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Direct injection analysis of polar micropollutants in natural drinking water sources with biphenyl liquid chromatography coupled to high-resolution time-of-flight mass spectrometry

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ABSTRACT

A method for the trace analysis of polar micropollutants (MPs) by direct injection of surface water and groundwater was validated with ultrahigh-performance liquid chromatography using a core-shell biphenyl stationary phase coupled to time-of-flight high-resolution mass spectrometry. The validation was successfully conducted with 33 polar MPs representative for several classes of emerging contaminants. Identification and quantification were achieved by semi-automated processing of full-scan and data-independent acquisition MS/MS spectra. In most cases good linearity ($R^2 \geq 0.99$), recovery (75% to 125%) and intra-day (RSD < 20%) and inter-day precision (RSD < 10%) values were observed. Detection limits of 9 to 83 ng/L and 9 to 93 ng/L could be achieved in riverbank filtrate and surface water, respectively. A solid-phase extraction was additionally validated to screen samples from full-scale reverse osmosis drinking water treatment at sub-ng/L levels and overall satisfactory analytical performance parameters were observed for RBF and reverse osmosis permeate. Applicability of the direct injection method is shown for surface water and riverbank filtrate samples from an actual drinking water source. Several targets linkable to incomplete removal in wastewater treatment and farming activities were detected and quantified in concentrations between 28 ng/L for saccharine in riverbank filtrate and up to 1 µg/L for acesulfame in surface water. The solid phase extraction method applied to samples from full-scale reverse osmosis drinking water treatment plant led to quantification of 8 targets between 6 and 57 ng/L in the feed water, whereas only diglyme was detected and quantified in reverse osmosis permeate. Our study shows that combining the chromatographic resolution of biphenyl stationary phase with the performance of time-of-flight high-resolution tandem mass spectrometry resulted in a fast, accurate and robust method to monitor polar MPs in source waters by direct injection with high efficiency.

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1. Introduction

Anthropogenic organic micropollutants (MPs) and their transformation products are ubiquitously detected in the aquatic environment [1–3]. MPs can preferentially remain in the water phase during environmental and water treatment processes based on their polarity and degree of persistency to (a)biotic degradation. These chemicals can reach drinking water, possibly triggering adverse effects on human health [4,5]. In the European Union, regulation to protect natural waters from hazardous substances is implemented, e.g. the Water Framework Directive [6]. However, most polar MPs known to occur in the aquatic environment are currently overlooked by these regulatory actions [7], resulting in the need for accurate, sensitive and robust analytical tools to efficiently monitor source waters.

Hybrid high-resolution mass analyzers (HRMS) such as linear ion trap (LTQ) Orbitrap and quadrupole time-of-flight (q-ToF) coupled to either liquid (LC) or gas chromatography (GC) are being increasingly applied to environmental samples [8–10]. HRMS has dramatically improved the potential for identification of small organic molecules, providing a resolving power, typically defined at full width at half maximum (FWHM), of 500,000 (at m/z 200) and 80,000 (at m/z 400) for modern Orbitrap and ToF detectors, respectively, and a mass deviation lower than 5 ppm for both precursors

and product ions [10]. HRMS can provide sensitivity comparable to that of low-resolution MS [10,11] and greater selectivity in full-scan acquisitions [12]. LC-HRMS/MS represents the obvious tool to screen for polar MPs in water samples in most cases, holding a pivotal role in the elucidation of unknowns [13,14] and offering robust quantitative performance [10].

So far, reversed-phase high-performance LC (RP-HPLC) with octadecyl carbon chain-bonded silica stationary phase (C18) and coupled to hybrid Orbitrap MS equipped with electrospray ionization (ESI) has been the most used setup to quantify small polar MPs in water samples [15–18]. The improved sensitivity and dynamic range of more recent q-ToF technology have widened the possibilities for quantitative applications with hyphenated HRMS [8,19,20]. Recent q-ToFs can be a tremendous asset when coupled to ultrahigh-performance liquid chromatography (UHPLC) [10], for its additional benefits in terms of throughput and chromatographic resolution [21]. Greater efficiency can be achieved by carrying chromatographic separation on core-shell stationary phases [22].

In this context, we explored the capabilities of UHPLC-ESI-q-ToF/MS to screen qualitatively and quantitatively for polar MPs in natural raw waters. The main objective of this study was to optimize and validate a high-efficiency target screening method to analyze polar MPs in drinking water sources at environmentally relevant concentrations by direct injection analysis. A second objective was to validate a generic solid-phase extraction (SPE) with hydrophilic-lipophilic balance (HLB) for applications requiring sub-ng/L detection limits. To the best of our knowledge we introduce the first accurate-mass screening method for polar MPs in source waters which conjugates LC-HRMS analysis by direct injection, UHPLC separation on a novel core-shell biphenyl analytical column, and semi-automated identification with high confidence and quantification from full-scan HRMS data and MS/MS data recorded in a data-independent acquisition (DIA). Direct injection analysis with UHPLC-ESI-q-ToF/MS should deliver satisfactory performance to detect trace concentrations of MPs with high efficiency thanks to minimum sample preparation, high chromatographic resolution with core-shell technology [22] and semi-automated identification and quantification. Furthermore hybrid ToF analyses result in identification with confidence higher than low-resolution MS thanks to full-scan MS and DIA MS/MS data [23], offering the advantages of posing no hard limits on full-scan acquisition, the possibility to analyze target and non-target compounds retrospectively, and to apply diverse data mining strategies.

The direct injection analysis method presented in this manuscript was validated for surface water and riverbank filtrate (RBF) with a set of 33 target analytes previously chosen to investigate the efficiency of removal of polar MPs by pilot-scale reverse osmosis (RO) treatment [24]. The compounds were selected from scientific literature data and included chemicals regarded as critical for RO and for the quality of source waters. RP chromatography was chosen not to overlook moderately polar MPs when investigating RO filtration, as hydrophobicity can result in incomplete chemical removal [25]. The biphenyl column was chosen for its aqueous stability, enhanced selectivity compared to phenyl stationary phases, higher selectivity than C18 for aromatic compounds and a larger electron cloud that promotes dipole-dipole interactions with polar analytes [26]. Shape selectivity and polarizability have been identified as the main factors affecting the retention and selectivity with biphenyl stationary phases, with π-π and polar-π being the main interactions involved [27]. The applicability of our screening method was demonstrated by (i) direct injection analysis of field samples from two drinking water sources consisting of river water and RBF and (ii) SPE followed by analysis of samples from a drinking water treatment plant where anaerobic RBF is treated by standalone RO.

2. Materials and methods

2.1. Standards, chemicals and stock solutions

Details are provided in the Supplementary material section S-1.

2.2. Sample matrices

RBF, surface water and RO permeate were provided by the drinking water company Oasen (Gouda, The Netherlands) and sampled at different production locations in the Dutch river Rhine basin. RBF and RO permeate grab samples were taken from a full-scale RO treatment plant fed with freshly abstracted bank filtrate from a site located in the province of Utrecht. The surface water grab samples were taken from the river Lek in the village of Lekkerkerk, The Netherlands. All samples were collected in 5 L polyethylene bottles and stored in the dark at 2 °C for not more than three months before any procedure was applied. Procedural blanks consisting of ultrapure water were prepared for each batch and treated as samples.

2.3. Sample preparation

For analysis of RBF and surface water by direct injection, 990 μL aliquots were transferred to a 2 mL luer polypropylene (PP) syringe fitted with a 0.22 μm disk filter (Nantong FilterBio Membrane Co., Ltd, Nantong, China) and spiked with 10 μL isotope-labeled standards to obtain a concentration of 2 μg/L. The filtrate was collected in 1.5 mL PP LC vials and analyzed. A generic solid-phase extraction method was validated for RBF and RO permeate by using Oasis HLB (150 mg) from Waters (Etten-Leur, The Netherlands). The cartridges were placed on a vacuum manifold, conditioned with 5 mL of MeOH and equilibrated with 5 mL of ultrapure water. Samples and procedural blanks, 100 mL (n = 4) were transferred to a 250 mL PP bottle, spiked to 50 ng/L with the working isotope-labeled stock mixture and loaded onto the cartridges with the aid of a vacuum pump. After loading, the cartridges were washed with 2 mL of ultrapure water and dried under vacuum for 15 min. The cartridges were then eluted with 4 × 2.5 mL of MeOH by gravity whenever possible or by means of vacuum. The extracts filtered with 0.22 μm PP filters (Filter-Bio, Jiangsu, China) and collected in 15 mL PP falcon tubes before evaporation to 0.5 mL under a gentle nitrogen flow. After evaporation, the extracts were transferred to 1.5 mL PP LC vials and stored in the dark at 2 °C. Prior to UHPLC-q-ToF/MS analysis the extracts were diluted 5 times in ultrapure water to be more compatible with the aqueous mobile phase used for chromatographic separation (see Section 2.4). The procedure resulted in an enrichment factor of 40 and a concentration of internal standards equal to 2 μg/L to match that of the standards used for the calibration series (see Section 2.5).

2.4. LC conditions and HRMS settings

The analyses were conducted with a UHPLC system (Nexera, Shimadzu, Den Bosch, The Netherlands) coupled to a Bruker Daltonics maXis 4G high resolution q-ToF/MS upgraded with HD collision cell and equipped with a ESI source (Wormer, The Netherlands). Before MS detection the analytes were separated along a reversed-phase core–shell Kinetex biphenyl LC column, having 2.6 μm particle size, pore size of 100 Å and dimensions of 100 × 2.1 mm (Phenomenex, Utrecht, The Netherlands). The mobile phases considered for this study were ultrapure water (eluent A) and MeOH (eluent B). The effects of including acetic acid or formic acid in eluent A were evaluated in terms of number of detectable analytes. The LC gradient expressed as B percentage was 0% at 0 min, 50% at 2.5 min, 100% at 5 and until 7 min. The total flow rate was 0.3 mL/min. The initial

conditions (100% A) were re-established for a 4-min equilibration pre-run between consecutive injections. For the analysis, 30 μL of sample were injected for positive ESI mode, whereas 40 μL were injected for negative ESI mode. The column oven and tray temperature were 40° and 15 °C, respectively.

The MS detector was internally calibrated before starting an analysis batch and additionally prior to any injection. This was achieved by infusing a 50 μM sodium acetate solution in H_2O:MeOH (1:1, v/v) with a loop injection of 20 μL and a loop rinse of 20 μL. Positive and negative ESI were achieved in separate runs with a resolving power of 30,000–60,000 FWHM. MS/MS data were recorded in broadband collision induced dissociation (bbCID) mode, a DIA mode in which all ions are fragmented by alternating low and high collision energy, nominally 6 and 25 eV, respectively. More details about MS settings and the reference masses used for MS calibration are given in the supporting info (Tables S-2, S-3 and S-4).

2.5. Target screening and quantification method

Full-scan and bbCID MS/MS data were processed with TASQ (Bruker Daltonics), a two stage algorithm for detection and quantification of target analytes against a user-built database [28]. The database required analytes formulas, retention times and qualifier ions. To select the optimum qualifiers, fragmentation data was generated by analyzing a mixture of standards in autoMSMS mode, a data-dependent acquisition (DDA) algorithm that discerns analytes peaks from background and automatically derives the MS/MS acquisition rate from precursor intensities over consecutive scans. These measurements were carried by applying 20 eV collision energy in positive and negative ionization, respectively. Automated annotation of the MS/MS spectra was performed with RMassBank [29]. The most intense fragments were manually inspected and checked in the bbCID MS/MS data. Following successful confirmation, the fragments were added to the database as qualifiers of their respective precursors. For analytes showing no fragmentation, adducts other then (de)protonated precursors and isotopic peaks were considered. Full-scan HRMS data were screened for the monoisotopic mass of the (de)protonated target along with $[M+Na]^+$ and $[M+NH_4]^+$ adducts and $[M-H+CH_3COOH]^-$ adducts. Extracted ion chromatograms (EICs) with a mass tolerance of 2 m Da for full-scan data and 5 m Da for bbCID MS/MS data were obtained for the target ions. The retention time window tolerance for quantifier ions was 0.2 min, whereas qualifiers had to deviate no more than 0.02 min from the retention time of their respective quantifier ion. Isotopologue peaks were scored with the *m*Sigma function which expresses the similarity between experimental and theoretical isotopic patterns calculated from the elemental composition of precursors and fragments. Low *m*Sigma values (<100) indicated good isotopic fit. For identity confirmation, the presence of at least one qualifier ion was set as mandatory. Calibration curves for quantification were calculated by analyzing ultrapure water spiked with 16 μg/L of target MPs and serially diluted to obtain 10 concentration levels, with 31.25 ng/L being the lowest concentration of the calibration series (Table S-5). All calibration levels contained 2 μg/L internal standards. Isotope-labeled internal standards were available for 14 compounds. Surrogate internal standards could be assigned to 10 compounds after consideration of structural similarities, a 1-min retention time window and 30% tolerance for procedural losses. For the remaining 11 analytes no internal standard could be used. Calibration lines had to be derived from at least 6 points whose recalculated concentrations were within 30% accuracy from the nominal spiked concentrations and had to display r-squared values greater than 0.99. Where quantification with internal standard could not be carried, an external standard calibration was used instead.

2.6. Method validation

The method was validated for the analysis of RBF and surface water via direct injection and for solid-phase extraction of RBF and RO permeate. Linearity, detection and quantification limits, intra-day and inter-day precision and procedural recoveries comprehensive of sample treatment and potential matrix effects were assessed in two non-consecutive days. The calibration series prepared as described in Section 2.5 were used to assess linearity. Due to the limited applicability of the signal-to-noise (S/N) approach to full-scan HRMS data [30], we have adopted our own strategy based on sensitivity, selectivity and qualifier/quantifier ion ratio. The instrumental quantification limits (IQL) were defined as the lowest concentration of the calibration series capable of generating a quantifier ion peak of at least 1000 intensity units, extracted from full-scan HRMS data with a mass window or ±2 m Da and with a resolving power of 30,000 FWHM. The qualifier ions were extracted from the bbCID MS/MS data with a mass window of ±5 m Da with a minimum resolving power of 20,000 FWHM and a minimum S/N of 3 was considered whenever possible. For IQL confirmation, the q/Q ion ratio had to deviate not more ±30% from the average ratio observed along different calibration points. The instrumental detection limits (IDL) were set at concentrations 3.3 times lower than the IQL.

For the direct injection method, limits of detection (MLD) and limits of quantification (MLQ), recoveries and precision were investigated in RBF and surface water (n = 4) at concentrations matching the 5 lowest points of the calibration series, i.e. 31.25, 62.5, 125, 250, and 500 ng/L. Non-spiked aliquots were analyzed to assess background concentrations. All samples were spiked with 2 μg/L internal standards and filtered before analysis. For confirmation of MQL values in different matrices, the lowest quantifiable level within 30% accuracy from its nominal concentration had to comply with the limits' criteria. The recovery values are reported as the average of the ratio between measured concentrations, subtracted for any background concentration detected in non-spiked samples, and nominal concentrations at levels equal or greater than MQL. Intra-day and inter-day precision are reported as the relative standard deviation (RSD) of replicate measurements at spike concentrations equal or greater than MQL. Recovery values between 75% and 125% with RSD lower than 20% and 10% for intraday and interday repeatability were considered satisfactory.

For the validation of SPE method, detection limit values, recoveries and precision were calculated by analyzing RBF and RO permeate samples (n = 4) spiked to 50 ng/L unlabeled and labeled standards. Labeled standards were also added to non-spiked samples and procedural blanks. To derive the MQLs and MDLs of the SPE procedure the IDLs and IQLs were corrected for the concentration factor and recovery values of the SPE procedure. Recovery values and precision were calculated analogously to the validation of the direct injection method.

3. Results and discussion

The optimum mobile phase consisted of a mixture of A, ultrapure water 0.05% acetic acid (v/v), and B, pure MeOH. When formic acid was used instead, (iso)phthalic acid, barbital and bisphenol A could not be detected possibly due to its lower p*K*a compared to acetic acid, which can result in less favorable conditions for deprotonation of weakly acidic analytes in negative ESI mode. The final chromatographic conditions provided sharp peaks with baseline lower than or equal to 0.1 min at FWHM for all analytes except acesulfame and PFBA, which displayed a baseline width of approximately 0.3 min at FWHM. The list of target analytes, their formulas, retention times, ESI mode, internal standards, quantifier and qualifier ions and their

Table 1
Direct injection analysis method performance (n = 4).

	Ultrapure water				Riverbank filtrate			Precision		Surface water			Precision	
	Linearity R²	Calibration range ng/L	IQL ng/L	IDL ng/L	MQL ng/L	MDL ng/L	Recovery (%) ± SD	Intraday RSD (%)	Interday RSD (%)	MQL ng/L	MDL ng/L	Recovery (%)	Intraday RSD (%)	Interday RSD (%)
1H-benzotriazole	0.995	31–4000	31	9	63	19	93 ± 16	16.8	7.2	63	19	83 ± 15	18.3	7.7
2-(methylamino)pyridine	0.998	31–4000	31	9	26	8	83 ± 13	15.3	3.3	54	16	86 ± 7	8.1	3.3
2-hydroxyquinoline	0.995	31–4000	31	9	31	9	61 ± 10	16.4	5.5	31	9	63 ± 6	10.2	4.1
4- hydroxyquinoline	0.996	31–4000	31	9	63	19	86 ± 4	4.6	1.4	63	19	95 ± 8	8.5	3.1
Tolyltriazole	0.995	31–4000	31	9	31	9	92 ± 8	8.6	3.1	63	19	93 ± 12	13.2	3.1
6- hydroxyquinoline	0.996	31–4000	31	9	63	19	78 ± 15	18.9	8.1	63	19	101 ± 18	17.9	7.6
Acesulfame	0.998	63–16000	63	19	117	35	128 ± 39	30.3	12.8	n/a	n/a	92 ± 13	14.0	4.9
Antipyrine	0.996	31–4000	31	9	63	19	106 ± 15	14.5	6.1	31	9	102 ± 5	4.8	1.1
Atrazine	0.997	31–4000	31	9	31	9	95 ± 7	7.2	2.3	31	9	95 ± 11	11.7	4.6
BAM	0.997	63–4000	63	19	125	38	110 ± 7	5.9	1.0	63	19	123 ± 23	18.7	7.8
Barbital	0.999	63–4000	63	19	276	83	66 ± 8	11.4	4.7	308	93	76 ± 7	9.3	4.0
Bentazon	0.999	31–4000	31	9	269	76	102 ± 18	18.0	4.5	238	76	111 ± 24	21.6	8.3
Bisphenol A	0.993	125–4000	125	38	250	76	96 ± 13	13.1	2.9	250	76	95 ± 1	10.6	4.3
Caffeine	0.996	63–4000	63	19	63	19	96 ± 14	14.1	4.1	63	19	96 ± 13	13.2	5.3
Carbamazepine	0.999	63–8000	63	19	63	19	108 ± 29	26.7	11.3	63	19	95 ± 7	7.9	3.1
Chloridazon	0.995	31–2000	31	9	31	9	91 ± 16	17.6	3.5	31	9	81 ± 6	7.4	2.0
DEET	0.996	31–2000	31	9	31	9	97 ± 12	12.8	4.0	31	9	93 ± 12	13.2	4.7
Diclofenac	0.995	31–8000	31	9	63	19	109 ± 24	22.0	9.1	63	19	112 ± 26	23.1	8.7
Diglyme	0.998	63–4000	63	19	50	15	86 ± 3	3.9	1.6	50	15	86 ± 5	5.7	1.7
Diuron	0.997	31–4000	31	9	31	9	99 ± 6	5.9	1.5	31	9	104 ± 2	19.0	8.2
HFPO-DA	0.998	31–16000	31	9	59	19	89 ± 15	17.2	4.7	59	19	92 ± 10	11.0	4.5
Ibuprofen	0.997	63–4000	63	19	63	19	104 ± 12	11.5	4.2	125	38	112 ± 11	10.1	3.9
Paracetamol	0.997	63–4000	63	19	63	19	93 ± 12	13.1	4.9	63	19	87 ± 12	13.5	4.7
PFBA	0.998	125–8000	125	38	133	9	79 ± 47	59.1	31.5	127	9	107 ± 57	53.6	27.7
PFOA	0.997	31–4000	31	9	56	19	106 ± 17	16.3	7.0	59	19	111 ± 12	10.8	4.3
Phenyl urea	0.999	63–4000	63	19	63	19	81 ± 31	38.2	16.8	63	19	92 ± 15	16.7	7.1
Saccharin	0.997	31–4000	31	9	21	9	90 ± 4	4.9	2.0	24	9	95 ± 6	6.5	2.8
Sulfamethazine	0.997	31–4000	31	9	31	9	91 ± 25	27.9	8.4	31	9	100 ± 25	24.8	6.5
Sulfamethoxazole	0.995	31–4000	31	9	31	9	90 ± 6	7.0	2.6	31	9	94 ± 5	5.8	2.3
Tetrabutylammonium	0.996	31–4000	31	9	31	9	95 ± 10	10.2	4.2	31	9	104 ± 19	18.2	7.6
Triethyl phosphate	0.996	31–4000	31	9	31	9	93 ± 13	14.2	5.9	31	9	97 ± 9	9.1	3.5
Tetrapropylammonium	0.994	31–4000	31	9	31	9	103 ± 12	11.9	4.6	31	9	111 ± 10	9.0	1.5
Triclosan	0.999	125–8000	125	38	n/a	n/a	n/a	n/a	n/a	125	38	155 ± 31	20.0	5.5

ratios is shown in table S-6 of the supplementary material. EICs of all target analytes and isotope-labeled compounds from injection of a standard are given in section S-7 of the Supplementary material. A 7-min chromatographic run with the resolving power of our HRMS detector was sufficient to obtain satisfactory separation. Acesulfame and triclosan were the earliest and latest eluting compounds and displayed a retention time of 2.9 and 6.3 min, respectively. This was in accordance with the retention-elution mechanism in reversed-phase chromatography, with acesulfame being the most hydrophilic compound with a log K_{ow} of −1.33, and triclosan the least polar with a log K_{ow} of 4.76. Indications about the dead volume were obtained from the retention time of metformin, which was 0.9 min. Isomer separation was satisfactory for the hydroxyquinolines and phthalic and isophthalic acid, whereas the 4- and 5-methyl-1H-benzotriazole could not be separated. Following this finding, only the 4-methyl-1H-benzotriazole was included in the working spike mixture used throughout this study. In the result section this compound is referred to as tolyltriazole and its concentration is the sum of the concentrations of both isomers. Good MS/MS data were obtained for all analytes except bisphenol A, diglyme and triclosan which showed no significant fragmentation in the working concentration range. Inspection of full-scan HRMS data revealed distinct adducts for bisphenol A and diglyme, i.e. $[M−H+CH_3COOH]^-$ and $[M+NH_4]^+$, respectively. These were used as qualifier ions along with the ^{37}Cl isotopic peak for triclosan. For HFPO-DA, instead, complete in-source fragmentation could be observed, with little to no detection of the $[M−H]^-$, therefore the $[M−C_3F_4O_3H]^-$ fragment, which displayed the highest signal intensity in full-scan HRMS data, was used as quantifier ion. As expected in HRMS analysis, satisfactory selectivity could be achieved for MS and MS/MS ions. Calibration curves obtained from at least six spiked concentrations in ultrapure water showed good linearity (expressed as r-squared values greater than 0.99) except for phthalic acid and isophthalic acid, for which linearity in the working concentration range could not be achieved. These compounds, although detectable, were not carried further on with the validation process. The dynamic range from IQL to highest calibration standard covered three orders of magnitude in signal intensity units to the higher end. Detector saturation could be observed following injection of a few hundreds of picograms on column for most analytes. Satisfactory linearity and qualifier ion ratios across the inspected calibration levels resulted in IQLs ranging from 31.2 to 125 ng/L and IDLs between 9 and 38 ng/L.

3.1. Direct injection validation results

The performance parameters assessed for validation of the direct injection method are summarized in Table 1.

In RBF 29 targets displayed recoveries values between 78% and 110%, 24 of which had RSD below 20% and 10% for intra-day and inter-day precision, respectively. In surface water 31 compounds were recovered from 76% to 123%, 27 of which had RSD values equal or lower than 20% and 10% for intra-day and inter-day precision, respectively. The lowest recoveries were observed for 2-hydroxyquinoline in RBF and surface water (61 ± 10% and 63 ± 6%) and barbital in RBF (66 ± 8%). The MQLs provided by the direct injection method in RBF ranged from 21 to 276 ng/L, whereas in surface water the range was 31 to 308 ng/L in surface water. For both matrices the median MQL value was 61 ng/L. An example of detection at MQL is given in Fig. 1.
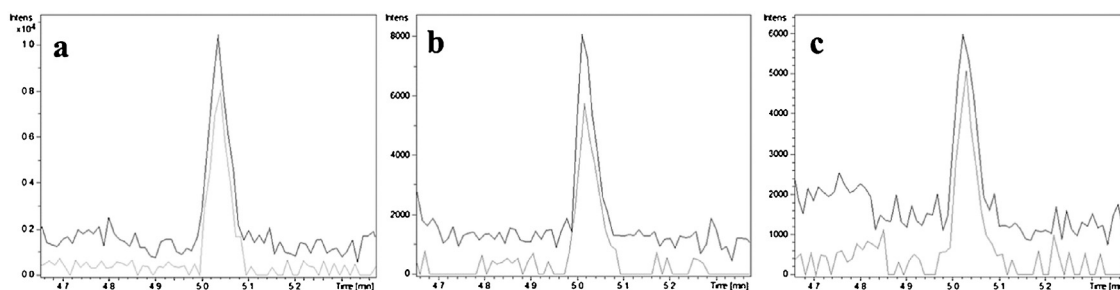
Fig. 1. EICs of 2-hydroxyquinoline (146.0600 ± 0.002, black signal) and its qualifier ion (128.0479 ± 0.002, grey signal) in ultrapure water (a), riverbank filtrate (b) and surface water (c) spiked at 31.25 ng/L.

The quantitative performance of the direct injection method was compared with that of other methods relying on HPLC coupled to low-resolution MS, for long regarded as the gold standard of quantitation. Hermes et al. published a multi-residue method for direct injection analysis of surface water and bank filtrate with hyphenated triple quadrupole (QqQ) MS sharing 13 analytes with our own target list [31]. The MQLs of these analytes ranged from 0.5 to 90 ng/L and from 1 to 75 ng/L in bank filtrate and surface water, respectively. In terms of reported MQLs, our methodology resulted in lower values for 1H-benzotriazole in both matrices. In bank filtrate we obtained comparable MQLs for 3 analytes (ibuprofen, saccharin and sulfamethoxazole) and higher MQLs for 9 analytes (acesulfame, caffeine, carbamazepine, DEET, diclofenac, diuron, tetrabutylammonium, tetrapropylammonium and triclosan). In surface water the MQLs obtained in the present study were comparable for 5 analytes (1H-benzotriazole, caffeine, ibuprofen, saccharin and sulfamethoxazole) and between 5 to 30 times higher than the reported values for 7 analytes (carbamazepine, DEET, diclofenac, diuron, tetrabutylammonium, tetrapropylammonium and triclosan). In another study UHPLC coupled to hybrid QqQ-MS provided better quantification limits for carbamazepine, diclofenac, paracetamol and sulfamethoxazole (0.2–6.8 ng/L) by injecting 100 μL of surface water [32]. For caffeine in surface water, the MQL obtained in our study were lower than those achieved with hybrid QqQ-MS by one order of magnitude [33]. Analogously, the MQLs achieved for atrazine in surface water and groundwater by direct injection with hyphenated QqQ-MS were higher than the MQLs validated in our study by a factor of 3 [34]. UHPLC coupled to quadrupole-linear ion trap MS was used to validate the direct injection analysis of pesticides and organic contaminant in treated wastewater [35]. Compared to our study, the MQLs were higher for diuron, comparable for 6 analytes (antipyrine, DEET, paracetamol, saccharin, sulfamethazine and sulfamethoxazole) and at least a factor of 5 lower for 4 analytes (acesulfame, atrazine, caffeine, carbamazepine).

Overall the MQLs achieved in the present study ranged from comparable to higher by one order of magnitude than those achieved by (hybrid) triple quadrupole MS and were comparable to quadrupole-linear ion trap MS. In a few instances lower MQLs than those found in scientific literature were obtained in the present study.

3.2. SPE validation results

The performance parameters and results of the validation of the SPE procedure are summarized in Table 2. In the development phase we observed poor recoveries and precision for acesulfame and PFBA (data not shown). These compounds were consequently excluded from the validation process. HFPO-DA and saccharin were not considered for SPE as they were added to the target list at a later stage. The majority of the remaining compounds used for
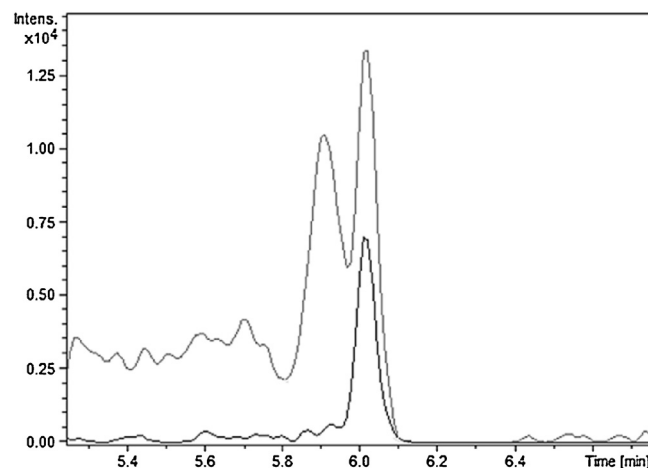

Fig. 2. EICs of ibuprofen (grey) m/z 205.1234 ± 0.002 and its bbCID MS/MS fragment m/z 161.1330 ± 0.005 (black) in a RBF sample spiked to 50 ng/L and extracted with SPE. The quasi-isobaric interference in the full-scan data can be seen at t_R 5.9 min.

SPE validation displayed good recoveries in the investigated matrices. In RBF recoveries within 78% and 114% were obtained for 24 analytes, 21 of which displayed satisfactory RSD for both intraday and interday precision. In RO permeate 26 targets had recoveries between 79% and 122% with RSD lower than 20% and 10% for intraday and inter-day precision, respectively. The lowest recoveries were observed for barbital (9 ± 2%), bentazon (15 ± 1%) and diglyme (46 ± 20%) in RBF, whereas in RO permeate the lowest recovery was observed for 2-hydroxyquinoline (66 ± 9%). The procedure could not be validated for bisphenol A in RBF due to large standard deviation of the recovery values. This resulted from high background concentrations in one of the two batches processed for validation. For ibuprofen in RBF, a quasi isobaric interference could be detected in full scan HRMS data within a mass deviation tolerance of 2 mDa or 5 ppm with a resolution of 30,000 FWHM. The chromatograms are shown in Fig. 2. Due to this interference, ibuprofen was quantified in all samples by setting the bbCID MS/MS ion as quantifier and the deprotonated adduct as qualifier. This approach didn't result in changes in the MQLs of ibuprofen as both full-scan and bbCID MS/MS ions displayed good linearity from 62.5 ng/L onwards. Overall the recoveries observed in both matrices were quite satisfactory, with the most accurate and precise parameters being obtained for the RO permeate. This could be expected given the much simpler matrix of RO permeate compared to the raw RBF.

3.3. Analysis of non-spiked field samples

The direct injection method was applied to screen river Lek water and RBF originated from the river Oude Rijn. This bank filtrate was also the feed water of an experimental RO-DWTP. The

Table 2
Solid-phase extraction method performance for riverbank filtrate and RO permeate (n = 4).

	Riverbank filtrate					RO permeate				
				Precision					Precision	
	MQL ng/L	MDL ng/L	Recovery % ± SD	Intraday RSD (%)	Interday RSD (%)	MQL ng/L	MDL ng/L	Recovery % ± SD	Intraday RSD (%)	Interday RSD (%)
1H-benzotriazole	0.74	0.23	96 ± 5	9.6	2.6	0.67	0.20	87 ± 4	10.2	2.3
2-(methylamino)pyridine	0.53	0.16	68 ± 16	12.6	10.5	0.52	0.16	67 ± 20	17.3	13.7
2-hydroxyquinoline	0.84	0.25	108 ± 5	4.2	2.1	0.51	0.16	66 ± 9	28.4	8.1
4- hydroxyquinoline	0.88	0.27	114 ± 10	7.0	3.8	0.77	0.23	99 ± 7	9.7	3.6
Tolyltriazole	0.80	0.24	103 ± 7	9.4	3.1	0.80	0.24	103 ± 6	9.6	2.7
6- hydroxyquinoline	0.86	0.26	111 ± 6	4.8	2.6	0.71	0.21	91 ± 7	6.8	3.7
Antipyrine	0.98	0.30	126 ± 9	11.4	3.4	0.80	0.24	103 ± 4	5.2	1.7
Atrazine	0.78	0.23	100 ± 6	5.2	2.8	0.73	0.22	94 ± 11	7.7	5.4
BAM	1.42	0.43	90 ± 4	8.1	2.0	1.46	0.44	93 ± 7	11.4	3.7
Barbital	0.14	0.04	9 ± 2	41.1	14.4	1.87	0.57	119 ± 4	4.4	1.6
Bentazon	0.12	0.04	15 ± 1	4.5	2.8	0.76	0.23	98 ± 9	3.1	3.9
Bisphenol A	2.59	0.79	83 ± 86	71.1	61.1	2.84	0.86	91 ± 7	12.3	4.0
Caffeine	1.35	0.41	86 ± 8	8.9	4.1	0.13	0.04	86 ± 9	9.4	5.0
Carbamazepine	1.50	0.45	95 ± 16	10.2	7.7	1.46	0.44	93 ± 11	7.9	5.1
Chloridazon	0.88	0.27	114 ± 5	2.9	2.1	0.75	0.23	97 ± 11	11.3	5.4
DEET	0.65	0.20	84 ± 6	7.3	3.4	0.61	0.19	79 ± 8	9.9	4.7
Diclofenac	0.67	0.20	86 ± 2	4.2	0.9	0.71	0.22	92 ± 5	5.3	2.6
Diglyme	0.72	0.22	46 ± 20	18.0	20.0	1.28	0.39	81 ± 7	20.1	5.2
Diuron	0.86	0.26	111 ± 6	3.4	2.6	0.74	0.23	96 ± 8	7.2	3.7
Ibuprofen	1.84	0.56	117 ± 27	9.0	10.3	1.46	0.44	93 ± 5	10.5	2.7
Paracetamol	1.53	0.46	97 ± 7	5.3	3.2	1.43	0.43	91 ± 5	10.5	2.6
PFOA	0.66	0.20	85 ± 20	14.5	10.8	0.87	0.26	112 ± 4	2.0	1.6
Phenyl urea	1.23	0.37	78 ± 6	10.0	3.4	1.50	0.45	95 ± 19	14.4	9.2
Sulfamethazine	0.79	0.24	102 ± 7	3.5	3.0	0.75	0.23	97 ± 11	9.0	5.4
Sulfamethoxazole	0.74	0.22	95 ± 4	6.0	2.0	0.81	0.24	104 ± 12	6.1	5.3
Tetrabutylammonium	0.80	0.24	103 ± 11	12.0	4.9	0.76	0.23	98 ± 9	17.2	5.0
Triethyl phosphate	0.61	0.19	79 ± 12	17.1	7.3	0.66	0.20	85 ± 5	8.3	2.9
Tetrapropylammonium	0.88	0.27	114 ± 12	6.4	4.6	0.76	0.23	98 ± 16	13.1	7.6
Triclosan	3.16	0.96	101 ± 14	6.4	4.5	3.81	1.16	122 ± 8	15.0	3.5

Table 3
Target screening results (n = 4).

	Direct injection		Solid-phase extraction	
	[a]SW ng/L	[b]RBF ng/L	[b]RBF ng/L	[c]ROP ng/L
1H-benzotriazole	73 ± 3[*]	n.d.	n.d.	n.d.
2-hydroxyquinoline	n.d.	n.d.	<MQL	n.d.
Tolyltriazole	68 ± 4[*]	n.d.	n.d.	n.d.
Acesulfame	1072 ± 17	n.d.	n.d.	n.d.
Antipyrine	<MQL	<MQL[**]	57 ± 1	n.d.
BAM	n.d.	n.d.	39 ± 2	n.d.
Bentazon	<MQL	<MQL	28 ± 1	n.d.
Carbamazepine	83 ± 4[*]	n.d.	n.d.	n.d.
Chloridazon	85 ± 7[*]	n.d.	6 ± 1	n.d.
DEET	< MQL	n.d.	n.d.	n.d.
Diglyme	< MQL	< MQL	22 ± 2	3.6 ± 0.2
HFPO-DA	70 ± 4	n.d.	n.d.	n.d.
PFBA	< MQL	n.d.	n.d.	n.d.
PFOA	n.d.	n.d.	9 ± 1	n.d.
Saccharin	n.d.	28 ± 5	n.d.	n.d.
Sulfamethazine	n.d.	n.d.	8 ± 1	n.d.
Triethyl phosphate	n.d.	n.d.	16 ± 2	n.d.

n.d.: not detected.
MQL: Method quantification limit, given in Tables 1 and 2 for direct injection and solid-phase extraction methods, respectively.
<MQL indicates that a peak was detected but the quantification was considered unreliable.

[a] Surface water.
[b] Riverbank filtrate.
[c] RO permeate.
[*] n = 3.
[**] Quantifiable in one replicate.

SPE procedure was applied to RBF and RO permeate samples. The results are shown in Table 3. Only those analytes are shown that were detected or quantified in at least one of the screened matrices. EICs of the target analytes detected and quantified in RBF and RO permeate are given in the Supplementary material (section S-8).
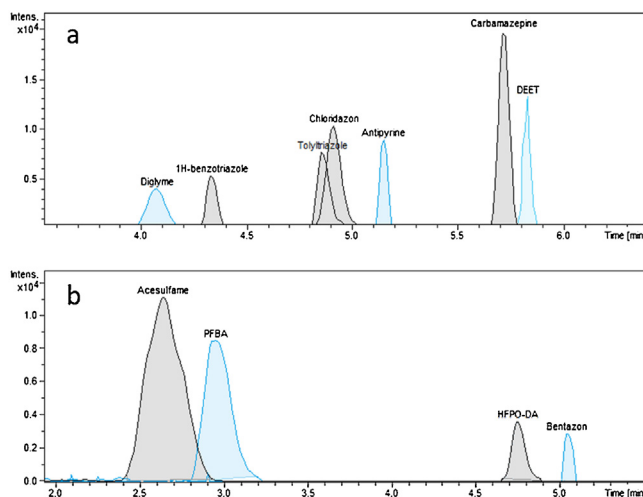
Fig. 3. Overlaid EICs of target analytes that could be quantified (grey) and those that were detected, albeit at concentrations below MQLs (blue) in non-spiked surface water samples analyzed in positive ESI mode (a) and negative ESI mode (b). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Screening river Lek samples by direct injection analysis led to the detection of antipyrine, bentazon, DEET, diglyme and PFBA, whereas 1H-benzotriazole, acesulfame, carbamazepine, chloridazon, HFPO-DA and tolyltriazole were quantified at concentrations between 68 ng/L (tolyltriazole) and 1 μg/L (acesulfame). EICs of the target analytes detected and quantified in surface water are shown in Fig. 3.

These findings are in reasonable to good agreement with scientific literature data. The anticorrosive agents 1H-benzotriazole and tolyltriazole have been detected and quantified in surface water

from the same area at higher concentration [16,36]. In accordance with recent literature data [37], we quantified HFPO-DA in the river Lek at 70 ± 4 ng/L. However, Gebbink et al. reported up to 433 ng/L about 30 km downstream, near an emission source. Tidal movement has been shown to occur up to the river Lek sampling point and may explain the levels of HFPO-DA observed in the present study [38]. Based on the identities of the MPs detected in surface water, the main emission pathways could be identified as (i) industrial wastewater treatment plants effluents and (ii) agricultural and livestock farming runoffs. Direct injection analysis of RBF samples led to the detection of antipyrine, bentazon, diglyme and triethyl phosphate at concentrations below MQL, whereas saccharin could be quantified at 28 ± 5 ng/L. The SPE procedure applied to the RBF samples resulted in the quantification of the analytes previously detected by direct injection analysis at concentrations from 6 ± 1 to 57 ± 1 ng/L. Additionally, BAM, chloridazon, diglyme, PFOA and sulfamethazine were also quantified after SPE within this concentration range and only 2-hydroxyquinoline was detected below MQL. The SPE method allowed the quantification of BAM in RBF at concentrations equal to MDL with direct injection, but the analyte could not be detected when RBF was directly injected. This could be explained by the effects of pre-concentration and clean-up resulting from the SPE procedure and by matrix ion suppression in direct injection analysis. BAM was not detectable in RBF spiked to 31 ng/L and directly injected for the validation study. The artificial sweetener saccharin, despite being quantified by the direct injection method, was not detected in the SPE extract. This compound is structurally related to acesulfame, which was excluded from the SPE protocol validation due to poor recoveries observed in the early development phase. These anionic analytes are likely not retained by the HLB sorbent at the conditions resulting from our extraction protocol. Dedicated SPE methods to improve the recovery values of acesulfame and saccharin with HLB sorbent can be found in the scientific literature [39,40]. The compounds detected in RBF were mostly small neutral hydrophilic and anionic MPs. In a recent publication about groundwater quality, antipyrine, bentazon and triethyl phosphate were found in riverbank filtrate from rural areas significantly more than in other groundwater types [41], thus supporting our findings. The other quantified targets, i.e. BAM [42], sulfamethazine [42,43] and the perfluorinated surfactant PFOA [44] were also in line with scientific literature in terms of water matrix occurrence and concentrations. The absence of cationic MPs in RBF might be explained by electrostatic sorption onto soils and natural organic matter [45,46]. Based on the identity of the MPs detected in the bank filtrate, possible sources of pollution could be (i) runoffs from agricultural and livestock farming sites, e.g. in the case of antipyrine, an antipyretic drug for veterinary use, the herbicide bentazon, the sweetener saccharin which is also used as livestock feed additive [47], the pesticide metabolite BAM, and the veterinary antibiotic sulfamethazine; (ii) industrial wastewater effluents, e.g. diglyme and triethyl phosphate; (iii) urban wastewater effluents, e.g. acesulfame. Diglyme was the only compound detected and quantified in RBF and RO permeate produced from it. RO membranes have been reported to effectively reject uncharged polar organics of molecular weight equal to or larger than 150 Da [48,49] and anionic MPs almost completely [47]. Therefore, for most compounds concentrations in the permeate might not be detectable even after SPE.

4. Conclusion

A UHPLC-q-ToF/MS system was used to validate a direct injection analysis method followed by semi-automated data treatment for the detection and quantitation of polar MPs in natural drinking water sources. The application of the direct injection method to environmental samples confirmed the presence of herbicides, sweeteners, pharmaceutically active compounds, anticorrosive agents and industrial chemicals in surface water and to a lesser extent in a RBF fed to a full-scale RO treatment plant. Analytes enrichment via a validated SPE protocol led to detection of further MPs and quantification of those previously detected by the direct injection method. These MPs were screened in RO permeate and not detected except for diglyme, whose concentration was 3.6 ng/L. For RBF, the validated methods should be complementarily applied to guarantee detection of more polar MPs not enriched by SPE, as shown by the case of acesulfame, PFBA and saccharin. Combining the detecting performance of ESI-q-ToF/MS with the efficiency of UHPLC separation and semi-automated data processing resulted in a fast, accurate, and robust analysis method suitable to monitor diverse polar contaminants in natural waters at environmentally relevant concentrations. The SPE method was suitable to further lower the detection limits of MPs in RBF and RO permeate by a factor of 40. The ability of the biphenyl stationary phase to exhibit good chromatographic resolution for analytes of different classes, polarity and structures, suggests its suitability for a larger number of compounds, e.g. analogues and metabolites. Furthermore, the core-shell biphenyl column should be compatible with HPLC applications given its sub-3 μm particle size and the subsequently generated backpressure [26]. The database of target compounds is *per se* extendable and could be used for suspect screening also in a retrospective way, for instance by incorporating accurate mass MS and MS/MS data of analytes of interest from open spectral libraries such as the MassBank [50]. Although our screening method relied on semi-automated data processing with vendor software, open-source alternatives exist, e.g. *enviMass* [51], and should be considered.

Declarations of interest

None.

Acknowledgments

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.chroma.2018.07.036.

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