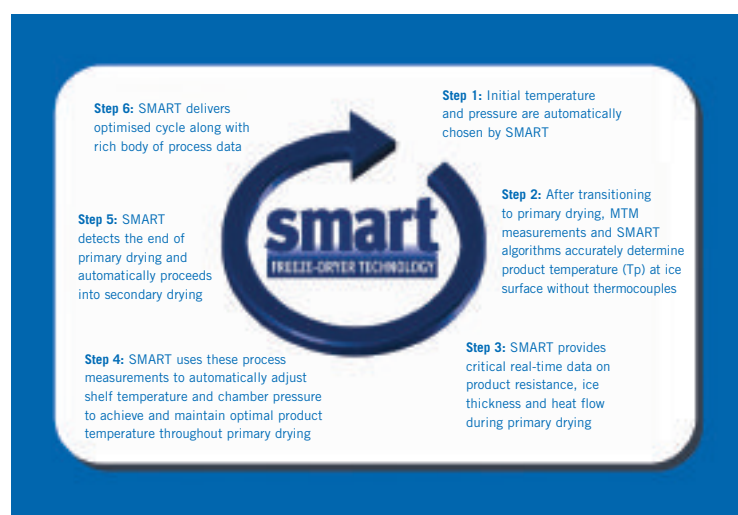
In practice, in order to get good MTM data, a minimum product surface area of greater than 300 square centimeters or three-quarters of a sample tray is required. Other requirements include the lyophilisation system being relatively leak-free, the sample being in an aqueous solvent, the recommended solids content being between three and 15 per cent and the optimal vial fill being 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 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 (T_g) or the collapse temperature (T_c) (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 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 software provides real-time data on the product resistance, ice thickness and heat transfer

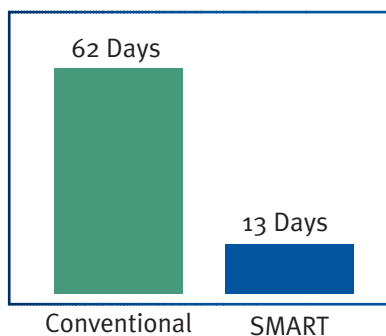
Figure 2: The SMART Freeze-Dryer Technology Process



Reduce freeze-dry cycle development time by 79%

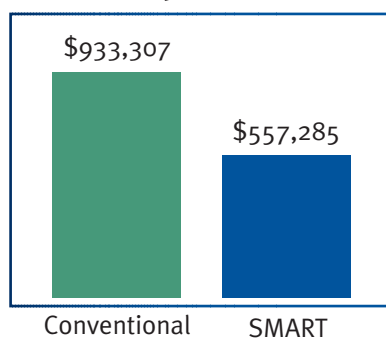
Introducing SMART Freeze-Dryer™ Technology

Time to Develop One Freeze-Drying Cycle



Results are based on independent testing at customer sites.

Annual Direct Development Costs



Based on reported average of 8 development programs per year.

SMART Freeze-Dryer Technology

enables skilled development scientists to accelerate and streamline the development of freeze-drying cycles for protein-based therapeutics.

Case studies from several premier life sciences organizations indicate breakthrough results:

- Cycle development time reduced by 79% or more.
- Annual cycle development cost savings of \$350,000 or more.
- Process data, such as product resistance and heat flow, available at the push of a button.
- Days shaved off freeze-drying cycles.
- PAT capabilities help understand process variables, support scale-up and answer regulatory questions.



SMART is available as a retrofit or on new LyoStar® II R&D and Process Development Freeze-Dryers.

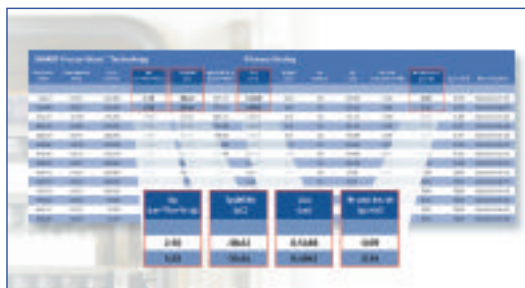
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Figure 3: The SMART Freeze-Dryer software provides real-time data on the product resistance, ice thickness and heat transfer flow during primary drying



flow during primary drying (see Figure 3). Using these process measurements, the shelf temperature and drying chamber pressure are automatically adjusted to maintain the optimal product temperature throughout primary drying. The end of primary drying is then detected and the process then automatically progresses into secondary drying. At the end of the process, an optimised lyophilisation cycle is delivered, 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 the 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.

CONCLUSION

SMART sample data output not only affords an optimised freeze-drying cycle, but also provides the user with the MTM data to better understand the freeze-drying process and troubleshoot freeze-drying protocols. Pharmaceutical manufacturers are being encouraged by

the FDA through their process analytic technology (PAT) initiative (4,5) to understand and control process parameters to build quality into product manufacturing by design. SMART Freeze-Dryer Technology is a PAT tool for identifying and reporting critical parameters during the product freeze-drying formulation process that can be later monitored during freeze-drying production to maintain product quality.

Developments are underway to improve the technology as a PAT tool. These improvements will allow MTM measurements to be collected on standard or currently-used freeze-drying cycles. Scientists will be able to run their standard freeze-drying cycles and collect MTM data including resistance measurements, product temperature calculations and heat-flow calculations. This additional data will provide significant advantages in trouble-shooting existing freeze-dryer cycles, and validating changes or adjustments to legacy protocols.

There continues to be an increasing need for improved methods in freeze-drying process development – especially with the continuing advancements in protein-based therapeutics. This, coupled with the FDA's PAT initiative, make the development of tools – such as SMART – important in developing robust freeze-drying protocols, and providing the critical data needed to identify parameters that require monitoring and controlling during product production.

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Figure 4: Results from two case studies of process development savings that were achieved by applying SMART Freeze-Dryer Technology

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	
Labour costs	\$36,060	\$2,412	\$33,648	
Material costs	\$93,750	\$75,000	\$18,750	
Total costs per development programme	\$130,810	\$78,412	\$52,398	
Development programmes per year	8	8	-	
Total annual cycle development costs	\$1,046,480	\$627,296	\$419,184	

Case #2 detail				
	Traditional approach	SMART approach	Savings	
Number of experimental runs performed	8	2	6	
Estimated development time (days)	63	16	47	
Analytical (DSC) costs	\$1,000	\$1,000	\$0	
Labour costs	\$30,480	\$2,820	\$27,660	
Material costs	\$25,000	\$25,000	\$0	
Total costs per development programme	\$56,480	\$28,820	\$27,660	
Development programmes per year	8	8	-	
Total annual cycle development costs	\$451,840	\$230,560	\$221,280	