GLASS DELAMINATION IN STERILE FORMULATIONS AND DRUG RECALLS: A REVIEW

*Kabirdas B. Ghorpade, Sharda M. Shinde
*Aurigene Pharmaceutical Services Limited, Miyapur (Telangana.)
2School of Pharmacy SRTM University, Nanded (Maharashtra)

Abstract:
Injectable formulations face continuing challenges of glass compatibility. To assure glass compatibility of the injectable formulation is an area of current interest. Most of the common and serious challenge of the glass compatibility is glass delamination. Glass delamination is basically degradation of the glass and formation the flakes as a result of the incompatibility with the product stored, storage condition, pharmaceutical processing which include the terminal sterilization and type of the glass container. Glass delamination should be taken very seriously as it is when present into the formulations it is directly related to the health of patient. In this review we discussed the factors affecting the glass durability, glass delamination effect on health and quality control of glass delamination and related drug recalls.

Corresponding author:
Kabirdas B. Ghorpade,
Aurigene Pharmaceutical Services Limited,
Miyapur (Telangana.)

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INTRODUCTION:
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 certain condition where chemical degradation of the drug occurs (1). The presence of foreign particles especially glass particles is undesirable in parenterals (4).

Due to the inertness of the glass it is commonly used for the packaging of parenteral formulation. (2). Despite having various advantages of glass as packaging material of parenteral formulations it possesses various serious disadvantages like glass incompatibility which results in delamination.

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 maximize the patient risk. Issue of glass delamination has caused several pharmaceutical complications which importantly includes drug recalls where manufacturers to voluntarily recall their drug products. Hence there is always need to proper check on the glass delamination of the packaging glass containers. Food and drug Administration suggests drug manufacturer to identify potential causes of the glass delamination by conducting the 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 the development of the injectable formulation the selection of the glass container is the key factor which minimize 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 include the sterilization method.

FACTORS AFFECTING INNER SURFACE GLASS DURABILITY OF GLASS
The resistance of the glass to aqueous corrosion shows the good stability of the injectable formulations.

Following are the factors which affects 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 into the solution. Glass used for pharmaceutical containers are 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 important step in the selection of the glass as packaging of pharmaceuticals. According to USP 1660 glass containers, they have different hydrolytic stability with the type and the composition.

The glass hydrolytic stability is the defined by the resistance to release of soluble elements into water under specified condition when 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 solution stored.

Type I Borosilicate glass is mainly used for the injectable formulations having acid, neutral and alkaline pH. They retain the resistivity after different pharmaceutical processing 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 suitable for the storage of non-aqueous injectable formulations and powder for injections 8.

CONVERTIN PROCESS
Two types of glass containers are there for the parenterals product molded containers and tubular glass containers. Molded glass containers are prepared by mold process and tubular glass containers are prepared by converting glass tubes into containers.

In the manufacturing of molded 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 cutter into pieces and transferred to the mold and next step is the pressing where 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 container have to undergo through two high heat treatment 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 base and shoulder region where extensive heat is applied to get the desired shape of the container which result 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.\(^{19}\)

**NATURE OF DRUG PRODUCTS**

Nature of the product in contact with the container during its shelf life may impact 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 this leading to a less resistant glass. Characteristics of drug product solution in contact with the glass may also impact glass delamination. 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 (≥8) cause the dissolution of 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. Presence of buffers in the drug product solution, such as phosphates and citrates, can interact with the glass containers causing the delamination. Terminal sterilization of the drug.

The pH dependent Corrosion of glass by chemicals (i.e., citrate, phosphate, acetate buffers) and have been known for decades \(^{23}\). Nature of formulation being stored - Alkaline and certain buffer solutions (citrate and tartrate) have higher tendency to aggravate the process of delamination. Ronald, et al., investigated the delamination/corrosion of glass by a pharmaceutical product having pH of 8.2 Authors have used three type-I borosilicate glass vials from two different vendors of which two vials (ammonium sulfate treated and the other one un-treated) were kept in contact with the product with pH of 8.2 and the remaining were used as a control. Vials were stored under 2 different temperature conditions 40°C and 30°C. Visible particulate matter was observed in vials contained 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.

Previous work investigated \(^ {12}\), reaction mechanism between silica glass and several silicate glasses with HF acid solution. Study showed the reaction rates varied with time and rate of agitation. The reaction was diffusion controlled.

In the glass grain test performed by Bohrer \(^ {13}\), it is found that the 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\(_2\), MGCL\(_2\), NAHCO\(_3\), NAH2PO4, KH2PO\(_4\) etc. the study shows and confirmed the major glass components extracted into the solutions. Among all above solutions NAHCO\(_3\) AND gluconate extracted highest amounts of glass components. The study also confirmed the ability of basic solutions to attack and dissolve the glass network.

White \(^ {15}\), 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 non-crustalline layers, and ion exchange.

Ion exchange is the most common mechanism of interaction between glass and product. Na\(^+\) ions which are present in glass can be replaced by the H\(^3+\) ions of the solution. This reaction is dominant in neutral and acidic solutions \(^ {16}\).

Another study showed the glass compatibility and performance characteristics of the glass after exposure of 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 the conditions glass delamination frequency was increased \(^ {18}\).

Investigated study suggests that increased levels of silicic acid precede glass degradation events, making Si levels in solution a primary indicator of glass degradation \(^ {24}\).

**CONTAINER SIZE AND VOLUME OF SOLUTION RATIO**

In most of the injectables formulations, containers are filled less 30% which enhance the risk of glass delamination due to unfavourable surface/volume ratio. As per USP test for glass surface chemical durability, 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 2020 decreasing the filling volume from 90% down to 30%
of the brimful capacity of the container and autoclaving the borocilicate 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 17. In the study investigated 20, the different impact of fill volume on leachable profile of the 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.

**PHARMACEUTICAL PROCESSING**

In the pharmaceutical injectable drug product manufacturing, terminal sterilization is the integral part of the process. During the terminal sterilization the glass container is subjected to high temperature (121°C) which may increases the chances of leachable from the container to the solution causing delamination.

Thirumangalathu R, 2015 investigated different dehydrogenation conditions were investigated to determine whether and how vial processing may impact the surface of glass vials as well as their potential to subsequent delamination. Besides standard depyrogenation conditions, vials were also investigated after depyrogenation with extended duration (1 h at 300°C) to simulate longer holding times in a sterilization tunnel, increased temperature.21

**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 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 (17).

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 Analyses glass surfaces to detect flakes or pitting defects. TEM is used to analyse thin delamination flakes. SIMS analyses the hydrogen diffusion into glass. ICP-MS measures the trace levels of glass components such as Sodium, Boron, Aluminium, 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 that observed with glass delamination. Flame Atom Absorption Spectrometry (FAAS) A state-of-the-art flame atom 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.

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

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

**DRUG RECALLS**

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 (25), due to the glass as particulate matters during the year 2018-19. And 2021-21.
Table 2: Drug recalls by USFDA due to glass delamination in 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 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:
Selection of glass containers for sterile formulations is due to its inertness is most widely accepted. Glass delamination is defined as degradation of surface glass, as from a vial, that produces glass flakes. There are various factors which affect the glass durability like glass composition, Nature of the product stored, Converting procedure of glass containers, pharmaceutical processing and the storage condition of the product. In this review we have discussed about the glass delamination and factors responsible for the same and quality control.

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CONFLICTS OF INTEREST
The authors declare no conflict of interest.

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