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## Review Article

# Glass Delamination in sterile formulations and Drug Recalls: A Review

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## Abstract

Injectable formulations are constantly facing continuing challenges of glass compatibility. To assure glass compatibility of the injectable formulation in the area of current interest. Most of the common and serious challenges of glass compatibility are glass delamination. Glass delamination is basically the degradation of the glass and formation of the flakes as a result of the incompatibility with the product stored. The other factors which contribute to glass delamination are the Type of glass container used, Storage condition, and Pharmaceutical Processings like terminal sterilization. Glass delamination should be taken very seriously as it is when present in the formulations it is directly related to the health of the patient. This review describes the Factors responsible for the glass delamination and its effect on patient health and the quality control analysis techniques of the same.

## Introduction

In the development of the injectable dosage forms, the selection of the glass container is the key factor that minimizes the risk of glass delamination. Other factors are also important which can enhance the chance of glass delamination such as type of the glass container, processing condition of the container, Product storage condition, nature of the drug product store, pharmaceutical processing mainly including the sterilization method. The selection of glass containers as a packaging material for injectables is a task of great interest. Glass material can be chemically and physically reactive in a certain condition where chemical degradation of the drug occurs [1]. Due to the inertness of the glass, it is commonly used for the packaging of the parenteral formulation [2]. Glass, in the form of ampules, bottles, cartridges, vials, and pre-fillable syringes, is the content material of choice for parenteral products [3]. The presence of foreign particles especially glass particles is undesirable in parenteral [4]. Despite having various advantages of glass as a packaging material of parenteral formulations it possesses various

serious disadvantages like glass incompatibility which results in delamination. Although having a tendency of glass to react it is the most widely accepted packaging material for Injectables [5].

It is the phenomenon wherein glass flakes are generated into the solution possibly due to the interaction between the glass material and the product stored and maximizing the patient risk. The issue of glass delamination has caused several pharmaceutical complications which importantly includes drug recalls where manufacturers voluntarily recall their drug products. Hence there is always a need to properly check on the glass delamination of the packaging glass containers. Food and Drug Administration suggests drug manufacturers identify potential causes of the glass delamination by conducting stability studies of the drug product within the intended glass containers. In the same way manufacturers also new techniques to determine the delamination propensity of glass. In general, the resistance of glass to aqueous corrosion is called glass durability [6]. The chemical durability of glass depends upon environmental conditions [7].

Factors affecting inner surface glass durability of glass [8].

The stability of the injectable formulations is related to the resistance of the glass to aqueous corrosion

Following are the factors which affect the inner surface durability of the glass

- Glass Composition
- Converting procedure of glass container
- Nature of the drug product stored
- Container size and volume of solution ratio
- Pharmaceutical processing

### Glass composition

Glass containers for injectable formulations are intended to come in direct contact with the solution. Glass used for pharmaceutical containers is either soda-lime glass or borosilicate glass. As per the composition, borosilicate glass contains boric acid, aluminum oxide, alkali, and alkaline earth oxides. The composition of the glass represents the resistance of the glass. Determination of the hydrolytic resistance for glass is an important step in the selection of the glass as the packaging of pharmaceuticals. According to USP 1660 glass containers, they have different hydrolytic stability with the type and the composition [9]. The glass hydrolytic stability is defined by the resistance to the release of soluble elements into water under the specified condition when the glass container is in contact with water. Higher the resistance of glass to the hydrolytic resistance lowers the risk of glass delamination due to the interaction between the glass container and the solution stored.

Type I Borosilicate glass is mainly used for injectable formulations having acid, neutral and alkaline pH. They retain resistivity after different pharmaceutical processes like terminal sterilization. Type II Glass is the treated soda-lime-silica glass with increased hydrolytic resistance as equal to type I Glass. Type III Glass is the soda-lime-silica glass having moderate hydrolytic resistance and is suitable for the storage of nonaqueous injectable formulations and powder for injections [10].

### Converting process

Two types of glass containers are there the parenteral product molded containers and tubular glass containers. Moulded glass containers are prepared by mold process and tubular glass containers are prepared by converting glass tubes into containers. In the manufacturing of moulded glass containers, the glass is undergone through high single heat treatment. It consists of three steps melting is the step where glass is melted by high heat treatment. Pouring is the second step where melted glass is cut into pieces and transferred to the mold and the next step is the pressing where the final shape of the container is achieved. Molded glass containers have a composition with low silicon content and high alkali

earth elements and have uniform chemical homogeneity. And on the other hand, tubular glass containers have to undergo two high heat treatments to get the required container design. The Glass tube is heated by flame to its softening point and pulled for elongating to form the desired shape. The glass delamination usually occurs in the base and shoulder region where extensive heat is applied to get the desired shape of the container which results in the evaporation of the alkali and borates. To obtain the desired resistance to the chemical attack the proper check on the container converting procedure is crucial [10,11].

### Nature of drug products

The nature of the product in contact with the container during its shelf life may impact the durability of the glass. This may contribute to drug product interaction causing the release of glass flakes. As the glass is exposed to water, the silicon oxide will leach into the product thus leading to a less resistant glass [12]. Characteristics of drug product solution in contact with the glass may also impact glass delamination [13]. Acidic solutions cause the dissolution of water and exchange of hydrogen ions with the alkali ions such as sodium and potassium ions. Highly basic solutions cause the dissolution of the silicon oxide layer. Excess Ammonium sulfate treatment of glass containers is a process to remove the excess alkali from the surface which can also cause delamination. The presence of buffers in the drug product solution, such as phosphates and citrates, can interact with the glass containers causing delamination. Terminal sterilization of the drug.

Corrosion of glass by chemicals in different pH environments (i.e., citrate, phosphate, acetate buffers) has been known for decades [14]. Nature of formulation being stored - Alkaline and certain buffer solutions (citrate and tartrate) have a higher tendency to aggravate the process of delamination.

Ronald, et al., investigated the corrosion of glass by a pharmaceutical product having a basic pH of 8.2. When ammonium sulfate treated vials containing the product solution having pH of 8.2 and stored under 2 different temperature conditions 40°C and 30°C. Visible particulate matter was observed in vials containing product after 30 days and 8 weeks of storage at 40°C and 30°C respectively. The particulate matter was found to be glass as identified using field-emission environmental SEM equipped with Xray analysis capabilities investigated the effect of formulation and process variables on the delamination process [15].

Previous work investigated [16]. Reaction mechanism between silica glass and several silicate glasses with HF acid solution. The study showed the reaction rates varied with time and extent of agitation. The reaction was diffusion controlled.

In the glass grain test performed by Bohrer [17]. It is found that all variety of the glass components into the solution they used. In this study, the solutions of the inorganic salts were used like NaCl, KCl, CaCl<sub>2</sub>, MgCl<sub>2</sub>, NaHCO<sub>3</sub>, NaH<sub>2</sub>PO<sub>4</sub>, KH<sub>2</sub>PO<sub>4</sub>, etc. the study shows and confirmed the major glass components extracted into the solutions. Among all the above solutions NaHCO<sub>3</sub> and gluconate extracted the highest amounts

of glass components. The study also confirmed the ability of basic solutions to attack and dissolve the glass network.

White [18]. Has identified five mechanisms to describe the corrosion of glass: congruent dissolution by simple dissociation, congruent dissolution by chemical reaction, incongruent dissolution with the formation of crystalline reaction products, incongruent dissolution with the formation of noncrystalline layers, and ion exchange.

Ion exchange is the most common mechanism of interaction between glass and product. Na<sup>+</sup> ions which are present in glass can be replaced by the H<sub>3</sub>O<sup>+</sup> ions of the solution. This reaction is dominant in neutral and acidic solutions [19].

Another study showed the glass compatibility and performance characteristics of the glass after exposure to cidofovir solution by observing glass surface characteristics by SEM before and after exposure of the drug product for stress and real-time stability storage condition. In both, conditions glass delamination frequency was increased [20].

Increased levels of silicic acid precede glass degradation events, making Si levels in solution a primary indicator of glass degradation [21].

### Container size and volume of solution ratio

In most of the injectables formulations, containers are filled less than 30% which enhances the risk of glass delamination due to unfavorable surface/volume ratio. As per the USP test for glass surface chemical durability, the Container size and volume of the solution can affect the durability of the glass, salt concentration, and pH. As per the study investigated by Bicker, decreasing the filling volume from 90% down to 30% of the brimful capacity of the container and autoclaving the borosilicate type I glass vials 1h at 121°C containing water and citric acid 0.024M. significantly increase the glass surface attack was experienced by the HCl 0.01M titration values [22]. The study showed the different impacts of fill volume on the leachable profile of the glasses filled with low fill volumes of water or salt solution. An alteration of the chemical durability occurs within the heel zone of the vials while using standard converting procedures [23].

### Pharmaceutical processing

In pharmaceutical injectable drug product manufacturing, terminal sterilization is an integral part of the process.

During the terminal sterilization, the glass container is subjected to high temperature (121°C) which may increase the chances of leaching from the container to the solution causing delamination. Thirumangalathu R investigated different depyrogenation conditions were investigated to determine whether and how vial processing may impact the surface of glass vials as well as their potential for subsequent delamination. Besides standard depyrogenation conditions, vials were also investigated after depyrogenation with extended duration (1h at 300°C) to simulate longer holding times in a sterilization tunnel, increased temperature [24].

### Quality control of glass delamination

Out of the conventional methods to evaluate glass durability titration and change in specimen weight were widely used. In the titration method, the acid required to neutralize the corrosion solution was measured. And in the other method called a change in specimen weight the mass of glass dissolved during corrosion was determined [9].

The extent of glass corrosion and chemical attack is assessed by analyses of the inner glass surface morphology, the concentrations of extracted elements in solution, and by identification of particles and flakes. The quality control test of the glass delamination includes Optical microscopy, Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM), Secondary Ion Mass Spectrometry (SIMS), and Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

Light microscopy is used to examine the intact glass container and determine if there is any presence of glass flakes in the drug product. SEM Analyzes glass surfaces to detect flakes or pitting defects. TEM is applied to analyze thin delamination flakes. SIMS analyzes the diffusion of hydrogen into the glass. ICP-MS measures the trace levels of glass components such as Sodium, Boron, Aluminum, Calcium, etc. In the drug product solutions. SEM coupled with energy dispersive X-ray spectrometry (SEM/EDS) is used to determine if the flakes are similar to those observed with glass delamination. Flame Atom Absorption Spectrometry (FAAS) A state-of-the-art flame atomic absorption spectrometer is used to measure sodium oxide. Stereo-Microscopy is used for the visual (optical) inspection of the vulnerable area in the heel region of the containers. Secondary Ion Mass Spectrometry (TOF-SIMS) is used For ion sputter depth profiling in glass delamination. See the following Table 1 for quality control testing of the glass delamination [25,26].

### Glass Delamination and Risk at Patient

The glass delamination is mainly due to the interaction between the solution into the container and glass material. This interaction results in the reduced potency or activity of the Active Pharmaceutical Ingredients. The formation of glass flakes, cracks can compromise the safety and efficacy of the drug product and can put the patient at risk [27]. Delamination in glass containers of medicines for parenteral use has resulted in numerous recalls lately. Although no case has become known where a patient has come to harm, the FDA sees the risk of vascular injury, embolism, and thrombosis through the glass particles [28].

### Drug recalls [29]

Glass delamination should be taken seriously as any foreign particulate injected may be hazardous. The issue of glass delamination has caused several pharmaceutical manufacturers to recall their drug products. Following are some examples of drug recall by USFDA, due to the glass as particulate matters during the year 2018-19. And 2021-21 Tables 2,3.

**Table 1:** Quality control of glass delamination.

| Parameter                               | Test parameter  | Analytical methods                        |
|---|---|---|
| Glass surface                           | Degree of surface pitting, chemical composition               | Transmission Electron Microscopy EM, SIMS |
| Extracted element into solution         | Conductivity/pH Individual and total extractable              | Conductivity/pH meter, ICP-MS,            |
| Visible and sub-visible glass particles | Particle number and size, particle morphology and composition | Particle size analyser, SEM-EDX           |

**Table 2:** Drug recalls by USFDA due to glass delamination in the year 2018-2019.

| Product Name   | Company Name  | Reason for Recall   |
|--|---|---|
| Piperacillin and Tazobactam for injection, USP 3.375 g                           | AuroMedics Pharma LLC   | particulate matter, identified as glass and silicone material particles |
| Vecuronium Bromide for Injection, 20 mg, Vecuronium Bromide for Injection, 10 mg | Sun Pharmaceutical Industries, Inc.                               | particulate matter identified as glass.                                 |
| Piperacillin and Tazobactam for injection, USP 3.375 g                           | AuroMedics Pharma LLC   | particulate matter, identified as glass and silicone material particles |
| Fluorouracil Injection   | Fresenius Kabi  | Potential for glass particulate   |
| Mycophenolate Mofetil for injection  | Par Pharmaceutical, Inc   | glass fragment after reconstitution.                                    |
| Sodium Bicarbonate Injection USP, 50 mEq/50 mL (1 mEq/mL),                       | Hospira, Inc., a Pfizer company                                   | presence of particulate matter confirmed as glass.                      |
| Labetalol Hydrochloride Injection, USP   | Due to Potential Of Cracked Glass At The Rim Surface Of The Vials | Hospira, Inc., a Pfizer company   |
| Ampicillin and Sulbactam for Injection USP                                       | AuroMedics Pharma LLC   | The product has been found to contain glass                             |

**Table 3:** Drug recalls by USFDA due to glass delamination in the year 2020-21.

| Product Name   | Company Name            | Reason for Recall                                       |
|--|-------------------------|---|
| Hydromorphone HCL Injection, USP   | Hospira, Inc.           | Due to The Potential for Empty or Cracked Glass Vials   |
| Daptomycin for injection 500mg   | Merck                   | Product contains particulate matter identified as glass |
| R.E.C.K. (Ropivacaine, Epinephrine, Clonidine, Ketorolac) 50 ml in Sodium Chloride-60 ml BD syringe    | QuVa Pharma, Inc.       | presence of particulate matter identified as glass      |
| Ketorolac Tromethamine Injection, USP, 30 mg/mL, and Ketorolac Tromethamine Injection, USP, 60 mg/2 mL | Fresenius Kabi USA, LLC | Presence of Particulate Matter identified as glass      |

## Conclusion

Glass compatibility with injectable formulations is the current topic as a challenge. Complete assurance is to be gained while selecting a glass material for injectable drug storage in an attempt to minimize glass delamination.

The concept is well explained in the literature. This review study makes understand the factors affecting the glass durability, quality control of the glass delamination and related drug recalls.

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