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Fast determination of arsenosugars in algal extracts by narrow bore high-performance liquid chromatography–inductively coupled plasma mass spectrometry

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ABSTRACT

The potential of narrow bore high-performance liquid chromatography (HPLC) with detection by inductively coupled plasma mass spectrometry (ICP-MS) for fast determination of arsenosugars in algal extracts was explored. The retention behavior of four naturally occurring dimethylarsinoylribosides on an anion-exchange microbore column was investigated, with the mobile phase flow rate ranging from 60 to 200 μL min^{-1}. A low sample consumption system consisting of a micronebulizer and a low inner volume cyclonic spray chamber was used as the interface between the micro-column and the ICP mass spectrometer. Both the high efficiency nebulizer, HEN, and the PFA micronebulizer were tested, with the former providing 20–50% greater sensitivity than PFA (depending on the liquid flow rate), but comparable limits of detection and slightly lower chromatographic resolution. With the setup employed and under the optimal conditions, a satisfactory separation of the arsenosugars was achieved in less than 5 min. The instrumental limit of detection was 0.20 μg As L^{-1} and the precision was better than 3% (RSD%, $n = 5$). The accuracy of the determination was verified by the analysis of a reference algal extract, obtaining values in good agreement with the reference ones.

1. Introduction

Arsenic occurs in many different chemical forms in the environment [1] and can bioaccumulate in algae and living organisms reaching levels in the 1–100 μg g^{-1} concentration range [2]. Inorganic arsenic can be alkylated and adenosylated by algae thus giving rise to organoarsenic compounds such as arsenobetaine and arsenosugars. Indeed arsenosugars are common constituents of marine samples [3,4]. These compounds, mostly water soluble, contain a 5-deoxypentose moiety and an arsinoyl or arsinothioyl group, attached to the C5 carbon, and a variety of side chains at the C1 position. Since arsenic compounds display very different degrees of toxicity, arsenic speciation is an important issue to evaluate the environmental impact caused by this element as well as its metabolization [5]. The most common means for carrying out arsenic speciation is through HPLC/ICP-MS coupling, generally employing ion exchange chromatography [6,7]. The determination of four naturally occurring arsenosugars in algae with anion-exchange chromatography and ICP-MS as element-specific detector was first reported by Raber et al. [8]. An Hamilton PRP X-100 anion-exchange column was used along with an aqueous solution of ammonium dihydrogen phosphate (20 mmol/L) of pH 5.6 as the eluent. The mobile phase was pumped at a flow rate of 1.5 mL min^{-1}. Isocratic elution by using ammonium hydrogen phosphate, ammonium carbonate or ammonium bicarbonate has also been reported [7]. Wuilloud et al. [9] employed an ionic exchange mechanism for arsenic speciation in Antarctic algae. A pneumatic concentric nebulizer adapted to a double pass spray chamber was employed, the mobile phase flow rate being 0.8 mL min^{-1}. With a gradient elution procedure, it was observed that the arsenosugars eluted in less than 15 (anionic exchange) to 25 (cationic exchange) min. At higher liquid flow rates (1 mL min^{-1}) with a pneumatic concentric nebulizer adapted to a cyclonic spray chamber the analysis time was shortened down to 12 min. Additional assays were made at even higher mobile phase flow rates (1.5 mL min^{-1}) [5].

To carry out arsenosugar determination, the mobile phases correspond to a diluted solution containing a salt or an organic solvent [10]. At the common liquid flow rates used in HPLC (*c.a.*, 1 mL min^{-1}) this solutions may cause a degradation in the system performance [11,12]. A way of overcoming these problems is to decrease the mass of solution introduced into the spectrometer. The so-called low sample consumption systems [13] are accessories able to work efficiently at liquid flow rates in the order of several tens of microlitres per minute. In this case a micronebulizer, such as

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the MicroConcentric nebulizer (MCN) and high efficiency nebulizer (HEN), is adapted to a low inner volume spray chamber, providing high analyte transport efficiency (from 10% up to 90%, depending on the flow rate) and reduced wash out times.

However, to work at low liquid flow rates can be detrimental from the point of view of peak resolution when dealing with speciation studies. To avoid this, microbore columns are available that are packed with smaller particles (*i.e.*, 3 μm) and/or lower inner diameters (*i.e.*, <2 mm) than conventional columns. So far, few studies have been carried out on the use of microbore columns for arsenic speciation analysis through ICP-MS [14–18]. Woller et al. [14] used an anion-exchange microbore column coupled with a MCN to simultaneously determinate inorganic arsenic and selenium species. At a 100 μL min^{-1} mobile phase flow rate, determination of As(III), As(V), Se(IV) and Se(VI) species in water samples was achieved in less than 4 min. These authors employed a double pass spray chamber (Scott type) having a high inner volume (roughly 100 cm^3).

A narrow bore reversed-phase HPLC column with ion-pairing was used by Pergantis et al. [15,16] to effect the determination of arsenite, arsenate, methylarsonate and dimethylarsinate as well as of some arsenic animal feed additives. A HEN was used to introduce the mobile phase at a flow rate as low as 40 μL min^{-1}. Castillo et al. [17] demonstrated the suitability of an anion exchange microbore column adapted to either a MicroMist nebulizer or a HEN for arsenic and selenium speciation in spiked waters. It was found that the former provided wider peaks than the latter because its transfer line had about a six times lower dead volume. This fact was in agreement with a previously published work [18].

To date, the use of narrow bore HPLC/ICP-MS for arsenosugars determination has never been reported. The only available reference is an application note from Thermo [19], which shows the determination of four common arsenosugars in a kelp seaweed (macroalgae) extract, using a 2.1-mm-ID C_{18} column. However, in this case a conventional glass pneumatic concentric nebulizer in conjunction with a single pass spray chamber equipped with an impact bead was used. As a result the mobile phase liquid flow rate (0.7 mL min^{-1}) was very close to usual values.

The main goal of the present work was thus to carry out the determination of the most common arsenosugars in algal extracts through a microbore column adapted to a low sample consumption system (down to 60 μL min^{-1}), consisting of a micronebulizer and a low inner volume cyclonic spray chamber (Cinnabar). The effect of the mobile phase flow rate on the main chromatographic parameters (capacity, efficiency, sensitivity) was investigated in the 60–200 μL min^{-1} range, using two micronebulizers (PFA and HEN) for comparison. The obtained analytical figures of merit were hence compared to those provided by a conventional column and the system finally applied to the determination of arsenosugars in a reference algae extract.

2. Experimental

2.1. Reagents and standards

Standard solutions containing 1000 mg As L^{-1} of each of the following compounds were prepared in Milli-Q water (Millipore, El Paso, TX, USA): arsenate as $Na_2HAsO_4{\cdot}7H_2O$ (Merck, Darmstadt, Germany); arsenite as $NaAsO_2$ (Merck) and methylarsonate as $Na_2CH_3AsO_3{\cdot}6H_2O$ (Chem Service, West Chester, PA, USA). Ammonium dihydrogen phosphate (p.a.) and aqueous ammonia solution (25%, Suprapur) were purchased from Merck. The reference algal sample was from a batch of *Fucus serratus* (brown alga) extracts obtained by Madsen et al. [20].

Table 1
ICP-MS instrumental conditions.

Parameter	Value
RF Power	1500 W
Plasma gas flow rate	14.5 L min^{-1}
Auxiliary gas flow rate	1.65 L min^{-1}
Nebulizer gas flow rate	1.0 L min^{-1}
Lens voltage	6.5–8.5[a]
Reaction cell rod offset	−8 V
Quadrupole rod offset	0 V
RF amplitude	150 V
Axial field voltage	300 V
Cell path voltage	−28 V
RP*a*[b]	0
RP*q*[b]	0.25
Dwell time	400 ms
Measured ions	$^{75}As^+$
	$^{77}ArCl^+$

[a] Optimized daily.
[b] Mathieu stability parameters of the cell's quadrupole: $a = 1.9 \times RPa$; $q = 0.95 \times RPq$.

2.2. Instrumentation

The system comprised a Perkin Elmer-Sciex (Concord, Ontario, Canada) Series 200 HPLC coupled to a Perkin Elmer-Sciex Elan DRC II, via a pneumatic nebulizer/cyclonic spray chamber system. Table 1 shows the ICP-MS instrumental conditions. The RF power and the nebulizer gas flow rate were optimized to obtain maximum sensitivity, while limiting oxides and double charge ions formation ($^{156}CeO^+/^{140}Ce^+ < 0.02$; $^{138}Ba^{2+}/^{138}Ba^+ < 0.03$). The other parameters were optimized for maximum ion transmission. The ion intensity at m/z 75 ($^{75}As^+$) was monitored using the time-resolved analysis software Chromera (Perkin Elmer-Sciex). Additionally, the ion intensity at m/z 77 ($^{40}Ar^{37}Cl^+$) was monitored to detect possible argon chloride ($^{40}Ar^{35}Cl^+$) interference at m/z 75. The interface between HPLC and ICP-MS was selected on the basis that the liquid conduction dead volume should not exceed 2% that of the chromatographic column. Both a HEN (model 170-A0.2) by Meinhard Inc. (Golden, Colorado, USA) and a PFA-ST micronebulizer by Elemental Scientific Inc. (Omaha, Nebraska, USA) were tested. Furthermore, a 20 cm × 0.025 cm ID transfer line was used to connect the output of the HPLC column to the nebulizer. In the case of the PFA-ST nebulizer a threaded, zero dead volume flanged fitting was used whereas for HEN, the capillary from the column was directly fitted to the nebulizer arm. Therefore, the extra column dead volume was about 26 and 13 μL when working with the HEN and PFA, respectively. These values were low as compared to that for the column (about 200 μL). The 20 cm^3 inner volume cyclonic spray chamber (Cinnabar) by Glass Expansion (Melbourne, Australia) was used.

2.3. Chromatographic conditions

Anion-exchange HPLC separations were performed on a Chromus Nucleosil SB HPLC column (100 mm × 2.10 mm ID, 5 μm), with a mobile phase of 60 mM aqueous ammonium dihydrogen phosphate of pH 5.9 (adjusted with aqueous ammonia), at a flow rate of 60–200 μL min^{-1}. Methanol was added to the mobile phase (2 + 98, v/v) to enhance the signal response. For the sake of comparison, a Hamilton PRP X-100 (250 mm × 4.1 mm ID, 10 μm) anionic exchange column was also employed at a 1.5 mL min^{-1} mobile phase flow rate. In this case, the mobile phase consisted of a 20 mM aqueous ammonium dihydrogen phosphate of pH 5.6.

The arsenic species determined were: 3-[5′-deoxy-5′-(dimethylarsinoyl)-β-ribofuranosyloxy]-2-hydroxypropylene glycol (*Arsenosugar 1*); 3-[5′-deoxy-5′-(dimethylarsinoyl)-β-ribofuranosyloxy]-2-hydroxypropyl-2,3-hydroxypropyl phosphate

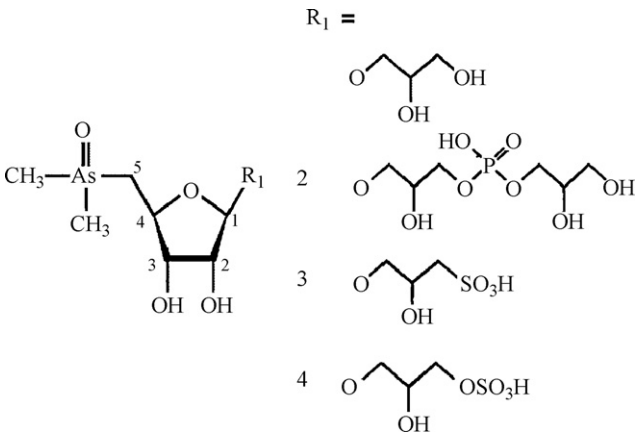

Fig. 1. Chemical structure of the investigated arsenosugars species.

(*Arsenosugar 2*); 3-[5′-deoxy-5′-(dimethylarsinoyl)-β-ribofuranosyloxy]-2-hydroxypropane sulfonic acid (*Arsenosugar 3*); 3-[5′-deoxy-5′-(dimethylarsinoyl)-β-ribofuranosyloxy]-2-hydroxypropyl hydrogen sulfate (*Arsenosugar 4*). The structures of these arsenic compounds are shown in Fig. 1.

3. Results and discussion

3.1. Effect of the mobile phase flow rate

The effect of the mobile phase flow rate was studied in a first place. Fig. 2 shows the chromatograms with the four arsenosugars peaks obtained at three different liquid flow rates. Peaks identification was based on Ref. [20]. Clearly the retention times decreased with increasing the mobile phase flow rate. Furthermore, the peaks became narrower and higher as the liquid flow rate went from 60 to 200 $\mu L\,min^{-1}$. It was observed that at the highest liquid flow rate tested, the time required to analyze a sample was just 5 min. This meant a significant shortening in the time required in other studies carried out at conventional flow rates with common ionic exchange columns [20]. Experiments carried out with narrow-bore C_{18} columns [19] showed that the time required to separate the four arsenosugars in a kelp extract was 2.5 min, shorter than that employed in the present work. However, a high flow rate (*c.a.*, 0.7 $mL\,min^{-1}$) was selected in that case. With the setup employed a good separation efficiency was possible even when working at 60 $\mu L\,min^{-1}$ (Fig. 2a). Concerning the effect of the flow rate on sensitivity, the variation of peak height and area while increasing the mobile phase flow rate from 60 to 200 $\mu L\,min^{-1}$ for arsenosugar 3 is presented in Fig. 3 (identical results were obtained for the other compounds). It can be seen that the higher the liquid flow rate the

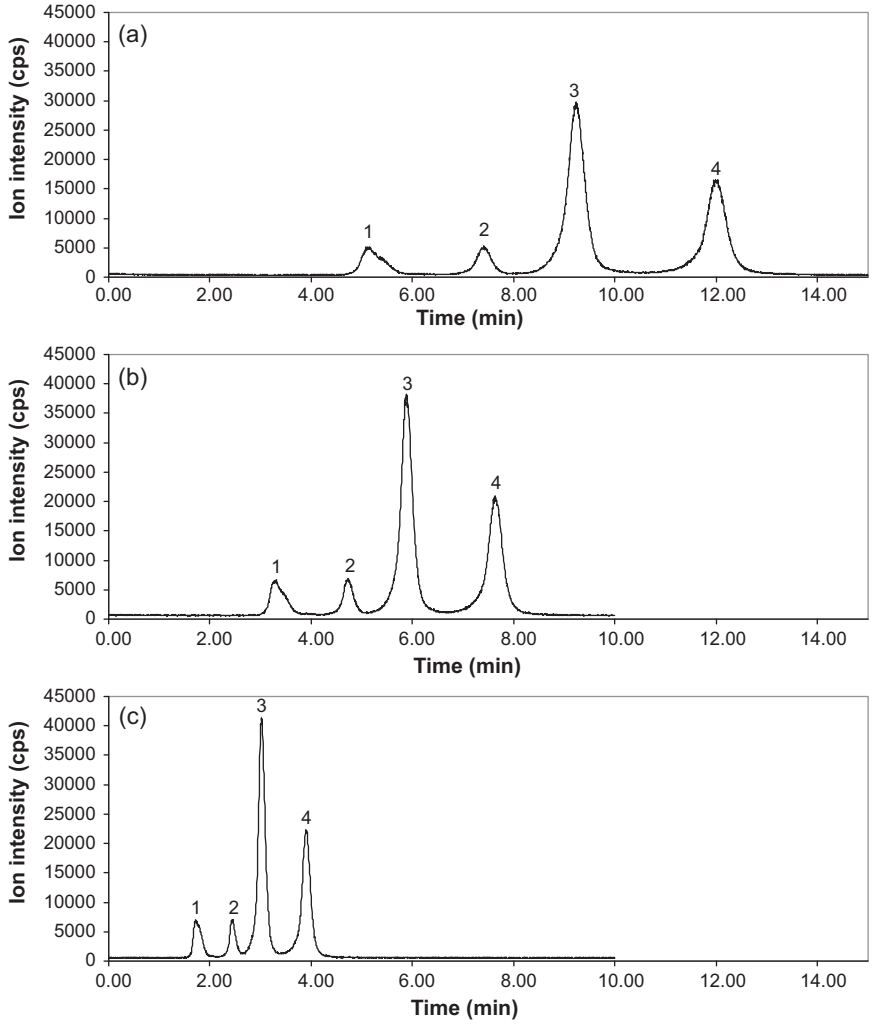

Fig. 2. Chromatograms obtained for the four organosugars detected in the algae sample at (a) 60 $\mu L\,min^{-1}$; (b) 100 $\mu L\,min^{-1}$ and (c) 200 $\mu L\,min^{-1}$ mobile phase flow rates. Nebulizer: PFA.

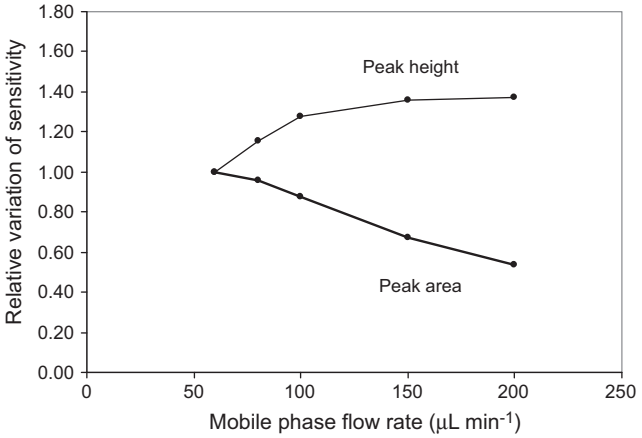

Fig. 3. Effect of mobile phase flow rate on sensitivity for arsenosugar 3. Nebulizer: PFA.

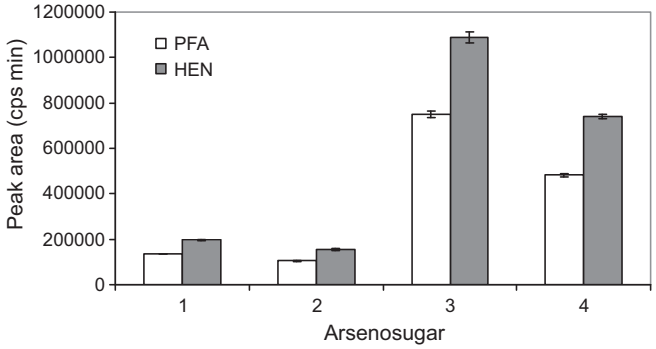

Fig. 4. Comparison of the sensitivities for the two nebulizers used. Mobile phase flow rate: 200 μL min^{-1}.

higher the peak. In relative terms peak height increased by a 40% as the liquid flow rate increased from 60 to 200 μL min^{-1}. This is explained on the basis of a lower peak dispersion in the column and the sample introduction system. This gives rise to a higher analyte concentration in the plasma and, hence, to a higher ionic signal. Unlike the peak height, the peak area decreased with increasing the mobile phase flow rate (about by a 50% as the liquid flow rate switched from 60 to 200 μL min^{-1}). This result can be attributed to several reasons. On the one hand tailing of the peaks became less marked as the flow rate increased and, on the other hand the column had less capability to retain the species on the active sites as the liquid flow rate went up [16]. Another factor not considered so far is that the analyte transport efficiency through the spray chamber decreases as the liquid flow rate is increased. This is a well known trend that has as a main consequence a decrease in the total mass of analyte delivered to the ionization source in those situations in which a given solution mass/volume is injected prior the nebulizer (*e.g.*, HPLC and flow injection analysis applications). Finally, it should be noted that the nebulizer gas flow rate was optimized at the highest sample uptake rate (200 μL min^{-1}). Hence, the increase in sensitivity (as peak area) with decreasing the mobile phase flow rate could be even greater than that displayed in Fig. 3.

3.2. Effect of the micronebulizer design

A comparative study about the effect of the nebulizer type on the performance was carried out. The HEN requires higher gas backpressure values to furnish a given gas flow rate than the PFA system. In fact, to reach a 1 L min^{-1} gas flow rate, the respective backpressure values were 10 and 4.5 bar. As a result finer aerosols are generated and higher ICP-MS sensitivities are expected for the HEN than for the PFA. However, it has been verified that despite this fact, the differences in terms of ICP-MS analytical figures of merit were less significant than expected according to the differences in terms of aerosol characteristics [21]. Fig. 4 compares the peak areas for these two devices, at the flow rate of 200 μL min^{-1}. Under this condition, the optimal gas flow rate was 1 L min^{-1} for both the nebulizers. As expected, the HEN provided a 50% higher sensitivity than PFA, irrespectively of the arsenosugars considered. The increase in terms of peak height was quite similar. However, the improvement in sensitivity by the HEN over the PFA decreased with lowering the flow rate (about 30% at 100 μL min^{-1} and about 10–20% at 60 μL min^{-1}). This result was consistent with an increase in the extent of solvent evaporation inside the spray chamber at low liquid flow rates. Obviously, at 60 μL min^{-1} the liquid to gas mass ratio was lower than at 200 μL min^{-1}. Hence, the differences in the characteristics of the aerosols generated by the two nebulizers were partially counterbalanced by the intensification in aerosol evaporation. Consequently, the total mass of analyte delivered to the plasma for the two nebulizers approached as the liquid flow rate decreased.

Another interesting result was found comparing the separation efficiency for the four arsenosugars and the two micronebulizers evaluated (Table 2). The number of theoretical plates (N) was obtained on the basis of the retention time (t_R) and the Half-Maximum Peak-Width (HMPW):

$$N = 5.54\left(\frac{t_R}{\text{HMPW}}\right)^2 \quad (1)$$

As expected, the N values increased as the retention time went up. The same could be stated as regards the liquid flow rate: generally, the higher this variable, the lower the N value. As regards the nebulizer design, it was found that at low liquid flow rates (*i.e.*, below 100 μL min^{-1}) the PFA nebulizer afforded higher N values than the HEN. This was due to the fact that the HMPW increased as switched from the PFA to the HEN. Note that retention times were not a function of the nebulizer design. However, at the highest liquid flow rate tested (200 μL min^{-1}) both nebulizers provided similar N and HMPW. These results could be ascribed to dissimilar dead volumes of the two nebulizers, which led to a different peak broadening at low liquid flow rates. It has been suggested that the dead volume of the HEN can be minimized by inserting a quartz or Teflon capillary through the solution arm [15,22]. However, since good peak separations were observed also by using the standard configuration, no attempt to further reduce the dead volume of the nebulizers was done.

Table 2
Number of theoretical plates for arsenosugars 1–4 at different mobile phase flow rates, using PFA or HEN.

Arsenosugar	60 μL min^{-1}		80 μL min^{-1}		100 μL min^{-1}		200 μL min^{-1}	
	PFA	HEN	PFA	HEN	PFA	HEN	PFA	HEN
1	640	370	620	440	520	440	390	350
2	3000	1710	2920	1850	2310	2020	1450	1510
3	3230	2580	2920	2330	3000	2210	1650	1700
4	4010	2830	3410	2460	3240	2710	2130	2130

Table 3
Comparison between the characteristics, operating conditions and analytical figures of merit provided by a microbore and a conventional column.

	Hamilton PRP X-100 250 mm × 4.1 mm ID 10 μm	Chromus Nucleosil 100 mm × 2.1 mm ID 5 μm
Mobile phase	20 mM $NH_4H_2PO_4$ pH 5.6	60 mM $NH_4H_2PO_4$ pH 5.9
Flow rate (mL min^{-1})	1.5	0.2
Sample volume (μL)	20	2
Analytical time (min)	22	5
Sensitivity (ppb^{-1})[a]	16,000	12,500 (PFA) 18,300 (HEN)

[a] Based on peak area values for arsenite, arsenate, methylarsonate and arsenosugars 1–4.

3.3. Comparison of narrow bore column with conventional column for arsenosugars determination

In most of the studies referring to arsenosugar determination the column employed has been the Hamilton PRP X-100 (250 mm × 4.6 mm ID, 5 μm) with aqueous ammonium phosphate as the mobile phase [7]. Table 3 shows a comparison between the Hamilton PRP X-100 column and the Chromus Nucleosil column used in the present work. The microbore column has been operated under the highest mobile phase flow rate because it has shown a good compromise between sensitivity and analysis time. A four times shortening in the analysis time was observed. At a seven times lower liquid flow rate and with a ten times smaller injected sample volume the microbore column was able to provide comparable sensitivities to those for the conventional one. This result can be ascribed both to a lower peak dispersion in the column and to a lower mobile flow rate that improved the analyte transport efficiency. Furthermore, the problems related with the salt build up at the sampler cone of the ICP-MS interface were reduced because the matrix load was 2.5 times lower.

3.4. Limits of detection and precision

LODs were obtained by recording the baseline of the chromatogram during a 1.3 min period of time. Then 3 s_b was calculated from 200 consecutive background measurements and divided by the sensitivity (taken as the peak height to arsenosugar concentration ratio). The HEN provided higher and noisier background signals than the PFA. This fact compensated for the improvement in sensitivity reported for the former. As a result LODs obtained with the two nebulizers were quite similar, about 0.2 ng As mL^{-1}, which is absolutely adequate for arsenosugars determination in algal extracts. In previous studies with conventional sample introduction systems as interfaces, the reported LODs for arsenosugars were 0.3–0.4 ng As mL^{-1} [19]. For other studies in which arsenic inorganic and organic species other than arsenosugars were separated the LODs achieved with a direct injection nebulizer (DIN) were of the same order as those encountered in the present work [18]. Precision was evaluated from five consecutive chromatograms. Relative standard deviation was included within the 1–3% range.

3.5. Analysis of a reference algal extract

The reference algal sample was analyzed and the results are summarized in Table 4. As it was previously mentioned, in order to obtain the calibration lines, arsenate, arsenite and methylarsonate standards were prepared. A satisfactory agreement between the obtained and reference concentration values was observed (the maximum deviation was about 5%), thus supporting the suitability of the interface employed to the fast determination of arsenosugars in algae extracts. These results also indicated the negligible effect of the arsenic chemical form on sensitivity.

Table 4
Arsenosugars content in the reference algal extract.

Arsenosugar	As content (μg)		
	Reference value	Found (PFA)	Found (HEN)
1	0.100 ± 0.004	0.106 ± 0.001	0.104 ± 0.002
2	0.086 ± 0.002	0.083 ± 0.002	0.088 ± 0.003
3	0.620 ± 0.024	0.599 ± 0.013	0.620 ± 0.015
4	0.400 ± 0.012	0.385 ± 0.006	0.421 ± 0.006

Note: Mobile phase flow rate: 200 μL min^{-1}; n = 5.

4. Conclusions

The use of narrow bore HPLC/ICP-MS in conjunction with a low sample consumption system allowed the accurate and precise determination of the major arsenosugars in algae, with comparable sensitivity as the conventional system, but with strongly reduced analytical times, lower sample and mobile phase volumes and minor matrix loading into the ICP and interface regions of the ICP mass spectrometer. Concerning the nebulizer type, the HEN provided 20–50% greater sensitivity than PFA but comparable limits of detection and slightly lower chromatographic resolution. Hence, the use of HEN, which needs an external gas line to provide the required high gas backpressure, did not appear to be advisable in this case. Finally, it is worth mentioning that no relevant effect of the arsenic species on sensitivity was observed, because a 10% maximum variation in sensitivity was found as a function of the arsenic chemical form. This fact allowed the quantification of arsenosugars using standard solutions of common anionic arsenic species (arsenite, arsenate and methylarsonate).

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