

RESEARCH ARTICLE

Aluminum elution and precipitation in glass vials: effect of pH and buffer species

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Abstract

Inorganic extractables from glass vials may cause particle formation in the drug solution. In this study, the ability of eluting Al ion from borosilicate glass vials, and tendencies of precipitation containing Al were investigated using various pHs of phosphate, citrate, acetate and histidine buffer. Through heating, all of the buffers showed that Si and Al were eluted from glass vials in ratios almost the same as the composition of borosilicate glass, and the amounts of Al and Si from various buffer solutions at pH 7 were in the following order: citrate > phosphate > acetate > histidine. In addition, during storage after heating, the Al concentration at certain pHs of phosphate and acetate buffer solution decreased, suggesting the formation of particles containing Al. In citrate buffer, Al did not decrease in spite of the high elution amount. Considering that the solubility profile of aluminum oxide and the Al eluting profile of borosilicate glass were different, it is speculated that Al ion may be forced to leach into the buffer solution according to Si elution on the surface of glass vials. When Al ions were added to the buffer solutions, phosphate, acetate and histidine buffer showed a decrease of Al concentration during storage at a neutral range of pHs, indicating the formation of particles containing Al. In conclusion, it is suggested that phosphate buffer solution has higher possibility of forming particles containing Al than other buffer solutions.

Keywords

Acetate buffer, aluminum, borosilicate glass, citrate buffer, extractables, histidine buffer, phosphate buffer

History

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Introduction

For injectable drugs, particularly for liquid injectables, components of the drugs are regularly in contact with the surface of the packaging systems which should protect the drug against any contamination from the external environment during storage. Therefore, it is essential to evaluate the physicochemical compatibility between the drug formulation and the packaging components in order to select appropriate primary packaging systems during the course of formulation development of injectable drugs^{1–3}.

Among the packaging materials that are compatible with injectable drug solutions, glass containers, such as vials or ampoules, have been widely chosen and used. Borosilicate glasses in particular are known to have good chemical durability and are used commonly in the pharmaceutical industry as the primary container⁴. However, these glass containers, even when made from borosilicate glass, can produce some undesirable events that unavoidably occur from being in contact with drug solutions in long-term storage⁵. Formation of particles in drug solutions is

well-known among drug manufacturers, as one of the events from incompatibility between a drug solution and glass container.

Some researchers have reported that some elements in drug solutions are known to induce the degradation of glass surfaces, which correlates with particle formation, as the result of delamination on the degraded surface⁶. Brown et al.⁷, Bacon et al.⁸ and Ernsberger⁹ evaluated glass corrosion focusing on phosphate buffer, citrate buffer and EDTA, respectively. Iacocca et al.¹⁰ also reported a correlation between glass corrosion and SiO₂ elution, using glutaric acid.

In addition to the delamination, in the case of storing glass vials containing drug solution, there is another mechanism to form particles during the storage; a precipitation due to chemical interaction between the drug solution and extractables from the glass vials. There are some researchers^{11–13} who reported the precipitation of the drug solution and there are also researchers^{14,15} who discussed extractables from the glass; however, there is less comprehensive information on the effect of the interaction between the drug solution and the extractables.

As we reported previously¹⁶, phosphate buffer solution in a borosilicate glass vial has the ability to form particles due to interactions with the aluminum (Al) that is eluted from the glass during storage. Silicon (Si) elution at the time the particles formed in phosphate buffer solution was 2–8 ppm and these values are thought to be lower than those from reports that mention about glass corrosion^{10,17}. These results suggest that the particles in

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phosphate buffer solution can be formed under a situation where glass degradation hardly occurs on the surface of glass vials. The issue of Al-phosphate complexes leading to particle formation should therefore be brought to the attention of researchers working on drug formulation.

Citrate buffer, acetate buffer, and histidine buffer are also selected for injectable drug products, especially biological drugs, in order to maintain the pH of the drug solution within the appropriate range from the point of view of drug stability. The ability of these buffers to elute Al from glass vials and induce particle formation should be evaluated.

In this study, we investigated the ability of the four aforementioned buffer solutions to elute Al from glass vials and the tendency to form Al-containing precipitates.

Materials and methods

Materials

Dibasic sodium phosphate, monobasic sodium phosphate, sodium chloride, citric acid, sodium citrate and acetic acid were all special-grade reagents purchased from Kanto Chemical (Tokyo, Japan) or Wako Pure Chemical Industries (Osaka, Japan). L-Histidine was of USP compendium quality purchased from Research Organics Inc. (Cleveland, OH). For pH adjustment, 1 mol/L or 0.1 mol/L of aqueous sodium hydroxide or aqueous hydrochloric acid were purchased from Kanto Chemical or Wako Pure Chemical Industries. Both aluminum oxide powder (α type, particle size 35–50 μm) and silicon dioxide (amorphous, particle size approximately 3–25 μm) were purchased from Kanto Chemical. The other chemicals were all commercially available, reagent-grade chemicals. All water used in this study was ultrapure water supplied by an ultrapure water system (Millipore, Billerica, MA).

Borosilicate (Type I) tubing glass vials (colorless, 10 mL) were obtained from Fuji Glass (Tokyo, Japan) without any special treatment on the surface. The glass vials were manufactured from glass tubes supplied by Nippon Electric Glass (Shiga, Japan). Plastic vials (Daikyo CZ resin, colorless, 10 mL) were obtained from Daikyo Seiko (Tokyo, Japan). For rubber closures, S10-F6, D777-1 and RB2-40 closures were obtained from Daikyo Seiko.

Buffer preparation

Phosphate buffer solutions were prepared from monobasic sodium phosphate or dibasic sodium phosphate and sodium hydroxide, citrate buffer solutions were prepared from citric acid and sodium hydroxide, acetate buffer solutions were prepared from acetate and sodium hydroxide, and histidine buffer solutions were prepared from histidine or histidine chloride and hydrochloric acid, respectively. All of the buffer solutions contained 0.9% sodium chloride, which served as a tonicity agent.

Preparing buffer solutions with aluminum (Al) ions

The given concentration of aluminum (Al) ions was prepared by diluting an Al standard solution for ICP 1000 mg/L (Kanto Chemical) with the buffer solution. To eliminate the amount of Al eluted from a glass vial, these solutions were stored in plastic vials.

Filling and storage of the sample solution

Rubber closures and plastic vials were washed with water and then autoclaved in a steam sterilizer (HV-25, Hirayama, Saitama, Japan) at 121 °C for 30 min. Glass vials were washed with water and then heat sterilized in a clean oven (DRC633FA, Advantec, Tokyo, Japan) at 310 °C for 1 h. Sample solutions were filtered by

a 0.22 μm Millex GV Durapore membrane filter (Millipore), then 10 mL was added to each vial in a clean bench, and the vial was immediately stoppered and capped. Each filled sample was stored at the given conditions or was heated to the given conditions in the steam sterilizer.

Preparing suspensions containing powders in buffer solution

Suspensions containing powder of aluminum oxide or silicon dioxide in the four kinds of buffer solution were prepared by suspending approximately 10–30 mg of the powder with 5 mL of buffer solution (50 mM, pH 5 or 7) in a plastic tube (Becton Dickinson, Franklin Lakes, NJ), and the tube was stored at 25 °C for 2 days or 6 months in a horizontal position.

Visual inspection

Each sample vial was inspected for insoluble particulate matter under a 5000 Lux light condition.

Particle counting

To confirm the results of visual inspection and to measure sizes of particles, laser particle-counting instrument PC-2300 (Spectrex, CA) was used. Features of this apparatus are described by Iacocca et al.¹⁰. Calibration was done using polystyrene spheres (4–5 μm , ca. 960 particles/mL). Prior to measurement, each vial exterior was wiped to remove surface contaminants and then the vial was gently swirled for ~3 s.

In this study, all vials, which particles were observed by visual inspection (detectable size: more than 200 μm), were confirmed to be detected more than 500 particles/mL using this apparatus.

Energy dispersive X-ray spectrometry (EDX) analysis

EDX analysis was performed under the same procedure as reported previously¹⁶, using SEM-EDX (JSM-5600LV JED-2140, JEOL, Tokyo, Japan).

Inductively coupled plasma (ICP) analysis

Al and Si concentrations were measured using inductively coupled plasma optical emission spectrometry (ICP-OES) (VISTA-PRO, Seiko Instruments, Chiba, Japan). To avoid effects of precipitating particles or the powders on measurement, each sample solution was filtered through a 0.45 μm Millex HV Durapore membrane filter (Millipore) prior to the measurement. The filtrates were transferred into a polypropylene 15 mL plastic tube (Becton Dickinson). Standard solutions were prepared by serial dilution of an ICP standard 1000 mg/L of multi-element IV (including Ag, Al, B, Ba, Bi, Ca, Cd, Co, Cr, Cu, Fe, Ga, In, K, Mg, Mn, Na, Ni, Pb, Sr, Tl and Zn) and an ICP standard 1000 mg/L of Si (Merck, Darmstadt, Germany) with 0.9% sodium chloride solution. The nominal detection wavelength for analysis was 396.152 nm for Al and 251.611 nm for Si. When measuring a sample just after conducting terminal sterilization, 1–10 mM of citrate buffer solution was added for the purpose of inhibition of precipitation of elements eluted before analysis.

Results and discussion

Observation of particles in various pH of phosphate buffer solutions in glass vials during storage

Table 1 shows the results of a visual inspection of the vials filled with pH 5–8 of phosphate buffer solution (10 and 50 mM) after storage at 40, 60 and 80 °C. Under the storage condition at 40 °C for 3 months, particles were detected only in the sample of 50 mM

Table 1. Results of visual inspection of phosphate buffer solution (10 and 50 mM) in various pHs.

Solution	Storage		Vials detected particles/vials inspected			
	Temperature	Period	pH 5	pH 6	pH 7	pH 8
Phosphate buffer (10 mM)	40 °C	3 months	0/5	0/5	0/5	0/5
	60 °C	1 month	0/5	0/5	2/5	0/5
		2 months	0/5	0/5	5/5	0/5
	80 °C	2 weeks	0/5	3/5	2/5	0/5
		1 month	5/5	5/5	5/5	5/5
Phosphate buffer (50 mM)	40 °C	3 months	0/5	0/5	3/5	0/5
	60 °C	1 month	0/5	2/5	3/5	0/5
		2 months	0/5	5/5	5/5	0/5
	80 °C	2 weeks	0/5	3/5	3/5	0/5
		1 month	5/5	5/5	5/5	5/5

at pH 7. At 60 °C for 2 months, particles were detected at pH 6 and 7 for 50 mM and pH 7 for 10 mM. At 80 °C for 1 month, all samples contained particles, and for 2 weeks, some particles were detected at pH 6 and 7 for both 10 and 50 mM. All samples which were detected particles visually (*ca* 200–2000 μ m) were observed to contain lots of subvisible (<50 μ m) particles, since laser-particle counting showed more than 500 particles/mL. It is noteworthy that average mean sizes of these particles were within a range of 5–10 μ m (data not shown) in comparison with the report which describes that average sizes of delaminated glass particles were approximately 20–25 μ m¹⁰, suggesting these particles in this study are different from delaminated glass particles.

These results indicate that the tendency for the particle formation depends on the temperature and pH. As reported previously¹⁶, particles formed from a phosphate buffer in glass vials after storage are thought to be complexes of phosphate and Al which are eluted from the surface of glass vials. In that study, we used phosphate buffer solution at pH 7 and 16 mM as phosphate. From the results of this study, it is thought that phosphate buffer solution at pH 6 and 7 has higher possibility of these particle formations than pH 5 and 8. Considering that 50 mM buffer solution at pH 6 formed particles at 60 °C for 2 months but 10 mM did not, the higher concentration is thought to form more particles.

Observation of particles in phosphate, citrate, acetate and histidine buffer solutions in glass vials during storage

Next, we performed another stability study using four kinds of buffer solutions; phosphate buffer, citrate buffer, acetate buffer and histidine buffer. The buffer solutions we used in this study were all 50 mM and pH 7 and were stored at 40, 60 or 80 °C for up to 3 months. The results of visual inspection after storage are shown in Table 2. In citrate buffer and histidine buffer, no particles were observed under these storage conditions. On the other hand, acetate buffer formed particles in the samples stored at 60 and 80 °C as well as phosphate buffer. The EDX analysis of the particles that were collected from the acetate buffer (60 °C, 2 months) showed Al and O, and hardly showed Si (data not shown). We confirmed the vials containing visually detectable size (*ca.* 200–500 μ m) also had lots of subvisible particles detected by laser-particle counting and these mean sizes were within a range of 5–10 μ m (data not shown).

These results suggest that not only phosphate buffer but also other buffer solutions are at risk to form particles containing Al. Comparing the time to form these particles between in phosphate and acetate buffers at 60 °C, the particles were formed in phosphate buffer earlier than in acetate buffer.

Table 2. Results of visual inspection of various buffer solutions (50 mM, pH 7).

Storage	Temperature	Period	Vials detected particles/vials inspected			
			Phosphate	Citrate	Acetate	Histidine
40 °C		2 months	0/5	0/5	0/5	0/5
60 °C		1 month	5/5	0/5	0/5	0/5
		2 months	5/5	0/5	2/5	0/5
80 °C		1 month	5/5	0/5	5/5	0/5
		2 months	5/5	0/5	5/5	0/5

Evaluation of eluting amount of Al and Si from glass vials by phosphate and other buffer solutions using heat treatment

To confirm if the pH of phosphate buffer has an effect on the eluting tendency of Al and Si from a glass vial, we measured the Al and Si concentrations in phosphate buffer solution just after extraction at a high temperature. The high temperature eluting study was conducted for a short time to prevent the concentrations of extracted ions from reaching critical time that lead to undesired effects such as precipitation.

Phosphate buffer solutions at various pHs (20 mM) were filled in glass vials. Heat treatment (105 °C, 60 min) was performed, and then each solution in the vial was transferred into a plastic tube, adding citrate buffer to inhibit precipitation of Al complexes. The results of Al and Si concentration using the ICP method were shown in Figure 1, showing that higher pH elutes both Al and Si higher in the range of pH 4–11. It is noteworthy that the ratio of Si to Al of the sample just after heating was approximately 10:1 in all of the tested samples having a detectable level of Al and Si (pH > 6). The glass vial used in this study was made of borosilicate glass tubing manufactured by Nippon Electric Glass. The amount of SiO₂ and Al₂O₃ in the glass from Nippon Electric Glass is 70–75 and 5–10%, respectively, and this formulation means that the ratio of Si to Al as an atomic element is estimated to be approximately 6–13¹⁶. The ratio of approximately 10 is quite similar to the ratio of the Si/Al concentration just after heating, suggesting that both Si and Al were eluted from the glass vials in ratios similar to composition of the borosilicate glass, at any pH level.

To compare eluting tendency of Al and Si from the glass vial among the four kinds of buffer solution (phosphate, citrate, acetate and histidine), measurement of Al and Si concentration was conducted in addition to the 20 mM phosphate buffer solution. The four kinds of buffer solution (50 mM) were filled in glass vials and heated (105 °C, 60 or 240 min), then Al and Si were measured in the same manner as mentioned above. As well as phosphate buffer solution, three other kinds of buffer solution showed that they elute Al and Si depending on their pH with the ratio of composition of the borosilicate glass (Figure 2).

Bacon et al.⁸ reported that higher pH of citrate buffer eluted higher Si in glass vials after terminal sterilization (121 °C, 60 min). Our results reveal that not only Si but also Al is eluted from the glass vials depending on the pH.

Figure 3 shows the results of Al and Si concentrations for 10 or 50 mM of the four kinds of buffer solutions (pH 7) after heating at 105 °C, 60 min. The order of eluting amounts of Al and Si from the four buffer solutions at pH 7 as follows; citrate > phosphate > acetate > histidine. In addition, higher levels of Al and Si are eluted from 50 mM citrate, phosphate and acetate buffers relative to 10 mM buffers indicating that elution from glass vials depends on the concentration of the buffering agents.

The four kinds of buffer have different pH-buffering capacity due to the differences of their pK_a , however, citrate buffer showed the highest Al and Si elution amounts at all pHs in this study. These results suggest that the eluting ability does not have a correlation with the buffering capacity.

From these results, it suggests that each buffer solution has its own eluting ability from glass containers depending on temperature, time and its concentration.

Evaluation of concentration of Al during storage after heat treatment

The four kinds of buffer solution in the glass vials as described in the previous section were stored at 5 °C for 5 months. After storage, the particles were observed only in the samples in the range of pH 6–9 of phosphate buffer, and in pH 6 and 7 of acetate buffer (data not shown). These particles were also detected by laser-particle counting. Each solution was filtered through a 0.45 μm filter, then the Al concentration of the filtrate was measured (Figure 4). Comparing the Al concentrations with the concentration before storage (i.e. just after heating), remarkable decreases of Al concentration were observed in the range of pH 6–9 of phosphate buffer and in pH 7 of acetate buffer. On the other hand, in citrate buffer and histidine buffer, little change was observed before and after storage.

It should be noted that the buffer conditions (pH 6, 7, 8 and 9 of phosphate buffer, and pH 6 and 7 of acetate buffer) in which the particles formed were identical to those in which Al concentration decreased. Previously, we reported that phosphate buffer solution

at pH 7 has the ability to form particles due to interactions with the Al that is eluted from the glass during storage¹⁶. In this section, we showed the pH range which has the ability to form particles in phosphate buffer. Besides, it is also revealed that particles containing Al form in acetate buffer. The citrate buffer solution, where a decrease in the Al concentration was not shown and particles did not form, is thought to keep Al from precipitation in the solution due to its chelating ability. In the case of histidine buffer solution, we were not able to reveal if histidine buffer has the ability to form particles, since the Al concentrations were very low before storage.

Evaluation of solubility of aluminum oxide and silica in the various buffer solutions

The solubility of powder of aluminum oxide and silicon dioxide (silica), simulated as materials of borosilicate glass, was measured in the phosphate buffer solution. The powder of aluminum oxide or silica was suspended with various pHs of phosphate buffer solution (20 mM) in plastic tubes and the tube was stored at 25 °C for 2 days. Each of the tubes was filtrated, then the Al concentration for aluminum oxide or Si concentration for silica of each filtrate was measured. These concentrations at various pHs are shown in Figure 5. Al concentrations at neutral pHs were lower than both at acidic and alkali pHs. On the other hand, Si concentration became higher along with the increase of pH of buffer solution. The tendencies of the solubility profile of both aluminum oxide and silica in the buffer solutions are considered reasonable; since it is well-known that aluminum oxide has both acid-soluble and alkali-soluble species and silica is more soluble as the pH increases in other common aqueous solutions. However, it is emphasized that the solubility profile of the Al concentration was absolutely different from the elution profile of Al ion from glass vials (Figure 2), showing the higher pH elutes higher Al. Furthermore, each Al concentration was remarkably lower than one-tenth of Si at pHs greater than 7. On the surface of the glass, Al is speculated to be forced to leach into the buffer solution in accordance with Si elution, especially at neutral pHs.

The solubility of powder of aluminum oxide and silica in the other three kinds of solution was also measured. The powder of aluminum oxide or silica was suspended with pH 5 or 7 of the buffer solution (50 mM) in plastic tubes and the tube was stored at 25 °C for 6 months. As shown in Figure 6, all of the buffer solutions at pH 7 showed a lower Al concentration than at pH 5. On the other hand, for silica, the buffer solutions at pH 7 showed a higher Si concentration than at pH 5. The Al concentration in phosphate, citrate, acetate and histidine buffer at pH 7 was 0.07, 0.31, 0.00 and 0.01 ppm, respectively, and the Si concentrations in these buffers were 14.2, 27.1, 6.3 and 8.5 ppm, respectively.

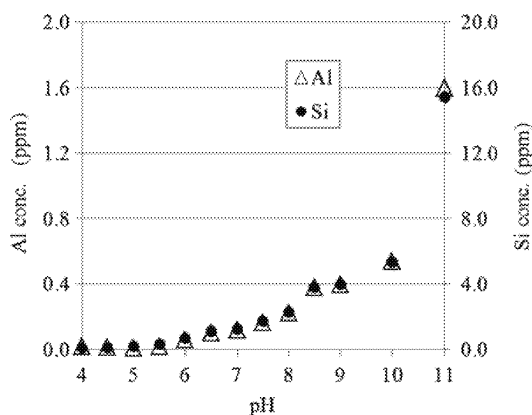


Figure 1. Al (opened triangle) and Si (filled circle) concentrations in phosphate buffer solutions (20 mM) in glass vials heated at 105 °C for 60 min.

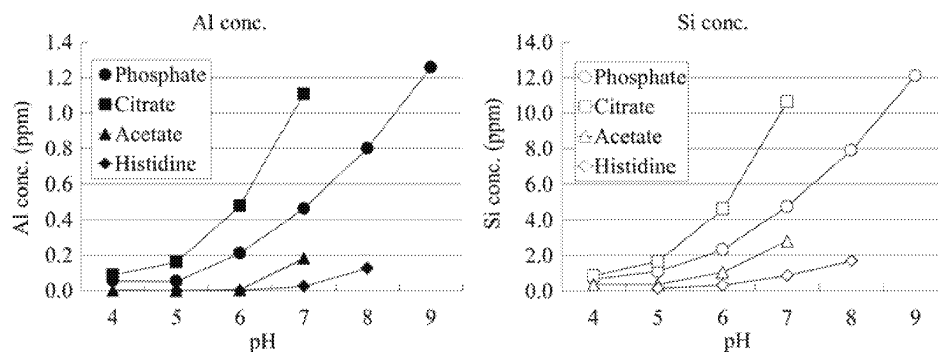


Figure 2. Al and Si concentrations in phosphate, citrate, acetate and histidine buffer solutions (50 mM) in glass vials heated at 105 °C for 240 min.

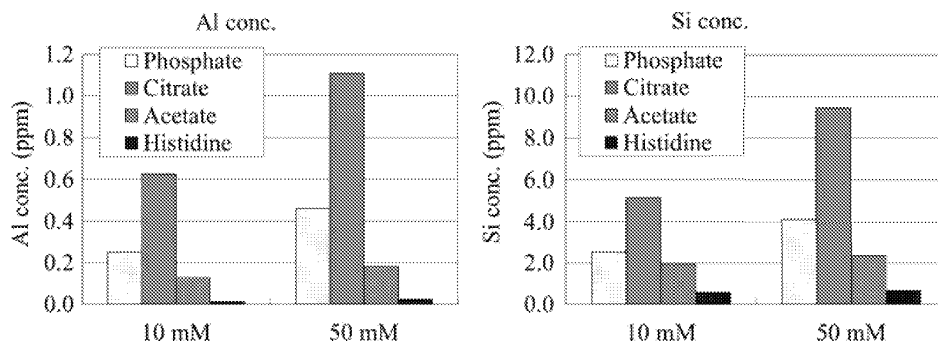


Figure 3. Al and Si concentrations in various buffer solutions (10 or 50 mM, pH 7) in glass vials heated at 105 °C for 240 min.

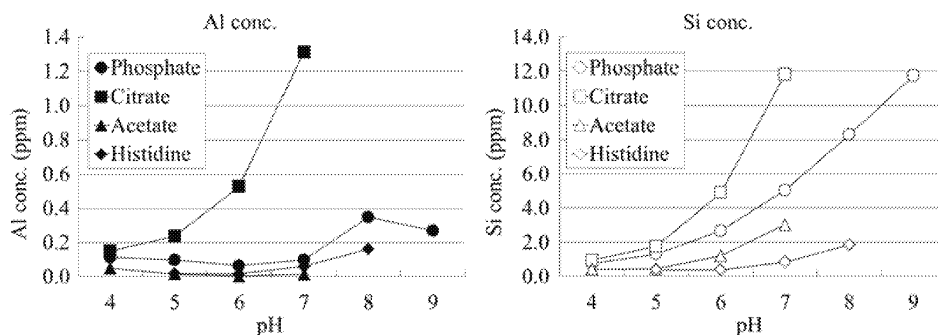


Figure 4. Al and Si concentrations in phosphate, citrate, acetate and histidine buffer solutions (50 mM) in glass vial stored at 5 °C for 5 months after heat treatment 105 °C for 240 min.

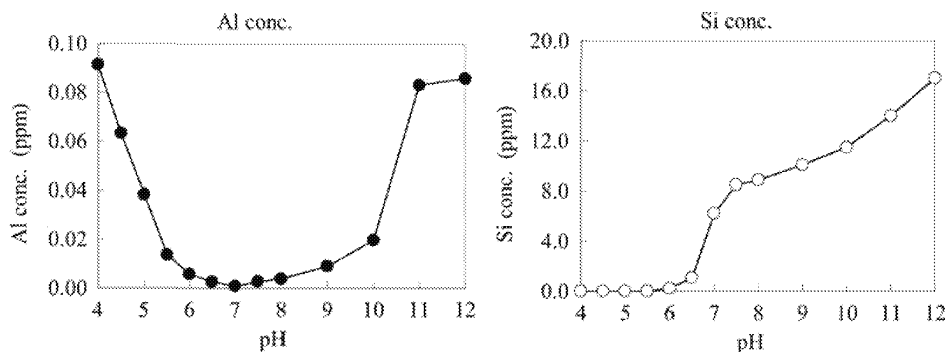


Figure 5. Al or Si concentration in suspensions of aluminum oxide powder or silica, respectively. All suspensions (in phosphate buffer, 20 mM) were stored at 25 °C for 2 days.

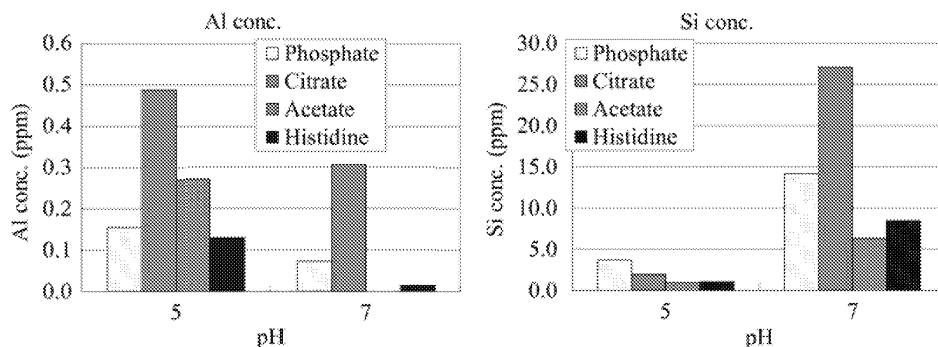


Figure 6. Al or Si concentrations in phosphate, citrate, acetate and histidine buffer solutions (50 mM). Left: Al concentrations in suspensions of aluminum oxide powder. Right: Si concentrations in suspensions of silica. Suspensions were prepared from phosphate, citrate, acetate or histidine buffer solution (50 mM) and were stored at 25 °C for 6 months.

At pH 7, each buffer solution showed different Al and Si concentrations, and the orders of both concentrations were the same (citrate > phosphate > histidine > acetate). It is noteworthy that the order has some similarities to the eluting study as shown in Figure 3 (citrate > phosphate > acetate > histidine). It is suggested that those eluting amounts of Al and Si into the buffer solutions in glass vials during storage has a correlation with the solubility of both aluminum oxide and silica.

On the other hand, at pH 5, it is speculated that Si would be eluted slightly from the glass vial due to low solubility of silica, regardless of buffer species. As a result, Al would be eluted slightly, although all buffer species have relatively high solubilities of aluminum oxide.

The phenomenon that Al and Si were eluted from glass vials in ratios similar to the composition of borosilicate glass although Si has high solubility, suggests that the coordination of Al with Si is tight and also suggests that the low solubility of Al contributes the chemical durability of the glass.

Effect of adding Al ions to the various buffer on the particle formation

In our previous report¹⁶, formation of particles containing Al, P and O was observed in phosphate buffer solutions by adding the Al ion. As well as phosphate buffer, we evaluated whether other buffers have a possibility to interact with the Al ion and to form precipitate particles.

One or 0.5 ppm of Al ions were added to the four kinds of buffer solution (20 mM; pH 4.0–11.0 for phosphate, pH 4.0–8.0 for citrate, pH 4.0–7.5 for acetate and pH 5.0–9.0 for histidine), and each solution was placed in a plastic vial and then stored at 5 °C for 1 month. The results of visual inspection are shown in Table 3. In the buffer solutions with 0.5 ppm of the Al ion, particles formed only in the phosphate buffer at the range of 6.0–9.0; on the other hand, with 1 ppm of the Al ion, particles formed not only in phosphate buffer but also in acetate buffer (pH 6.5 and 7.0) and histidine buffer (pH 7.0, 7.5 and 8.0). No particles were observed in all pHs of citrate buffer. As a result of the EDX analysis of the particles that were collected from the acetate buffer (pH 6.5) and histidine buffer (pH 7.5), these particles contained at least Al and O (data not shown). It is difficult to confirm whether these particles contained acetate and histidine buffer species since EDX does not clearly detect carbon (C). However, these results suggest the possibility that acetate buffer and histidine buffer form some particles containing Al at a certain pH range.

Furthermore, the Al concentration in the filtrate of each buffer solution adding 0.5 ppm of the Al ion after 1 month storage at 5 °C was measured (Figure 7). For phosphate, acetate and histidine buffer, the Al concentrations decreased from 0.5 ppm

at neutral pH. On the other hand, for citrate buffer, Al concentrations did not decrease in all the pHs in this study. These results suggest that each buffer has a different ability to maintain Al ion soluble, thus particle formation is observed at the pHs with low solubility for Al complexes. In this study, acetate buffer and histidine buffer solution with additional 0.5 ppm of the Al ion did not show particles although the Al concentration in neutral pHs decreased remarkably. The results suggest that these buffer solutions with 0.5 ppm of the Al ion at neutral pHs might have certain particles which contain Al, but the particles are too small or too slight to be detected.

Conclusions

In this study, the ability of eluting the Al ion from glass vials, and tendencies of precipitation containing Al were investigated using various pHs of phosphate, citrate, acetate, and histidine buffer.

Through heating, all of the buffers showed that Si and Al were eluted from glass vials in ratios similar to the composition of borosilicate glass at any pH. This suggests that each buffer solution has its own eluting ability from glass which is the container for this solution, depending on the eluting temperature, time and its concentration. In addition, during storage after the heating, the Al concentration of certain pHs of phosphate and acetate buffer solution decreased, suggesting the formation of particles containing Al. In citrate buffer, Al did not decrease over time in spite of the high elution. From the results, where the Al solubility profile between aluminum oxide and borosilicate glass was different, it is speculated that the Al ion may be forced to leach into the buffer solution according to Si elution on the

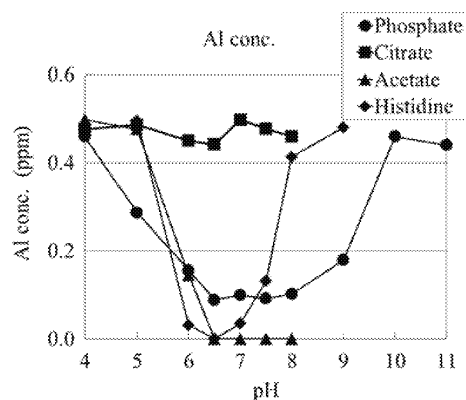


Figure 7. Al concentration of filtrate of phosphate, citrate, acetate and histidine buffer solutions (20 mM) with 0.5 ppm of Al ion, stored at 5 °C for 1 month.

Table 3. Results of visual inspection of various buffer solutions (20 mM) with Al ion.

pH	Particle (White particle) detection							
	Phosphate		Citrate		Acetate		Histidine	
	0.5 ppm Al	1.0 ppm Al	0.5 ppm Al	1.0 ppm Al	0.5 ppm Al	1.0 ppm Al	0.5 ppm Al	1.0 ppm Al
4.0	No	No	No	No	No	No	No	No
5.0	No	No	No	No	No	No	No	No
6.0	Detected	Detected	No	No	No	No	No	No
6.5	Detected	Detected	No	No	No	Detected	No	No
7.0	Detected	Detected	No	No	No	Detected	No	Detected
7.5	Detected	Detected	No	No	No	No	No	Detected
8.0	Detected	Detected	No	No	No	No	No	Detected
9.0	Detected	Detected	No	No	No	No	No	No
10.0	No	No	No	No	No	No	No	No
11.0	No	No	No	No	No	No	No	No

surface of glass vials. When Al ions were added to the buffer solutions, phosphate, acetate and histidine buffer showed a decrease of Al concentration during storage at a neutral range of pHs, indicating the formation of particles containing Al.

In conclusion, it is suggested that phosphate buffer solution has higher possibility of forming particles containing Al than other buffer solutions, since phosphate buffer elutes higher Al than acetate and histidine buffer and has the ability to interact with Al. Citrate buffer, known as a chelating agent, does not have the possibility to form particles although it elutes the highest Al out of these buffer solutions. Acetate and histidine buffers have a lower risk to form particles than phosphate due to the poor eluting ability. The results from this study will provide a number of pharmaceutical researchers working on drug formulation with additional information about selecting buffer solutions from the perspective of particulate matter formation.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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