Miniaturization of Freeze Drying: Process Optimization in the LyoCapsule Using Innovative PAT

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The development of an appropriate freeze-drying cycle for drug products is usually performed in a laboratory scale freeze dryer, such as SP Scientific's LyoStar™ 3 using several hundred vials per shelf.

Recently, Dr Alexandra Braun, GILYOS GmbH, presented a webinar describing data on the benefits of using a miniaturized lyophilizer (LyoCapsule™, SP Scientific) that can freeze-dry as little as seven vials at a time for early stage cycle optimization. This tech note summarizes the data presented in the webinar and includes a selection of questions from the Q&A session.

Small-scale miniaturization

Miniaturization of freeze-drying has obvious benefits for early stage development of drugs when many optimization studies can be performed with limited availability of active pharmaceutical ingredient (API), particularly in the case of biopharmaceuticals. Additionally, reducing material consumption minimizes financial risk and with less vials to test, preparation and processing time can be decreased. However, it is not just in early development where the benefits of small scale lyophilization can be seen, at later stages the scaling down of existing conditions can benefit troubleshooting more easily with the knowledge that the final cycle conditions can be scaled back up again.

Optimization challenges

Cycle optimizations with mid-scale equipment often encounter several limitations. In many cases, the use of partial loads or placebo runs is associated with deviating heat and mass transfer conditions resulting in less representative freeze-drying behavior.

There are numerous factors that influence these limitations and the product performance during any scaling up of the lyophilization process. The freeze dryer characteristics can determine product quality. Radiation levels will affect heat transfer according to the size and shape of the chamber and in doing so create the 'edge effect' whereby vials on the outer edge will receive more radiation than the center vials. Freezing behavior can differ between lab and manufacturing freezers driving a different nucleation temperature and higher drying temperature. Even the differing monitoring tools can influence optimization decisions.

Miniaturization using innovative technologies

Using the LyoCapsule, it is possible to transfer to mid-scale laboratory or pilot scale equipment easily overcoming many of these challenges. The LyoCapsule's process parameters have been adapted to simulate drying in larger freeze dryers with individual wall and shelf temperature controls. It is also equipped with innovative process analytical tools (PAT), for example ControLyo® for controlled nucleation, Manometric Temperature Measurement (MTM), SMART™ that enables cycle design in one experiment, Tunable Diode Laser Absorption Spectroscopy (TDLAS) that calculates water vapor concentration and flow velocity and TEMPRIS® wireless sensors, enabling smooth transfer of the developed cycle to larger freeze dryers during scale-up.

Dr Braun presented data that compared heat transfer characteristics between the standard LyoStar and the miniaturized LyoCapsule freeze dryer. Preliminary studies examining the use of the MTM-SMART feature of the LyoCapsule for cycle design of various formulations were also discussed.

To understand the impact of wall temperature on product temperature, the average heat transfer coefficient (Kv) was calculated for all edge and center vials of both the LyoStar and the LyoCapsule. The actual wall temperature can be adjusted in the LyoCapsule and variations of this temperature were included in the comparison. In Dr Braun's studies, higher edge Kv values were measured than at the center in the LyoStar. In the LyoCapsule, there were minimal differences to LyoStar values when the wall temperature was equal to the product temperature. It is, therefore, possible to use the LyoCapsule to evaluate the product temperature profile under selected conditions to use in the LyoStar.

Apart from the wall temperature adjustments of the LyoCapsule, other technologies, such as MTM-SMART enable the LyoCapsule to function effectively. The principle of MTM-SMART involves, determination of vapor pressure of ice and product resistance based on input parameters such as product information, that are used to adjust shelf temperature and chamber pressure and control and optimize the product temperature throughout the drying.

Dr Braun and her team evaluated MTM-SMART in the LyoCapsule and the LyoStar, examining the impact of wall temperature on product temperature and characteristics, reproducibility of MTM and with other formulations (Braun A, Gieseler H, submitted for publication, 2019) (Figure 1). Modifying the wall temperature of the LyoCapsule enabled a comparable target product temperature than that of the LyoStar (Figure 2). In a triplicate run, the similar recipe design led to a reproducible cycle with a homogenous product temperature profile.

Summary

The LyoCapsule can be used as a complementary tool that facilitates optimized cycle development with low material consumption. Heat input can be modified by adjusting wall temperature to enable optimized product temperature profiles. Dr Braun's preliminary experiments suggest a combination of MTM-SMART and other PAT Tools incorporated in the miniaturized LyoCapsule make it possible to not only optimize cycle conditions for early stage drug product development, but also to systemically scale-up the lyophilization process to pilot/ laboratory scale operations.

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

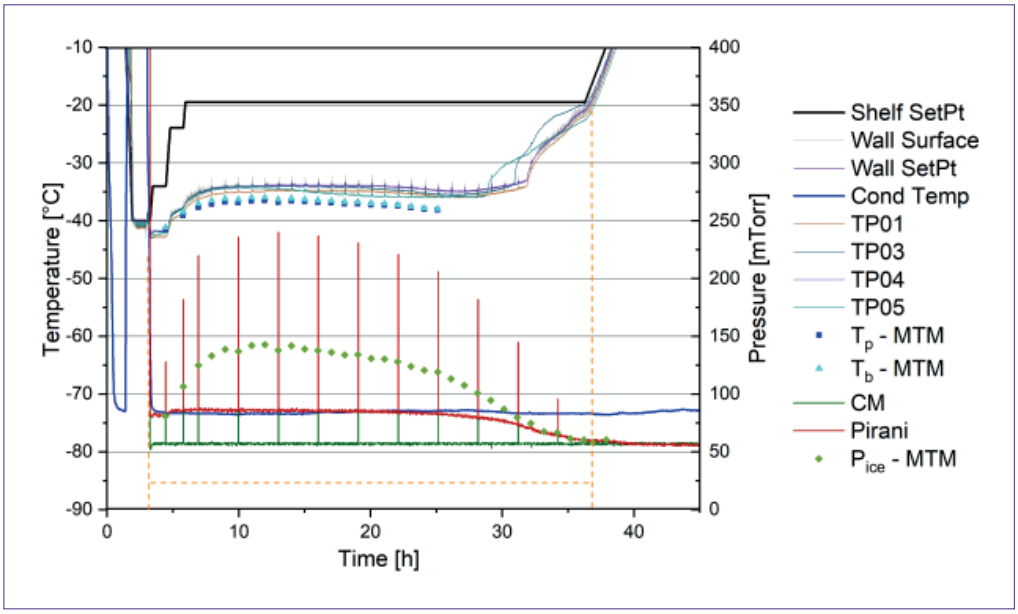

Figure 1. SMART cycle for a 50 mg/ mL sucrose formulation in the LyoCapsule.
The vapor pressure of ice was in good agreement with the Pirani for endpoint detection. Product temperature calculated by MTM showed similar only a small deviation from the product temperature profiles measured by thermocouples.

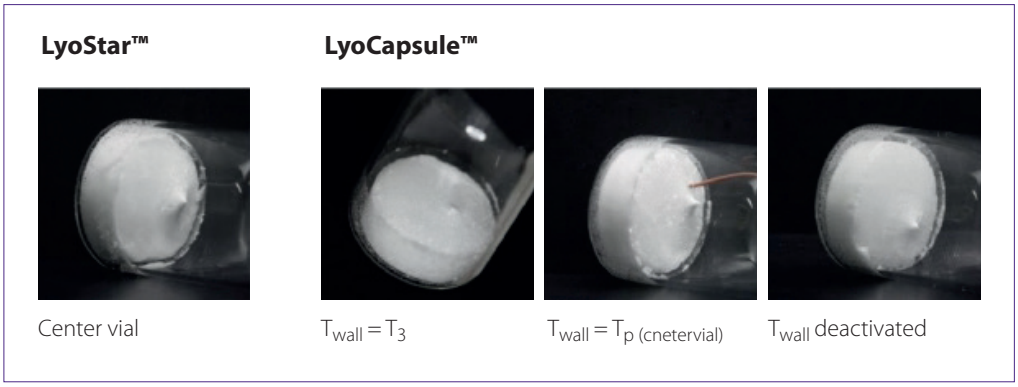

Figure 2. Comparisons of cake morphology after lyophilization.
Lyophilization of 50 mg/ mL sucrose was comparable in the LyoCapsule and the LyoStar, even when modifying the wall temperature.

Q&A Session

1. **How did you determine Kv values? Did you calculate Kv values using MTM?**
   The Kv values were determined gravimetrically which enable comparisons between Kv values of individual vials in both freeze dryers and distinguish between vials at different positions to assess the heterogeneity of the batch. Using MTM, batch averaged Kv values are obtained.
2. **What is the nucleation temperature for your runs in LyoCapsule in comparison to the nucleation temperature in a LyoStar?**
   Nucleation temperatures measured by thermocouples in the LyoCapsule are comparable to those measured in a LyoStar with no significant impact of the wall temperature setting, but there can be a nucleation difference of the vials with no invasive thermocouple.
3. **Can we simulate choked flow in the LyoCapsule?**
   This would be very difficult because there is a large duct diameter in relation to chamber size and condenser volume in the LyoCapsule. Due to the small surface area of the LyoCapsule shelf, it could be difficult to load high amount of sample into the chamber to provoke choked flow or a condenser overload.
4. **Can you use the same ramp rate, temperature and vacuum compared to other freeze dryers?**
   Yes, similar ramp rates can be applied for appropriate cycle transfer. For shelf temperature and vacuum even higher ramp rates can be achieved in the LyoCapsule than in the LyoStar.
5. **Would there be any benefits to using aluminum foil inside the door?**
   There are stainless steel door and walls in the LyoCapsule with comparable emissivity. As wall temperature can be controlled, I would not expect any problems with this.
6. **Did you experience limits with SMART like the larger machines?**
   So far, I have not experienced any additional limitations for SMART in the LyoCapsule compared to larger dryers. The typical limits that have been described with MTM, such as water reabsorption in case of highly concentrated amorphous solids apply to all dryers.
7. **Does LyoCapsule have a controlled nucleation option?**
   Yes, the LyoCapsule uses ControLyo technology (also used in the LyoStar) that ensures all vials nucleate simultaneously.
8. **When considering vials, do you have to cover the rest of the space with empty vials to shield the product vial?**
   Empty vials are not necessary in the LyoCapsule as wall temperature can be adjusted to overcome issues of atypical radiation.