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Optimization of a dispersive liquid–liquid microextraction followed by liquid chromatography-diode array detection method for the determination of parabens in surface waters

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ABSTRACT

An analytical method for optimizing the extraction of methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP) and butylparaben (BtP) in water using dispersive liquid–liquid microextraction followed by high-performance liquid chromatography-diode array detection was developed. Full factorial design 2^3 with central point evaluated the interaction between the extraction solvent, disperser solvent, and sample volumes for the extraction tests. The desirability function was used to obtain the optimal condition for the extraction of parabens. Acetone and decanol were used as disperser and extraction solvents, respectively. The optimized results showed: 10 mL/700 µL/90 µL respectively for the sample volume/disperser solvent/extraction with global desirability (*D*) value above 0.80, and extraction recovery values of 43.30%, 68.00%, 86.30% and 94.70% for MeP, EtP, PrP and BtP, respectively in a pH range between 5.0 and 6.0. The method exhibits good linearity, correlation coefficients (*r*) varying from 0.9957 to 0.9989, limit of detection, (0.5–1.0 µg L^{-1}), limit of quantification, (1.0–2.0 µg L^{-1}). All the parabens showed recovery rates of approximately 88%–115%. The method was successfully applied to determine parabens in surface water samples collected in the Brazilian semi-arid region (Ceará State, Brazil). The study area has high eutrophication levels and the results showed the occurrence of parabens in 60% of the samples, suggesting a possible anthropogenic contamination source.

Keywords: Parabens; Dispersive liquid–liquid microextraction; Experimental design; Desirability; Surface waters

1. Introduction

Environmental monitoring of so-called emerging contaminants has a great interest in the scientific community, mainly by recognizing their effects on aquatic toxicity, genotoxicity, endocrine disruption as well as selection of resistant pathogenic bacteria [1–6]. Among them, it can be mentioned parabens, which are chemical compounds derived from 4-hydroxybenzoic acid, obtained from its esterification with alkyl substituents, ranging from methyl to butyl [7,8].

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Parabens are widely used as preservatives in various pharmaceutical formulations, and their use is mainly justified by their broad spectrum of antimicrobial activity, low cost, high solubility in cosmetic emulsions and good chemical stability at pH values commonly used in these formulations [9–13]. However, studies reported that parabens can be classified as endocrine disruptors in humans. It was identified their presence in mammary neoplastic cells [14], besides correlated disturbances in the concentration of female hormones with their exposure [15,16]. Parabens when applied under skin are rapidly absorbed and metabolized by the carboxylesterase enzyme, having as its main metabolite the p-hydroxybenzoic acid, derived from the paraben hydrolysis process, which also has estrogenic activity, but less than the respective ester [17,18]. However, it is possible to bioaccumulation the parabens in several human tissues, justified by their excessive use [19]. Several studies indicated the presence of parabens in human placenta tissue, breast milk, amniotic fluid, blood plasma and urine [20–23].

Parabens are introduced into the aquatic environment from wastewater treatment plants discharges, which the presence of higher contamination levels depends on several factors such as geographical location, climatic conditions, and the efficiency of these treatment plants [24,25]. Most of the technologies used in Brazilian's STPs (sewage treatment plants) are conventional biological types, especially stabilization ponds, activated sludge systems and anaerobic reactors, such as upflow anaerobic sludge blanket [26]. However, several investigations have shown that organic compounds such as parabens are frequently not removed during conventional biological wastewater treatment and not biodegraded in the environment. Their insufficient removal from the STPs is mentioned as the major source of their release into the environment, so it is necessary to remove them from sewage before their release into water bodies [27].

Although the occurrence of parabens for preservative use has been studied extensively, their impact and environmental distribution began to be reported from the 1990s onwards, where parabens were detected in waters of an industrial wastewater treatment plant in Sweden [28]. Still in Europe, in the waters of the Aveiro River (Portugal) the presence of propylparabens and butylparabens was identified [29] and butylparabens and propylparabens were detected in waters of the Turia River (Spain) as well as in waters intended for human consumption [30]. In Asia, Li et al. [31] analyzed the waters from the Beijing River (China) and detected the presence of eight parabens, including octylparaben, identified for the first time in surface waters. In Latin America (South Brazil region), the presence of parabens was first identified in 2013 in surface waters. Silveira et al. [32], found several pharmaceuticals and personal care products, among them methylparaben (MeP), in concentrations of 7.6–29.8 μg L^{-1}. In the same year, in the Southeast region of Brazil, Luizete [33] detected 0.21 μg L^{-1} of MeP also in surface waters. Despites there are several studies about the occurrence of parabens in Brazil, there is no data about the presence of these compounds in surface waters in the North and Northeast region of Brazil until to date [34,35]. This study is the first to conduct a survey on the presence of parabens in the Northeast region of Brazil, which is marked by a semi-arid climate and also a low hydric precipitation and evapotranspiration rates, contributing to a greater risk of anthropogenic contamination of its water resources [36,37].

Several analysis methods have been developed for the detection and quantification of parabens in aqueous matrices such as surface water, groundwater, drinking water and domestic and/or industrial effluents. Among them, high-performance liquid chromatography (HPLC) is by far the most widely used [38] in combination with various types of detectors such as spectrophotometric ultraviolet-visible (UV-Vis) and mass spectrometry [39,40]. However, because paraben concentration reaches trace levels in these matrices, the preconcentration and extraction steps are generally required prior to analysis.

Liquid–liquid extraction (LLE) methods are widely used despite the environmental, and financial negative impacts and high consumption of carcinogenic solvents [41–43]. In order to minimize such impacts, an LLE miniaturization was developed in the 90's, a liquid phase microextraction [44] and, in 2006, a variant of this technique, dispersive liquid–liquid microextraction (DLLME) [45], aiming at pre-concentration/extraction of polycyclic aromatic hydrocarbons in water.

In the DLLME method, a mixture at appropriate proportions of extraction and disperser solvents is rapidly injected into the aqueous sample to form a cloud point (cloudy solution). Then, the solution is centrifuged, and the organic phase (containing the analyte) is removed for identification/quantification by an appropriate technique. It is necessary that the disperser solvent have chemical affinity both in the extraction solvent (organic phase) and in the sample (aqueous phase) and the extraction solvent is immiscible in the sample. The addition of a disperser solvent to the extraction solvent will promote an increased dispersion of it in the sample, contributing to the increase of the surface area between the analyte of interest and the extraction solvent (organic phase), improving the extraction efficiency [46].

The main advantage of the DLLME method is due to the short extraction time, which depends on partition equilibrium [47]. In addition, different factors affect the extraction process by DLLME, such as extraction solvent, dispersing solvent, sample volumes, pH, ionic strength, agitation and extraction time [25,45,48].

In this connection, univariate studies were widely used to evaluate the DLLME parabens extraction method [49,50]. However, experimental design has gained increasing importance in the optimization of extraction/preconcentration processes, since it allows the design of an optimal response, as well as the synergistic effect of the interaction between the factors [51–53]. Besides being fast and economical since fewer tests are usually performed without losing the reliability of the results.

Based on the above, the aim of this study is to optimize a method for analysis of methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP) and butylparaben (BtP) in water using DLLME followed by HPLC-DAD (diode array detector) and factorial design as a tool to investigate the variables that affect the extraction process as well as the evaluation of the occurrence of parabens in surface waters in the state of Ceará, Brazil.

2. Experimental

2.1. Reagents and materials

Acetone, methanol, 1-decanol HPLC grade solvents were acquired from Merck (Darmstadt, Germany). NaCl was purchased from Vetec (Diadema, Brazil). The preservatives methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP) and butylparaben (BtP) were purchased from Sigma-Aldrich (Steinheim, Germany). From individual stock solutions (1,000 mg L^{-1}) of parabens in methanol, multi-component solution (50 µg L^{-1}) in water were prepared and deionized using a Milli-Q® system (Millipore Direct-Q3, MA, USA).

2.2. Instrumentation

Chromatographic analyses of the parabens were carried out with a high-performance liquid chromatography Shimadzu 20A Prominence (Kyoto, Japan) coupled with diode array detector UV-Vis SPD-M20A Shimadzu (Kyoto, Japan). The chromatographic separation of the parabens was performed on a ZORBAX-ODS C18 column Agilent (250 mm, 4.6 mm ID and 5 µm particle size). It was used, as mobile phase, methanol and water acidified with 1% acetic acid (70:30 v/v) at a flow rate of 1 mL min^{-1} in isocratic mode, column temperature of 30°C, injection volume of 20 µL and detection at 256 nm.

2.3. Selection of the solvents

The extraction and disperser solvents are the main factors that affect the extraction process. Thus, previous studies were conducted to select the best pair of extraction/disperser solvents. The extraction solvents were selected in decreasing order of polarity, 1-octanol and 1-decanol, and disperser solvents were: acetonitrile, methanol, and acetone [25,46]. The initial tests were performed using the synthetic multielement solution at 50 µg L^{-1} concentration of each paraben in deionized water. The volume of 1 mL of extraction/disperser (0.1 mL/0.9 mL) solvents pairs was added to 10 mL aliquot of the multielement solution, with the following extraction/disperser solvent pairs: 1-decanol/acetone, 1-decanol/acetonitrile, 1-decanol/methanol, 1-octanol/acetone, 1-octanol/acetonitrile, and 1-octanol/methanol. The mixture was shaken using a vortex mixer (Kasvi, Paraná, Brazil) for 2 min. A cloudy solution formed and then, was centrifuged for 5 min at 4,000 rpm (Eppendorf AG, Hamburg, Germany). The organic phase supernatant was carefully removed using a glass microsyringe (Agilent, Delaware, USA) and injected in the chromatographic system HPLC-DAD according to the conditions previously established. The extraction/disperser solvents pair with the best extraction efficiency was selected for the optimization study of extraction, calculated from the recovery of parabens in the extraction phase.

2.4. Experimental design

For the optimization of DLLME parabens extraction with the selected solvents pair, it was applied a full factorial design 2^3 to evaluate the factors: sample volume (V_{sam}), the volume of the extraction solvent (V_{ext}) and volume of the disperser solvent (V_{disp}), with high (+) and low (–) levels, and a central point that corresponds to the average values of each variable, as specified in Table 1. The high and low levels were selected from preliminary studies.

The responses obtained were treated by the software Statistica 6.0 (StarSoft, Oklahoma, EUA) using the desirability function [54,55] to assess the optimal condition for parabens extraction. The enrichment factor (EF) of each paraben in the extraction phase was used as the response variable, and calculated according to the methodology of Rezaee et al. [45], is defined as the ratio between the concentration of each paraben in the extraction phase (P_{ext}) and the initial concentration of each paraben in the aqueous phase (P_{aquo}), according to Eq. (1):

$$\mathrm{EF} = \frac{P_{ext}}{P_{aquo}} \tag{1}$$

The concentration of parabens in the extractor phase was obtained by comparing peak areas obtained from an external calibration curve prepared from a standard solution of parabens in concentrations from 2.0 to 8.0 mg L^{-1} solubilized in 1-decanol. All the experiments were done randomly and in triplicate.

According to the responses obtained from experimental design, an optimal condition was sought in which it could favor a maximum of simultaneous extraction of parabens, for this, the desirability function developed by Derringer and Suich [54], was applied. In this function, a mathematical procedure is performed to identify the best condition of simultaneous extraction among the answers that are being evaluated in this factorial design. The responses of the factorial design are converted into values between 0 and 1, called individual desirability (D_i). In this model, 0 represents the undesirable value, which corresponds to the lowest response obtained from factorial design, and the response transformed into 1 corresponds to the best response obtained from factorial design, the most desirable value, that is, that corresponds to the maximum EF value obtained in the extraction of parabens. Therefore, the desirability function involves the transformation of each estimated response variable (in this case, the EF values) to a desirable value D_i where $0 \le D_i \le 1$. The D_i for each paraben studied was obtained according to Eq. (2):

$0, \text{ if } \mathrm{EF} \le L$

$$D_i = \left[\frac{(\mathrm{EF} - L)}{(H - L)^W}\right], \text{ if } L < \mathrm{EF} < H \tag{2}$$

$1, \text{ if } \mathrm{EF} \ge H$

Table 1
Factors and levels used in the factorial design 2^3

Factors (mL)	High level (+)	Low level (–)	Central point (mL)
V_{sam}	12.50	7.50	10.00
V_{disp}	1.20	0.60	0.90
V_{ext}	0.20	0.10	0.15

where EF is the answer for each factorial design, L and H are the lowest and the highest EF value obtained in each design, respectively, and W is the weight given for each experimental design result. In this study, the value of $W = 1$ was applied, since it sought to identify the experimental conditions with the highest EF responses, equally for all parabens, considering that all parabens had the same relevance in this study.

After transforming the predicted values of the dependent variables (EF) in different combinations levels of the variables in a predicted value of D_i, these were combined from the geometric mean, according to Eq. (3), in order to obtain a single value, defined as global desirability (D):

$$D = \left(D_{i1} \times D_{i1} \times \ldots D_{\text{in}}\right)^{1/n} \tag{3}$$

where the values of D_{i1} to D_{in} correspond to the D_i values obtained for each paraben and "n" corresponds to the number of responses obtained from D_i, which in this study corresponds to 4, the number of analytes evaluated. The D value provides a general assessment of the combined response levels where $0 < D < 1$. It is noteworthy that, as a geometric function was used, if $D_i = 0 \therefore D = 0$, which corresponds to the lowest EF value (L) obtained in this design.

2.5. DLLME extraction

In the experimental design, an adequate volume of sample solution of parabens at 50 μg L^{-1} was transferred to a Falcon tube, NaCl PA was added in a proportion of 10% (w/v) and shaken in vortex mix for 2 min (Kasvi, Paraná, Brazil). The appropriate volume of acetone/decanol mixture was added to the tube in the proportion required by the experimental design in question and the mixture was shaken by a vortex mixer (Kasvi, Paraná, Brazil) for 2 min. The cloudy solution formed was centrifuged for 5 min at 4,000 rpm (Eppendorf AG, Hamburg, Germany). The organic phase supernatant was carefully removed by a glass microsyringe (Agilent, Delaware, USA) and injected into the HPLC-DAD.

2.6. Analytical figures of merit

To ensure that the DLLME extraction methodology was properly optimized, the following analytical performance parameters were evaluated according to ANVISA [56], and ICH guideline [57]: selectivity, linear range (LR), correlation coefficient (r), limit of detection (LOD), limit of quantification (LOQ), precision and accuracy (recovery %).

2.7. Real sample analysis

The proposed method was applied to the determination of parabens in eleven surface water reservoirs, located in the state of Ceará, in the Northeastern region of Brazil. The sampling sites and location are shown in Fig. S1 and Table S1. These reservoirs are responsible for the water supply of the fifth most populous city in Brazil (Fortaleza), with more than 2,680,000 habitants [58]. Its climate is classified as semi-arid with average rains of 1,500 mm/y, but the high potential evapotranspiration is 2,300 mm/y, causing a negative climate hydric balance [59], making it essential to monitor the quality of these water resources due to their high scarcity. The samples were collected between 2018 and June 2019 and were filtered in a nylon membrane filter of 0.45 μm (Millipore, Massachusetts, USA), and stored at 4°C until the microextraction procedure was optimized.

3. Results and discussion

3.1. Selection of the solvent extraction

Several factors can influence the extraction process by DLLME, among them, there are: the selection of the extraction and disperser solvents, volumes of extraction and disperser solvents, extraction time, agitation, pH and ionic strength [45,60,61]. However, the choice of extraction and disperser solvents, as well as their uses in appropriate proportions, are the main factors for a more efficient DLLME extraction process. Therefore, preliminary studies were carried out at choosing the most suitable extraction solvents, including the characteristic such as low toxicity, low water solubility and good affinity with parabens, and lower cost.

The results obtained showed extraction efficiency for the 1-decanol/methanol pair (36.5%–73.8%), and 1-decanol/acetone (34.1%–74.7%) as shown in Table 2.

Both decanol/methanol and decanol/acetone extraction/disperser solvents pairs showed similar recovery values (Table 2). Despites both acetone and methanol solvents have low environmental and health risks when compared to acetonitrile [62,63], 1-decanol/acetone was selected as extraction/disperser solvents pair due to the acetone lower toxicity (chronic exposure) and also lower cost when compared to methanol [64]. Some studies report that acetone as a disperser solvent produces solutions with more uniform and stable cloud point for a long period [65,66].

In the present study, a formation of a more stable cloud point was observed for the tests that used decanol as one of the solvents pair, this might be due to the lower solubility of 1-decanol in water, which might provide a greater separation of analytes from the aqueous phase.

3.2. Optimization of DLLME conditions

Table 3 shows the results obtained from the experimental design, that is, the EF obtained for each paraben and their respective relative standard deviations (RSD) under the previously established conditions. The EF varied from 20 (MeP) to 66 (PrP) times, depending on the paraben.

To measure the main effects of the studied variables and their interactions with each other, an analysis of variance (ANOVA) was performed with a statistical significance value less than 0.05, with a 95% confidence level being shown on the graph of Pareto, Fig. 1. The R-squared statistic indicated that the model explains variability in EF of 88.13%, 98.87%, 97.58% and 93.49% for MeP, EtP, PrP and BtP, respectively. Fig. 1 also revealed that extraction solvent showed to be the most relevant variable for parabens, except for the MeP, since its effect did not exceed the significance limit (red line).

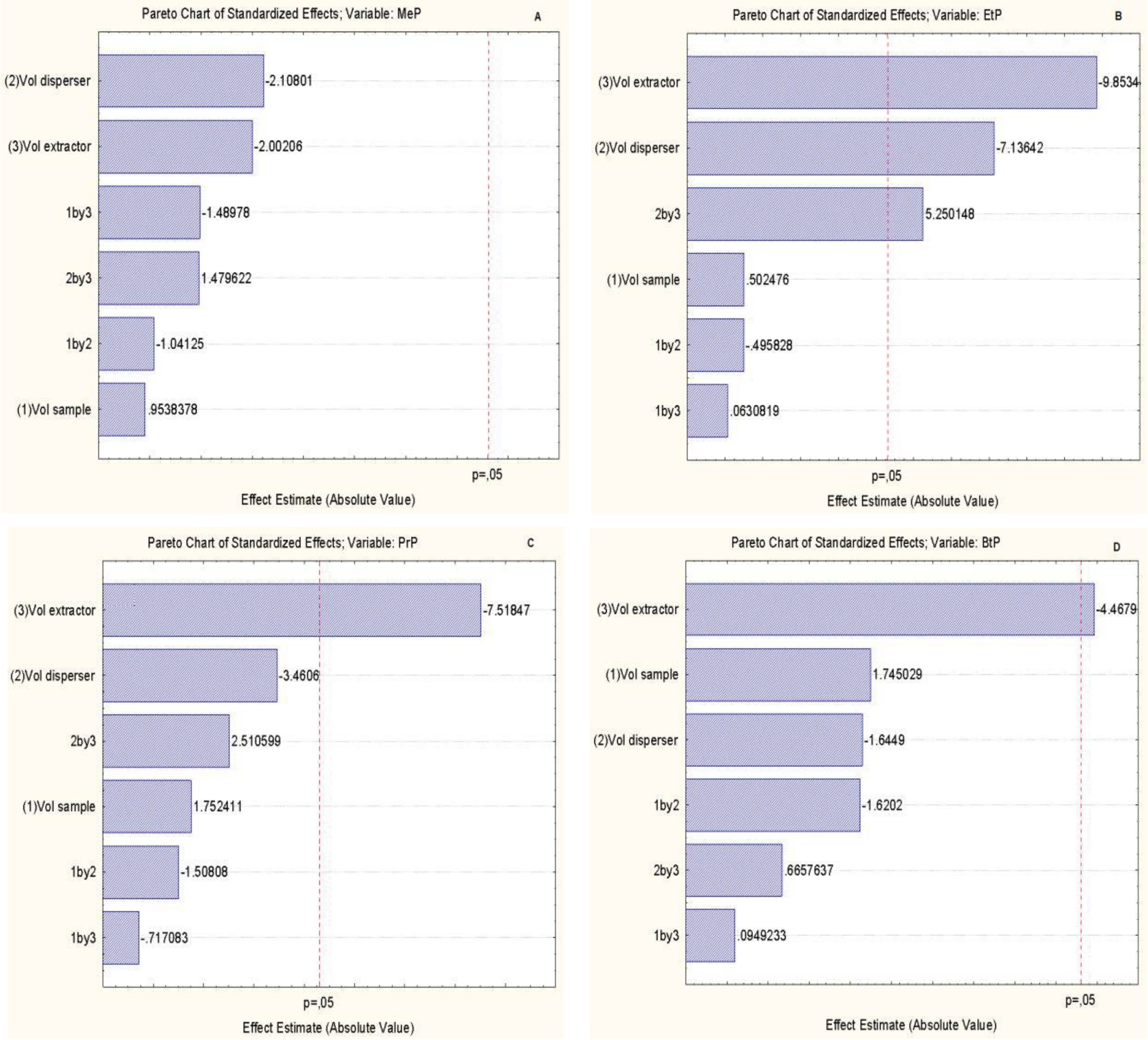

Fig. 1. Pareto graphs of the effects (A) MeP, (B) EtP, (C) PrP and (D) BtP.

Among the studied parabens, MeP has lower aliphatic chain, that is, greater polar character, thus, its interaction with the organic phase is the lowest, a fact also confirmed by the lower EF values obtained. It was found that an increase in the volume of decanol had a negative effect on all parabens, decreasing the EF, which was expected, since it causes the dilution of the analyte in the organic phase. However, this effect was more significant to EtP, PrP and BtP as they have a higher lipophilicity, and consequently, higher values of partition coefficients, which culminates in a greater interaction with the extraction solvent and thus, a greater dependence on it [51,67]. Following the same trend, an increase in the volume of disperser solvent also contributes negatively to all parabens, however, with a significant negative effect only for EtP (Fig. 1B).

For BtP (Fig. 1D), the sample volume has a slightly greater positive effect when compared to the other parabens, in others word the higher the sample volume the higher the EF value, this might be due to the solubility of BtP in water, which is the lowest of all parabens, about 10 times smaller than that for MeP [17,68], therefore, a larger volume of sample gives a greater availability of butylparaben in water and, thus, allows a greater extraction. It is concluded that, for all parabens, the proportion of solvent extraction/disperser has a positive interaction, suggesting that the most significant factor is the proportion that they keep among themselves [45,69].

3.3. Desirability function

In Fig. 2, the *D* function parameters for the present study are plotted. The smaller the disperser and extraction solvent volumes are, in relation to the sample volume (A and B), the greater the EF, moreover, the influence of the sample volume suggests that, even under low sample volumes, the desirability already reaches satisfactory values above 0.8. Such observation becomes relevant when the availability of sample volume for analysis is small.

For the *D* relative to the volume variation of the extraction × disperser solvents (Fig. 3), the relationship between linearity and proportionality is observed and at the same time inversely proportional to the EF, that is, the smaller the volumes of both, the greater the EF value, and it might reach desirability values close to 1. However, the effects of the disperser solvent variation are more complex, since, according to the studies, an increase in the volume of disperser solvent might result in a greater solubility of the analytes in the aqueous phase, decreasing the EF, however, low volumes of disperser solvent might hinder the formation of the cloud point, also contributing to decrease of the extraction efficiency [70].

It was possible to conclude that the proportion of 10 mL/700 µL/90 µL for sample volumes/disperser solvent/extraction solvent, respectively, was more efficient, since in these conditions, the desirability was above 0.80 and it was considered from acceptable to excellent in all variables [54,71]. Extraction tests were carried out with lower volumes than 90 µL, however these presented difficulties at the time of collection for subsequent injection into the chromatographic system. The average volume collected in the extraction by DLLME under optimized conditions was 71 µL measured with the injection microsyringe in the chromatographic system.

3.4. pH effect

The pH effect is relevant in DLLME when the analytes of interest have ionizable groups. As parabens are esters derived from benzoic acid, they have ionizable groups [44,67]. Therefore, it is relevant to study the effect of pH on the distribution of these in the extraction solvent, since, strictly speaking, the higher its concentration in the non-ionized form, the greater the EF. Fig. 4A represents the percentual of extraction recovery (ER%) of parabens as a function of pH variation, being obtained according to the equation:

$$\text{ER\%} = \text{EF} \times \frac{V_{\text{ext}}}{V_{\text{sample}}} \times 100 \qquad (4)$$

where V_{ext} and V_{sample} are the volumes of the extraction phase (decanol) collected after extraction by DLLME and sample, respectively, already in the optimized conditions of the experiment. As can be seen, regardless of the pH studied, BtP has the highest values of ER% while MeP has the lowest, which is justified by the fact that with the increase in the aliphatic chain, there is also an increase in the

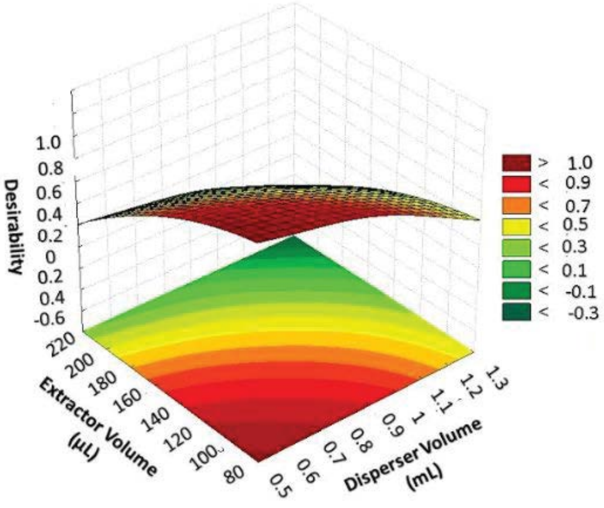

Fig. 3. Desirability graph obtained in the experimental design of paraben extraction optimization by DLLME (disperser × extraction).

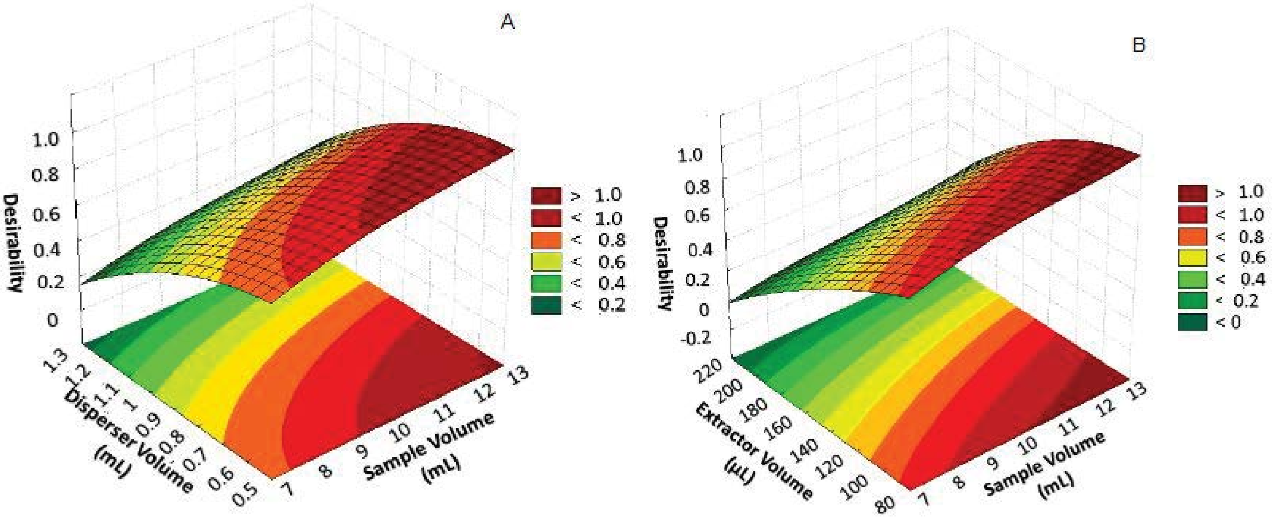

Fig. 2. Desirability graph obtained in the experimental planning of optimization of paraben extraction by DLLME (A) disperser × sample and (B) extraction × sample.

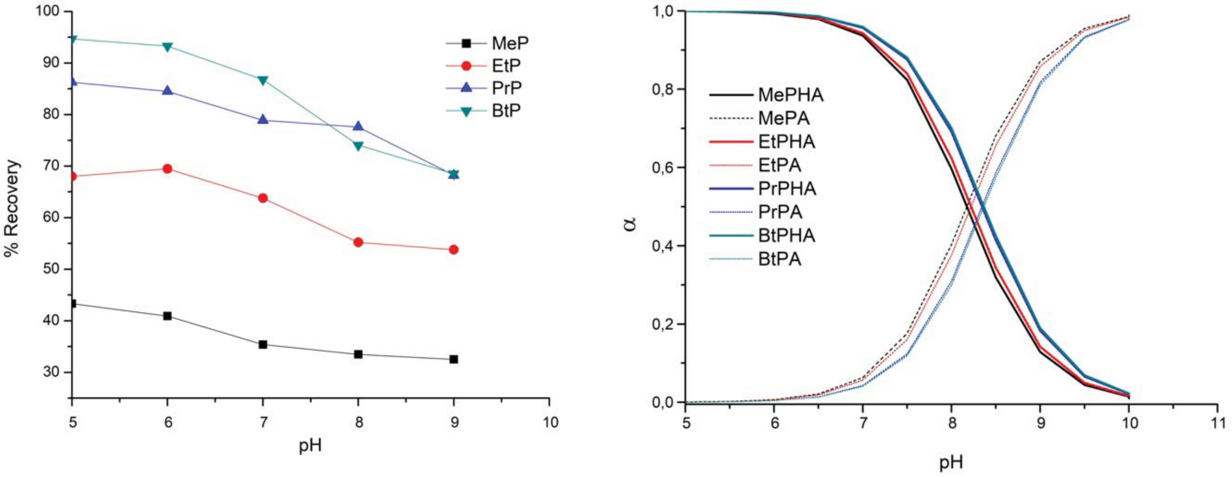

Fig. 4. Effect of pH on ER% of parabens by DLLME (A) and diagram of distribution of parabens as function of pH, where HA is the acid form and A⁻ is the deprotonated form (B).

nonpolar character of the analyte providing greater interaction between it and the extraction phase of similar polarity.

For all parabens studied, the increase in pH contributes to a decrease in ER%. As can be seen in Fig. 4A, which corresponds to the species distribution diagram for the pH range under study, pH values above 6.5 favors the deprotonation of the hydroxyl group of parabens, to such an extent that, at pH values above 8.2, their availability in non-ionized form corresponds to less than 50%, which significantly contributes to the reduction of ER%. At pH values below 6.0 the availability of parabens in the non-ionized form is maximum (99.5%). Thus, optimization of the paraben extraction by DLLME must be performed in the range of $5 < pH < 6$ to obtain the highest values of ER%.

3.5. Analytical figures of merit

The selectivity was evaluated by the association of the retention time (R_t), purity tests and peak similarity in addition to the comparison of the UV spectra of the samples with parabens standard solution. Fig. 5 shows the overlapping chromatograms of a sample from Pacoti reservoir and the same sample spiked with 5 μg L^{-1} of parabens, after extraction by DLLME. Fig. 5 also shows the chromatograms of the samples from Batente and Macacos reservoirs, where EtP and EtP and BtP were detected, respectively (Table 2).

The spectra generated from the paraben standard were saved in the software database of the HPLC-DAD equipment, and later compared with the spectra of the samples. As example, Fig. S2 presents the comparison of the Pacoti reservoir UV-Vis spectra and the standard spectra of parabens. The DAD detects absorption in the UV-Vis, through several arrays of photodiodes, obtaining information about a variety of wavelengths at once. If two analytes have similar retention times, it is possible to distinguish them using HPLC-DAD by comparing their absorption spectra, in addition to calculating the percentage of similarity between the spectra and their purity [5,26]. No interference was observed in the studied parabens. The HPLC-DAD software also indicated a similarity percentage greater than 89% for all evaluated parabens, in addition to revealing that all peaks had a 100% purity level.

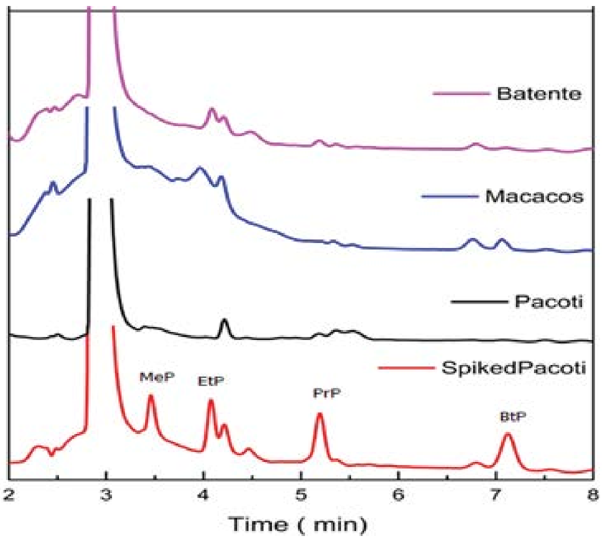

Fig. 5. Overlap chromatograms from prepared samples obtained in matrix (black), 5 μg L^{-1} spiked matrix (red) and Batente (pink) and Macacos (blue) reservoirs.

The Student's test was used at a 95% confidence level in order to evaluate the adjustment of the calibration equations [26]. The linear models for calibration curves showed a good fit for all parabens, with correlation coefficients (r) varying from 0.9957 to 0.9989 (Table 4). The LOD was estimated by successive dilutions, which started from the lowest point of the calibration curve to the lowest level of detection for each compound to consider the signal-to-noise ratio (S/N) at approximately 3:1. The LOQ was determined as the lowest spiked level that can be analyzed in the sample with accuracy and precision [72]. The LOD ranged from 0.5 to 1.0 μg L^{-1} and LOQ was 1.0 to 2.0 μg L^{-1}.

The precision of the method was assessed by repeatability. Accuracy was assessed by recovery experiments with three replicate analyses of the spiked surface water samples in levels 5.0, 25.0 and 60.0 μg L^{-1} for all analytes. The repeatability was reported by the relative standard deviation (RSD%) and accuracy by recovery % both shown in Table 5. All the parabens showed recovery rates of approximately 88%–115%. All analytes show RSD values below 15%. The main guides recommend 70%–120% recovery and RSD ≤ 20% [56,57].

The performance of the proposed method is summarized in Table 6 and compared with literature data. Comparing the LOD and LOQ values obtained with different analytical techniques, the proposed method showed improved sensitivity in relation to fabric phase sorptive extraction (FPSE) and HPLC-DAD detection [73]. The sensitivity in DLLME-HPLC-DAD was lower than rotating disk sorptive extraction (using Oasis® HLB as the sorbent phase) followed by gas chromatography-mass spectrometry (RDSE-GC-MS) [74] and solid-phase extraction followed by liquid chromatography-tandem mass spectrometry (SPE-LC-MS-MS) [75], due to their better robustness of the detection system. However, the proposed method showed similar recoveries for all parabens, it requires a small amount of sample, without the need for any complex steps, such as derivatization or clean-up. The DLLME-HPLC-DAD method besides being simple and fast uses minimal hazardous reagents, it needs lower energy consumption and lower cost, hence it can be used as a green alternative for the analysis of the parabens in monitoring environmental program, as long as the limits of sensitivity are considered [40,63].

Table 2
Efficiency of DLLME extraction of a synthetic sample containing parabens in different pairs of extraction/disperser solvents

Solvents Extr./Disp.	Recovery – *R*%			
	MeP	EtP	PrP	BtP
Decanol/Acetone	34.1	53.7	68.1	74.7
Decanol/Acetonitrile	33.8	55.1	65.5	66.2
Decanol/Methanol	36.5	55.8	70.2	73.8
Octanol/Acetone	32.3	49.6	63.5	70.1
Octanol/Acetonitrile	30.3	48.5	62.6	66.9
Octanol/Methanol	33.1	48.2	58.4	65.8

3.6. Real sample analysis

Table 7 shows the average concentrations of parabens and the respective standard deviation of the 11 surface water samples analyzed. The presence of MeP and PrP was not detected in the analyzed samples. EtP concentrations were found in the reservoirs: Batente (0.47 μg L^{-1}), Gavião (0.51 μg L^{-1}), Macacos (0.55 μg L^{-1}), Pacajús (0.77 μg L^{-1}), Riachão (0.62 μg L^{-1}), and BtP concentrations were found in the reservoirs: Macacos (0.96 μg L^{-1}), Maranguapinho (0.59 μg L^{-1}) and Sítios Novos (0.61 μg L^{-1}). However, all MeP and PrP concentrations were below the LOQ of the

Table 3
Experimental design results

Exp.	MeP		EtP		PrP		BtP	
	EF[a]	RSD[b]	EF	RSD	EF	RSD	EF	RSD
1	20.87	3.52	27.94	3.82	30.35	5.76	36.58	8.58
2	24.57	6.66	32.82	6.34	41.01	4.62	45.46	4.01
3	23.14	2.61	29.51	2.58	32.94	0.77	41.20	0.31
4	48.61	4.65	54.67	6.49	62.97	2.47	65.95	3.07
5	22.75	3.43	25.75	2.93	28.03	3.7	30.36	0.82
6	23.41	0.34	34.99	8.14	42.11	11.39	50.72	2.97
7	25.73	1.18	29.97	2.57	30.14	2.51	33.27	2.47
8	29.35	12.09	51.15	5.87	49.66	9.62	48.00	4.01
CP	32.67	0.12	36.75	0.10	40.08	2.75	45.18	1.20

[a]extraction factor; [b]relative standard deviation ($n = 3$).

Table 4
Quantitative features of the proposed method for analysis of parabens in surface waters by DLLME

Analyte	Range (μg L^{-1})	Calibration equation	LOD[a] (μg L^{-1})	LOQ[b] (μg L^{-1})	R^c	T_{calc}^{d}	T_{crit}^{e}	Test F^f
MeP	5–75	$y = 5.6114\text{E}6x - 842.7602$	1.0	2.0	0.9957	21.59	2.78	1,869.04
EtP	5–75	$y = 8.1357\text{E}6x + 5{,}956.6088$	0.5	1.0	0.9989	42.59	2.78	8,588.06
PrP	5–75	$y = 8.8467\text{E}6x + 11{,}045.5894$	0.5	1.0	0.9967	24.72	2.78	3,361.22
BtP	5–75	$y = 8.8013\text{E}6x + 21{,}913.0099$	0.5	1.0	0.9974	27.59	2.78	3,800.12

[a]limit of detection (S/N = 3); [b]limit of quantification; [c]correlation coefficient; [d]Student's *t* parameter calculated; [e]critical Student's *t* parameter at 95% confidence level ($\alpha = 0.05$; $n = 6$; $\nu = n-2$); [f]calculated *F* parameter.

Table 5
Results from the accuracy and precision of the proposed method for analysis of parabens in surface waters by DLLME

Analyte	Recovery %			RSD%		
	5 μg L^{-1}	25 μg L^{-1}	60 μg L^{-1}	5 μg L^{-1}	25 μg L^{-1}	60 μg L^{-1}
MeP	95.27	96.69	91.19	13.17	8.97	0.24
EtP	97.67	112.31	104.14	9.59	5.14	2.13
PrP	88.76	91.68	94.22	13.87	4.09	6.39
BtP	102.43	96.44	114.78	2.54	4.10	1.16

Table 6
Comparison of analytical performance data of the proposed method and other techniques in determination of parabens in water samples

Method	Analyte	LOD μg L^{-1}	LOQ μg L^{-1}	Sample mL	Recovery %	EF	Reference
FPSE-HPLC-DAD	MeP	2.85	9.5	10	96.3	95.4	[73]
	EtP	–	–		–	–	
	PrP	2.98	9.85		104.9	83.3	
	BtP	2.75	9.15		103.2	102.4	
RDSE-GC-MS	MeP	0.02	0.6	20	79.5	–	[74]
	EtP	0.02	0.8		82.1	–	
	PrP	0.04	0.12		82.1	–	
	BtP	0.06	0.15		91.4	–	
SPE-LC-MS/MS	MeP	0.024	0.08	250	79.0	–	[75]
	EtP	0.024	0.08		92.0	–	
	PrP	0.012	0.04		74.0	–	
	BtP	0.012	0.04		77.0	–	
DLLME-HPLC-DAD	MeP	1.0	2.0	10	43.3	48.0	This study
	EtP	0.5	1.0		68.0	75.6	
	PrP	0.5	1.0		86.3	95.9	
	BtP	0.5	1.0		94.7	105.2	

proposed method. In 60% of the analyzed samples, the presence of at least one type of paraben was identified, which might suggest anthropogenic contamination source.

As it is the first study to analyze parabens in the north and northeast of Brazil, there is no way to compare the evolution of the contamination of these water resources in relation to the presence of parabens. However, some authors have identified the presence of other emerging contaminants, which tend to be associated with anthropogenic contamination, such as bisphenol-A and ethinylestradiol in waters in Sao Luiz/MA [76] and Moreira [77] detected the presence of hormones 17β-estradiol and 17α-ethinylestradiol in a concentration range between 0.44 to 0.91 μg L^{-1} in the Gavião reservoir in Fortaleza/CE, the same as in this study.

Table 7 also shows the trophic status index of these reservoirs made available by the Water Resources Management Company (COGERH) in the state of Ceará and obtained according to the methodology proposed by Carlson [78] and adapted by Paulino et al. [79] for the management of reservoirs in the semi-arid of Ceará. Most of the them where the presence of parabens were detected eutrophic or mesotrophic, which corroborates the possibility of anthropogenic contamination, arising from the disposal of treated and untreated sewage and wastewater in cities and industries, located near or on the banks of these reservoirs [80].

4. Conclusion

In this study, multivariate experimental design was applied to optimize the extraction of parabens by DLLME in water. With the optimization, technique provided high enrichment factors for parabens analyzed, making the method more sensitive, besides contributing to the lower consumption of organic solvents, less exposure to them and minimal amount of sample. The most relevant factor for the extraction process is the proportion of solvent extraction/disperser. The proportion of sample volume has a less significant effect on the extraction process by DLLME.

Furthermore, the DLLME-HPLC-DAD method was successfully validated and the use of DAD as a detector for HPLC has proved to be a powerful tool in the determination and identification of compounds as it allows the online acquisition of their UV spectra.

Lastly, the DLLME-HPLC-DAD method was applied to determine parabens in surface water samples that are

Table 7
Results of the parabens analysis from different reservoirs of surface waters of Ceará, Brazil

Reservoirs	Level trophic[a]	MeP ± SD[b]	EtP ± SD[b]	PrP ± SD[b]	BtP ± SD[b]
		µg L^{-1}	µg L^{-1}	µg L^{-1}	µg L^{-1}
Acarape do Meio	Mesotrophic	ND	ND	ND	ND
Araçoiaba	Eutrophic	ND	ND	ND	ND
Batente	Eutrophic	ND	0.47 ± 0.08	ND	ND
Gavião	Mesotrophic	ND	0.51 ± 0.07	ND	ND
Itapebussu	Oligotrophic	ND	<LOD	ND	<LOD
Macacos	Eutrophic	ND	0.55 ± 0.04	ND	0.96 ± 0.33
Maranguapinho	Eutrophic	ND	ND	ND	0.59 ± 0.09
Pacajús	Mesotrophic	ND	0.77 ± 0.10	ND	ND
Pacoti	Eutrophic	ND	ND	ND	ND
Riachão	Eutrophic	ND	0.62 ± 0.04	ND	<LOD
Sítios Novos	Eutrophic	ND	<LOD	ND	0.61 ± 0.09

[a] Trophic State Index; [b] standard deviation (n = 3); ND = not detected.

used for human consumption, in Northeastern region of Brazil. The results showed that 60% of the studied samples are contaminated with parabens. These water resources are found in the semi-arid region of Brazil, where water availability is low, making it essential to monitor these and other contaminants to improve the quality of life of the population who depends on them.

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Supplementary information

Optimization of a dispersive liquid–liquid microextraction followed by liquid chromatography-diode array detection method for the determination of parabens in surface waters

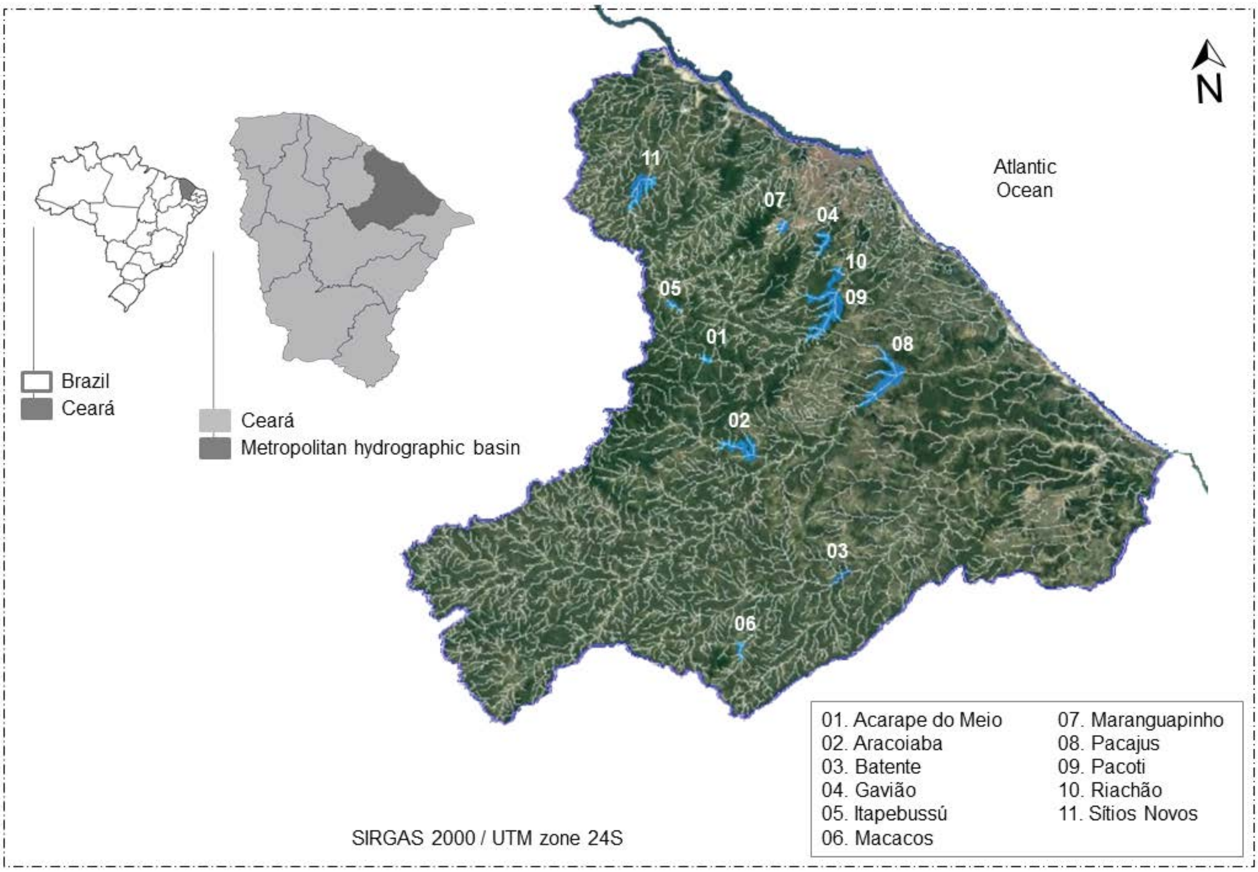

Fig. S1. Location of the surface water reservoirs analyzed, in the State of Ceará, Brazil.

Table S1
Identification and geographic coordinates of the surface water samples

Number	Reservoirs	City	Latitude* S	Longitude* W
1	Acarape do Meio	Redenção	–4.19366	–38.79973
2	Araçoiaba	Araçoiaba	–4.40239	–38.69906
3	Batente	Morada Nova	–4.65133	–38.49205
4	Gavião	Pacatuba	–3.90686	–38.55701
5	Itapebussu	Maranguape	–4.06028	–38.90159
6	Macacos	Ibaretama	–4.80240	–38.71086
7	Maranguapinho	Maranguape	–3.87925	–38.65152
8	Pacajús	Pacajús	–4.22245	–38.38713
9	Pacoti	Horizonte	–4.04323	–38.53842
10	Riachão	Itaitinga	–4.00000	–38.52616
11	Sítios Novos	Caucaia	–3.77200	–38.96261

*Global Positioning System (GPS) coordinates georeferenced by COGERH and cartographic projection SIRGAS 2000/UTM zone 24S.

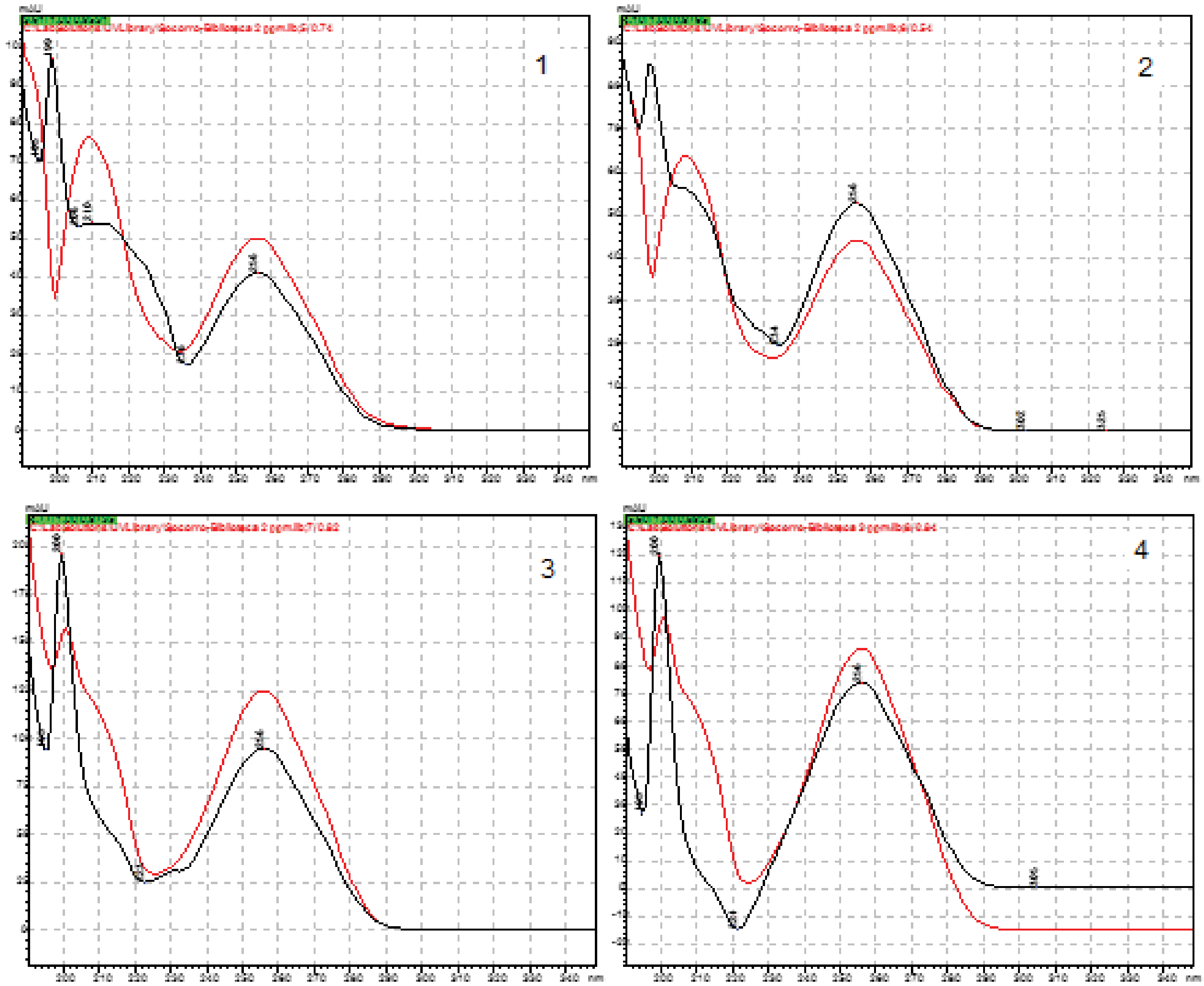

Fig. S2. Absorption spectra of a standard solution of 5 μg L^{-1} of parabens (red) and of a sample from the Pacoti reservoir spiked with 5 μg L^{-1} of parabens (black) obtained after extraction by DLLME with DAD, being: MeP (a), EtP (b), PrP (c) and BtP (d).