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RESEARCH

Failure of Glass Tubing Vials during Lyophilization

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ABSTRACT Lyophilization is a commonly used and often preferred method for preparing certain drug products. In this process, the liquid pharmaceutical product is packaged in glass vials, frozen, and then dried via sublimation at low pressures. One problem that can be encountered during lyophilization is the occasional failure of the glass vial, a condition that will be referred to in this paper as "lyo-breakage." Lyo-breakage, while relatively rare, can be a serious problem, as it results in lost product, additional costs to remediate any spillage, and inspection time to ensure that all broken vials are discarded. Some companies have suggested that lyo-breakage is related to thermal stress and, subsequently, can be reduced through changes to the thermal properties of the vials. In this paper, we will show that when the most common form of lyo-breakage occurs, the stresses in the glass are caused by an internal force from product expansion during freezing and not due to thermal stress from processing temperatures.

KEYWORDS: Borosilicate glass, Fracture diagnosis, Fracture patterns, Lyophilization, Thermal shock, Internal force.

LAY ABSTRACT: Lyophilization, or freeze drying, is often the preferred method for preparing certain drug products following manufacture. In this process, the liquid pharmaceutical product is packaged in a small glass cylindrical container called a vial, frozen, and then dried at low pressures. One problem that can be encountered during lyophilization is the occasional failure of the glass vial. While relatively rare, this failure can result in lost drug product, additional costs to clean up any spillage, and increased inspection time to ensure that all broken vials are discarded. The data presented in this paper demonstrate that when the most common form of lyophilization-associated breakage occurs, the stresses in the glass are caused by an internal force from drug product expansion during freezing and not due to thermal stress on the glass from processing temperatures.

Introduction

Lyophilization consists of changing a liquid pharmaceutical product into a dry solid "cake" by means of a freeze/dry process. This involves reducing the temperature of the liquid content in a glass vial over a period of several hours while holding the vial at atmospheric pressure. Once the liquid product is frozen, the pressure surrounding the vial is reduced to a relatively low value and a slight amount of heat is added to sublime the frozen water. The temperature and pressure are then returned to normal atmospheric values to complete the drying process. Occasionally, there can be a problem with failure of the vial (either cracking or complete breakage) during this process, and that failure will be termed "lyo-breakage" in this paper. The process during which this type of failure occurs is the same as what others in the literature have termed "freeze–thaw" breakage (1).

It is possible that lyo-breakage can occur on both molded and tubing vials, although the preponderance of problems that we have encountered is with broken tubing vials. We anticipate that this is not necessarily related to the physical characteristics of tubing vials compared to molded vials but rather to the predominant use of tubing vials for pharmaceuticals that undergo the lyophilization process.

Properly diagnosing the cause of vial failures is complicated, as there can be several distinctly different types of breakage occurring during lyophilization. These breakage types have different causes and require different corrective actions. This paper will focus on the more common type of lyo-breakage of

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Figure 1

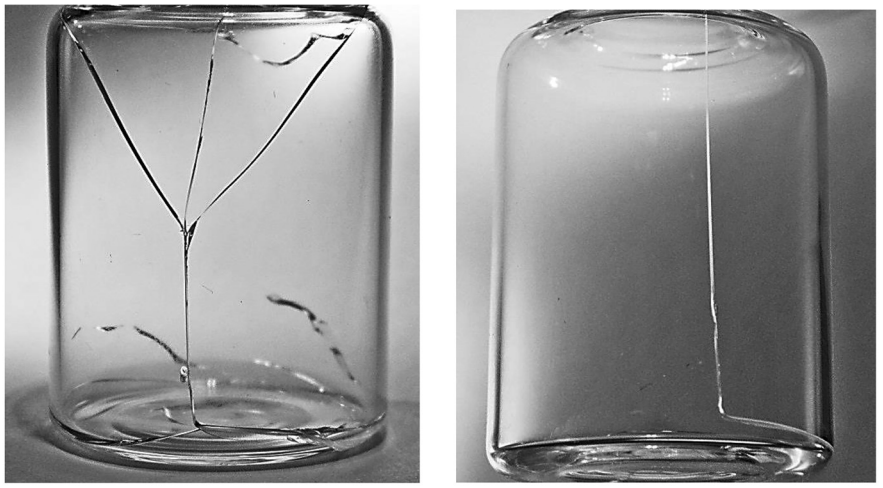
Lyo-breakage: typical fracture patterns from commercial practice.

tubing vials, which, in our experience with fracture diagnosis of vial breakage during lyophilization, manifests in a majority of instances by the fracture pattern shown in Figure 1. This pattern is characterized by a vertical fracture in the lower sidewall region sometimes with forking above and/or below the origin site, which occurs on the outside glass surface.

Lyo-breakage has been investigated to some extent in previous studies. In 1993, this type of breakage was attributed to differences in the coefficient of expansion of the frozen product in comparison to the glass vial (2). More recently, this type of breakage was attributed to the number of degree-hours of subzero exposure of the vial during lyophilization (3). A thorough study involving detailed testing was undertaken using a strain gage that was mounted to a vial and subjected to a simulated lyophilization cycle (1,4). These studies quantified the existence of a significant strain in the glass during both freezing and subsequent thawing of the product that was created by a notable expansion of the frozen pharmaceutical product.

While previous published papers and our laboratory experience have provided information relative to the failure of glass vials during lyophilization, some misconceptions in the industry exist about the manner in which lyo-breakage occurs. For example, lyo-breakage is sometimes ascribed to outward-directed forces related to the expansion of the frozen product against the inside surface of the glass vials. Other times, breakage is attributed to thermal differentials that are assumed to occur between the inside and outside glass surfaces during lyophilization.

The purpose of this paper is to offer a definitive explanation of the forces that are acting on the glass vials when the more common type of lyo-breakage occurs. This explanation will be based on studies of the fracture patterns that are observed on vials after breakage. Fractography is a well-known and valued means of understanding the forces that are involved in any glass article at the time of failure. When forces act on a glass object, the glass elastically deforms (strain), which in turn results in the creation of both compressive and tensile stresses. These stresses are uniquely distributed in the glass depending on design factors, glass thickness distribution, and the type of force being applied to the object. Glass only fails under the influence of tensile stresses, and cracks will propagate in directions normal to the distribution of the tensile stresses. Thus, the crack pattern will be unique to the type of force that was acting on the glass object at the time of failure and can be used to identify the force after the fracture event.



a) Failure at relatively high pressure

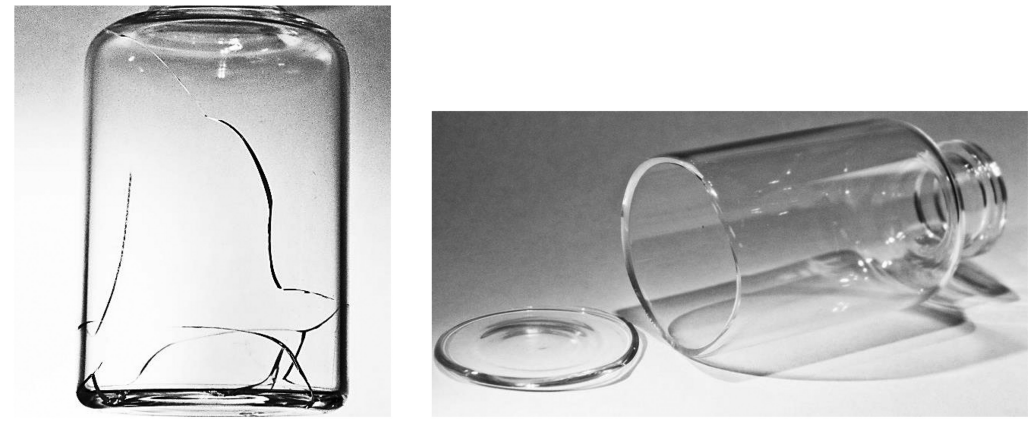
b) Failure at relatively low pressure

Figure 2

Examples of vials that failed due to an internal pressure force.

Examples of different crack patterns of broken glass vials are shown in Figures 2 and 3. The vials in Figure 2 were broken by an internal pressure force that was created by filling the vials to overflowing with water and subjecting the filled vials to hydraulic pressure. The pressure was initially low and was increased until the vial failed. The fracture pattern consisted of a vertical crack that could exhibit branching above and below the precise location where the fracture originated. The vial in Figure 2A exhibited extensive fracturing, which is typical of relatively high pressures. The vial in Figure 2B failed at a much lower pressure and exhibited a relatively simple pattern consisting of only a straight vertical crack with looping in the lower end.

The vials in Figure 3 were broken by a thermal shock force that was created by vials that had been heated in an oven and then immersed in a cold-water bath. The fracture pattern consisted of many meandering cracks



a) Failure at relatively high temperature differential

b) Failure at relatively low temperature differential

Figure 3

Examples of vials that failed due to a thermal shock force.

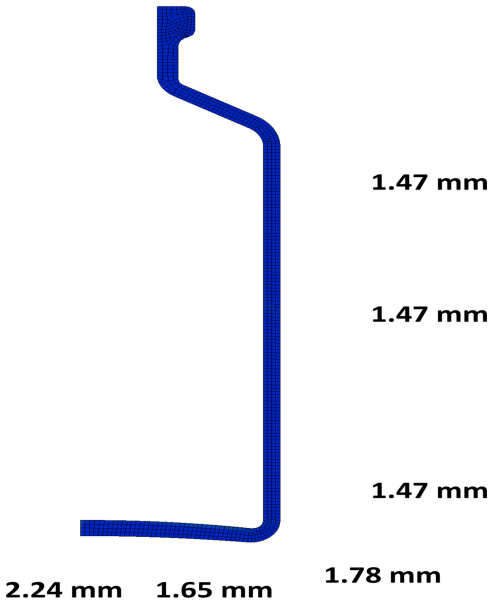


Figure 4

Glass thickness distribution.

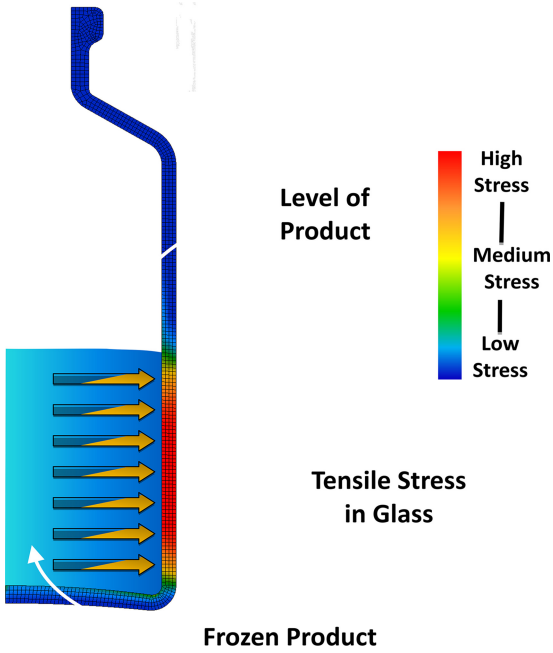


Figure 5

Finite element analysis of tensile stress pattern due to expansion of frozen product.

throughout the sidewall and base regions. The vial in Figure 3A exhibited extensive cracking in the sidewall indicative of a relatively high temperature differential at the time of failure. The vial in Figure 3B failed at a much lower temperature differential and exhibited a relatively simple pattern consisting of only a single circumferential crack around the base of the vial.

Discussion

Based on the fracture diagnosis techniques summarized in the published literature (5–8) and as shown by the examples in Figures 2 and 3, it was concluded that the fracture patterns shown in Figure 1 are uniquely characteristic of breakage caused by a force applied to the inside surface of a vial causing it to expand outward. To confirm this conclusion, a finite element computer stress analysis (FEA) of a tubing vial that had been produced under normal commercial operations was undertaken. The profile and glass thickness distribution of the vial used in these analyses is shown in Figure 4. In these analyses, a 3D symmetrical model was created using Solidworks, and the model was then imported into Autodesk® Simulation for the purpose of performing the FEA. The horizontal force simulated the expansion of water when it freezes into ice. The results of the FEA in Figure 5 show that the outward expanding force generates tensile stresses of nearly equal magnitude on both the inside and outside glass surfaces consistent with the expansion of a thin-walled cylinder in which the thickness is much less than the cylinder diameter. Fracture origins will occur in this region on the outside surface owing to a greater likelihood of having flaws of sufficient severity on this surface compared to the inside surface, consistent with previous findings (2).

Fracture diagnosis of origins from numerous 51 expansion borosilicate tubing vials that broke during typical commercial lyophilization has shown that the tensile breaking stresses range from 27.6 to 69.0 MPa, as determined from measurements of the physical dimensions of fracture origin mirrors (5) and as shown in Figure 6. The relationship between the dimensions of a fracture mirror and the breaking stress, σ in MPa, is given in Shand's book (9):

$$\sigma = 1.87/r^{1/2} \quad (1)$$

where r in meters is the mirror radius (1/2 of the mirror diameter) as shown in Figure 6. The proportionality constant, 1.87 MPa/$m^{1/2}$, is for borosilicate glass, which is being considered in this example.

The breaking stresses that were calculated from fracture analysis of vials that were broken in normal

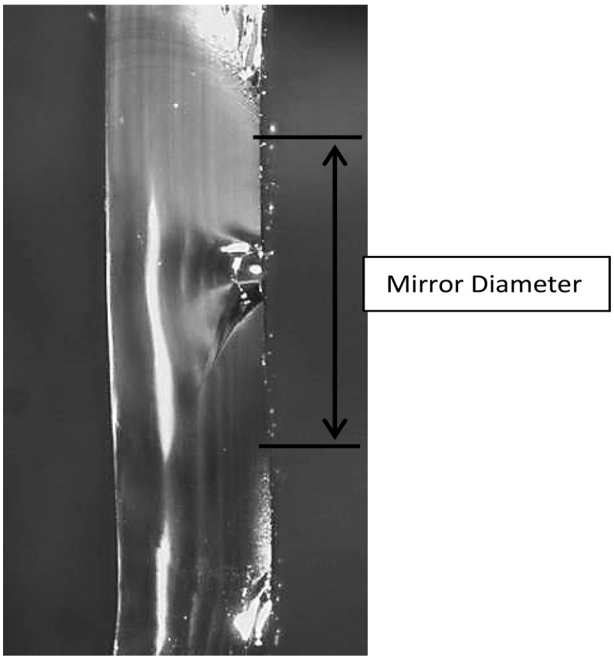


Figure 6

Fracture origin mirror from a lyo-breakage vial.

lyophilization are on the same order of magnitude as the stresses calculated from the data of Milton (4) and Jiang (1). Based on their measured strain levels and assuming the use of borosilicate glass, stress levels ranging from 20.0 to 29.0 MPa were calculated, which they attributed to the expansion of the frozen product. Thus, the fracture pattern and the breaking stresses indicate that the most likely cause for the most common form of lyo-breakage is from the outward expansion of the frozen product.

Even with this information, it is necessary to consider the assertion that lyo-breakage is caused by stresses generated by temperature gradients that are assumed to be created during the lyophilization process. If a thermal gradient were the major factor that caused lyo-breakage, the fracture pattern would consist of meandering cracks in the sidewall and bottom regions with origins that would most likely be located on the outside glass surface in the bottom or heel areas as discussed in the literature (5,7,8) and as shown in Figure 3. This is in direct contrast to the fracture pattern that is observed for vials that break during commercial operations as shown in Figure 1.

Breaking stresses from thermal gradients were also considered relative to the failure of glass vials during lyophilization. For a rapid change in the surface temperature of a thin-walled cylinder (10), the magnitude of stress that is generated in the glass, σ, is given by:

$$\sigma = E\alpha\Delta T/2(1 - \acute{\upsilon}) \quad (2)$$

where E is Young's modulus of the glass, α is the coefficient of thermal expansion of the glass, $\acute{\upsilon}$ is Poisson's ratio, and ΔT is the temperature difference between the outside and inside glass surfaces. Rearranging this equation to create a stress index value (stress generated per unit temperature difference) gives:

$$\sigma/\Delta T = E\alpha/2(1 - \acute{\upsilon}) \quad (3)$$

For a typical 51 expansion borosilicate composition that is used for pharmaceutical tubular vials, E is 69.0 GPa, $\acute{\upsilon}$ is 0.22, and α is 51×10^{-7} cm/cm/°C. Using these values in eq 3 gives a stress index value of 0.23MPa/°C. This stress index value can be used to calculate the temperature differential that would be required to cause failure if the glass strength is known or it can be used to calculate the magnitude of stress that would be generated in the glass if the temperature differential is known.

During a normal lyophilization process, vials filled with a pharmaceutical product are placed on shelves inside a lyophilization chamber. Refrigerant, such as liquid nitrogen, passes through cavities in the shelves, slowly cools the bearing surface region of the vials via conduction, and cools the environment surrounding the filled vials via convection. Because the total cooling time of a filled vial from room temperature to approximately −40°C typically requires a few hours to complete, it is assumed that any temperature gradients that might be created in the glass between the inside and outside surfaces of the vials would be very small.

To test this hypothesis, eq 3 was used to estimate the temperature gradient that would be required to generate the stress magnitudes that have been observed for numerous commercial breakage incidents. To achieve a total breaking stress of 27.6 MPa, a temperature differential of 125°C between the inside and outside surfaces of the glass vial would be required. For a breaking stress of 69.0 MPa, a temperature differential of 314°C would be required. It is unlikely that such high temperature gradients would be generated in the glass due to the manner in which filled vials are slowly cooled in normal commercial lyophilization processes.

Thus, the expected fracture pattern and the overall magnitude of stress for thermal gradient breakage are inconsistent with the observations of commercial practice.

Laboratory Tests

As a means of further investigating the load types that can lead to lyo-breakage, three laboratory tests were performed. In all tests, 51 expansion type borosilicate tubing vials of 70 mL capacity were used. These samples had been selected from commercially produced tubing vials exhibiting the design shown in Figure 1 and with normal thickness profiles for the sidewall and bottom regions as shown in Figure 4. To normalize and control the glass surface strength during these tests, the entire outside sidewall and bottom surfaces of the vials were first manually abraded with emery paper consisting of 150 grit silicon carbide particles. This abrasion results in a glass surface strength of approximately 28 MPa for the load durations that were encountered in these studies (11).

Freezer Test

Abraded vials were divided into two groups of 24 samples each. In the first group, 40 mL deionized water was introduced into the vials, and the vials were left unclosed. In the second group, the vials were empty and unclosed. Both groups were placed into a freezer (−18°C) for 6 h, a time and temperature that were sufficient to solidly freeze the water in the filled vials as noted by visual observations.

Under these test conditions, the filled vials experienced an outward-directed force on the inside glass surface that was created by the expansion of the water as it froze. It was assumed that thermal gradients would be miniscule since the temperature change of the vials would be very gradual, and the inside and outside glass temperatures would remain essentially equal during the entire time period. The unfilled vials experienced no physical or significant thermal stresses.

After storage, the vials were removed and visually inspected for the presence of cracking or complete failure. Twenty-three of the filled vials broke during this test, and all broken vials were examined to document the extent and nature of the fracture pattern. None of the unfilled vials failed.

Liquid Nitrogen Immersion Test

Abraded vials were divided into two groups for these tests. For the first group, 40 mL deionized water was introduced into five vials, which were left unclosed. The second group consisted of eight vials that were empty and unclosed. Both groups were physically held by the finish and were individually immersed up to the lower neck region in liquid nitrogen (−196°C) for 3 min. During immersion, care was used to assure that none of the liquid nitrogen was allowed to enter the unclosed finish of the test vials. It was visually observed that the water in the filled vials froze in about 2 min of this time interval.

Under these test conditions, the filled vials experienced an outward-directed force on the inside glass surface that was created by the expansion of the frozen water and a substantial thermal shock proportional to a temperature differential of 217°C (room temperature vials, at 21°C, immersed into liquid nitrogen, at −196°C). The unfilled vials experienced only a substantial thermal shock.

After testing, the vials were removed and visually inspected for the presence of cracking or complete failure. Two of the filled vials broke during this test, and both of them were examined to document the extent and nature of the fracture pattern. None of the unfilled vials failed.

Oven to Water Bath Test

Because this test initially involved heating the vials to elevated temperatures, all of these tests were undertaken with empty, unclosed vials. The vials were placed into an oven at 218°C. After 30 min, the vials were individually removed and, within 3 s, transferred by the finish and physically held in a room temperature water bath (21°C) for 30 s with the water level at the lower portion of the neck. Care was taken to assure that water did not enter the open portion of the vials during testing. Four vials total were used in this test.

Under these test conditions, the vials experienced a substantial thermal gradient of 197°C (heated vials, at 218°C, immersed in room temperature water, at 21°C) but no outward-directed mechanical force, as the vials were empty.

After testing, the vials were removed and visually inspected for the presence of cracking or complete

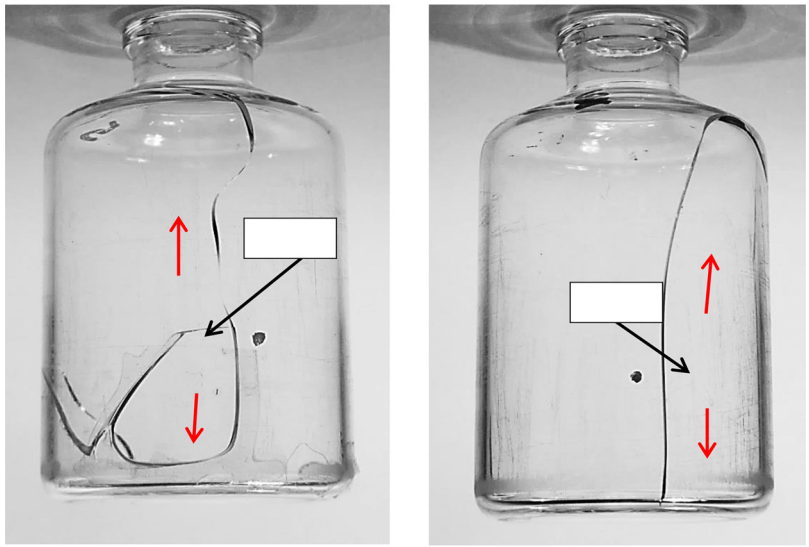


Figure 7

Typical fracture pattern from freezer test breakage.

failure. All four vials broke during this test, and they were examined to document the extent and nature of the fracture pattern.

Results of Laboratory Tests

Freezer Test (Outward-Directed Force Only)

Of the 24 filled vials, 23 failed, and a representative example of the fracture pattern is shown in Figure 7. These failures occurred only after the vials had been in the freezer for sufficient time for the water to freeze. None of the vials failed within the first few minutes of insertion into the freezer. In addition, there were no failures of the 24 empty vials, indicating that the thermal stresses experienced by the vials were miniscule (less than the surface strength of the abraded glass).

The breakage pattern shown in Figure 7 consisted of a single vertical sidewall fracture with a fracture origin on the outside glass surface in the lower sidewall area consistent with the superposition of tensile stress created by the expanding ice with the surface damage created by the emery paper abrasion. This fracture pattern was identical to the pattern that is typically observed on the most common type of breakage that occurs during lyophilization as shown in Figure 1.

Liquid Nitrogen Immersion (Combination of an Outward-Directed Force Plus a Significant Thermal Gradient)

None of the eight empty vials failed, indicating that the thermal stresses did not exceed the surface strength of the abraded vials and therefore were relatively low in magnitude. Two of the five filled vials failed, and a representative example of the fracture pattern of the vials that broke in this test is shown in Figure 8. This fracture pattern was the same as was observed for the freezer test (Figure 7). It was noted during this test that the failures occurred at about 2 min of immersion when the water had frozen, thereby exerting an outward force on the vial. During the first minute of immersion when the thermal shock would be the greatest and the water had not yet frozen, no failures were noted. Thus, based on the visual observations and on the similarity of the fracture pattern to the freezer test, it was concluded that the outward expansion force of the frozen water was the sole cause of failure in this test, and thermal stresses did not contribute to the breakage.

Oven to Cold Bath Thermal Shock Test (Thermal Gradient Only)

A representative example of the fracture pattern of the four vials that broke in this test is shown in Figure 9. The fracture pattern was very complex and consisted of numerous meandering fractures in the sidewall

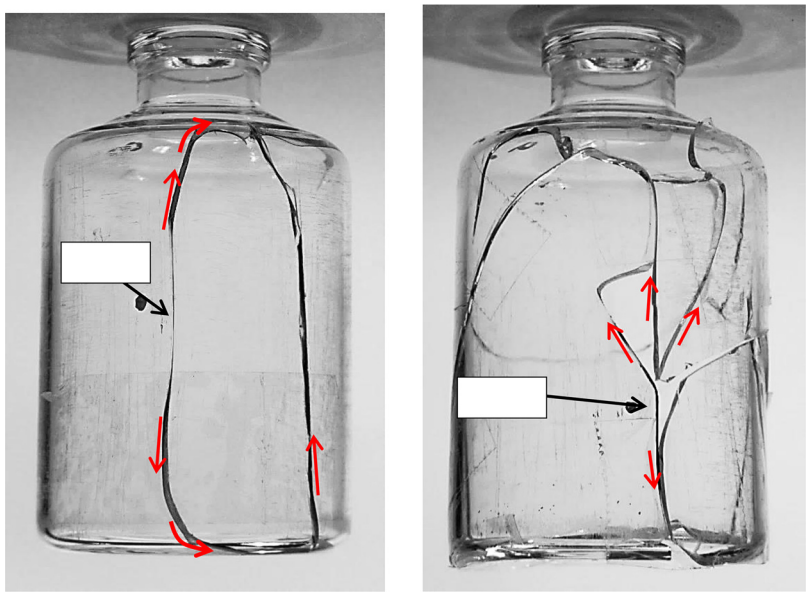


Figure 8

Typical fracture pattern from liquid nitrogen immersion breakage.

region plus a circumferential crack around the bearing surface. This fracture pattern substantially differs from the pattern that was observed in the previous two laboratory tests (see Figures 7 and 8) and from the fracture pattern that is typically observed in the most common form of lyo-breakage that occurs during commercial practice, as shown in Figure 1. The fracture pattern observed in this test was consistent with the unique pattern that is expected from failures due to the creation of a thermal gradient between the inside and outside glass surfaces as noted in the literature (5) and as observed from the exemplar fracture pattern in Figure 3.

Conclusions

Based on the nature of the fracture patterns, on the measured breaking stresses of tubing vials that fail during commercial lyophilization, and on the calculated stress values from thermal differentials, it was

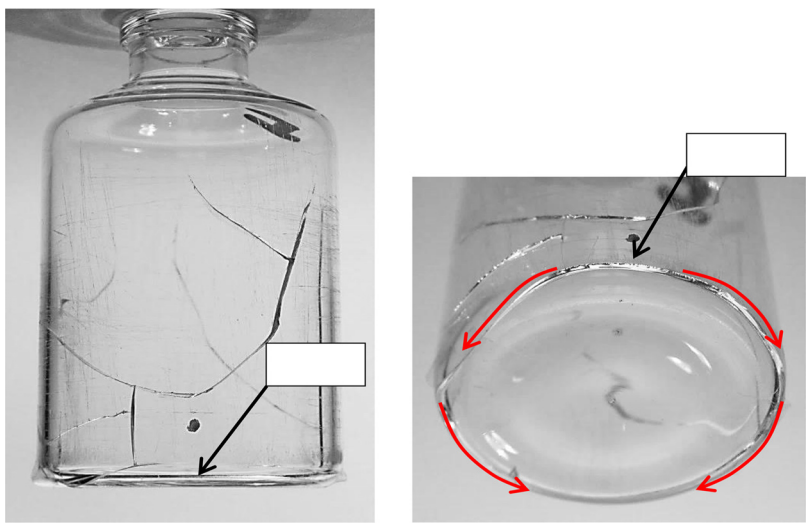


Figure 9

Typical fracture pattern from oven to cold-water bath test breakage.

concluded that the common type of lyo-breakage discussed in this paper is due to the outward expansion force generated by the frozen pharmaceutical product and not due to thermal gradients. Thus, changes to the thermal properties of the glass vials (design changes to the vials or the use of glass having a lower coefficient of thermal expansion) are unlikely to make any significant difference in the frequency of breakage that may be experienced in typical lyophilization processes.

Solutions to lyo-breakage can be best realized by performing detailed fracture analyses. Such analyses will clearly differentiate the cause of breakage as either due to excessively high forces due to the expanding product or due to low glass strength caused by problems during vial production, transportation, or filling.

Conflict of Interest Declaration

The authors declare that they have no competing interests.

References

1. Jiang, G. E.; Akers, M. Mechanistic Studies of Glass Vial Breakage for Frozen Formulations I. *PDA J. Pharm. Sci. Technol*. **2007**, *61* (6), 441–451.

2. Williams, N. A.; Guglielmo, J. Thermal Mechanical Analysis of Frozen Solutions of Mannitol and Some Related Stereoisomers. *PDA J. Pharm. Sci. Technol.* **1993**, *47* (3), 119–123.

3. Chow, E. J.; Kitaguchi, B.; Trier, M. Effects of Subzero Temperature Exposure and Supercooling on Glass Vial Breakage. *PDA J. Pharm. Sci. Technol*. **2012**, *66* (1), 55–62.

4. Milton, N.; Gopalrathnam, G.; Craig, G. D.; Mishra, D. S.; Roy, M. L.; Yu, L. Vial Breakage during Freeze-Drying: Crystallization of Sodium Chloride in Sodium Chloride-Sucrose Frozen Aqueous Solutions. *J. Pharm. Sci*. **2007**, *96* (7), 1848–1853.

5. Quinn, G. D. *Fractography of Ceramics and Glasses*; Special Publication 960-16e2; National Institute of Standards and Technology: 2007; Chapters 4, 5, 7.

6. ASTM C1678–10: Standard Practice for Fractographic Analysis of Fracture Mirror Sizes in Ceramics and Glasses, March 2010.

7. Bradt, R. C.; Tessler, R. E. *Fractography of Glass*; Plenum Press: 1994; pp 207–252.

8. Lomax, J. Fracture Analysis as an Aid to Quality Improvement. *Glass,* March, **1972**, 1–6.

9. Mecholsky, J. J.; Rice, R. W.; Freiman, S. W. Predictions of Fracture Energy and Flaw Size in Glasses from Measurements of Mirror Size. *J. Am. Cer. Soc*. **1974**, *57* (10), 440.

10. Shand, E. B. *Glass Engineering Handbook*; McGraw-Hill Book Co.: New York, 1958; p 112.

11. Mould, R. E.; Southwick, R. D. Strength and Static Fatigue of Abraded Glass Under Controlled Ambient Conditions: II Effect of Various Abrasions and the Universal Fatigue Curve. *J. Am. Cer. Soc*. **1958**, *42* (12), 582.

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