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Fast and sensitive determination of per- and polyfluoroalkyl substances in seawater

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ABSTRACT

In this work, a novel, fast, and sensitive method was developed for perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS) and PFOS precursor's determination in seawater. The proposed method consists in a vortex-assisted liquid-liquid microextraction (VALLME) combined with liquid chromatography (LC) and LTQ-Orbitrap high resolution mass spectrometry (LTQ-Orbitrap HRMS) determination. Several parameters affecting both the HPLC-LTQ Orbitrap HRMS determination and the VALLME were studied, with special attention to blank contamination problem. The use of LTQ-Orbitrap-HRMS in full mode, quantifying the target analytes using the exact mass, provides a very powerful detection in terms of sensitivity and specificity maintaining all the information provided by the full mass spectra, allowing, also, the identification of non-target substances. The use of matrix-matched calibration, together with labelled surrogate standards, minimize matrix effects and compensate potential recovery losses, resulting in recoveries between 95 and 105%, with excellent sensitivity (quantitation limit between 0.7 and 6 ng L^{-1}) and precision (4–10%). The proposed method requires only 35 mL of sample and 100 μL of extracting solvent, is fast and avoids the use of other solvents to obtain the dispersive cloudy solution, simplifying the procedure and improving the existing procedures for the determination of per- and polyfluoroalkyl substances (PFASs) in seawater in terms of green analytical chemistry. The method was successfully validated by participating in a proficiency test assay provided by the National Measurement Institute of the Australian Government for the determination of PFOA, total PFOS and linear PFOS in waters. A revision of the state of the art in the last twelve years of methods for the analysis of PFASs in seawater and other types of water was performed, and a critical comparison between the developed method and the previously published was included. Finally, the method was applied to the analysis of samples from Ría de Vigo, a sensitive and semiconfined coastal area located in the northwest of Spain. PFOS, N-methyl perfluorooctanesulfonamide (*n*-MeFOSA) and *N*-ethyl perfluorooctanesulfonamide (*n*-EtFOSA) were detected in samples at levels lower than the maximum allowable concentration (MAC) established by Directive 2013/39/EU, but above the annual average (AA) levels.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are a group of anthropogenic chemicals, consisting of an alkylated hydrophobic chain fully or partially fluorinated, hydrophilic group terminated. This configuration provides to PFASs simultaneous hydrophobicity and lipophobicity. Moreover, these substances present a great chemical and thermal stability. Due to their properties, as water and lipid repellents and stability, PFASs have been widely used as surfactants in industry for surface treatment, paper coatings, performance chemicals etc [1,2]. The "long chain" perfluroalkyl sulfonic acids ($C_nF_{2n+1}SO_3H$, $n \geq 6$) and perfluoroalkyl carboxylic acids ($C_nF_{2n+1}COOH$, $n \geq 7$) and their corresponding anions, have demonstrated to be more bioaccumulative than the short-chain analogues [3]. According to the OCDE 2002 report [4] perfluorooctane sulfonic

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acid (PFOS) is persistent, bioaccumulative and toxic to mammalian specie. Repeated exposures result in hepatotoxicity and mortality.

The wide usages, resistance to degradation, bioaccumulation, toxicity, and persistence of PFASs have resulted in their consideration as global environmental contaminants [5]. As consequence, PFOS and its salts have been listed under Annex B (restricted use) of the Stockholm Convention in 2009 [6,7] and included in water Directive 2013/39/EU as priority substances in the field of water policy. The maximum allowable concentration (MAC) for PFOS and its derivatives in surface waters (not inland) established by the water Directive is 7,2 $\mu g\,L^{-1}$.

Presence of PFASs in seawater is caused by discharges of treated or untreated wastewater effluents or river flows [8], urban runoff following rain episodes, atmospheric deposition of volatile precursors and subsequent transformation, or direct application of fire-fighting foams containing PFASs, among others [9]. Although PFASs are diluted in the open seawaters, the continuous input, and their persistence cause that some PFASs have been detected in open seas and coastal areas [8,10–12]. In the last years few papers have focussed its aim on the study of PFASs in seawater samples. PFOS and perfluorooctanoic acid (PFOA) are the most frequently measured PFASs in waters (Table 1). In this work, FOSA (perfluorooctanesulfonamide), N–EtFOSA (*N*-ethyl perfluorooctanesulfonamide) and N–MeFOSA (*N*-methyl perfluorooctanesulfonamide) were included, in addition to the most frequently measured PFOS and PFOA, because of their importance. FOSA, used as protective coatings, is a precursor of PFOS that is frequently detected in water monitoring programs (20% of samples) [13]. *N*–EtFOSA is a termiticide (Sulfluramid) still in use in some countries in insecticide formulations [14]. It is a precursor of FOSA, and its major degradate is PFOS. N–MeFOSA is also a precursor of FOSA (and PFOS), and both (N-EtFOSA and N-MeFOSA) are scarcely determined in water samples [15]. For these reason, we found the determination of these compounds very interesting.

The low concentrations (few $ng\,L^{-1}$) reported in the literature for these compounds in water samples makes necessary the use of a pre-concentration step for their analysis. The pre-concentration method most frequently used for the determination of PFASs in water samples is the solid phase extraction (SPE) of a high volume of sample (between 250–1000 mL), being the Oasis HLB cartridges the most popular device [11,12,16–19] (Table 1). Other sorbents used for the SPE are Oasis Wax [20,21], C_{18} [22], styrene divinylbenzene (SDVB) [23], Strat X-AW cartridges [13] or mixed hemimicelles [24]. This procedure (SPE) requires high volumes of sample, involves several steps, increasing the risk of PFASs contamination (mainly PFOA) by the contact of the sample and extracts with many laboratory materials [17,23], and frequently is time consuming. The use of microextraction techniques like in-tube SPME [25], dispersive liquid – liquid microextraction (DLLME) [27] or vortex-assisted liquid-liquid microextraction (VALLME) [26,27] for the determination of PFASs in water samples is still scarcely extended, possibly due to the low limit value established in the environmental regulations. These techniques allow a considerable reduction of the volume of sample (0.8–40 mL), are fast, involve few steps, reducing the sample handling and also the risks of contamination [28]. Dispersive liquid–liquid microextraction, was introduced by Rezaee et al. in 2006 [29] and is based on the extraction of analytes in aqueous samples by an appropriated mixture of extraction solvent and dispersant agent producing a cloudy solution. In order to avoid the use of two different solvents, one for the extraction and the other to obtain the dispersion, some authors suggest replacing the dispersant by an agitation step to achieve the formation of the cloudy (VALLME) [30,31]. By this way the DLLME is simplified and only the most appropriate extraction solvent needs to be selected. That was the approach used for this work.

The chromatographic determination is often performed by HPLC tandem mass spectrometry with electrospray ionization in negative mode, with few exceptions using LC–ToF–MS [19], LC-Orbitrap Tribrid HRMS [20] or even GC–MS with derivatization [32]. The LTQ–Orbitrap used in this work is a hybrid mass spectrometer that combines the linear ion trap and the Orbitrap. HRMS on LTQ–Orbitrap system in full-scan mode has demonstrated to be the most powerful determination approach in terms of sensitivity and specificity [33].

One of the main problems in the determination of PFASs at trace levels is the difficulty to keep blank levels at minimum, due to the potential presence of these compounds in the plastic equipment and materials used in the laboratory such as tubing, fitting, filters, septa, etc. All the steps (sampling, storage, extraction, and determination) must be carefully controlled trying to avoid Teflon® and other components that could introduce blank signal, hampering the achievement of the low detection limits required for the determination. In this work a careful selection of materials and analytical conditions was performed in order to maintain the procedural blanks at minimum. In addition, a reduction of the instrumental contamination was achieved by changing the mobile phase Teflon filters by glass filters.

The aim of this work is to develop a fast and sensitive method especially suitable for the determination of PFOS, PFOA, and PFOS precursors in seawater in order to evaluate their presence in marine environment.

As far as we know, this is the first work that combines a miniaturized extraction technique with the LTQ-Orbitrap determination of PFASs in seawater, allowing the reliable quantitation of the linear and branched isomers of PFOS and PFOA and the identification of non-target analytes. The proposed VALLME-LC-LTQ-Orbitrap HRMS method has been validated by an in-house procedure, and also by participating in a proficiency test report organized by the National Measurement Institute of the Australian Government.

The optimized method was applied to the analysis of samples from Ría de Vigo (Galicia, Spain). This estuary is affected by an intense outflow of nutrients which produces a consequent high primary productivity. It is surrounded by small and dispersed villages and also affected by Vigo city (>300,000 inhabitants) with medium industrial development and significant port operation. All this, added to geographic and oceanographic characteristics that do not permit a good level of water exchange with the ocean, could lead to an accumulation of certain contaminants within the estuary.

2. Experimental

2.1. -Reagents and standards

Individual standards of sodium perfluoro – 1 –octanesulfonate (L–PFOS), perfluoro–n–octanoic acid (PFOA), *N*–methyl perfluorooctanesulfonamide (N–MeFOSA), N–ethyl perfluorooctanesulfonamide (N–EtFOSA), N–ethyl $-d_5$perfluorooctanesulfonamide (d – N–EtFOSA–M), sodium perfluoro–1– [1,2,3,4 $-^{13}C_4$] –octanesulfonate (MPFOS) and perfluoro–n– [1,2,3,4 $-^{13}C_4$] –octanoic acid (MPFOA) 50 μg/ml in methanol from Wellington Laboratories (Canada). Perfluoro – 1 – octanesulfonamide (FOSA) and perfluoro–1–[$^{13}C_8$]octanesulfonamide 50 $\mu g\,mL^{-1}$ in isopropanol were also supplied by Wellington Laboratories. Stock standards were stored at −18 °C in polypropylene screw vials with ethylene-propylene o – ring (Deltalab, Spain). Cap vials were also tested for the storage, with polypropylene septa, but this system is not useful for the long term storage because solvent losses by evaporation were detected. The labelled standards were used as surrogates.

Table 1
Summary of papers about PFASs extraction in water samples.

Compounds	Type/Volume	Extraction	Determination	%R (%RSD)	M-LOQ (ng L^{-1})	Ref.
PFOA, PFOS	surface/0.8 mL	In-tube SPME	LC–ESI–MS/MS(−)	81–85 (2.5–6.2)	1.5–3.2	[25]
PFOA, PFOS	surface and tap/1 L	SPE (Presep-C Agri)	HPLC–ESI/MS/MS (−)	94.8–106 (3.1–5.4)	0.1	[49]
PFOS, PFOA	river/500 mL	SPE Oasis HLB (200 mg)	HPLC–ESI–MS/MS (−)	69–97 (2–7)	0.05–1	[17]
PFOS/PFOA/PFNA/PFDA	river/500 mL	SPE Oasis HLB Sep-pack (200 mg)	HPLC–MS/MS–ESI (−)	73–88(7.5–11.8)	0.5–3	[16]
PFOS/PFOA and other	wastewater/500 mL	SPE C18	HPLC–MS/MS–ESI(−)	8–102 (0.4–12)		[22]
PFASs	wastewater/900 mL	LLE with MTBE		80–93 (0.8–9)	0.94–2.3	
PFOS,PFOA, PFCAs, PFSAs	river, tap, wastewater/5 mL	On-line SPE C_{18}	UHPL-MS/MS	76–134 (10–30)	1–20	[48,50]
PFOS, PFOA	river, 1L	SPE Oasis HLB	LC–MS/MS ESI-	107–120	0.1	[18]
PFASs	tap/250 mL	SPE SDVB	LC–MS/MS ESI-	85–112 (0.9–5.0)	2.9–14	[23]
PFOS, PFOA and other PFASs	river/500 mL	SPE Mixed hemimicelles	LC–MS/MS ESI-	57–105 (2–8)	LOD:0.05–0.28	[24]
PFOS and other PFASs	river/200 mL	SPE Wax	LC—Orbitrap Tribrid HRMS	62–103 (1–7)	0.02–1.87	[20]
PFOS and PFPAS	surface/500 mL	SPE Oasis Wax	LC–MS/MS	87–112 (1.1–8.7)	LOD:0.05–1	[21]
PFOS and PFAAS	tap,surface/250 mL	SPE LiChrolut EN + derivatization	GC–MS	95–100 (5–6)	0.1–0.5	[32]
PFOS, PFOA and other PFASs	river, 100 mL	Magnetic solid phase extraction (MSPE)	UHPLC–MS/MS ESI-	89–111 (0.8–4.1)	0.01–0.06	[51]
PFOs, PFOA, other PFASs, hormones, plasticizers. . .	tap, river/10 mL	UA-DLLME-SFO	HPLC–MS/MS ESI-	84–105 (1–16)	4	[27]
PFOS	tap,surface/20 mL	VALLME	LC–MS ESI–	90–105 (1–10)	5.3	[26]
PFOS, PFOA, FOSA and other PFASs	river/0.350 mL	On-line SPE Poros HQ	UHPLC–MS/MS	91–101 (2–9)	10–50	[47]
PFOS, PFOA and other PFASs	seawater/1 L	SPE	UPLC–MS/MS ESI –	60–122 (3–11)	LOD:0.6–3 pg L^{-1}	[8]
PFOS, PFOA and other PFASs	seawater/500 mL	SPE Oasis HLB	HPLC–MS/MS ESI-	85–136	LOD:0.2–2	[11]
PFOS, PFOA, FOSA, and other PFASs	seawater/250 mL	SPE Oasis HLB	LC-ToF-MS	96–108 (6–19)	2–200	[19]
PFOS and PFOA	Surface and wastewater	SPE	HPLC-Q-Exactive Orbitrap	98–113 (2–4.5)	i-LOQ:0.05–0.35 pg	[52]
PFOS, PFOA, FOSA and other PFASs	Seawater/35 mL	VALLME	HPLC-LTQ-Orbitrap	95–105 (3.9–10)	0.66–1.1 6.6 PFOA	This work

PFPA: perfluorinated phosphonic acids; PFAAs: perfluoroalkyl acids, PFASs: per- and polyfluoroalkyl substances. UA-DLLME-SFO: Ultrasound assisted dispersive liquid-liquid microextraction- solidification of a floating organic drop.

Working standards (individuals and mixtures) were prepared from stock solutions by dilution in a mixture methanol:water (75:25) (M:W mixture from now on), and stored refrigerated (4 °C) in 8 mL Nalgene vials. Diluted standards were fresh prepared every two months to ensure the stability of standards (23 months at 5 °C [34]).

For the extraction, 1-Octanol Chromasolv® (grade HPLC 99%) was from Sigma-Aldrich Co. (Madrid, Spain), dichloromethane SpS was from Romil (Cambridge, UK) and *n*-hexane Suprasolv® was from Merck Millipore (Germany). HPLC mobile phases were methanol LC–MS grade from Fisher Chemical (Loughborough, UK). Water was purified with a Direct 5 Milli Q system (Millipore, Bedfore, MA, USA). Ammonium acetate was from Sigma-Aldrich (MO, USA). Seawater samples were used for the optimization of the analysis method. Sodium chloride purissime for analysis (Riedel-de Haën) was used for the proficiency test samples.

2.2. Sampling

Samples were collected in Ría de Vigo (Galicia, Spain), a semi-confined coastal area affected by high industrial and port activities. The sampling campaigns were carried out in spring and autumn of 2015 (sampling points showed in Fig. 5 map). Superficial (1m) and depth water samples (5 m above the bottom) were collected. Samples collected using a glass pitcher were stored in 1L amber glass bottles at 10 °C until arrival at the laboratory, where they were stored at −20 °C until further analysis.

2.3. VALLME

For the extraction of seawater samples, aliquots of 35 mL of water were introduced in a 50 mL centrifuge tube and then spiked with 20 μL of the labelled surrogate standards (50 μg L^{-1}). The extraction was performed by agitation using 100 μL of 1 – octanol as extracting solvent in an agitation plate Vibrax-VXR by IKA (Staufen, Germany) during 5 min at 1800 rpm. We replace the use of a dispersing solvent by using agitation to disperse the immiscible extracting solvent in water. Then, the organic phase was separated by centrifugation (Eppendorf 5804, Madrid, Spain) at 3500 rpm for 3 min. The fine droplets of 1 – octanol were collected with a glass Pasteur pipette and the volume was adjusted to 1 mL with a M:W mixture (75:25) due to the immiscibility of the 1–octanol with the LC mobile phase. To remove any solid particles that might interfere in the analysis and damage the instrument, the extract was passed through a polypropylene 0.2 μm OlimPeak syringe filter (Teknokroma, Barcelona, Spain) before LC injection.

2.4. HPLC–LTQ–Orbitrap determination

Separation of PFASs was performed with a Luna C_{18} 150 × 2 mm × 3 μm (Phenomenex, USA) column with a constant temperature of 40 °C. Water with 2 mM of ammonium acetate (pH = 6) and methanol were selected as mobile phases. The initial ratio of methanol was 40%, maintained 1 min after which the ratio of MeOH increased to 90% in 14 min and held 5 min. Finally, the ratio returns to 40% and held 8 min. The column flow was 220 μL min^{-1}.

Table 2
Analytical performance characteristics of the VALLME-HPLC-ESI-LTQ-Orbitrap HRMS proposed method. R. time: retention time; M-LOD: method detection limit; M-M-LOQ: method quantification limit. Samples spiked at 0.05 μg L^{-1} level for trueness and precision (repeatability, n = 6).

	M/Z theoretical	M/Z measured	Mass Error (ppm)	M/Z confirm	R. time (min)	M-LOD (ng L^{-1})	M-LOQ (ng L^{-1})	Linearity (μg L^{-1})	Trueness (%)	Precision (%RSD)	Uncertainty (%)
PFOA	412.96698	412.96530	4.068	413.97067	13.4	3.0	6.6	M-LOQ-12 (r = 0.9990)	97	4.4	11.2
PFOA-C13 (SU)	416.98022	416.98079	1.366	417.32291	13.4	–	–				
PFOS	498.93066	498.93106	0.802	499.93402	14.57	0.22	0.66	M-LOQ-12 (r = 0.9997)	95	3.8	13.2
PFOS-C13 (SU)	502.94373	502.94430	1.133	503.94772	14.53	–	–				
FOSA	497.94690	497.94812	2.450	498.95078	16.76	0.37	1.13	M-LOQ-12 (r = 0.9995)	105	6.7	15.9
M8FOSA (SU)	505.97345	505.97403	1.146	507.97012	16.76	–	–				
N-MeFOSA	511.96271	511.96268	0.058	512.96637	18.39	0.29	0.87	M-LOQ-12 (r = 0.9986)	103	10	22.1
N-EtFOSA	525.97852	525.97839	0.247	526.98212	19.08	0.26	0.79	M-LOQ-12 (r = 0.9973)	97	3.9	20.2
d-N-EtFOSA (SU)	531.00958	531.00964	0.113	532.01410	19.22						

Su: surrogate. *Instrumental blank signal.

Phase A was prepared fresh every 48 h as the EPA method 537 recommends. The injection volume selected was 20 μL in a loop of 25 μL.

Determination of PFASs was performed in an LC-LTQ Orbitrap (Thermo-Finnigan, Waltham, MA, USA) with electrospray negative ionization (ESI) (metal needle distance: D, sheath gas: 20 au (arbitrary units), auxiliary gas:5 au, source temperature 300 °C). The ions were acquired in the full scan mode and the exact mass $[M-H]^-$ (mass tolerance 5 ppm) was used to quantify each compound (Table 2) with resolution R > 30000.

In order to reduce the instrumental blanks (for PFOA mainly), the Teflon mobile phase filters were replaced by glass filters. Other changes typically used for blank reduction (replacement of tubes or bypass of degasser) could not be applied, and for this reason the presence of PFOA in the blank was not totally avoided.

2.5. Quantification and quality control

PFASs were identified by retention-time matching and accurate mass (mass tolerance 5 ppm) ("*m*/*z* measured" for quantitation and "*m*/*z* confirm" for confirmation (Table 2)). Quantification was performed by matrix matched calibration using each surrogate labelled standard to correct the signal of each compound (d–N–EtFOSA corrects N–EtFOSA and N – MeFOSA). The use of matrix-matched calibration, together with surrogate standards, minimizes matrix effects and compensates potential recovery losses. The regression curves were constructed with 9 calibration points between 0.5 and 300 ng L^{-1}. Linearity was good in that range with linear correlation coefficients (r) ranging between 0.9995 and 0.9999. Chromatographic control was performed by injection of two standard solutions (10 and 100 ng L^{-1}) containing all target compounds, and an instrumental blank for each batch (12 samples).

Procedural blanks are free of target compounds except for PFOA. These procedural blanks were reduced for PFOA as much as possible. All the material was rinsed with methanol before the use. Also, the glass vials with Teflon septa were replaced by polypropylene screw vials with ethylene-propylene o-ring, the PTFE septa of the centrifuge tubes by polyethylene stoppers and some liquid chromatograph instrument parts were replaced avoiding Teflon® in all the material. With all these precautions PFOA presence in the procedural blanks was reduced but not totally eliminated. For example, by replacing the mobile phase Teflon® filters by glass filters the PFOA procedural blank was reduced from 5.1 ± 1.3 ng L^{-1} to the definitive procedural blank of 3.0 ± 0.66 ng L^{-1}. The procedural blanks were systematically controlled to maintain this value.

3. Results and discussion

3.1. Study of the HPLC–LTQ–Orbitrap-HRMS parameters

Gradient conditions were assayed, using water and methanol as mobile phases, modifying also the concentration of ammonium acetate in both phases between 0 mM and 20 mM. The best results were obtained, using water (2 mM ammonium acetate) and methanol. The total gradient takes 28 min. Although some papers reports the necessity of using a higher proportion of ammonium acetate (20 mM) to maintain the stability of the retention times [23], we verify that with the selected conditions and the chromatographic column used in this work, the retention times are stable enough (variability <3%) to provide confidence in the identification of all target compounds. Mobile phases with ammonium acetate need to be prepared fresh every 48 h to maintain the proportion of ammonium acetate avoiding losses by volatilization.

The Orbitrap electrospray ionization (ESI) source parameters (distance of the metal needle, auxiliary and sheath gas flow, and

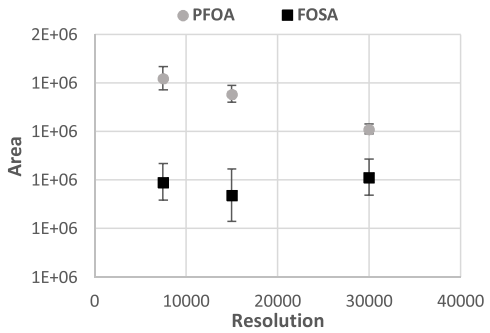

Fig. 1. Resolution effect. Concentration of standard injected 2 μg L^{-1}.

source temperature) were studied in order to find the conditions that provide the best sensitivity. The auxiliary and sheath gas flows have a little effect (negative) on the sensitivity of the selected compound, and for this reason the lower assayed values were selected (auxiliary: 5 au and sheath gas: 20 au). Regarding the metal needle distance, the best results were obtained with D distance. Source temperature is the parameter that has more influence on the PFASs response with opposite effect depending on the compound. The response increases with the temperature for PFOS, whereas decreases for PFOA (high signal decrease at 400 °C) and PFOSA. In order to improve PFOS signal maintaining a good sensitivity for PFOA and PFOSA, 300 °C was selected as source temperature. The electrospray voltage was 3.6 kV, and the capillary and tube lens voltages were −32 V and −7.24 V respectively.

Regarding the HRMS parameters, only resolution was studied. For the ion trap the automatic gain control (AGC-IT) and the maximum injection time (IT) were set at $5e^{+5}$ and 250 ms respectively, whereas for the Orbitrap the automatic gain control was set at $5e^{+7}$ and the maximum injection time at 50 ms. Resolutions of >30,000, >15,000 and >7500 were tested injecting a standard of PFASs (n = 3). A higher response was obtained for PFOA as the resolution decreases. Small variations were observed for PFOS, FOSA, N-MeFOSA and N-EtFOSA (Fig. 1). A lower value of resolution means a worse selectivity, and in this case only supposes an improvement in PFOA responses. Taking into account that de detection and quantitation limits for this compound depends on the blank signal, which also increase its response, we decided to set the resolution at > 30000 (FWHM) in the range *m*/*z* 400–550.

The use of MS/MS mode was discarded because as it was previously reported [33], the high stability of PFOS provides fragment ions of poor intensity and limited specificity (*m*/*z* 80 and *m*/*z* 99) in the LTQ-Orbitrap and therefore, it has not any advantages over the full scan HRMS mode. On the other hand, the full scan acquisition allows the identification of other compounds of interest in the samples, not possible in MS/MS acquisition.

Other parameters studied were the injection volume and the injection solvent. 10, 15, 20 and 25 μL were tested as injection volume. As it was expected, the response increases as the volume increases. Nevertheless, because 25 μL is the total volume of the loop, when 25 μL are injected there is a worsening in peak shape and therefore, a loss of sensitivity. For this reason 20 μL was selected as injection volume.

The injection solvent mixture was also studied because it is important to obtain a good peak shape and to avoid adherence to the LC – MS system [21]. Although the response of PFOS, PFOA and FOSA remains almost constant when the percentage of MeOH variates (Fig. 2), an important decrease in signal was observed for *n*-MeFOSA and *n*-EtFOSA when the percentage of MeOH was lower than 75% (50–60% decrease for 40% of MeOH). Moreover, when the solvent injected was 100% MeOH, broad peaks were obtained. Thus, the solvent selected for the injection was M: W (75:25).

Using these optimized conditions, an adequate chromatographic separation and peak signal of the linear and branched isomers of PFOS were achieved (see chromatogram of the proficiency test sample in Fig. 4a).

3.2. Study of the extraction procedure

VALLME is a highly advantageous technique for the analysis of seawater samples. The presence of salts in this matrix can cause clogging when other extraction methods, involving solid phases, are used and frequently it is necessary to include a prefiltration step. The filtration of water samples can result in losses by adsorption of PFASs on the filters [35], and even cause contamination by PFASs [36]. For these reasons, this step must be avoided. The presence of salts is not an inconvenient for VALLME, on the contrary, improves the separation of the aqueous and the organic phase. Also, the solubility of PFOS in water (pure water 680 mg L^{-1}) decreases significantly in seawater (12.4 mg L^{-1}), improving the transference of PFOS from the aqueous phase to the organic phase (PFOS solubility in octanol 56 mg L^{-1})[37], and therefore the extraction efficiency.

The selection of the appropriate extraction solvent is a key step in VALLME optimization. The proper solvent must have high affinity for PFASs and immiscibility with water. Moreover, it is also recommended that the solvent has lower density than water for a better recovery of the organic drop. With the purpose of avoid the use of a second solvent to obtain the dispersion, in this work the formation of the cloudy solution was obtained by agitation, simplifying the procedure.

The first studies to select the extraction solvent were performed using polypropylene centrifuge tubes (50 mL) in order to avoid the presence of Teflon® material. The procedure for these studies was the same as described in 2.2 section. Because of their water immiscibility, the organic solvents tend to form a single micro drop when they are added to a water sample; therefore, an agitation (5 min, 1800 rpm) was needed to break down the drop of organic solvent and to improve the dispersion process. Dichloromethane, hexane and octanol were tested. After the extraction, centrifugation (3 min at 3500 rpm) was used to separate the two phases again. The assay using 300 μL of dichloromethane was discarded because of the difficulty in the organic phase removal. Very poor extraction efficiency (lower than 10%) was obtained with 400 μL of hexane, so this solvent was also discarded.

1-Octanol (100 μL) was then assayed, because this solvent had previously provided good results for PFOS [26] or alkylphenols [30], but in this case the 1-octanol remained adhered to the walls of the tube, hampering the proper recovery of the organic phase. In order to improve the 1-octanol separation and the recovery of target compounds, some assays were performed modifying the ionic strength [38] (adding about 0.025 g of ammonium chlorine or ammonium acetate) or modifying the pH [26] (adding hydrochloric or sulfuric acid). However, the 1-octanol drop was still difficult to recover because it remained adhered to the walls of the polypropylene tubes, and therefore the extraction efficiency of the compounds was poor (≤10%). Finally, the use of polypropylene tubes was discarded and glass tubes were used. The PTFE septa of the tubes were replaced by polyethylene stoppers to avoid PFOA blank contamination and to prevent splashing.

The assays performed using the glass centrifuge tubes, with no addition of salts or acids, allow a good recovery of the 1-octanol drop. The recovered octanol need to be diluted by rising up to 1 mL of M:W (75:25) mixture due to the immiscibility of the 1-octanol with the LC mobile phases. The volume of 1-octanol was maintained in 100 μL because higher volumes were not miscible with the M:W mixture. Extraction time of 5 min was selected, because it was enough to obtain good extraction efficiency (68–88% without surrogate correction).

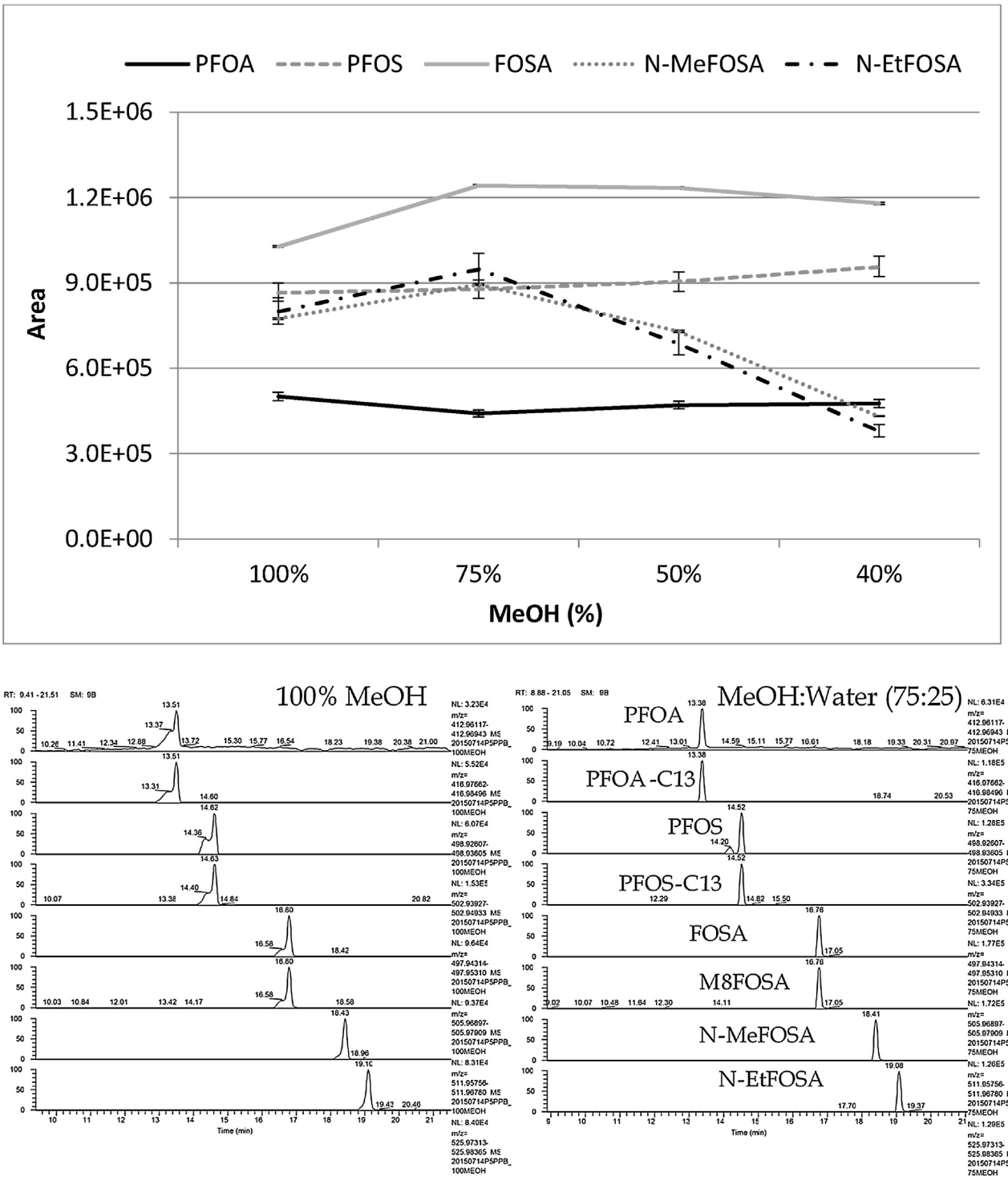

Fig. 2. Graph and chromatogram showing the injection solvent effect. Concentration of standard injected 50 μg L^{-1}.

The final extract was passed through a polypropylene 0.2 μm OlimPeak (Teknokroma, Spain) syringe filter to remove any solid particles that could damage the LC instrument and might interfere in the determination. Losses of target analytes were not observed in the filtration step achieving about 90% recovery for all the PFASs.

3.3. Matrix effect evaluation

When electrospray ionization mass spectrometry is used, the presence of co-extracted matrix or interfering compounds can cause unexpected signal enhancement or signal suppression of the analytes (matrix effect). Matrix effect can heavily affect the reproducibility, the linearity and the accuracy of the method, and for this reason is important to evaluate if a measurement is affected by matrix effect, and if so, try to avoid it, or correct the effect [39].

The absolute matrix effect (ME) [40] was evaluated by comparing the response of the pure solution standard with a post-extraction spiked sample according to the equation $ME\,(\%) = \frac{R_3}{R_1} \times 100$, were R_3 is the response of a post spiked sample, and R_1 is the response of a pure standard. ME (%) higher than 100% indicates

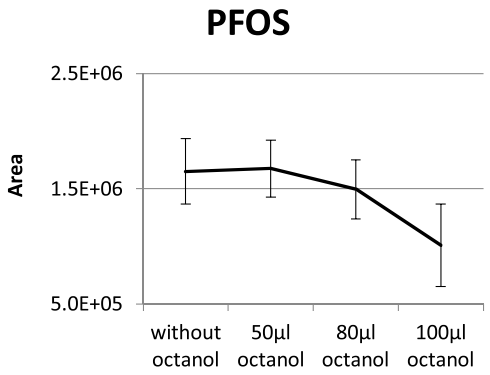

Fig. 3. Influence of the presence of 1-octanol in the injected standards. Concentration of standard injected 2 $\mu g\,L^{-1}$.

a signal enhancement, whereas values lower than 100% indicates signal suppression. No matrix effect was observed for PFOA, FOSA, N-MEFOSA and N-EtFOSA, with ME (%) between 91 and 95%; however signal suppression was observed for PFOS, obtaining a value of 66%. In order to identify the source of this ME, we tested the effect of octanol in PFASs signal by injecting PFASs standard without octanol, and adding 50 µL, 80 µL and 100 µL of 1-octanol to the standard. As can be seen in Fig. 3, the presence of 1-octanol in the standard inhibits the signal (decrease in signal of 40% for PFOS), and therefore, the presence of 1-octanol in the extracts can act as interfering causing the signal suppression detected for this compound.

The use of isotopic labelled surrogate standards to correct the matrix effect is recommended, since matrix effect should not affect the relative efficiency of ionization of the analyte and its stable isotope-labeled IS [40]. In our case, matrix effect was corrected for PFOS (ME = 102%), but a worse result was obtained for PFOA (ME = 85%). For this reason, matrix matched calibration was selected for quantification, using a seawater sample without PFASs content, and correcting the signal using the labelled surrogate standards. With this quantification approach we obtained good and reproducible accuracy (95–105% recoveries with uncertainty lower than 25%) using 100 µL of 1-octanol for the extraction in glass tubes.

3.4. Analytical performance characteristics

The proposed method (scheme included in Suppl. Fig. 1S) was validated in terms of linearity, detection (M-LOD) and quantification (M-LOQ) limits, precision and trueness. For linearity test, a curve was fitted by spiking a seawater sample (without PFASs) at 8 concentration points (between 0.1 and 12 $\mu g\,L^{-1}$). Good linearity of the method was obtained between M-LOQ and 12 $\mu g\,L^{-1}$ with linear correlation coefficients (r) ranging between 0.9973 and 0.9997. The M-LOD and M-LOQ for PFOA were calculated using the average procedural blank signal and 3 times and 10 times the standard deviation of the blank signal, respectively. For the remaining PFASs M-LODs were calculated as 3 × Sy/x/b and M-LOQs as 10 × Sy/x/b, where Sy/x is the standard error of the estimate and b is the slope of a curve obtained by spiking a clean sample at low values (between 0.25 and 300 $ng\,L^{-1}$). The sensitivity achieved (M-LOQ< 7 $ng\,L^{-1}$) is enough to determine the PFASs at the maximum concentration level established by Directive 2013/39/EU for this kind of water (7200 $ng\,L^{-1}$).

Trueness was determined using the analytical recoveries of spiked samples (n = 5) at 0.05 $\mu g\,L^{-1}$ level. The proposed procedure showed good recoveries (95–105%) for all the PFASs (Table 2). Additionally, three samples were spiked at 1 $ng\,L^{-1}$ and 10 $ng\,L^{-1}$ levels (n=3) to verify the trueness at LOQ levels, obtaining recoveries ranged 91 and 107% at 1 $ng\,L^{-1}$ (PFOA not measured below LOQ) and between 91 and 105% at 10 $ng\,L^{-1}$ level. Fig. 4b) shows a chromatogram of a negative sample spiked at 5 $ng\,L^{-1}$, a level close to the LOQs including the m/z and the mass error with respect to the theoretical m/z. Also, the mass spectra obtained for this spiked sample can be seen in Fig. 2S

The precision of the method was evaluated by determining the repeatability and the intermediate precision. The repeatability was calculated as within – day RSD, using 6 replicates of spiked seawater samples (0.05 $\mu g\,L^{-1}$) analysed with the proposed method during the same day and the same analyst and equipment. The repeatability obtained, expressed as RSD, was satisfactory for all the PFASs (Table 2), with values lower than 10%. The intermediate precision (IP) of the method was calculated as between – day RSD of concentrations over the course of 3 months (11 replicates of 0.05 $\mu g\,L^{-1}$ spiked water samples). A good intermediate precision, with%RSD lower than 14% in all cases, was obtained. The uncertainty (U) of the analytical method was also estimated on the basis of in-house validation data according to the EURACHEM/CITAC guide for all target compounds at 0.05 $\mu g\,L^{-1}$ level. The main sources of uncertainty were identified and quantified and combined uncertainty (coverage factor k = 2, for a 95% of confidence) was calculated as $U = k\sqrt{u_1^2 + u_2^2} + |\mu - \bar{x}|$, where the uncertainties associated with the spiked sample ($u_1 = C_{sample}*\sqrt{\left(\frac{S_{standard}}{C_{standard}}\right)^2 + \left(\frac{S_{pipette}}{V_{pipette}}\right)^2 + \left(\frac{S_{flask}}{V_{flask}}\right)^2 + \left(\frac{S_{balance}}{m_{standard}}\right)^2}$), precision ($u_2 = \frac{S_{prec}}{\sqrt{N}}$) and trueness $|\mu - \bar{x}|$ were taken into account. The relative expanded uncertainty calculated for the whole method at 0.05 $\mu g\,L^{-1}$ level was lower than 23% for all the PFASs (Table 2).

3.5. Proficiency test validation

Although there is a reference material certified for PFOS and other perfluoroalkyl substances in drinking water (IRMM-428), it cannot be considered fully representative of a surface water sample which, following the definition laid down by the Water Framework Directive, must include suspended particulate matter and/or more or less dissolved organic matter (i.e. humic and fulvic acids) [41]. For this reason, we decided to participate in a proficiency test that includes surface water, to perform a more adequate validation of the developed method.

The interlaboratory validation was performed by participating in the proficiency test assay (AQA16-06) provided by the National Measurement Institute of the Australian Government (2016). In this test, 24 international laboratories analyse PFOA and PFOS (linear and total) in two water samples. Sample A is a contaminated water from a contaminated site (surface water), whereas sample B is an autoclaved tap water spiked with standard solutions of PFOA and PFOS. Samples were received refrigerated in HDPE bottles.

Taking into account the range of concentration expected, only 10 mL of water were extracted. Using the developed method a low recovery of PFOA-C_{13} was observed. PFOA has a water solubility of 3400 $mg\,L^{-1}$ in water. In order to decrease the solubility of PFOA and improve the extraction of this compound and the surrogate, 0.35 g of NaCl were added to the sample to reproduce the salinity of the seawater. By this way a good extraction (89–106% recoveries) was achieved (Table 3). Linear and total PFOS could be determined due to the appropriate separation of the linear and branched isomers (Fig. 4A). As can be seen in Table 3, satisfactory values of |*Z-score*| were obtained ($|z| \leq 2$ satisfactory). All the |En-score| values were below 1 and therefore also satisfactory. These results are relevant, because in previous interlaboratory assays reported in the literature for PFASs in water samples, only the 48% of the laboratories for PFOA and 67% for PFOS obtained |z| score values ≤2 [42]. That brings to light the fact that although there are many procedures published in the literature for the determination of PFASs in water samples, not all these procedures are validated and checked by

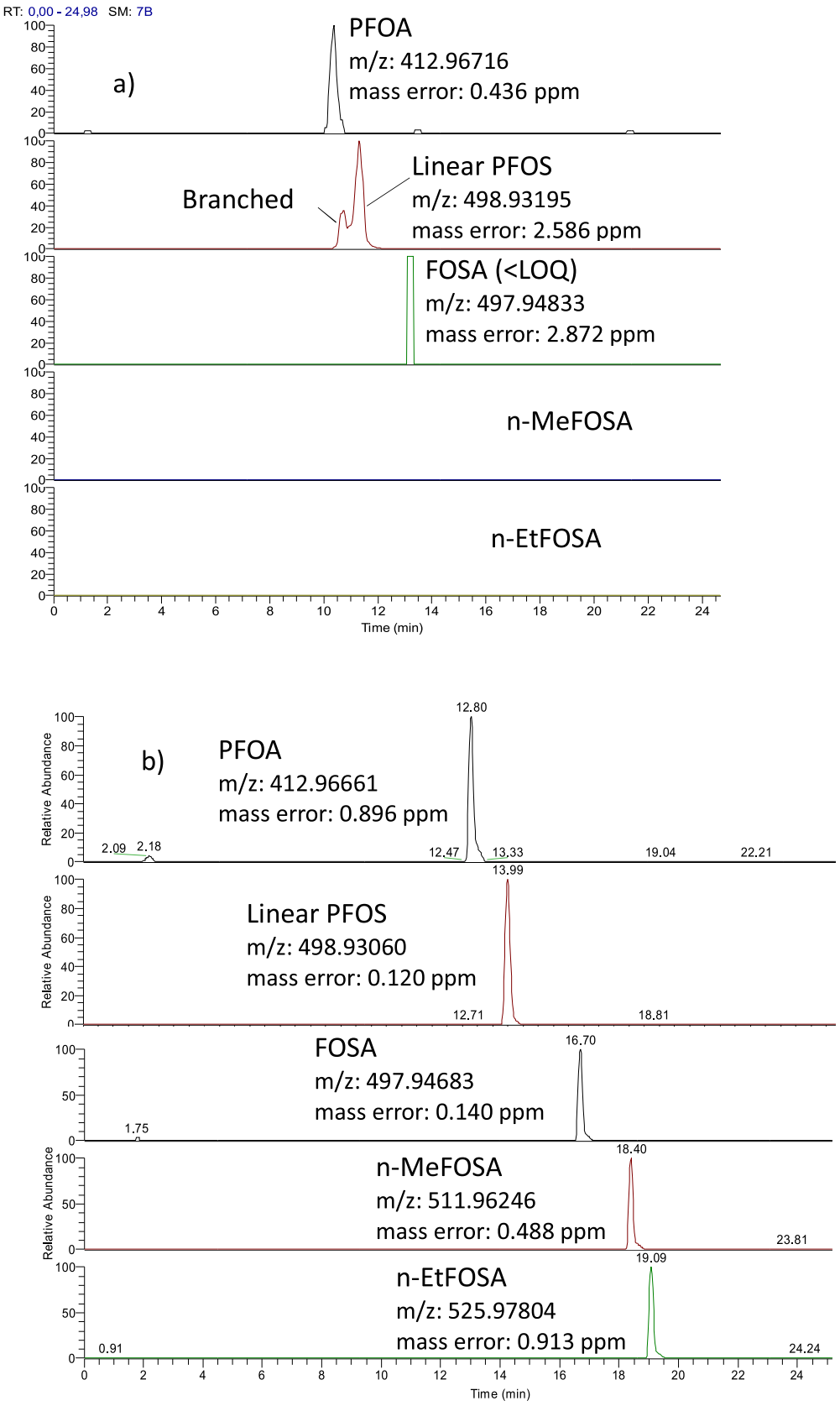

Fig. 4. Chromatograms with the *m*/*z* for each compound and the mass error with respect to the theoretical *m*/*z*: a) proficiency test sampleB; b) negative sample spiked at 5 ng L^{-1} level.

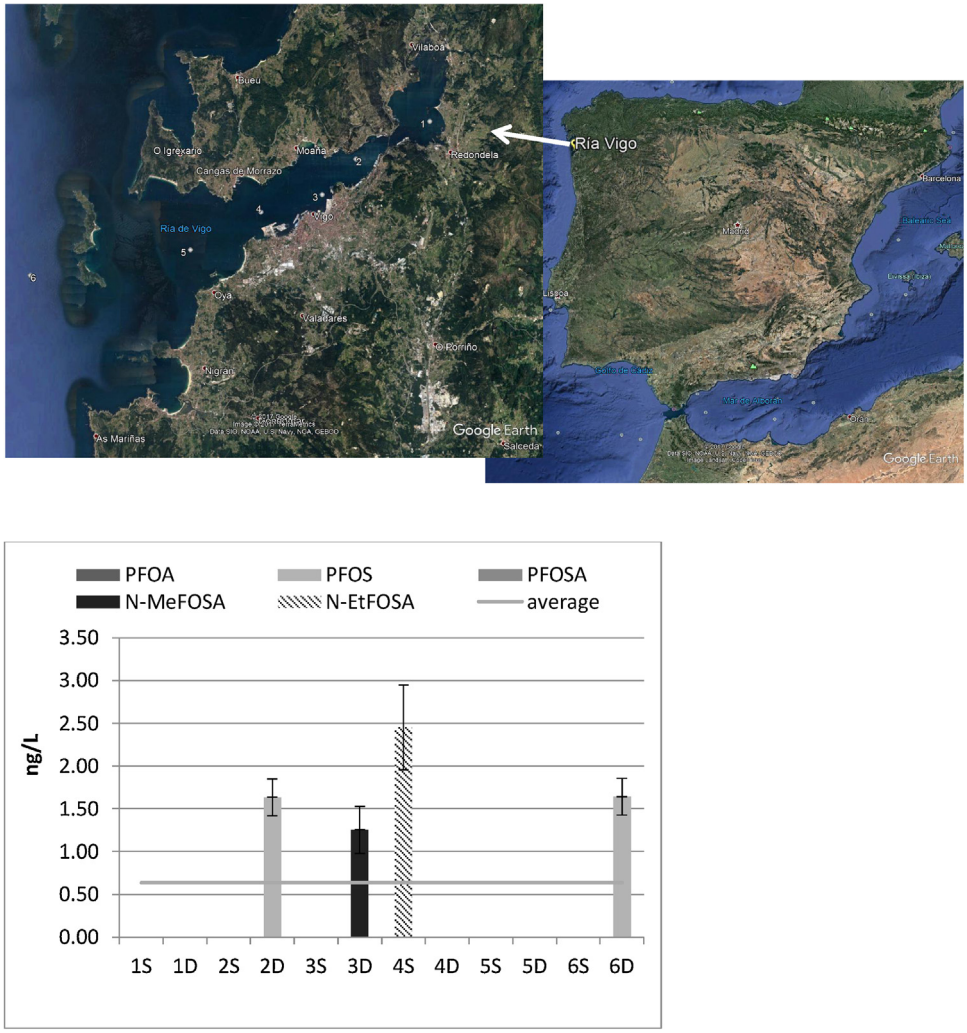

Fig. 5. Ría de Vigo sampling points and results.

Table 3
Proficiency test (AQA16-06) provided by the National Measurement Institute of the Australian Government (2016) results.

	Compound	Concentration (μg/L)	U (μg/L)	Asigned value (μg/L)	z-Score	En-score
Sample A	Linear PFOS	1.90	0.25	1.65	0.8	0.6
	PFOA	0.087	0.010			
	Total PFOS	2.54	0.33	3.00	−0.8	−0.7
Sample B	Linear PFOS	4.70	0.62	4.5	0.2	0.2
	PFOA	10.02	1.12	10.83	−0.4	−0.6
	Total PFOS*	5.60	0.74	6.5	−0.7	−0.7

Total PFOS*: sum of linear and branched isomers.

external sources, such as interlaboratory assays or proficiency test, and those that participate, not always achieve good results.

The assigned value in the assay was determined from robust average of participants results following the procedure described in ISO 13528:2015. In sample A there is not assigned value for PFOA because few laboratories were able to report a numeric value due to the low concentration level of the target compound.

The good results obtained in the test performed using surface and tap water demonstrate the applicability of the proposed method also for the analysis of surface and tap waters by adjusting the salinity of the sample to 0.035 g mL^{-1}.

3.6. Analysis of samples

The VALLME–LC–LTQ–Orbitrap HRMS method proposed in this work was successfully applied to the analysis of samples from Ría de Vigo estuary (Galicia, Spain). 6 Sampling points were collected from the inner to the outside of the estuary and surface (S) and depth (D) samples were analysed for each point.

As can be seen in Fig. 5, PFOA and PFOSA have not been detected in any of the analysed samples above their quantitation limits. PFOS was detected in sample 2D and 6D, both depth samples. Sample point 2 is located near to a fiberglass shipyard, and that could be the source of PFOS. *n*-MeFOSA and *n*-EtFOSA were detected in samples 3D and 4S respectively. N-EtFOSA is an insecticide (sulfluramid) typically used for cockroach and ant control. The presence of *n*-MeFOSA could be justified by the influence of sailing and ports. N-MeFOSA and *n*-EtFOSA are precursors of PFOSA, and this is a precursor of PFOS; thus, presence of these compounds can be relevant because it can lead to future PFOS presence. Moreover, these compounds are considered insoluble in water, and for this reason are scarcely found in water samples, and as far as we know, its pres-

ence was only previously reported in literature at very low levels (pg L^{-1}) in the North Sea [43].

All the samples were below the maximum allowable concentration (MAC) for perfluorooctane sulfonic acid and its derivatives (PFOS) established by Directive 2013/39/EU (7200 ng L^{-1}), but at levels higher than the annual average stablished by the directive (0.13 ng L^{-1}), and for this reason the monitoring of PFASs in this area could be of interest.

Finally, the levels of PFASs detected in the studied area (0.64 ng L^{-1} and <12.6 ng L^{-1} for PFOs and PFOA respectively) were similar or lower than those reported in the literature in similar areas. For example, levels of 2.2/1.8 ng L^{-1} for PFOS and 7.3/11.6 ng L^{-1} for PFOA were reported in Ebro and Guadalquivir Rivers respectively [44]; 1.86 ng L^{-1} for PFOS and 0.118 ng L^{-1} for PFOA were reported in Cantabrian Sea [8]. Also in Guanabara Bay (Brasil) the concentration of PFASs detected was similar (0.56 ng L^{-1} for PFOS and 1.76 ng L^{-1} for PFOA)[10]. Higher levels were reported in Sheldt Estuary (26.65 ng L^{-1} of PFOS and 23.5 ng L^{-1} of PFOA)[19], Estuary and north coast of Bohai Sea (China) (between not detected to 30.9 ng L^{-1} of PFOS and 2.58–81.7 ng L^{-1} of PFOA)[11], or Tokyo Bay (21 ng L^{-1} of PFOS and 167 ng L^{-1} of PFOA)[12].

3.7. Comparison with previous methodologies

The main difference between the proposed method and the already published, lies in the fact that the entire procedure was especially developed for the specific analysis of PFASs in seawater samples. Few papers about method development for the determination of PFASs in water perform the optimization specifically for seawater, and, as far as we know, until now all of the papers about PFASs in seawater samples use classical procedures like SPE [8,11,12,19,45,46], but none of them miniaturized sample treatment. Seawater samples have some special characteristics, different from other surface waters, and for this reason the methods optimized for other surface waters not always are the most appropriate for the analysis of seawater samples. As it was explained in Section 3.2, presence of salt in the seawater samples is advantageous in VALLME extraction, so the filtration is avoided, reducing the risks of possible losses or contaminations. Moreover, contrary to the traditional off-line SPE procedures, with the VALLME method proposed in this work no evaporation step is necessary, avoiding losses of the volatile precursor's *n*-MeFOSA and *n*-EtFOSA [45]. For all these reasons, the proposed extraction method overcomes those difficulties and it is advantageous for the analysis of PFASs in seawater samples.

Comparing the proposed method with methods designed for any kind of water sample, the M-LODs and M-LOQs obtained with the proposed method using only 35 mL of sample were comparable to those reported using solid phase extraction and higher sample volumes, as can be seen in Tables 1 and 2. The achievement of very low detection limits using low volume of sample is mandatory for monitoring programs involving several sampling points and a great number of samples, that should be stored refrigerated. Better detection limits were obtained only by extraction of 1 L of sample. Some other approaches using low sample volumes were in-tube SPME (0.8 mL) [25], on-line SPE (0.35 mL, but achieved worse LODs that the obtained with the proposed method [47], or 5 mL but a worse precision [48]), UA-DLLME-SFO (10 mL) [27] or VALLME (20 mL) [26], but none of these approaches were applied to seawater samples.

Moreover, in those works using low volumes of sample, data were acquired in MS/MS mode. The main advantage of using Orbitrap HRMS detection instead of the more conventional triple quadrupole MS detection is that we can perform the acquisition in full scan mode and quantify the target analytes using the exact mass, avoiding any interference, which is essential for the achievement of low detection limits. On the other hand, there is not loses of information, and therefore the identification of other related non target compounds, like PFASs precursors, is possible, improving the analytical information of the sample.

The proposed VALLME procedure allows determining not only the frequently measured PFOS and PFOA, but also FOSA, N-EtFOSA and N-MeFOSA because of their importance as contaminants and also as precursors of FOSA and PFOS. Also the method is faster than the SPE and LLE classical procedures, allowing the extraction of 18 samples per day, and cheap, because does not need the use of sorbents or expensive equipment for sample treatment. Moreover, we avoid the use of a dispersing solvent used in DLLME and simplify the procedure by using agitation to obtain the dispersion.

All these improvements were achieved providing excellent accuracy, precision and sensitivity, similar than the obtained with the procedures previously published in the literature, as can be seen in Table 1.

4. Conclusions

The method proposed in this work for the determination of PFASs in seawater is fast, simple, easy and with high sensitivity (M-LOQ <7 ng L^{-1}) using a low volume of sample (35 mL) and solvents (0.85 mL). The proposed VALLME approach is really suitable for the reliable analysis of seawater samples, because the presence of salt in the sample improves the extraction, and does not supposes an inconvenient for the extraction in the opposite to SPE procedures.

The use of LTQ-Orbitrap-HRMS in full scan mode, quantifying the target analytes using the exact mass, provides a specificity maintaining all the information obtained in the full spectra, which allow the identification of non-target compounds. Excellent recoveries (95–105%) and quantification performances for all target compounds were obtained by using matrix-matched calibration and labelled surrogate standards correction. Good results were obtained in the proficiency test performed for PFOA, linear PFOS and total PFOS ($|z| < 1$), demonstrating the reliability and applicability of the method, not only for the determination of PFASs in seawater, but also in other types of waters by adjusting the salinity of the sample. Moreover, because of the simplicity of the procedure a high number of samples can be extracted per day, and consequently the method proposed can be useful for monitoring programs.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.chroma.2018.04.049.

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