Strategy to Evaluate the Performance of Lyophilization Stoppers

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Introduction

Lyophilization, the process of dehydrating a material through freezing, sublimation, and desorption, is commonly used to extend the shelf life of biologic drug products. Since one of the objectives of lyophilization is to extend the shelf life, long-term performance testing of any lyophilization containment system is essential. That testing must include not only measurement of container closure integrity (CCI), but also of the system's ability to maintain the targeted drug product water content and to inhibit moisture ingress. Within a glass vial container closure system, the stopper composition plays a critical role.

This poster discusses a strategy for two-year evaluation of four types of lyophilization stoppers (two bromobutyl elastomers, two chlorobutyl elastomers) in both 13mm and 20mm sizes, paired with borosilicate glass vials and aluminum seals. Lyophilization was performed in a commercial chamber using a solution blend of 20 mg/ml mannitol and 40 mg/ml sucrose – nitrogen backfill was to 11.6 psi. Evaluation comprised of:

- CCI (unsealed) – ability to maintain vacuum (24 hrs.)
- CCI (sealed) – ability to maintain vacuum
- Water vapor pressure in headspace
- Water content of cake
- Water content of stopper

The strategy proved effective in demonstrating that while all systems maintained acceptable CCI and water levels, composition of stopper does influence water level of drug product.

Objectives

- Discuss the strategy for an experimental outline to evaluate the performance of lyophilization stoppers.
- Examine the utility of laser-based headspace analysis to measure container system pressure.
- Discuss the merit of performing feasibility studies to identify issues before the commencement of long-term studies.

Materials

- 2R and 10R borosilicate glass vials in various blow back features (NBB, EBB and ABB)
- Various formulations of 13mm and 20mm lyophilization stoppers
- 13mm and 20mm Flip Off® CCS Seals
- Mannitol and Sucrose
- Hull Model 8FS12C lyophilizer

Testing Equipment/Methodology

- Karl Fischer (KF) Coulometric Titrator for Cake and Stopper moisture analysis
- Lighthouse FMS – Moisture/Pressure Headspace Analyzer for the headspace moisture and pressure analysis
- Laboratory benchtop lyophilization simulator

Feasibility Evaluation

- Pop-up experimentally performed to measure pop-up potential. Vials can have an American blowback, European blowback or No blowback feature. These features of the vial help maintain the stability of the stopper in the vial while being lyophilized. And help prevent the stopper from "popping" back up after being seated.

Lyophilization and Testing Design

Samples are loaded into the chamber

Samples are lyophilized

Samples are placed on stability

Samples are pulled and tested

destructive

- moisture/pressure in headspace
- KF on lyo cake and stopper

non-destructive

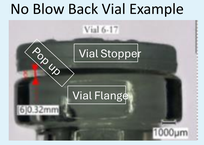
- moisture/pressure in headspace and returned to stability

Experimental Outline Using Benchtop Lyo Simulator

Lyo Chamber (simulator)

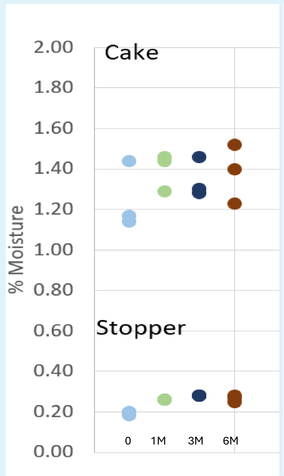
Stoppers Compressed into Glass Vials by Chamber Plates

No Blow Back Vial Example

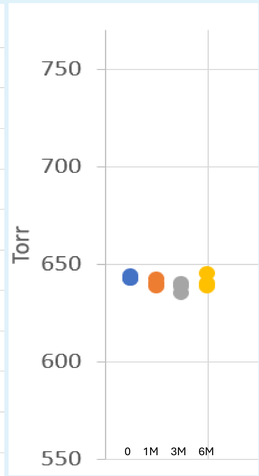


European Blow Back Vial Example

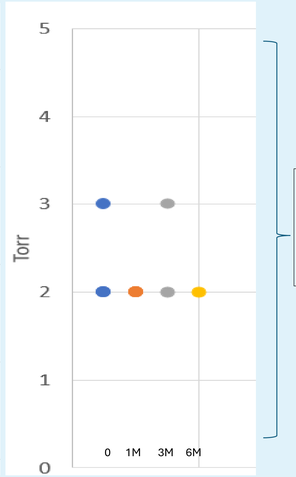
Moisture



HS Pressure in Test Vial



HS Moisture in Test Vial



N=3 Destructive Testing at each timepoint

Discussion & Conclusions

- The study was designed to monitor the moisture transition in a container closure system (CCS) after being lyophilized.
  - ✓ Evaluate initial compatibility with stopper configuration
  - ✓ Monitor moisture transition in the CCS through a 24-month life cycle
  - ✓ Monitor change in vacuum and moisture pressure in the CCS over a 24-month life cycle
- The samples were divided and stored at 25°C/60%RH after being lyophilized
  - One set was first tested for headspace (HS) moisture and pressure (nondestructive) and then that same vial was disassembled, where the cake and the stopper were each tested for moisture by Karl Fischer titration
  - The other set was only tested for headspace moisture and pressure and then placed back on stability for continuous monitoring in an unopened system.
- The data between the destructive moisture/pressure vials was comparable to the moisture/pressure in the unopened vials.
- The traceability of the residual moisture in the cake and the stopper showed similar trends and appear to be leveling off at the 6-month timepoint.
- After 12 months the vacuum pressure shows that the vials are relatively unchanged from the original established vacuum.

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