Analytical Chemistry

Development and validation of an analytical method for detection and quantification of benzophenone, bisphenol A, diethyl phthalate and 4-nonylphenol by UPLC-MS/MS in surface water

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ABSTRACT

Guandu River is the main water source for 9 million inhabitants in Rio de Janeiro city and some others included in the metropolitan region of the Rio de Janeiro State, Brazil. Here, the development of a chromatographic method and its application to assess the occurrence of 4-nonylphenol (4NP), benzophenone (BP), bisphenol A (BPA) and diethyl-phthalate (DEP), known as endocrine disruptors (EDs), is reported. Sample were prepared by solid phase extraction (SPE) with C18 cartridge and methanol as elution solvent. Validation of analytical method followed the United States Environmental Protection Agency protocol (USEPA 8000D guide) and selectivity, matrix effect, linearity, precision, accuracy, robustness, limit of detection (LOD) and limit of quantification (LOQ) were evaluated. The recovery was greater than 90%, accuracy was found between 80% and 115% and relative standard deviation (RSD) below 11.03%. LOQ ranged from 10.0 to 50.0 ng L^{-1}, while the LOD ranged from 0.87 to 5.72 ng L^{-1}. The coefficients of determination (R^2) were greater than 0.99 for all compounds within a linear ranges of 10.0 to 500 ng L^{-1} for 4NP and BP and 50.0 to 500 ng L^{-1} for BPA and DEP. The method was therefore considered selective and robust for all micropollutants. Matrix effect was observed for BP, 4NP and DEP. The developed method was applied to analyze five samples collected monthly during 2018 at a selected sampling point of a river in Rio de Janeiro State. The maximum concentrations found for BPA, BP, DEP and 4NP were 182.04, 286.20, 2.56×10^3 and 13.48 ng L^{-1} respectively. These values are high enough to justify an investigation on the presence of these micropollutants in drinking water as well as to extend the monitoring for the search of similar pollutants and their metabolites.

INTRODUCTION

The availability of water resources in the world is gaining increasing attention. It is frequently associated to climatic factors (drought, climate changes), as well as by the increasing demand for clean water (due to the intense population growth) and decreasing quality. The latter is a direct consequence of the pollution promoted by domestic, rural and industrial activities. Approximately half of the world's population currently suffers from moderate and 10% from extreme water scarcity (*Banjac et al., 2015*; *Estrada-Arriaga et al., 2016*; *Johnson et al., 2016*; *Cunha, Araujo & Marques, 2017*; *De Araujo, Bauerfeldt & Cid, 2017*; *De Araujo et al., 2019*).

Concerns about exposure to the endocrine disruptors (EDs) micropollutants have been increasing over the years due to the possible damage that can be caused to exposed organisms. (*Meyer, Sarcinelli & Moreira, 1999*; *Bila & Dezotti, 2007*; *Cirja et al., 2008*; *Vela-Soria et al., 2014*; *Rodríguez-Gómez et al., 2015*; *Caldas et al., 2016*;*Vela-Soria et al., 2014*; *Starling, Amorim & Leão, 2019*). According to the United States Environmental Protection Agency (USEPA), an ED is "an exogenous agent that interferes with the synthesis, secretion, transport, metabolism, binding or elimination of the body's natural hormones, which are responsible for homeostasis, reproduction, development and/or behavior'' (*Bila et al., 2007*; *Camilleri et al., 2015*; *Kabir, Rahman & Rahman, 2015*).

The disruption of endocrine functions may be associated with interference in the synthesis, secretion, transport, binding, action or elimination of the natural hormones of organisms, thus triggering a new hormonal response. By mimicking the action of an endocrine hormone, a substance exaggerates or improperly triggers a false stimulus, causing a damage to the exposed organisms even at low concentrations (*Bila & Dezotti, 2007*; *Castro-Correia & Fontoura, 2015*, *Rodríguez-Gómez et al., 2015*).

The main sources of EDs in water bodies are punctual (such as domestic and industrial effluents) or diffuse (such as pesticides from agricultural areas). Several investigations report the recalcitrance of many of these compounds to degradation in wastewater treatment plants and in treatability studies. Due to the ineffectiveness of most wastewater treatment systems, micropollutants in the effluents are discharged into the receiving water bodies, in concentration levels which are high enough to cause chronic toxicity or to trigger an endocrine reactions (*Funasa, 2014*; *Camilleri et al., 2015*; *Castro-Correia & Fontoura, 2015*; *Dias et al., 2015*). Some EDs, such as bisphenol A (BPA), 4-nonylphenol (4NP), benzophenone (BP) and phthalates, such as diethylphthalate (DEP), have attracted the attention of the scientific community due to the frequent detection and quantification of these analytes in water samples, for example in raw sewers or treated waters. 4NP is a byproduct from the biological degradation of alkylphenol polyethoxylates, widely used as nonionic surfactants in household cleaning products (*Moreira et al., 2011*; *De Araujo, Bauerfeldt & Cid, 2017*). DEP is a synthetic substance used as an ingredient in cosmetic formulation and to increase the flexibility of plastic materials used in the manufacture of toys, household items, auto parts and others (*Viecelli et al., 2011*; *Farajzadeh & Mogaddam, 2012a*; *Farajzadeh & Mogaddam, 2012b*). BPA is a degradation product of some polymers, such as polycarbonates and epoxide resins, and is used as an antioxidant in polyvinyl

chloride (PVC) plastics (*Chen et al., 2011*; *Doerge et al., 2011*; *Bomfim et al., 2015*). Finally, BP is commonly found in UV filter formulations despite its well-known disruptive endocrine activity proved by in vivo and in vitro assays assays (*Vela-Soria et al., 2014*; *Wang et al., 2017*).

For a quantitative assessment of the quality of surface water concerning the concentration levels of these EDs, accurate analytical methods are required. (*Giesy et al., 2002*; *Silveira et al., 2013*; *Arbeláez et al., 2015*; *Caldas et al., 2016*; *Starling, Amorim & Leão, 2019*). Preparation of water surface water samples, prior to the analytical determination of these four EDs, is required and solid phase extraction (SPE) is the most applied method. However, liquid–liquid Extraction (LLE), solid phase micro extraction (SPME), dispersive liquid–liquid microextraction (DLLME), SPE online, stir bar sorptive extraction (SBSE) are often reported (*Farajzadeh & Mogaddam, 2012a*; *Farajzadeh & Mogaddam, 2012b*; *Zaater, Tahboub & Sayyed, 2014*; *Selvaraj et al., 2014*; *Wu et al., 2015*; *Caballero-Casero, Lunar & Rubio, 2016*; *Olatunji et al., 2017*; *Rozaini et al., 2017*; *De Araujo, Bauerfeldt & Cid, 2018*; *Barreca et al., 2019*; *He & Aga, 2019*; *Król & Dudziak, 2019*). The quantitative analysis is frequently performed by the liquid chromatography coupled to mass spectrometry (LC-MS/MS) and gas chromatography coupled to mass spectrometry (CG-MS) techniques, although other detectors of other kinds coupled to the liquid chromatography are used, such as liquid chromatography with ultraviolet detection (LC-UV), liquid chromatography with diode array detection (LC-DAD) and liquid chromatography with fluorescence detector (LC-FLD) (*Zgoła-Grześkowiak et al., 2009*; *Chen et al., 2010*; *Lou et al., 2012*; *Ciofi et al., 2014*; *Padhye et al., 2014*; *Camilleri et al., 2015*; *Terzopoulou, Voutsa & Kaklamanos, 2015*;, *Asati, Satyanarayana & Patel, 2017*; *Comtois-Marotte et al., 2017*; *De Araujo, Bauerfeldt & Cid, 2018*. The realization that conventional water and sewage treatment systems do not completely remove most of these micropollutants opens a discussion of a possible worrisome public health problem, since micropollutants may be present in the water supply (*Matsuo et al., 2011*; *Moreira et al., 2011*; *Silveira et al., 2013*; *Tran, Hu & Ong, 2013*; *Dai et al., 2014*; *Mann et al., 2016*; *Valls-Cantenys et al., 2016*; *Tröger et al., 2018*; *Starling, Amorim & Leão, 2019*).

The Guandu river basin is the key source of water supply for approximately 9 million inhabitants in the metropolitan region of Rio de Janeiro State (*Cetesb, 2011*). In the basin, Guandu river is the most important component. Rio dos Poços, Queimados, Macaco, Ribeirão das Lajes rivers, among others, are also part of the Guandu basin. Pollution of these rivers is potentialized by the discharge of untreated (or only partially treated) urban and industrial effluents. The runoff from agricultural areas also contributes to pollution of the Guandu river basin. A large part of the sewage discharged into the tributaries of the basin has the water damming area for collection and subsequent treatment and distribution. Thus, the studied site (dam to collect water for supply), is characterized by being a region with a complex matrix, due to the amount of untreated sewage that is discharged in the region.

Previous investigations concerning the Guandu basin waters revealed the presence of three psychoactive drugs (bromazepam, clonazepam and diazepam) in most samples (*De Araujo et al., 2019*) and the presence of 4NP in relatively high concentrations (*De Araujo,*

Bauerfeldt & Cid, 2018). The need for the development of a new analytical methodology arises due to the complexity of the matrix as described above and also by the scarcity of previously published works concerning this site. Another investigation (*Dias et al., 2015*) revealed that 20–50% of the Guandu river water samples presented estrogenic activity expressed as 17β-estradiol (E2) equivalents or E2-EQ. Additionally, after treating the water in a conventional water treatment plant, estrogenic activity was still found in 8% of the water samples in levels higher than the reference established by the authors as 1 ng L^{-1} E2-EQ. These findings strongly indicate the importance of developing proper analytical methods for the determination of EDs, particularly for monitoring of the Guandu river, which is of high relevance in terms of water supply and receives heavy discharge of treated and untreated urban sewage and industrial effluents.

Therefore, the objective of the present study is to develop and validate an analytical method based on LC-MS/MS to determine four EDs: BP, BPA, DEP and 4NP in the Guandu river basin, Rio de Janeiro State, Brazil.

MATERIALS & METHODS

Chemical and reagents

BP, BPA, DEP and 4NP, with 99% purity, were purchased from Sigma-Aldrich (St. Louis, USA). Methanol, acetonitrile (LC–MS grade) and ammonium hydroxide (28.0–30.0%) were purchased from J.T. Baker® (Phillipsburg, USA). Ultrapure water was obtained from a Milli-Q Direct 8 (Millipore®). SPE cartridges were used to promote the clean-up and pre-concentration of the analytes in the preparation of real samples. The SPE cartridges Bond Elut C18® (500 mg/3 mL) were purchase from Las do Brasil (Brazil).

Instrumentation and software

Analyses were performed using an ultra-performance liquid chromatography (UPLC-MS/MS) (Waters Milford, MA, USA) equipped with an Acquity UPLC binary pump liquid chromatograph with a Xevo TQD MS/MS triple quadrupole detector, autosampler and column temperature controller. Details on the chromatographic method are described elsewhere (*De Araujo et al., 2019*).

Electrospray ionizations in positive and negative modes (ESI+ and ESI- respectively) were used as ionization source. The drying gas, as well as the nebulizing gas, was nitrogen generated by pressurized air in a Nitrogen Generator Genious NM32LA (Peak, USA). The nebulizing gas flow was 50 L h^{-1} whereas the desolvation gas flow was 1100 L h^{-1}.

To operate in the MS/MS mode, the collision gas was argon 99.99% (Air Products, Brazil) in the collision cell. The optimized values were as follows: capillary voltage 3.2 kV; source temperature 150 °C; desolvation temperature 600 °C. For quantification and identification, the best collision energies were optimized to promote more intense signals used in multiple reaction monitoring (MRM) mode. Thus, two transitions were selected: one transition with the highest signal intensity was selected for quantification and another transition, with the lower signal intensity, for identification. Table 1 shows the optimized MRM transitions for the EDs with their respective retention times (Tret). The software

Table 1 Endocrine disruptor class, log Kow and UPLC-MS/MS parameters.

Analyte	Class	Log K_{ow}[a]	Tret (min)	Ionization	Transitions MRM, *m/z* (CE[b], eV)	
					Quantification	**Identification**
BP	PCP[c]	3.18	4.01	Positive	316 > 105 (15)	316 > 77 (30)
BPA	Plasticizer	3.22	3.77	Negative	227 > 212 (18)	227 > 133 (25)
DEP	Plasticizer	2.42	3.81	Negative	223 > 149 (20)	223 > 177 (10)
4NP	Surfactants	5.76	5.05	Negative	219 > 106 (21)	219 > 119 (34)

Notes.
[a]http://www.chemspider.com.
[b]CE, collision energy.
[c]Personal care product.

MassLynx (Waters, USA), version 4.1, performed analytical instrument control, data acquisition and treatment.

Preparation of the laboratory matrix control sample

A composite sample (control sample) was prepared in order to gather all possible interferents and matrix effect that we should find in real samples collected. Surface water samples were collected at four different locations along the Guandu River: Paracambi (PBI; −22.663144; −43.742502), Seropédica (SER; −22.806417; −43.626079), Nova Iguaçu (NIG; −22.817486; −43.624333) and Rio de Janeiro (RIO; −22.897108; −43.734804) in order to gather all possible interferents and matrix effect that we should find in real samples collected. The sites are characterized by rural, industrial and high population density areas. This composite control sample was prepared by filtration on glass fiber filter (1.00 μm pores size) followed by the SPE procedure. The target analytes were not detected, in comparison to the non-spiked matrix (sample control) and spiked matrix (sample control spiked with limit of quantification (LOQ) values for each analyte). Thus, the composite sample has been adopted as the matrix control for the validation and sample preparation tests.

Sample preparation

The sample preparation procedure, previously developed in our laboratory (de (*De Araujo, Bauerfeldt & Cid, 2018*), was applied aiming at the extraction, cleaning and concentration of EDs and optimized in order to achieve its best performance concerning the recovery of BP, BPA and DEP and also the necessity of promoting greater concentration factor thus, obtaining lower limits of quantification and detection (at the ng L^{-1} level, for environmental monitoring purposes). Different sample volumes (250, 500 and 1,000 mL) were evaluated. During these tests, the maximum load the cartridge was capable of adsorbing was evaluated. Each test was carried out in triplicate. Three solutions were prepared by spiking of the BP, BPA, DEP and 4NP standards to the matrix control sample at the same concentration level of 25.0 μg L^{-1} but with different volumes. Thus, each solution percolated by the cartridge had a different analyte mass (6.25 μg, 12.5 μg and 25.0 μg). After percolation, an aliquot of the eluate was taken and injected into the UPLC-MS/MS and the presence or absence of signals was verified, allowing to conclude whether the analytes were completely adsorbed by cartridge. Tests for other elution volumes and two-step elution with the same final

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volume also performed. Each test was carried out in triplicate. In all tests the cartridge was conditioned with 5.00 mL of methanol followed by 5.00 mL of ultrapure water.

Method validation

All validation experiments were performed according to the USEPA 8000D guidelines (*Usepa, 2018*). The parameters selectivity, precision (relative standard deviation - % RSD), accuracy, LOQ, limit of detection (LOD), linearity, matrix effect and robustness were evaluated as previously described (*De Araujo et al., 2019*).

Spiked matrix control samples were prepared, using of the filtered composite control sample, at concentration levels of 50.0 ng L^{-1} (low), 250 ng L^{-1} (medium) and 500 ng L^{-1} (high) in two days (intra-day 1 and 2) and submitted to SPE procedure. The precision and accuracy of the analytical method were determined by analyzing sets of 5 replicates of the spiked matrix control samples. The extracts were injected in triplicate in the UPLC-MS/MS. The precision of the method was evaluated in terms of the % RSD. Accuracy was calculated by comparing the measured concentration with the nominal concentration as the mean recovery percent (%).

The LOQ is defined for each analyte as the lowest concentration level that can be quantified with RSD <20% and accuracy found within the range from 70–130%. The LOD for the 4NP, was calculated according to (*Shrivastava & Gupta, 2011*), while for the BPA, BP and DEP, the LOD were calculated based on the standard deviation of the blanks replicates, according to (*Usepa, 2014*).

Six-point analytical curves were obtained by analysis of spiked matrix control samples at concentration levels between 50.0 to 500 ng L^{-1} for BPA and DEP and 10.0 to 500 ng L^{-1} for BP and 4NP. All spiked matrix control samples were subject to extraction and clean-up procedures. Similar procedure was performed used ultrapure water for the preparation of the standards for comparision. F-test was applied in order to evaluate the matrix effect, based on the calibration factors, with a confidence limit of 95% and 24 degrees of freedom.

The robustness of an analytical method is the ability of the method be not affected by small variations in method execution parameters. Robustness provides an indication of method reliability during routine application (*Eurochem, 2014*). To evaluate the robustness of the method, change of the flow of the mobile phase was chosen. Samples previously used in the linearity assay were taken and the mobile phase flow was changed from 0.40 mL min^{-1} to 0.30 mL min^{-1}. Thus, two analytical curves with different flows were obtained. Based on the same concept of the calibration factor described in the matrix effect, it was possible to evaluate, through the *F* test, if the analytical curves presented any significant difference, assuming a confidence limit of 95% and 24 degrees of freedom.

Application of the developed method to real surface water samples
Sampling location and procedure

Five composite surface water samples of 4.0 L each were collected monthly from a selected sampling point at Guandu river, NIG, Rio de Janeiro State for five months (April to August 2018). The sampling point was in the dammed area used as a source for water abstraction for treatment and distribution. The sampling procedure, preservation and transport conditions followed the instructions of the Brazilian National Guide for Collection and Preservation
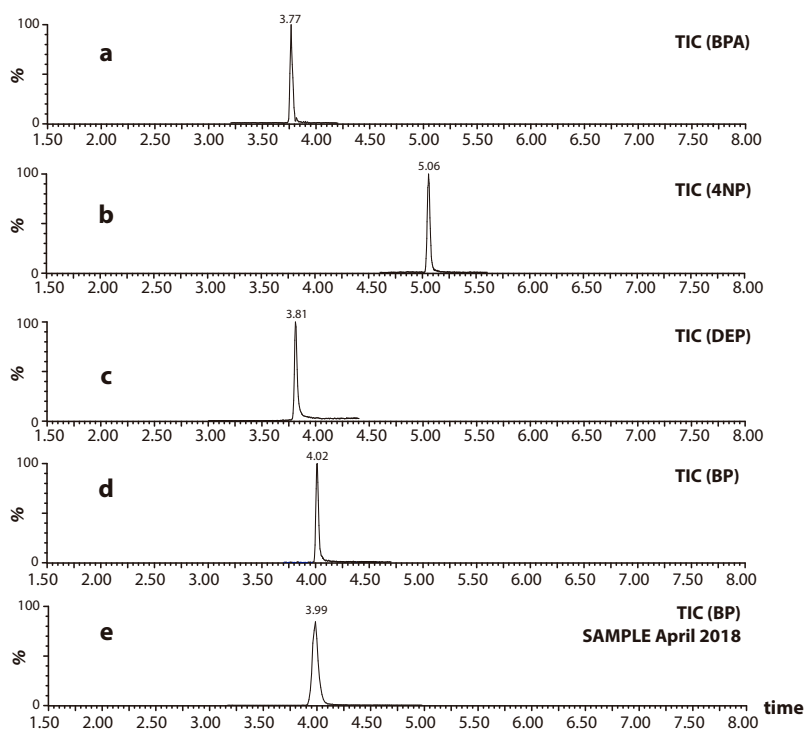
Figure 1 UPLC-MS/MS total ion chromatograms (TIC) of each endocrine disruptor under studyat10.0 µg L-1. (A) BPA; (B) 4NP; (C) DEP; (D) BP; (E) sample of april/2018.

of Environmental Samples (*Ceteb, 2011*). Samples were collected in a 4.0 L amber vial, with enough volume to perform the determination assays and to store for further testing, if necessary. At the time of collection, with the help of a HORIBA U-52 multiparameter probe, temperature, pH, Oxidation Reduction Potential (ORP), conductivity, turbidity, dissolved oxygen and dissolved total solids were measured.

RESULTS AND DISCUSSION

Determination by UPLC-MS/MS

The MS/MS operation mode was described. As above mentioned, the two most intense transitions were selected for the identification and further quantification of the target analytes. The highest intense transition was used for quantification and the second, for identification. The retention time, class, log K_{ow}, MRM transitions and collision energy for each compound analyzed are described in Table 1.

Figure 1 presents the UPLC-MS /MS total ion chromatograms (TIC) of the four EDs analyzed in this work and a sample where the BP was quantified in April 2018. The total running time was 8.0 min.
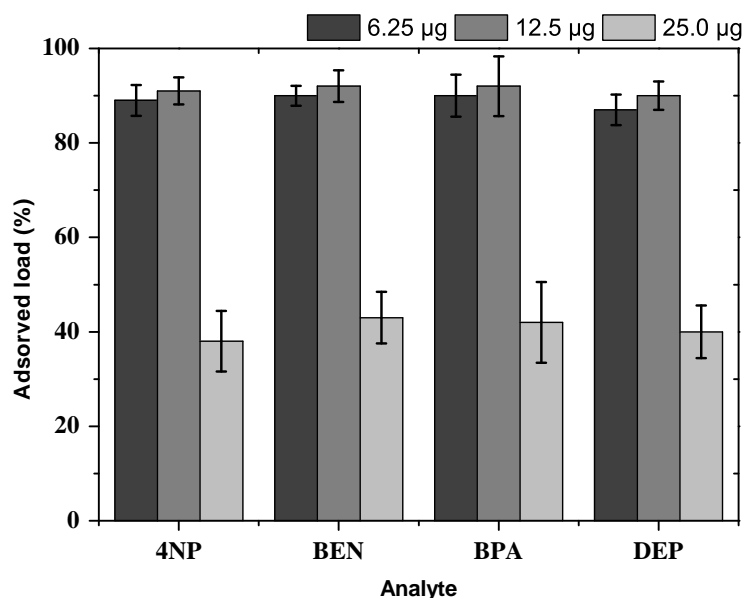
Figure 2 **Maximum load (in mass) a cartridge is able to adsorb.**

Optimization of the SPE sample preparation step

The optimization of the SPE procedure was performed in order to guarantee the conditions for the best recovery of the analytes under study. Figure 2 illustrates the maximum load the cartridge is able to adsorb.

As can be seen from Fig. 2, the maximum retention of the cartridge is 12.5 µg. Thus, the sample volume of 500 mL was selected, since the expected concentration of micropollutants in surface water samples is less than the saturation capacity of the cartridge.

In order to achieve 70–130% recovery as recommended by the USEPA 8000D Guide (*Usepa, 2018*), two volume of solvent were tested and elution in one and two steps was also tested (Fig. 3).

As it can be seen from Fig. 3, the adoption of a two-step elution using the four mL (2 × two mL) elution volume led to a gain in the recovery of the analytes, which are, however, still below the recommended range (70–130%), as recommended by the USEPA 8000D Guide (*Usepa, 2018*). Alternatively, the elution volume was increased to five mL and an increase in the recovery of all analytes was observed. In order to promote better recovery values, the 2.5 mL two-step elution was tested and, as shown in Fig. 4, an increase in the recovery rate of all analytes was noted, being all analytes within the recommended recovery range (*Usepa, 2018*).

The increased recovery is achieved with two-step elution since this is similar to solid–liquid extraction. Efficient extraction of analytes from solid to extracting liquid is guaranteed by repeated extractions. Neutral compounds can have substantial distribution coefficient (K_D) values, making extraction easier. On the other hand, organic compounds that form hydrogen bonds with water, are partially soluble in water or are ionogenic (weak acids or bases), may have lower K_D, thus hindering their complete extraction, which requires
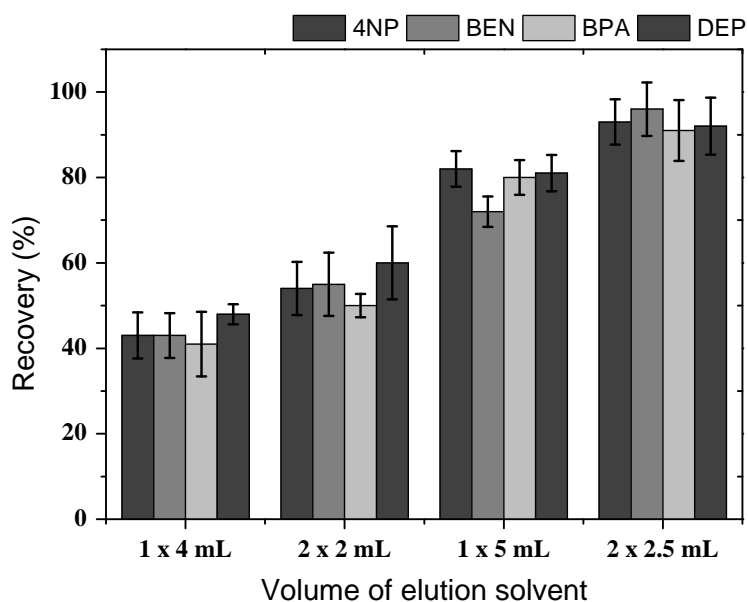
Figure 3 **Effect of the solvent volume and sequential elution on the recovery.**

numerous extractions. Additionally, the sample matrix may contain influence on the value of K_D (*Mitra, 2003*).

Method validation

Validation of the analytical method was performed by analyzing spiked matrix control samples and was assessed in agreement to the recommendation in the USEPA 8000D guide (*Usepa, 2018*).

Selectivity

The selectivity of the method was established by analysis of non-spiked (Blank) and spiked matrix control sample at the LOQ values (50.0 ng L^{-1} for BPA and DEP and 10.0 ng L^{-1} for BP and 4NP). The chromatograms (Fig. 4) were evaluated and the existence of a signal was verified in the chromatograms of the non-spiked matrix control sample (Blank) with intensity lower than the signal intensities of the respective LOQs.

Thus, the selectivity of the method was considered satisfactory, since the non-spiked matrix control sample (Blank) showed signals with lower intensities than the analyte signals, at the LOQ level, for each analyte, causing no interference in the quantification.

Precision and accuracy

Intra-day and inter-day precision and accuracy were established by analyzing spiked matrix control sample ($n = 5$) at three different concentrations: 50.0 ng L^{-1} (low), 250 ng L^{-1} (medium) and 500 ng L^{-1} (high), in two consecutive days (intra-days 1 and 2.) Results for the inter-day precision were found between 1.46 and 10.32% for 4NP and BP respectively. Regarding the accuracy, results were obtained between 80.43 and 104,32% for DEP and BP respectively (Table 2). Results were satisfactory and within the recommended values
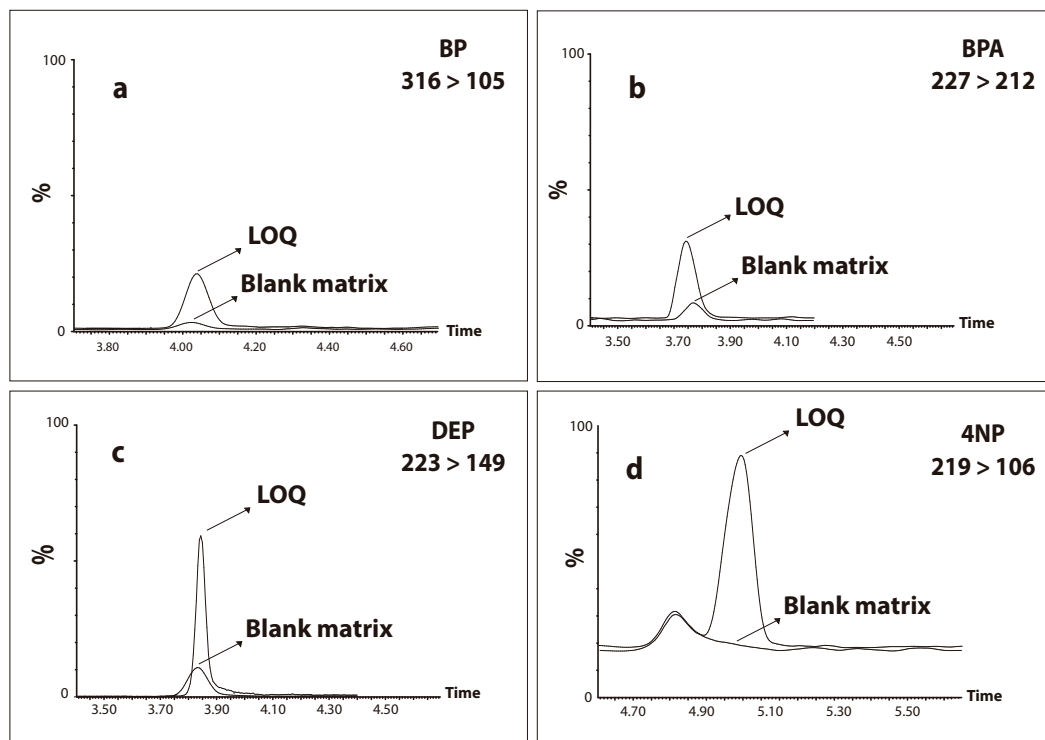
Figure 4 **UPLC-MS/MS chromatograms of each ED from a positive sample of surface water with the corresponding LOQ and a non-spiked matrix control sample (blank matrix).** (A) BP; (B) BPA; (C) DEP; (D) 4NP.

(RSD < 20%; accuracy between 70 and 130%) (*Usepa, 2018*). The precision and accuracy values of the method are quite consistent with other reports (*Chen et al., 2010*; *Li et al., 2012*; *Selvaraj et al., 2014*; *De Araujo, Bauerfeldt & Cid, 2017*; *De Araujo, Bauerfeldt & Cid, 2018*).

Linearity

Analytical curves were prepared with both matrix control sample and ultrapure water, containing analytes in concentrations levels ranging from 50.0 to 500 ng L^{-1} for BPA and DEP and 10.0 to 500 ng L^{-1} for BP and 4NP. Results are shown in Table 3. The R^2 coefficients range from 0.992 to 0.999 for BP and DEP respectively, indicating excellent linearity for all analytes.

Matrix effects must be investigated in quantitative LC-MS/MS determinations (*Postigo, De & Barceló, 2008*; *Gros & Petrovic, 2009*; *Gros, Rodríguez-mozaz & Barceló, 2012*). As above mentioned, matrix effect was evaluated from F values (F_{calc}) resulting from the comparison of the calibration factors (Fc) calculated for each analyte from the analytical curves obtained from standards prepared with ultrapure water and matrix control samples (see Table 4).

Calculated F values for BP, DEP and 4NP are greater than the critical F value, suggesting that the analytical curves are not statistically equal. Thus, the matrix must be showing

Table 2 Accuracy and precision of target compounds in surface water.

| | Intra day | | | | | | | | Inter day | | | |
| | day 1 | | | | day 2 | | | | | | | |
Comp	Spiked level (ng L^{-1})	Found (ng L^{-1})	RSD (%)	Rec (%)	Spiked level (ng L^{-1})	Found (ng L^{-1})	RSD (%)	Rec (%)	Spiked level (ng L^{-1})	Found (ng L^{-1})	RSD (%)	Rec (%)
	50	46.71	4.74	93.42	50	57.61	1.85	115.22	50	52.16	1.85	104.32
BP	250	266.56	5.94	106.62	250	208.73	11.03	83.49	250	245.78	10.32	98.31
	500	435.52	3.87	87.71	500	419.47	4.10	83.89	500	429.01	4.92	85.80
	50	49.86	3.55	99.71	50	48.26	4.83	96.52	50	49.06	2.16	98.11
BPA	250	210.36	3.97	84.15	250	216.53	1.64	86.61	250	213.45	1.64	85.38
	500	419.65	6.70	83.93	500	405.08	5.00	81.02	500	412.36	5.00	82.47
	50	53.68	4.93	107.37	50	47.01	4.70	94.01	50	50.35	3.43	100.69
DEP	250	213.02	4.66	85.21	250	219.85	2.31	87.94	250	201.08	2.29	80.43
	500	490.30	1.38	98.06	500	469.95	2.73	93.99	500	480.12	2.73	96.02
	50	46.44	0.89	92.87	50	46.42	1.46	92.84	50	46.43	1.46	92.86
4NP	250	239.23	2.08	95.69	250	207.63	5.55	83.05	250	223.43	5.55	89.37
	500	412.49	4.62	82.51	500	493.95	4.92	98.79	500	453.22	4.92	90.64

Notes.

[a] Mean value from quintuplicate samples injected in triplicates (in total, 30 measurements).

Table 3 LOQ, LOD, slope, intercept, determination coefficients (R2) for linearity tests.

| Comp | LOQ | LOD | intra day | | | | | | inter day | | |
| | | | day 1 | | | day 2 | | | | | |
	ng L^{-1}	ng L^{-1}	slope	intercept	R^2	slope	intercept	R^2	slope	intercept	R^2
BP	10.00	5.72	658.40	2,413.01	0.993	654.63	2,453.46	0.992	651.01	2,634.58	0.992
BPA	50.00	5.61	30.43	−66.06	0.998	30.50	−59.79	0.997	30.47	−63.10	0.997
DEP	50.00	2.71	2,037.53	10,208.03	0.996	2,075.22	9,314.53	0.999	2,053.88	9,848.56	0.996
4NP	10.00	0.87	66.91	−27.53	0.999	62.28	17.99	0.998	64.55	−3.43	0.996

Table 4 Evaluation of matrix effect.

| Comp | Ultrapure water | | | Matrix (surface water) | | | Fcalc[a] |
	Slope	Intercept	R^2	Slope	Intercept	R^2	
BP	368.65	2,248.66	0.990	798.01	1,433.27	0.992	50.46
BPA	13.76	40.48	0.992	32.74	−98.94	0.992	1.00
DEP	651.86	5,357.51	0.993	2,201.35	9,873.76	0.993	12.14
4NP	18.68	21.57	0.990	65.83	4.63	0.996	6.22

Notes.

[a] Fcritical = 1.98. (interval of confidence: 95%).

significant influence on the determination of these analytes. Thus, it is strongly suggested that an analytical curve prepared in a spiked matrix is adopted for the determination of BP, DEP and 4NP. An alternative should be found on the adoption of the standard addition method. For BPA, the calculated F value is lower than the critical F value,

Table 5 Evaluation of matrix effect.

Comp	Control			Flow			Fcalc[a]
	Slope	Intercept	R^2	Slope	Intercept	R^2	
BP	798.02	1,433.27	0.992	766.14	1,442.23	0.995	1.08
BPA	32.74	−98.94	0.992	28.87	−47.91	0.994	1.01
DEP	2,201.35	9,873.75	0.993	2,221.35	6,678.87	0.990	1.03
4NP	65.83	4.63	0.997	61.14	2.35	0.995	1.17

Notes.
[a] Fcritical = 1.98. (interval of confidence: 95%).

suggesting that the analytical curves in ultra-pure water and spike matrix are equivalent. Even though, quantification of all analytes was performed by comparison with the spiked matrix analytical curves.

Limit of quantification and limit of detection

LOQ were determined for each analyte, according to the validation criteria. LOQ values are 10.0 ng L^{-1} for BP and 4NP and 50.0 ng L^{-1} for BPA and DEP. LOD, defined according to the literature (*Shrivastava & Gupta, 2011*; *Eurochem, 2014*), varied between 0.87 and 5.72 ng L^{-1} for 4NP and BP respectively. LOQ and LOD values are shown in Table 3.

Current legislation recommends maximum permitted levels for some EDs in water. According to the USEPA 816-F-09-004 (*Usepa, 2009*), the threshold concentration level for di(2-ethylhexil) phthalate (DEHP), an ED that can cause reproductive difficulties, liver problems and increased risk of cancer, is 0.60 µg L^{-1}. The threshold value for 4NP in freshwater samples is 28.00 µg L^{-1} and in saltwater it is 7.00 µg L^{-1} according to USEPA 822-R-05-005 (*Usepa, 2005*). An analytical method for the determination of 4NP in the same basin has been previously reported (*De Araujo, Bauerfeldt & Cid, 2018*). However, comparisons between LOQ and LOD are not possible due to the difference between hyphenated techniques (LC-DAD and UPLC-MS/MS). Nevertheless, the reported LOQ and LOD values, obtained from SPE-LC-MS/MS technique, are similar to some previously reported limits, in investigations using similar hyphenated techniques (*Li et al., 2012*; *Camilleri et al., 2015*; *Wooding, Rohwer & Naudé, 2017*; *Chang et al., 2018*).

Robustness

The same standards used for the linearity test were analyzed under two different mobile phase flow conditions (0.40 and 0.30 mL min^{-1}), in order to investigate the robustness of the method. *F* test was applied showing no significant difference for the calibration factors. Table 5 illustrates the results for the robustness of the method. As can be seen from Table 5, the developed method proved to be robust for all analytes.

Application in real samples

Table 6 shows the physicochemical parameters, obtained from analysis of the samples at collection sites, in April, May, June, July, and August 2018.

A chromatogram of the environmental samples is shown in Fig. 5, in which the quantification of the four EDs in the collected surface water sample can be seen. The results are presented in Table 7.

Table 6 Physicochemical characteristics of the samples measured on site during sampling.

Parameter/Date	April 13	May 11	June 08	Min–Max
Time	9:47 AM	10:57 AM	10:08 AM	9:47–10:57
Temperature (°C)	26.11	24.54	23.41	23.4–26.1
pH	7.25	7.05	7.49	7.05–7.49
ORP[a] (V)	0.16	0.18	0.17	0.16–0.18
Condutivity (mS cm^{-1})	0.12	0.13	0.12	0.12–0.13
Turbidity (NTU)	16.47	8.54	5.41	5.41–16.5
DO[b] (mg L^{-1})	6.81	7.47	7.96	6.81–7.96
TDS[c] (g L^{-1})	0.021	0.063	0.081	0.021–0.081

Notes.

Obs: July and August: probe under maintenance.
[a] Oxidation Reduction Potential.
[b] Dissolved Oxygen.
[c] Total dissolved solid.

BP was detected (below LOQ) in one sample (July) and quantified in the other four samples (April, May, June, August); 4NP was detected in all samples but quantified in only one (July); BPA was quantified in four samples and DEP was quantified in all five samples.

In Guandu river, the range (min–max) found for DEP was 259.40–2. 56×10^3 ng L^{-1} (the maximum value being 10 times higher than the threshold value for drinking water according to the USEPA 816-F-09-004 regulation (*Usepa, 2009*). For proper quantification of DEP in the samples, it was necessary to dilute the samples prior to the SPE procedure, in order to guarantee that the concentration of DEP could be found within the linear range. With regard to the European regulations, the European Union has included 4NP, octylphenol (OP) and DEHP in the list of the 33 priority substances in environmental waters and has established maximum concentrations levels (based on environmental quality standards) at 300 ng L^{-1} for 4NP, at 100 ng L^{-1} for OP and at 1.30×10^3 ng L^{-1} for DEHP (*Dévier et al., 2013*).

DEP is often found in formulations of medicines, perfumes, nail polishes, shampoos, toys and other consuming goods (*Gómez-Hens & Aguilar-Caballos, 2003*; *Viecelli et al., 2011*). Phthalates are of great concern today due to their intensive utilization, especially for the purpose of increasing the flexibility and strength of plastic packaging; however phthalates are not chemically bound to the packaging plastic, which facilitates the release from the plastic into aqueous matrices (*Farajzadeh & Mogaddam, 2012a*; *Farajzadeh & Mogaddam, 2012b*). The main source of DEPs found in surface water is the untreated or insufficiently treated sewage and industrial effluents discharged into water bodies. Another source of environmental contamination is the leaching from plastic waste disposed in open dumps or uncontrolled landfills, when the environmental conditions (pH, temperature, contact time among other conditions) are in favor of the leaching of phthalates once the plastics are in contact with water (*Bošnir et al., 2007*; *Souza et al., 2012*).
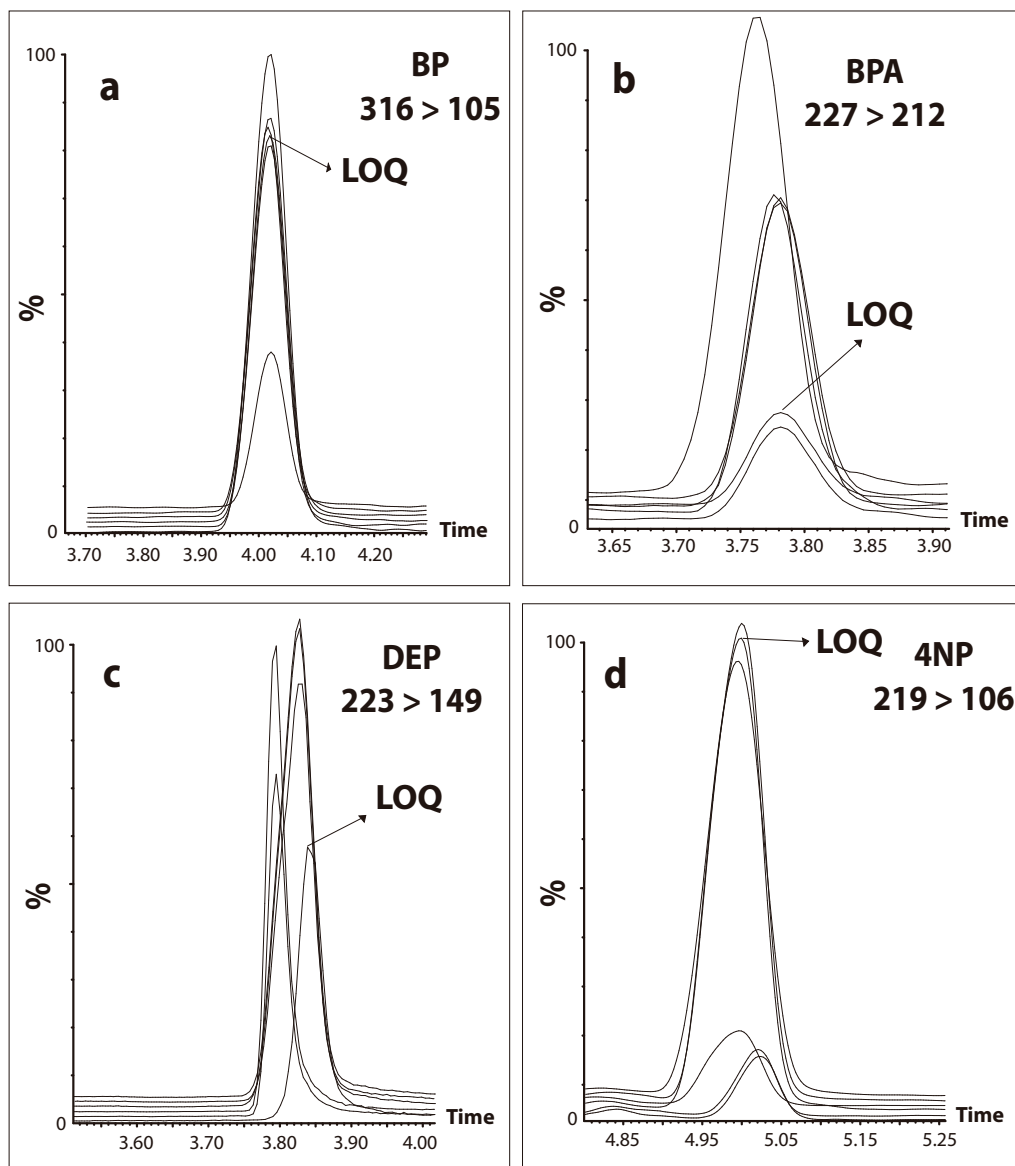
Figure 5 Chromatograms of each ED for samples collected between April and August 2018. (A) BP; (B) BPA; (C) DEP; (D) 4NP.

CONCLUSIONS

The present study describes the optimization and application of an analytical method for the determination of four EDs in surface water samples using SPE for sample cleaning, extraction and pre-concentration and subsequent analysis by UPLC-MS/MS. There was an optimization of the sample volume percolated by the SPE cartridge. The elution volume was also optimized considering sequential elutions. Bond Elut C18 cartridge was used for analyte extraction. The sample preparation was efficient (recovery >90% and RSD <11.03%) for extraction, pre-concentration and clean-up of BP, BPA, DEP and 4NP from

Table 7 Determination of BP, BPA, DEP and 4NP in surface water (ng L^{-1}).

Compound	April	May	June	July	August	Mean	Max	Min
BP	286.20	42.36	41.66	d[a]	d[a]	123.41	286.20	41.66
BPA	182.04	76.25	65.14	57.32	d[a]	95.18	182.04	57.32
DEP	1.30×10^3	456.77	259.40	2.56×10^3	545.19	1.02×10^3	2.05×10^3	259.40
4NP	d[a]	d[a]	d[a]	13.48	d[a]	–	–	–

Notes.
[a]detected (value < LOQ).

surface water samples. UPLC-MS/MS analysis allowed the simultaneous determination of the four EDs in a fast-chromatographic run (8 min). In addition, the method was selective, robust and sensitive, with relatively low LOQ values, found within the ranges commonly reported in the literature. Analytical curves were developed with coefficient of determination greater than 0.99. Matrix effect was verified for three out of four analytes: BP, DEP and 4NP. For these EDs, the adoption of the standard addition method is highly recommended.

The method was applied for the determination of the EDs in surface water samples from a very important water supply source in the Rio de Janeiro State. The maximum concentrations of BP, BPA, DEP and 4NP in five samples collected monthly during a five-month period in 2018 were 286.20, 182.04, 2.56×10^3 and 13.48 ng L^{-1}.

Finally, based on the results and the lack of regulation in Brazil and many other countries in the world regarding threshold values for these EDs, monitoring of other relevant water bodies must be done, followed by ecological and human health risk assessment. Moreover, the concentration levels found in the water samples are high enough to justify future investigations on the presence of these micropollutants in drinking water as well as to extend the monitoring for the search of similar pollutants and their metabolites.

Funding
This study was supported by the Coordination and Improvement of Higher Level or Education Personnel (CAPES) to Frederico Goytacazes de Araujo (1589040/2016), by the National Council for Scientific and Technological Development (CNPq Process 308.335/2017-1) to Marcia Marques and the Carlos Chagas Filho Research Support Foundation (FAPERJ) (E-26/202.894/2018 and E-26/202.793/2015) to Marcia Marques and Eduardo Monteiro Martins, respectively. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures
The following grant information was disclosed by the authors:
Coordination and Improvement of Higher Level or Education Personnel (CAPES): 1589040/2016.

National Council for Scientific and Technological Development (CNPq Process: 308.335/2017-1.
Carlos Chagas Filho Research Support Foundation (FAPERJ): E-26/202.894/2018, E-26/202.793/2015.

Competing Interests

Marcia Marques is an Academic Editor for PeerJ.

Author Contributions

- Frederico Goytacazes de Araujo conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.
- Glauco Bauerfeldt, Marcia Marques and Eduardo Monteiro Martins conceived and designed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the paper, and approved the final draft.

Data Availability

Raw measurements are available in the Supplementary Files.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj-achem.7#supplemental-information.

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