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Accelerated Extractable Studies of Borosilicate Glass Containers

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ABSTRACT: This article describes the use of an accelerated extractable procedure for borosilicate glass containers. The procedure, which is very similar to a protocol developed by a PDA Task Force, includes the monitoring of Si, Na, K, Al, Ba, Ca, Mg, Fe, and Zn in the extracts as well as measurements of pH change and total extractables. Unlike the PDA protocol, which uses H_2O as the sole extraction solution, the procedure outlined in this report used a variety of unbuffered ($pH \simeq 4$, H_2O, $pH \simeq 6.5$, $pH \simeq 8.0$, $pH \simeq 9.5$, and $pH \simeq 10.4$) and buffered ($pH = 8$ and $pH = 10$) aqueous extraction media. Studies were completed for several borosilicate glasses, including a mixture of tubing vials, molded vials, and ampoules from US and European suppliers. Results of these studies are presented in this article and are discussed in terms of the interactions between borosilicate glasses and aqueous solutions.

Introduction

Glass containers used in the pharmaceutical industry are durable, but cannot be considered inert. When it is placed in contact with a solution, a variety of interactions can occur, including ion exchange or selective leaching, glass dissolution, pitting, solution concentration, precipitation, stable film formation, surface layer exfoliation, weathering, stress corrosion, and erosion corrosion (1). Glass/media interactions have been studied over sixty years, and during this time period several hundred articles, numerous reviews (1-9), and two extensive bibliographies (10-11) have been published.

Glass corrosion has been a very important subject in a variety of fields outside the pharmaceutical industry (1-34). For example, the weathering of glass has been extensively studied to determine if glass processing costs can be reduced without sacrificing durability and to develop optimum methods for preserving historic windows and glass treasures. The wide use of glass electrodes for chemical analyses and glass columns for chromatographic separations has promoted a detailed characterization of glass/media interactions. Finally, the leaching of glass and other glass corrosion mechanisms have been studied in relation to the storage of radioactive wastes as glasses and the use of glass fiber optics for communication purposes.

Numerous kinds of glasses, types of media, and exposure conditions have been used in studies from these other disciplines (1-34). Borosilicate glasses (USP Type I), soda-lime glasses (USP Types II and III), fused quartz, Vycor glass, simulated nuclear waste glasses, and binary or ternary glass mixtures of oxides have been examined. The medium used for most studies was H_2O, although aqueous solutions containing various salts or chelating agents, acidic media, and alkaline solutions have also been used. In terms of the environmental conditions reported in these studies, glasses were exposed to the media for long time intervals (2-3 years) at room temperature (25°C) or for significantly shorter time intervals (1 hour to 30 days) at elevated temperatures (70-200°C).

The results of weight loss measurements, solution analyses, and various surface analytical measurements from studies in nonpharmaceutical fields (1-34) have led to a good understanding of the qualitative and quantitative characteristics of glass/media interactions. In addition, some of these studies have also provided the scientific basis for the different water attack, glass extraction, and powdered glass tests used by the parenteral industry (4).

Glass and its interactions with solutions have also been important topics in the pharmaceutical industry. Although the pharmaceutical bibliography represents only a small subset of the overall glass bibliography from all disciplines, several articles (35-40) have reviewed the material in relevant pharmaceutical papers. In general, both review and individual articles have listed the composition of pharmaceutical glasses (36-38, 40-42), have discussed the types of interactions between glass containers and pharmaceutical solutions (35-41, 43-48), or have described the various protocols for glass testing (39-40, 44-46).

Concerning the composition of pharmaceutical glasses, a PDA report on Glass Containers (37), *Technical Methods Bulletin No. 3*, described the classification of parenteral glasses according to the USP classification system and the glass manufacturers' designations. Representative compositions of common pharmaceutical glasses were

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also provided in this report. In addition, this Technical Methods Bulletin contained a discussion of factors that can be used for the selection of a glass container and a review of identification test methods for glass containers used by the parenteral industry.

In the case of glass/product interactions many authors have taken the knowledge about glass/media interactions acquired from other fields and have directly applied the information to glass compositions and media used in the pharmaceutical industry. One aspect of glass/product interactions, glass extractables, has been the focus of several papers. The nature of the extractables, the mechanisms by which they arise, and the factors affecting them have been the topics for discussion in these articles (35, 37, 39, 41, 43, 45, 47). However, drug absorption and other glass/product interactions have also been thoroughly discussed, especially in the review by Wang and Chien (38).

As mentioned above, several extraction procedures have been developed for pharmaceutical containers (39–40, 44–48). Similar to glass extractable experiments used in other disciplines, the medium used in most of the protocols is H_2O. In addition, most procedures utilize accelerated extraction conditions where the glass containers are exposed to the extraction solution at an autoclave temperature (121°C) for relatively short time intervals (1–20 hours). However, extraction conditions using lower temperatures (25–70°C) for significantly longer time intervals (3–4 months) have occasionally been used (47). Finally, the types of extractable measurements have involved total extractable alkali, pH shifts, and specific elemental analyses.

Among the various extraction procedures used for pharmaceutical containers, the PDA Extractable Protocol (39) is probably the most general. It is very similar to the USP Water Attack test (49) with one major exception. It uses the same extraction medium, H_2O, and it subjects the containers to the same exposure conditions, 121°C for one hour, as that of the compendial test. However, the protocol includes the monitoring of several elements such as Na, Al, K, Ca, Ba, Fe, Mg, Zn, and Si in the extracts. In addition, the procedure includes measurements of the pH change and the extractable weight and suggests methods of identifying the materials leached from glasses. In contrast, the USP Water Attack test contains only one measurement, a pH titration which is indirectly related to extractable alkali.

It is particularly noteworthy that water is the only extraction medium specified in the PDA Extractable Protocol. However, the PDA Task Force on Glass Extractives noted that the procedure, in principle, could be used with other extraction solutions although some of the tests such as pH change, extractable weight, and the monitoring of certain elements may not be applicable for some extraction media (39). In our glass extractable experiments we have used the PDA protocol, but we have used a variety of unbuffered (pH $\simeq$ 4, H_2O, pH $\simeq$ 6.5, pH $\simeq$ 8.0, pH $\simeq$ 9.5, and pH $\simeq$ 10.4) and buffered (pH = 8 and pH = 10) aqueous extraction media. This report contains the results of our studies with many different US and European borosilicate parenteral glass containers.

Experimental

The extraction studies were done in two different laboratories, one in Crawley, UK and the other in Kalamazoo, MI. Similar experimental procedures were used in both laboratories with the exception of the methods used for some of the elemental analyses.

Preparation of Extraction Media

In addition to High-Purity H_2O (e.g., Milli-Q® Grade Water), which is the extraction medium specified in the PDA protocol (39), other unbuffered (pH $\simeq$ 4, pH $\simeq$ 6.5, pH $\simeq$ 8.0, pH $\simeq$ 9.5, and pH $\simeq$ 10.4) and buffered (pH = 8 and pH = 10) aqueous extraction media were also used. With the exception of water, the unbuffered systems were prepared by adjusting the pH of a High-Purity H_2O solution using a dilute solution of hydrochloric acid (Anachemia; AristaR) or lithium hydroxide (Alpha Products; AristaR). The pH = 8 buffer was prepared by adjusting the pH of a 0.01*M* solution of Tromethamine (2-amino-2-hydroxymethyl-1,3-propanediol); whereas, the pH = 10 buffer was a 0.05*M* sodium carbonate/0.05*M* sodium bicarbonate solution.

The water and the reagents used to adjust the pH were chosen so that the elemental concentration in each unbuffered extraction medium was $\leq$ the appropriate detection limit for each of the nine elements analyzed. Similar precautions were taken for the preparation of the buffered media, and the concentration of Si was $\leq$ detection limit. The detection limits for each element are noted in a later section of this report.

Preparation of Samples

All containers were treated as specified in the PDA protocol (39). In particular, all vials and ampoules were rinsed twice with High-Purity H_2O.

Preparation of Standard Solutions

An aqueous standard stock solution of certified purity was acquired for each element from a commercial source (Spex Industries Inc., National Bureau of Standards, or Scientific Products). For example, the standard stock solution for Na was a 1000-ppm Na solution that was obtained from Spex Industries Inc. In general, the elemental concentration of each stock standard solution was approximately 1000 ppm for the element of interest.

As specified in the PDA protocol (39), working standard solutions were prepared fresh daily from the stock solutions and were stored in acid-rinsed (1 + 1 HNO_3) polyethylene bottles. With the exception of Mg, the working standard solutions were very similar to those noted in the PDA protocol (39). In the case of Mg, the working standard solutions were prepared using 0.6% La.

Extraction Procedure

The extraction procedure was very similar to the one specified in the PDA protocol (39). First, the pH of each extraction medium was measured just prior to the experiment. Before measuring the pH, 10 mg of reagent grade KCl was added and dissolved in a 10 mL aliquot of the extraction medium.

Next, the rinsed sample containers were filled to their nominal capacity with the extraction medium. A minimum of twenty vials or amoules was used for each experiment. More than twenty of the smaller volume containers were used in order to obtain a volume of 200 mL, which was necessary to complete the various analyses described below.

After all the containers were filled, each was covered with a polypropylene (PP) beaker. The PP beakers, which were used as covers, had been previously rinsed twice with High-Purity H_2O and had been exposed to H_2O under autoclave conditions (121°C for 1 hour).

Finally, the filled and covered containers were autoclaved for one hour at 121 ± 1°C. After the containers were cooled, the contents of all glass containers were emptied into an acid-rinsed (1 + 1 HNO_3) polyethylene bottle.

Analyses of Extracts

The combined extracts were subjected to several measurements. A summary of the analytical procedures used in the US studies, which were very similar to those reported in the PDA protocol (39), is given below.

a. pH: The pH of each extract was measured immediately after the extracts were pooled together. Before measuring the pH, 10 mg of reagent grade KCl was added and dissolved in a 10 mL aliquot of the extract.

b. Elemental Analyses: For the analyses of Na, K, Fe, and Zn, an aliquot of the sample extract was analyzed using the appropriate atomic absorption (AA) procedure. The concentrations were determined using an air/acetylene flame and the following AA bands: Na, 589.0 and 589.6 nm peaks; K, 766.5 m band; Zn, 213.9 nm peak; and Fe, 248.3 nm band. Dilution of some samples was necessary in order to perform some of the measurements in a suitable concentration range.

For the AA determinations of Ba and Al, each extract was analyzed in the presence of 1500 ppm NaCl. A blank was prepared in the same manner. The concentrations were determined using a nitrous oxide/acetylene flame and the appropriate AA bands (Al, 309.3 nm; Ba, 553.6 nm). All the Al and Ba measurements were obtained using scale expansion (10×).

Ca and Mg were analyzed in the presence of 0.6% La. A blank was prepared in the same manner. The concentrations were determined using an air/acetylene flame and the appropriate AA bands (Ca, 422.7 nm; Mg, 285.2 nm).

The modifications to the Heteropoly Blue Method, noted in the PDA protocol (39), were used for the analysis of Si (as SiO_2). The band at ≃650 nm was used for all the measurements. Also, an extra step, the addition of 0.1 mL of 1 + 1 H_2SO_4 prior to the addition of the 1 + 1 HCl to the solutions, was used in the Si determinations of the pH ≃ 10 buffered media.

c. Miscellaneous Measurements: Each extract was measured for total extractables by transferring a 100 mL aliquot of the extract to a tared evaporating dish, evaporating the solution on a steam bath to dryness, drying the dish in an oven at 105°C for one hour, cooling it in a desiccator, and weighing it. A blank was treated in the same manner using extraction medium that had not been exposed to glass containers. The total extractables, in mg per 100 mL of solution, was reported as the difference between the amount found in each extract and the blank. Some of the sample and blank residues from the measurements for total extractables were also analyzed by X-ray fluoresence and infrared spectroscopy.

The analytical procedures used in the UK studies were the same as those described above with some noteworthy exceptions. In the UK experiments, analyses for Al, Ba, Ca, Mg, Fe, Zn, and Si were performed using graphite furnace AA procedures instead of the AA flame methods and the Heteropoly Blue Method used in the US studies.

Elemental Analyses: Accuracy, Linearity Range, and Detection Limits

Information pertaining to the accuracy, linearity range, and detection limit of each elemental assay is essential to properly evaluate the results of any extraction study. In principle, a number of variables can affect the accuracy of any elemental determination. However, since the level of extractables found in most glass extractable studies is usually small, there was probably only one factor, the matrix effect of the extraction medium, that could have significantly affected the elemental analyses reported in this report.

To determine if the accuracy of each elemental analysis was adequate, standards, which had been prepared at equivalent concentrations in water (pH ≃ 6.0) and three unbuffered aqueous solutions (pH ≃ 2.0, pH ≃ 4.0, and pH ≃ 10.0), were analyzed. In these studies, a deviation not greater than 10% between the absorbance of standards prepared in H_2O and those prepared at different pH levels was defined as acceptable. The results are shown in Table I. For each of the elements that were analyzed, two different concentrations of standards were examined. The results for most elements were considered acceptable. For those elements (Mg and Na) for which absorbances were not equivalent, some adjustments in the sample preparations were made to overcome unequal response problems. For example, as noted above, all of our Mg determinations were made in the presence of 0.6% La. The procedure for Mg, which is specified in the PDA protocol (39), does not include the addition of La, and this could lead to difficulties if a wide range of pH values were used (see Table I). It is also noteworthy that the addition of KCl to the solutions used for Na determinations was not used even though the data in Table I indicates such a modification would have been desirable. One reason for omission of the KCl addition was that none of our glass studies were done for pH ≃ 2, where the largest absorbances differences in the Na analyses were observed. Another reason is that analytical grade KCl contains a small amount of NaCl, and this leads to a significant bias (≃0.050 absorbance units; ≃0.2 ppm) in the data reported for Na. It is true that the data could have been corrected for the bias. Indeed, a correction was applied to the Na (w/KCl) data shown in Table I. However, the correction was comparable to the values found for Na in some glass extractable experiments, and, consequently, the uncertainty in the measure-

TABLE I. Absorbance Values of Elemental Standards at Different pH Values

Element	Standard (ppm)	Absorbance H_2O pH ≃ 6.0	pH ≃ 2.0	pH ≃ 4.0	pH ≃ 10.0
Na	0.2	0.048	0.086	0.063	0.060
	0.4	0.093	0.144	0.105	0.099
Na[a]	0.2	0.049	0.053	0.050	0.055
(w/KCl)	0.4	0.097	0.099	0.100	0.102
Mg	0.1	0.028	0.040	0.032	0.018
	0.2	0.078	0.080	0.077	0.066
Mg[b]	0.1	0.053	0.058	0.055	0.053
(w/La)	0.2	0.105	0.109	0.104	0.103
K	0.4	0.030	0.038	0.037	0.034
	1.0	0.116	0.121	0.122	0.120
Ca[b]	0.2	0.011	0.012	0.011	0.011
	0.4	0.021	0.022	0.022	0.022
Al[c]	1.0	0.0034	0.0039	0.0038	0.0035
	2.0	0.0078	0.0078	0.0077	0.0076
Ba[c]	0.4	0.0047	0.0050	0.0050	0.0050
	1.0	0.0140	0.0140	0.0140	0.0140
Zn	0.2	0.047	0.048	0.047	0.045
	0.4	0.095	0.094	0.094	0.094
Fe	1.0	0.039	0.039	0.038	0.038
	2.0	0.076	0.074	0.074	0.074
SiO_2	1.0	0.095	0.095	0.090	0.100
(650 nm)	3.0	0.280	0.270	0.265	0.275

[a] With 1000 ppm KCl. Data corrected for presence of Na in KCl.
[b] With 0.6% La.
[c] With 1000 ppm KCl.

ments of low Na determinations would probably not have been significantly better had the KCl addition been utilized.

Si standards were also prepared at equivalent concentrations in unbuffered (pH ≃ 8 and pH ≃ 10) and buffered (pH ≃ 8 and pH ≃ 10) aqueous solutions and analyzed using the Heteropoly Blue Method. The results for Si were acceptable as long as the extra step, the addition of H_2SO_4 described earlier, was used for the measurements of the pH ≃ 10 buffered media.

The concentration range in which a linear response was observed for each element is shown in Table II. The detection limit for each element depended upon the method used for the determination and is also shown in Table II. In general, the graphite furnace AA methods, which were used in the UK studies, had significantly lower detection limits than the flame AA procedures.

TABLE II. Linearity Range and Detection Limits for Elemental Assays

Element	Linear Range (ppm)	US Studies Detection Limit (ppm)	UK Studies Detection Limit (ppm)
Al[a]	0–40.0	≃0.1–0.3	≃0.005
Ba[a]	0–25.0	≃0.1–0.3	≃0.005
Ca[a]	0–5.0	≃0.1	≃0.005
Mg[a]	0–0.5	≃0.01–0.02	≃0.005
Na[b]	0–1.0	≃0.06	≃0.06
K[b]	0–2.0	≃0.05	≃0.05
Fe[a]	0–5.0	≃0.1	≃0.005
Zn[a]	0–1.0	≃0.02	≃0.007
Si[c]	0–2.5	≃0.1	≃0.01

[a] US Studies: Flame AA; UK Studies: Graphite Furnace AA.
[b] US Studies: Flame AA; UK Studies: Flame AA.
[c] US Studies: Heteropoly Blue Method; UK Studies: Graphite Furnace AA.

Discussion

Extractable Protocol

Table III provides a comparison of the key features of the extraction procedure used in our studies with those of

TABLE III. Accelerated Procedures for Glass Extractables

	USP Water Attack Test	PDA Extractable Protocol	Extractable Procedure, This Study
Extraction medium	H_2O	H_2O	H_2O Unbuffered H_2O (pH ≃ 4–10) Buffered H_2O (pH ≃ 8–10)
Extraction conditions	Autoclave 121 ± 1°C 1 hr	Autoclave 121 ± 1°C 1 hr	Autoclave 121 ± 1°C 1 hr
Extract analyses	Total alkali	pH change Na, Al, K, Ba, Ca, Fe, Mg, Zn, Si Total extractables ID methods	pH change Na, Al, K, Ba, Ca, Fe, Mg, Zn, Si Total extractables ID methods

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