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Evaluation of Glass Delamination Risk in Pharmaceutical 10 mL/10R Vials

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ABSTRACT

Glass delamination is characterized by the dissociation of glass flakes from the glass surface. Since glass delamination is time dependent, 5 vial types were investigated to assess delamination under accelerated stress conditions published as quick tests in literature and compared to stress testing recommended per United States Pharmacopoeia <1660>. A broad panel of analytical techniques was employed to test the solution for visible/subvisible particles and leachables and characterize topography and composition of the surface. The vial types showed significant differences in surface durability when applying the same stress conditions. An increase in glass leachables and change in topography were shown for uncoated vials. An indication for an elevated delamination risk was confirmed for Expansion 33 vials only by the compiled analytical data set including particle assessment and change in elemental composition of the near glass surface investigated by dynamic secondary ion mass spectrometry. The delamination test protocols differ in test solution, handling, and time. Before choosing the most appropriate protocol to predict delamination propensity and mimic real-time conditions, long-term storage data are needed. A combination of analytical techniques to study the risk for long-term corrosion of glass is highly recommended covering the 3 aspects: visible/subvisible particle assessment, solution analysis, and surface characterization.

Introduction

In recent years, glass particles, so-called lamellae, have been observed in a couple of parenteral products filled in glass containers. These visible glass particles resulted in product recalls due to the parenteral administration of the products to ensure patients' safety.[1-3] Therefore, biopharmaceutical industry and regulatory agencies nowadays pay considerable attention to particle formation, especially to glass delamination from glass containers for therapeutic parenteral products, including biologics.[4,5] An informal monograph in the United States Pharmacopoeia (USP <1660>[6]) has been released in 2012 to provide guidance for pharmaceutical industry related to evaluating glass delamination.

Glass delamination is described in literature.[7-11] It is characterized by the dissociation of glass in the form of sheets and flakes from the product contact surface. White and Zoitos have suggested different mechanisms to describe the corrosion of glass[12]: (1) congruent dissolution by simple dissociation or by chemical reaction with the solvent referred to as homogeneous dissolution in this article. This leads to enhanced concentration of the respective glass elements in the formulation. Concentrations of the ions are equivalent to the weight ratios of the elements in the bulk glass. (2) Incongruent dissolution with the formation of crystalline reaction products or the formation of noncrystalline layers and (3) ion exchange. Mechanism (2) results in ion concentrations in the solution, which are significantly different from the bulk concentrations (inhomogeneous dissolution).

The predominant mechanism depends on the solution in contact with the glass surface. When glass surfaces are exposed to water, the glass surface is hydrated and an alkali-depleted,

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silica-rich layer is formed.[13] This involves an ion exchange between hydrogen ions from the water and alkali ions in the glass. The presence of water promotes hydrolysis of the silicon-oxygen bond, forming a silica-gel layer. At higher pH values, the mechanism of glass dissolution is assumed to change from the leaching of alkali elements to the dissociation of the silicate network.[6]

Glass delamination in vials for parenteral products on the one side depends on the glass composition and the glass/vial manufacturing processes,[7,11] and on the other side, process conditions during drug product manufacturing[14-16] such as terminal sterilization[10] of glass vials and potentially depyrogenation after vial washing.[17] In addition, the dosage form and formulation (compound,[9] pH,[4,18] ionic strength,[17,18] and buffer components[19,20]) and storage conditions (temperature and time)[21-23] impact the risk and likelihood for glass delamination during a product's shelf life. For example, liquid (refrigerated and ambient) formulations are expected to interact stronger with the glass surface compared to dried (lyophilized) formulations and thus would be considered a higher risk for delamination. Frozen formulations in comparison to dried formulations would also be of higher concern for delamination given that freezing and thawing can pose stress on the vial.[15] Jiang et al.[15] have reported that freeze/thaw cycles of protein formulations may induce formation of glass lamellae by mechanical stress due to rapid movement of the frozen plug from the glass surface at temperatures below −50°.

Glass delamination is evident by visible glass flakes (particles) in solution and can show up as subvisible particles (SVPs).[4] Delamination is a matter of time, and glass particles may only occur after months or years of drug product storage. If delamination is observed in vials, it is assumed to occur mostly at areas where heat was applied during the vial forming process, that is, at the bottom and shoulder of a vial.[24] These areas have a lower hydrolytic/chemical resistance and form so-called reaction zones when in contact with the drug product. This is also why glass delamination is likely less of an issue for syringes, given that these areas are usually located outside of the product contact region of the glass barrell.[25] By applying extreme stress conditions to glass containers,[6,17,18,24,26] glass delamination can be accelerated. These accelerated test methods may provide a rough evaluation of the potential and the risk for delamination of the respective glass vial. These conditions, however, do not necessarily relate to actual long-term storage at intended conditions. For the time being, these tests are unable to predict likelihood of occurrence or even time point of glass delamination but are used to assess the relative risk of occurrence and to determine the risk for glass delamination of a given container. These tests are thus of value for the general assessment of the glass container to be chosen.

The present study assesses stress protocols to accelerate glass delamination in pharmaceutical glass vials. First, the interior surface of 5 different vial types was characterized after using established stress conditions to force glass delamination. Second, the 3 applied accelerated delamination tests were compared. A broad panel of conventional and advanced analytical techniques was employed for testing the (1) stressed solutions, for example, visible and SVPs by light obscuration and Micro-Flow Imaging (MFI), particle identification by scanning electron microscopy with energy dispersive X-ray spectrometry (SEM-EDS), pH shift, and leaching of elements from the glass by inductively coupled plasma spectrometry (ICP) and (2) characterizing the inner vial surface after particular stress treatment by colorimetric staining, SEM, and dynamic secondary ion mass spectrometry (D-SIMS). The results obtained were further related to results of a delamination study performed in alignment with USP chapter <1660>, section Screening Methods to Evaluate Inner Surface Durability.[6]

Materials and Methods

Glass Vials

Five vial types in a 10 mL/10R format were used in the present study. Table 1 summarizes the nominal glass composition, thermal expansion coefficient, the presence and type of coating surface modification, and the surface properties of these vials as provided by the vendors.[27] Uncoated Expansion 33 and Expansion 51 vials were purchased at Schott North America, Inc. (Elmsford, NY) and Schott AG (Müllheim, Germany), respectively. Three vial types of 51 expansion glasses with an additional interior surface modification, which are referred to as Siliconized, TopLyo™, and Type I plus® vials, were obtained from Adelphi Healthcare Packaging (Haywards Heath, UK). The vials are referred to as “surface-modified” vials rather than “coated” vials in the following as the terminology “coated” suggests only a physical application of material that can be easily removed or extracted. All vials comply with hydrolytic class I.

Preparation of Vials for Stress Test

Washing of Vials

Vials were washed with water for injection (WFI) (~75°C) in a Belimed LA280 cleaning and disinfectant instrument (Belimed Sauter AG, Sulgen, Switzerland) and allowed to dry under laminar air flow for several hours (<24 h).

Table 1
Summary of Chemical Composition and Physical Data of Investigated Glass Vials as Provided by the Vendors[27]

Trade Names	Expansion 33	Expansion 51	Siliconized	TopLyo	Type I plus
Chemical glass composition	(wt.%)	(wt.%)	(wt.%)	(wt.%)	(wt.%)
SiO_2	81	75	75	75	75
B_2O_3	13	10.5	10.5	10.5	10.5
Al_2O_3	2	5	5	5	5
Na_2O	3.5	7	7	7	7
CaO	–	1.5	1.5	1.5	1.5
K_2O	0.5	–	–	–	–
Thermal expansion coefficient	$3.3 \times 10^{-6}\ K^{-1}$	$4.9 \times 10^{-6}\ K^{-1}$	$4.9 \times 10^{-6}\ K^{-1}$	$4.9 \times 10^{-6}\ K^{-1}$	$4.9 \times 10^{-6}\ K^{-1}$
Layer	No	No	$SiOCH_3$	$Si_aO_bC_cH_d$	SiO_2
Layer thickness	–	–	~10-60 nm[a]	~40 nm	100-200 nm
Coating method	–	–	Baked-on	PICVD	PICVD
Surface property	Hydrophilic	Hydrophilic	Hydrophobic	Hydrophobic	Hydrophilic

PICVD, plasma-impulse chemical vapor deposition.
[a] Theoretical calculation based on the amount of sprayed-on silicon emulsion assuming homogeneous silicon layer.