

EVALUATION OF PISTON MOVEMENT AND CONTAINER INTEGRITY UNDER SEVERE STORAGE CONDITIONS IN PLASTIC AND GLASS PREFILLED SYRINGES

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ABSTRACT

Purpose: The shipment and storage of biopharmaceuticals in prefilled syringes (PFS) places new demands on PFS performance. Studies compared package integrity of glass and plastic PFS: piston movement was evaluated under reduced pressures to simulate transport by air in non-pressurized holds, and container closure integrity was tested on PFS that had been frozen or frozen and thawed, since some biopharmaceuticals are stored and transported in the frozen state. Piston release and travel forces were also measured in plastic PFS since in order to be competitive with siliconized glass PFS, the functional characteristics of plastic PFS must meet or exceed the criteria established for glass PFS.

Methods: To examine piston movement under reduced pressures, glass and Daikyo Crystal Zenith® (CZ) plastic 1 mL PFS were filled with water with consistent bubble size. Syringes were mounted vertically in an acrylic vacuum leak detector box which could be evacuated to a desired vacuum level. Metrics and photography were performed to gauge piston movement. Separately, container closure integrity was tested on frozen, and frozen and thawed glass and plastic syringes using a dye ingress assay. Siliconized glass and plastic 1 mL Luer Lock (LL) PFS were filled with sucrose solution and frozen at -20°C. One-half of each type was thawed before testing; the rest were tested without thawing. Piston release and travel forces in both glass and plastic LL syringes were measured on an Instron Material Testing System after filling and piston placement.

Results: Under reduced pressure equivalent to 16,000 feet altitude, pistons in neither glass nor plastic PFS moved. However, when pressure was reduced to the equivalent of 18,000 feet altitude, only pistons in glass PFS moved (9-9.5mm). When the pressure was further reduced, equivalent to 21,500 feet altitude, pistons in plastic syringes also moved. When container closure integrity was tested on filled frozen syringes, syringes made of plastic or glass did not leak. In addition, no leakage was detected in glass or plastic syringes frozen and then thawed at room temperature. Piston release and travel forces in plastic syringes remained relatively consistent during long-term storage while those in glass syringes showed more variability between syringes and greater fluctuation in both forces as a function of distance.

Conclusions: Prefilled syringe systems made of CZ plastic which utilize Flurotec®-laminated pistons are silicone-free and offer several advantages for packaging of biopharmaceuticals. The reduced pressure at high altitudes may cause piston movement and provide a pathway for microbial ingress as the piston returns to its original position when the reduced pressure is removed. Pistons in siliconized glass PFS moved readily under these conditions compared to the plastic syringe system, perhaps due to CZ's silicone oil-free feature. While both CZ and glass syringes maintained container closure integrity after freeze/thaw, plastic is break-resistant, providing advantages for low temperature storage and transport of biopharmaceuticals, and the absence of silicone eliminates the possibility of silicone-induced aggregation of sensitive biologics. In addition, the piston release and travel forces in plastic syringes remained relatively consistent during long-term storage at room temperature or at 4-8°C while those in glass syringes showed more variability, possibly due to the redistribution of silicone over time.

INTRODUCTION

In order to develop a better understanding of the mechanical properties of prefilled syringes made of CZ, we have carried out tests to evaluate the

performance characteristics of these syringes under different conditions. These data will allow potential users to decide whether CZ silicone oil-free prefilled syringes may be more advantageous than ones made from glass for their specific application. In addition, this information could help to suggest possible new uses for this versatile packaging material.

In this study we tested whether the pistons in siliconized glass and CZ prefilled syringes filled with water showed movement under increasingly reduced pressures: 8,000 feet (typical of pressurized aircraft), 16,000 feet (typical of feeder aircraft) as well as under more rigorous conditions (18,000-21,500 feet). An understanding of the effects of high altitude on package integrity has important implications for the shipment of prefilled syringes since reduced pressure could induce piston movement and provide a pathway for the ingress of airborne contaminants including microorganisms. Packaged products transported in non-pressurized holds via the feeder aircraft network can be exposed to altitudes as high as 16,000-19,000 feet and packages carried by truck over mountain passes may experience altitudes as high as 12,000 feet.

We also investigated whether CZ as well as glass syringes (a) frozen with water or (b) frozen and then thawed, maintained their container closure integrity. Demonstration of package integrity would provide pharmaceutical manufacturers with the option to store and ship labile biologics in the frozen state in syringes filled for single-dosage use rather than in vials, which are better suited for multiple dosing.

In addition to studying piston movement under reduced pressure, we compared the piston release force and travel force in LL prefilled syringes made of CZ with ones made from siliconized glass. The LL syringes were tested over a two-year time frame to assess the effect of storage on syringe performance.

METHODS

Piston Movement under Reduced Pressures

Sample preparation:

Three each of 1 mL long prefilled syringes made of siliconized glass or CZ plastic were filled with 1.1 mL Milli-Q water by drawing the liquid into the syringe through the needle. The bubble in each syringe was adjusted to a height of 2.5 mm by drawing up the plunger to admit air into the barrel and the needle cover was replaced.

Details of piston migration experiment:

The three siliconized glass or CZ syringes filled with water were mounted vertically, tip down, in the chamber of a Haug Pac-Vac Leak Detector made of acrylic (Figure 1). A vacuum pump was used to evacuate the chamber and the desired vacuum could be controlled by a valve mounted between the pump and the chamber. A vacuum gauge provided a reading of the vacuum inside the chamber in inches Hg which was converted to the equivalent altitude using a conversion chart provided in the instrument manual. In the first stage the pressure was reduced to 22.24 inches Hg (equivalent to 8,000 feet elevation). In the second stage the pressure was reduced to 13.71 inches Hg (equivalent to 16,000 feet elevation) and permitted to remain there for several minutes. The pressure was further reduced until movement of the pistons was observed. The vacuum was then released and the pressure in the chamber returned to atmospheric pressure (29.92 inches Hg). The time to complete each run was approximately 20 minutes. Photographs were taken during the entire process to document movement of the pistons. A Sony DSLR-A100 digital camera was used.

Figure 1. Haug Pac-Vac Leak Detector



Measurement of piston movement:

To estimate the distance that the pistons moved, the photographic files were downloaded into Windows Picture Viewer and magnified using the 'Zoom In' button. The pictures were printed and the ruler in each photograph was used to estimate the distance from the bottom of the piston to the liquid surface.

Determination of piston weight:

A total of 10 pistons used in CZ syringes and 10 for glass syringes were individually weighed on a Mettler Model AT261DR balance. The mean and standard deviation of the measurements were calculated automatically.

Integrity of Siliconized Glass and CZ Prefilled Syringes after Freezing

Sample preparation:

Ten each of siliconized glass and CZ 1 mL LL syringes were filled with Milli-Q water. An 18 gauge needle was used to draw 1.2 mL of liquid into each syringe and the bubble was adjusted to a height of approximately 1 mm. The needle was removed and replaced with a protective cap. The syringes were placed vertically, tip down, in plastic racks and frozen at -21°C.

Measurement of closure integrity:

Closure integrity was tested on both frozen and frozen/thawed syringes using a dye ingress assay based on conditions described in the European Pharmacopoeia 6th Edition (Section 3.2.9). Syringes were immersed in a 1 g/L solution of methylene blue R and the external pressure was reduced by 27 kPa for 10 minutes. After returning to atmospheric pressure, the syringes remained immersed for 30 minutes. The syringes were then rinsed and inspected for traces of colored solution. 5 of each set of 10 syringes were thawed at room temperature before testing while the remaining 5 were tested without thawing.

Piston Release and Travel Forces in CZ and Siliconized Glass Syringes

Sample preparation:

CZ 1 mL LL syringes and competitive glass 1-3 mL LL syringes were filled with water and the pistons were vacuum placed by Hyaluron Contract Manufacturing using SV-122 filling equipment. The target fill volume for both the syringe sets was 1.0 mL. The samples were shipped to West Pharmaceutical Services in Lionville, Pa., for evaluation. The samples were divided and stored at room temperature (RT) or 4-8°C. Syringes stored under these conditions were tested over a period of 24 months. Pistons used with CZ syringes were laminated with Daikyo Flurotec® film; pistons tested with glass syringes were silicone-coated except for the drug contact surface which was Flurotec®-laminated.

Measurement of piston release and travel forces:

The samples were tested for piston release and travel force using an Instron Material Testing System (MTS). Prior to testing, the 4-8°C samples were equilibrated for 1 hour at room temperature. The nozzle caps were removed and a B-D PrecisionGlide 27G½" needle was affixed to the nozzle end of each syringe for testing. The appropriate plunger rods were threaded into the pistons for testing and the syringes were fixed to the syringe fixture of the MTS with the needle/nozzle end positioned downward. The syringes were tested at a rate of 304.8 mm/min (12 in/min) to measure the piston release and travel (sliding) force.

RESULTS AND DISCUSSION

Piston Movement under Reduced Pressures

Under reduced pressures up to the equivalent of 16,000 feet in altitude, no movement of the pistons in the siliconized glass or CZ syringes was observed. However, when the pressure was reduced to the equivalent of 18,000 feet in altitude, the pistons in the siliconized glass syringes showed significant movement toward the flange end (Figure 2) while there was no observable movement of the pistons in the CZ syringes (Figure 3). Only when the pressure was further reduced to the equivalent of 21,500 feet in altitude was there movement of the pistons in the CZ syringes (Figure 3). When the vacuum was released, the pistons in the glass syringes returned to close to their original positions, while the pistons in the CZ syringes did not. These observations are summarized in Table I.

Figure 2. The effect of low pressure on piston movement in siliconized glass syringes

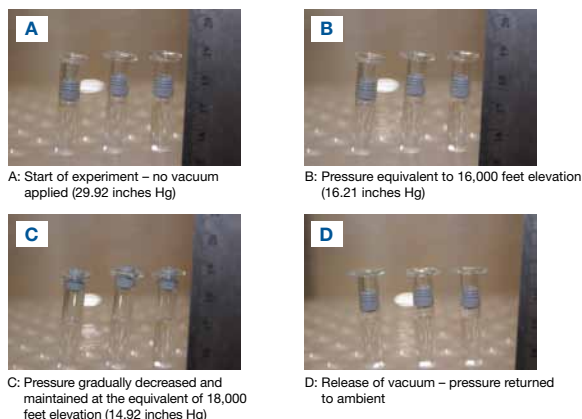


Figure 2: Glass prefilled syringes filled with water were mounted vertically in a Haug Pak-Vac leak detector. The chamber was gradually evacuated and the pressure inside the chamber was monitored via a vacuum gauge. Photographs were taken to document piston movement and the distances migrated by the pistons were measured using the ruler mounted to the right of the syringes in each photograph.

Figure 3. The effect of low pressure on piston movement in CZ syringes

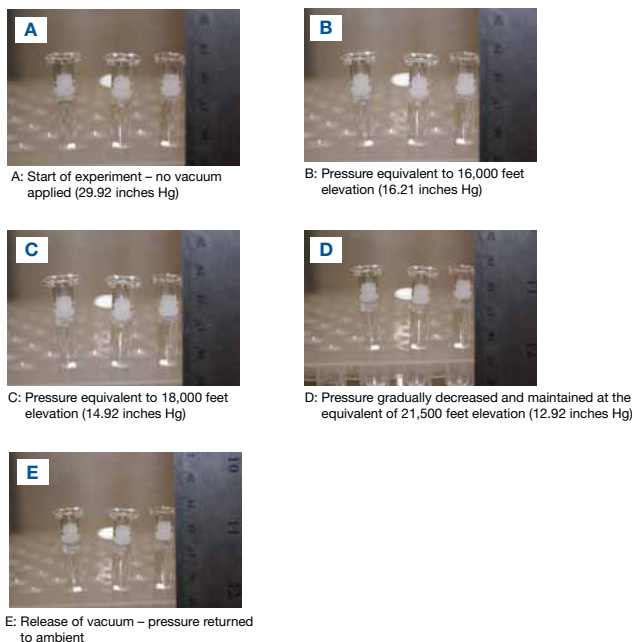


Figure 3: Plastic prefilled syringes filled with water were mounted vertically in a Haug Pak-Vac leak detector. The chamber was gradually evacuated and the pressure inside the chamber was monitored via a vacuum gauge. Photographs were taken to document piston movement and the distances migrated by the pistons were measured using the ruler mounted to the right of the syringes in each photograph.

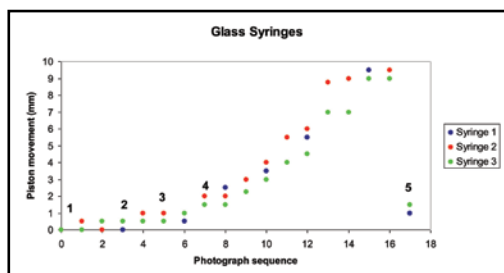
Table I: The effect of reduced air pressure on piston movement in prefilled syringes

Stage	Glass				CZ			
	Gauge (in. Hg)	Pressure (in. Hg)	Altitude (feet)	Piston Movement	Gauge (in. Hg)	Pressure (in. Hg)	Altitude (feet)	Piston Movement
I	7.68	22.24	8000	No	7.68	22.24	8000	No
II	13.71	16.21	16000	No	13.71	16.21	16000	No
III	15.00	14.92	18000	Yes	15.00	14.92	18000	No
IV	-	-	-	-	17.00	12.92	21500	Yes
V	0	29.92	0	Yes	0	29.92	0	No

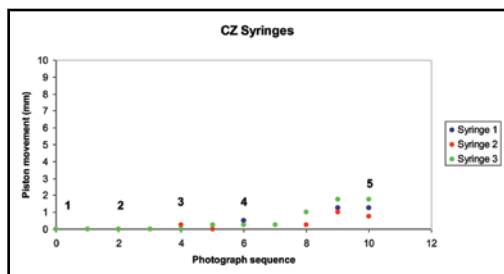
Note: The pressure in the chamber was calculated by subtracting the reading on the vacuum gauge from 29.92 inches Hg, the air pressure at sea level. The altitude corresponding to the reading on the vacuum gauge was extrapolated from a graph of vacuum gauge reading vs. altitude in the instrument manual.

To quantify piston movement in glass and CZ prefilled syringes as a function of pressure, photographs from each experiment were printed out and the distance from the bottom of the piston to the liquid surface was measured. Figure 4 shows that the pistons in the glass syringes had moved 9-9.5 mm under reduced pressure while those in the CZ syringes had moved less than 2 mm. When the vacuum was released, the pistons in the glass syringes returned to within 1.5 mm of their starting positions. The positions of the pistons in the CZ syringes, however, did not change.

Figure 4: Piston movement in prefilled syringes under reduced pressure



- 1: Starting position – no vacuum
- 2: 8,000 feet elevation
- 3: 16,000 feet elevation
- 4: 18,000 feet elevation
- 5: Vacuum released



- 1: Starting position – no vacuum
- 2: 8,000 feet elevation
- 3: 16,000 feet elevation
- 4: 21,500 feet elevation
- 5: Vacuum released

Figure 4: Glass and plastic prefilled syringes filled with water were mounted vertically in a Haug Pac-Vac leak detector which was gradually evacuated. Photographs were taken during the evacuation (see Figures 2 and 3) to record piston movement. These were printed in order to measure the distances migrated by the pistons using the ruler present in each photograph.

These results have important implications for the evaluation of prefilled syringes for use in transport of drugs by air. Since the pistons in glass syringes return to close to their original positions following repressurization, it would not be possible to determine solely by inspection whether significant movement of the pistons had actually occurred during transit. In contrast, in CZ syringes if there were a breach, one would be able to see that the piston had not returned to its original position.

The two types of pistons were weighed to determine whether less of a pressure differential was required to move the pistons in the glass syringes merely because they weighed less. However the pistons used in the siliconized glass syringes are 26% heavier (274 mg vs. 218 mg) than the pistons used in the CZ syringes. Therefore, lower weight cannot explain the relative ease of movement of the pistons in the siliconized glass syringes under reduced pressure. Movement of the pistons in the glass syringes is most likely due to the lubricating effect of the silicone coating.

Container Closure Integrity of Siliconized Glass and CZ LL Prefilled Syringes after Freezing

When container closure integrity was tested on frozen syringes using an assay based on dye exclusion, none of the five syringes made of glass or CZ showed signs of leakage. In addition, no leakage was detected in glass or CZ syringes which had been frozen and then thawed prior to testing. These results (summarized in Table II) raise the possibility that prefilled syringes can be used to both ship and store labile biologics in the frozen state. While both CZ and glass syringes maintained container closure integrity after freeze/thaw, plastic is also break-resistant, providing advantages for low temperature storage and transport of biopharmaceuticals, and the absence of silicone eliminates the possibility of silicone-induced aggregation of sensitive biologics.

Table II: Container closure integrity in Luer Lock prefilled syringes

Syringe	Passed test	
	Frozen	Frozen/Thawed
Glass	5/5	5/5
CZ	5/5	5/5

Note: Container closure integrity was determined using a dye ingress assay based on conditions described in the European Pharmacopoeia 6th Edition (Section 3.2.9).

Piston Release and Travel Forces in CZ and Siliconized Glass Syringes

The piston release and travel forces were measured in LL syringes made of glass and plastic. The force profiles shown in Figure 5 are cumulative data of the average of twenty samples at each time point, over a 24 month time period. The CZ 1 mL LL syringes exhibited a more consistent travel force than the glass 1-3 mL LL syringes after storage at RT or 4-8°C. The profiles of the glass syringes, particularly ones which were stored at room temperature, show considerable “chatter” or fluctuations in both piston release and travel forces. This phenomenon is indicative of inconsistencies in the silicone coating within the barrels of the siliconized syringes. These may be due to redistribution of the silicone with time or the presence of “dry spots,” the result of improper siliconization of the barrel (Eakins, 2009; Eakins, 2010). It is likely then, that the absence of silicone in CZ syringes results in travel forces which are more predictable and consistent over time.

Figure 5: Piston release force and travel force in CZ and glass LL syringes

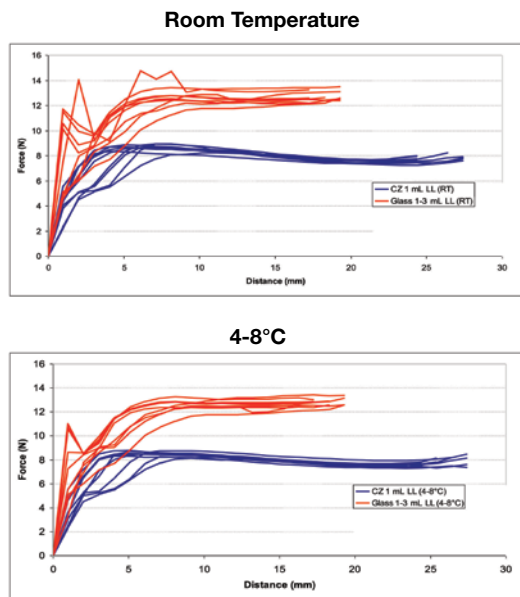


Figure 5: CZ 1 mL LL syringes and competitive glass 1-3 mL LL syringes were filled with 1 mL water and the pistons were vacuum placed by Hyaluron Contract Manufacturing using SV-122 filling equipment. The samples were divided and stored at room temperature (RT) or 4-8°C. Syringes stored under these conditions were tested over a period of 24 months, with time points at 0, 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 18 months, and 24 months. 20 syringes were tested per time point. The samples were tested for piston release and travel force using an Instron Material Testing System (MTS). Prior to testing, the 4-8°C samples were equilibrated for 1 hour at room temperature. The nozzle caps were removed and a B-D PrecisionGlide 27G½" needle was affixed to the nozzle end of each syringe for testing. The syringes were tested at a rate of 304.8 mm/min (12 in/min) to measure the piston release and travel (sliding) force.

SUMMARY

- Prefilled syringe systems made of CZ plastic were found to provide advantages over glass PFS in several tests. Most likely, these benefits can be attributed to CZ's lack of silicone and the use of Flurotec®-laminated pistons.
- Under reduced pressure equivalent to 18,000 feet in altitude, the pistons in siliconized glass syringes showed movement toward the flange end of the syringe barrel. Under the same conditions there was no movement of the pistons in CZ syringes. However, upon further reduction in pressure equivalent to 21,500 feet in altitude, the pistons in the CZ syringes showed movement. Following repressurization, the pistons in siliconized glass syringes returned to close to their original positions; the position of the pistons in the CZ syringes did not change. These results suggest that there may be less risk of microbial contamination of drug products shipped in plastic vs glass PFS.
- Syringes made of glass or plastic maintained container closure integrity after freezing at -21°C. In addition, when syringes made of glass or plastic were frozen and then thawed, container closure integrity was still maintained. This attribute will allow shipment and storage of labile biologics in the frozen state in syringes, which are better suited for single doses than vials which are preferable for multiple dosing.
- Measurement of piston release and travel forces in CZ LL syringes indicates that these forces are more consistent over time after storage at room temperature or at 4-8°C than in syringes made of glass. The fluctuations in both the piston release and travel forces, particularly in ones stored at room temperature, are indicative of inconsistencies in the silicone coating ("dry spots"), the result of improper siliconization, as well as the redistribution of the silicone layer with time. It is likely, therefore, that the absence of silicone in CZ syringes is responsible for travel forces which are more predictable and consistent over time.

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