Savillex Technical Note
Flash Freezing in Fluoropolymer Bottles

Summary

Flash freezing is the process of rapidly lowering the temperature of a liquid so that larger ice crystals do not have the chance to form. These larger crystals can potentially damage proteins and other critical components of the liquid. Flash freezing is a common process for freezing bulk drug substance (BDS) and can lead to failure of typical BDS containers.

A standard method for flash freezing BDS is to immerse it in a liquid nitrogen bath. However, few product containers are designed to survive this flash freezing. Most containers used to store BDS have glass transition temperatures well above -196°C, and many containers structurally fail during the rapid descent through the glass transition. Even worse, these failures are rarely detected until after the container is thawed, which can be days if not weeks or months after the freezing is completed.

Conversely, fluoropolymer materials typically do not change structurally after a typical flash freezing process. Therefore, a container system manufactured from fluoropolymers has the potential to not only survive flash freezing, but to continue to retain the same functionality it had when at room temperature.

This technical note outlines a study performed to test the integrity of fluoropolymer bottles being subjected to a flash freezing process down to liquid nitrogen temperatures (-196°C). The protocol was modeled after one used to flash freeze licensed biopharmaceutical products at a major pharmaceutical company. Bottles were frozen and then tested for integrity to ensure no structural breaches and no loss of closure seal. Bottles were also observed during the freezing process to ensure the bottles did not collapse; a common problem seen in bottles which lack the structural integrity required during flash freezing.

Not All Fluoropolymer Bottles are Made the Same

The container closure system of the Purillex® bottles has a superior design, which ensures a better seal and better protection of contents, even under flash freeze conditions. No cap inserts are used, ensuring single material contact with critical BDS product. The identical fluoropolymer resin is used for both the bottle and closure. Both the bottle closure and preform are injection molded, ensuring precision functionality between bottle and closure (Figure 1).

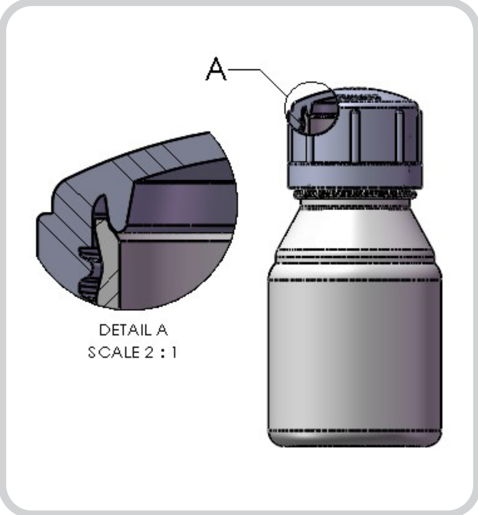

Figure 1: Injection Molded Bottle and Closure Ensures Precise Engagement and Closure Integrity

Purillex bottles are made using a proprietary two-step stretch blow molding process (Figure 2). A bottle preform is injection molded, ensuring precision closure dimensions. The preform is then blown into a bottle while protecting the neck, lip, and threads. This ensures the critical dimensions of the bottle neck are maintained, allowing a precision seal.

1. The preform is preheated and loaded into the mold
2. Stretch rod is lowered inside the preform
3. Air passes through the stretch rod, which is slowly lowered as the bottle is blown

Figure 2: Stretch Blow Molding Process

Bottle Flash Freeze Test Procedure

Fourteen 1,000 mL (1 L) Purillex PFA bottles were selected for testing from the same bottle lot. All bottles underwent a thermal pretreatment consisting of a dry heat exposure cycle at 250°C for 120 minutes. This cycle was chosen as worst-case in terms of temperature and exposure time. Two additional control bottles were also exposed to the identical cycle, then immediately leak tested to 15 psig. This was to ensure the thermal pretreatment did not, on its own, cause bottle integrity issues.

Each test bottle was filled with purified water to the minimum working volume of 200 mL and preconditioned at 21°C overnight. This volume was chosen as worst-case for headspace air; in theory, more entrapped air in the bottle will increase the likelihood of bottle integrity failure due to rapid air pressure decrease.

Bottle closures were tightened to the standard torque using a calibrated dial torque wrench. Each closure was brought to the proper torque and held at the value for 10 seconds.

Six of the test bottles were then submerged in dry ice for 24 hours. After the 24-hour exposure, each bottle was visually inspected for integrity.
Six of the test bottles were submerged in a liquid nitrogen bath for 30 minutes. After the bottles were removed from the bath, each bottle was visually inspected for integrity.

All 12 test bottles were then thawed for a minimum of 24 hours prior to leak testing.

Table 1 shows the bottles selected and the freeze cycle for each.

	Exposure	
Bottle	Dry Ice	LiN2
1		x
2	x	
3		x
4	x	
5		x
6	x	
7		
8		
9		x
10	x	
11		x
12	x	
13		x
14	x	

Table 1: Bottle Exposure Matrix

Hydrostatic Test Procedure

Note: 200 mL water remained in bottles after submersion test and was present during the integrity testing.

Each closure was drilled, and a fitting was tapped into the closure. Caution was used to ensure the closure did not loosen or tighten during drilling and fitting installation. A pressure line was attached to the fitting, the bottle was supported in an inverted position, and was pressurized to 2 psi. After a five-minute period, the threaded area was inspected using backlighting to inspect for any water droplets. The container was then pressurized to 15 psi, and after another 5-minute period, the threaded area was inspected using backlighting to inspect for any water droplets.

Results

The two control bottles tested to ensure the dry heat preconditioning process did not compromise bottle integrity passed the leak testing method. They were also inspected to ensure no physical deformity of the closure thread area.

All six bottles submerged in dry ice for 24 hours maintained integrity. All six of these bottles passed the hydrostatic leak testing method at both test pressures after submersion.

All six bottles submerged in liquid nitrogen for 30 minutes maintained integrity. All six of these bottles passed the hydrostatic leak testing method at both test pressures after submersion.

Four of the bottles (#2, 6, 10, and 14) were submerged in liquid nitrogen a second time for 30 minutes and again inspected for wall collapse. The bottles were again thawed for a minimum of 24 hours and hydrostatically tested at 2 and 15 psig using the test method described above. All four of the bottles maintained integrity and again passed the hydrostatic leak testing method at both test pressures.

Conclusions

Evidence from this test protocol indicates that Savillex 1 L Purillex PFA bottles are suitable for dry heat sterilization at 250°C for 120 minutes and then flash freezing down to liquid nitrogen temperatures (-196°C) with no bottle collapse and no loss of bottle integrity. Several of the tested bottles passed integrity testing after exposure to a second flash freezing cycle.

This is a testament to the structural durability of fluoropolymer materials when exposed to temperature extremes. It is also illustrative of the strength and reliability of the Purillex bottle seal technology.

Savillex
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