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Silicate release from glass for pharmaceutical preparations

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Abstract

Glass is made of polymeric silica and other minor components, which are necessary for turning the silica into a material more easily moldable and resistant to temperature changes. Glass containers for pharmaceutical usage are classified according to their resistance to a chemical attack, a test carried out in the presence of water and heat. The test is designed to show the released alkalinity, a variable dependent on the amount of sodium oxide, one of the minor components added to the glass mass. In this work, the release of silica from glass by action of constituents from pharmaceutical formulations was investigated. The study included products used in large volumes and usually stored in glass containers. Solutions of amino acids, electrolytes, glucose, oligoelements and others such as heparin and sodium bicarbonate were individually stored in glass containers and heated at 121 °C for 30 min, as in the water attack test. The test was also carried out only with water, where the pH varied from 2 to 12. The released silicate was measured either by photometry or atomic absorption spectrometry, depending on the nature of the sample. The results showed that silicate is released during the heating cycle even if the contact is with pure water only. The pH exerts a considerable influence on the release, being that the higher the pH, the higher the silica dissolved. An elevated pH, however, is not the only factor responsible for silica dissolution. While in the solutions of NaCl, KCl, Mg Cl_2 and $ZnSO_4$ and in most of the amino acids, the concentration of silicate was as high as in pure water (0.1–1.0 mg Si/L). In the solutions of sodium acetate, bicarbonate and gluconate, its concentration was much higher, over 30 mg Si/L. These results were confirmed by the analysis of commercial products, where in solutions of amino acids the level of silicate ranged from 0.14 to 0.19 mg Si/L. On the other hand, calcium gluconate, sodium bicarbonate and potassium phosphate presented silicate levels from 1 to 4 mg/L. Although silica is not considered a toxic substance for humans, it is necessary to be aware of its presence in solutions for parenteral nutrition due to the direct introduction into the bloodstream and the large volume usually administrated, even to pre-term infants.

Keywords: Glass; Silicon; Parenteral nutrition; Contamination

1. Introduction

Although silicon is not recognized as a toxic species for humans and is even used as a food additive, the toxicological effects of silica are not well documented. It is considered an essential element for humans, and its mode of action is related to the formation of bones, although silicon has been found in the aorta, skin, tendons, and nails (Austin, 1977; Carlisle, 1986). The normal plasma silica levels are reported as being ca. 170 μg/L (20–209 μg/L) (Peters et al., 1999; Gitelman and Alderman, 1990; Lugowski et al., 1998). Since the kidneys play the main role in silicon excretion (Berlyne et al., 1986; Reffitt et al., 1999), patients with chronic renal failure present increased plasma silicon levels (Adler et al., 1986; Berlyne et al., 1986; Gitelman and Alderman, 1990). Moreover, high silicon levels have been found in commercial dialysate, caused by either inadequate removal of silicon during the water treatment or the usage of contaminated dialysis concentrates (D'Haese et al., 1995).

As with other essential trace elements, certain forms of silicon are toxic, being the toxic effects mainly related to lung diseases, where silicosis is caused by the aspiration of small particles of silica (Witschi and Last, 1996).

There are also adverse effects of silicon, related to hemodialysis patients (Hosokawa et al., 1990), probably due the way as silicon enters in the organism. While the silicon present in food and water is selectively absorbed in the gastrointestinal tract, its introduction directly into the bloodstream, as it occurs in hemodialysis, faces no barriers. The parenteral via is also the

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way how silicon enters in the body when it is present in pharmaceutical preparations for intravenous administration. Although the data available indicate that silicon toxicity is low, it is important to know how much silicon is administrated to patients along with intravenous formulations.

Glass from packaging material may be a source of silicon to the organism. Glass containers for injectables should be chemically stable. This stability is reached by adding certain constituents to common glass, which reduces its interaction with water (Bacon, 1986). Although highly resistant, it should not be assumed that glasses in general are not soluble in aqueous solutions. Even those glasses that exhibit excellent chemical durability in water may be readily dissolved if exposed to substances such as hydrofluoric acid which are able to attack the glass network (Shelby, 1997).

Glass is made of polymeric silica. In order to lower the melting temperature (∼2000 °C) of the pure silica glass, sodium oxide is added to the glass melt. The reaction between silica and sodium oxide turns silica into silicate and reduces the melting temperature to a values below 1600 °C since the polymeric silica chains are interrupted according to the Eq. (1) (Scholze, 1988).

$$\equiv \text{Si–O–Si} \equiv + \text{Na}_2\text{O} \rightarrow \equiv \text{Si–O–Na} + \text{Na–O–Si} \equiv \quad (1)$$

Silicate glasses are more prone to react with water than pure silica glass. A two-dimensional representation of both structures is shown in Fig. 1, where is possible to see the rupture in the silica network due to presence of sodium (and calcium) atoms bound to terminal oxygen atoms. These are points in the network that weaken the hydrolytic resistance of glass.

In a previous study, we have shown that, in spite of complying pharmacopeial requirements of releasing very low alkalinity (hydrolytic resistance test), glasses also release other of their constituents, for which no tests are prescribed (Bohrer et al., 2004).

Due to their large volume, nutrition and infusion solutions are the parenterally administered pharmaceuticals that present the most adverse effect when containing contaminants. The volume given to a patient on a total parenteral nutrition (TPN) regimen may reach 3000 mL per day depending on the body weight. Moreover, TPN is administered to the critically ill or to patients with compromised metabolic and organ function, aggravating the deleterious effect of the contaminants.

In this work, the presence of silicon in formulations for parenteral nutrition stored in glass containers was investigated. Since the dissolution of silicate glass may occur by action of constituents either in association or not with heating for the sterilization of products already bottled, the study was conceived to show the influence of these variables on the amount of silicon that can be leached into finished formulations for parenteral nutrition.

2. Materials and methods

2.1. Apparatus

A Varian SpectrAA-200 atomic absorption spectrometer equipped with a GTA-100 graphite furnace and an autosampler (Melbourne, Australia), a PerkinElmer Lambda 16 spectrophotometer (Überlingen, Germany), a Phoenix AV50 autoclave (São Paulo, Brazil) and a Digimed pH meter D-20 (São Paulo, Brazil) were used.

2.2. Reagents

The water used was distilled, deionized and further purified in a Milli-Q high purity water device (Millipore, Bedford, USA). All working standard solutions were prepared from commercial silicate standard solutions containing 1000 mg/L (Merck, Darmstadt, Germany). The substances used in the tests were listed in Table 1. All substances were of analytical grade or USP and were

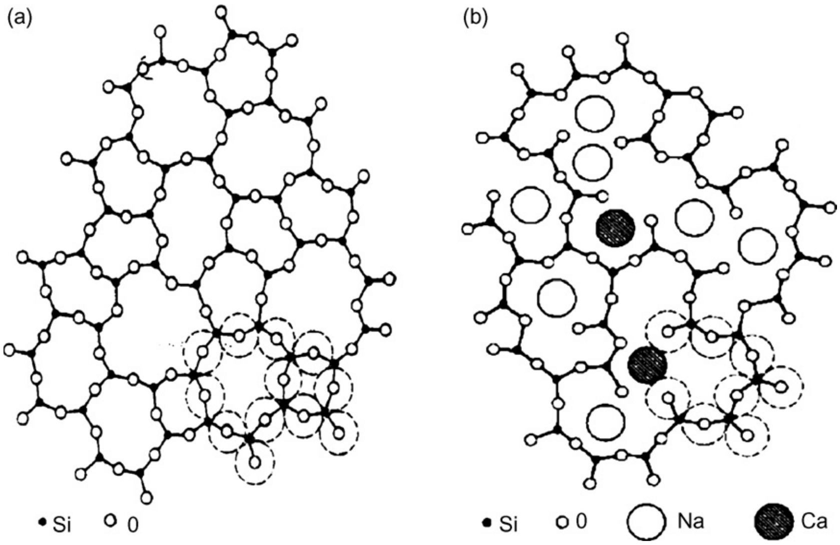

Fig. 1. Schematic representation of a two-dimensional structure for (a) pure silica glass and (b) silicate glass. A fourth oxygen atom would be located above or below each silicon atom in the three dimensional structure (Adapted from Shelby, 1997).

Table 1
Manufacturer, purity and concentration (after preparation) of the substances analyzed in the experiment

Substance	Concentration	Manufacturer	Purity	Method of analysis
Acetic acid	0.8%	Vetec	p.a.	AAS
Alanine	13.70 g/L	Aldrich	p.a.	Photometry
Arginine	9.20 g/L	Aldrich	p.a.	Photometry
Asparagine	1.30 g/L	Aldrich	p.a.	Photometry
Aspartic acid	8.90 g/L	Merck	p.a.	AAS
Calcium chloride	10%	Merck	p.a.	Photometry
Chromium chloride	0.005%	Merck	p.a.	Photometry
Glucose	10%	Merck	USP	AAS
Glutamic acid	4.60 g/L	Merck	p.a.	AAS
Glycine	7.90 g/L	Aldrich	p.a.	Photometry
Heparin	5000 UI/mL	Sigma	p.a.	AAS
Histidine	5.20 g/L	Aldrich	p.a.	AAS
Isoleucine	5.10 g/L	Aldrich	p.a.	AAS
Leucine	8.90 g/L	Aldrich	p.a.	AAS
Lysine	7.90 g/L	Aldrich	p.a.	AAS
Magnesium chloride	10%	Merck	p.a.	Photometry
Magnesium sulfate	50%	Merck	p.a.	Photometry
Manganese sulfate	0.12%	Merck	p.a.	Photometry
Methionine	3.80 g/L	Merck	p.a.	AAS
N-Acetyl-tyrosine	1.60 g/L	Aldrich	p.a.	AAS
Ornitine	3.20 g/L	Aldrich	p.a.	Photometry
Phenylalanine	5.10 g/L	Aldrich	p.a.	AAS
Potassium chloride	10%	Merck	USP	Photometry
Potassium hydrogenophosphate	2 meq/mL	Merck	USP	AAS
Proline	8.90 g/L	Aldrich	p.a.	Photometry
Serine	2.40 g/L	Aldrich	p.a.	Photometry
Sodium acetate	2 meq/mL	Merck	USP	AAS
Sodium bicarbonate	8.4%	Merck	USP	AAS
Sodium chloride	10%	Merck	USP	Photometry
Sodium dihydrogenophosphate	0.5 mol/L	Merck	USP	AAS
Sodium gluconate	10%	Fluka	p.a.	AAS
Threonine	4.10 g/L	Vetec	p.a.	AAS
Tryptophan	1.80 g/L	Sigma	p.a.	AAS
Valine	4.80 g/L	Aldrich	p.a.	AAS
Zinc sulfate	1.1%	Labsynth	p.a.	Photometry

furnished by different suppliers, which are also listed in Table 1. HNO_3 (65%, 1.40 g/mL) from Merck was further purified by sub-boiling distillation, and after that stored in a plastic bottle. Oxalic acid, hydrochloric acid, ammonium molybdate, sodium hydroxide, 1-amino-2-naphtol-4-sulfonnic acid, sodium sulfite, and sodium bissulfite were all from Merck.

2.3. Contamination control

To avoid contamination, only plastic materials were used. All laboratory ware (pipette tips, volumetric flasks, etc.) was immersed for at least 48 h in a 10% (v/v) HNO_3/ethanol solution and shortly before use was washed with Milli-Q purified water.

To avoid contamination from the air, all steps in the sample and reagent preparation were carried out in a class 100 clean bench.

2.4. Silicate measurement

Silicon was determined either by photometry or by graphite furnace atomic absorption spectrometry (GF AAS), after optimization of both procedures for the investigated samples. Both methods were optimized for the determination of silicate in the presence of the substances investigated in this study.

Photometric determination: the method used was the molybdate method, described in Standard Methods (Eaton et al., 1995). The solutions consisted of 7.5% (m/v) oxalic acid; 10% (m/v) ammonium molybdate, with a pH adjusted to 7–8 with NaOH 0.1 mol/L; HCl diluted 1:1 with water. The solution of the reducing agent, 1-amino-2-naphtol-4-sulfonnic acid, was prepared by dissolving 250 mg of the acid along with 500 mg of sodium sulfite in 25 mL of water and mixing this solution with a solution of sodium bissulfite containing 15 g of salt in 75 mL of water. This solution is stable for 24 h and must be stored under refrigeration (4 °C). To prepare standards and samples for determination, 2.5 mL silicate standard or sample was added to a 10 mL volumetric flask, followed by 50 μL HCl solution and 100 μL ammonium molibdate solution. After 5 min 100 μL oxalic acid solution was added and the flask was left for 10 min. Finally, 100 μL of the reducting solution was added, the volume was completed, and after 5 min, the absorbance was read at 815 nm against a blank prepared using 2.5 mL purified water.

AAS determination: a pyrolytic coated furnace with L'vov platform and argon as purge gas were used for the measure-

Table 2
Temperature program for the atomic absorption spectrometer operation for Si measurement

Step	Temperature (°C)	Time (s)	Gas flow (L/min)
1	85	5	3.0
2	95	40	3.0
3	120	10	3.0
4	900	6	3.0
5	900	2	0.0
6[a]	2700	2.1	0.0
7	2700	2	3.0

[a] Read.

ments. The wavelength was set at 251.6 nm, the lamp current was 10.0 mA, and the spectral slit width 0.2 nm. Background absorption was corrected using a deuterium lamp. The temperature program used is described in Table 2. A sample volume of 20 μL was used in all measurements. Adequate pyrolysis and atomization temperatures for the Si measurement in the presence of some matrix constituents were investigated. For this purpose, pyrolysis and atomization temperature curves of solutions containing 100 μg/L of pure Si and Si in the presence of 1 g/L glycine, and 1 g/L NaCl were established separately.

The choice of one of the methods was based on recovery tests. For this, individual solutions of each substance were prepared (as described in Table 1), followed by the addition of 400 μg/L silicate for the photometric measurements and 50 μg/L for the AAS measurements.

2.5. *Analysis of the raw material*

All substances included in the study were analyzed to determine their level of contamination by silicate. For the analysis, the solutions were prepared in polyethylene volumetric flasks in the concentration of that they are used commercial formulations. This information is also given in Table 1. Heparin was dissolved to give a solution with the same UI/mL (5000) as the commercial product. All samples were prepared in triplicate and the measurement was taken just after the preparation. Silicon measurement was carried out by AAS or photometry.

2.6. *Heating cycle*

Ten-milliliter new glass ampoules for injectables (Schott, Germany) were employed. Both clear glass ampoules (75% SiO_2, 10.5% B_2O_3, 7% Na_2O and 5% Al_2O_3) and amber glass ampoules (70% SiO_2, 7% B_2O_3, 7% Na_2O and 6% Al_2O_3) were utilized in the assays.

Before filling, the ampoules were rinsed three times with the solution to be stored. The ampoules were sealed by fusion of the glass and heated at 121 °C in an autoclave for 30 min. After cooling down they were opened and the silicon was measured by AAS or photometry. The silicate already present as an impurity in the substances (determined according to Section 2.5) was subtracted from the measured. The experiment was carried out in triplicate. Five ampoules of each type filled only with pure water were also submitted to the sterilization procedure.

2.7. *Influence of the pH on the silicate extraction*

Three ampoules of each type (clear and amber) were filled with aqueous solutions of different pH, from 2 to 12, adjusted with 1.0 mol/L HCl or 1.0 mol/L NaOH. The ampoules were submitted to the heating cycle and the silicate concentration in each ampoule was measured by spectrophotometry.

2.8. *Analysis of commercial products*

Commercial formulations stored in glass containers were analyzed for their silicate content. As they have different compositions and are from different brands, this information is given in Table 4. For all products, at least three samples of the same batch were analyzed, and the reported results correspond to the mean value calculated from these replicates. Five commercial formulations stored in plastic containers were analyzed as well. The results are also presented in Table 4.

3. Results and discussion

3.1. *Silicate measurement*

Since different samples were to be analyzed, recovery tests were carried out with all of them using both techniques, photometry and AAS.

Preliminary tests were done in order to determine the optimal conditions for the photometric determination of silicate using the ammonium molybdate method in the presence of the investigated substances. Tests were done with different concentrations of ammonium molybdate and reducing agent. The concentrations that give the best result for the majority of the samples are those described in Section 2.4.

The measurement of Si by GF AAS began with the investigation of adequate pyrolysis and atomization temperatures in different sample matrices. As this can be very time-consuming, three different kinds of matrices were chosen for this investigation: a pure Si solution, and Si in the presence of inorganic and organic matrices, namely, 1 g/L NaCl and 1 g/L glycine. No significant differences in the Si response were observed due to the presence of the matrix constituents (Fig. 2) with respect to the

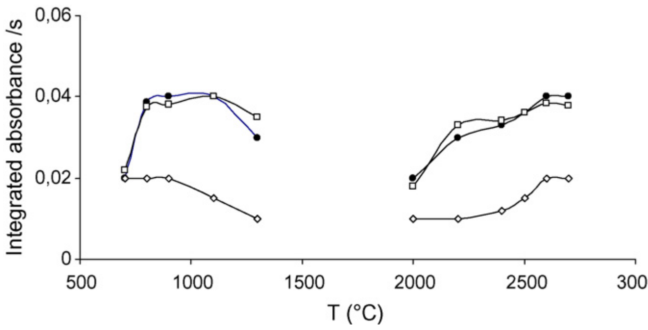

Fig. 2. Pyrolysis and atomization curves for Si (0.5 ng) in aqueous solutions. Atomization temperature for pyrolysis curves: 2700 °C. Pyrolysis temperature for atomization curves: 900 °C. (●) Silicon; (□) Silcon + 1 g/L glycine; (◊) Silicon + 1g/L sodium chloride.

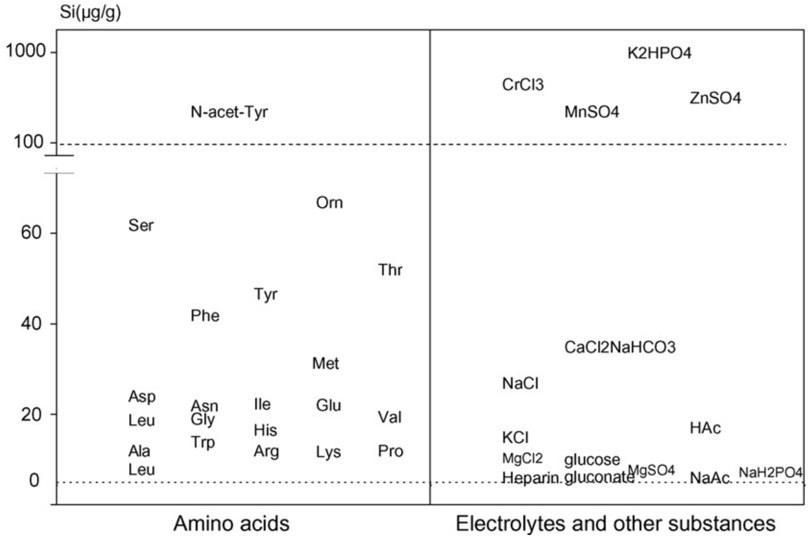

Fig. 3. Silicon level in substances used in formulations for parenteral nutrition.

best pyrolysis and atomization temperatures. Therefore, 900 °C was chosen as the pyrolysis temperature, and the atomization temperature was fixed at 2700 °C for all samples.

The figures of merit determined for both methods are presented in Table 3. Linear calibration curves were obtained for aqueous solutions with a Si concentration range between 50 and 600 μg/L for the photometric method and between 10 and 300 μg/L for the AAS method. The relative standard deviations obtained for five measurements of aqueous solutions ranged from 1% to 3%. For samples containing some formulation components (1 g/L NaCl, 1 g/L glycine or 1 g/L glucose) the relative standard deviation ranged from 1% to 8%. The limit of detection (LOD), which is defined as three times the standard deviation of 10 measurements of a blank solution divided by the slope of the calibration curve, was 8 and 0.2 μg/L Si for the photometric method and AAS method, respectively. Since for the photometric measurement the sample is diluted 4 times (2.5 mL in a 10-mL volumetric flask) the LOD for the original sample is 32 μg/L.

3.2. Recovery tests

Since no reference materials containing silicate and these matrices are available, recovery tests were carried out using the photometry method and GF AAS to choose the adequate method for each sample. The results of this experiment are depicted in Fig. 1 in the Supplementary material. While GF AAS enabled the measurement of Si in almost all samples, the photometric measurement was subject to some interference. Amino acids do not interfere either in the GF AAS or in the photometric determination. As could be expected, in the presence of acetate, bicarbonate, and all phosphate salts the photometric determination failed, since these species are known for interfering in silicate determination using the ammonium molybdate method (Eaton et al., 1995). On the other hand, the measurement in the presence of chloride and sulfate salts was not possible by GF AAS (see the low Si absorbance in the presence of NaCl in Fig. 2). The method used for the analysis of each individual sample is identified in Table 1.

Table 3
Figures of merit for the measurement of Si by photometry and GF AAS

Parameter	Method	
	Photometry	GF AAS
Analytical range	50–600 μg/L	10–300 μg/L
Analytical curve	$y = 0.0306x + 0.0005$	$y = 0.0031x + 0.0007$
Regression (r^2)	0.999	0.991
Precision (aqueous solution)	1%	3%
Precision (samples[a])	1–2%	5–8%
LOD[b]	8 μg/L	0.2 μg/L (4 pg)

[a] 1 g/L NaCl, 1 g/L glycine, or 1 g/L glucose.

[b] LOD = limit of detection (3 σ, $n = 10$).

3.3. Raw material

Silica was found as an impurity in all investigated substances. Fig. 3 shows that while the silicate concentration in amino acids ranged between 7 and 57 μg/g, it reached almost 1000 μg/g

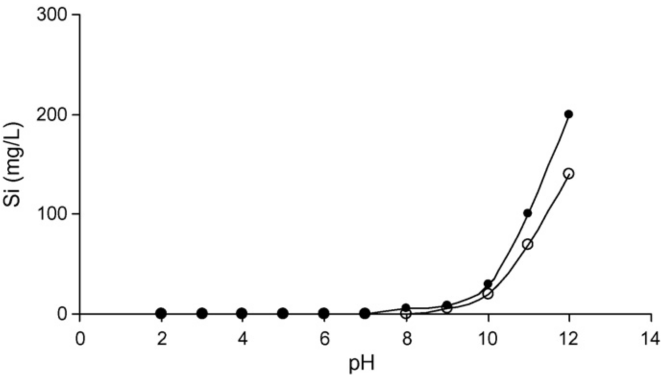

Fig. 4. Influence of the pH on silica dissolution from: (●) clear and (○) amber glass ampoules during the heating cycle for sterilization (121 °C, 30 min) into aqueous solutions.

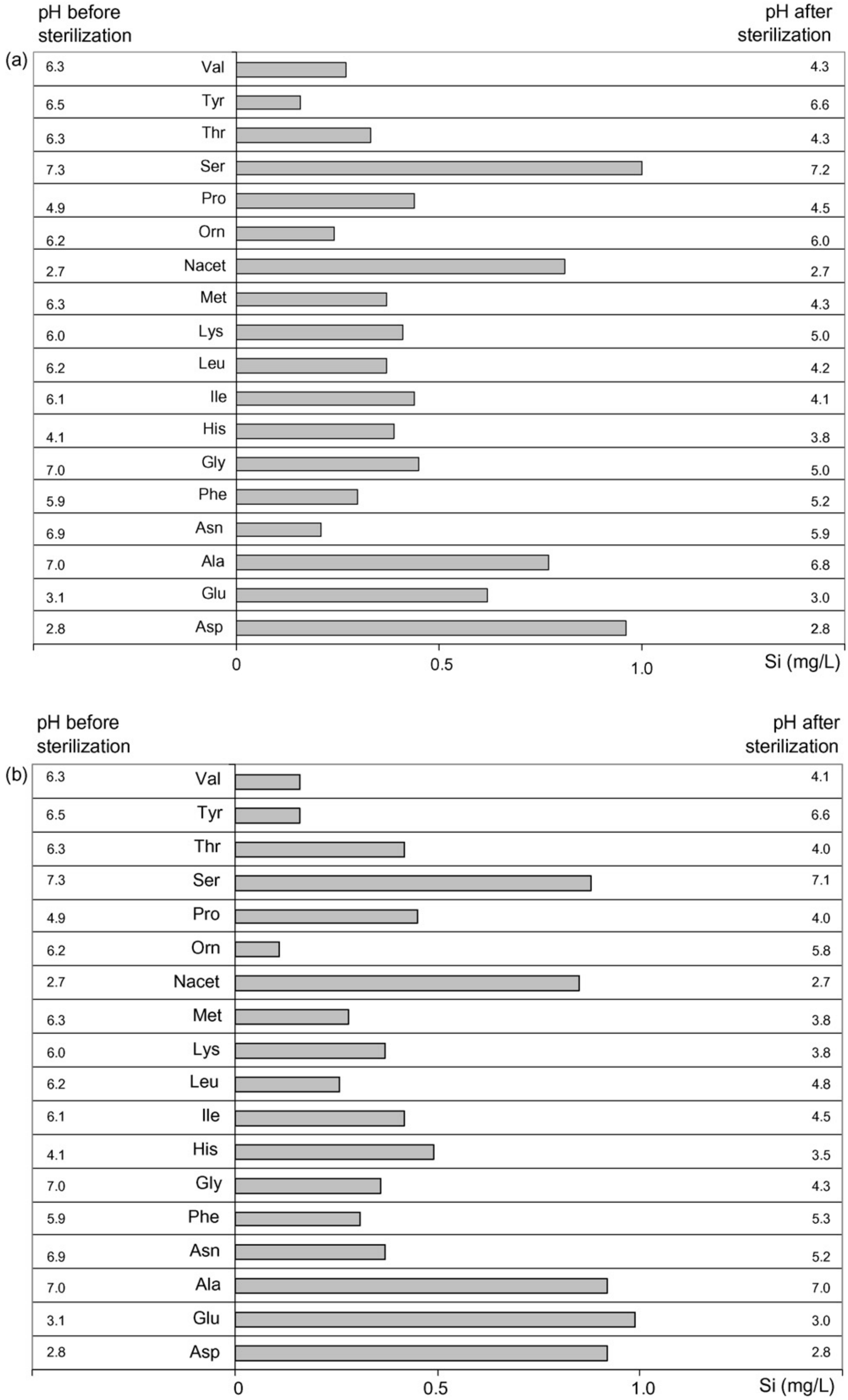

Fig. 5. Silica extracted from: (a) clear and (b) amber glass ampoules during the heating for sterilization (121 °C, 30 min) of solution of amino acids used in parenteral preparations.

among the salts. Since pharmacopoeias do not establish limits for silicate in raw substances and silica may be used as a desiccant agent, some of these high silicate levels might be due to its addition as an undeclared preservative.

3.4. Silicate release during heating

The first heating test was carried out with the ampoules filled with pure water. The results showed that even pure water is able to dissolve some silica from the glass surface. An average of 156 ± 36 μg/L silicate was found in the water after the sterilization of clear glass ampoules and 83 ± 16 μg/L was extracted from amber ampoules. These results are in agreement with the glass composition, since the clear ampoule contains 75% silica, whereas the amber ones contain 70% silica.

Although it is known that extreme pH levels usually result in the rapid dissolution of glass and that silicate glasses begin to dissolve rapidly at pH levels higher than 9 and lower than 1 (Scholze, 1988), the influence of the pH on the dissolution of the glass ampoules used in this work was also evaluated. The test intended to show how much of the glass dissolution was caused by the pH and how much was caused by the action of the substance itself. In commercial solutions for parenteral nutrition, both extremes of pH can occur, although the upper range is more frequent. Solutions of phosphates and gluconate may present pH levels of over 8 and bicarbonate and acetate of over 10. On the other hand, trace element solutions generally present a pH below 3, depending on the salts used. The experiment showed that, considering only the influence of the pH, glass dissolution increased exponentially with the pH of the solution above a pH

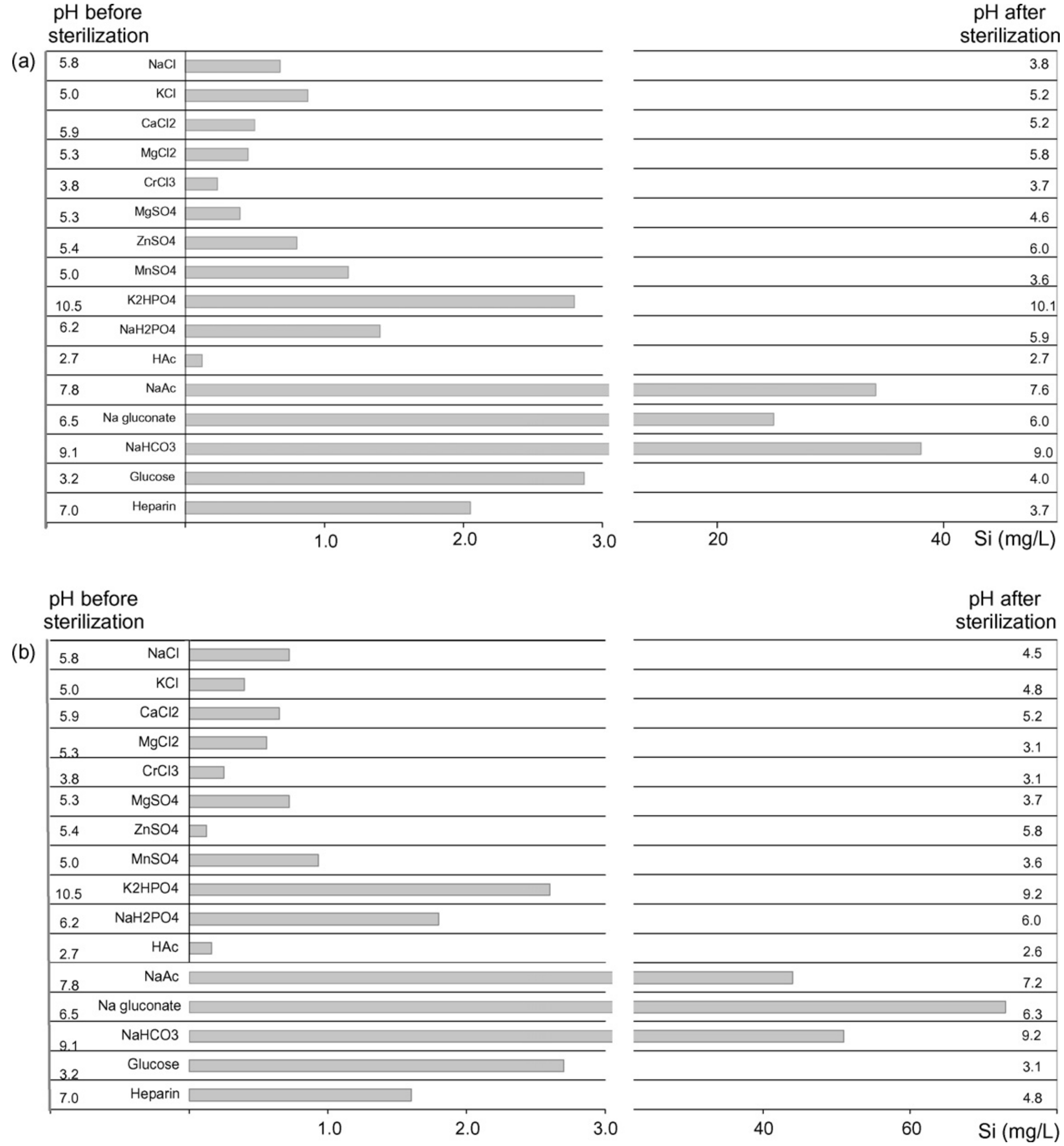

Fig. 6. Silica extracted from: (a) clear and (b) amber glass ampoules during the heating cycle for sterilization (121 °C, 30 min) of solution of electrolytes and other substances used in parenteral preparations.

of 8 (Fig. 4). It is possible to see in Fig. 4 that the influence of the pH is the same for both clear and amber glass.

Fig. 5 shows the silicate found in solutions of amino acids after the heating procedure. The silicate concentration in these solutions was higher than that in pure water, showing that the substances have an influence on the dissolution of glass. Since the amino acids do not present solutions with extreme pH levels, the simple presence of the amino acids was able to increase glass dissolution. Although the amino acids behave in the same way for both types of glass, the amount of silicate leached from the clear ampoules was higher than that from the amber ampoules. This is in agreement with the results for pure water, probably for the same reason: clear glass contains more silica than amber glass.

Fig. 6 shows the concentration of silicate found in the solutions of electrolytes and the other investigated substances, after the sterilization procedure. The results showed that among the salts, the pH, although not being the only influence, played the most important role on the glass dissolution. With the exception of glucose and gluconate, all the other solutions that dissolved high amounts of silicate presented pH levels over 8. The relatively low amount of silicate found in potassium hydrogenophosphate, solution presenting the highest pH, is probably related to the amount of salt in solution, which is very little compared to the others. On the other hand, sodium dihydrogenophosphate solution, which pH is 6.2, presented considerable amount of silicate. It seems, that glucose, gluconate, and phosphate are themselves able to react with silica and promote glass dissolution, since the amount of silicate in these solutions is much higher than in the correspondent water sample with the same pH.

Bacon and Ragon (1959) showed that anions such as citrate, gluconate, oxalate, tartrate and malate attack the sulfur-treated soda-lime glass. They also showed that citrate and gluconate are able to attack borosilicate and very high silica glasses, even when keeping the pH of the solutions at 7. The authors concluded that the action of these anions may be related to the formation of soluble complexes with silicon in neutral solutions.

Table 4
Silicate found in comercial formulations stored in glass and plastic containers

Product	Product concentration	Manufacturer	Si concentration μg/L (±S.D.)[a]
Water sterile for injection	–	Geyer	280 ± 13
Water sterile for injection	–	Geyer	240 ± 9
Water sterile for injection	–	Geyer	220 ± 12
Water sterile for injection	–	SEM	292 ± 25
NaCl	20%	Halex Istar	875 ± 45
KCl	10%	Santisa	217 ± 21
KCl	19.1%	Geyer	264 ± 18
$MgSO_4$	50%	Geyer	360 ± 22
$MgSO_4$	50%	Ariston	225 ± 18
$NaHCO_3$	8.4%	JP	3623 ± 98
$NaHCO_3$	8.4%	JP	4154 ± 306
Sodium phosphate	0.5 mol/L	Geyer	1360 ± 210
Sodium phosphate	0.5 mol/L	Geyer	2800 ± 112
Potassium phosphate	2 meq/mL	Braun	923 ± 78
Sodium acetate	2 meq/mL	Braun	1260 ± 56
Sodium acetate	2 meq/mL	Index	1220 ± 107
Calcium gluconate	10%	Ariston	1230 ± 141
Calcium gluconate	10%	Halex Istar	2833 ± 134
Ped-element	Oligoelements	Darrow	520 ± 46
Ad-element	Oligoelements	Darrow	239 ± 21
Lipovenos	10% soy oil	Fresenius	65 ± 3
Pediamino PLM	10% amino acids	B.Braun	145 ± 7
Nefroamino AEH	7.2% amino acids	B.Braun	141 ± 9
Aminoped	10% amino acids	Fresenius	175 ± 11
Aminosteril Hepa	8% amino acids	Fresenius	170 ± 8
Aminoplasmal L 10 A	10% amino acids	B.Braun	172 ± 13
Priméne	10% amino acids	Clintec	142 ± 10
Dipeptiven	20% alanyl-glutamine	Fresenius	192 ± 17
Glucose	50%	Ariston	630 ± 23
Glucose	25%	Merck	423 ± 65
Heparin	5000 UI/mL	Eurofarma	376 ± 25
Heparin	5000 UI/mL	Roche	415 ± 22
Water for injection[a]	–	Equiplex	12.7 ± 0.4
KCl[a]	10%	Isofarma	25.1 ± 1.2
Glucose[a]	50%	Fresenius	13.2 ± 2.2
Potassium phosphate[a]	2 meq/mL	Aster	33.5 ± 7.8
Travasol[a]	10% amino acids	Baxter	n.d.

S.D.: Standard deviation ($n = 3$), n.d.: not detected.

[a] Formulations stored in plastic containers.

Glass dissolution may be attributed to the reaction of the silica with water according to the Eq. (2):

$$SiO_{2(glass)} + H_2O \rightarrow H_2SiO_{3(solution)} \qquad (2)$$

In the presence of hydroxyl ions the reaction can be accelerated, following the Eq. (3):

$$SiO_{2(glass)} + 4\,OH^- \rightarrow SiO_4{}^{2-}{}_{(solution)} + H_2O \qquad (3)$$

According to Shelby (1997), several processes have been observed during the dissolution of glasses in aqueous solutions. If the glass contains any alkali or other highly mobile ions, the ion exchange between these ions and the protonic species (H_3O^+) from the solution can occur. Since all commercial silicate glasses contain alkali ions, the initial step in their dissolution usually involves this process. The increase in the pH of the solution due to the ion exchange process (Eq. (4)) increases the solubility of the silica in the solution, according to Eq. (3). If both reactions occur, at the end of the dissolution process silicate may be released in solution without any significant change in the pH.

$$-Si–O–Na_{(glass)} + H_2O_{(solution)} \rightarrow -Si–O–H + Na^+{}_{(solution)} + OH^- \qquad (4)$$

In this study, the pH of the solutions did not increase. In Figs. 5 and 6 it is possible to see that it remained the same or even decreased after the heating cycle.

3.5. *Commercial formulation*

Table 4 shows the results of the analysis of commercial infusion solutions and solutions for parenteral nutrition. As could be expected, Si was found in all samples, being gluconate, bicarbonate, phosphates, and acetate the most contaminated. On the other hand, very little silica was found in lipid emulsions. Probably because of their lower water content, the interaction of the formulation with the glass surface is reduced even during the heating cycle. Moreover, the low Si content of the formulations stored in plastic containers helps to reinforce the fact that glass is the main source of this element in such products. Since the formulations present similar compositions, the contribution of raw material in silicate contamination in infusion and parenteral formulations is very low when compared to glass.

4. Conclusion

Substances commonly used in parenteral nutrition present silica as an impurity. Levels between 0.6 and 730 μg/g were found among salts and levels between 7 and 107 μg/g were found among amino acids.

The heating of glass containers for the sterilization of bottled products promotes the release of silica from the glass surface. The extent of this process is greatly influenced by the pH and the nature of the solution being sterilized. The silicate dissolution increases exponentially during the heating cycle for solutions with pH levels above 8. Although amino acids dissolve approximately three times more silica than pure water, practically all of them present the same behavior, probably because the pH of their solutions does not surpass 7. Among salts, different behaviors were observed. Whereas in solutions of sodium and potassium chloride the release of silicate is lower than 1 mg/L, in solutions of gluconate, acetate, bicarbonate, and phosphate the amount can be higher than 50 mg/L.

Silicate is present in all commercial solutions for parenteral nutrition stored in glass containers. Although it is not a toxic species, pharmacists and physicians must be aware that silicate might be present in large amounts in parenteral preparations stored in glass containers, mainly because of their direct administration into the bloodstream.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijpharm.2007.12.025.

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