Equipment capability of freeze-dryers and its relevance to the graphical design space for primary drying

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The capabilities of a freeze dryer can change with differences in design. This is particularly important when users are transferring cycles from lab-scale to commercial-scale freeze dryers. Each freeze dryer has its own limitations and it is important to understand these limitations to avoid the risk of product failure when scaling-up the production.

Recently, Dr. Jayasree M. Srinivasan from Baxter BioPharma Solutions presented a webinar discussing how to measure and compare equipment capabilities of lab-scale and production-scale freeze dryers in order to define optimal design space parameters. This tech note summarizes the webinar and includes a selection of questions from the Q&A session.

Determining design space for optimal product lyophilization

Optimal product and processes can be represented graphically, defined by boundaries that represent the limitations of the freeze-drying conditions. One boundary is the critical product temperature required before collapse occurs and the second boundary is equipment capability. The area underneath the boundaries represents the design space and ensures the product is safely produced (Figure 1). The plot of chamber pressure and sublimation rate is dependent on vial heat transfer coefficient (K_v) and product resistance (R_p) which will establish the relationship between the controlled parameters and product temperature.

Changes in the design or function of the freeze dryer itself or any process deviations can alter freeze-drying cycle properties and result in product failure. Sublimation requires consistent and homogenous heat controlled by the shelf temperature to regulate the freeze-drying process, any inconsistencies in shelf temperature can result in uncontrolled freeze drying. In

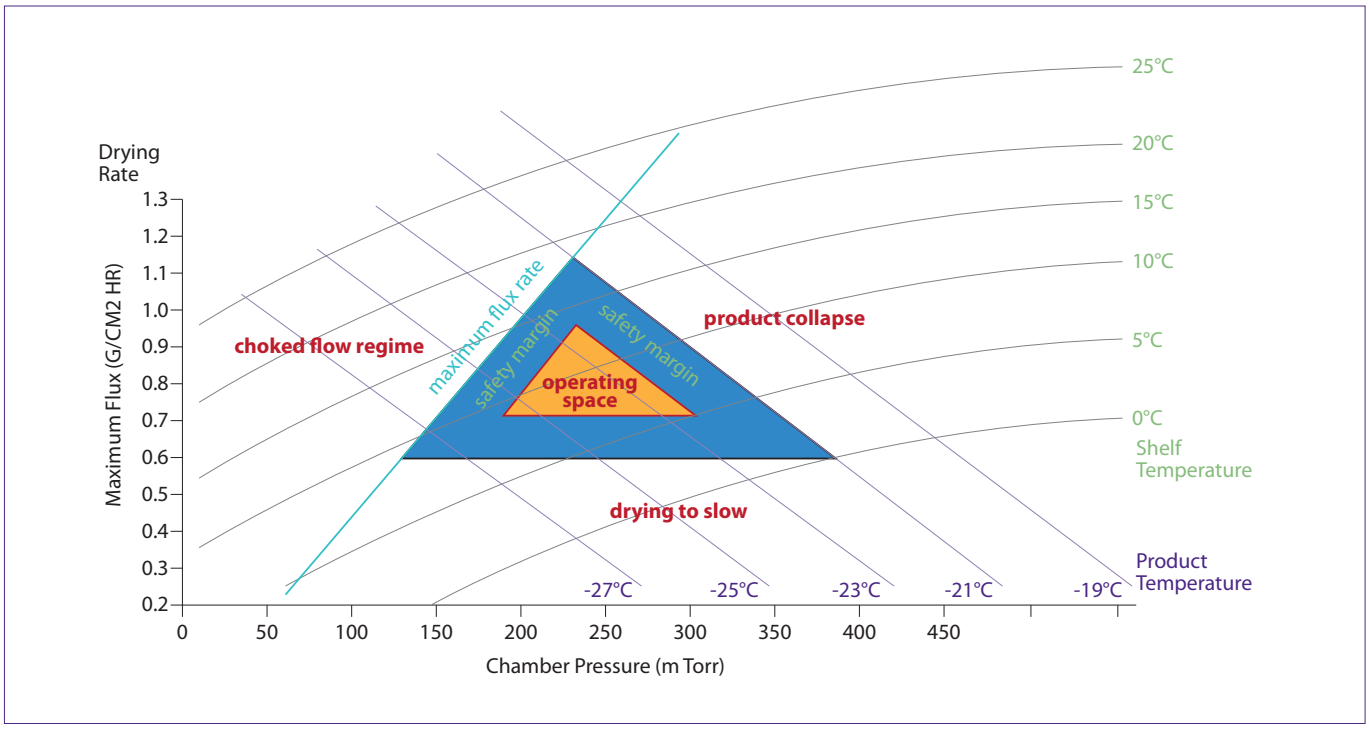

Figure 1: Design space of the freeze-drying process. A multidimensional representation of equipment capability limit and product knowledge

addition, process deviation can be caused by fluid problems in the refrigeration and varying dynamics of water vapor flow from chamber to condenser.

These critical product parameters are important whether it is in early stage development, pilot clinical stages or commercial manufacturing. However, transferring from one stage to another might require repeated optimization if the freeze dryers are not fully characterized for their capabilities.

Comparative freeze dryer capability study

Dr. Srinivasan set up a study to examine the capability of two lab-scale freeze dryers (LyoStar™ II, SP Scientific) (Figure 2) and three production-scale freeze dryers (one LyoMax® 9 and two LyoMax® 20s, IMA Group). There are several methods that exist to determine the mass flow rate during sublimation and the easiest is the Tunable Diode Laser Absorption Spectroscopy (TDLAS) method. The studies described in this tech note utilized a TDLAS as a flow meter for mass flow determination. Measuring the maximum mass flow rate identifies the choked point (the limit of velocity of water vapor that flows through the spool piece [duct] between the chamber and condenser of the freeze dryer).

Figure 2: LyoStar 3 (the next generation to LyoStar II)

Compatible capabilities of laboratory and production freeze dryers

Maximum sublimation rates were measured as a function of chamber pressure after increasing the shelf temperature at each pressure point, until the chamber pressure was no longer in control ("choked" flow). Comparing two LyoStar II freeze dryers revealed that the capability curves of sublimation rates were superimposable indicating equivalent performance. Extending this experiment to compare the LyoStar with the two LyoMax freeze dryers demonstrated that the production freeze dryers (LyoMax 9 and 20) had more capability than lab-scale freeze-dryers and supported higher sublimation rates, therefore, lab-to-production technical transfer would be easily achievable (Figure 3). The capability of the LyoMax 9 was in fact better than that of the LyoMax 20 due to the smaller shelf surface area.

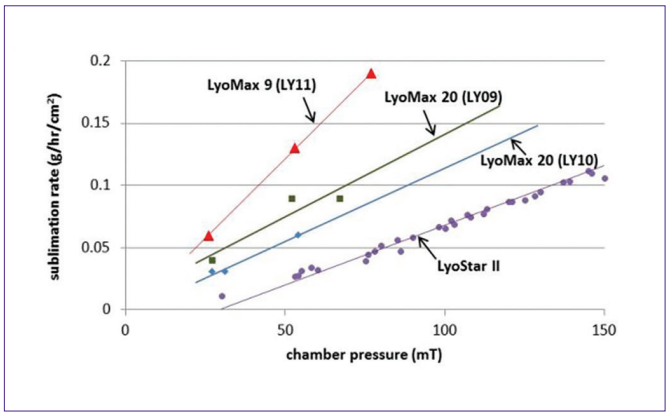

Figure 3: Comparison of Capabilities of LyoStar II® and LyoMax® Freeze-dryers

Comparable lyophilization between lab and product freeze dryers using same cycle conditions

Dr. Srinivasan went on to demonstrate the scalability from LyoStar to LyoMax. Lyophilization which was carried out using a formulation of amorphous API (124.2 mg/mL) and mannitol (32 mg/mL), and batches of 300 vials in the LyoStar II and 11,000 vials in the LyoMax freeze dryers. The same cycle conditions, developed with the LyoStar II, were used in both freeze dryers. There was very good agreement in mass flow rate data (collected using TDLAS) between the two freeze-dryers. The maximum rate achieved during this study for both the LyoStar II and the LyoMax freeze dryers indicated they were operating at 20 and 30%, respectively, of their maximum capability which implies they will not reach the choke point under the process conditions used.

Reproducibility of two batches using the same formulation and same lyophilization cycle conditions was measured in the LyoMax 9. It was found that the maximum flow rates and

time to reach them were similar (1.37 g/sec and 1.33 g/sec, respectively after 0.5 hours).

Summary

Two lab-scale (LyoStar II) and three production-scale freeze dryers (LyoMax) were compared for their equipment capabilities. It was found that the LyoMax 9 and 20 were more capable than the LyoStar II with all the freeze dryers operating at 20-30% capability suggesting that the lyophilization process can be easily scaled-up between a lab- and production-scale freeze dryer.

Equipment capabilities and batch reproducibility was also demonstrated in the LyoStar II and the LyoMax 9, respectively providing further evidence of robust equipment functionality for both types of freeze dryers.

This information can be illustrated graphically on a design space plot identifying the safe zone where cycle conditions will produce an optimized product. Deviation into areas outside this region can lead to choked flow rates and product failures.

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

Q&A Session

1. **What is the ratio of the duct diameter to chamber volume or mass flow where choked flow becomes impossible?**
   We have not determined that ratio.
2. **Would you favor dm/dt via TDLAS vs MTM to fill up the Pikal equation and Kv determination?**
   We at Baxter routinely use the TDLAS for mass flow rate determination. We prefer this technique due to its ease of use and non-destructive nature of the measurements.
3. **Can you explain why it has to be -45°C for water freezing?**
   We typically use -40°C to -45°C to freeze formulations to ensure batch uniformity so all vials are frozen completely prior to sublimation.
4. **Why does your example lyo cycle start pulling vacuum at -15°C during thermal treatment, rather than -45°C?**
   If the primary drying shelf temperature is warmer than -15°C (or any annealing temperature), it is not necessary to freeze the formulation back down to -40°C before pulling a vacuum. You can initiate vacuum at the annealing temperature. Freezing it to -40°C would only extend the cycle time.
5. **Has Baxter WW standardized on TDLAS for pilot equipment, even in Belgium?**
   No, we have not. Bloomington is the only Baxter facility that has the TDLAS capability.
6. **Why do you need to know the weight of the water when using TDLAS for choke limit determination?**
   The TDLAS estimates the total mass flow rate data. We also measure the weight loss gravimetrically (weights before and after drying) as a way to check the accuracy of the TDLAS. A variance of 3-5% is typical.
7. **How full do we need to fill the tray with H_2O?**
   For lab-scale freeze dryers, we use 1.5-2 L of Milli-Q water for each lyo tray.