Paper spray-atmospheric pressure photoionization-high resolution mass spectrometry for the direct analysis of neutral fluorinated compounds in waterproof impregnation sprays

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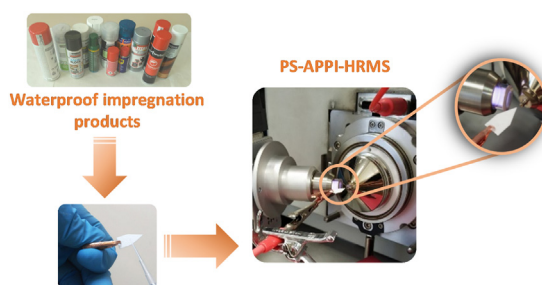[b] Water Research Institute (IdRA), University of Barcelona, Montalegre 6, E-08001, Barcelona, Spain

HIGHLIGHTS

- APPI combined with a PS-based technique has been proposed for the first time.
- Low-cost and fast method for the screening of non-polar and low polar compounds.
- The use of a dopant as spray solvent helps to ionize non-polar PFAS by APPI.
- PS-APPI allows the efficient ionization of all studied families of neutral PFAS.
- Neutral PFAS were found in 7 out of 16 waterproof impregnation sprays.

GRAPHICAL ABSTRACT

ARTICLE INFO

ABSTRACT

In this work, paper spray (PS) is combined with atmospheric pressure photoionization-mass spectrometry (PS-APPI-MS) for the determination of non-polar and low polar compounds, such as the neutral per- and polyfluorinated alkyl substances (PFAS). The proposed PS-APPI-MS method has been developed for the analysis of fluorotelomer alcohols (FTOHs), fluoroctanesulfonamides (FOSAs) and fluorooctane sulfonamido-ethanols (FOSEs), using both negative ion mode and high-resolution mass spectrometry (HRMS). The most critical working parameters (i.e., UV-krypton lamp position, sample drying time, spray dopant solvent and spray voltage) have been evaluated to study both the ionization behaviour and ionization efficiency. The best results were achieved using dopant-assisted PS-APPI-HRMS with toluene as dopant solvent. The most intense ions observed in the mass spectra, $[M–H]^-$ for FOSAs and $[M+O_2]^{-\bullet}$ for FTOHs and FOSEs, were selected and proposed for fast screening and quantitative analysis of target compounds in waterproof impregnation sprays samples using internal standard calibration method and being able to detect down to $\mu g\ L^{-1}$ levels. The satisfactory values of the method quality parameters (detection capability, repeatability, trueness and linearity) demonstrated the good performance of the PS-APPI-HRMS method and allowed the identification and quantitation of some FTOHs (6:2 FTOH, 7-Me-6:2 FTOH, 8:2 FTOH, 10:2 FTOH) and N-MeFOSE at mg L^{-1} in some of the waterproof impregnation spray products analyzed. This low-cost PS-APPI-HRMS method allows a fast screening, with minimum sample preparation, of non-polar and low polar compounds simultaneously, which can significantly improve the throughput on routine laboratories.

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1. Introduction

In the last years, the use of ambient ionization mass spectrometry techniques (AIMS) has shown an important increase, probably due to its attractive characteristics to perform direct analysis of samples in the open air with minimal or even no previous sample treatment [1] AIMS techniques promote straightforward analysis with emphasis on simplicity, low cost and short analysis time. Among AIMS techniques, paper spray ionization-mass spectrometry (PSI-MS) is one of the easiest and simplest. A liquid sample deposited onto a triangular shaped paper is analyzed by adding a solvent and applying a high voltage, which produces a spray of charged droplets in the apex of the triangle paper [2]. Because PSI-MS is based on the electrospray ionization mechanism, its applications have been generally limited to the analysis of polar and moderate polar compounds (amines, amides, ketones or acids) that can be easily protonated or deprotonated in liquid-phase before being transferred into the gas-phase *via* ion evaporation [3]. Recently, some authors have proposed the use of some strategies to favour the ionization of a wider range of compounds. For instance, Li et al. [4] reported the use of non-polar solvents to favour the ionization of insoluble drugs, peptides, nucleotides, and phospholipids as solids from the paper, whereas Kim et al. [5] proposed these non-polar solvents to ionize low- and non-polar aromatic compounds. Both authors agree that the main ionization mechanisms may involve field desorption ionization and/or chemical ionization by corona discharge on the paper tip. The monitoring of environmental and food contaminants and the evaluation of risk of human exposure to persistent pollutants frequently require the analysis of a large number of samples, although in many studies only few of them are positives. Under this scenario, the direct analysis of samples by AIMS methods could play an important role by detecting the positive samples and assisting in the workload of control laboratories. PS-based methods might help to achieve these goals, as has already been shown for other ambient MS methods that were applied in research areas such as food, environmental, forensic and clinical analysis [6–10], and demonstrated their feasibility for both qualitative and quantitative analysis of polar and moderate-polar compounds in raw samples.

Per- and polyfluorinated alkyl substances (PFAS), which comprise a huge group of chemicals that are characterized by a totally or partially fluorinated alkyl chain with a terminal functional group, have been used in many industrial and consumer products due to their special chemical properties such as hydrophobicity, lipophobicity, non-sticking and highly fire resistance, among others [11–15]. Within this family of compounds, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are of great concern because of their persistence, toxicity and potential bioaccumulation in organisms, as well as their biomagnification through the food chain [16–18]. From a regulatory point of view, PFOA and PFOS have been included by the Stockholm Convention as persistent organic pollutant in Annex A and B, suggesting their elimination and production restrictions, respectively [19,20]. Over the last years, other fluorinated compounds such as fluoroctanesulfonamides (FOSAs), fluoroctane sulfonamido-ethanols (FOSEs) or fluorotelomer alcohols (FTOHs), among others, have substituted these PFAS. Although some of them show lower toxicity, they can degrade into the persistent PFAS, therefore their monitoring is of interest [14,21]. Related to human exposure, there are few available data about PFAS content in consumer products, which are the main source of emission of these compounds into the environment. In addition, there is a lack of information about PFAS employed in consumer products such as impregnation products, cleaners, polishers and lubricants [22,23]. Besides, this information is often hidden by the data owner, making it less accessible [24]. Regarding the analytical

methods used to determine these families of compounds, FTOHs, FOSAs and FOSEs have been analyzed by both gas chromatography (GC) [25–28] and liquid chromatography (LC) [29,30] mainly coupled to mass spectrometry (MS). In the GC-MS analysis both electron ionization (EI) and chemical ionization (CI) have been used, although high fragmentation and poor ionization efficiency were reported for some of these compounds. In LC-MS, electrospray ionization (ESI) has been the ionization technique most currently used, although atmospheric pressure chemical ionization (APCI) and atmospheric pressure photoionization (APPI) have also recently been proposed to overcome some of the ionization problems observed in ESI for FTOHs and FOSEs [11]. Concerning AIMS methods, so far none have been reported for these families of neutral PFAS, maybe due to the difficulties for their ionization under electrospray-based mechanisms. However, alternative ionization methods can be considered for the development of AIMS methods for these analytes to improve high-throughput quality control laboratories.

The present study explores the feasibility of a new AIMS approach that combines paper spray with APPI and high-resolution mass spectrometry (PS-APPI-HRMS) for the rapid analysis of FTOHs, FOSEs and FOSAs. The results obtained with the PS-APPI-HRMS method are compared with those achieved using the conventional PSI-HRMS setup in order to understand the evaporation/ionization mechanism involved in this new approach. Finally, the proposed PS-APPI-HRMS method has been applied for the determination of neutral PFAS in commercial waterproof impregnation spray products.

2. Materials and methods

2.1. Materials, reagents and standards

For paper spray experiments, Whatman 31ET chromatography paper (W31) obtained from Sigma-Aldrich (Steinhein, Germany) and copper clips purchased from Muller Electric (Akron, OH, USA) were used. Regarding solvents, acetonitrile (ACN), methanol (MeOH) (LC-MS Chromasolv® grade), ethanol (EtOH) (Chromasolv® for HPLC gradient grade) and dimethylformamide (DMF) (anhydrous grade) were purchased form Sigma-Aldrich (Steinheim, Germany). Concerning solvents used as dopants, toluene and chlorobenzene (Chromasolv® Plus HPLC) were also acquired from Sigma-Aldrich, while anisole and acetone (pesticide residue analysis grade) were supplied by Fluka® Analytical (St. Louis, MO, USA), whereas tetrahydrofuran (PHOTREX™) was purchased from J.T. Baker (Deventer, Holland). The purity of all solvents used was higher than 99.8%.

FTOHs, FOSAs and FOSEs selected as target compounds for this study are shown in Fig. 1. Fluorotelomer alcohol standards (FTOHs), 1H, 1H, 2H, 2H-perfluorohexan-1-ol (4:2 FTOH), 1H, 1H, 2H, 2H-perfluorooctan-1-ol (6:2 FTOH) and 1H, 1H, 2H, 2H-perfluoro-7-trifluoromethyl-octan-1-ol (7-Me-6:2 FTOH) were acquired from Flurochem, Ltd. (Derbyshire, UK), whereas 1H, 1H, 2H, 2H-perfluorodecan-1-ol (8:2 FTOH) and 1H, 1H, 2H, 2H-perfluorododecan-1-ol (10:2 FTOH) were purchased from Alfa Aesar GmbH & Co KG (Karlsrube, Germany), at a purity higher than 96%. Regarding FOSEs and FOSAs standards, 2-(*N*-Methylperfluoro-1-octanesulfonamido)-ethanol (*N*-MeFOSE), 2-(*N*-ethylperfluoro-1-octanesulfonamido)-ethanol (*N*-EtFOSE) and *N*-methylperfluoro-1-octanesulfonamide (*N*-MeFOSA) were supplied by Wellington Laboratories, Inc. (Guelph, Ontario, Canada) as individual standard solutions (50 mg L^{-1} in methanol, ≤ 98%), while *N*-ethylperfluoro-1-octanesulfonamide (*N*-EtFOSA) (99%) was obtained from Dr. Ehrenstorfer GmbH (Augsburg, Germany). Internal standards used for quantitation of FTOHs, 1H, 1H-pentadecafluoro-1-octanol (7:1

FA), 1H, 1H-perfluoro-1-nonanol (8:1 FA), 1H, 1H-perfluoro-1-decanol (9:1 FA) and 1H, 1H-perfluoro-1-dodecanol (11:1 FA) were obtained from Fluorochem LTd. For the quantitative analysis of FOSA and FOSEs we used commercially available labelled standards, 2-(N-Ethyl-*d5*-perfluoro-1-octane-sulfonamido)-ethan-*d4*-ol) (*d9*-N-EtFOSE) and N-ethyl-*d5*-perfluoro-1-octanesulfonamide (*d5*-N-EtFOSA) solutions (50 mg L^{-1} in methanol, supplied by Wellington Laboratories Inc.). Individual stock solutions (1 mg mL^{-1}) for FTOHs and N-EtFOSA were prepared in methanol and stored at 4 °C, while the working standard solutions were prepared weekly by appropriate dilution of the stock standard solutions in methanol and stored at 4 °C until their analysis.

2.2. Instrumentation

The home-made PS-APPI-HRMS setup used in this work is shown in Fig. 2. A triangular piece of W31 paper, 10 mm (height) by 8 mm (base width), was held using a cooper clips with the apex in line with the inlet of the mass spectrometer at a distance of 4 ± 1 mm. The krypton lamp (Syagen, Santa Clara, CA, USA) used in APPI emitted photons at 10.0 and 10.6 eV energy and it was set at an angle of 30° and a distance of 1 cm from both the triangle paper apex and the MS inlet. The analysis of both standard solutions and liquid samples was performed loading aliquots of 10 μL onto the W31 paper and letting it dry for 2 min. Later, 70 μL of toluene (spray solvent) were deposited onto the base of the triangle paper with a pipet. The high voltage applied to the cooper clip for PS-APPI-HRMS analysis was 2.5 kV to generate a spray of microdroplets before the photoionization and the ions generated were recorded for 2.5 min.

Mass spectrometry analyses were performed using a quadrupole-Orbitrap mass spectrometer (Q-Exactive, Thermo Fisher Scientific, San Jose, CA, USA). High-resolution mass spectra were acquired using both negative-ion full-scan (HRMS) and product ion scan (MS/HRMS) modes. Precursor ions were fragmented in the higher-energy collisional dissociation (HCD) cell using normalized collision energies (NCE %) that ranged from 10 to 37%. Orbitrap operated in profile mode within 50−700 *m/z* range and at a mass resolution of 70,000 FWHM (full width at half maximum at *m/z* 200) for both full-scan and product ion scan. All ions were assigned applying a mass accuracy criterion lower than 5 ppm. Automatic gain control (AGC) was set at 10^6 and 10^5 for HRMS and MS/HRMS experiments, respectively, and the maximum injection time was set at 300 ms. The S-lens radiofrequency level and the capillary temperature were fixed at 50% and 300 °C,

respectively. Nitrogen (99.95% pure, Air Liquide, Madrid, Spain) was used as collision gas and precursor ions were isolated using an isolation window of 1 *m/z* in the quadrupole. Xcalibur™ software *v*3.1 (Thermo Fisher Scientific, San José, CA, USA) was used for data acquisition and data processing.

Accurate mass calibration was performed in the Q-Exactive mass spectrometer every 72 h using electrospray ionization and a calibration solution that contained caffeine, MRFA peptide, Ultramark 1621 and butylamine in acetonitrile/methanol/water (2:1:1, *v/v*) with 1% (*v/v*) formic acid.

2.3. Samples

Sixteen commercial waterproof impregnation spray products of different brands were collected from local supermarkets (Barcelona, Spain). Prior to PS-APPI-HRMS analysis, an adequate volume of a standard solution containing the internal standards were added to samples. The mixture (sample with internal standards) was shaken in a vortex for few seconds before depositing an aliquot of 10 μL onto the W31 paper. No further sample manipulation was performed before the analysis.

2.4. Data analysis

The quantification of the samples was done by using the internal standard method and calibration standard solutions prepared in methanol at concentrations ranging from 0.05 to 110 mg L^{-1}. An unweighted least squares curve fitting adjusted with a linear regression was carried out by plotting the ratio of analyte and internal standard areas in front of the ratio of analyte and internal standard concentrations (5 mg L^{-1} for 7:1 FA, 8:1 FA, 9:1 FA and 11:1 FA, and 0.4 mg L^{-1} for d$_7$-N-EtFOSA and d$_9$-N-EtFOSE). Additionally, the samples were measured by triplicate and standard deviation (SD) was determined to provide the uncertainty of the final concentrations.

3. Results and discussion

3.1. PS-APPI vs PSI behaviour of FTOHS, FOSAs and FOSEs

The ionization behaviour of FTOHs, FOSEs and FOSAs by paper spray using both approaches, standard PSI and PS-APPI, have been explored in this work using the same home-made paper spray setup. To perform both PSI and PS-APPI-HRMS experiments with
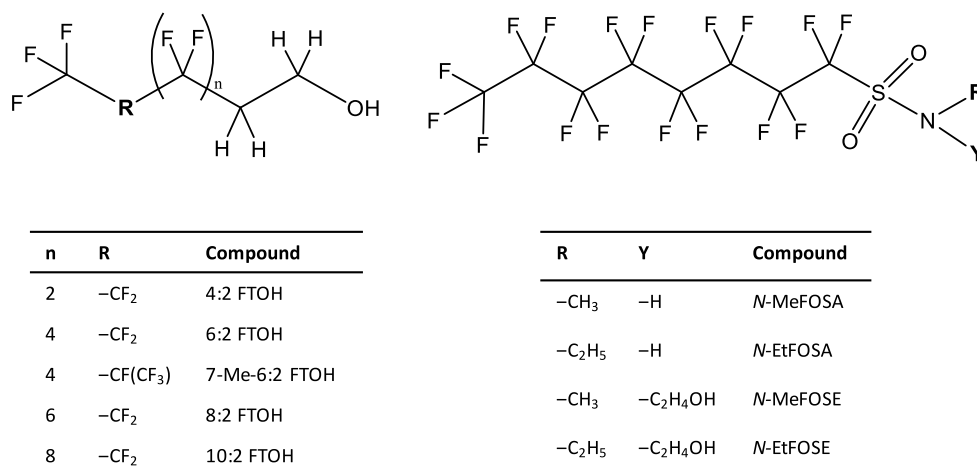

n	R	Compound
2	−CF$_2$	4:2 FTOH
4	−CF$_2$	6:2 FTOH
4	−CF(CF$_3$)	7-Me-6:2 FTOH
6	−CF$_2$	8:2 FTOH
8	−CF$_2$	10:2 FTOH

R	Y	Compound
−CH$_3$	−H	N-MeFOSA
−C$_2$H$_5$	−H	N-EtFOSA
−CH$_3$	−C$_2$H$_4$OH	N-MeFOSE
−C$_2$H$_5$	−C$_2$H$_4$OH	N-EtFOSE

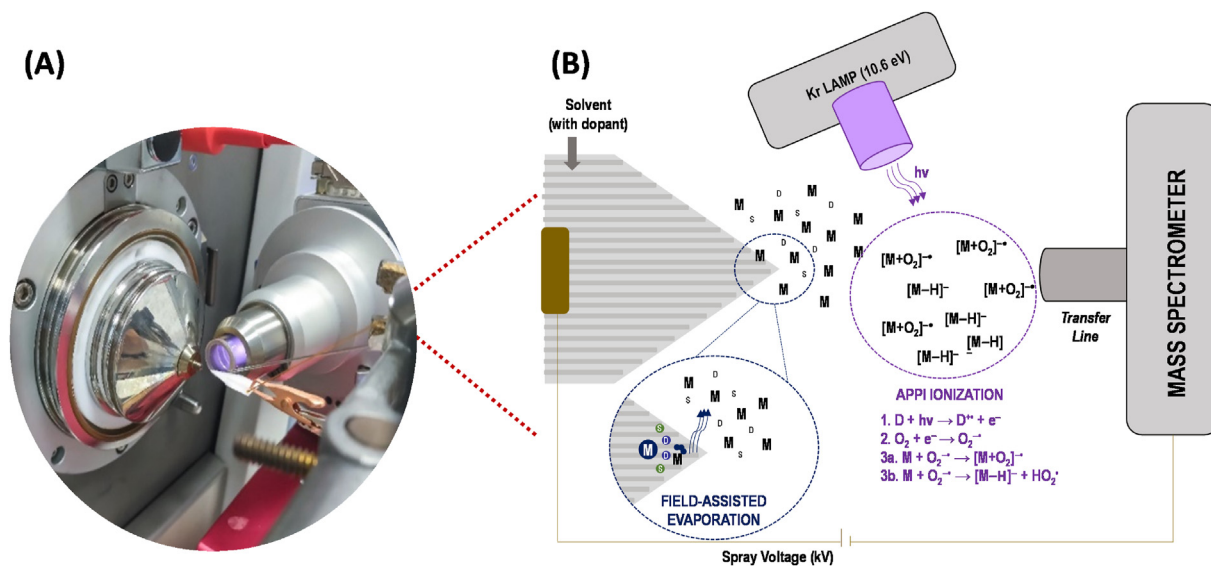**Fig. 1.** Chemical structures of the studied neutral PFAS.

Fig. 2. (A) Home-made experimental setup of voltage-assisted paper spray atmospheric pressure photoionization source. (B) Scheme of the ionization process and mechanism by PS-APPI (M: molecule, D: dopant, S: solvent). The figure is not drawn to scale.

the same setup, a krypton lamp was installed at the position described in the instrumentation section (Fig. 2). This krypton lamp was only switched-on during PS-APPI experiments. For these studies, 10 μL of a methanolic standard solution containing the analytes (10 mg L^{-1} for FTOHs and 5 mg L^{-1} for FOSAs and FOSEs) were deposited on the triangle paper and analyzed by using several solvent mixtures (acetonitrile, toluene, methanol and acetone) and applying high-voltages within the range of 2−4 kV. After the first experiments, none of the target compounds was detected in positive ion mode neither in PSI-HRMS (krypton lamp switched-off) nor in PS-APPI-HRMS (krypton lamp switched-on). Thus, further studies of neutral PFAS by PSI-HRMS and PS-APPI-HRMS were focused on negative ion mode.

Concerning the analysis of PFAS by PSI-HRMS in negative ion mode, the best results were obtained using methanol/toluene (9:1, *v/v*) as spray solvent and 3.5 kV as spray voltage. At these conditions, FOSAs were ionized (Fig. 3A) *via* proton abstraction [M–H]$^{-}$, while no ions were observed for FTOHs and FOSEs. These results are in agreement with those previously observed when using ESI. These ESI studies showed the difficulties to generate deprotonated ions [M–H]$^{-}$ from FTOHs and FOSEs and how they could only be ionized *via* adduct formation with ionic mobile phase components [11,12]. Although, the ionization mechanism taking place in paper spray under negative ion mode is still not well-understood, some authors [5,31] reported that other ionization mechanisms, in addition to electrospray, can also take place for non-acidic/basic compounds that have low polarity and high electron affinity. The ionization mechanisms involved could be initiated by corona discharge processes [31]. To evaluate this possibility, several non-polar organic solvents (acetone, toluene, cyclohexane and hexane) were tested to prevent electrospray-based mechanisms in PSI. As occurred before, only FOSAs were ionized using non-polar solvents, obtaining the best responses when using toluene/cyclohexane (3:1, *v/v*) and a spray voltage of 2.5 kV (see Electronic Supplementary Material, ESM; Fig. S1). At these conditions, the abundances of FOSAs ions were almost two orders of magnitude lower than that observed using mixtures including polar solvents, which favour the ionization of FOSAs by electrospray-based mechanisms. However, the low intensity of the [M–H]$^{-}$ when using non-polar solvents would indicate that the ionization might be produced *via* corona discharge at the apex of the triangle shaped paper.

Since previous studies performed in the research group showed that FTOHs and FOSEs can be efficiently ionized *via* LC-APPI-MS [11], the krypton lamp was switched-on to achieve the ionization of these compounds by PS-APPI-HRMS. In this new approach, the solvent used in paper spray played two important roles, as solvent to extract and transport the analytes from the sample point to the apex of the triangle shaped paper and as dopant solvent in the dopant-assisted APPI process. Fig. 3B shows the averaged mass spectrum (from 0.5 to 1.5 min) obtained for a standard mixture of neutral PFAS. As can be seen, FTOHs and FOSEs generated the characteristic superoxide adduct ions [M+O$_2$]$^{-\bullet}$ as it was previously reported in LC-APPI-MS [11]. The ionization mechanism of FTOHs and FOSEs might be initiated by the electrons released during the toluene photoionization process, which can be later captured by the atmospheric oxygen to form the superoxide radical ions [O$_2$]$^{-\bullet}$. No thermal-assisted evaporation was required in the PS-APPI setup, so field-assisted evaporation could be responsible for the transfer of neutral molecules from the paper substrate to the gas-phase, where they could later interact with superoxide radical ions [O$_2$]$^{-\bullet}$ to yield the superoxide adduct ion [M+O$_2$]$^{-\bullet}$ [32]. Regarding FOSAs, the ions observed in PS-APPI-HRMS were also [M–H]$^{-}$ and their signals were even higher than that observed using standard PSI-HRMS (Fig. 3B). As occurred for FTOHs and FOSEs, the field-assisted evaporation of FOSAs followed by their dopant-assisted photoionization in the gas-phase could be responsible for the increase in the ion responses in PS-APPI-HRMS.

Tandem mass spectrometry with the full-scan acquisition of product ions at high-resolution (MS/HRMS) was used to characterize the ions observed in both PSI-HRMS and PS-APPI-HRMS and to confirm the presence of these families of compounds in real samples (see ESM, Table S1). All product ions observed in the MS/HRMS mass spectra were consistent with those previously reported using LC-APPI-MS/MS [11,33] and GC-APPI-HRMS [34] for these families of compounds.

3.2. PS-APPI-HRMS method optimization

To maximize the ion intensity in PS-APPI-HRMS, several operational parameters such as the krypton lamp position (angle α and distance d), the spray solvent composition and the spray voltage were optimized using 8:2 FTOH and *N*-EtFOSA as model
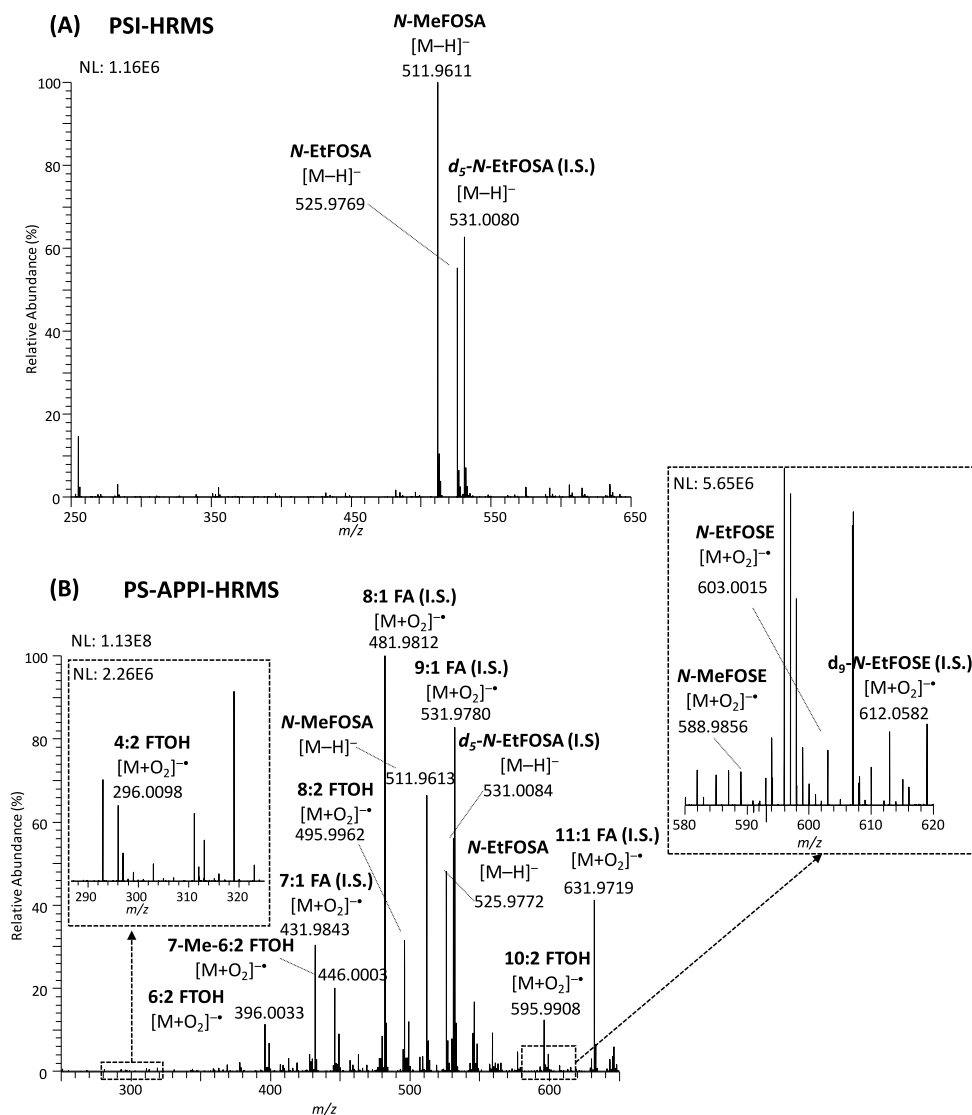
Fig. 3. Paper spray mass spectra obtained from 10 μL of a standard solution containing a mixture of target compounds prepared in pure methanol (10 mg L^{-1} for FTOHs and 5 mg L^{-1} for FOSAs and FOSEs) and deposited onto the paper substrate. (A) PSI-HRMS: methanol/toluene (9:1, v/v) as spray solvent and 3.5 kV as spray voltage. (B) PS-APPI-HRMS: toluene as spray solvent and a spray voltage of 2.5 kV. These mass spectra were averaged from data acquired within the time period of 0.5–1.5 min.

compounds (deposition of 10 μL of a 10 mg L^{-1} standard mixture solution prepared in methanol onto the triangle shaped paper).

The ions generated from 8:2 FTOH and *N*-EtFOSA were only observed within an angle (α) between 20° and 45° and a distance from the paper tip (d) between 0.3 and 1.5 cm. Fig. 4A shows the variation of ion abundance in front of the angle and the distance tested. As can be seen in this figure, the optimal ion signal is observed at the position of 30° (angle α) and 1 cm (distance d). Moreover, several spray solvents, such as toluene, acetone, chlorobenzene, tetrahydrofuran and anisole, which could act as dopants, were tested to study their effect on the analyte response. Fig. 4B depicts the ion intensity observed using the different solvents and as can be seen toluene provided the highest signal for both 8:2 FTOH and *N*-EtFOSA, although chlorobenzene and anisole also produced a relative intense ion signal for *N*-EtFOSA, because they might favour proton abstraction from this analyte.

The spray/dopant solvent may also help to facilitate both the extraction of analytes from the sample and their transport to the paper tip. To this end, toluene was mixed with other cosolvents

(acetonitrile, cyclohexane, tetrahydrofuran, methanol, ethanol, or dimethylformamide) at different percentages (from 25% to 75%). However, any of the mixtures provided a significant signal improvement over 100% toluene. Therefore, toluene was selected as the optimum solvent for the analysis of neutral PFAS by PS-APPI-HRMS and it was used to evaluate the effect of the spray voltage over the ionization efficiency of analytes. As an example, Fig. 4C shows the changes on the relative abundances of the ions generated for some neutral PFAS (4:2 FTOH, 6:2 FTOH, 10:2 FTOH, *N*-MeFOSA and *N*-EtFOSE) by PS-APPI-HRMS using spray voltages ranging from 0.5 to 4.0 kV. Regarding shorter fluoroalkyl chain FTOHs (4:2 FTOH and 6:2 FTOH), the highest ionization efficiency was observed at approximately 2.5 kV, whereas for 10:2 FTOH and, especially, for FOSAs and FOSEs, the response was higher when increasing the spray voltage (ca. 3.0 kV). This fact may be related to the vapour pressure of analytes. Less volatile analytes may require a stronger electric field (higher spray voltages) at the tip of the paper to promote the desorption of neutral molecules to the gas-phase when using nonpolar solvents. Therefore, as a compromise, a
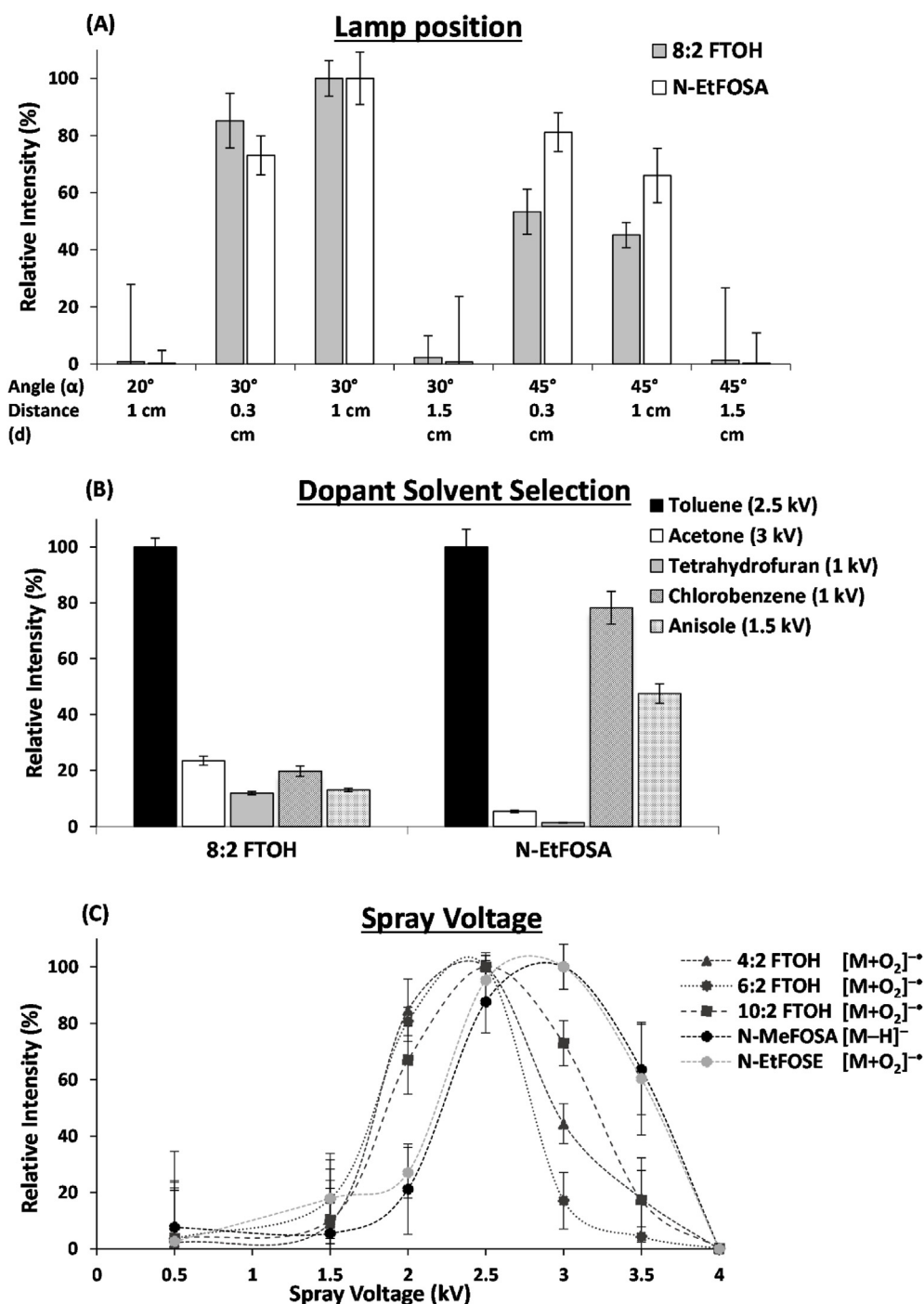
Fig. 4. Effect of (A) lamp position, (B) dopant solvent selection, (C) spray voltage over the PS-APPI-HRMS response of the analytes.

spray voltage of 2.5 kV was selected to achieve a sensitive method for the simultaneous determination of all neutral PFAS.

Under the optimal PS-APPI-HRMS conditions, a standard mixture containing the nine target compounds at a concentration of 10 mg L^{-1} for FTOHs and 5 mg L^{-1} for FOSAs and FOSEs were analyzed. Interestingly, differences on their chronogram profiles were observed within the acquisition time (2.5 min) (Fig. 5). For all FTOHs, the ion signal was more intense within 0.2−2.0 min. However, the ion response of 4:2 FTOH (m/z 296.0101) decreased over the time, while that of 10:2 FTOH (m/z 595.9909) increased over the same period of time. In contrast, the response of the less

volatile FOSEs (m/z 588.9857 and m/z 603.0014) and FOSAs (m/z 511.9619 and m/z 525.9775) significantly raised at the end of the chronogram. This behaviour could be related to both the relative volatility of these compounds and the variation in the size of the droplets of the spray generated at the tip of the paper. The high volatility of some compounds could make easier their transfer into the gas phase, even when the presence of large amount of solvent favoured the generation of relatively large droplets. However, when the solvent runs out over the time, the droplets become much smaller, which facilitates the desolvation process and the transfer of high molecular weight compounds to the gas phase. Furthermore,

the absence of solvent at the end of the recorded period might increase the electrical field at the tip of the paper, which could also favour the field-assisted evaporation of the less volatile analytes [3,35,36].

3.3. Analysis of waterproof impregnation sprays by PS-APPI-HRMS

Before the PS-APPI-HRMS analysis, the deposited sample onto the triangle shaped paper should let it dry. However, the volatility of target compounds limited the maximum drying time of the sample on the paper substrate. Blank samples spiked with target compounds were analyzed using different drying periods (0.5−10 min). The highest signal for the analytes was achieved after letting the sample dry on the paper triangle at room temperature for 2 min (see ESM, Fig. S2). Longer drying times produced a significant decrease on the response of FTOHs, especially for 4:2 FTOH (the more volatile one), due to the loss of analytes by evaporation before starting the PS-APPI-HRMS determination. Regarding ion signal variability (RSD %), it increased with drying time and was lower than 17% for drying times below 2 min for all the compounds except for 4:2 FTOH (RSD 32%) due to its high volatility. Although this variability is acceptable, some authors have proposed the use of a Teflon tube covering the paper [37] or an on-substrate derivatization [38] to reduce losses due to the evaporation, especially of highly volatile analytes, and thus improve the performance of the measurements.

Internal standard method was used to quantify the neutral PFAS in order to allow the correction of both signal variability and possible matrix effects. The internal standards used were d_5-*N*-EtFOSA and d_9-*N*-EtFOSE for FOSAs and FOSEs and 7:1 FA, 8:1 FA, 9:1 FA and 11:1 FA for FTOHs, being the calibration curves linear ($R^2 > 0.998$) within the studied concentration range. Quality parameters such as limits of detection and quantitation as well as precision and bias were estimated and the results obtained are summarized in Table 1. Method limits of detection (MLODs) and quantitation (MLOQs) based on the signal-to-noise (S/N) ratio of 3 and 10, respectively, were estimated by spiking a blank waterproof impregnation spray sample with target compounds at low concentration level. For most of neutral PFAS, the estimated MLODs ranged from 3 to 27 μg L^{-1}, except for 4:2 FTOH that was higher (315 μg L^{-1}) due to its high volatility. These MLODs are at least 5 to 10 times lower than the concentration levels generally found for neutral PFAS in impregnating agents, which are currently above mg L^{-1} levels [21,22]. Replicated analyses (n = 5) at two concentration levels (low level: 0.08−0.6 mg L^{-1} and 2 mg L^{-1} for 4:2 FTOH, high level: 2−25 mg L^{-1} and 50 mg L^{-1} for 4:2 FTOH) were performed to
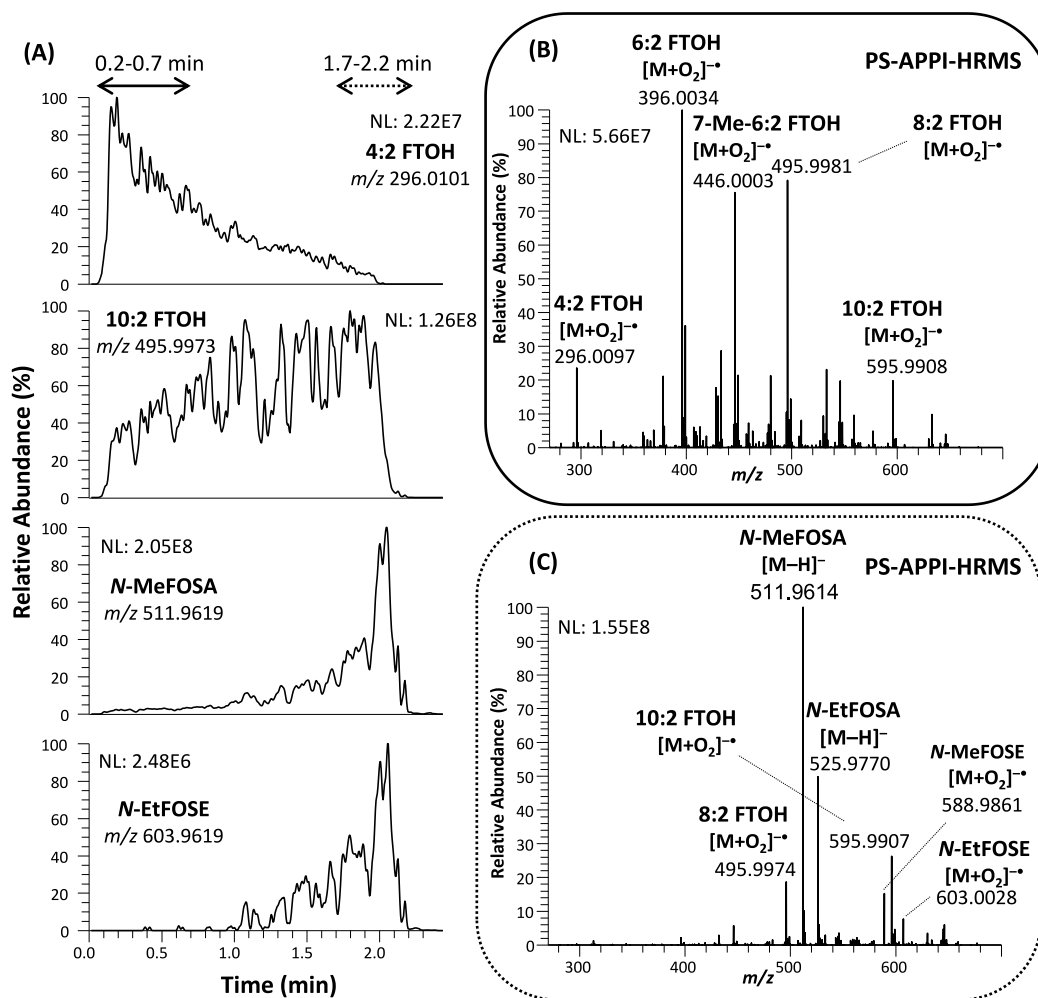

Fig. 5. Chronograms and mass spectra obtained in the PS-APPI-HRMS analysis of a mixture of target compounds (10 μg mL^{-1} for FTOHs and 5 μg mL^{-1} for FOSAs and FOSEs). (A) Selected ion current profiles for 4:2 FTOH, 10:2 FTOH, *N*-MeFOSA and *N*-EtFOSE (mass error: 5 ppm), (B) averaged mass spectrum obtained from data acquired between 0.2 and 0.7 min, (C) averaged mass spectrum obtained from data acquired between 1.7 and 2.2 min.

Table 1
Quality parameters of the PS-APPI-HRMS method.

Analyte	MLOD (μg L^{-1})	MLOQ (μg L^{-1})	Calibration range (mg L^{-1})	R^2	ΔSlope (%)[a]	Precision (RSD, %)		Trueness (Re. Bias, %)	
						Low Level[b]	High Level[c]	Low Level[b]	High Level[c]
4:2 FTOH	315	1000	1−110	0.9978	5	32	20	39	7
6:2 FTOH	25	85	0.15−60	0.9995	−6	13	5	18	0.2
7-Me-6:2 FTOH	27	90	0.15−60	0.9998	−3	9	4	12	0.3
8:2 FTOH	6	20	0.05−60	0.9984	3	9	9	9	9
10:2 FTOH	6	20	0.05−60	0.9995	0.2	5	2	5	2
N-MeFOSA	3	10	0.05−5	0.9998	−5	6	4	11	0.3
N-EtFOSA	3	10	0.05−5	0.9993	7	12	1	17	0.7
N-MeFOSE	12	40	0.05−5	0.9999	−6	10	9	10	0.2
N-EtFOSE	12	40	0.05−5	0.9999	1	18	4	16	0.2

[a] Defined as relative difference between external calibration and matrix matched slopes.
[b] Low level: 0.08−0.6 mg L^{-1} and 2 mg L^{-1} for 4:2 FTOH.
[c] High level: 2−25 mg L^{-1} and 60 mg L^{-1} for 4:2 FTOH.

Table 2
Concentration of neutral PFAS found in waterproof spray products using PS-APPI-HRMS.

Sample	Detected compound	Ion assignment	Accurate mass (*m/z*)	Mass accuracy (ppm)	Concentration $\pm$ SD (mg L^{-1})
WP-01	n.d.	−	−	−	n.d.
WP-02	n.d.	−	−	−	n.d.
WP-03	6:2 FTOH	[M+O$_2$]$^{-\bullet}$	396.0032	1.3	0.27 $\pm$ 0.01
	8:2 FTOH	[M+O$_2$]$^{-\bullet}$	495.9956	3.4	0.057 $\pm$ 0.003
WP-04	6:2 FTOH	[M+O$_2$]$^{-\bullet}$	396.0024	3.3	25 $\pm$ 1
	7-Me-6:2 FTOH	[M+O$_2$]$^{-\bullet}$	445.9910	2.0	0.34 $\pm$ 0.01
	8:2 FTOH	[M+O$_2$]$^{-\bullet}$	495.9972	0.2	0.08 $\pm$ 0.002
	10:2 FTOH	[M+O$_2$]$^{-\bullet}$	595.9905	0.7	0.2 $\pm$ 0.02
WP-05	6:2 FTOH	[M+O$_2$]$^{-\bullet}$	396.0033	1.0	0.172 $\pm$ 0.009
	N-MeFOSE	[M+O$_2$]$^{-\bullet}$	588.9856	0.2	0.63 $\pm$ 0.04
WP-06	6:2 FTOH	[M+O$_2$]$^{-\bullet}$	396.0024	3.3	167$\pm$5[a]
WP-07	6:2 FTOH	[M+O$_2$]$^{-\bullet}$	396.0024	3.2	102$\pm$1[a]
WP-08	n.d.	−	−	−	n.d.
WP-09	6:2 FTOH	[M+O$_2$]$^{-\bullet}$	396.0020	4.3	<MLOQ
WP-10	n.d.	−	−	−	n.d.
WP-11	8:2 FTOH	[M+O$_2$]$^{-\bullet}$	495.9949	4.8	<MLOQ
WP-12	n.d.	−	−	−	n.d.
WP-13	n.d.	−	−	−	n.d.
WP-14	n.d.	−	−	−	n.d.
WP-15	n.d.	−	−	−	n.d.
WP-16	n.d.	−	−	−	n.d.

[a] Sample diluted with acetone for analyte quantitation.

evaluate the precision (concentration intra-day repeatability as relative standard deviation, RSD %) and the trueness (relative bias, %) of the method. For most of the compounds, RSD (%) values were lower than 18% and bias were below 18%, except for 4:2 FTOH. The high volatility of this compound could be the responsible for the higher values calculated, an RSD of 32% and a bias of 39%. Additionally, the matrix effect was considered negligible for these types of samples since the differences between the slopes achieved by an external and matrix matched calibration were lower than 7%.

FTOHs, FOSAs and FOSEs were determined by PS-APPI-HRMS in 16 waterproof impregnation spray samples purchased from local stores in January 2019. Any label of the 16 samples analyzed indicated the use of neutral PFAS as an ingredient in these products. Internal standards (0.4 mg L^{-1} for d_5-*N*-EtFOSA and d_9-*N*-EtFOSE and 5 mg L^{-1} for FAs) were added to the sample after transferring it to an Eppendorf tube. Prior to the analysis of the sample, procedural blanks were carried out to avoid potential contamination of the samples due to the material used during the sample manipulation. The sample raw data were acquired in both PS-APPI-HRMS for the quantitation of identified compounds (mass accuracy less than 5 ppm) and PS-APPI-MS/HRMS for confirmatory purposes (see ESM, Table S1). If necessary, positive samples containing neutral PFAS at concentration levels above the calibration range were adequately diluted in acetone to quantify target compounds within

the linear calibration range used. Table 2 lists the samples analyzed and the neutral PFAS identified along with the quantitative results obtained by PS-APPI-HRMS. Among the waterproof impregnating spray samples, the presence of neutral PFAS was detected in seven samples. FTOHs were identified in the 7 positive samples, being the 6:2 FTOH the most frequently detected at concentrations ranging from 0.27 to 167 mg L^{-1}. Fig. 6 shows as an example the PS-APPI-HRMS and PS-APPI-MS/HRMS spectra obtained in the analysis of sample WP-06. In this sample, 6:2 FTOH was present at a concentration of 167 $\pm$ 5 mg L^{-1} and it was confirmed by tandem mass spectrometry (see ESM, Table S1). In some of the samples, more than one neutral PFAS were found at important concentration levels (i.e., WP-03 and WP-04) which may suggest the use of technical formulations in the production of these waterproof impregnation spray products. As an example, the mass spectra of one of these samples (WP-04) is shown in Fig. S3 (ESM). The concentration levels of FTOHs found in this study are in agreement with those reported for commercial impregnation products analyzed in Norway (0.5−330 mg L^{-1}) [22] and Switzerland (0.8−9400 mg L^{-1}) [23]. Moreover, *N*-MeFOSE was only detected (0.63 $\pm$ 0.04 mg L^{-1}) in one waterproof impregnation spray sample (WP-05), while FOSAs were not detected in any of the tested products.
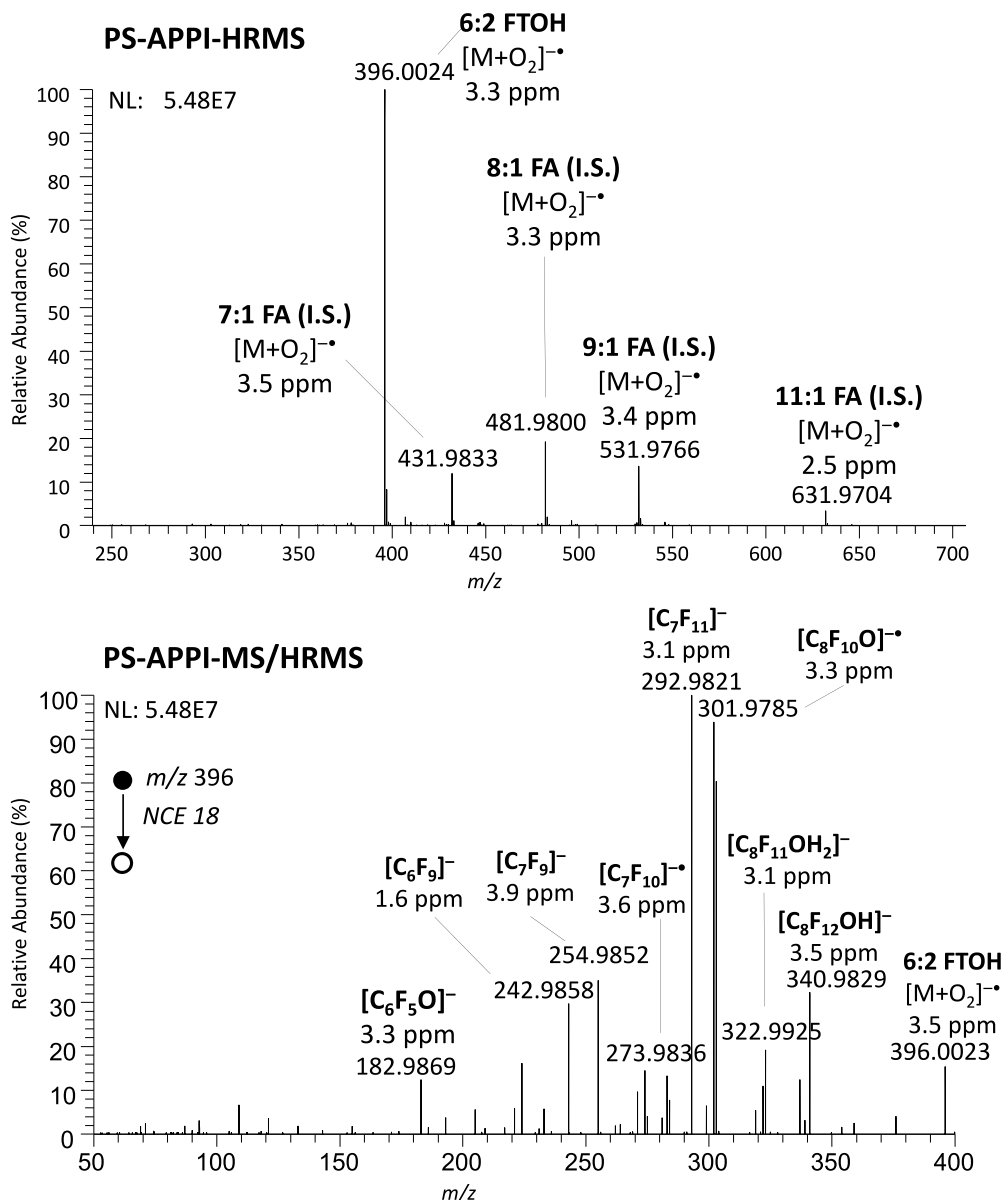
Fig. 6. PS-APPI-HRMS(/MS) spectra of a positive waterproof impregnation spray sample (WP-06) where 6:2 FTOH was identified at a concentration of 160 $\pm$ 4 mg L^{-1}.

4. Conclusions

In this work, the combination of APPI with the PS-based technique has demonstrated to be an effective approach to overcome the ionization problems observed for FOSEs and FTOHs using the standard PS setup. Under PS-APPI conditions, FTOHs and FOSEs have shown a high tendency to generate superoxide adduct ions $[M+O_2]^{-\bullet}$ while the deprotonated molecule ion $[M-H]^-$ has been mainly detected for FOSAs. The krypton-lamp position (set horizontally at 30 °C and at 1 cm from the sharp tip) as well as the spray solvent (toluene) and the spray voltage (2.5 kV) have been the most critical working parameters to obtain the best signal intensity. Method quality parameters, such as MLODs (at low µg L^{-1} levels), linearity ($R^2 > 0.998$), intra-day precision (RSD% <18%) and trueness (relative errors <18%) have demonstrated the good performance of the PS-APPI-HRMS method proposed. Moreover, the analysis of waterproof impregnation sprays by PS-APPI-HRMS

revealed the presence of several neutral PFAS up to mg L^{-1} levels, being the presence of 6:2 FTOH the most abundant one. These results demonstrated the potential of the proposed PS-APPI-HRMS method for the fast determination of these neutral fluorinated compounds in waterproof impregnation sprays, but the method could be further applied for fast monitoring of neutral PFAS in other samples to study the human exposure to these substances. Further studies should be performed to evaluate the general applicability of PS-APPI for the analysis of other low polar/non polar compounds.

CRediT authorship contribution statement

R. Seró: Conceptualization, Investigation, Validation, Formal analysis, Writing − original draft. **J.F. Ayala-Cabrera:** Conceptualization, Methodology, Investigation, Validation, Formal analysis, Writing − original draft. **F.J. Santos:** Conceptualization, Methodology, Supervision, Project administration, Writing − review &

editing. **E. Moyano:** Conceptualization, Methodology, Supervision, Project administration, Writing − review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aca.2022.339720.

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