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Extractables Testing of Aluminosilicate and Borosilicate Glass Containers

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When it comes to required extraction studies (1) for new glass compositions that are starting to enter the parenteral packaging market, manufacturers naturally have questions about the suitability of these new products. One extraction study potentially answers these questions.

Extraction studies are necessary because glass containers, which are frequently considered inert, react with aqueous solutions at relatively low rates in most parenteral drug applications.

Extraction methods for glass assess the durability of the container surface to any number of solution chemistries, often accelerated using elevated temperatures. Solution analysis then quantifies the amount of glass constituents that have reacted or dissolved from the container into solution.

Compendial chapters offer methods to quantify the hydrolytic resistance of glass containers for pharmaceutical packaging (2–4). These methods involve an accelerated treatment (e.g., autoclave) of containers filled with pure water followed by titration of the reacted solution (5). A separate, quantitative analysis of the non-titrated, post-autoclave solution provides the concentrations of elements extracted from the interior of the glass container. While not an exhaustive representation of container extracts from all conditions (3), these are perhaps the most commonly referenced set of extraction conditions.

Although compendial chapters group results by nominal container volume and set numerous unique limits, glass corrosion literature has demonstrated that extracted solution concentrations are a result of glass surface area and true solution volume

diluting the response (6). It is therefore helpful to compare extract concentrations from dissimilar container shapes by normalizing the results to the glass surface area-to-solution volume ratio (SA/V).

The chemical durability of glass containers (i.e., resistance to corrosion) depends on many factors, including bulk composition, changes in surface chemistry produced during manufacturing (e.g., converting), the solution chemistry of reaction and the time and temperature of exposure (3,7). For many years, glass vials used for parenteral packaging were mostly composed of borosilicate composition; durable, boron-free aluminosilicate containers have been introduced for use in parenteral packaging (8). Chemical strengthening with molten salt is used to improve the mechanical performance of borosilicate and aluminosilicate glass packaging components.

In this study, the aluminosilicate containers used were chemically strengthened. Regarding glass composition, hydrolytic resistance of silicate glasses generally depends on the relative amounts of oxides identified as network formers (e.g., SiO_2 , B_2O_3), intermediates (e.g., Al_2O_3), and alkali/alkaline-earth modifiers (e.g., Na_2O , K_2O , CaO , MgO). In general, higher-silica glasses exhibit greater chemical durability, additions of alumina can improve durability in certain cases, and the addition of excess alkali

oxides and boron ($\text{R}_2\text{O} + \text{B}_2\text{O}_3$) can have a negative effect on hydrolytic resistance (7). Other extractables may be a result of property modifiers (e.g., oxides of barium or iron) or fining agents (e.g., oxides of arsenic or tin) used in glass manufacturing, and from impurities in raw materials. The glass containers used in this study were commercially available borosilicate and aluminosilicate products designed specifically for use in primary pharmaceutical packaging. All three container types used in this study meet the Type I performance criteria (titration limit) for the surface hydrolytic test outlined in USP <660> Containers—Glass. The major components in each glass are outlined in Table 1 below.

Although both glass tubing and/or formed containers may be used to characterize materials of construction, an extractables analysis of a primary packaging component must include testing of the final containers such as vials ready for drug fill. Containers that are molded or converted must be included in an extractables analysis in order to evaluate effects of the tube-to-vial converting process which can produce chemical heterogeneities across the container surface. These regions of variable chemical composition may lead to differences in chemical durability, which are undesirable, and these effects can only be evaluated in the final container.

Table 1 Oxide Components of Glasses Studied

Glass Type	SiO_2	Al_2O_3	B_2O_3	Na_2O	K_2O	CaO	MgO
Aluminosilicate A	✓	✓	×	✓	✓	✓	✓
Borosilicate B	✓	✓	✓	✓	×	✓	×
Borosilicate C	✓	✓	✓	✓	✓	✓	✓

✓ = present in bulk glass, × = not present

In certain cases, such chemical heterogeneities in borosilicate glass containers have been shown to produce delamination of silica-rich lamellae from the surface into the drug product (9,10). Often, these heterogeneities are caused by the volatilization of alkali and boron from the glass during the converting process and subsequent deposition resulting in a surface enriched in excess alkali and boron.

The vials used in this study were converted from size matched tubing and were converted to the same overall dimensions. The tubes were suitably closed with PTFE and silicone stoppers to hold liquid. Vials and tubes were filled with ultrapure water, and autoclaved with a hold of one hour at 121°C according to procedures outlined in USP chapter <660> and ISO 4802

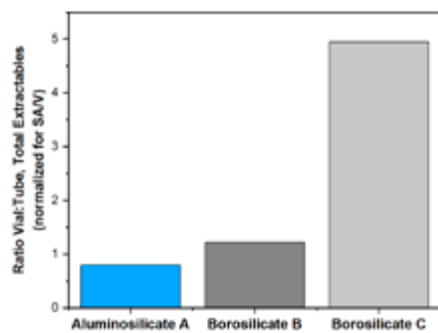


Figure 1 Ratio of Total Extractables for Vials and Tubes of Three Different Glasses (The higher ratio for the borosilicate samples indicates a greater change in surface chemistry during the tube-to-vial converting process. Concentrations of extractables have been normalized for differences in SA/V.)

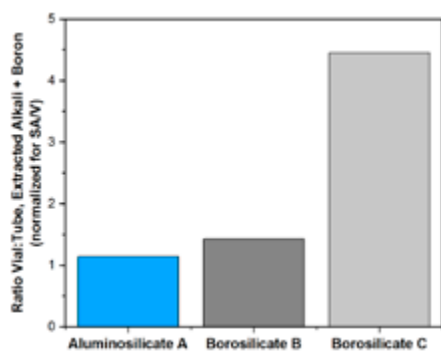


Figure 2 Ratio of Extracted Alkali+Boron for Vials and Tubes of Three Different Glasses

(2,4,6). The reacted solution samples were then analyzed quantitatively by ICP-MS. Concentrations were normalized for wetted surface area-to-fill volume to account for differences in container geometry.

To illustrate the effects of the converting process on chemical durability, extractables of formed vials and tubing are compared in **Figure 1** and **Figure 2**. For both borosilicate vials tested, the total concentration of extractables was greater than that of the parent glass tubing (even when normalized for differences in SA/V between the vials and tubing). This increase in total extractables after converting is due to changes in surface chemistry from the converting process. In **Figure 2**, only the relative concentrations of extracted alkali and boron are compared, and the vial-to-tube ratios of these extracted species were greater for the Borosilicate B and Borosilicate C containers/tubes than for the Aluminosilicate A containers/tubes.

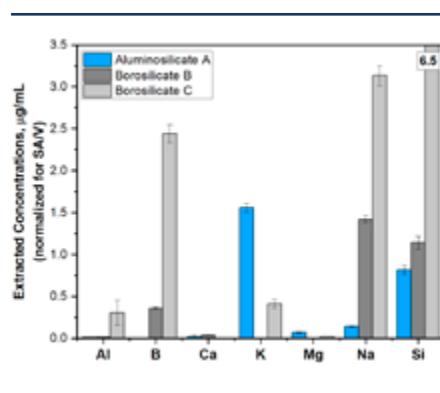


Figure 3 Extractables Profiles for Three Vial Types Measured by ICP-MS and Normalized by SA/V (Concentrations greater than the chosen scale are labeled individually.)

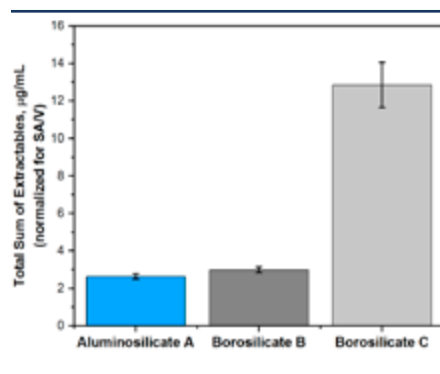


Figure 4 Total Sum of Extractables for Three Vial Types Measured by ICP-MS and Normalized for SA/V

The extractables profiles for size-matched vials are presented in **Figure 3** and include only extracted elements with a reported concentration greater than 0.01 ppm ($\mu\text{g}/\text{mL}$). A comparison of the total amount of extractables for each vial type is presented in **Figure 4**. The Aluminosilicate A containers exhibited lower concentrations of extracted aluminum and silicon than the (aluminum-containing) borosilicate containers. If the extracted amount of silicon, boron and aluminum is considered as a measure of breakdown of the glass network during corrosion, the extractables profile for Borosilicate C indicates it is the least chemically durable of the three container types tested. Alkali (Na, K) and boron components in glass have significantly higher dissolution rate in water compared to other glass components, so it is helpful to consider their extracted concentrations together rather than separately (7). The data in **Figure 3** shows that extracted Na+K+B is greater for both Borosilicate B and Borosilicate C than for Aluminosilicate A.

Despite a greater amount of extracted potassium for Aluminosilicate A, the comparison of total levels of extracted alkali+boron indicates that the Borosilicate B and Borosilicate C containers demonstrate a weaker resistance to corrosion in water compared to Aluminosilicate A. The Aluminosilicate A vials exhibited the lowest concentration of total extractables, overall.

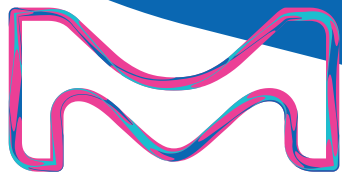
In short, the extractables analysis shows Aluminosilicate A to have a high degree of chemical durability and more uniform surface chemistry after converting, further reinforcing its suitability for use in parenteral packaging applications.

[Editor's Note: The authors' company will be exhibiting at the *2018 PDA Annual Meeting*.]

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