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ORIGINAL ARTICLE

Methods to determine Arsenic, Aluminium and Tin in Meglumine Antimoniate (Glucantime®) by Graphite Furnace Atomic Absorption Spectrometry using surface response optimization

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ABSTRACT

This work presented new methods for the determination of aluminium, arsenic and tin in a pentavalent antimonial drug (Glucantime®) by graphite furnace atomic absorption spectrometry (GF AAS). The samples of Glucantime® was added to triton X-100 (4:1) to prevent carbonaceous residues inside the graphite tube that was observed without triton use. The choice of the modifiers were made by univariated selection testing (using the furnace program as described by the manufacturer), permanent ruthenium, iridium, rhodium, zirconium, titanium, tungstenium and tantalum (500 µg of each) inside of an L'vov platform inserted in a pyrolitic graphite tube. The best pyrolysis and atomization temperatures were obtained by a surface response made by a program as described by the manufacturer. For aluminium, the best pyrolysis and atomization temperatures (AT) were 1238 and 2583 ºC using Ir as permanent modifier; for arsenic: 1390 and 2610 ºC, also using iridium as the permanent modifier, while for tin, pyrolysis and AT were 614 and 2526 ºC, with Ru, the permanent modifier. The limits of detection and quantification were 2.54 and 7.27 µg L^{-1} for Al; 0.23 and 0.77 µg L^{-1} for As and 0.19 and 0.63 µg L^{-1} for tin. Recoveries for all metals (n=21 for each metal) were between 97.4 and 102.8% for Al; 100.0 and 104.5 for As and 102.3 and 105.2 for Sn. The higher intra- and inter-assay precision (n=7 for intra and 21 for inter assay, for each analyte), were 3.5% (intra) for tin to 7.1% (inter-assay) for As. For the analysis, using the proposed methodologies for the five lots of Glucantime®, average concentrations were between 50.83 and 110.00 µg L^{-1} for Al, 159.81 and 382.97 ng L^{-1} for As and 84.40 and 616.17 µg L^{-1} for Sn.

Key words: *Glucantime, aluminium, arsenic, tin, graphite furnace atomic absorption spectrometry, permanent modifiers.*

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INTRODUCTION

Leishmaniasis is a tropical disease affecting 12 million people worldwide in impoverished areas and results in substantial health problems or death of an estimated 400,000 people per year [1]. Leishmaniasis, from the genus Leishmania, is caused by a protozoan parasite transmitted by the bite of the infected female phlebotomine sandflies. Wild and domesticated animals and humans themselves can act as a reservoir of infection. The Leishmania parasite appears as a motile promastigote in the sandfly's stomach and soon transforms into an anamastigote once engulfed by host macrophages [2]. Glucantime®, a pentavalent antimonial drug, is commonly used as a first-line for treatment of leishmaniasis [2].

Studies have shown that the presence of inorganic impurities in formulated drugs and raw materials used in pharmacies may represent a risk to public health as a result frequent intake of these substances, even at low levels, which can pose serious health problems [3-4]. Therefore, there is concern that heavy metal

contamination with substantial amounts of elements such as aluminium (Al), arsenic (As) and tin (Sb) during processing and packaging of Glucantime® may pose a public health problem in patients receiving treatment with this drug.

Aluminium has been long known to be neurotoxic, with mounting evidence that chronic exposure is a factor in many neurological diseases, including dementia, autism, and Parkinson's disease [5].

Arsenic and many of its compounds are especially potent poisons. Arsenic disrupts ATP production through several mechanisms. At the level of the citric acid cycle, arsenic inhibits pyruvate dehydrogenase and by competing with phosphate it uncouples oxidative phosphorylation, thus inhibiting energy-linked reduction of NAD+, mitochondrial respiration, and ATP synthesis. Hydrogen peroxide production is also increased, which might form reactive oxygen species and oxidative stress. These metabolic interferences result in death from multi-system organ failure probably from necrotic cell death, not apoptosis. A post mortem, one may observe brick red colored mucosa due to severe hemorrhage [6].

In humans inorganic arsenic is reduced nonenzymatically from pentoxide to trioxide, using glutathione (GSH) or it is mediated by enzymes. Reduction of arsenic pentoxide to arsenic trioxide increases its toxicity and bioavailability [7].

Arsenic compounds are widely used and have long been recognized as toxicants [8]. Arsenic is a constituent of many foods such as meat, fish, poultry, grains and cereals [9]. In excessive amounts, arsenic causes gastrointestinal damage and cardiac damage. Chronic doses can cause vascular disorders such as black foot disease [9].

Tin is a suspected reproductive toxicant and exposure to it has the potential to negatively affect the human reproductive system. The severity and nature of its adverse effect is variable and can be influenced by factors such as sex, level of exposure and individual sensitivity to the chemical. Effects on the female reproductive system can include menstrual problems, alteration of sexual behavior, puberty onset, length of pregnancy, menopause onset, infertility and lactation problems. Effects on the male reproductive system can include altered sexual behavior and fertility and problems with sperm shape or sperm count [10]. Mechanisms of toxicity of tin include inhibition of enzyme activity and protein synthesis, alterations in nucleic acid function, and changes in cell membrane permeability [10].

Flores et al. [11] drew attention to the fact that routine quality control of drugs with the appropriate methods to detect heavy metals has been traditionally neglected. Contamination of antimonials with heavy metals such as lead, arsenic and tin is not expected unless poor quality control of manufacturing process allows the use of impure salts.

In this work, we present the results of new methods for Al, As, and Sn determinations in Glucantime®, using Triton X-100 to prevent carbonaceous residues inside of a graphite tube by GF AAS (graphite furnace atomic absorption spectrometry) with Zeeman background correction.

METHODOLOGY

Instrumentation

The integrated absorbances were performed in an atomic absorption spectrometer, Spectra 220 from Varian (Victoria, Australia), equipped with a graphite furnace, an autosampler EL 98013384-2C, and a polarized Zeeman background correction. Hollow cathode lamps (HCL) of Al from Jarrel Ash (Boston, USA, Part number 45452), were operated at a 20 mA current, 0.5 nm slit and a wavelength of 392.6 nm; for As, the HCL was purchased from Varian (Victoria, Australia Part number 5610100300), and operated at a 12 mA current with a 0.5 nm slit and a wavelength of 143.7 nm; for Sn, the HCL lamp was also purchased from Varian (Victoria, Australia Part number 5610106100), operated at 15 mA with a 0.5 nm slit and a wavelength of 235.5 nm. Argon 99.996% (White Martins, Belo Horizonte, MG, Brazil) was used as the purge gas with a flow rate of 250 mL min^{-1}. Graphite tubes with L'vov platforms (Varian, Part Number 01-900327-0) were used for all studies.

Chemical and reagents

Deionized water (resistivity of 18.2 Ω cm^{-1}) was obtained with a Milli-Q System (Millipore, Bedford, MA, USA) and was purified immediately before use for the preparation of all solutions. Nitric acid (trace metal grade) was obtained from Merck (Darmstadt, Germany). Solutions (1000 mg L^{-1}) of iridium, niobium, tantalum, titanium, ruthenium, rhodium and zirconium were obtained from Fluka (Fluka, Buchs, Switzerland), used at 1 mol L^{-1} in hydrochloric acid. Tungsten, in the same solution, was acquired from Merck (Titrisol, Merck). Plastic bottles, autosampler cups and other ware were cleaned by soaking in 20% v/v HNO_3 for one day, rinsing several times with Milli-Q water, then left to dry. The autosampler washing solution, containing 0.05% v/v Triton X-100 (Merck) plus 0.1% v/v isopropanol (Sigma-Aldrich, São Paulo, Brazil), was used to avoid analyte adsorption onto the surface of the container and clogging of the capillary sampling tip, as well as to improve the dispersion of the sample solution onto the platform. Al, As and Sn stock solutions (1000 mg L^{-1}) were prepared from Titrisol Merck ampoules in 5% v/v nitric acid.

Samples and sample treatment

The samples of Glucantime® used in this study were obtained from Health Department of the Minas Gerais State, Brazil. In initial studies have shown that after introduction of the Glucantime® sample without any treatment, carbonaceous residues had formed above the L'vov platforms inside of the graphite tubes. This problem was eliminated by diluting the Glucantime® samples of the injectable drug with Triton X-100. We used a 4:1 dilution, i.e. four parts of Glucantime® with one part of Triton X-100 5% v/v. The final concentrations of Triton X-100 in the samples were a 1 % v/v. A similar problem with carbonaceous residues in sample with high carbon content was observed and eliminated also using Triton addition to the samples, as has been previously reported [12-26].

L'vov platform treatment with permanent modifiers

The graphite tubes were treated independently with 500 µg of each studied permanent modifier (Zr, Ir, Rh, Ru, Nb, W, Ti and Ta) by applying 50 mL of each metal solution (1000 mg L^{-1}) onto the platform and submitting them to a furnace temperature program 10 times for the platform treatment, as previously described [27-28].

Optimization strategies

In all optimization steps, 20 µL of the prepared Glucantime® samples diluted with Triton X-100, as described elsewhere, was used. Several experiments were performed to choose the appropriate modifier to measure aluminum, arsenic and tin in the samples. The integrated absorbance measures and background signals of these samples were obtained employing independent L'vov platforms inside the graphite tubes treated with before mentioned permanent modifiers by using the temperature program as recommended by the manufacturer. A tube without permanent modifier was also employed. This tube was used with the equipment adjusted in accordance with the manufacturer to measure the response and to verify if the equipment demonstrated an integrated absorbance response consistent with an acceptable level.

LOD and LOQ calculations

The limits of detection (LOD) and quantification (LOQ) for all analytes (Al, As and Sn) were calculated after 10 measurements of the blank of the calibration curves. The level zero of the aqueous calibration curves were used for arsenic and tin, and the Glucantime® plus Triton X-100 (4:1 v/v), for aluminium. The LOD was calculated as 3 s/a, while the LOQ was 10 s/a, where *s* is the standard deviation of ten measurements of the blank of the appropriate calibration curve and *a* is the slope of the aqueous or matrix matching calibration curves.

RESULTS AND DISCUSSION

Choice of the best permanent modifiers for each analyte

The selected samples for the preliminary studies had previously contained the three analytes, and therefore, no spiking was required. This is an excellent advantage because the analytes will be linked to the original sample substances. The best sensitivity with repeatability and low background signal were observed with permanent Ir (500 µg) for aluminium and arsenic (Fig. 1 and 2). For tin, the best modifier was Ru permanent (500 µg) on the L'vov platform. All other modifiers and combinations presented very low relative sensitivity. We chose these modifiers for the construction, with the Varian surface response program, to optimize the best pyrolysis and atomization temperatures for each analyte. All of these studies were done using a temperature program suggested by the manufactures of the used equipment.

Optimization of the pyrolysis and atomization temperatures

After the choosing for the best modifiers for Al, As, and Sn, the surface responses were obtained to optimize the best pyrolysis and atomization temperatures for each analyte in each diluted Glucantime®sample as presented in item 2.3. As was observed by the surface responses (generated by the SRM Wizard surface generation program, installed in the equipment), the best pyrolysis and atomization temperatures were 1,238 and 2,583ºC, respectively, for aluminium using permanent iridium (500 µg) as presented in Figure 1. For arsenic, the best pyrolysis and atomization temperatures, also using permanent iridium as a modifier, were 1,390 and 2,610 ºC, respectively, as presented in Figure 2, while for tin, the best pyrolysis and atomization temperatures, using permanent ruthenium (also 500 µg deposited above the L'vov platform), were 614 and 2,526 ºC, as show in the Figure 3. The absorption pulses, obtained for each analyte, using these modifiers and temperatures, are illustrated in Figures 4, 5 and 6 for Al, As and Sn, respectively.

The characteristic masses (m_o) obtained using these optimized programs for each analyte were (5.0 ± 0.8 pg) for aluminium (recommended mass by the manufactures is 5.0 pg for standard solutions of Al); (10.1 ± 0.9 pg) for arsenic (recommended mass is 10 pg) and (6.7 ± 1.1 pg) for tin (recommended mass is 5.0 pg). Considering that the obtained characteristic masses (n=6), obtained through the calibration points of the employed calibration curves, the results can considered good as the real characteristic masses were obtained directly in the diluted Glucantime® samples, and when compared with the recommended

characteristic masses (obtained in new equipment and using standard analytes solutions), the obtained m_{os} were in very good agreement for all the studied analytes.

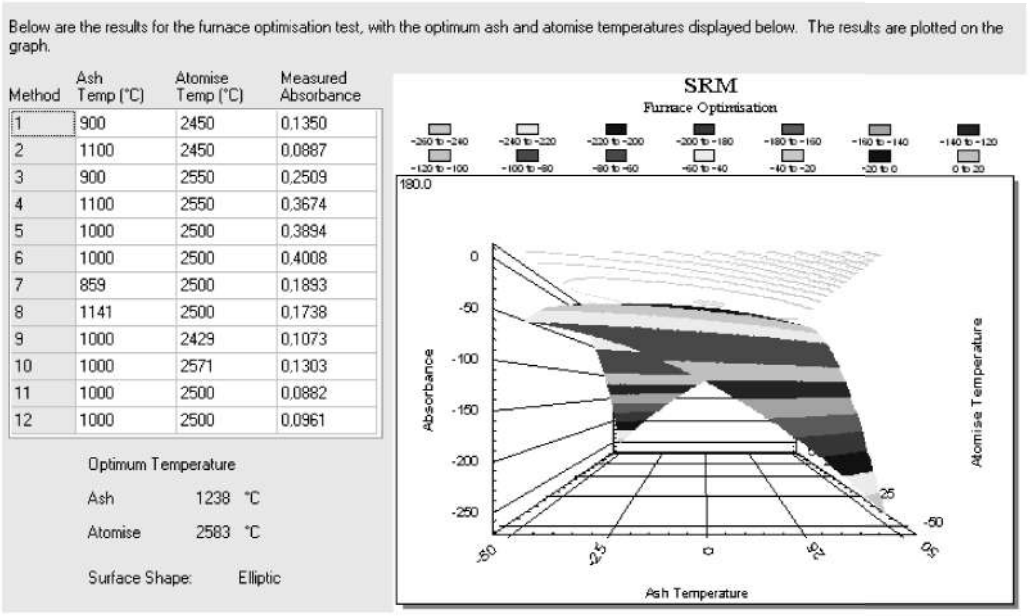

Figure 1. Surface response for Al in a sample of Glucantime® plus Triton X-100 (4:1) using Ir (500 µg) as permanent modifier inside a L'vov platform.

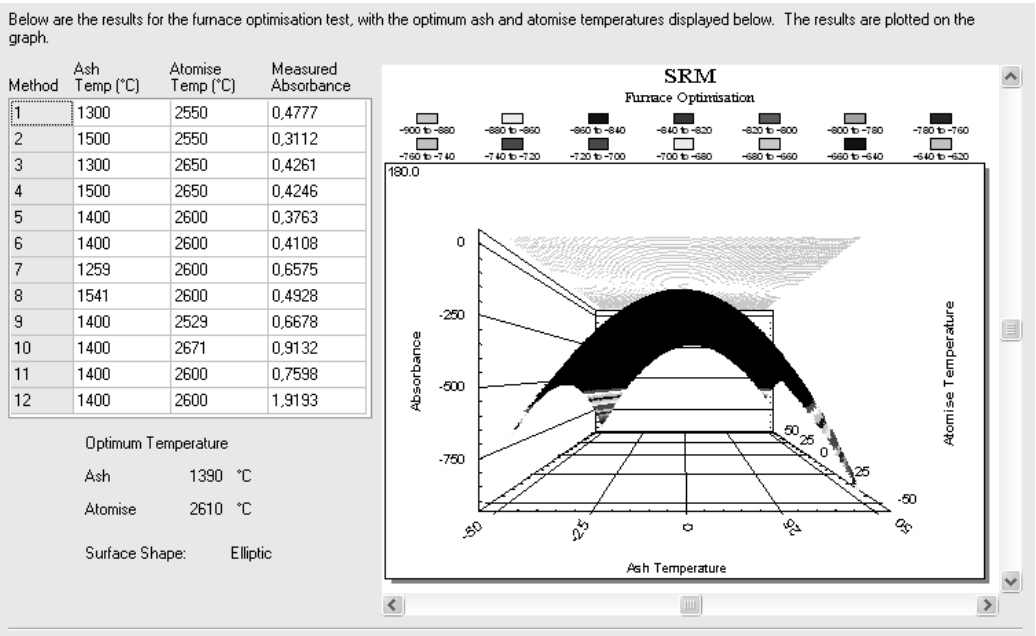

Figure 2. Surface response for As in a sample of Glucantime® plus Triton X-100 (4:1) using Ir (500 µg) as permanent modifier inside a L'vov platform.

Below are the results for the furnace optimisation test, with the optimum ash and atomise temperatures displayed below. The results are plotted on the graph.

Method	Ash Temp (°C)	Atomise Temp (°C)	Measured Absorbance
1	600	2350	0,5580
2	800	2350	0,5917
3	600	2450	0,7505
4	800	2450	0,7119
5	700	2400	0,6651
6	700	2400	0,5950
7	559	2400	0,5545
8	841	2400	0,5709
9	700	2329	0,5516
10	700	2471	0,6190
11	700	2400	0,6210
12	700	2400	0,7314

Optimum Temperature

Ash 614 °C

Atomise 2526 °C

Surface Shape: Elliptic

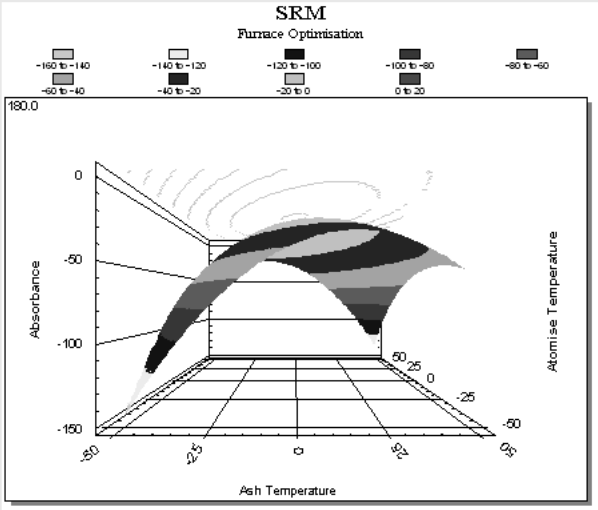

Figure 3. Surface response for Sn in a sample of Glucantime® plus Triton X-100 (4:1) using Ru (500 µg) as permanent modifier inside a L'vov platform.

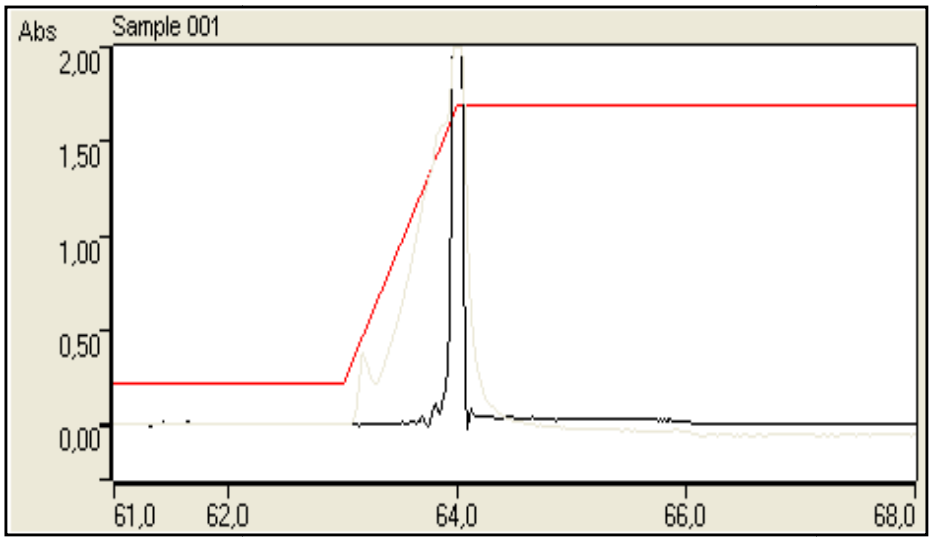

Figure 4. Absorption pulse for 0.3 ng of Al in Glucantime® plus Triton X-100 (4:1), using Ir (500µg) as permanent modifier.

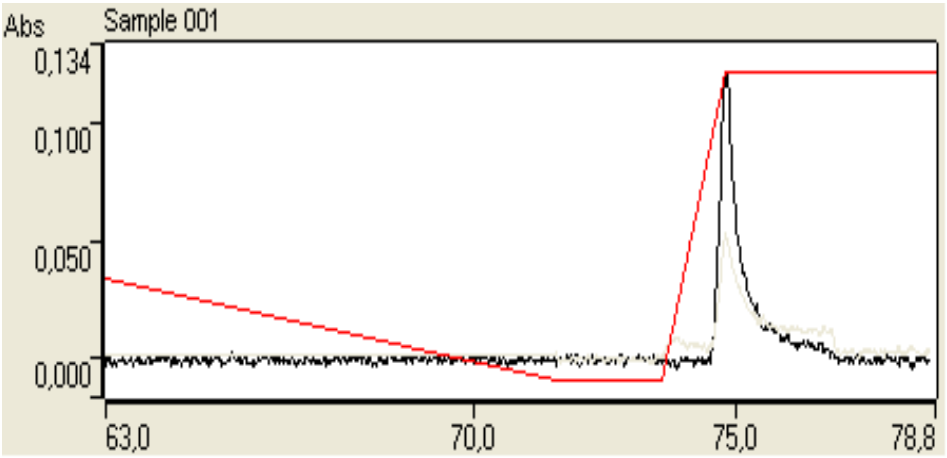

Figure 5. Absorption pulse for 0.3 ng of As in Glucantime® plus Triton X-100 (4:1), using Ir (500µg) as permanent modifier.

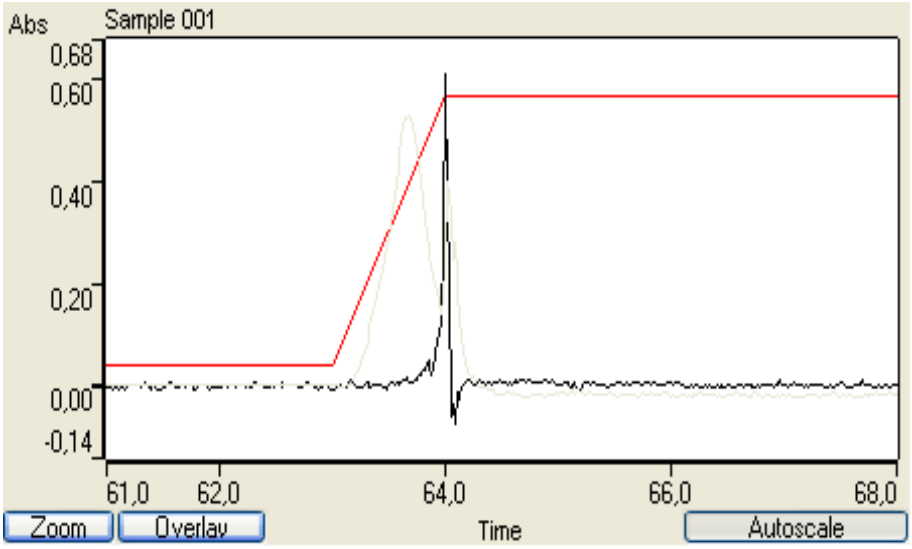

Figure 6. Absorption pulse for 2.7 ng of Sn in Glucantime® plus Triton X-100 (4:1), using Ru (500µg) as permanent modifier.

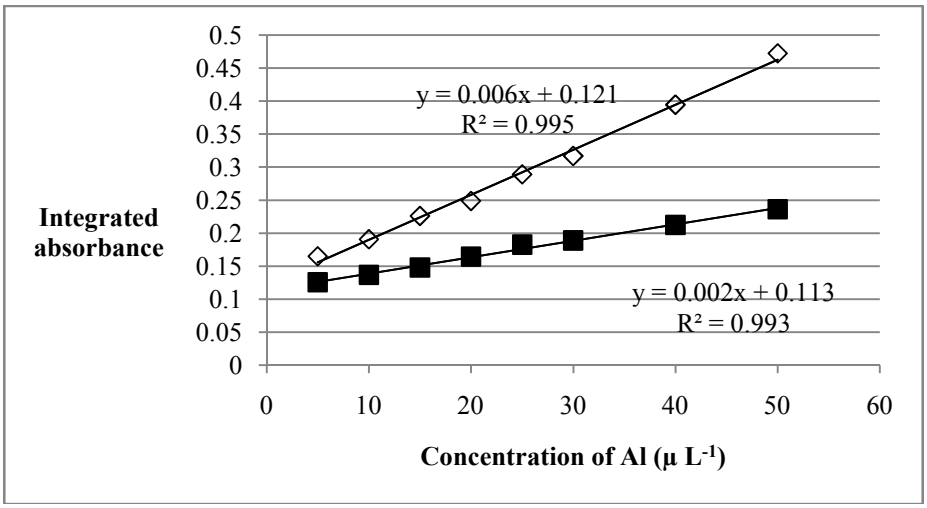

Figure 7. Calibration curves for Al by aqueous solutions and matrix matching (in Glucantime® plus Triton X-100, 4:1) (◊ matrix matching calibration and ■ aqueous calibration).

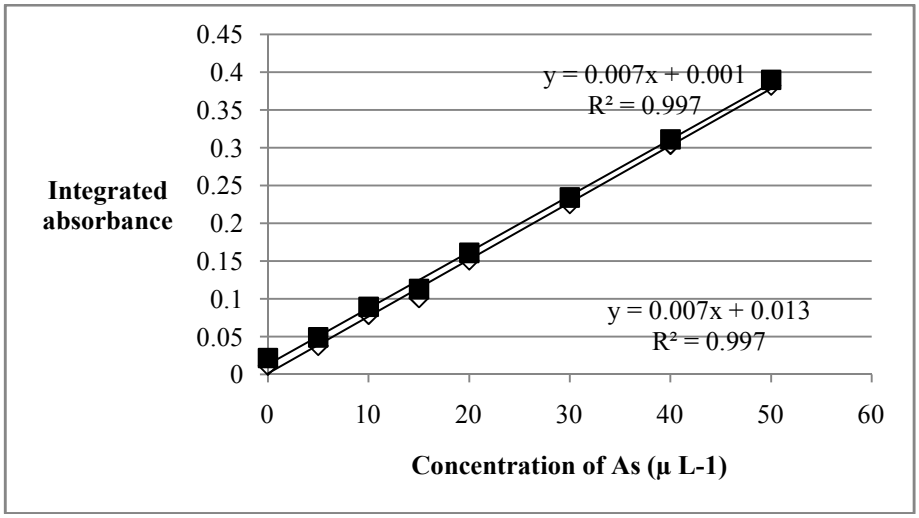

Figure 8. Calibration curves for As by aqueous solutions and matrix matching (in Glucantime® plus Triton X-100, 4:1) (◊ aqueous calibration and ■ matrix matching calibration).

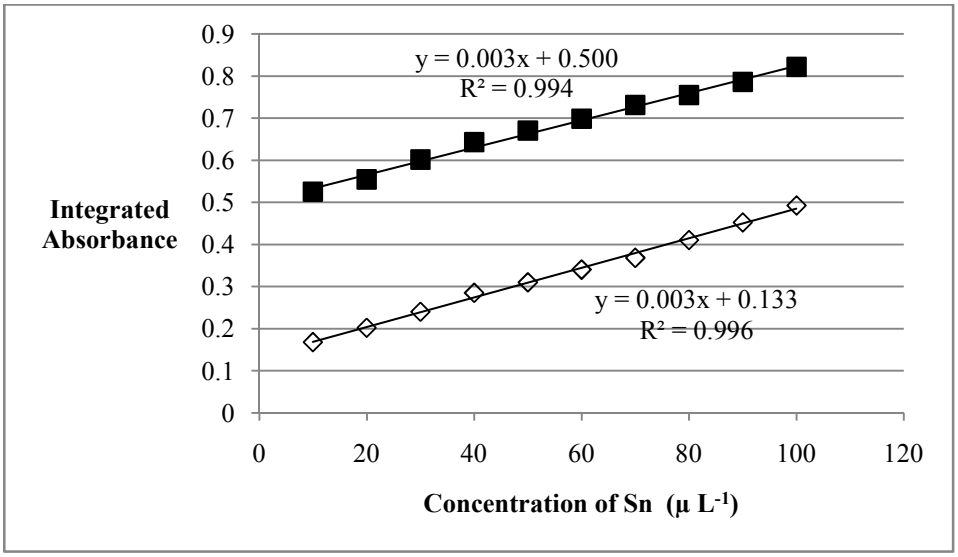

Figure 9. Calibration curves for Sn by aqueous solutions and matrix matching (in Glucantime® plus Triton X-100, 4:1) (◊ aqueous calibration and ■ matrix matching calibration).

Analytical figures of merit

Table 1 presents the furnace temperature program for determining the analytes (Al, As and Sn) in Glucantime® (with 1 % v/v of Triton X-100). The pre-drying and drying steps were carefully optimized to avoid sputtering, thus preventing the samples from spilling out of the graphite tube. This step received special attention, because Triton X-100 use is a surfactant, and when introduced into the graphite furnace, it avoids the formation of carbonaceous residues inside the tube and above the L'vov plataform, and thus, avoids clogging of the oven and the direct passage of lamp light beam while not interfering in the correct measurement of the integrated absorbance. To evaluate the possibility of matrix effects, three curves, using matrix matching calibration (in Glucantime® plus Triton X-100) and three aqueous curves, were obtained within a range of 0 to 50 µg L^{-1} for aluminum using the optimized temperatures and times as described in the furnace temperature program. For arsenic, the same curves were also made in the range of 0 to 50 µg L^{-1}. For tin, the same curves presented a range of 0 to 100 µg L^{-1}. The aqueous calibration curves were done by appropriate dilution of aluminium, arsenic and tin standard stock solution (1,000 mg L^{-1}) in deionized water, maintaining the final solution at 2%v/v HNO_3. The range of the calibration curves were thus chosen for covering the entire linear range by the equipment, according to the manufacturer.

In Figure 7, the average for each curve is presented for Al, while in Figures 8 and 9, As and Sn are presented, respectively. As can be observed visually in Figure 7, the average curves were not parallel. But the matrix effect was evaluated by comparing the averages of the angular and linear coefficients of these curves using statistical tools (F and Student's t tests). These tests revealed that the curves did not present statistically significant differences at a 95 % confidence level, which indicates the absence of matrix effect for As and Sn (Figures 8 and 9, respectively). Therefore, all of the subsequent studies for these analytes were conducted using aqueous calibration curves. For aluminium, the tests revealed statistically significant differences at a 95 % confidence level for the curves, which indicates the presence of matrix effect. Therefore, all of the subsequent studies were carried out using matrix matching calibration curves. Table 2 presents the findings for the main parameters of merit for the proposed methods.

The LOD and LOQ were 2.54 and 7.27 µg L^{-1} for Al; 0.23 and 0.77 µg L^{-1} for As and 0.19 and 0.63 µg $L^{-1}$for Sn, respectively.

Romero *et al* [29] examined the high frequency of skin reactions in patients treated with Meglumine Antimoniate (MA) contaminated with heavy metals. In their study, the authors present concentrations as determined in two lots of MA, but do not present the limits of detection and quantification for either Sb(III), As, Cd or Pb.

Flores and co-workers [30] proposed a method to determine total arsenic by batch HG-AAS (hydride generation atomic absorption spectrometry) in MA. In their study, a LOD of 0.8 ng for total As was obtained. In our study, considering that the volume introduced in the furnace was 20 µL, the obtained LOD for As was 0.23 µg L^{-1} or 0.005 ng.

Precision was evaluated through intra- and inter-assay studies. The intra-assay coefficient of variation (CV) was calculated using the standard deviation of the reference sample spiked with 15, 25, and 35 µg L^{-1}

of Al, and for As, 20, 50, and 80 μg L^{-1} of Sn, divided by the average of the respective concentrations, and then multiplied by 100. Such determinations were performed separately in seven replicates of one sample of diluted Glucantime® (Glucantime® plus Triton X-100) on the same day and read in triplicate. To calculate the inter-assay coefficient of variation, the same procedure was repeated with seven replicates of the same sample and readings in triplicates over three different days. The higher average CV for the intra- and inter-assay precision was 5.8±0.9 % and 6.5±1.4 % for Al; 7.0±1.8 % and 7.1±2.3 % for As and 6.4±2.2 % and 6.8±2.5 % for Sn. These results are presented in Table 3.

Accuracy was evaluated by recovery studies with Glucantime® sample diluted as previously described and spiked with 15, 25, and 35 μg L^{-1} of Al and As and 20, 50, and 80 μg L^{-1} of Sn. Recoveries showed results (presented in Table 4), ranging from 97.4±10.0 to 102.8±7.4 % for Al; 100.0±3.5 to 104.5±3.2 % for As and 102.3±4.6 to 105.2±2.1 % for Sn.

Analytical application

Aluminium, arsenic and tin concentrations were determined in 5 lots of Glucantime® samples using the optimized experimental conditions and aqueous calibration curves (for As and Sn) or matrix matching calibration curve (for Al). Table 5 presents these results.

Romero et al [29] included a discussion about the high frequency of skin reactions in patients with Leishmaniasis treated with Glucantime® contaminated with heavy metals (trivalent antimony, arsenic, cadmium and lead). According to the authors, their data showed that the frequency of skin reaction, an unusual adverse event, was greater in patients treated with the drug containing a high concentration of lead, cadmium and arsenic. Arsenic, lead and cadmium have also been linked as a cause of contact allergy [31]. Pentavalent antimony could cause a generalized rash but the phenomenon is rare even with prolonged exposure to the maximum recommended dose [32]. The authors suggest that a more plausible hypothesis would be reactions due to arsenic, lead or cadmium.

In a study done by Flores et al [30], which evaluated four lots of Glucantime® as part of their proposed methodology, the arsenic concentrations were between 0.48 and 1.27±0.08 mg L^{-1} for manufacturer 'A' and 9.6±0.7 and 78.9±2.7 mg L^{-1} for manufacturer 'B'. According to the authors, as the MA is administrated in an injectable form, the presence of As posses a greater risk factor for people undergoing treatment. In view of this, arsenic control must be made routinely to ascertain the quality of drugs used for leishmaniasis treatment.

Table 1: Optimized furnace temperature program for the determination of Al, As and Sn in Glucantime® plus Triton X-100.

Step	Number	Temperature (°C)	Time (s)	Ar flow rate (L min^{-1})
Drying	1	85	5	0.3
	2	95	40	0.3
	3	120	10	0.3
	4	600	10	0.3
	5	600	50	0.3
Pyrolysis	6	1238[a], 1390[b], 614[c]	0.8	0
Atomization	7	2583[a], 2610[b], 2526[c]	2.0	0
Cleaning	8	2700	2.0	0.3

a = Al; b = As and c = Sn.

Table 2: Analytical figures of merit for the determination of Al, As and Sn in Glucantime® plus Triton X-100.

Parameter	Results		
Regression equations, *n*=3	Abs =(0.0060x±0.0012) C_{Al} + (0.121±0.010		
	Abs=(0.070±0.0030)C_{As}+ (0.006±.0008)		
	Abs = (0.0092 ± 0.0005)C_{Sn} + (0.004 ± 0.002)		
Analyte	Al	As	Sn
R^2 (n=3)	0.9940 ± 0.0009	0.9940±0.0015	0.9992 ± 0.0010
Linear range (μg L^{-1})	0 – 50.0	0 – 50.0	0 – 100.0

LOD (µg L^{-1})	2.54	0.23	0.19
LOQ (µg L^{-1})	7.27	0.77	0.63
Characteristic masses (pg)	5.0 ± 0.8	10.1 ± 0.9	6.7 ± 1.1

Table 3: Coefficients of variation for intra-assay and inter-assay obtained for the determination of Al, As, and Sn in Glucantime® by GF AAS

Al concentration (µg L^{-1})	CV intra-assay (%, n=7)	CV inter-assay (%, n=21)
15.0	4.7±1.2	6.5±1.4
25.0	4.6±1.4	4.9±1.2
35.0	5.8±0.9	5.2±1.1
As concentration (µg L^{-1})	CV intra-assay (%, n=7)	CV inter-assay (%, n=21)
15.0	7.0±1.8	7.1±2.3%
25.0	4.8±2.4	5.8±1.8%
35.0	6.7±1.6	6.3±3.4%
Sn concentration (µg L^{-1})	CV intra-assay (%, n=7)	CV inter-assay (%, n=21)
20.0	4.0±0.8	6.8±2.5
50.0	6.4±2.2	6.6±2.6
80.0	3.5±1.6	4.8±2.2

Table 4: Recoveries of Al, As and Sn from spiked Glucantime® samples by GF AAS

Concentration of Al (µg L^{-1})	Recovery, % (n=21)
15.0	101.0±15.4
25.0	97.4±10.0
35.0	102.8±7.4
Concentration of As (µg L^{-1})	Recovery, % (n=21)
05.0	100.0±3.5%
25.0	104.5±3.2%
35.0	101.7±4.9%
Concentration of Sn (µg L^{-1})	Recovery, % (n=21)
20.0	102.3±4.6
50.0	103.2±6.8
80.0	105.2±2.1

Table 5: Levels of Al, As and Sn obtained from Glucantime® samples (n=5 sample lots) with the proposed methods for different lots with varying expiration dates

Samples	Al Levels (µg L^{-1})	As Levels (ng L^{1})	Sn Levels (µg L^{1})
A1	50.83±0.13	204.44±0.40	227.67±0.50
A2	93.50±0.30	382.97±0.60	616.17±0.13
A3	107.67±0.20	285.71±0.20	393.17±0.40
A4	60.75±0.20	176.93±0.30	84.40±0.20
A5	110.00±0.30	159.81±0.50	179.67±0.60

CONCLUSION

The presented methods to determine Al, As and Sn in Glucantime®, using the graphite furnace atomic absorption spectrometry, were very simple and requires only a ampoule dilution of Glucantime® with

triton X-100 to prevent the formation of carbonaceous residues inside of graphite tubes. The sensitivity for all analytes can be considered satisfactory with low limits of detection and quantification, especially for arsenic and tin. Aluminum can be determined using just matrix matching calibration, but it is not difficult to obtain matrix matching calibration using a Glucantime® ampoule plus triton X-100 as a blank for all points of the calibration curves. We could read all samples with interpolation inside the same curve. For arsenic and tin, we used aqueous calibration and matrix matching calibration for aluminium. The use of permanent modifiers (permanent iridium for As and permanent ruthenium for tin), appear to destroy matrix during the pyrolysis stage. The same does not seem to occur for Al was not found a modifier that does not present matrix effect. Because aluminium possesses a matrix effect, none of the tested modifiers were able to successfully destroy the interfering effects of atomization of this analyte in the glucantime samples. The surface response program is a very interesting tool for achieving the best pyrolysis and atomization temperatures for all analytes in the Glucantime® sample. The accuracy and precision were very good, and when analyzing the five different lots of Glucantime®, using the proposed methodology, the results varied between 50.83 to 110.00 μg L^{-1} for Al; 159.81 to 328.97 ng L^{-1} for As and 84.40 to 616.17 μg L^{-1} for Sn.

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