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Spectrophotometric determination of trace aluminium content in parenteral solutions by combined cloud point preconcentration–flow injection analysis

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A cloud point preconcentration and flow injection (FI) analysis methodology for aluminium(III) determination has been developed. The analyte in the initial aqueous solution was complexed with Chrome Azurol S (CAS) in the presence of the cationic surfactant benzyldimethyltetradecylammonium chloride (BDTAC). The absorption spectroscopic characteristics of the ternary complex [Al(III)–CAS–BDTAC] were examined in detail. The preconcentration step was carried out by means of the non-ionic surfactant polyethylene glycol *p*-nonylphenyl ether (PONPE 7.5). The enriched analyte solution was injected into an FI system using an HPLC pump. The chemical variables affecting the analytical performance of the combined methodology were studied and optimised. The developed approach was successfully applied to the determination of trace amounts of aluminium in parenteral solutions without previous treatment. Under the optimum experimental conditions, 99.9% extraction was achieved for a preconcentration factor of 50**.** The limit of detection was 1.12×10^{-7} mol l^{-1}. The calibration plot was linear over at least two orders of magnitude of aluminium concentration. The developed coupled methodology, which thoroughly satisfies the typical requirements for pharmaceutical control processes, is appropriate for monitoring the aluminium concentration in parenteral nutrition.

Introduction

Aluminium is recognised as an important toxic substance causing considerable morbidity and mortality, particularly in patients with chronic renal failure. Diseases that have been associated with aluminium include dialysis dementia, renal osteodystrophy and Alzheimer's disease. Aluminium also has an effect on red blood cells, parathyroid glands and chromosomes. The main clinical manifestations of aluminium toxicity include progressive encephalopathy, osteomalacia, microcytic hypochromic anaemia and cholestasis. Many sources have been shown to be contaminated with aluminium. These include the water used for dialysis, medicines containing aluminium, such as aluminium-containing phosphate binding gels, total parenteral nutrition solutions, processed human serum albumin, intravenous fluids in infants and other environmental and industrial sources.[1–3]

Long-term total parenteral nutrition (TPN) patients can inadvertently receive significant amounts of aluminium present as contaminant in TPN. Many of the solutions for parenteral nutrition have an aluminium content which exceeds the suggested threshold concentration of 25 μg l^{-1} recommended by the American Society for Clinical Nutrition (ASCN) and the American Society for Parenteral and Enteral Nutrition (ASPEN).

Although electrothermal atomic absorption spectrometry (ETAAS) and inductively coupled plasma atomic emission spectrometry (ICP-AES) are the most commonly used techniques in the determination of trace level metals, the aluminium concentration in parenteral solutions is not compatible with the limit of detection of such techniques. Consequently, a preconcentration step is essential. Spectrophotometry continues to enjoy wide popularity. The common availability of the instrumentation, the simplicity of procedures and the speed, precision and accuracy of the technique still make photometric methods an attractive alternative. In particular, spectrophotometry has become the most widely used detection technique in flow-injection analysis (FIA).[4–8] FIA is particularly appropriate when only a small amount of sample is available (pharmaceuticals, biological fluids, environmental samples), when a rapid analysis is needed and especially when the number of samples to be analysed is significant.

In the last decade, increasing interest has been shown in developing surfactant-based methods in all fields of analytical chemistry. Aqueous micellar solutions have been used in, among other fields, spectroscopy, the electroanalytical field and separation science.[9-15]

Aqueous solutions of many non-ionic surfactant micellar systems become turbid over a narrow temperature range when the experimental conditions are changed. This temperature is named the cloud point temperature. Above the cloud point, the solution separates into two phases: one, very small in volume, the surfactant-rich phase, and the other, the bulk aqueous solution, containing surfactant monomers. The use of micellar systems as an alternative to other techniques of separation offers several advantages, including low cost, safety and high capacity to concentrate a wide variety of analytes of widely varying nature with high recoveries and very high concentration factors.[16-25] From an analytical point of view, the surfactant-rich phase can be used to separate and/or preconcentrate different analytes before their injection into any hydrodynamic analytical system.

The use of chelating reagents in combination with the FI technique for the determination of aluminium has appeared in various publications.[21–23] The sensitivity (2 mg l^{-1}) of the standard fluorimetric method for aluminium determination recommended by the *British Pharmacopoeia*[26] is not suitable for determining aluminium at the levels normally found in TPN solutions. Also, such a technique involves the use of organic

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solvents. The aim of this work was to develop a cloud point extraction–flow injection method for monitoring aluminium in parenteral solutions. The metal is complexed with Chrome Azurol S (CAS) in the presence of cationic surfactant benzyldimethyltetradecylammonium chloride (BDTAC), extracted with polyethylene glycol *p*-nonylphenyl ether (PONPE 7.5) (a non-ionic surfactant) and then injected in an adequate carrier for the spectrophotometric determination. The effect of the several experimental variables affecting the method sensitivity and stability were investigated in detail. The optimised procedure was applied to examine the aluminium content in commercially available parenteral solutions.

Experimental

Reagents

A 1 mg ml^{-1} stock standard solution of Al(III) was prepared from its nitrate salt of analytical-reagent grade purity (Merck, Darmstadt, Germany). Working standard solutions were standardised by a potentiometric method.[27]

A 3.5×10^{-3} mol l^{-1} solution of CAS (Merck, Buenos Aires, Argentina) was prepared by dissolution in and dilution to 10 ml with doubly distilled water.

A 0.5 mol l^{-1} acetate buffer solution was prepared, the desired pH being obtained by the addition of dilute $HClO_4$ or NaOH solution (Merck).

All solutions were prepared with ultra-high-quality water obtained from a Barnstead Easy pure RF compact ultrapure water system. For FIA, all solutions were de-gassed by ultrasonication (Testlab, Argentina).

All other reagents were of analytical-reagent grade. The non-ionic surfactant PONPE 7.5 was supplied by Tokyo Kasei Industries (Tokyo, Japan), the cationic surfactant BDTAC by Fluka (Buchs, Switzerland) and HPLC grade acetonitrile by Merck.

Solution A was prepared following the procedure described by Silva *et al.*[28] by mixing 10 ml of PONPE 7.5, 10 ml of $NaClO_4$ (Merck, Darmstadt, Germany) (1 mol l^{-1}) and 40 ml of distilled ethanol and diluting to 100 ml with doubly distilled water.

Apparatus

The experimental set-up for FIA consisted of a Beckman System Gold Programmable Solvent Module 126 HPLC pump and a Rheodyne injection valve with a 20 μl loop. Detection was carried out with a Beckman System Gold 168 diode array detector. System Gold software was used for data acquisition.

A Hewlett-Packard spectrophotometer with 10 mm optical path cells (4 or 0.4 ml capacity) was used to perform the absorptiometric batch measurements. A Shimadzu RF 500 spectrofluorimeter with 10 mm optical path cells was used to perform the fluorimetric standard method.

pH values were measured with an Orion 940 pH meter equipped with a glass combined electrode. A centrifuge was used to accelerate the phase separation process.

Recommended procedure. CPE and spectrophotometric determination

An aliquot of metal ion solution (50 μl), 0.01 ml of CAS solution (3.5×10^{-3} mol l^{-1}), 0.5 ml of BDTAC solution (0.2% w/v), 0.2 ml of acetate buffer solution (0.5 mol l^{-1}, pH 6.3) and 0.5 ml of solution A were placed in a graduated centrifuge tube and the mixture was diluted to 10 ml with doubly distilled water. The solution obtained was centrifuged for 5 min at 3500 rpm (1852.2*g*). After phase separation, a surfactant rich phase of 200 μl was obtained. Then, 200 μl of acetonitrile were added in order to decrease the viscosity of the sample. The resultant solution was injected into a stream of carrier [70% acetate buffer 1×10^{-2} mol l^{-1}, pH 6.3–30% acetonitrile] at a flow rate of 0.7 ml min^{-1} and the FI responses were recorded at 554 nm. The FI configuration allows the analysis of about 20 samples per hour. Table 1 summarises the optimum experimental conditions for the spectrophotometric determination of aluminium.

Sample procedure

All experiments were carried out following the recommended procedures, but aliquots of parenteral solution in addition to spiked samples were analysed.

Results and discussion

Effect of experimental variables on spectrophotometric procedure and optimisation

With the aim of elucidating the outstanding features of complex formation, the ternary Al(III)–CAS–BDTAC system was studied in the absence of non-ionic micelles.

Nature of cationic surfactant additive. A cationic surfactant was added to the system in order to achieve quantitative cloud point extraction of the Al(III)–CAS complex. Several cationic surfactants (quaternary ammonium salts) were tested so as to select the one producing the best results regarding micellar enhancement and stability. BDTAC showed the best performance.

Influence of order of reagent addition. The best order of reagent addition proved to be metal aliquot, chromogenic reagent, cationic surfactant and buffer solution. Complete complex formation was achieved at the moment of mixing with absorbance measured at 554 nm. The complex was stable for at least 24 h.

Chelating reagent and cationic surfactant concentrations. Stoichiometry. Fig. 1 and 2 show the results of the experiments carried out in order to determine the optimum chromogenic reagent–cationic surfactant–metal ion relation. In different experiments, the CAS and the BDTAC concentrations were modified (CAS, 0–1.3×10^{-5} mol l^{-1}; BDTAC, 0–5.2×10^{-6} mol l^{-1}). Other experimental variables were kept constant: metal ion, 7.4×10^{-7} mol l^{-1}; pH, 6.3 (acetate buffer, 1.0×10^{-2} mol l^{-1}). The absorbance was measured at the wavelength of maximum absorption of the complex (631 nm).

Table 1 Experimental conditions for CPE-FI determination of aluminium

CPE Step—	
Equilibration temperature	298 K
Centrifugation time	5 min
Working pH	6.3
Buffer solution	Acetate buffer (0.01 mol l^{-1})
Surfactant	PONPE 7.5 (0.5 ml Solution A)
FI step—	
Surfactant rich phase diluting agent	Acetonitrile (200 μl)
Flow rate	0.7 ml min^{-1}
Carrier composition	70:30 [acetate buffer (1×10^{-2} mol l^{-1}, pH 6.3)– acetonitrile]
Working wavelength	554 nm

Above a reagent to metal ion excess of 10 : 1, there was no variation in the sensitivity and stability of the complex. The stoichiometry of the CAS–BDTAC–Al(III) ternary complex, determined by the Yoe–Jones method,[29] was 7 : 4 : 1.

Effect of experimental variables on CPE parameters and optimisation

Selection of extractive surfactant. Several non-ionic surfactants were tested: TX-100 (Merck), TX-405 (Fluka), Igepal CO 720 (Aldrich, Milwaukee, WI, USA), Tween 80 (Sigma, St Louis, Mo, USA), PONPE 10 (Tokyo Kasei Industries) and PONPE 7.5. On the one hand, none of the results demonstrated quantitative extraction, and on the other, the critical points of the surfactants tested were too high with the risks of complex decomposition and poor extraction efficiency during the centrifugation step.

A possible explanation of the extraction behaviour of PONPE 7.5 is the existence of microscopically ordered structures in the surfactant-rich phase, such as liquid crystals, which can distinguish slight differences in molecular size, shape and structural factors.[30,31] PONPE 7.5 has been successfully used as an extracting surfactant for metals chelates.[14, 28, 31, 32.] The cloud point of the studied system with PONPE 7.5 is near room temperature (14.5 °C), offering advantages in terms of the experimental procedure. For this particular case, substantial operative advantages were attained, because phase separation occurred spontaneously at room temperature.

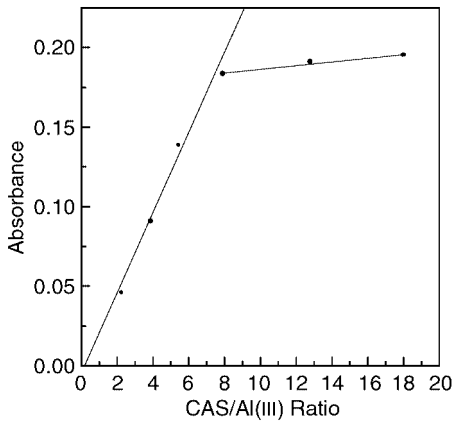

Fig. 1 Effect of reagent excess. $C_{Al(III)} = 7.4 \times 10^{-7}$ mol l^{-1}; C_{BDTAC} = 0.01% v/v; pH = 6.3; $C_{buffer\ agent} = 1 \times 10^{-2}$ mol l^{-1}; working wavelength, 631 nm.

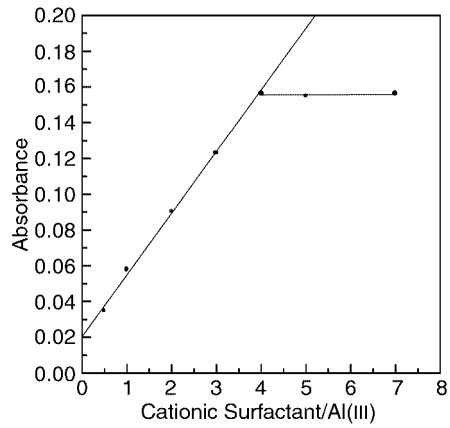

Fig. 2 Effect of cationic surfactant excess. $C_{Al(III)} = 7.4 \times 10^{-7}$ mol l^{-1}; $C_{CAS} = 7.4 \times 10^{-6}$ mol l^{-1}; pH = 6.3; $C_{buffer\ agent} = 1 \times 10^{-2}$ mol l^{-1}; working wavelength, 631 nm.

Ionic strength. Ionic strength has no notable effect on the extraction efficiency and sensitivity within the interval μ = 0.005–1 mol l^{-1}.

Effect of pH. Trials were carried out in order to locate the optimum pH range for the quantitative extraction of the complex. Each desired pH value was obtained by the addition of $HClO_4$ and/or NaOH solution in the presence of buffer. The results are shown in Fig. 3. As can be seen, the extraction begins at pH 4.6 and starts to decrease at pH 7.0. A pH of 6.3 was chosen.

Effect of surfactant concentration. The variation of the extraction efficiency was studied within the surfactant concentration range 0.1–2.0% w/w. Quantitative extraction was observed at PONPE 7.5 concentrations > 0.3%. A 0.5% w/w surfactant concentration (0.5 ml of solution A) was chosen as optimum. A preconcentration factor of 50 was achieved. Under the optimum experimental conditions, the extraction was quantitative (99.9%, successive extraction method). This could be ascribed to the fact that the preconcentrated (Al(III)–CAS–BDTAC) ternary complex has no charge, and it is consequently located in the micelle core.

Effect of centrifugation time. A centrifuge time of 5 min was selected as optimum as complete separation occurred within this time and no appreciable improvements were observed for longer times.

Optimisation of FI parameters

Selection of the diluting agent for the surfactant-rich phase and carrier composition. Different solvents for the surfactant-rich phase were tried so as to select the one producing the optimum results concerning sensitivity. The very high viscosity of the surfactant rich phase (*ca.* 20 cP) was drastically decreased with a diluting agent. Methanol was tested, but decomposition of the complex was observed. The best results were obtained with acetonitrile, and at least 200 µl of the diluting agent must be added to the surfactant rich phase. The effect of the composition of the diluting agent on sensitivity was studied within the range 0–100% for different mixtures of buffer and acetonitrile.

The carrier composition in the FI procedure was investigated in order to obtain the optimum analytical performance. Different buffer-to-acetonitrile ratios were tested.

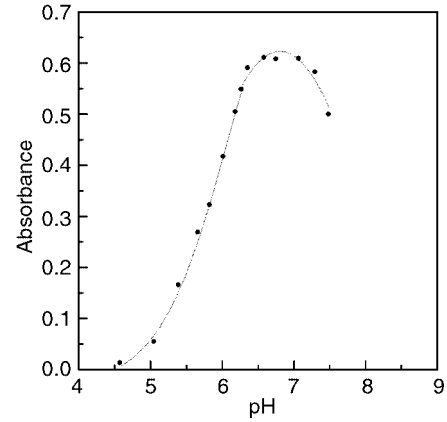

Fig. 3 Effect of pH. $C_{Al(III)} = 7.4 \times 10^{-7}$ mol l^{-1}; $C_{CAS} = 7.4 \times 10^{-6}$ mol l^{-1}; C_{BDTAC} = 0.01% v/v; $C_{buffer\ agent} = 1 \times 10^{-2}$ mol l^{-1}; $C_{PONPE\ 7.5}$ = 0.5% w/w; surfactant rich phase diluting agent, 200 µl of acetonitrile; carrier, 70 + 30 acetate buffer (0.01 mol l^{-1}, pH 6.3)–acetonitrile; flow rate, 0.7 ml min^{-1}; working wavelength, 554 nm.

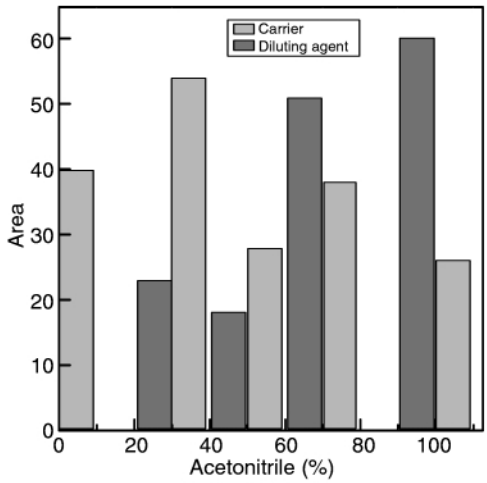

Fig. 4 Effects of diluting agent and carrier composition. Light grey bars: $C_{Al(III)}$ = 7.4 × 10^{-7} mol l^{-1}; C_{CAS} = 7.4 × 10^{-6} mol l^{-1}; C_{BDTAC} = 0.01% v/v; $C_{buffer\ agent}$ = 1 × 10^{-2} mol l^{-1}; $C_{PONPE\ 7.5}$ = 0.5% w/w; carrier, 70 + 30 acetate buffer (0.01 mol l^{-1}, pH 6.3)–acetonitrile; flow rate, 0.7 ml min^{-1}; working wavelength, 554 nm. Dark grey bars: $C_{Al(III)}$ = 7.4 × 10^{-7} mol l^{-1}; C_{CAS} = 7.4 × 10^{-6} mol l^{-1}; C_{BDTAC} = 0.01% v/v; $C_{buffer\ agent}$ = 1 × 10^{-2} mol l^{-1}, $C_{PONPE\ 7.5}$ = 0.5% w/w; surfactant rich phase diluting agent, 200 μl of acetonitrile; flow rate, 0.7 ml min^{-1}; working wavelength, 554 nm.

Fig. 4 shows the effects of both diluting agent and carrier composition; 100% acetonitrile was selected as the best diluting agent, and a 70 + 30 buffer–acetonitrile carrier was chosen.

Determination of aluminium using FI. A solvent programmable module was used instead of a peristaltic pump with the purpose of minimising the dispersion effect and optimising the sensitivity. The results were highly satisfactory. A high reproducibility was achieved; peak areas can be repeated with % error < 0.9 (RSD). In contrast, analytical parameters (linearity, detection limit, instrumental and method precision and accuracy) were unsatisfactory when a peristaltic pump was used.

A calibration plot was constructed under the optimum experimental conditions. Beer's law is obeyed for the range 2 × 10^{-7} –2.5 × 10^{-5} mol l^{-1} Al(III). The statistical parameters were as follows: y = (0.9 ± 0.7) + (3.6 × 10^7 ± 5.0 × 10^5) x, where y is the integrated area and x is the aluminium concentration in mol l^{-1}; correlation coefficient r = 0.9994; p = 4.92 × 10^{-10}; n = 8.

The limit of detection[33] (LOD) was 1.12 × 10^{-7} mol l^{-1} . The calibration graph for a 20 μl injected sample was linear over at least two orders of magnitude. The phase volume ratio (V_s/V_w, the ratio of the volume of the surfactant rich phase to that of the aqueous phase) was 0.02.

Determination of aluminium in parenteral solution. In order to validate the proposed methodology, the developed procedure was applied to the determination of aluminium in parenteral solution samples and some aluminium-spiked samples. The procedures were carried out in parenteral solutions without any previous treatment. Table 2 gives the results obtained for spiked samples and Table 3 for commercial parenteral solutions samples.

The effects of representative potential interfering species (at the concentration levels at which they might occur in the samples studied) were tested. Commonly encountered matrix components such as alkali and alkaline earth elements generally do not form stable complexes and are not extracted into the surfactant rich phase. Even though iron is normally present in TPN solutions at trace levels, Fe(III) could be tolerated up to at least 1 × 10^{-4} mol l^{-1}.

Table 2 Determination of aluminium in spiked NaCl parenteral solution samples

Sample No.	Al(III) added/ μg l^{-1}	Al(III) found[a]/ μg l^{-1}	s^b	Recovery (%)[c]
I	0.0	6.9[d]	0.058	—
II	5.1	11.5[e]	0.018	90.19
III	10.2	17.1[f]	0.012	100.0

[a] n = 6. [b] Standard deviation. [c] 100 (found −6.9)/ added. [d] 2.56 × 10^{-7} mol l^{-1}. [e] 4.26 × 10^{-7} mol l^{-1}. [f] 6.34 × 10^{-7} mol l^{-1}.

Table 3 Concentrations of aluminium in commercial parenteral solutions (95% confidence interval; n = 6)

	Al concentration/mol l^{-1}	
Sample	Proposed method[a]	Standard method[26]
Ringer physiological solution[a]	4.2 ×10^{-7}	Not found
Ringer physiological solution[a]	6.7 ×10^{-7}	Not found
NaCl physiological solution[b]	2.5 ×10^{-7}	Not found

[a] Na^+ 145.5 mequiv. l^{-1}; K^+ 1.3 mequiv. l^{-1}; Ca^{2+} 2.7 mequiv. l^{-1}; Cl^- 149.5 mequiv. l^{-1}. [b] Na^+ 145 mequiv. l^{-1}; K^+ 145 mequiv. l^{-1}.

Conclusions

The *in situ* cloud point extraction procedure represents a promising approach in the area of pharmaceutical monitoring. A simple, inexpensive, efficient, safe, versatile and non-polluting method was developed.

The use of the programmable solvent module for FIA led to a substantial improvement of the analytical performance of the method. The developed procedure has much improved speed, sensitivity, reproducibility and cost per analysis compared with typical FI methodology. Dispersion was substantially minimised.

The results of this study clearly show the potential and versatility of this method, which could be applied to monitoring aluminium in various samples of environmental, toxicological, medical and forensic interest.

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