Significance of Aluminium Release from Type I Borosilicate Glass Containers

Alberto Biavati[1], Paolo Amadei[1], Arianna Ferrarini[1], Michele Poncini[1], Luca Zalaffi[1], Maura Mantovani[2]

[1] Bormioli Rocco e Figlio SpA, Fidenza, Italy
[2] Azienda Unità Sanitaria Locale, Parma, Italy

Corresponding author: Alberto Biavati, Bormioli Rocco e Figlio SpA, Via Martiri della Libertà 1, 43036 Fidenza (PR), Italy

ABSTRACT

Aluminium is the third most abundant element in the lithosphere after silicon and oxygen and may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Alumina (Al_2O_3), as a glass network former, is very important to improve the chemical inertia of glass towards aqueous solutions attack. The release of aluminium from borosilicate glass comes from the dissolution of a very thin superficial layer of the glass during the hydrolytic attack. The aluminium release from type I glass containers of different composition was compared after autoclaving of 1 h at 121 °C according to the European Pharmacopoeia (EP) 6. This autoclaving cycle corresponds to approximately 5 years of contact between the glass surface and the solution at ambient temperature. USP 32 fixes a limit of 25 µg/l for large volume solutions used for total parenteral nutrition; EP 6 fixes a limit of 15 µg/l for solutions for peritoneal dialysis and of 10 µg/l for sterilised water for use in the manufacture of dialysis solutions, where very large volumes are involved. 200 µg/l (ppb) is the limit for aluminium in human albumin. Sodium lactate solution for parenteral dosage forms has a limit of 0.1 µg/ml (ppm). The aluminium release from other packaging materials (polyolefins etc.) was not determined but apparent discrepancies were evidenced on the basis of the very high permissible limits of release of EP 6 and USP 32 (1 µg/ml) for these materials. To evaluate the significance of aluminium intake from type I glass containers, some large volume parenteral therapies were evaluated. Due to the small volumes coming from type I glass containers, aluminium loading from glass was assessed to be negligible.

KEY WORDS

- Aluminium release
- Glass chemical durability
- Parenteral nutrition
- Polyethylene for containers
- Polyolefins for containers
- Polypropylene for containers
- Type I glass containers

ZUSAMMENFASSUNG

Bedeutung der Freisetzung von Aluminium aus Behältern aus Typ-1-Borosilikatglas

Aluminium ist das dritthäufigste Element in der Lithosphäre nach Silizium und Sauerstoff und kann nach längerer parenteraler Zufuhr bei gestörter Nierenfunktion eine giftige Wirkung haben. Aluminiumoxid (Al_2O_3) ist eine Strukturkomponente von Glas und sehr wichtig für die chemische Trägheit gegenüber wässrigen Lösungen. Die Freigabe von Aluminium aus Borosilikatglas wird von der Auflösung einer dünnen Glasschicht während des hydrolytischen Angriffes verursacht.

Die Abgabe von Aluminium aus Glasbehältern der hydrolytischen Klasse I von verschiedener Zusammensetzung wurde nach 1 h Autoklavierung bei 121 °C bestimmt gemäß Europäischem Arzneibuch (EP) 6. Dieser Autoklavierzyklus entspricht einem Kontakt zwischen Glasoberfläche und Lösung bei Raumtemperatur über eine Zeitspanne von ca. 5 Jahren. Für großvolumige Lösungen z. B. zur parenteralen Ernährung bestimmt die USP 32 einen Grenzwert von 25 µg/l. Die EP 6 setzt Grenzwerte von 15 µg/l für Lösungen für die Peritonealdialyse und 10 µg/l für steriles Wasser fest, das für die Herstellung von Dialyselösungen verwendet wird. 200 µg/l (ppb) ist der Grenzwert für Aluminium in Albumin zur Anwendung am Menschen.

Für Natriumlactat zur parenteralen Anwendung gilt ein Grenzwert von 0,1 µg/ml (ppm). Die zulässige Freisetzung von Aluminium aus anderen Verpackungsmaterialien (Polyolefine etc.) ist nicht bestimmt worden. Große Diskrepanzen werden aus den nach EP 6 und USP 32 zulässigen sehr hohen Abgabegrenzen (1 µg/ml) für diese Materialien erkennbar.

Um die Bedeutung der Aluminium-Aufnahme aus Glasbehältern der hydrolytischen Klasse I zu bewerten, wurde eine Reihe von Infusionstherapien mit großen Volumina überprüft. Wegen der geringen Mengen wurde der Beitrag der Gläser zur Aluminium-Aufnahme und -akkumulation als unbedeutend bewertet.

Pharm. Ind. 72, No. 12, 2144–2147 (2010)

Pharm. Ind. 72, Nr. 12, 2144–2147 (2010)

1. Introduction

Elements in traces include metals in concentration below 1 µg/g of biologic liquids. They are often essential for human metabolism, but their loading or unbalance can give undesired side effects. Among them Cu, Zn, Cr, Mn, Co, Mo, Se, F, etc. can be mentioned [1]. Whenever prolonged infusion therapies with large amounts of solutions are involved, mainly in case of total parenteral nutrition, loading of elements even present in traces is likely from any different source including glass and plastic packaging materials that comes in contact with the pharmaceutical preparations often for prolonged times.

In particular aluminium may reach toxic levels if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature and they require large amounts of calcium and phosphate solutions which may contain traces of aluminium and other elements in traces. Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminium in greater amounts than 4 to 5 µg per kg body weight per day accumulate aluminium at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of total parenteral nutrition products and of the lock-flush solutions used in their administration.

Aluminium is the third abundant element in the lithosphere after silicon and oxygen and therefore its presence at least at trace levels everywhere is understandable.

Aluminium oxide (alumina) Al_2O_3 is a glass network former and a very important component of every kind of borosilicate glass (type I containers, tubing glass for ampoules, Pyrex glass, etc.), to improve the chemical inertia of glass towards aqueous solutions attack.

The alumina content of glass (i.e. the Al_2O_3 % w/w in the bulk) is not always significative of the aluminium release, since the chemical durability of the glass depends strongly on the whole glass composition.

For example a low resistance borosilicate can release more aluminium even if its aluminium content is lower than in another high resistant borosilicate glass, due to their different chemical durability.

In commercial borosilicate glass, alumina content usually ranges from 2.5 % (Pyrex) up to 6 %. Usually the alumina content (tubing and moulded glasses) is around 5 %.

The ions release from glass surface during hydrolytic attack follows an S-shaped curve up to a limit dissolution rate, so that for example at the half of the autoclaving time, the release will be lower than the half of the release found after a complete autoclaving cycle.

Previous works demonstrated that the releasing mechanism follows a dissolution process with a ratio between the released elements similar to their ratio in the glass composition, excluding sodium ion that is released in higher amount due to its higher availability to ion exchange with water [2, 3].

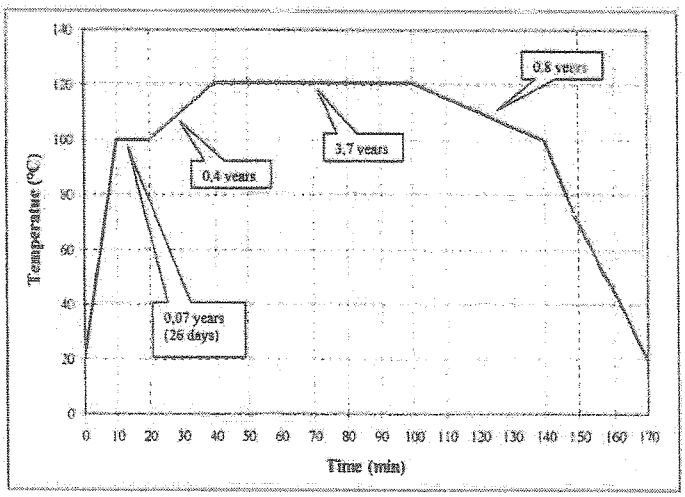

Fig. 1: EP 6 autoclaving test cycle with the correlation time–room temperature of each step.

The autoclaving cycle according to the European Pharmacopoeia (EP) 6 (Fig. 1) and its correlation with the time of contact at ambient temperature between the glass surface and the aqueous solution was experienced to follow with a good approximation the Lyle equation [2]:

$$\text{Log } h_1 = \text{Log } h_2 + (T_2 - T_1)/22.4$$

$h_{1,2}$ time (h) at temperature $T_{1,2}$ with $T_2 > T_1$

Injectables conditioned in vials of type I glass usually have a shelf life of 2 years or no longer than 3 years, so the aluminium release is expected to be lower than that obtained after a complete autoclaving cycle of 1 h at 121 °C.

2. Materials and methods

Tests have been conducted in type I borosilicate moulded glass containers ranging from 10 to 100 ml. The glass composition is shown in Table I. Hydrolytic release tests were conducted using the method indicated by the European Pharmacopoeia 6th ed., with autoclaving at 121 °C for 1 h by a laboratory autoclave Asal Vapormatic 770.

High purity deionised water having a conductivity lower than 0.2 µS was freshly prepared for each test from a mixed resins deioniser Elettracqua RD60.

Bottles were filled up to 90 % of their brimful capacity and capped with laboratory Petri dishes made of Pyrex glass.

Hydrolytic attack solutions were analysed by ICAP Thermo Fisher Scientific 6300 DUO for aluminium release at the wavelengths 167.079 nm and 309.278 nm. The working standard solutions were prepared from commercial standard so-

Table I

Type I glass composition (% W/W).

SiO_2	71 %
Al_2O_3	5 %
CaO	1 %
BaO	2 %
B_2O_3	12 %

lutions containing 1 000 mg/l of aluminium (Carlo Erba Reagenti, Milano, Italy). To avoid possible contamination, only Pyrex laboratory ware autoclaved at least twice were used. Reagents and solutions blanks were always prepared to check for the analytical background.

Internally treated containers, for example by silicone resins, were not considered since in this case the attack solution does not interact with the glass surface, but with a polymer layer altering the ion release. The analysis of any possible release of organics or siloxanic fragments did not concern the purposes of this work.

3. Results

A preliminary work was done to check the practical detection limit for aluminium in water solution with the adopted instrumental conditions, that was determined to be 7 ppb at the wavelength of 167.079.

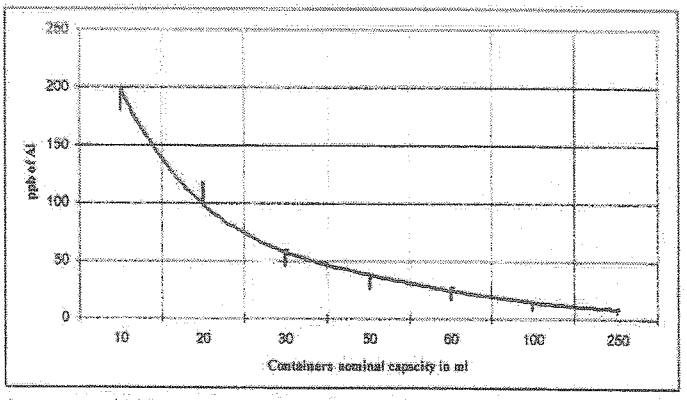

Fig. 2: Moulded containers: aluminium release correlation with volume after autoclaving 1 h at 121 °C according to EP 6.

At least 4 containers of the same production lot for capacities higher than 50 ml and from 6 to 10 containers for lower capacities were used for each test. At least three replicates on separate days were performed for each capacity in order to obtain a good data reliability.

Considering the container capacity, aluminium release was experienced to decrease from 200 ppb to 15 ppb, from 10 to 100 ml container capacity and to values lower than 10 ppb in 250 ml containers, according to the curve shown in Fig. 2. Data variation is also depicted in the graph.

Together for comparison were autoclaved also some containers of capacity 30 and 100 ml, of type I low alumina (Al_2O_3 3.6 % instead of 5 %) borosilicate glass. Aluminium release was determined to be approximately 60 to 70 % of the plotted aluminium amounts.

On the other side it has been determined that borosilicate type I glasses having a lower alumina content – and therefore a lower release of aluminium – show an higher release of other elements present in the glass composition (i.e. boron, zinc, etc.) following approximately the dissolution mechanism of the silica network components [3].

For comparison some type II soda lime glass containers of capacity 100 and 250 ml were also analysed in the same conditions for aluminium release. No aluminium trace was detected and so the release estimated to be lower than 5 µg/l.

4. Discussion

As expected, the container capacity affects strongly the aluminium release of the glass – considering that the lesser the capacity, the higher the surface/volume ratio with the consequent increase of the concentration of the released elements, according the exponential curve of Fig. 2.

The practical significance of the aluminium release at the "trace" levels shown above, must be compared to the USP 32 and EP 6 Pharmacopoeias regulations.

USP 32 fixes a limit of 25 µg/l (0.025 ppm) for large volume solutions used in total parenteral nutrition (TPN).

EP 6 fixes a limit of 15 µg/l (0.015 ppm) for solutions for peritoneal dialysis and of 10 µg/l (0.010 ppm) for sterilised water for use in the manufacture of dialysis solutions, haemofiltration and haemodiafiltration solutions, therapies where very large volumes are involved.

Haemodialysis solutions and sodium lactate solutions for parenteral dosage forms have a limit of 100 µg/l (0.10 ppm). Human albumin has a limit of 200 µg/l (0.20 ppm). Vaccines for human use (i.e. tetanus, diphtheria, hepatitis, allergen products, etc.) have a limit of 1.25 mg per dose. Considering polymeric packaging materials used for injectables, aluminium release is regulated in EP 6 as follows:

- polypropylene for containers and closures for preparations for parenteral and ophthalmic use have a release limit of 1 µg/ml (1 ppm);
- polyethylene with additives for containers for preparations for parenteral use and for ophthalmic preparations have a release limit of 1 µg/ml (1 ppm);
- polyolefins have a release limit of 1 µg/ml (1 ppm).

Aluminium release in the above materials is determined after boiling 1 h 100 g of the polymeric material with 250 ml of HCl 0.1 M while stirring.

No aluminium release is regulated for glass and for polyethylene-vinyl acetate for containers and tubing for TPN preparations.

It is to point out that most of the large volume glass containers are of type II and polymeric containers are used for very large volume infusions.

Type II glass is a soda lime glass surface treated in order to obtain a complete superficial alkali depletion. Aluminium release from type II glass containers is hardly detectable (< 5 µg/l) for the following reasons:

- very high superficial chemical durability after alkali depletion due to a silica content higher than 90 %,
- glass bulk contains approximately 2 % of alumina (less than a half of the amount contained in borosilicate glass),
- high ratio of volume-to-surface area (the higher the volume, the lesser is the surface area in contact with the pharmaceutical preparation).

Pharm. Ind. 72, Nr. 12, 2144–2147 (2010)

Type I glass container is the best choice whenever the pH of the injectable solution is around 7 or between 7 and 8.

The examination of some of the most common therapies that involve large volume parenterals lets understand the practical contribution of type I glass to the global aluminium intake and loading in the most exposed patients [4].

Case 1

Example for a peritoneal dialysis solution. Other contemporary therapies, i. e. via digestive tract etc., are excluded.

Type II glass and polypropylene containers:

Glucose 1.5 – 7.5 %
Na^+ 140 mEq/l (3.2 g/l)
Acetate 45 mEq/l (2.6 g/l)
Ca^{++} 4 mEq/l (0.08 g/l)
Mg^{++} 1.5 mEq/l (0.02 g/l)
Cl^- 101 mEq/l (3.6 g/l)

Ampoules 1 – 10 ml:

Sodium heparine 50 – 100 U
Papaverin 4 % 1 ml
Xilocain 2 % 1 ml
K^+ 0 – 3.5 mEq/l (0 – 0.14 g/l)

Daily volume: 2 liters.

In case of impaired liver or kidney function:

Type II glass containers:

Proteins solution (L-aminoacids) 1.5 l/day

Ampoules 1 – 10 ml:

ACE inhibitors
Insulin
Antibiotics etc.

Parenteral nutrition (see Case 3).

Case 2

Scalded patients (over 40 %, 70 kg body weight). Other contemporary therapies, i. e. via digestive tract etc., are excluded.

Polypropylene containers:

Ringer lactate 11.2 l
(Parkland formula: 4 ml × weight × %)

Type II glass containers:

Proteins solution (L-aminoacids) 1.5 l/day
Glucose 5–30 % 1 l

Type I glass containers:

Albumin 20 %, 50 ml
Sodium bicarbonate 250 ml

Ampoules 1 – 10 ml:

Immunoglobulins

Parenteral nutrition (see Case 3)

Case 3

Example for parenteral nutrition of a male adult of 70 kg body weight.

Type II glass containers:

Glucose 50 % 1 l
Aminoacids 10 % 1 l
Electrolytes solution (Na^+, K^+, Cl^-, Mg^{++}, P) 500 ml

Polypropylene containers:

Lipids 20 % 250 ml

Ampoules 1 – 10 ml:

Vitamins

The above examples are only indicative of the complexity of the therapeutic strategies, always matched to the specific situation of the clinical patient context.

Considering the release from Fig. 2 we can try to calculate the aluminium intake from moulded glass containers. The calculus result is rounded in excess as above mentioned, considering that the expiry time of the pharmaceutical preparations are 3 years or less and the worst ageing conditions equivalent to EP 6 autoclaving test simulates approximately 5 years.

Supposing the use of a pharmaceutical preparation with one type I glass 50 ml vial, its contribution will be:

$$35\ \mu g \times 50\ ml / 1\,000\ ml = 1.75\ \mu g$$

Case 1: 3 liters per day estimated. Practical contribution to the daily intake: 1.75 / 3 = 0.58 µg/l (limit: 15 µg/l)

Case 2: 14 liters per day estimated. Practical contribution to the daily intake: 1.75 / 14 = 0.125 µg/l (limit: 15 µg/l)

Case 3: 4 liters per day estimated. Practical contribution to the daily intake: 1.75 / 4 = 0.44 µg/l (limit: 15 µg/l)

5. Conclusions

The presence of aluminium in the water and in the raw materials even in small traces is quite probable being aluminium the third most abundant element in the lithosphere; moreover it is tolerated with limitations in some injectables (vaccines) as it is used in their preparation. The comparison between the limits for large volume solutions and the limits of the aluminium release for some polymeric materials shows an apparent discrepancy since these materials are widely used in large volume therapies.

Aluminium is a very important glass network former and stabiliser, and that is why the aluminium is hardly released from glass. In both EP 6 and USP 32 aluminium contamination is ruled in large volume therapies due to the enhanced risk of intake and loading, but it is a matter of fact that the risk of aluminium intake from glass is negligible due to both the negligible extractable amounts and the small volumes involved from type I glass containers compared to other different origins.

REFERENCES

[1] Harrison's Principles of Internal Medicine. New York: McGraw-Hill; 1999.

[2] Biavati A. Correlation between hydrolytic ion release and pH changes in type II glass containers. *Pharm Ind.* 1997;59(2):175 – 178.

[3] Guadagnino E, Verità M, Furlani C, Polzonetti G. Aluminium release of pharmaceutical glass containers: determination by GFAAS in the extract solutions and study of the inner surfaces by XPS and SIMS. *Glastechnische Berichte.* 1991;64(7).

[4] Bartoccioni F. Terapia 2008. 31th ed. Roma: La Treggia Edizioni srl.; 2007.

Work was presented at Pharmapack, Paris, January 21 and 22, 2009.