Applicability of the LyoCapsule Mini Freeze Dryer for Pharmaceutical Product Formulation and Process Development

Emily Gong and William Kessler
Physical Sciences, Inc. 20 New England Business Center, Andover, MA 01810

Introduction

The development of biopharmaceuticals often requires lyophilized formulations to produce stable drug products.[1] Development of a drug formulation and lyophilization (freeze drying) process begins with laboratory experiments followed by scale-up to larger lyophilizers. A challenge during formulation and process development is the limited supply of and cost of producing sufficient Active Pharmaceutical Ingredient (API). Significant amounts of API may be required to properly screen formulations for freeze drying feasibility, understand critical product attributes, and define product and process design space to create a robust freeze-drying process. Placing a few vials within a larger freeze dryer does not provide representative drying conditions due to atypical radiation conditions created when vials are not situated in a close-packed formation or when vials do not fill the freeze dryer shelf surface.[2] Atypical radiation effects lead to differences in product temperature histories and drying times resulting in non-representative cycles.

Another restriction of current lab-scale lyophilizers is their limited ability to emulate larger lyophilizers due to differences in radiative effects from warmer, non-temperature-controlled surfaces between lab and production-scale lyophilizers.[3] Also, differences in the product resistance to drying (R_p) created due to differences in ice nucleation temperatures between laboratory and the sterile, low particle conditions in manufacturing-scale operations leads to differences in product temperatures and drying times.[4] Adjustments must be made to shelf temperatures and drying times to compensate for differences in drying heterogeneity (due to the larger ratio of edge to center vials in a lab-scale dryer) and R_p to produce high quality pharmaceutical product.

The LyoCapsule™ Freeze Dryer (seven 20cc vial) miniature product chamber freeze dryer was developed to bridge the gap between laboratory and manufacturing-scale lyophilizers. As shown in Figure 1, the LyoCapsule™ Freeze Dryer contains a small freeze drying chamber with a cylindrical inner chamber and utilizes wall temperature control to emulate the radiation conditions of edge or center vials. It has the ability to freeze-dry a relatively small number of vials under heat and mass transfer conditions typically encountered in larger freeze dryers. It is outfitted with process analytical technology tools (thermocouples, capacitance manometers, Pirani gauge, Manometric Temperature Measurement (MTM) and Tunable Diode Laser Absorption Spectroscopy (TDLAS)) that enable the use of scientific and engineering principles for successful process scale up and economically viable drug product manufacturing. In addition, it may also be a valuable tool to "scale down" a process cycle from a large freeze dryer to a smaller freeze dryer to investigate process failures using a limited amount of API.

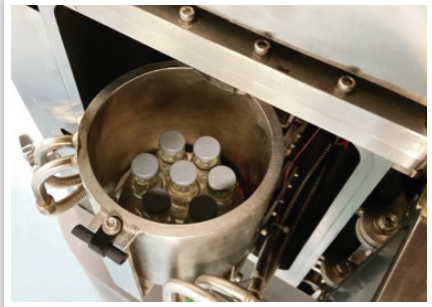

Figure 1. Inner cylindrical chamber of the LyoCapsule™ Freeze Dryer with temperature-controlled shelf and wall.

Methods

Experiments were performed in both the LyoCapsule™ Freeze Dryer and the lab-scale LyoStar 3 Freeze Dryer (both manufactured by SP Scientific, Stone Ridge, NY). A 5% mannitol (Sigma) formulation was used for all cycles. The LyoCapsule™ Freeze Dryer was loaded with seven 20cc vials and the LyoStar 3 Freeze Dryer was loaded with 112 filled 20cc vials surrounded by a row of empty "dummy" vials and placed on the middle shelf. The fill volume of the 5% mannitol solution was 5mL in both dryers. For all cycles, product temperatures of edge and center vials were measured using 36-gauge thermocouple probes (SP Scientific) placed at the bottom center of the vial. For experiments in the LyoStar 3 Freeze Dryer, the temperature of the metal band that forms the bottomless tray (band temperature) was measured with thermocouple probes (Omega) placed on the inside wall of the band. During experiments in the LyoCapsule™ Freeze Dryer, the wall temperature was controlled either to match the center vial temperature (CVT) during the cycle (real-time feedback control) or to emulate the temperature of the metal band in the LyoStar 3 Freeze Dryer using a pre-programmed recipe. TDLAS water vapor mass flow data was collected for all cycles.

Experimental Results

This study's focus was to demonstrate the application of this new lyophilizer to emulate the product temperature history of a larger laboratory dryer often used for process development. The aim was to compare the radiation environment of the LyoStar 3 process development freeze dryer to the LyoCapsule™ Freeze Dryer. Similar experiments were reported by Obeidat et al.[5]

However, a second generation LyoCapsule™ Freeze Dryer was used in this study. Improvements include changes to the shelf geometry from square to cylindrical to eliminate corner effects and the creation of an inner chamber that has the ability to slide out from the main chamber for ease of loading vials and placing thermocouples.

First, a freeze drying cycle was performed in the LyoStar 3 Freeze Dryer to determine primary and secondary drying times, product temperature profiles of edge and center vials, and the band temperature profile. Then, the same cycle was performed in the LyoCapsule™ Freeze Dryer with the wall temperature controlled either to follow the CVT or to emulate the band temperature in the LyoStar 3 Freeze Dryer. The drying chamber pressure was maintained at 100mTorr for all cycles. Comparisons of product temperature profiles between the LyoStar 3 Freeze Dryer and the LyoCapsule™ Freeze Dryer are shown in Figure 2.

When the wall temperature in the LyoCapsule™ Freeze Dryer was controlled to match the CVT, product temperatures and primary drying times of both edge and center vials (Figure 2A) in the LyoCapsule™ Freeze Dryer resembled those of center vials observed in the LyoStar 3 Freeze Dryer. When the wall temperature in the LyoCapsule™ Freeze Dryer was controlled to emulate the band temperature in the LyoStar 3 Freeze Dryer, the product temperature and primary drying time of the edge vials (Figure 2B) in the LyoCapsule™ Freeze Dryer closely resembled the edge vials in the LyoStar 3 Freeze Dryer. Additionally, the center vial in the LyoCapsule™ Freeze Dryer more closely resembled the LyoStar 3 Freeze Dryer edge vials than the center vials.

TDLAS data was collected for all three freeze drying cycles. Figure 3 shows the TDLAS-determined water vapor mass flow and integrated water removed. The water vapor mass flow profiles for the two cycles performed in the LyoCapsule™ Freeze Dryer indicated a difference in primary drying time. The data show an increased primary drying time for the cycle where the wall temperature was set to follow the CVT (Figure 3B) compared to the cycle where the wall temperature was set to emulate the band temperature in the LyoStar 3 Freeze Dryer (Figure 3C). This further validates the product temperature data shown in Figure 2. Further analysis will utilize TDLAS data to explore differences in product resistance between the LyoCapsule™ Freeze Dryer and the LyoStar 3 Freeze Dryer.

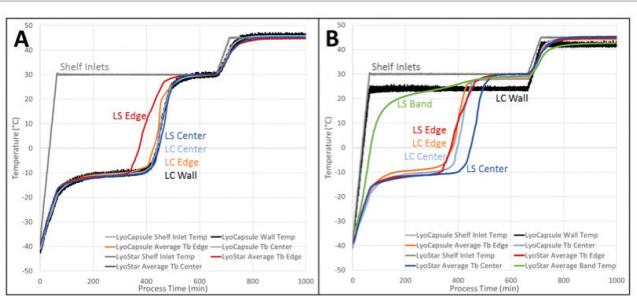

Figure 2. Product temperatures comparisons during primary and secondary drying between the LyoCapsule™ Freeze Dryer and the LyoStar 3 Freeze Dryer for 5% mannitol. A) The wall temperature of the LyoCapsule™ Freeze Dryer was set to follow the CVT. B) The wall temperature of the LyoCapsule™ Freeze Dryer was set to emulate the band temperature in the LyoStar 3 Freeze Dryer. LC and LS denote LyoCapsule™ Freeze Dryer and LyoStar 3 Freeze Dryer respectively.

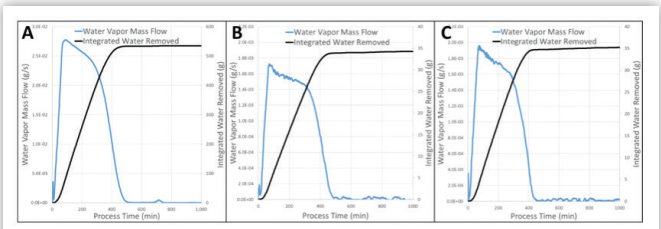

Figure 3. TDLAS data for water vapor mass flow (g/s) and integrated water removed (g) for 5% mannitol in A) the LyoStar 3 Freeze Dryer, B) the LyoCapsule™ Freeze Dryer with the wall temperature set to follow the CVT, and C) For the LyoCapsule™ Freeze Dryer with the wall temperature set to emulate the band temperature in the LyoStar 3 Freeze Dryer.

Conclusions

Technology transfer of lyophilization cycles from laboratory to production-scale dryers typically involves preserving product temperature histories. This is usually accomplished by maintaining the same drying chamber pressure setting and adjusting the shelf temperatures and drying times. This study focused on demonstrating the application of the LyoCapsule™ Freeze Dryer for emulating product temperature history between two laboratory dryers using adjustments to the radiation environment in the LyoCapsule™ Freeze Dryer to emulate center and edge vial drying conditions in the LyoStar 3 Freeze Dryer. Vials in both dryers were exposed to similar particle-laden environments, likely resulting in similar product resistance to drying values (although these have not yet been assessed). We have shown that product temperature histories and drying times can be conserved between the LyoCapsule™ Freeze Dryer and LyoStar 3 Freeze Dryer through controlling the wall temperature.

The LyoCapsule™ Freeze Dryer can be a powerful tool for formulation and process development for lyophilized pharmaceuticals. The LyoCapsule™ Freeze Dryer can be used to ensure that critical formulation collapse temperature is not exceeded during primary drying, define proper shelf temperature and pressure selection for effective sublimation processes, plan process scale-up and perform "scale-down" experiments to troubleshoot issues encountered in commercial freeze dryers while utilizing minimal API.

References

1. Wang, W. (2000). Lyophilization and development of solid protein pharmaceuticals. International journal of pharmaceutics, 203(1), 1-60.
2. Patel, S. M., Jameel, F., & Pikal, M. J. (2010). The effect of dryer load on freeze drying process design. Journal of pharmaceutical sciences, 99(10), 4363-4379.
3. Pikal, M. J., Bogner, R., Mudhivarthi, V., Sharma, P., & Sane, P. (2016). Freeze-drying process development and scale-up: scale-up of edge vial versus center vial heat transfer coefficients, Kv. Journal of pharmaceutical sciences, 105(11), 3333-3343.
4. Rambhatla, S., Ramot, R., Bhugra, C., & Pikal, M. J. (2004). Heat and mass transfer scale-up issues during freeze drying: II. Control and characterization of the degree of supercooling. AAPS PharmSciTech, 5(4), 54-62.
5. Obeidat, W. M., Sahni, E., Kessler, W., & Pikal, M. (2017). Development of a mini-freeze dryer for material-sparing laboratory processing with representative product temperature history. AAPS PharmSciTech, 1-11.