Software Tools for Pharmaceutical Lyophilization Process Development

Emily Gong
Senior Research Scientist, Physical Sciences, Inc.
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Lyophilization is a complex process, and development of optimized processes that are economical and robust can be costly and time-consuming. Lyophilization cycles must produce quality product across and between batches, and therefore, must account for process heterogeneity. Many companies lack the tools, staff, and experience in pharmaceutical freeze-drying which can lead to inefficient drying cycles, failed batches, increased costs, and delays in drug production. Accurate and easy-to-use software modeling tools can alleviate some of these issues and speed up the scale-up process.

Recently, Emily Gong, Senior Research Scientist, Physical Sciences Inc., Andover, MA, USA presented a webinar describing a software modeling tool that PSI, along with its collaborators (University of Connecticut, University of Massachusetts Lowell, Purdue University, Genentech and Merck), has developed to optimize conditions for the primary drying cycle and while accounting for heterogeneity within and between batches of drug products. This tech note summarizes the webinar and includes a selection of questions from the Q&A sessions.

Sources Of Heterogeneity

Before developing the software, it was important to understand one of the major challenges of lyophilization - heterogeneity of the freeze-drying process between vials and between batches. Some of these variations are due to the difference in radiative heat input between vials on different positions of the shelf or between different vial geometries (Figure 1).

It is common to observe a lower product temperature within a vial in the center of a shelf compared to the outer edge due to differences in radiative heat input. Edge vials "view" the warmer dryer walls and receive higher heat input from radiation. The edge vials limit the shelf temperature set point because the critical product temperature should not be exceeded, while the center vials dictate the total drying time as they are colder and therefore dry slower.

Figure 1: Variation in radiative heat input from dryer surfaces is dependent on viewing factors (based on vial position on shelf).

Another source of heterogeneity is stochastic ice nucleation during the freezing process. The temperature at the onset of ice nucleation impacts product resistance, and therefore, drying rates. Although technologies now exist that can reduce this uncontrolled ice nucleation, the effect on product resistance still needs to be considered when designing a freeze-drying process.

Other variations in the process include variation in the surface temperature of the shelf and variations in fill volumes that lead to variations in heat transfer and drying time.

Primary Drying Heat And Mass Transfer Model

The aim of PSI and its collaborators was to develop user-friendly software for primary drying process development and scale-up that accounts for heterogeneity and statistical variation.

Physical Sciences Inc., created this primary drying development software based on two publications from the University of Connecticut, Pikal et. al., Impact of Natural Variations in Freeze-Drying Parameters on Product Temperature History: Application of a Quasi Steady-State heat and Mass Transfer and Simple Statistics, *AAPS PharmSciTech*, 2018, and Pikal et al., Freeze-Drying Process Development and Scale-up: Scale-Up of Edge Vial Versus Center Vial Heat Transfer Coefficients, K_V, JPharmSci, 2016. This program relies on the heat and mass transfer steady state model of freeze drying in vials and includes statistical variation in product temperature and drying time across the batch. This information can then predict location-dependent distribution of product temperature and drying time as well as batch average results.

User-friendly Software to Optimize Primary Drying Cycle Process Development

In the webinar, Ms. Gong describes details of input parameters and examples of the visual output. Vial heat transfer coefficients are input for the center, inner edge, and outer edge vials at three different chamber pressures. These values are fit to a well-accepted equation for vial heat transfer as a function of pressure enabling calculations of the heat transfer coefficients at different chamber pressures. Product resistance is input as a function of dry layer thickness. The software provides drop-down menus for common excipients to guide novice users, but users can also input product specific information.

Additional inputs include vial geometries, fill parameters, and equipment capability limits. With the information provided, users can iteratively model different process conditions to minimize primary drying time while maintaining key product parameters (Figure 2).

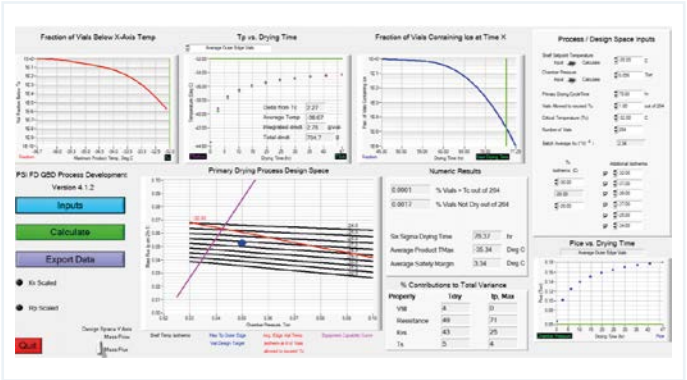

Figure 2: *Heterogeneous primary drying process development model results*

As part of a Quality by Design (QbD) process development approach, the software also provides a design space and estimate the percentage of vials that may collapse and those that do not complete primary drying for different process conditions (shelf temperature, chamber pressure and drying time).

To effectively utilize the software model, the following values need to be determined:

1. The product critical temperature, T_c needs to be independently defined using differential scanning calorimetry (DSC), thin-film transmission or bulk solid optical coherence tomography freeze-drying microscopy
2. An experimental value of the vial heat transfer coefficient (K_v) is estimated by freeze-drying deionized (DI) water at several chamber pressures
3. The product resistance (R_p) is calculated using a TDLAS water vapor mass flow rate sensor with a conservative cycle to avoid product collapse
4. The freeze dryer equipment capability limits determined through experiments, calculations, or historical data

These values were input into the model to enable calculations to define the desired target product temperature profiles and the predictions were confirmed through laboratory-scale experiments.

Case Studies

Model validation experiments were performed using excipient drug formulations and drug substance provided by Genentech and Merck to validate the model with industry-relevant formulations. Both industry drug substance case studies described in the webinar used the SP Hull LyoStar 3 freeze dryer with 264 vials in the middle shelf (center 198, outer edge 44, inner edge 22).

Case study 1

The first case study discussed in the webinar involved a protein active pharmaceutical ingredient (API) with a total solid content of 3.9% w/v. The collapse temperature of the product was determined to be -39°C through previous freeze-drying microscope studies and the vial was filled to 3 mL at a depth of 0.85 cm.

After an initial conservative experiment #0, which was run to determine the product resistance, experiment #1 was run at the same conditions as experiment #0 (-30°C and 50 mTorr), and experiments #2 and #3 were run to test the model over a range of shelf conditions (-25°C and -20°C, respectively).

The R_p data from experiment #0 was used in conjunction with K_v values determined from DI water experiments to develop predictions for product temperatures for the three different shelf temperatures. The results demonstrated that there was relative consistency of R_p among experiments and ≤ 1°C difference in product temperature between the model and each experiment for all vial classes from the edge to center as shown in Figure 3.

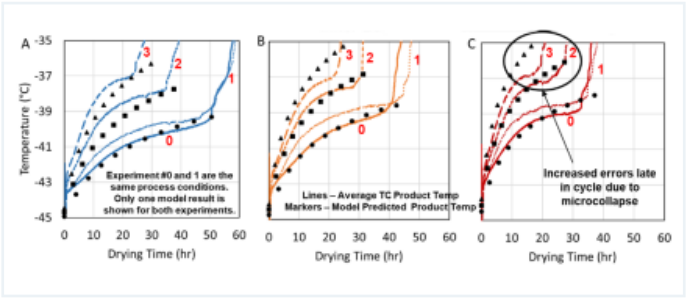

Figure 3: *Accuracy of model predicted product temperatures compared to experimental results over a range of shelf temperatures*

Case study 2

The second case study also involved a protein API with a solid content of 4.7% w/v. The collapse temperature of the product was higher at -23°C and the volume of the product was greater (5.2 mL with a fill depth of 1.47 cm).

Experiment #0 was again used to determine product resistance. A conservative condition with a T_s of -35°C and a chamber pressure of 50 mTorr. Experiment #1 was run at aggressive conditions suggested by our industry partners (0°C and 150 mTorr) and experiments #2 - #4 were run at conditions based on the model results for a collapsed temperature of -23°C (based on freeze-drying microscopy) or -26°C (based on a T_g' from DSC) with the shelf temperature changing from -13°C to -21°C at a constant chamber pressure of 65 mTorr.

As shown in Figure 4, the results demonstrated changes to R_p between experiments due to microcollapse. Although no visible changes in cake morphology were observed, consistent with macrocollapse, some shrinkage in the dried product was observed.

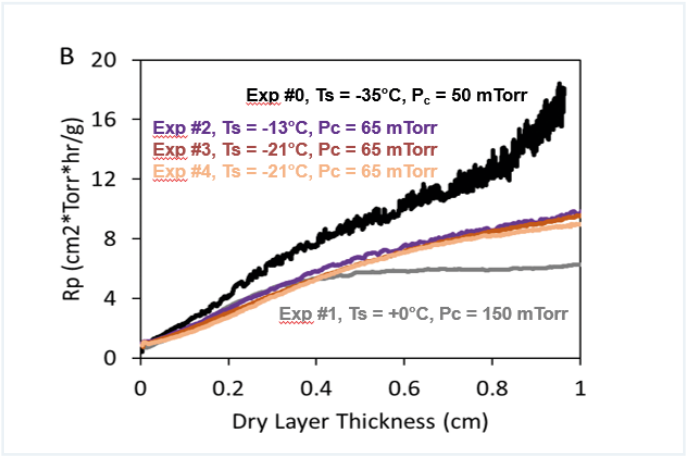

Figure 4: *Product resistance, case study #2*

Thermocouple data from individual vials was analyzed and declines in product temperature during some of the cycles were consistent with a drop in R_p, indicating microcollapse, and a drop in product resistance resulting in an increase in sublimative cooling. When using the product resistance data from experiment #0 to define the model inputs, the error in product temperature prediction was approximately 1.5°C. However, using in-process R_p values calculated from the data of the modelled cycle, it lowered the error to approximately 1°C for outer edge vials and 0.4°C for inner edge and center vials. The difference is due to the higher degree of microcollapse in warmer edge vials.

Primary drying time for both case studies, determined using sample probes in individual vials, were predicted accurately for all vial classes when the correct product resistance values are used for the model inputs.

Conclusions

This user-friendly software makes it easy to model a wide range of process conditions to determine optimal freeze-drying cycles. The software is capable of predicting the product temperature within a ± 1°C and primary dying end time when benchmarked against industry-relevant formulations.

However, the case studies highlighted the need for accurate model inputs for acceptable predictive capabilities, especially for R_p. Future improvements to the software are planned to reduce the work required to define these model inputs and will also include location-dependent R_p inputs, all of which will enhance its power as a predictive tool.

Initial pilot-scale experiments using this predictive modelling software and a larger freeze dryer, SP Hull LyoConstellation™ S20, have been promising and will be the focus of future validation efforts.

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

Acknowledgements

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Q&A Session

1. **You mentioned that a decrease in R_p with increasing L_{dry} suggests microcollapse. Is this also detectable in the product temperature recording via decrease in temperature?**

   Yes, we observed a reduction in product temperatures toward the end of the cycle due to the decreased product resistance and increased sublimative cooling. This was most apparent in outer edge vials which were warmer and underwent a higher degree of microcollapse.

2. **I assume these experiments are done with uncontrolled ice nucleation? Would the primary drying time be improved with controlled nucleation?**

   Yes, we did not use controlled ice nucleation. While we did not explore the effect of controlled nucleation, literature does suggest that it would reduce product resistance and lead to shorter primary drying times. Additionally, it would lead to lower heterogeneity between vials which would allow for a more aggressive cycle as you would not need to account for as much variation in the process. If you had resistance data for both controlled and stochastic ice nucleation, the model presented would be useful for determining the predicted percentage of vials that would be dry at a given time for both freezing methods.

3. **What differences in the design space do you see between using a batch average K_v and location-dependent K_v?**

   The only difference in the design space for the heterogeneous model versus a more standard batch average design space is that a single product temperature isotherm is shown representing the average edge vial temperature for the user defined number of vials allowed to exceed the critical temperature. For process development using only a batch average K_v, you have to include safety margins, often estimated or determined empirically, to account for the edge vials being warmer than the center vials. With location-dependent K_v inputs, a data-based approach is used to determine drying conditions that will ensure all vials remain below the critical temperature and complete primary drying.

This work has now been published. Please see: Bogner, R., Gong, E., Kessler, W. et al. A Software Tool for Lyophilization Primary Drying Process Development and Scale-up Including Process Heterogeneity, I: Laboratory-Scale Model Testing. AAPS *PharmSciTech* 22, 274 (2021). https://doi.org/10.1208/s12249-021-02134-3

935 Mearns Road, Warminster, PA 18974, USA | scientificproducts.com
+1-800.523.2327 | hello@spindustries.com