Characterization of Pre-filled Syringe Container Closure Integrity in Deep-Cold Storage Conditions

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Abstract

Pre-filled syringes (PFS) offer usability and other benefits but also present heightened Container Closure Integrity (CCI) risks for products requiring frozen storage. A range of PFS configurations were characterized for CCI at deep-cold storage temperatures using a laser headspace analyzer test method after conditioning at the target temperature in a CO_2 rich environment. Empirical CCI measurement data was combined with theoretical modeling and *in-situ* imaging to characterize and build a mechanistic understanding of the impact of these deep-cold temperatures on CCI.

The glass transition temperature (T_g) of the stopper elastomer is a critical consideration in maintaining CCI in glass syringes. Use of polymer syringe barrels can enable storage at temperatures below the T_g.

Introduction

- Container closure integrity (CCI) is critical to the quality and sterility of drug products and is typically measured during batch release and stability testing.
- CCI can be compromised by defects in the container components or failure of sealing interfaces allowing unwanted egress or ingress of gases, fluids or microbial contaminants.
- The plunger-barrel interface of a PFS is high risk area for CCI as it relies on radial contact pressure between the two components.
- Differences in material properties between the stopper and syringe barrel, combined with changes in these properties at low temperatures heighten CCI risk during deep cold storage.
- These low temperature related CCI breaches reseal when returned to higher temperatures and cannot be detected by most CCI methods.

Methods

Laser headspace analysis (CO_2) combined with pre-conditioning at the target temperature in a CO_2 rich atmosphere enabled detection of temperature related *transient* CCI breaches.

Figure 1 Laser headspace analyzer (Lighthouse), Temperature cycling unit (Tenney) and *in-situ* imaging set-up (Stress Engineering Services). A range of stoppers were evaluated with different outer diameters.

Calibration standards and control samples were used throughout to ensure the dependability of the CCI testing results.

A novel imaging method was used to visualize stopper rib contact with the barrel at target temperatures.

The study included glass and COC polymer syringes in 1mL long and standard formats and a range of coated and uncoated stoppers in 1mL and 1-3mL sizes.

Results

Figure 2 Overall CCI results for 1mLL glass syringes with *in-situ* images.

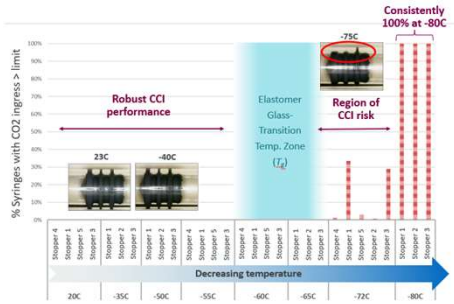


Figure 2 shows the results for the 1mL long glass syringe barrels (similar results were seen with the 1mL standard glass syringes). CCI performance was broadly equivalent across all stoppers with robust CCI above the stopper elastomer T_g and some degree of CCI loss below T_g. The *in-situ* images of stoppers in barrels at different temperatures confirm contact between the stopper ribs and barrel walls is lost at temperatures below the T_g.

Figure 3 Overall CCI results for 1mLL COC syringes with in-situ images

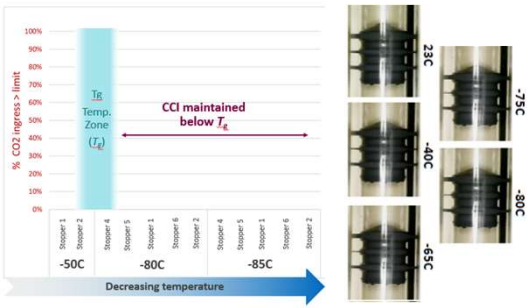
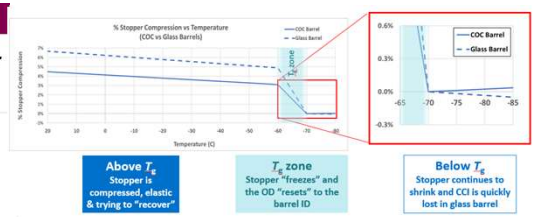


Figure 3 shows the results for the 1mLL format with COC syringes along with in-situ images showing CCI and stopper contact being maintained down to -85°C.

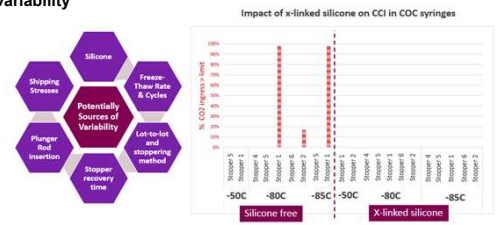
Figure 4 Approximation of the effects of passing through the stopper T_g, and the difference between glass and COC syringes



Critical material property changes occur to the stopper as the syringe passes through the T_g of the elastomer formulation (Figure 4). The stopper becomes "glassy" and loses its elastomeric properties, dramatically reducing the contact pressure between the ribs and the barrel wall. For glass syringes, this results in loss of CCI immediately below the T_g but for COC syringes it does not. This difference in behavior may be explained by shrinkage of the COC barrel at a rate faster than the "glassy" stopper (the coefficient of thermal expansion is much in the glassy state below T_g).

Numerous potential sources of variability in CCI performance were evaluated for the glass and COC syringes and different stoppers tested (Figure 5).

Figure 5 Below T_g, CCI can be impacted by sources of variability



In general, the results confirm robust CCI performance above the elastomer T_g and CCI impact around or below the T_g, particularly with glass syringes

Conclusions

- CCI can be maintained in glass PFS formats at storage temperatures above the T_g. With COC polymer syringes, CCI can be maintained at colder temperatures, with -85°C tested in this study.
- The T_g of the plunger stopper is the most critical factor in maintaining CCI in frozen storage conditions, especially for glass syringes. The material property changes that occur at this temperature result in a dramatic loss sealing contact pressure between the stopper ribs and barrel wall.
- For polymer syringes, the CTE of the COC is also an important factor. When the PFS drops below the T_g of the stopper, the CTE of the elastomer decreases so much that it becomes lower than that of the COC. This means that with further reductions in temperature, the COC barrel will shrink more than the stopper, increasing contact pressure.
- CCI must be demonstrated for all container systems during product development and commercialization under the applicable processing, shipping and storage conditions

References

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