CORNING
Valor® Glass

TECH NOTE

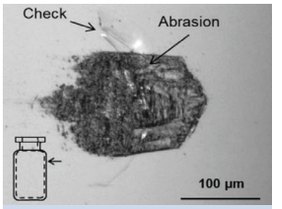
Description of Particulate Defects in Glass Containers by Mechanism of Formation

Parenteral products are expected to be "essentially free" of particles[1], however, products are recalled each year for particle-related issues.[2] Regarding glass containers, there are five primary mechanisms that produce particles that can be considered either mechanically-derived or chemically-derived.[3 4] By understanding the formation mechanism of the various particles generated from glass containers, drug manufacturers can more accurately identify solid defects and choose the appropriate response to reduce their occurrence and and reliably deliver safe and effective parenteral products to patients.[5]

MECHANICALLY-DERIVED PARTICLES

Mechanically-derived particles are created during the manufacturing and processing of glass containers by physical contact and mechanical forces. Frictive and normal forces exerted upon the containers throughout the entire pharmaceutical filling process may generate glass particles, glass fragments, and/or chips from abrasions or breakage.[6 7]

Glass Abrasions	
Mechanism	Glass particles due to abrasion from blunt frictive damage
Size	Subvisible to visible
Frequency	For bulk applications with high contact, if abrasions are present, they will exist and be consistent across most containers.
Location	Any – inside or outside
Composition	Composition of the glass container
Examples	Glass-to-glass contact or glass-to-material contact during glass production, converting process, transit, and on pharmaceutical manufacturing lines. In addition to the particles generated, surface abrasions or flaws can lead to cracks and breakage.
Mitigation Techniques	Particle generation, due to abrasion, can be minimized by improvements to packaging, adjustments to the manufacturing line (to reduce glass-to-glass or glass-to-metal contact and/or applied loads), and application of protective coating of the container exterior.



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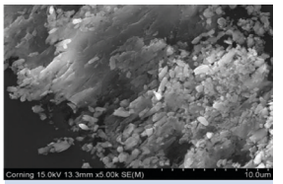
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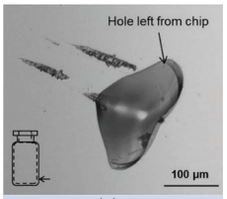
Figure 1: Optical microscope image (a) shows abrasion, chatter checks on the exterior glass surface, and SEM image (b) shows the morphology of the abraded small glass particles as a result of glass-to-glass contact.

Glass Particles/Chips Due to Breakage	
Mechanism	Glass breaks due to the presence of surface flaws and application of stress during tube forming, tube-to-container converting, or pharmaceutical filling operations creating glass particles and/or chips.
Size	Small subvisible particles to large visible chips
Frequency	Sporadic
Location	Any – inside or outside
Composition	Composition of the glass container
Examples	Non-smooth flow of containers or increased line pressure resulting in application of stress on containers on filling lines. Misaligned or damaged equipment (e.g., filling needle strikes on the flange, bent rails on capping machine) may result in impact to the container.
Mitigation Techniques	The tube forming and container converting processes must be optimized to minimize the generation of glass particles. Pharmaceutical filling lines may be adjusted to ensure proper sizing and smooth flow of containers. Utilize high strength containers produced by state-of-the-art converting and chemical strengthening processes. Fewer particles are produced by containers that reduce damage using low coefficient of friction exterior coatings.



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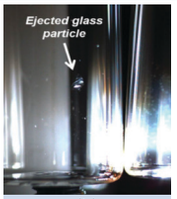

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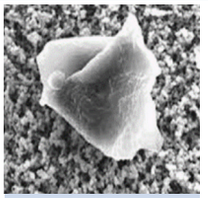
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Figure 2: Image (a) shows representative damage of missing glass chips on the surface of a glass vial processed on a conventional bulk filling line. Image (b) shows a glass particle ejected from the inner surface during vial-to-vial impact. Image (c) shows an SEM micrograph of a glass particle deposited on filter paper.

CHEMICALLY-DERIVED PARTICLES

Particles can be produced in glass containers by chemical interactions between the glass surface and the solution it holds. Some factors that influence the production of these particles include: the drug product, solution pH, processing conditions, altered glass surface chemistry, contamination, and others.[8 9]

Delamination of Chemical Heterogeneity	
Mechanism	Delaminated flakes (or "lamellae") result from preferential corrosion of glass surface heterogeneities that were produced during the converting process. The interaction of these low durability regions with the drug formulation may result in altered reaction zones that eventually detach and release into solution.
Size	Subvisible to visible flakes with a high aspect ratio (typically thinner than 1µm up to several hundred microns wide)
Frequency	Sporadic
Location	Lamellae may be present in solution or adhered to the strongly heated tubular container inner surface (e.g., heel).
Composition	Typically alkali-depleted, hydrated silica-rich flakes
Examples	Corrosion of lower-durability heterogeneities are typically produced in the heel of a tubular borosilicate vial during converting. Any solution especially corrosive to low durability region (acid, base, or neutral) may cause the low durability region to delaminate.
Supporting Details	Although many factors influence the occurrence of delamination, a container that is susceptible to delamination will contain regions of altered surface chemistry on the inner surface. Typically, these heterogeneities are enriched in sodium and boron at the surface. The propensity for a glass container to delaminate can be evaluated by determining the chemical durability ratio (CDR).[10]
Mitigation Techniques	It is important to select a container with uniform internal surface chemistry such as one formed in molded process. Another option is an aluminosilicate glass container that eliminates the risk of delamination through the removal of boron from the glass composition.

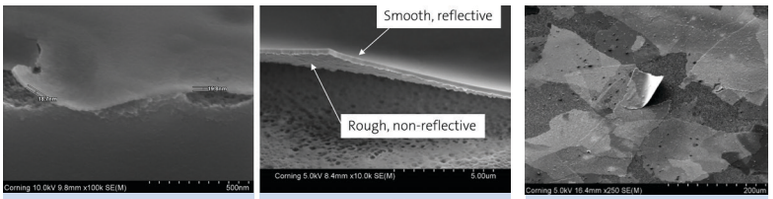


Figure 3: SEM images (a&b) of delaminated flakes attached to the glass wall in the heel area. The top surface is smooth, reflective and the underlying surface is rough, non-reflective. SEM image (c) of delaminated flakes from a 10mL tubular Type I borosilicate vial, separated from the test solution onto filter paper. Flakes were produced using the ALF procedure recommended by Sloey.[11]

Chemical Precipitation	
Mechanism	The formation of inorganic particles is possible when solutions are saturated with components of the precipitating phase.
Size	Subvisible to visible
Frequency	Consistent across many containers, detected during initial compatibility screening
Location	May be in solution and/or on container walls
Composition	Elements in ratios that differ from the composition of the container glass, and may contain API or excipients.
Examples	When elements are present at high concentrations, precipitates (e.g., Ba_2SO_4, $MgAl_xSi_yOH_z$) may form. The particles will have different elemental ratios than the bulk glass (e.g., high Mg / Si ratio relative to bulk glass) and may contain API or excipients.
Supporting Details	Precipitates form when solutions become saturated with respect to the components of the precipitating phase. These components may be contributed from various sources (e.g., sulfate from excipient, Al from stopper, Ba from glass). If the precipitate contains components of the drug product (API or excipient), it may be termed compound. Temperature changes affect solubility relationships and can prompt a stable solution at room temperature to form precipitates upon cooling. Precipitated particles may be crystalline or amorphous and may assume flake-like, high-aspect morphologies like delamination flakes. Precipitate phases can be distinguished from delamination by monitoring for declining solution concentrations of key elements over time, or comparing elemental ratios relative to the parent glass.
Mitigation Techniques	Select a container with uniform surface chemistry that is chemically durable to acids and bases. Do not overly accelerate screening studies relative to product use conditions (e.g., pH, temperature). Choose ingredients and components (e.g., excipient, stopper, glass) that release less of the precipitating elements.

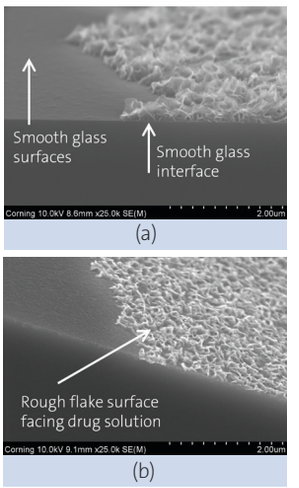
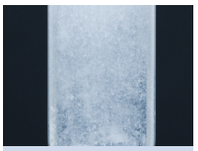


Figure 4: SEM image of a vial interior surface after exposure to a pH 11.6 solution for 28 days at 60°C with a precipitated deposit intact. This precipitate is deposited from the corroding solution onto the glass surface in all regions of solution contact (not localized to the heel region as with delamination). Image (a) is a tubular vial and image (b) is a molded vial.



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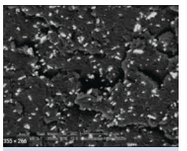

(b)

Figure 5: Image (a) barium sulfate $BaSO_4$ precipitates appear as a fine white haze during optical inspection. Electron micrograph (b) of barium sulfate from PEEK Biomaterials Handbook, 2012.[12]

Poor Glass Durability	
Mechanism	The interaction occurs over the entire container surface in contact with the solution. The result is a surface of altered chemistry (e.g., hydrated, silica-rich regions) which is detached and released into solution. This type of failure is distinguished from "delamination" as it is a result of generally low durability of the glass composition and entire inner glass surface regardless of the forming process.
Size	Subvisible to visible flakes (up to several hundred microns)
Frequency	Uncommon but affects the entire lot of glass, detected during initial compatibility screening
Location	The entire inner surface in contact with solution is at risk.
Composition	Varies; typically alkali-depleted, silica-rich flakes
Examples	A soda lime container filled with strongly basic solutions at elevated temperatures may result in the generation of these flakes.
Supporting Details	This failure occurs with the combination of insufficient durability of the glass composition and aggressively corrosive formulations.
Mitigation Techniques	It is important to select a container with high acid resistance and high alkali resistance.

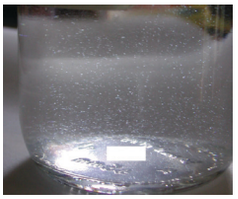

Figure 6: Image of flakes in a low durability Type II infusion molded bottle with suspension of brilliant, needle-shaped flakes after extraction with 0.9% KCl solution at 121 C for 1 hour.[13]

CONCLUSION

Particles in parenteral drugs are undesirable, and it is important to distinguish particles generated in glass containers by their formation mechanism. Particles may be mechanically-derived or chemically-derived. The risk of generating each type of particle can be mitigated by understanding the specific mechanism of formation. Chemically strengthened aluminosilicate glass containers with an external, protective, low-friction coating eliminate the risk for delamination, reduce the risk of damage and breakage, and enable smoother movement through filling lines.

FOR MORE INFORMATION OR ADDITIONAL INQUIRIES

please reach out to pharma@corning.com or visit www.corning.com/valor.

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