BioPharma Solutions

white paper edition

Methods for Determining Equipment Capability of Freeze-Dryers

Baxter

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Introduction

Parenteral drugs are routinely administered in the solution form when the drug product exhibits acceptable stability. However, there are cases where the long-term shelf life of a drug product solution is undesirable. One way of addressing the stability issue is by lyophilizing it in to a solid form. Lyophilization is a drug manufacturing process that involves freezing the formulation, drying the frozen ice under vacuum, and subsequent removal of unfrozen residual water. The pharmaceutical freeze-drying technique is constantly evolving to achieve improvements through a better understanding of the product and process conditions and the efficiency of the equipment. During the lyophilization development of a drug product, a graphical design space, that establishes a relationship between process variables and product physical attributes, is developed (see Figure 1 at the end of the document). The design space uses parameters inherent to the drug product and those associated with the container and equipment used. The blue trace (Figure 1) represents the capability of the freeze-dryer to support mass transfer during sublimation.

It is critical that the capability of dryers is well understood to transfer a lyophilization process from lab-scale to full-scale in manufacturing successfully. The limiting factor for any freeze-dryer is a phenomenon called "choked flow", when the velocity of water vapor in the duct that connects the product chamber with the condenser approaches the speed of light (360 m/sec). It is essential that this data is available for a freeze-dryer to design an efficient lyophilization cycle development.

Literature references for choked flow in a freeze-dryer are scarce. Patel *et. al.* described the use of the ratio of chamber pressure to condenser pressure as an indicator of choked flow, with the threshold being 2.5 (Reference 1). Any pressure ratio greater than 2.5 indicates a choked flow. Computational fluid dynamics modeling was used to predict "choked flow" by Kshirsagar *et. al.* the results of which compared well with experimental results (Reference 2).

This white paper describes two experimental methods of determining "choked flow", namely the minimum controllable pressure method and choke point method. A Tunable Diode Array Laser Absorption Spectroscopy (TDLAS) was used as a flow meter to measure the mass flow rate during sublimation. The TDLAS is installed in the connecting duct as depicted (Figure 2).

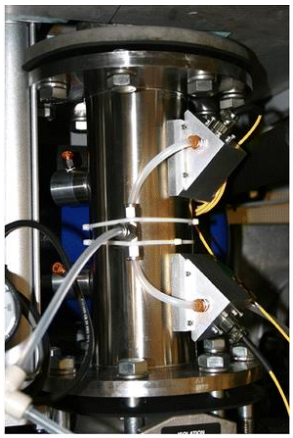

Figure 2. TDLAS Hardware Installed in the Duct Area of a LYOSTAR III Freeze-Dryer.

A LYOSTAR III freeze-dryer (SP SCIENTIFIC INDUSTRIES INC.) was evaluated for this study. (Table I) describes the duct dimensions for a LYOSTAR III freeze-dryer.

Parameter	Dimension
Process path (cm)	13.1
Duct angle (deg)	45
Duct area (cm^2)	74.36
Duct radius (m)	0.0486
Duct distance (m)	0.12

Table I. Duct Dimensions for a LYOSTAR III Freeze-dryer

Minimum Controllable Pressure Method

Three lyophilization trays were filled with 2 L of water each and frozen to -45°C until ice slabs were formed. The chamber of the freeze-dryer was evacuated to 10 mTorr (most lab-scale freeze-dryers are unable to control such a low pressure, so the flow is always choked throughout this experiment). A steady state was established. The chamber pressure that the freeze-dryer can control is the minimum controllable pressure at -45°C. The shelf temperature was increased in increments of 10 °C, steady state was established at each temperature setpoint, and the corresponding mass flow rate was noted.

The lyo in-process data is provided in (Figure 3).

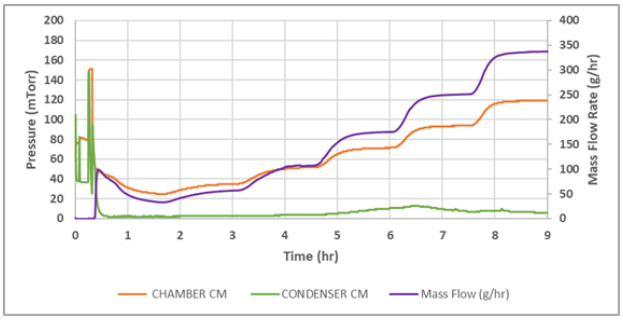

Figure 3. Lyo In-process Data Indicating Pressure and Mass Flow Rate as a Function of Time Using the Minimum Controllable Pressure Method.

The chamber pressure was not in control the entire duration of the experiment. The ratio of chamber pressure and condenser pressure remained greater than 3:1. Both these phenomena indicates choked flow.

The steady state mass flow rate (g/hr) and the observed chamber pressure at each shelf temperature is provided in (Table II).

Shelf Temp. (°C)	Pressure (mTorr)	Mass Flow Rate (g/hr)
-45°C	25	35.3
-35°C	35	56.4
-25°C	52	107
-15°C	72	174
-5°C	94	251
5°C	119	336

Table III. Summary of Shelf Temperature and Mass Flow Rate at Each Pressure Setpoint for Minimum Controllable Pressure Method.

Choke Point Method

Three lyophilization trays were filled with water as described in the minimum controllable pressure method and frozen to -45°C until ice slabs were formed. The chamber was evacuated at 45 mTorr. When a steady state was established, step changes to the shelf temperature were made until choked flow was observed. The process was repeated for the desired number of pressures setpoints.

The lyo in-process data is provided in (Figure 4).

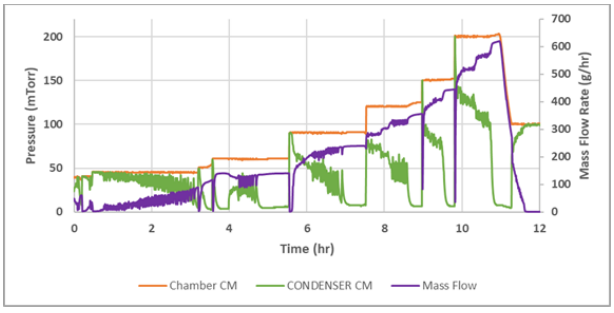

Figure 4. Lyo In-process Data Indicating Pressure and Mass Flow Rate as a Function of Time Using the Choke Point Method.

Unlike the minimum controllable pressure method, the chamber pressure (orange trace) remained in control even at chamber to condenser pressure ratios that would indicate a choked flow, so the pressure ratio was used as the choke point indicator for this method.

The shelf temperature and mass flow rate when choked flow was observed at each pressure setpoint are summarized in (Table III).

Shelf Temp (°C)	Pressure (mTorr)	Mass Flow Rate (g/hr)
-30°C	45	87.7
-20°C	50	110
-20°C	60	139
-5°C	90	239
10°C	120	353
20°C	150	443
20°C	200	618

Table IIIII. Summary of Shelf Temperature and Mass Flow Rate at Each Pressure Setpoint for Choke Point Method.

Comparison of the Two Methods

Comparison of the mass flow data obtained using the two methods indicated an excellent agreement (Figure 5).

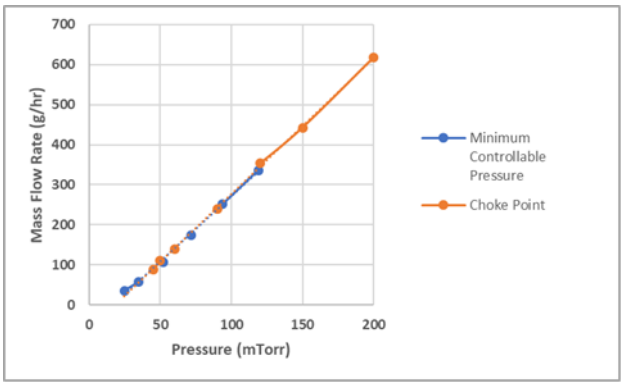

Figure 5. Comparison of Minim Controllable Pressure and Choke Point Methods.

The condenser temperature remained at <-70°C throughout the two experiments indicating that it was not overloaded.

Practical Considerations

The studies described here examined two methods of testing the equipment capability of a freeze-dryer. The minimum controllable pressure method is easier and quicker to conduct than the choke point method. In addition, in the choke point testing, the chamber was in control even at chamber to condenser pressure ratios (indicating a choked flow), rendering the minimum controllable pressure method more reliable.

References

[1]Patel, S. M.; Chaudhuri, S.; Pikal, M. J. "*Choked Flow and Importance of Mach I in Freeze-drying Process Design*", Chemical Engineering Science, 2010; 65: 5716-5727.

[2]Kshirsagar, V.; Tchessalov, S.; Kanka, F.; Hiebert, D.; Alexeenko, A. *"Determining Maximum Sublimation Rate for a Production Lyophilizer: Computation Modeling and Comparison with Ice Slab Tests"*, Journal of Pharmaceutical Sciences, 2019; 108: 382-390.

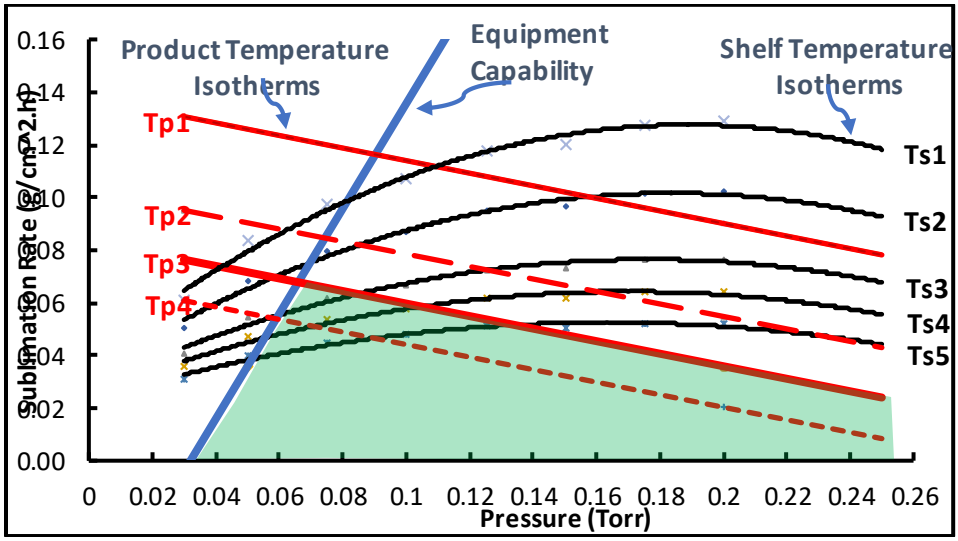

Figure 1. *Representative Design Space Indicating the "Safe Zone" in Green. Any Combination of Chamber Pressure and Shelf Temperature Within this Zone will Provide Acceptable Freeze-dried Solids. The Blue Line Represents the Equipment Capability Curve for the Freeze-dryer.*

Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, Illinois, USA 60015
Email: biopharmasolutions@baxter.com www.baxterbiopharmasolutions.com

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