SP Hull LyoStar® 4.0 Freeze Dryer for Rapid Lyophilization Cycle Development and Scale-up

Incorporating the Line-of-Sight™ Approach

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Introduction

Each part of the freeze-drying process has a large impact on product quality and integrity. With the advance of technologies and more sophisticated tools, there is a better understanding of the product early in the development process, and how to measure and record parameters that affect the final product. However, even with this knowledge, scaling-up can be an ongoing challenge for manufacturers, particularly for lyophilized biologic drugs. Differences in freeze-drying equipment performance, controls system and operation can occur between development and production scales, leading to time consuming and costly re-optimizations of lyophilization parameters to achieve successful freeze-drying of the product.

SP Hull LyoStar 4.0 R&D & Process Development Freeze Dryer

One area of lyophilization, that in the past required a considerable amount of trial-and-error, is cycle development. Recently, Dr Ian Schmitz, Portfolio Manager for Pharmaceutical Freeze Drying and Zak Yusoff, PMP Manager Global Technology Applications presented a webinar on improving the empirical nature of cycle development using SP's Line of Sight (LoS) suite of technologies, process analytical technology (PAT) tools and equipment design. This product bulletin highlights SP's latest lyophilizer, the SP Hull LyoStar® 4.0 for rapid lyophilization cycle development, optimization and scale-up. This product bulletin includes a summary of the webinar and a selection of questions from the Q&A sessions.

Cycle Development

One of the most important aspects of cycle optimization is formulation development and characterization. Choices of excipients and their ratios to Active Pharmaceutical Ingredients (API) need to be rationalized alongside optimization of other freeze-drying agents, such as cryoprotectants, lyoprotectants, buffers, tonicity agents that aid the lyophilization process. All these factors can affect the viability of the end-product and lead to product failures if not identified appropriately[1&2]. Characterization of the product formulation during these optimizations is performed through several commonly available methods for thermal analysis, such as modulated differential scanning calorimetry (mDSC) and freeze-drying microscopy (FDM) to identify critical parameters of glass transition (T_g'), eutectic (T_{eu}) and collapse (T_c) temperatures. Performing small scale formulation studies on the different ratios of excipients to API is strongly encouraged to select the most optimized product for lyophilization and ensure the formulation is robust to withstand the stresses during freezing and drying process.

Scaling-Up Lyophilization

After cycle development and knowledge of the laboratory stability batches either through accelerated or real time stability testing, the selected product is transferred to a larger lyophilizer for production. At this stage, knowledge of the equipment capabilities[3] needs to be established to scale-up the product seamlessly including an understanding of the effects of any heat transfer differences in the lyophilizer chambers. This helps re-create the product temperature profile obtained from the research and development (R&D) lyophilizer[4].

A comparison of an R&D lyophilizer of approximately 140 vials per shelf to a production freezer of more than 1,380 vials per shelf suggests that variation between vials or batches will have a greater effect in production. The most common scale-up issues relate to ice nucleation and vial heat transfer coefficient, K_v. Inconsistency in the container manufacturing process can impact the K_v from lot to lot. It affects changes in the size of ice crystal formation which impacts primary and secondary drying times and result in protein

aggregation which can affect long term stability. Shelf temperature variation create gradients of temperature across batches of vials and can impact product temperature.

Two key determinants of product temperature are: the K_v which is measured via the sublimation rate and as a function of chamber pressure which can vary according to vial location in the lyophilizer; and product resistance (R_p) which is the resistance to vapor flow through the dried product layer during primary drying and provides information about cake morphology[5]. In addition to the type of vial and specific formulation, the R_p is also influenced by the rate of freezing and ice nucleation temperature. These parameters can be measured using PAT tools, such as the non-invasive LyoFlux* Tunable Diode Laser Absorption Spectroscopy (TDLAS), manometric temperature measurement (MTM), and calculated using Tempris* wireless sensors from product temperature data to make reliable comparisons when scaling-up to larger lyophilizers.

As the cost of APIs is high and complex biological APIs require special handling prior to, during and after the lyophilization process, deciding on optimal conditions that translate from small-scale to production lyophilizers can be challenging. Some level of modelling should be incorporated into the development effort and during scale-up process once the information discussed above, such as the K_v and R_p are determined experimentally, or using the PAT tools as mentioned. There are several modelling algorithms, such as LyoCalculator (a development version of Dr. Pikal's Excel file), LyoPRONTO (Purdue University, USA) or LyoModelling Calculator (SP Industries/UConn) that can help calculate product temperature based on the critical parameters determined above once the K_v and R_p are known or estimated. The goal of the transfer is to maintain the product temperature profile obtained during the development process in the receiving lyophilizer. Maintaining the thermal profile is critical to a successful scale-up and transfer.

Line of Sight™ (LoS) Approach to Development and Scale-Up

Recognizing the inherent challenges of scale-up, SP has created LoS which consists of a suite of technologies, PAT tools, and equipment design that enables the user to develop a freeze-dried product in R&D and seamlessly **scale it up to commercial manufacturing**. It utilizes SP's range of scalable technologies and equipment that create a data-rich environment across all scales of freeze-drying systems (Figure 1). This also facilitates greater control and understanding of the freezing process which creates an expanded design space with defined sets of operating variables needed to maintain batch consistency.

Efficient scaling up of production requires mimicking of the product temperature profile between development stages supported by stability data, providing true batch average values of product temperatures, qualifying equipment capabilities as part of the performance qualification, and determining accurate and reliable critical parameters, such as K_v and R_p.

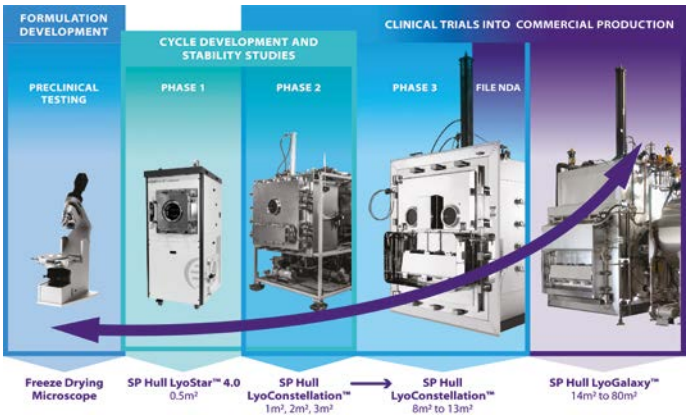


Figure 1: *Lyophilization Scale-up From Formulation to Full Commercialization*

There are four main technologies that are embedded in the LoS equipment that facilitate the attainment of these goals providing an accurate comparison between all scales of manufacturing from tens to thousands of vials:

1. **LyoFlux* TDLAS** - gives an accurate measurement of vapor mass flow
2. **Tempris* wireless sensors** - monitor product temperature using the same probe for R&D as for large scale lyophilization
3. **ControLyo® Nucleation Technology** - gives precise control over ice nucleation within the whole batch of samples and across different stages of production
4. **SMART™ Freeze-Drying Technology** - MTM primary drying optimization determines cake resistance, vapor pressure and temperature at the ice interface

LyoFlux* TDLAS

Efficient use of a lyophilizer is one of the most important aspects of lyophilization and LyoFlux* provides many features that can contribute to a reduction in down-time to days rather than weeks. Its non-invasive sensor measures water vapor concentration and flow velocity from which the product temperature (T_p) can be derived at the ice interface for a specific formulation. From these measurements, process design space parameters, such as K_v and R_p can be calculated based on the mass and heat transfer

equations at steady state for a specific product in one experiment as opposed to the traditional multiple runs. In addition, TDLAS considers all vials to provide accurate batch representation further saving time on individual vial measurements throughout the chamber.

ControLyo® Nucleation Technology

The degree of supercooling is a challenge when scaling up lyophilization as it is difficult to keep this constant between lyophilizers due to the controlled particulate level in an aseptic environment, such as in Grade A or ISO 5 clean rooms classification. ControLyo® technology utilizes an inert gas and a series of pressurization and depressurization steps for instantaneous, controlled ice nucleation in all vials in the product chamber at a higher temperature[6&7]. This minimizes supercooling and yields the largest possible ice crystals which lead to shorter drying times. The added advantage of ControLyo® is that it can be fitted, or retrofitted, to any freeze-dryer enabling interchangeable optimization parameters for lyophilization from early to late stages of development and commercialization. Additionally, the parameters used for the ControLyo® process can be easily quantified and validated.

Tempris* Wireless Sensors

Traditionally, thermocouple (TC) wires have been used to measure product temperatures in freeze dryers, but these are difficult to position within vials creating unreliable data and create issues with sterility and use with automatic or semi-automatic loading system. Tempris* sensors enable wireless real-time temperature measurements across all scales of lyophilization. With no trailing wires, they are more stable and allow for better positioning in the vial.

SMART™ Freeze-Drying Technology

SMART™ freeze-drying technology is a patented PAT tool using the manometric temperature measurement (MTM) technique to determine information, such as freeze-dried cake resistance, vapor pressure and product temperature at the ice interface, are some of the information you can calculate from the MTM measurement. This technology has been shown to save precious development time by replacing the empirical nature of the traditional trial-and-error approach to cycle development.

SP Hull LyoStar® 4.0 Freeze Dryer

The **LyoStar 4.0 is a R&D and process development lyophilizer** ideal for rapid lyophilization cycle development, optimization and scale-up. It is an updated version of the LyoStar 3 that is designed to mimic a full-scale production lyophilizer so that it can support rapid scale-up and enhance speed to market of biopharmaceutical products. It includes the PAT tools discussed above augmenting SP's Line of Sight™ suite of technologies. This enables highly accurate data to be collated for product and process understanding which is critical for scale-up and product life cycle management.

New Enhanced Features of SP Hull LyoStar 4.0

1. Greater Environmental Impact

- One enhancement of LyoStar 4.0 is using compliant refrigerant R449A that lowers the Global Warming Potential (GWP) compared to R404A that is used in the LyoStar 3. However, it runs slightly warmer than R404A, so this needed to be considered when designing the LyoStar 4.0. To alleviate this, an additional fan has been added to remove the warmer air from the heating coil and an additional set of coils to dissipate the heat. Due to high GWP for the R404A refrigerant, the cost of ownership of the LyoStar 3 will increase because of market availability and future sourcing.

2. Standardized Configuration

- All LyoStar 4.0 units have been standardized geometrically to configure to any cleanroom/isolator. This will facilitate easy adaption to any configuration selected by the customer whether it is a standalone unit, cleanroom design, or interface with an isolator.
- The LyoStar 4.0 is only available with a pressurized chamber. This allows ControLyo® to be installed onto any lyophilizer. Whereas the LyoStar 3 is available with either pressurized or non-pressurized product chambers, this has now been standardized
- Shelf distance is now standardized and is comparable to the SP Hull LyoConstellation lyophilizer series (S10–S30) to augment transfer between units during product development
- Standardized equipment and components help to improve the availability of service parts which shortens lead times and routine maintenance.

3. Flexibility for Customers

- Technologies can now be added to every unit either at purchase or later so that the customer doesn't need to make the decision at the time of purchase. This is designed as a "plug and play" concept whereby the units can be upgraded easily in the field.

4. User Benefits

An elevated vacuum pump has increased accessibility for easier routine maintenance

- Noise levels of the lyophilizer have been reduced to a maximum of 70 – 75 dBa

- Emergency off (EMO) switch has been applied to the front and back of the units so that the power can be turned off immediately in case of any emergency
- The LyoS™ 2.0 software now runs on the Windows10 operating system with a GE iFix version 6.1 and the latest Allen Bradley PLC to enable updates more easily. The software is fully compatible with all SP's instrumentation and is 21 CFR Part 11 capable

All these additional features discussed above are provided including the standard lyophilizer unit components listed in Box 1.

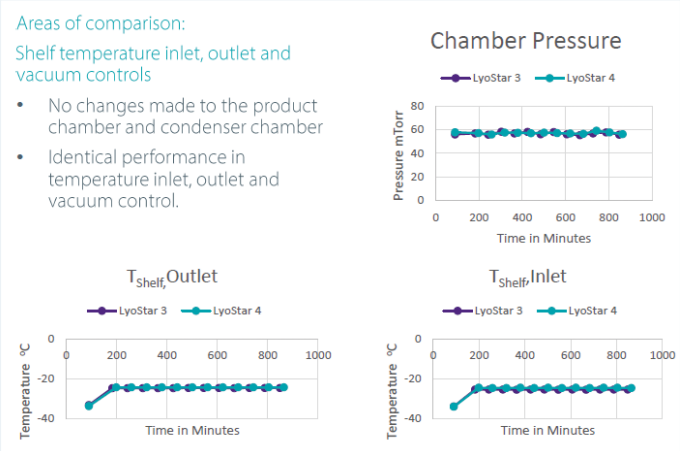


Figure 2: *Performance Comparison of LyoStar 3 and LyoStar 4.0 Lyophilizers*

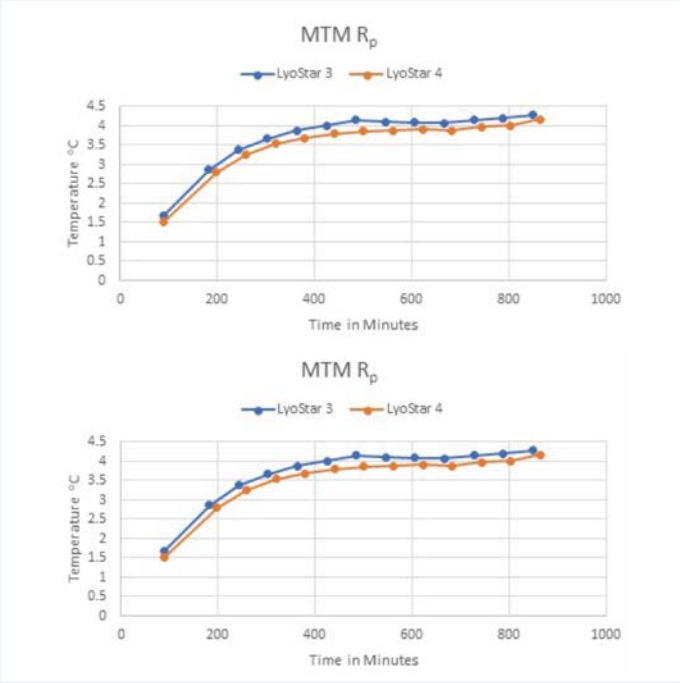


Figure 3: *: Comparison of MTM-T_p and MTM-R_p for 5% Sucrose in 20 mL Tubing Vial in LyoStar 3 and LyoStar 4.0*

Comparing chamber pressure and shelf temperatures between the LyoStar 3 and 4.0 revealed identical performances for shelf temperature control at the shelf inlet and shelf monitoring at the outlet, and vacuum control (Figure 2). Exploring this further with a 5% sucrose formulation and measuring various critical parameters using SMART™-MTM, there were no reported differences in performance between the LyoStar 3 and 4.0 (Figure 3). This further confirms that changes made in the LyoStar 4.0 do not impact performance, ideal for LyoStar 3 users who have developed their products in a LyoStar 3 lyophilizers.

Conclusion

It is important to understand much of the basic information required for cycle development and incorporate them into your product's development from the initial research stages to large scale manufacturing.

Where possible, integrating the latest technologies and PAT tools with a data driven approach benefits the accuracy and reliability of the freeze-drying process, creates robust cycles, and a better understanding of product and process for product life cycle management. This also reduces the time required for re-optimization when scaling-up production.

The upgrades of instrumentation within the LoS suite, including the launch of LyoStar 4.0 and the LyoConstellation series for production manufacturing, continue to form part of SP's full line capabilities. SP can provide equipment for the entire vial journey from vial washing to filling, lyophilizing (if required) to packaging and transporting of the final process activities (Figure 4).

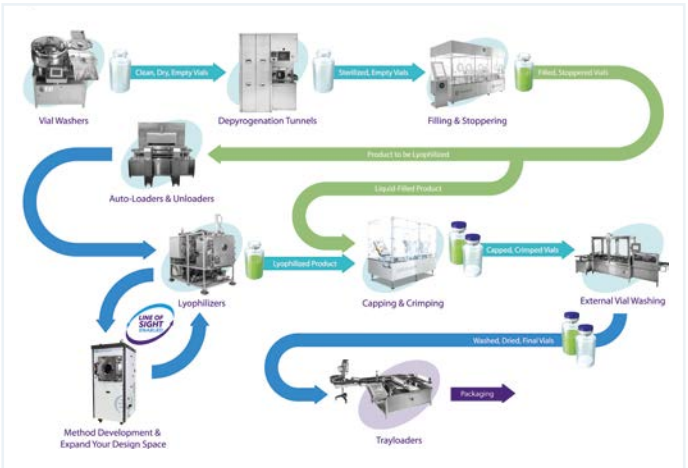


Figure 4: *Modular or Integrated Full Fill-Finish Aseptic Processing Equipment*

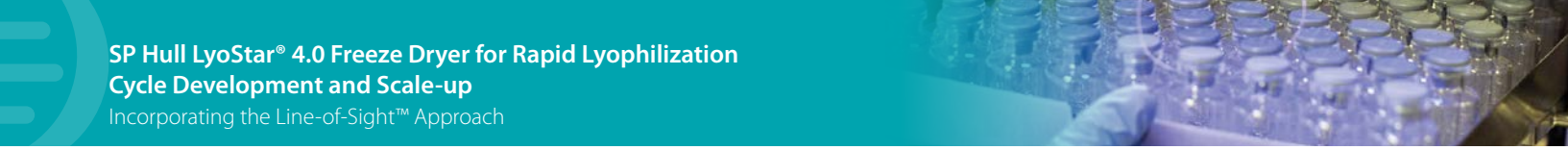
LyoFlux* is a registered trademark of Physical Sciences Inc., Andover, MA, USA and used by permission
Tempris* is a registered trademark of iQ-mobil solutions GmbH, Holzkirchen, Germany and used by permission

References

1. Interplay of Formulation Components on Excipient Functionality During Lyophilization – Dr. Bhushan Munjal, Ph.D. February 2021- https://www.spscientific.com/Webinars/Archives/
2. Buffer and Excipient Selections Dos and Don'ts for Rapid Throughput Formulation Development – Dr. Jeff Schwegman, Ph.D. September 2020 - https://www.spscientific.com/Webinars/Archives/
3. Equipment Capability of Freeze Dryers and Its Relevance to the Graphical Design Space for Primary Drying – Dr. Jayasree Srinivasan, Ph.D. September 2019 - https://www.spscientific.com/Webinars/Archives/
4. https://www.europeanpharmaceuticalreview.com/article/1263/lyophilization-cycle-robustness-and-process-tolerances-transfer-and-scale-up/ - Serguei Tchessalov, & Nicholas Warne, 19 June 2008
5. Factors that Influence Product Resistance and Methods to Measure Product Resistance – Dr. Robin Bogner, Ph.D. March 2020 - https://www.spscientific.com/Webinars/Archives/
6. Investing in the future of freeze-drying for biologic drugs – Zak Yusoff. As first published in Spinco Cutting Edge December 2018
7. Adoption of Controlled Ice Nucleation Technology, ControLyo® - From R&D to Commercial Manufacturing – Ian Whitehall, SP Industries. March 2020 - https://www.spscientific.com/uploadedFiles/PPC_Pages/SP%20Scientific%20Freeze%20Drying%20White%20Paper%20FINAL%20Mar20.pdf

Box 1: Standard Features of all SP Hull LyoStar 4.0 Lyophilizers

- SMART™-MTM and Auto-MTM technology incorporated into all lyophilizers
- All lyophilizers are ControLyo® ready
- Low Global Warming Potential (GWP) refrigerant
- Cascade refrigeration enables a shelf temperature as low as -70°C and condenser temperature of -85°C
- Capacitance manometer & Pirani vacuum gauges in product chamber for accurate endpoint detection
- Capacitance manometer in condenser chamber facilitates lyophilizer troubleshooting
- 16 thermocouples, stoppering and pneumatic isolation valve
- Compatible technologies including LyoFlux* and Tempris*
- One click printing of batch reports in PDF format
- Simple to install shelf latching kits to increase shelf inter-distant for larger vials



Q&A Session

1. **What temperature would you recommend for annealing for ice crystal growth?**

   The annealing temperature should be between the ice melting temperature and the glass transition temperature of the freeze concentrate and should be held for several hours. (Wang et al, 2012 https://www.americanpharmaceuticalreview.com/Featured-Articles/122325-Stabilization-of-Lyophilized-Pharmaceuticals-by-Process-Optimization-Challenges-and-Opportunities/)

2. **Can you adapt SP's LyoS software to work on an existing HMI and PLC? For example, an existing manufacturing lyophilizer does not have operating software.**

   This should be looked at on a case-by-case basis. The input/out (I/O) structure must be assessed so the controls system can be retrofitted with the LyoS software. This includes, but not limited to, the PLC components and the human machine interface (HMI).

3. **How do you evaluate the lyo appearance of sucrose 5% in LyoStar 3 and LyoStar 4.0?**

   The evaluation of the lyophilized cake appearance was based on visual inspection. We inspected for sign of shrinkage, looking at fill line in comparison to the cake height, check for major cracks and cake consistency from vial to vial. Unfortunately, we do not have any automated inspection equipment or analytical instrumentation to determine residual moisture content.

4. **What is preferable Pirani and CM pressure differential to determine the primary drying end point?**

   Pirani and capacitance convergence is one of the techniques that can be used for determining the primary drying endpoint. However, the value of PAT tools is beyond determination of primary drying endpoint. PAT tools enable users to monitor product temperature especially in a production environment to ensure product quality is met. Product temperature is one of the important quality attributes that is rarely monitored.

5. **Is Tempris specific to LyoStar or can it be used in any lyophilizer?**

   Tempris is a product that SP offers through partnership with IQ-Mobile. SP has performed integration into our SCADA system for data collection and archiving. It can be used on other lyophilizers and most commonly as a standalone instrument or integrated to a controller.

6. **Do you have experience in processing products that require plastic packaging of single use, i.e., single use eye drops for dry eyes or diabetic applications?**

   Beyond lyophilization equipment, SP has a complete solution for fill finish for sterile and non-sterile applications including ophthalmic, nasal spray, powder fill, or micro dosing into unique medical devices. SP i-Dositecno is our sister company specializing in fill finish equipment and has worked with many types of pharmaceutical containers.

7. **For the small scale lyophilizer you mentioned, is it representative of the large-scale ones?**

   SP designs the equipment to mimic most production equipment including surface finishes, external condenser with isolation valve, and controls system to ensure good instrumentation practices in our design. As we stated in the webinar presentation, the tools and techniques go beyond the R&D lyophilizer. SP incorporates these technologies into all scales of our lyophilizers so scaling up from R&D to commercial production can be done in a more efficient way supported by data along the progression of your product life cycle.

To view the full webinar, please go to the archived webinars on our website https://www.spscientific.com/Webinars/Archives/.

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