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Rapid Determination of Parabens in Water Samples by Ultra-high Performance Liquid Chromatography Coupled to Time of Flight Mass Spectrometry

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An analytical methodology has been developed and validated for the purpose of identifying and quantifying four parabens (methylparaben, ethylparaben, propylparaben and *n*-butylparaben) in water samples. The combination of rotating disk sorptive extraction (RDSE) technology with ultra-high performance liquid chromatography (UHPLC), along with electrospray ionization source (ESI) and time of flight mass spectrometry (TOF/MS) in trap mode, allowed for eliminating derivatization processes and a reduction of the chromatographic time required, achieving a greener analytical method. In this method, detection limits and precision (%RSD) were lower than 0.018 μg L^{-1} and lower than 9.7% for all the parabens, respectively, being better than similar works. Matrix effect and absolute recoveries were studied in tap and sewage water samples to observe suppressions of the signals for all analytes, and absolute recoveries were around 60%. This methodology was applied to the analysis of two sewage samples (punctual and composite) obtained from locations in Santiago, Chile.

Keywords Rotating-disk sorptive extraction (RDSE), parabens, UHPLC-ESI-TOF/MS, matrix effect, water samples

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Introduction

Parabens is the name given to a group of *p*-hydroxybenzoic acid (PHBA) esters that include methylparaben (MP), ethylparaben (EP), propylparaben (PP) and *n*-butylparaben (BP), among others. They are considered ideal preservatives because of their wide spectrum of anti-microbial activity, preventing the product from being affected by microorganisms, fungi or bacteria.[1] In addition, they are highly stable in regard to variation in pH, relatively safe to use, and have low production costs. Owing to these characteristics, they have been incorporated in products of daily use such as cosmetics, pharmaceutical drugs and foods.[2-4]

Parabens are found in low concentrations in a large variety of products to which the population and the environment are exposed. Recent studies have shown that parabens produce reproductive disorders in animal and human models.[5] In 2004, Darbre *et al*. found the presence of parabens in human breast tumor tissue at a concentration of between 4 – 20 ng g^{-1} and, thus, it is speculated that they may influence the growth and development of tumors.[6-8] Regarding environmental issues, many personal care chemicals are continuously released into the aquatic media through domestic sewage; therefore, this has given rise to growing concerns about their potential long term effects on wildlife.[1,8-10]

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According to the literature, several analytical methods have been proposed to detect parabens contributing to more efficient and greener technologies.[11] Extraction and desorption process are habitually considered the most crucial steps in analytical methods, as evidenced by the impact on results accuracy. For that reason, the extraction and desorption of parabens from aqueous samples were chemometrically optimized in a previous study developed by Becerra-Herrera *et al*.[12] by using the rotating disk sorptive extraction (RDSE) technique. Another study was then later developed using RDSE and cork as a sorbent phase, making a greener method.[13]

Liquid chromatography combined with mass spectrometry (LC-MS) has become one of the most extensively used techniques for the determination of parabens in aqueous matrices, due to its high sensitivity and specificity.[14] Currently, ultra high performance liquid chromatography (UHPLC) is becoming more commonly used and in combination with electrospray ionization source (ESI) and mass spectrometry (MS), they both can provide a significant increase in method sensitivity and feasibility, as well as a reduction of the analysis time.[15,16] Of the different mass analyzers available, the most frequently used include triple quadrupole (MS/MS), time of flight (TOF) and Orbitrap.[17-19] This last one allows for obtaining a full-scan product ion spectra with accurate masses of fragment ions, providing structural information of the compound. The identified compound structure is confirmed by comparing changes between experimental masses of fragment ions, which originate from parent ions, and exact molecular masses.[20]

The aim of this study is to develop a chromatographic method

for UHPLC-ESI-TOF/MS that permits identifying and quantifying four parabens: MP, EP, PP and BP in aqueous samples. The research includes the study of mobile phases using different solvents, mobile phase flows, injection volumes, injection mode, and ESI in positive and negative ion mode. The ion suppression/enhancement effect was studied and the different responses of each compound to this matrix effect were discussed. The eco-efficiency of the method proposed was calculated and compared with others, demonstrating that it is the greenest method, and deserves consideration as an excellent green analytical chemistry method. Lastly, this method was applied to analyze sewage samples from two locations in Santiago, Chile, in order to identify and quantify the parabens in real samples.

Experimental

Reagents and chemicals

Water from a Millipore Milli-Q Plus water system (Billerica, MA) was used throughout the experiment. Methyl paraben, ethyl paraben, propyl paraben, and *n*-butyl paraben were purchased from Sigma-Aldrich (Milwaukee, WI, USA). The standard stock solution of each analyte (200 mg L^{-1}) was prepared separately in methanol (MeOH) (Fisher Scientific, Fair Lawn, NJ, USA). Nitrogen with a purity of ≥99.999% was purchased from Linde (Santiago, Chile) and it was used in the final extract evaporation. Methanol (LC/MS grade, 99.8% purity), acetonitrile (ACN) (LC/MS grade, 99.8% purity), and ammonium acetate were supplied by Merck. The Oasis® HLB extraction cartridges were obtained from Waters Corporation (Milford, MA, USA).

Sample preparation

An extraction method (RDSE) specifically designed for extracting parabens from wastewater samples was used.[12] In this process, Oasis® HLB sorbent (50 mg) was loaded on the disk cavity. Before extraction, the disk containing the sorptive phase was placed inside the beaker and conditioned with ethyl acetate, methanol and Milli-Q water, and stirred at 2000 rpm for 5 min each.[12]

For extraction, 20 mL of a sample at pH 6 (buffered with HCl 1 M) with 5% methanol were added to the beaker and the disk was rotated at 2900 rpm for 70 min at room temperature. These conditions were previously optimized by Becerra-Herrera *et al.*[12] The effects of pH value and % methanol on the extraction of parabens were studied; pH values and % methanol ranging from 2 to 10, and 0 to 15%, respectively, were checked; and the optimal values were found to be pH 6 and 5% methanol. After extraction, the disk was placed into a 15-mL beaker containing 5 mL of methanol as a desorption solvent and stirred twice for 10 min at 2000 rpm. Afterwards, the methanol extract containing the concentrated analyte was evaporated under a N_2 stream to dryness.[12] At the end, the extract was redissolved in 500 µL of methanol and it was filtered through a 0.22-µm pore size and 13 mm diameter nylon filter. Ten microliters of this solution were injected into the UHPLC-ESI-TOF/MS.

In the samples study, 60 mL of water sample was necessary to perform the analysis in triplicate (20 mL × 3).

UHPLC-ESI-TOF/MS analysis

A PerkinElmer Flexar FX-15 ultra-performance liquid chromatography system (PerkinElmer, USA), with a binary pump system, a vacuum degasser, a cooling autosampler, and a thermostated column compartment, was used to perform chromatographic analysis.

Separation was carried out using an analytical column Brownlee SPP-C18 (2.1 × 75 mm, 2.7 µm) (PerkinElmer, USA), which was kept at 20°C. Moreover, optimum separation was achieved thanks to a binary mobile phase gradient at a flow rate of 0.3 mL min^{-1}, and the injection volume was 10 µL. Solvents were (A) water/ammonium acetate (5 mM) pH 6.5, and (B) methanol. In this sense, the program required 1.5 min to equilibrate the system prior to injecting the sample (0% B). After that, the gradient elution program was as follows: 0 – 1 min, 0 – 90% B; 1 – 2 min, 90 – 95% B; 2 – 3 min, 95 – 100% B; 3 – 4 min, 100% B.

The identification and quantification of parabens were both obtained using an AxION 2 TOF MS system equipped with a Dual Probe Electrospray Ionization Source (ESI) and controlled by Chromera Software and TOF MS Driver Software (PerkinElmer, USA).

During this process, the source working conditions were: capillary exit –100 V, capillary voltage 6000 V, gas flow rate 10 L min^{-1}, drying gas temperature 300°C and nebulizer pressure 80 psi. Acquisition function was in Trap mode, setting the parameters "IG Exit Low" and "Trap/Pulse Delay" at 6 and 19 µs, respectively so as to improve the sensibility of the analysis. LC/MS accurate mass spectra were recorded across the range 100 – 1200 *m/z* in negative mode. The identification and quantification of the four parabens was performed using the commercial standards indicated above.

Results and Discussion

Method optimization to determine parabens

In order to perform an optimal extraction of parabens from water, different chemical and preconcentration factors were examined. Variables were studied in tap water spiked with a known concentration of parabens to evaluate the matrix effect, among others.[12]

Taking into account that the TOF analyzer is combined with an electrospray ionization source, the ionization of analytes should be assisted by using an appropriate mobile phase to achieve the efficient deprotonation and separation of the parabens. At this point, it is pertinent to work within a range of pH 2 to 9 since the best column stability is located between these values.

Bearing this information in mind, different mobile phases (methanol, acetonitrile, water mixed with formic acid, acetic acid and ammonium acetate) in gradient programs were tested. Figure 1 shows the amplitudes achieved when different mobile phases were studied. As can be seen, pH values were from 2.3 to 6.5. Working with pH 6.5, 5 mM of ammonium acetate was added to an aqueous phase, stabilizing the pH water and allowing for obtaining better results. Higher pH values were not analyzed as the use of higher salt concentration is not recommended for the column stability and lifetime. Comparing the organic modifier, amplitudes obtained using acetonitrile were lower than using methanol. Suitably, methanol was selected as the organic modifier. It is pertinent to highlight that stability in retention times was also better using mobile phases containing methanol, as well as the higher peak area and peak shape of the analyzed compounds.

In order to optimize the identification and quantification of parabens in standard solutions and sewage samples, mobile phase flows (0.2, 0.3, 0.4 and 0.5 mL min^{-1}), two injection volumes (5 and 10 µL) and three injection modes (partial loop, fixed loop and µL-pick up) were tested. The combination of

0.3 mL min^{-1} flow rate, 10 µL injection volume, and partial loop injection showed optimal compounds separation within 4 min (Fig. 2). ESI in positive and negative ion mode was also evaluated, observing that all compounds were ionized in negative mode.

Knowing the advantages in the use of trap mode, detection was monitored using this option.[21]

Table 1 shows the empirical formula, exact mass, theoretical and experimental *m/z* in negative mode, error (ppm) and retention time (min) for each compound. As evidenced, ppm error was smaller than 1.2 for all the studied compounds, proving the TOF/MS reliability.

It should be noted that the use of the Dual Probe Electrospray Ionization Source presents a great improvement over conventional Electrospray Ionization Sources allowing for both calibration and sample analysis simultaneously. Thus, the mass precision is guaranteed, reducing the error (ppm).

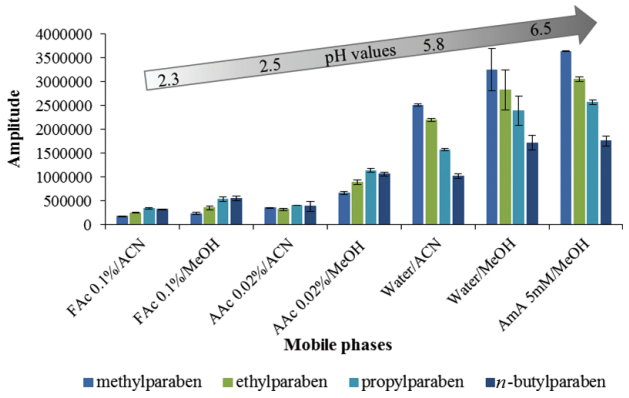

Fig. 1 Amplitudes achieved when different mobile phases were tested in UHPLC-ESI-TOF MS (FAc: formic acid; AAc: acetic acid; AmA: ammonium acetate). The arrow indicates the pH increment using the different mobile phases.

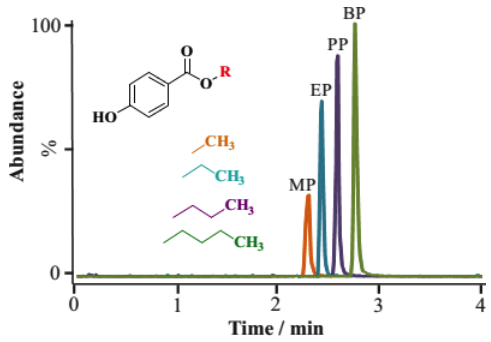

Fig. 2 Extracted ion chromatograms of parabens in a multi-standard solution containing 500 µg/L of each analyte.

As detailed in Table 1, all parabens have different *m/z* values, supporting their determination by liquid chromatography in similar times even at the same time. Additionally to the UHPLC, the AxION 2 TOF MS system has a connected syringe pump, whereby the sample may be directly infusioned into the ESI-TOF MS without using the UHPLC. In Fig. 3, a mass spectrum of 4 parabens obtained using a syringe pump is shown. The use of this syringe pump allows for identifying the existence of parabens in samples in 10 s. Due to the mechanism of the syringe pump, it is impossible to perform a calibration curve that would allow quantification of parabens, however, a preliminary screening of the presence of the parabens in a sample could be performed. Furthermore, thanks to the use of a TOF MS analyzer, the stability of *m/z*, the ppm error, and the isotopy of each compound could be checked, ensuring the determination of each compound and eliminating possible interferences. It is remarkable that, avoiding HPLC use, some sample pretreatment steps can be omitted, reducing requirements for reagents and time, and allowing for performing a screening of different kinds of liquid samples (urine, milk, juice, *etc.*).

Calibration curve, LOD and LOQ, and method precision

With the purpose to assure both a suitable identification and a quantification of the studied compounds, the figures of merit of the chromatographic method were studied. The calibration curves, correlation coefficients, detection limits (LODs) and quantification limits (LOQs) were obtained by LC-TOF/MS analysis with an extracted ion chromatogram (EIC) mode of deprotonated molecular ion. Linearity was scrutinized by the injection of standard solutions at eight concentration levels from 10 to 500 µg L^{-1}. Coefficients of correlation (r^2), method precision, LODs and LOQs have been detailed in Table 2.

The precision of this method, expressed in terms of relative standard deviation (%RSD), was evaluated for each compound, performing the whole procedure (extraction process and determination of compounds in UHPLC-ESI-TOF MS) 10 times with parabens at concentration levels of 250 µg L^{-1} in sewage.

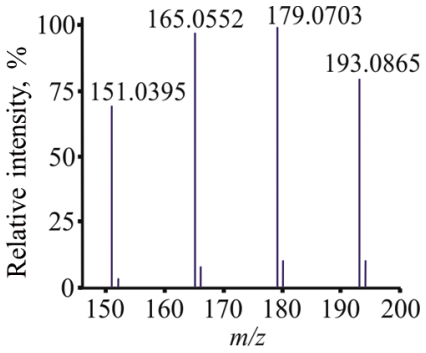

Fig. 3 Mass spectrum of methylparaben (151.0395), ethylparaben (165.0552), propylparaben (179.0703), and *n*-butylparaben (193.0865) obtained by direct infusion.

Table 1 Formula, theoretical and experimental mass/charge (*m/z*), error (ppm) and retention time (min) of the compounds

Compound	Formula	Exact mass	Theoretical *m/z* [M–H]$^-$	Experimental *m/z* [M–H]$^-$	Error, ppm	Retention time/min
Methyl paraben	$C_8H_8O_3$	152.0473	151.0394	151.0395	–0.7	2.42
Ethyl paraben	$C_9H_{10}O_3$	166.0629	165.055	165.0552	–1.2	2.53
Propyl paraben	$C_{10}H_{12}O_3$	180.0786	179.0708	179.0703	–1.1	2.64
n-Butyl paraben	$C_{11}H_{14}O_3$	194.0943	193.0864	193.0865	–0.5	2.75

Repeatability values lower than 9.7% were achieved for all compounds (Table 2).

The LODs and LOQs of the method were determined by injecting a calibration curve in matrix (sewage) between 5 and 50 μg L^{-1}. Resulting in values ranging from 0.008 to 0.018 and 0.027 to 0.055 μgL^{-1}, respectively.

To study matrix effect (ME) and recovery (Re), a technique previously defined was developed to evaluate these processes independently.[21] Thus, making use of Eqs. (1) and (2) for matrix effect and recovery, respectively, precise values were acquired in tap water and sewage:

$$ME\ (\%) = 100 \times (Ax_{S2} - Ax_{S3})/Ax_{S1} \quad (1)$$

$$Re\ (\%) = 100 \times (Ax_{S4} - Ax_{S3})/Ax_{S2} \quad (2)$$

where Ax_{S1}, Ax_{S2}, Ax_{S3} and Ax_{S4} correspond to the abundances (A) obtained for the parabens (x) from samples S1 (multi-standard solution of 500 μg L^{-1} of each paraben); S2 (tap water/sewage extract obtained using RDSE that had been enriched with 500 μg L^{-1} of the parabens before injection); S3 (extract obtained directly from a tap water/sewage sample); and S4 (extract obtained from a tap water/sewage sample enriched with 12.5 μg L^{-1} of each paraben).

On the one hand, as Table 2 shows, all compounds had an ME value lower than 100, meaning that all compounds had experienced suppression in these responses, showing similar values in tap water and sewage. On the other hand, absolute recovery values were different in tap water and sewage, with values being better when tap water was tested.

Real sample analysis

In order to assess the efficiency of the proposed method, it was applied to the analysis of sewages samples obtained from different places in Santiago, Chile. In each location, a punctual (P) sample (collected by a specialist between 10:00 and 11:00 am) and a composite (C) sample (collected at any time over 24 h) were taken. All samples were prepared in triplicate and injected three times into UHPLC-ESI-TOF MS.

As shown in Table 3, methylparaben and *n*-butylparaben were found in all punctual and composite samples, with lower concentrations in composite samples. Propylparaben showed the highest concentrations, being similar in punctual and composite samples. As an example, an extracted ion chromatogram of parabens in a punctual sewage sample (S-1P) is shown in Fig. 4. This information might indicate that the concentrations obtained in composite samples are lower due to the dilution of the sample (collected over 24 h).

Eco-efficiency and comparison with previous methodologies

Considering the analytical eco-scale proposed by Galuszka *et al.* in 2012,[26] which is based on the assignment of penalty points to the parameters of an analytical process. This parameter joined to recoveries, LOD, and %RSD of this work and similar previous works reported in the literature are compared in Table 4. According to this scale, an ideal green analysis has a

Table 2 Coefficients of correlation (r^2), method precision, LODs, LOQs, matrix effect (ME) and recovery (Re) for each paraben

Compound	Linearity, r^2	(%RSD) SW	LOD/ μg L^{-1}	LOQ/ μg L^{-1}	ME, % TW	ME, % SW	Re, % TW	Re, % SW
Methylparaben	0.998	2.5	0.018	0.055	61.2	62.3	59.8	53.1
Ethylparaben	0.999	2.8	0.014	0.043	75.2	82.6	61.4	60.9
Propylparaben	0.997	9.7	0.010	0.031	67.8	71.2	67.1	57.1
n-Butylparaben	0.997	9.5	0.008	0.027	72.4	78.1	64.7	62.3

Table 3 Parabens concentrations (μg L^{-1}) in punctual (S-1P and S-2P) and composite (S-1C and S-2C) sewage samples

Sample	Methylparaben	Ethylparaben	Propylparaben	*n*-Butylparaben
S-1P	4.338 ± 0.846	n.d.	14.317 ± 1.008	0.895 ± 0.272
S-1C	0.631 ± 0.107	n.d.	14.905 ± 6.070	0.666 ± 0.169
S-2P	2.956 ± 1.216	n.d.	2.455 ± 0.452	0.504 ± 0.016
S-2C	1.754 ± 0.848	n.d.	n.d.	0.440 ± 0.149

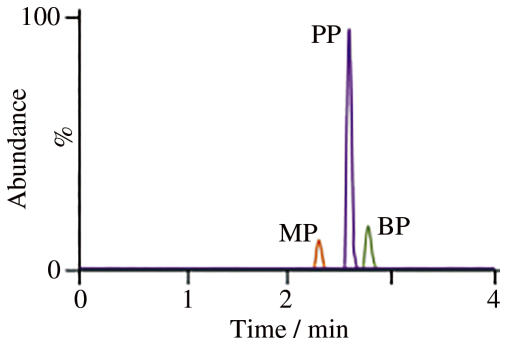

Fig. 4 Extracted ion chromatogram of parabens in a punctual sewage sample (S-1P).

Table 4 Comparison of chromatographic time, LOD, recoveries (%), %RSD and eco-efficiency of different analytical methods for the extraction and determination of parabens

Analytical method	Chromatographic time/min	LOD	Re, %	%RSD	EE	Ref.
LC-MS/MS	5	0.03 - 0.06 ng g^{-1}	82 - 108	13.8	94	22
SM-SLLME-UHPLC-QqQ	10	0.1 - 0.2 ng mL^{-1}	91 - 106	8	90	23
MLPDE-HPLC-UV	7	0.285 - 1.112 mg kg^{-1}	93.7 - 107.9	5.2 - 5.3	95	24
BaμE-HPLC-DAD	20	0.1 μg L^{-1}	85.6 - 100.6	<10.2	95	25
RDSE-GC-MS	14	0.02 - 0.05 μg L^{-1}	79 - 91	2 - 9	95	12
RDSE-HPLC/MS	8	0.24 - 1.81 μg L^{-1}	80 - 115	4.7 - 16	97	13
RDSE-UHPLC-TOF/MS	4/0.2[a]	0.008 - 0.018 μg L^{-1}	59.8 - 67.1	2.5 - 9.7	97	This work

LLE: liquid-liquid extraction; SM-SLLME: stir-membrane solid-liquid-liquid micro-extraction; MLPDE: matrix liquid-phase dispersion extraction; BaμE: bar adsorptive micro-extraction. a. Time necessary when direct infusion was employed.

value of 100 points. For each parameter of the analytical procedure (quantity of reagent, hazard, energy and waste), penalty points are assigned, allowing to classify the methodology within green chemistry.

Penalty points have a value of 3 for the methodology developed combining RDSE and HPLC-TOF/MS, which means that the analytical scale has a value of 97, positioning it as an excellent green methodology. As detailed in Table 4, the eco-efficiency (EE) of this work compared with other methodologies is excellent, mainly due to the low volume of solvents used and the reduction in the chromatographic time. It is noteworthy that chromatographic time was lower than in the reported studies, and it was reduced three times in comparison to the method proposed by the authors.[12] In addition, LOD and %RSD were also better in this study. Comparing the proposed method with other previously reported studies using RDSE with green sorbents and HPLC-MS/MS,[12] the EE is similar but this method obtained a better LOD and chromatographic time. A combination between both methods (one for extraction method and the other for analysis method) would be an excellent green method. Recoveries were lower than in other studies but it only represented the extraction method, which was the same previously developed by Becerra-Herrera *et al.*[12] The lower values in this study can be a result of matrix effect when UHPLC-TOF/MS was used to determine parabens, as the method has not been studied previously for these compounds in any reported work.

Conclusions

A rapid and green methodology for the identification and quantification of parabens in water samples has been purposed.

The RSDE method combined with an UHPLC-ESI-TOF/MS showed fruitful results in terms of RSD%, ppm error, matrix effect, recovery and LOD. The method enabled a concomitant reduction in analysis time, as well as elimination of the derivatization process. The designed method grants reliable identification and quantification of four parabens in only 4 min.

To validate the methodology, these compounds were determined in punctual and composite sewage samples. This platform can be used to perform a screening of parabens in samples in 10 seconds by direct infusion.

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