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A New Glass Option for Parenteral Packaging

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TECHNICAL ABSTRACT: Glass is the ideal material for parenteral packaging because of its chemical durability, hermeticity, strength, cleanliness, and transparency. Alkali borosilicate glasses have been used successfully for a long time, but they do have some issues relating to breakage, delamination, and variation in hydrolytic performance. In this paper, alkali aluminosilicate glasses are introduced as a possible alternative to alkali borosilicate glasses. An example alkali aluminosilicate glass is shown to meet the compendial requirements, and to have similar thermal, optical, and mechanical attributes as the current alkali borosilicate glasses. In addition, the alkali aluminosilicate performed as well or better than the current alkali borosilicates in extractables tests and stability studies, which suggests that it would be suitable for use with the studied liquid product formulation.

KEYWORDS: Glass, Parenteral, Extractables, Borosilicate, Aluminosilicate, Stability.

LAY ABSTRACT: The physical, mechanical, and optical properties of glass make it an ideal material for packaging injectable drugs and biologics. Alkali borosilicate glasses have been used successfully for a long time for these applications, but there are some issues. In this paper, alkali aluminosilicate glasses are introduced as a possible alternative to alkali borosilicate glasses. An example alkali aluminosilicate glass is shown to meet the requirements for packaging injectable drugs and biologics, and to be suitable for use with a particular liquid drug.

Introduction

Alkali borosilicate glasses have been used for drug packaging for over 90 years (1) because of their good chemical durability, hermeticity, strength, cleanliness, and transparency (2). These glasses are readily formed into vials, syringes, cartridges, ampoules, and bottles for storing and transporting various pharmaceutical solids, suspensions, and solutions. Overall, this glass family functions relatively well, and many billion doses are delivered safely each year (3), but there are some issues.

One issue is glass breakage (4, 5). The formation of a crack in the glass container can compromise the sterility of the drug, and has the potential to generate glass particles that can end up in the drug. Breakage results when an applied force induces tensile stresses in the glass container that propagate flaws. The pro-

pensity for glass breakage is greatly increased when critical flaws are present on the exterior surface of the container. Such flaws can be introduced during the manufacturing, transportation, or filling processes—especially when the glass containers are in contact with one another.

Another issue is delamination. Delamination is a specific type of glass corrosion that produces glass flakes. While it has been consistently observed for more than 50 years in soda-lime silicate glasses (1, 6), delamination has been only occasionally observed in pharmaceutical borosilicates, although the frequency has seemed to increase significantly in recent years (4). The published studies suggest that delamination in alkali borosilicate glasses results from phase separation and/or evaporation loss of the boron and alkali species from the glass surface during the high-temperature tube conversion process (7, 8). Phase separation refers to the transformation of a homogeneous glass into heterogeneous glass with two or more distinct glass compositions upon heating above the annealing temperature.

Another issue is variation in hydrolytic performance (9–11), which is a measure of the chemical durability

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TABLE I

The ASTM Target Composition for Type 1B Alkali Borosilicate Glass, the Analyzed Compositions of Various Type 1B Alkali Borosilicate Glasses In Use Today, Plus a Qualitative Description of the Alkali Aluminosilicate Family of Glasses

Darker shading indicates major components of the glass composition, while lighter shading indicates unintentionally added trace elements. Cells without shading indicate <0.01 weight% present. The compositions were determined by direct dissolution of commercial glass packaging (tubing, vials, syringes, etc.) in a concentrated hydrofluoric acid solution followed by ICP-OES (Inductively Coupled Plasma-Optical Emission Spectrometry) and ICP-MS (Inductively Coupled Plasma-Mass Spectrometry) analyses.

	Weight %								
	<i>ASTM Type 1B</i>	Borosilicate A	Borosilicate B	Borosilicate C	Borosilicate D	Borosilicate E	Borosilicate F	Borosilicate G	Aluminosilicate
SiO ₂	73	71.70	74.60	70.10	74.00	75.40	74.30	75.00	✓
Al ₂ O ₃	7	6.61	5.56	3.41	6.15	2.02	5.60	5.72	✓
B ₂ O ₃	10	11.50	10.90	12.40	11.10	11.30	10.70	10.60	0.00
Na ₂ O	6	6.40	6.93	5.91	7.29	7.87	7.14	6.97	✓
K ₂ O	1	2.35	0.04	2.80	0.90	1.13	0.78	0.77	✓
MgO	0.3	0.30	0.06	0.01	0.00	0.01	0.01	0.00	✓
CaO	1	0.56	1.47	1.03	0.68	0.02	0.45	0.40	✓
BaO	<2	0.00	0.00	2.73	0.02	0.32	0.01	0.00	✓
ZnO		0.00	0.00	0.97		0.96			0.00
CeO ₂						0.53			
Fe ₂ O ₃		0.092	0.046	0.049	0.040	0.021	0.031	0.021	✓
TiO ₂		0.028	0.018	0.027	0.018	0.015	0.020	0.017	✓
ZrO ₂		0.033	0.032	0.038	0.045	0.092	0.038	0.046	✓
SnO ₂		0.000	0.000	0.000					✓
As ₂ O ₅	0.1	0.000	0.083	0.000			0.000	0.000	0.000
Cl		0.045	0.002	0.075			0.210	0.190	

of the glass in neutral solutions. Chemical durability depends on many factors, including the pH of the solution and the composition of the glass. In general, silicate glasses are most durable in neutral solutions, and are much more durable in acidic solutions than in basic solutions, owing to different corrosion mechanisms (1, 12, 13). And while the relationship between composition and durability is quite complex, the main trends for commercial alkali borosilicates are fairly well known. First, increasing the silica content serves to improve the durability in acid environments, but does little to affect the durability in basic solutions. The addition of alkali and alkaline earth oxides (which is done to improve the meltability) degrades the chemical durability. To counteract some of this negative impact to chemical durability, aluminum oxide and/or boron oxide can be added, but there are limits. Aluminum oxide additions strongly increase the viscosity, which can be detrimental to forming, and too much boron oxide can lead to even worse chemical durability [some high-borate glasses are even readily soluble in water (14)]. In the case of boron oxide additions, the maximum chemical durability occurs when the molar

ratio of alkali oxide (in excess of alumina) to boron oxide is between 0.2 and 0.4. The variation in hydrolytic performance (vial-to-vial or lot-to-lot) is thought to arise from variations in bulk composition (which result from the fact that an ASTM glass designation (15) like Type 1A or Type 1B does not denote one specific composition—see Table I for an example) and/or variations in surface composition (which can result from differences in the high-temperature tube conversion process).

These and other issues have led the industry to consider changes—for example, the addition of inorganic barrier coatings, changes to the process to minimize contact between containers (i.e., ready-to-use containers), the use of ion exchange, and even a switch from glass to plastic. In this paper, alkali aluminosilicate glasses are introduced as a possible alternative.

Results and Discussion

To be a viable alternative, the alkali aluminosilicate glass must meet all of the current compendial require-

ments, and must pass suitability-for-use testing with each specific drug. In addition, it would be advantageous for the alkali aluminosilicate glass to be free of undesirable components (e.g., arsenic), to have good chemical durability against strong acids and bases, and to have thermal and physical properties similar to the current alkali borosilicates to make it compatible with existing processes and equipment.

As shown in Table I, the alkali aluminosilicates considered here have most of the same oxide components as the alkali borosilicates in use today. The main difference is the absence of boron oxide. In addition, some borosilicate compositions use arsenic oxide—a known carcinogen (16)—for fining (bubble removal during melting), and its presence justifies the need for the arsenic limit test described later. In the alkali aluminosilicate glasses, arsenic oxide was avoided altogether by using tin oxide for fining.

The following sections compare an example alkali aluminosilicate glass to various alkali borosilicate glasses currently used in the pharmaceutical industry, in five different areas: compendial requirements; resistance to strong acids and bases; physical, mechanical, and optical properties; thermal properties; and suitability for use.

Compendial Requirements

As a starting point, any glass intended for use in parenteral packaging must meet all of the compendial requirements. The U.S. and European Pharmacopeias (USP and EP) provide criteria to define glasses suitable for pharmaceutical packaging.

Most notably, chapters USP <660> and EP 3.2.1 describe hydrolytic tests (now harmonized) for the as-formed glass surface and for glass grains. While the grains tests study the bulk glass and are used primarily as an identity test, the glass surface tests study the as-formed surface of the actual container thereby capturing the impact of the high-temperature tube conversion process. Figure 1 shows the hydrolytic performance for the alkali aluminosilicate vials and three different alkali borosilicate vials as measured using the glass surface tests for ~3 mL vials. The results show considerable variability among the Type 1B borosilicates, ranging from barely meeting the requirement (<1.3 mL of titrant) to easily passing (~0.5 mL of titrant). The results also provide an example of how the high-temperature tube conversion process can af-

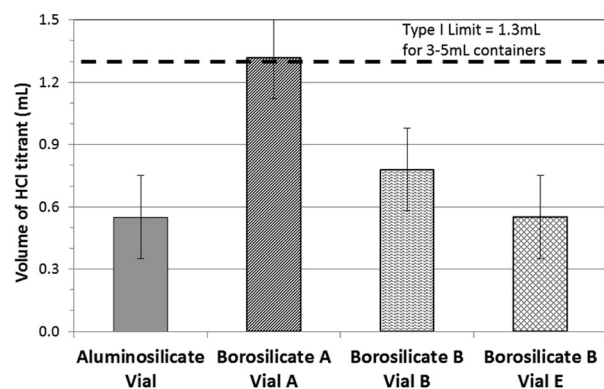


Figure 1

Hydrolytic testing results (USP <660> Surface Glass Test, EP3.2.1 Test A) of ion-exchanged alkali aluminosilicate 3 mL vials and three different alkali borosilicate 3 mL vials. Error bars indicate typical measurement variation in a control population.

fect hydrolytic performance. Vial B and Vial E, which were converted from the same Borosilicate B tubing using different conversion processes, show significant differences in hydrolytic performance. And finally, the results show that the hydrolytic performance of the alkali aluminosilicate vials is as good as the best alkali borosilicate vials in this study. These results show that the hydrolytic performance described in USP and EP chapters for alkali borosilicate glasses can be achieved by alkali aluminosilicate glasses.

The same pharmacopeial chapters also provide threshold concentrations for extractable arsenic. In the glass surface tests, the extractable arsenic concentration must be less than 0.1 µg/g. While it is possible to pass this limit test with low concentrations of arsenic in the glass, ideally no arsenic would ever be added. Because the alkali aluminosilicate glasses do not contain arsenic, they should intrinsically meet this requirement. Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) measurements confirm that arsenic is below the detection limit of 0.050 µg/g in extracted solution for the alkali aluminosilicate glasses.

Resistance to Strong Acid/Base

Although chemical durability against strong acids and bases is not an explicit pharmacopeial requirement, many drug products are not neutral solutions. In addition, the mechanisms behind good hydrolytic performance stem from good acid and base durabil-

TABLE II

Thermal, Physical, Mechanical, and Optical Properties and Associated Test Methods of a Few Alkali Borosilicate Glasses and the Alkali Aluminosilicate Glass

	units	TEST METHOD	Type 1B			Type 1A	Aluminosilicate
			Borosilicate A	Borosilicate B	Borosilicate C	Borosilicate H	
Strain Point ($10^{14.5}$ P)	$^{\circ}\text{C}$	ASTM C336-71/2010	525	530	537	525	556
Anneal Point (10^{13} P)	$^{\circ}\text{C}$	ASTM C336-71/2010	560	565	576	560	608
Softening Point ($10^{7.6}$ P)	$^{\circ}\text{C}$	ASTM C338-93/2008	780	785	767	825	870
Working Point (10^4 P)	$^{\circ}\text{C}$	ASTM C965-96/2012	1164	1160		1260	1292
(0–300 $^{\circ}\text{C}$) Thermal Expansion	10^{-7} K^{-1}	ASTM E228-11	52	49	53	33	69
Density	g/cm^3	ASTM C693-93/2008	2.34	2.34	2.41	2.23	2.39
Refractive Index	@ 589nm	various methods	1.49	1.492		1.473	1.493
Stress-Optic Coefficient	$10^{-6} \text{ mm}^2 \cdot \text{N}^{-1}$	ASTM C770-98/2008		3.4		4.0	3.05
Young's modulus	GPa	ASTM C623-92/2010		73		63	71
Poisson's ratio	-	ASTM C623-92/2010		0.2		0.2	0.2

ity. Therefore, glasses with good acid and base durability are expected to show less drug product–container interactions and fewer extractables for a wide range of drug products (including those with neutral pH).

The German Institute for Standardization (DIN) and the International Organization for Standardization (ISO) provide standard tests for strong acid and base durability testing of glass surfaces. DIN 12116 (Testing the resistance of glass to attack by boiling hydrochloric acid solution, and classification) describes a method for characterizing the acid durability of as-formed glass surfaces. Tubing samples (prior to conversion) of both the alkali aluminosilicate and alkali borosilicate glasses were prepared and tested according to DIN 12116. The results were the same for both types of glasses; all of the samples were class S1 in acid resistance ($<1.5 \text{ mg}/\text{dm}^2$). Class S1 indicates the best performance in this test, associated with the minimum weight loss under the test conditions.

ISO 695 (Glass—Resistance to attack by a boiling aqueous solution of mixed alkali—Method of test and classification) also describes a method for characterizing as-formed glass surfaces. This test was also performed on various tubing samples of alkali borosilicate and alkali aluminosilicate glasses. The results showed a small advantage for the alkali aluminosilicate glass. All the alkali borosilicate samples were identified as class A2 ($75\text{--}175 \text{ mg}/\text{dm}^2$), while the alkali aluminosilicate samples were identified as class A2 or better.

Physical, Mechanical, and Optical Properties

In addition to chemical durability, there are many other properties that make glass the preferred material for parenteral packaging. For example, the containers must have a high elastic modulus (and associated low strain) to withstand the container-to-container contact that occurs during the manufacturing, transportation, and filling processes. In addition, the containers must have good transparency to enable the optical inspection needed to ensure a consistent and defect-free product/dose.

Many material attributes including density, refractive index, and Young's modulus were measured on alkali borosilicate and alkali aluminosilicate glasses. Table II shows the specific material attributes, test methods, and results for various alkali borosilicate glasses and the alkali aluminosilicate glass. The results show that the physical, mechanical, and optical attributes for the alkali aluminosilicate are similar to those for the various alkali borosilicates. It is therefore expected that alkali aluminosilicate glasses will perform similarly to alkali borosilicates in terms of drug product inspection, alignment during high-speed filling, and other processes that depend on these physical, mechanical, and optical properties of the container.

Thermal Properties

The thermal properties of a glass affect both the container forming processes (prior to filling) as well as several drug manufacturing processes (during and after filling). For example, the high-temperature thermal properties of a glass influence its ability to be formed

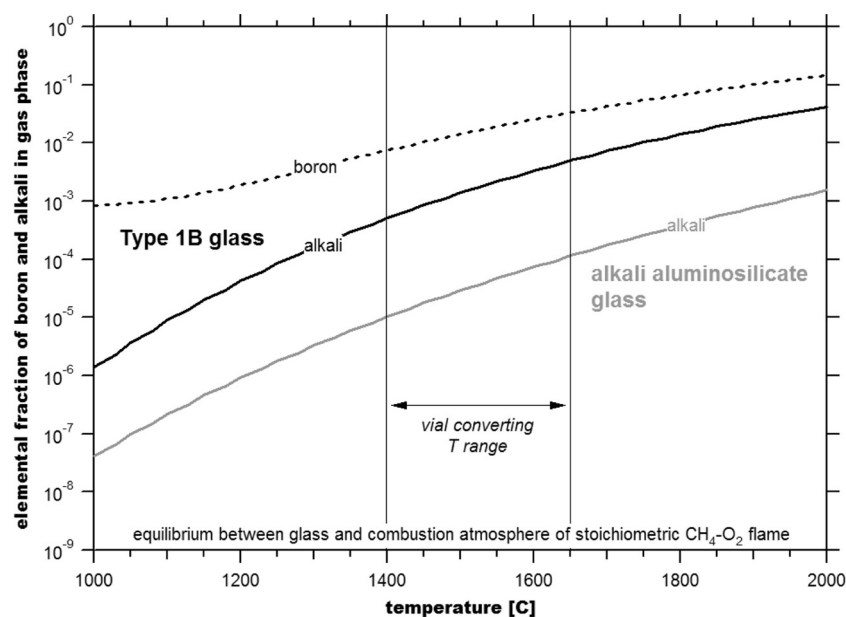


Figure 2

Estimated loss of boron and alkali species from a Type 1B alkali borosilicate glass and the alkali aluminosilicate glass over a range of temperature in a stoichiometric flame. Plot shows the elemental fraction of boron and alkali in the gas phase at equilibrium.

into tubing and to be converted from tubing into complex shapes, as well as the extent of evaporation loss during these processes. And the low-temperature thermal properties influence the upper temperatures for depyrogenation processes and heat transfer efficiency during lyophilization processes.

The results in Table II show that the thermal attributes of the alkali borosilicate glasses vary over a fairly wide range, consistent with the fairly wide variation in their composition (refer to Table I). The results also show that the alkali aluminosilicate glass has a somewhat higher working point and thermal expansion than the Type 1A and Type 1B alkali borosilicates studied. Although some alkali aluminosilicate glasses have already been successfully converted to final shapes (vials, cartridges, syringes, etc.) using existing equipment, some improvements in glass handling, forming, and manufacturing processes may be needed to industrialize alkali aluminosilicate glasses for use in parenteral packaging.

For lyophilization processes, the most important material attribute is thermal diffusivity to enable efficient heat extraction. The thermal diffusivity of the alkali aluminosilicate and various commercial alkali borosilicate glasses were measured via a microflash

method between -40 and $+40$ °C, and the results show no significant difference over this temperature range. The similar thermal diffusivity suggests that heat transfer during lyophilization should be equivalent for the two glass families.

As discussed in the Introduction, literature references point to phase separation or evaporation loss of boron and alkali species as the possible root causes of delamination in alkali borosilicates. It is difficult to evaluate the difference in phase separation behavior between the two glass families, because while phase separation is possible in alkali borosilicates, it is suppressed by the addition of aluminum oxide, and phase separation does not occur in typical alkali aluminosilicate glasses. It is, however, possible to estimate the difference in evaporation loss of boron and alkali species between the two glass families. Thermodynamic modeling (17) was used to estimate the relative loss of boron and alkali species from a Type 1B alkali borosilicate glass and the alkali aluminosilicate glass when exposed to a stoichiometric flame. The results, presented in Figure 2, show that evaporative losses are much lower (by 2–3 orders of magnitude) for the alkali aluminosilicate glass. These results suggest that delamination might be less of an issue in alkali aluminosilicate glasses.

TABLE III

Vial Types, Surface Treatments, Solution Chemistries, and Acceleration Conditions Evaluated in the Extractables Study

Vial Types	Surface Treatments	Solutions	Storage Temperatures	Acceleration
<ul style="list-style-type: none"> Aluminosilicate Borosilicate A, Vial A Borosilicate B, Vial B Borosilicate B, Vial E Borosilicate B, Vial F 	<ul style="list-style-type: none"> Non-treated 3% ammonium sulfate Ion-exchange 	<ul style="list-style-type: none"> pH 7.0, 25mM citrate buffer pH 8.0, 25mM phosphate buffer pH 6.0, 10mM Histidine buffer Water for Injection (WFI) 	<ul style="list-style-type: none"> 25°C 37°C 50°C 	<ul style="list-style-type: none"> Non-autoclaved 1hr autoclave at 121°C

Suitability for Use

The regulatory bodies for pharmaceutical packaging generally review three separate tests for confirmation of drug–container compatibility: (1) extractables studies, (2) leachables data, and (3) stability testing. *Extractables* refers to organic or inorganic substances that are part of the container and may become part of the drug or biologic product during contact. Extractable species are generally identified during accelerated studies (elevated temperatures, increased solution concentration, exaggerated pH, etc.) with representative, but not necessarily active, solutions. *Leachables* defines a subset of extractables that enter the product during non-accelerated, normal storage with active drug or biologic solution (2). Finally, *stability testing* encompasses a variety of tests that verify that the potency, pH, degradates, sterility, appearance, and so on, are all acceptable after storage (accelerated or non-accelerated).

There is no standard protocol for extractables testing because the testing is generally adapted to the partic-

ular packaging materials and the drug or biologic of interest (18). For example, glasses are generally extracted using aqueous solutions with various pH, buffer concentration, and solution chemistry, whereas rubber stopper materials might be extracted using organic solvents (i.e., ethanol, hexane, ethyl acetate). Studies can be performed under accelerated conditions (achieved, for example, by increasing temperature and/or pressure) or non-accelerated conditions.

Table III shows the range of vial types, surface treatments, solution chemistries, storage temperatures, and autoclaving conditions used in the current extractables study. Note that ion-exchange was only performed on the alkali aluminosilicate vial, and ammonium sulfate treatment was only performed on the Borosilicate B, Vial F.

The results of the water for injection (WFI) extraction study are listed in Table IV and plotted in Figure 3. The results show that the alkali aluminosilicate vial has comparable or lower extractables than the alkali borosilicate vials. Despite the change in alkali identity

TABLE IV

Average ICP-MS Concentrations for Vials Autoclaved and Stored in Water for Injection (WFI) at 25°C for 8 Weeks

Values shown in italics indicate the detection limit of the ICP-MS method; in those cases, standard deviation values are not applicable. Sn is not included in the table because it was not detected in any of the samples at any temperature (detection limit for Sn is 0.01 ppm).

ug/g	Aluminosilicate		Borosilicate A Vial A		Borosilicate B Vial B		Borosilicate B Vial E		Borosilicate B Vial F	
	Mean	Pooled SD	Mean	Pooled SD	Mean	Pooled SD	Mean	Pooled SD	Mean	Pooled SD
Al	0.07	0.02	0.71	0.13	0.12	0.01	0.03	0.01	0.07	0.01
B	<i>0.20</i>		1.82	0.12	<i>0.20</i>		<i>0.20</i>		<i>0.20</i>	
Ca	0.16	0.06	0.20	0.03	0.12	0.06	0.08	0.02	0.19	0.05
K	1.13	0.05	0.45	0.02	<i>0.05</i>		0.07	0.01	0.06	0.02
Mg	0.10	0.01	0.10	0.00	<i>0.01</i>		<i>0.01</i>		0.08	0.00
Na	0.70	0.04	3.18	0.12	3.79	0.06	2.48	0.05	1.20	0.04
Si	1.21	0.11	8.61	0.43	1.75	0.15	0.37	0.01	0.95	0.16

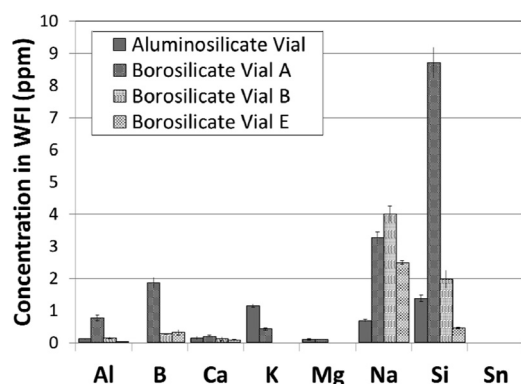


Figure 3

Plot of ICP-MS solution concentrations for metals extracted from alkali borosilicate and alkali aluminosilicate glass vials into WFI after autoclaving and 8 weeks of storage at 50 °C. Error bars represent the pooled standard deviation.

(sodium to potassium), the total amount of alkali released (and the corresponding impact upon solution pH, as reflected by the hydrolytic performance shown in Figure 1) is lower for the alkali aluminosilicate than for the alkali borosilicate vials.

Leachables tests generally show lower concentrations of the same species observed in extractables tests. Unfortunately, owing to the long times involved, the leachables study for this particular combination of container and liquid drug product formulation was not complete at the time of publication. But based on the results of the extractables tests, the expectation is that the alkali aluminosilicate will perform at least as well as the current alkali borosilicate.

A stability study was performed to check the compatibility of the alkali aluminosilicate vials with a specific liquid drug product formulation. Accelerated storage conditions were used to make it easier to see any potential detrimental effects. After sufficient stability data were collected (four time points over 6 months), the degradation kinetics were determined using several stability-indicating methods. The results from one of the stability-indicating methods are shown in Figure 4. The results show that the degradation kinetics for the alkali aluminosilicate vial are within the 2-sigma limit of the historical mean for the commercial alkali borosilicate vial typically used with the selected liquid drug product formulation. Similar results were obtained for the other stability-indicating methods that were used in this study (results not shown). These results suggest that the alkali

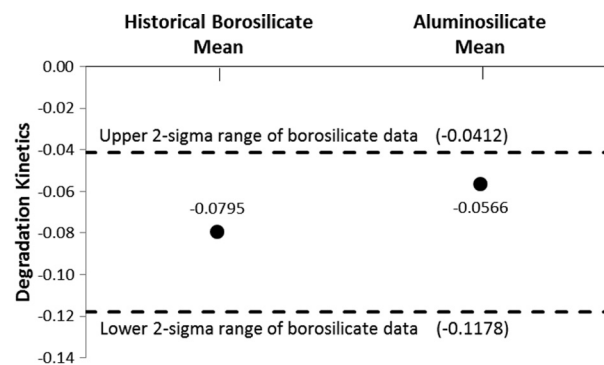


Figure 4

Product degradation kinetics under accelerated storage conditions for one stability-indicating assay when stored in standard alkali borosilicate vials (Historical Mean) and alkali aluminosilicate vials.

aluminosilicate vials would be suitable for use with the studied liquid drug product formulation.

Summary

Alkali aluminosilicates were proposed as an alternative to alkali borosilicates for parenteral packaging, and an example glass was compared to various alkali borosilicate glasses currently used in the pharmaceutical industry. The results show that this glass meets the compendial requirements, and the hydrolytic performance was equivalent to the best alkali borosilicate vial tested. Results from the strong acid and base durability tests suggest that this glass will be compatible with a wide range of drug and biologic chemistries. And results from extractables tests and stability studies suggest that this glass would be suitable for use with the studied liquid drug product formulation. Notably, this glass showed comparable or lower extractables, and indistinguishable degradation kinetics, compared to the current alkali borosilicate glasses.

In addition, this glass was formulated without arsenic or halides, which makes it an environmentally-friendly option. And the new glass prevents phase separation and minimizes evaporation losses, which are thought to contribute to delamination. Taken together, the results suggest that this alkali aluminosilicate glass is suitable for pharmaceutical packaging, and may offer some advantages over the current alkali borosilicate glasses.

Conflict of Interest Declaration

The authors declare that they have no competing interests.

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