Heat Transfer Adjustment in a Scale-Down 7-Vial Micro Freeze Dryer for At-Scale Lyophilization Cycle Development and Optimization

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Purpose

Lyophilzation cycle development, optimization, and scale-up is mainly influenced by how heat enters the product through the vial during drying. Vial heat transfer coefficients (K_v) in commercial scale lyophilizers are typically lower than laboratory scale units, resulting in longer cycle durations, lower drying product temperatures and throughput, and more expensive processes. It is often difficult to monitor drying performance at-scale. Thus, transfer of an optimal laboratory cycle to a commercial unit typically results in non-optimal commercial performance and unknown response to process deviations.

We have implemented the use of a small-scale 7-vial Micro Freeze Dryer (MicroFD) that has the capability to accurately control and monitor heat transfer into the vials. We demonstrate the ability to fine-tune the MicroFD K_v to match the K_v of center vials in a laboratory scale unit. The resulting lyophilization performance between scales results in equivalent product temperature profiles and critical quality attributes (CQAs) for the same drying process. The proposed workflow demonstrates how manipulation of K_v in the MicroFD enables cycle development, optimization, and quality by design (QbD) of at-scale lyophilization processes using only 7 product vials. By simply changing the MicroFD K_v, laboratory, pilot, and commercial unit cycles may be simulated using only 7 product vials for tremendous API savings as long as at-scale heat transfer coefficients are well characterized.

Methods

Water sublimation tests were used to measure K_v values on a 7-vial lyophilizer (MicroFD, Millrock Technologies) and a 304-vial laboratory lyophilizer (Lyostar III, SP Scientific). All vials were weighed before and after an abbreviated lyophilization primary drying cycle to determine the positional dependence of K_v. The temperature controlled blocks in the MicroFD were set to different temperatures to determine conditions that produced a K_v that matched center vials in the Lyostar III. Using the previously determined block temperature, equivalent placebo and monoclonal antibody (mAB) drug product lyophilization cycles were performed in the Lyostar III and MicroFD.

Results

The MicroFD is designed with precision machined, temperature controlled aluminum blocks that make direct contact with the outer vials. These blocks are designed to mimic vial-to-vial contacts that control inter vial heat transfer. The K_v for the MicroFD was measured for multiple block temperature settings. A block temperature was determined that resulted in the same K_v as center vials in the laboratory scale Lyostar III lyophilizer. Using the fine-tuned MicroFD block temperature, placebo and mAb drug product lyophilization batches were executed using the same drying parameters and formulations on each instrument. The center vials in the Lyostar III and the 7 vials in the MicroFD had completely overlapping product temperature profiles with equivalent primary drying time and average product temperatures. Additionally, the cake quality measured via visual inspection, SSA, and mass transfer coefficients measured via product temperature profiles were nearly identical.

Conclusion

A workflow is demonstrated using a scale-down 7-vial lyophilizer to simulate at-scale lyophilization development and optimization. The temperature of aluminum blocks in contact with product vials in the MicroFD were manipulated to yield a K_v that matches the at-scale unit. Equivalent lyophilization performance between the scale-down lyophilizer and a laboratory lyophilizer were demonstrated for placebo and mAb drug products. The workflow is being developed to include pilot and commercial lyophilizers.