Analytica Chimica Acta 1063 (2019) 159–166

Contents lists available at ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Single drop microextraction in a 96-well plate format: A step toward automated and high-throughput analysis

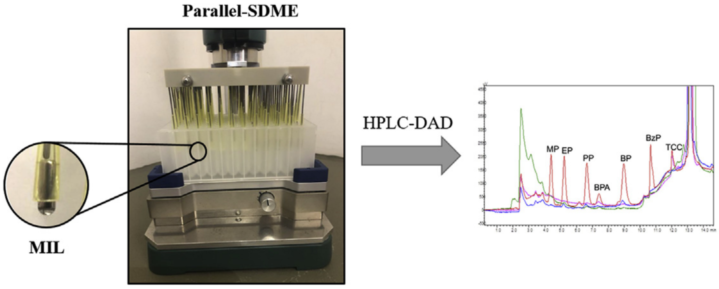
Gabriela Mafra [a], Augusto A. Vieira [a], Josias Merib [b, **], Jared L. Anderson [c], Eduardo Carasek [a, *]

[a] Departamento de Química, Universidade Federal de Santa Catarina, Florianópolis, SC, 88040-900, Brazil
[b] Departamento de Farmacociências, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, 90050-170, Brazil
[c] Department of Chemistry, Iowa State University, Ames, IA, 50011, USA

HIGHLIGHTS

- A novel magnetic ionic liquid-based methodology named Parallel Single Drop Microextraction (Pa-SDME) is proposed.
- The semi-automated methodology exhibited high-throughput and environmentally-friendly aspects.
- This configuration allows for the extraction of up to 96 samples simultaneously.
- Very satisfactory stability and analytical performance were obtained.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 21 November 2018
Received in revised form
31 January 2019
Accepted 4 February 2019
Available online 21 February 2019

Keywords:
Magnetic ionic liquids
Parallel single drop microextraction
Sample preparation
Endocrine disrupters compounds
High-throughput
96-well plate

ABSTRACT

In this study, an innovative and high-throughput parallel-single-drop microextraction (Pa-SDME) using the $[P^{+}_{6,6,6,14}]_2[MnCl_4^{2-}]$ magnetic ionic liquid (MIL) as extraction phase is demonstrated, for the first time, in the determination of methylparaben, ethylparaben, propylparaben, bisphenol A, butylparaben, benzophenone and triclocarban from environmental aqueous samples. This experimental setup comprised of a 96-well plate system containing a set of magnetic pins which aided in stabilizing the MIL drops and enabled the simultaneous extraction of up to 96 samples. Using this low-cost experimental apparatus, the sample throughput was lower than 1 min per sample. This novel approach exhibits a number of advantages over classical SDME approaches, particularly in maintaining a stable solvent microdrop and facilitating high-throughput analysis. Experimental conditions were carefully optimized using one-factor-at-a-time and multivariate designs. The optimal conditions employed 5.38 ± 0.55 mg (n = 10) of MIL, a sample volume of 1.5 mL at pH 6, and dilution in 20 µL of acetonitrile. The analytical parameters of merit were determined under the optimized conditions and highly satisfactory results were achieved, with LODs ranging from 1.5 to 3 µg L^{-1} and coefficients of determination higher than 0.994. Intraday and interday precision ranged from 0.6 to 21.3% (n = 3) and 10.4–20.2% (n = 9), respectively, with analyte relative recovery in three aqueous samples ranging between 63% and 126%.

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* Corresponding author.
** Corresponding author.
E-mail addresses: josias@ufcspa.edu.br (J. Merib), eduardo.carasek@ufsc.br (E. Carasek).

https://doi.org/10.1016/j.aca.2019.02.013

1. Introduction

Sample preparation plays a critical role in chemical analysis, especially in trace-level determination since it is generally necessary to obtain preconcentration of the analytes and eliminate potentially interfering compounds from the matrix to ensure precise and accurate results [1]. Traditional liquid-liquid extraction (LLE) and solid-phase extraction (SPE) approaches can be laborious, time-consuming, and generally require large quantities of organic solvents and/or samples. Therefore, current trends toward simplification and miniaturization of sample preparation steps focus on designing novel and innovative microextraction approaches [2]. Microextraction techniques have provided a significant improvement in sample preparation since these techniques allow for both enrichment and isolation of the analytes in a single step. Ideally, these techniques should exhibit speed and be simple, low-cost, and compatible with a wide range of analytical instrumentation [1,3].

In this regard, several techniques have been developed, particularly based on solvent microextraction (SME), as demonstrated by Dasgupta [4] and Cantwell [5] in the 1990s. Single-drop microextraction (SDME) was the first SME mode of application. Typically, SDME involves the use of a few microliters of an organic solvent microdrop maintained on the tip of a microsyringe, which is exposed directly in the liquid matrix or in the headspace above the sample. Following extraction, the microdrop is withdrawn and transferred to the analytical instrument [6]. The main advantages of SDME include good extraction capacity, rapid mass transfer, versatility, low-cost and little to no carryover effects [7]. However, some significant drawbacks have also been observed, specifically regarding the instability of the microdrop in the direct-immersion mode under high stirring rates, elevated temperatures and long microextraction times [8,9].

In SME approaches, the extraction solvent has a significant influence on the extraction efficiency. Conventional solvents such as 1-octanol, n-hexane, toluene, dodecane and hexadecane exhibit drawbacks mainly related to the extraction selectivity and high volatility, which can hinder the extraction efficiency and precision [10–14]. As a result, alternative solvents such as ionic liquids (ILs) have been evaluated in a number of microextraction procedures [15,16].

ILs are organic molten salts which have melting points at or below 100 °C and possess numerous advantageous physicochemical properties such as low or negligible vapor pressure at room temperature, high viscosity and chemical/electrochemical stability. Moreover, the chemical structures can be tailored to enhance interactions with specific classes of compounds, and the large possibilities of combination of cations and anions increase the range of applicability of these solvents [17]. Studies involving IL extraction solvents in SDME, in both HS and DI modes, have been reported for the determination of a variety of analytes including PAHs [16], sulfonamides [18], polychlorinated biphenyls [19], antidepressants [20], as well as trace elements [21,22] in several environmental and biological matrices.

Recently, an interesting subclass of ILs, called MILs has been exploited in a number of analytical applications. MILs are produced by incorporating a paramagnetic component in the IL structure (in general, transition or rare-earth metal anions or metal complexes) and exhibit a strong response to an external magnetic field. Due to their paramagnetic properties, MILs have an advantage of simplifying an extraction method and minimizing sources of error due to their rapid recovery from the sample solution with the aid of a rod magnet [23]. The application of MILs as extraction solvents in SDME offers advantages including no longer requiring a micro-syringe to form the microdrop, which enables larger volumes of droplet in comparison to the conventional solvents used in SDME as well as significant enhancement in microdrop stability [24]. These magnetic solvents are extensively used in catalytic processes [25] and engineering [26], but also have been exploited in sample preparation including DLLME [27–30], SDME [24,31,32], and other related techniques [33,34].

The development of automated analytical procedures which provides reduced analysis time, higher sample throughput and greater reproducibility through reduction of human error are highly desirable [13,35–39]. An important advancement to facilitate high-throughput analysis is the use of a 96-well plate system, a powerful tool that allows for the simultaneous analysis of up to 96 samples in parallel, reducing substantially the extraction/desorption time required in the sample preparation step [11,40–42].

This study reports for the first time a parallel-SDME/MIL-based (Pa-SDME) analytical methodology which combines the magnetic properties, drop stability, and extraction capacity of the trihexyl(tetradecyl)phosphonium tetrachloromanganate (II) ($[P^{+}_{6,6,6,14}]_2[MnCl_4^{2-}]$) MIL when coupled with a 96-well plate to facilitate high-throughput analysis by producing a low-cost apparatus capable of analyzing a series of samples simultaneously. The endocrine disrupting compounds methylparaben, ethylparaben, propylparaben, butylparaben, bisphenol A, benzophenone and triclocarban were selected as model analytes for the development of this low-cost method with separation/detection performed by HPLC-DAD. The optimizations were conducted through the evaluation of one-factor-at-a-time and using multivariate strategies, and the determination of the analytical parameters of merit for each analyte was carried out under optimal conditions. This innovative experimental setup is a first step in the development of fully automated MIL-based microextraction techniques, in which the features of these solvents are explored and combined with high-throughput procedures.

2. Experimental

2.1. Reagents and materials

High-purity analytical standards ($\geq$98%) of methylparaben (MP), ethylparaben (EP), propylparaben (PP), butylparaben (BP), bisphenol A (BPA), benzophenone (BzP) and triclocarban (TCC) were purchased from Sigma-Aldrich (St. Louis, MO, USA). High-performance liquid chromatography (HPLC) grade acetonitrile (ACN), acetone and methanol (MeOH) were purchased from Merck (Kenilworth, NJ, USA). The reagents trihexyl(tetradecyl)phosphonium chloride ($[P^{+}_{6,6,6,14}][Cl^{-}]$) (97,7%) Aliquat® 336 (mean molecular weight 442.0) and manganese (II) chloride tetrahydrate ($MnCl_2 \cdot 4H_2O$) (98%) were obtained from Sigma Aldrich. Additionally, hydrochloric acid and sodium hydroxide were purchased from VETEC (Rio de Janeiro, RJ, Brazil) to prepare solutions of 0.1 mol L^{-1} in order to adjust the pH of the samples. Ultrapure water (18.2 MΩ cm) was purified by the Mega Purity water purification system (Billerica, MA, USA). Aqueous samples were filtered with the aid of MT ™ Membrane Filters (0.45 μm HA) purchased from Merck Millipore Ltd. (Tullagreen, Carrigtwohill Co Cork, Ireland).

Individual stock solutions of the analytes were prepared at a concentration of 1000 mg L^{-1} in MeOH. In addition, working solutions containing a mix of the analytes at concentrations of 100 mg L^{-1} and 10 mg L^{-1} were prepared by diluting appropriate amounts of the stock solution in MeOH.

2.2. Synthesis of the extraction phase (MIL)

Synthesis of the magnetic ionic liquid (MIL) was carried out through the addition of 0.5 equivalent of $MnCl_2 \cdot 4H_2O$ and 1 equivalent of $[P^{+}_{6,6,6,14}][Cl^{-}]$ or $[Aliquat^{+}][Cl^{-}]$ in 10 mL of dichloromethane, according to previous studies [28]. The reaction was conducted at room temperature (21 °C) during 24 h under constant agitation. The product was dried overnight in a vacuum oven at 70 °C; additional details can be found elsewhere [29,31]. Characterization of the MILs was performed according to a previous study [28] with UV data included in Supporting Information.

2.3. Instrumentation

Liquid chromatography was performed using a Shimadzu LC-20A system (Tokyo, Japan). The HPLC was comprised of a Rheodyne manual injector with sample loop of 20 µL, two LC-20AT pumps, a DUG-20A$_3$ degasser, and a SPD-20 UV/Vis detector. The LC separation was carried out by a Thermo Scientific C18 analytical column (250 mm × 4.6 mm i.d. x 5.0 µm) (Waltham, MA, USA) with a flowrate of 1 mL min^{-1}. The gradient mode used in the analysis consisted of water (A) 50% and ACN (B) 50% (0–4 min), then the concentration of mobile phase A was reduced to 10% A (4–5 min) and maintained up to 17 min, followed by increasing the concentration of mobile phase B to 100% (17–23 min) to cleaning the LC system. From 23 to 23.5 min B percentage was decreased again to 50% and, this ratio was kept until the end of the analysis (26 min). The wavelengths monitored were 260 nm, 226 nm, 255 nm and 265 nm for parabens, BPA, BzP and TCC, respectively.

A semiautomatic 96-well plate system, obtained from Brüder Mannesmann Werkzeuge (Remscheid, NRW, Germany), was used to perform the extractions/dilution studies. Neodymium magnets (N35, 3 mm × 8.5 mm, 0.595 T) were purchased from Ímã Shop (São Paulo, SP, Brazil).

2.4. Magnet-based 96-well plate system

The lab-made extraction apparatus is based on neodymium magnet rods that are fixed in the pins of a conventional extraction blade of a 96-well plate system with pipette tips as guiding tubes and epoxy glue. Therefore, the produced blades exhibit the capacity of maintaining a certain amount (mg) of MIL during the SDME procedure due to the magnetic properties of the solvent. This configuration is capable of performing a series of extraction and desorption/dilution steps using a relatively large amount of extraction solvent and maintaining the stability of the microdrop, even with high stirring rates in direct-immersion mode. A scheme of the new configuration used in this study is shown in Fig. 1.

2.5. Optimization of the Pa-SDME/MIL-based approach

Optimizations were conducted through the evaluation of one-factor-at-a-time and the use of multivariate strategies. In this study, an average mass of 5.38 ± 0.55 mg (n = 10) corresponding to 10 µL of [P$^+_{6,6,6,14}$]$_2$[MnCl$_4^{2-}$] or [Aliquat$^+$]$_2$[MnCl$_4^{2-}$] was used. The analyte concentrations were kept at 500 µg L^{-1} and the sample volume was fixed at 1.5 mL. The extraction efficiency for each MIL was evaluated by extractions (n = 3) of the analytes in ultrapure water. Extraction time (30, 60, 90, 120 and 150 min) and sample pH (3, 6 and 9) were optimized using a Doehlert design that consisted of 9 experiments, these levels were chosen based on previous studies in which both variables were also examined [28,31]. The MILs evaluated are soluble in organic solvents such as ACN; therefore, allowing for the compatibility with the HPLC system. The dilution volume of ACN was evaluated by one-factor-at-a-time using 20, 50 and 80 µL (n = 3). All statistical analyses were performed using StatSoft Statistic 8.0 (Round Rock, TX, USA) and Microsoft Excel 2016 (Redmond, WA, USA).

2.6. Pa-SDME/MIL-based approach procedure

Firstly, a certain amount of MIL was weighed in each spot of a 96-well plate. Therefore, the blade comprised of a series of neodymium magnets was put in contact with the extraction phase. Due to the strong response to the magnetic field, the mass of MIL initially weighted was attracted and kept in the rod magnets. These blades containing approximately 5 mg of [P$^+_{6,6,6,14}$]$_2$[MnCl$_4^{2-}$] placed at the base of each magnetic pin were immersed in the vials with a sample volume of 1.5 mL at pH = 6 and containing the analytes (Fig. 1). The extraction was carried out for 90 min using continuous shaking of 500 rpm, followed by dilution. In the end of the extraction time, the extraction blades containing the magnetic rods were withdrawn, simultaneously, from the sample solution and the vials containing the samples were replaced by vials containing acetonitrile to the dilution step. In this step, the brush containing the magnetic pins and the MIL enriched with the analytes was immersed in a new well plate with 20 µL of ACN in each vial, followed by injection of the diluted solution into HPLC-DAD. The rinsing step was performed in 96-well vials containing 50 µL of acetone for a few seconds. This procedure was repeated between every new extraction/dilution cycle.

2.7. Analytical figures of merit and application in environmental aqueous samples

Figures of merit such as linear range, trueness, precision, enrichment factor, limit of detection (LOD) and limit of quantification (LOQ) were determined using the optimized extraction conditions. Calibration curves were constructed using the method of standard addition for each analyte at seven concentration levels (n = 3), in this case, known concentrations of analytes were added to the samples and subjected to the extractions. The LOQ was established as the first concentration of the calibration curves which provided satisfactory results for precision (≤20%), and the LOD was obtained through the division of LOQ by 3.3. The precision of the method was calculated based on the relative standard deviation (RSD). The enrichment factor (EF) was used to evaluate the extraction performance of the method and was calculated according to Equation (1) below:

$$EF = \frac{C_{MIL}}{C_{initial}} \tag{1}$$

where C$_{\text{MIL}}$ is the concentration of the analytes in the MIL droplet following the extraction and C$_{\text{initial}}$ is the initial concentration of analyte in the aqueous solution.

Intraday precision (n = 3) was evaluated at three concentrations (LOQ, 50 µg L^{-1} and 500 µg L^{-1}) for each analyte, and interday (evaluated in 50 µg L^{-1}) was carried out in three consecutive days (n = 9). In this step, to evaluate the RSD using random positions of the 96-well plate, different extraction positions (n = 6) were chosen according to Fig. S-5 of the Supporting Information, and extractions in lake water samples spiked with the analytes at 50 µg L^{-1} were performed. Trueness of the method was evaluated through relative recovery assays using samples of lake, stream and swamp spiked at three concentrations (LOQ, 50 µg L^{-1} and 500 µg L^{-1}). The reported lake constantly receives urban and hospital waste and it's in eutrophic conditions as shown in Figure S-6. The samples were collected in different locations near Federal University of Santa Catarina. These aqueous samples were filtered and immediately analyzed.

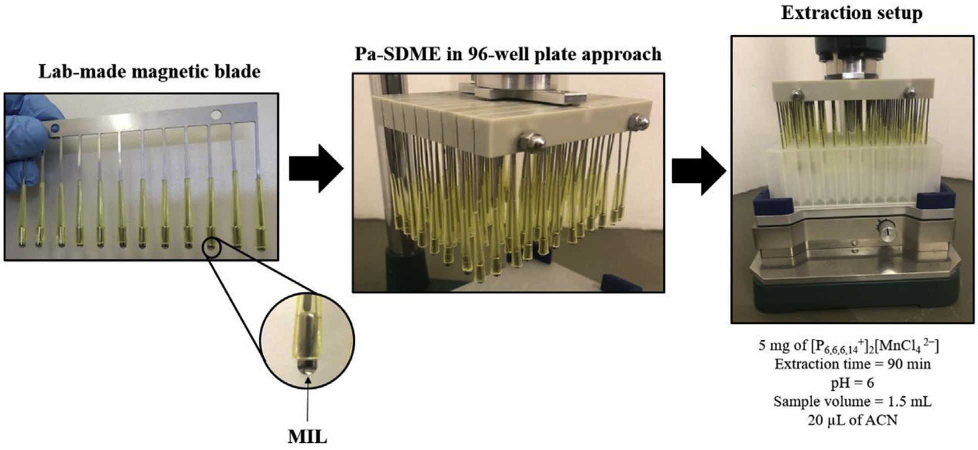

Fig. 1. An overview of the extraction procedure using the novel Pa-SDME/MIL-based approach.

3. Results and discussion

3.1. Extraction efficiency comparison

The nature of the extraction phase plays an important role in solvent microextraction process; therefore, the choice of an adequate extraction phase is one of the most important parameters that need to be optimized in SDME procedures. The extraction phase directly affects the distribution coefficient, and its physicochemical properties can also greatly affect the extraction kinetics. Desirable characteristics of a good extraction phase include high stability, affinity for the analytes and low volatility [6]. Thus, an experiment evaluating the extraction efficiency and drop stability was performed regarding two MILs, including $[P^{+}_{6,6,6,14}]_2[MnCl_4^{2-}]$ and $[Aliquat^{+}]_2[MnCl_4^{2-}]$. As can be observed in Fig. S-7 higher extraction efficiency for the analytes were obtained when $[P^{+}_{6,6,6,14}]_2[MnCl_4^{2-}]$ was employed, except for TCC.

On the other hand, when $[Aliquat^{+}]_2[MnCl_4^{2-}]$ was employed, higher values of RSD were observed, probably associated to the lower stability of anchorage of this MIL on the magnet. Based on these results, $[P^{+}_{6,6,6,14}]_2[MnCl_4^{2-}]$ was chosen for further optimizations since it provided enhanced extraction efficiency when compared with $[Aliquat^{+}]_2[MnCl_4^{2-}]$.

3.2. Evaluation of pH and extraction time

As previously described [43], adjusting the sample pH is very important when ionizable compounds are analyzed. Therefore, as the $[P^{+}_{6,6,6,14}]_2[MnCl_4^{2-}]$ MIL is hydrophobic, pH optimization to obtain non-ionized forms of the analytes which are preferably extracted by this phase is important. The extraction time is another variable that can significantly affect the analytical response. Since SDME is an equilibrium technique (non-exhaustive), a certain time is needed for analyte mass transfer to occur and result in high enrichment factors and acceptable precision [31].

Therefore, a Doehlert design was performed to evaluate the influence of the sample pH and extraction time using the geometric means of the chromatographic peak areas for all the analytes as the response. Sample pH was examined at 3, 6, 9 while extraction time was studied at 30, 60, 90, 120 and 150 min. A response surface obtained with this optimization is shown in Fig. 2.

As the pKa of the analytes studied range from 8.2 to 12.8, this variable did not show influence using a significance level of 5% (see ANOVA in Tables S−1). Thus, pH 6 was chosen for further experiments. In addition, the response surfaces obtained based on the chromatographic peak area for each analyte are also shown in Supporting Information (Figure S-8), in which a similar trend is possible to be observed for all the analytes. Regarding the extraction time, higher analytical responses were obtained in the range of 90 min−120 min, as can be observed in Fig. 2. Therefore, aiming at efficient extractions an extraction time of 90 min was selected for further experiments.

3.3. Evaluation of dilution solvent volume

In this step, ACN was used as dilution solvent prior to injection of the MIL in the chromatographic system. Volumes of 20, 50 and 80 µL of ACN were examined and a bar graph consisting of the normalized peak areas of each analyte is shown in Fig. 3, with experiments carried out in triplicate. In this case, the highest chromatographic peak area of each analyte (obtained with 20, 50 or 80 µL of ACN) was considered as 100%, and the other values were related this highest chromatographic peak area. Small amounts of dilution solvent are desirable in order to avoid excessive dilution of the analytes. Thus, 20 µL of ACN was selected since it provided the lowest dilution of the analytes.

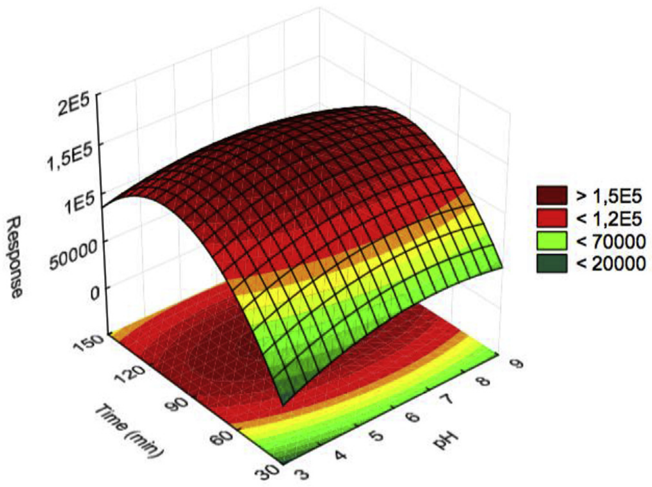

Fig. 2. Response surface for the Doehlert design obtained with the following parameters: pH and extraction time performed in 1.5 mL of ultrapure water spiked with 500 µg L^{-1} of each analyte, 5 mg of $[P_{6,6,6,14+}]_2[MnCl_{4-2}]$ and the dilution was carried out with 50 µL of acetonitrile.

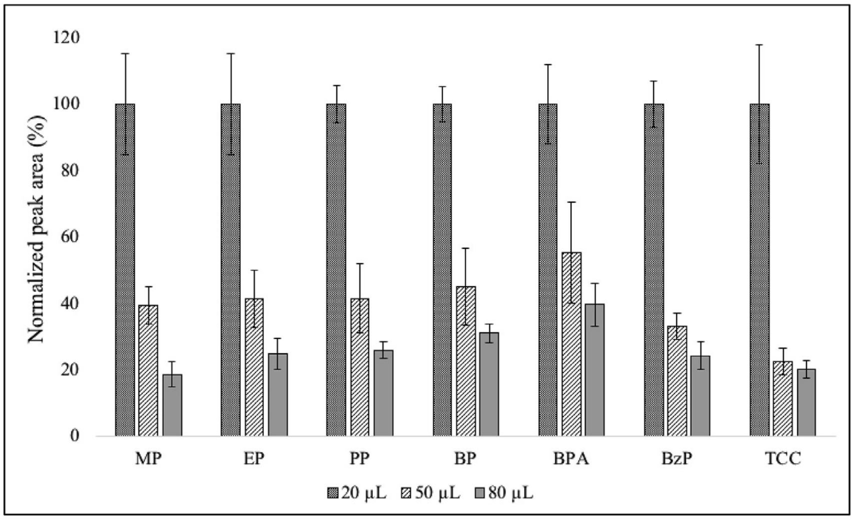

Fig. 3. Univariate optimization of dilution volume of acetonitrile for the Pa-SDME/MIL approach. Extractions were performed in 90 min, with 1.5 mL of ultrapure water spiked with 500 µg L^{-1} of each analyte and 5 mg of $[P_{6,6,6,14+}]_2[MnCl_{4-2}]$.

3.4. Analytical figures of merit and analysis of samples

Since the extraction/dilution conditions were optimized for the extraction of the analytes using the proposed methodology, determination of the analytical parameters of merit were assessed. The values for each analyte are shown in Table 1.

According to Table 1, values in agreement with validation guidelines were achieved for all analytes [44,45]. The LOD obtained for TCC was 3 µg L^{-1} while a LOD of 1.5 µg L^{-1} was achieved for all other analytes; coefficients of determination (R^2) ranged from 0.994 to 0.999. The intraday RSD values ranged from 1% to 21% and interday precision ranged from 10% to 20%. The interday precision results also showed that the use of different positions of the 96-well plate provided good reproducibility and that any position can be chosen without hindering the analytical features of the method. These results were in agreement with previously studies from Chatzimitakos et al., 2016, that quantified phenolic endocrine disrupting compounds in sewage, river and lake water samples using the $[N_{8\ 8,8,1}][FeCl_4]$ MIL and HPLC-DAD [33].

For trueness evaluation, samples of lake (1), stream (2) and swamp (3) water were spiked at different concentrations and subjected to the proposed method (n = 3); the results are shown in Table 2. The relative recovery in these samples ranged from 63% to 126%. It is important to mention that most of these values are in agreement with validation guidelines [44,45]. When these samples were analyzed without spiking any amount of the analytes no chromatographic signals corresponding to the studied compounds were detected. Fig. 4 shows chromatograms of blanks from the samples of lake, stream, swamp water and for a sample containing each of the analytes at concentration of 50 µg L^{-1}.

3.5. Analytical features of the proposed method

To point out some analytical features of the new configuration proposed, Table 3 shows a comparison with previously reported procedures for the determination of the compounds studied in environmental aqueous samples.

Based on the data reported in Table 3, the proposed procedure exhibits very interesting analytical features when compared to previously reported methods, particularly with regard to the sample throughput (0.94 min per sample) which can be achieved using the 96-well plate system during the 90 min of total sample preparation time (extraction/dilution). In order to determine the total analysis time is also important to mention the chromatographic run of 26 min. In addition, only 1.5 mL of sample was used, offering an important advantage when a large amount of sample is not available. Moreover, no cross contamination was observed when multiple extractions were performed. After each extraction/desorption cycle, the magnetic rods and vials used in the microextractions were properly washed and rinsed with acetone and water to avoid any contamination issue.

Table 1
Analytical parameters of merit of Pa-SDME/MIL-based method using $[P^{+}_{6,6,6,14}]_2[MnCl_4^{2-}]$ as extraction solvent.

Analyte	Linear equation	R^2	EF	LOD[a] (µg L^{-1})	LOQ[b] (µg L^{-1})	Linear range (µg L^{-1})	Precision (intraday)[c], n = 3 (%)			Precision (interday)[c], n = 9 (%)
							LOQ µg L^{-1}	50 µg L^{-1}	500 µg L^{-1}	50 µg L^{-1}
Methylparaben	y = 729.1x + 1157.7	0.994	11	1.5	5	5–500	11	16	17	13
Ethylparaben	y = 757.0x − 1611.6	0.998	11	1.5	5	5–500	12	21	20	14
Propylparaben	y = 771.1x − 4024.7	0.998	14	1.5	5	5–500	13	15	21	16
Butylparaben	y = 739.8x − 468.2	0.999	14	1.5	5	5–500	14	1	15	20
Bisphenol A	y = 391.5x − 2725.4	0.999	11	1.5	5	5–500	20	9	7	17
Benzophenone	y = 649.6x + 1190.2	0.996	10	1.5	5	5–500	10	4	10	10
Triclocarban	y = 95.5x + 2183.3	0.999	14	3.0	10	10–500	8	17	11	14

[a] LOD = LOQ/3.3.

[b] LOQ first concentration of the calibration curve.

[c] Intraday and interday precision values were calculated based on the RSD.

Table 2
Relative recovery of the analytes and RSDs for lake, stream and swamp water samples (n = 3).

Analyte	Lake water sample			Stream water sample			Swamp water sample		
	LOQ (%)	50 μg L^{-1} (%)	500 μg L^{-1} (%)	LOQ (%)	50 μg L^{-1} (%)	500 μg L^{-1} (%)	LOQ (%)	50 μg L^{-1} (%)	500 μg L^{-1} (%)
Methylparaben	100 ± 15	80 ± 2	80 ± 15	74 ± 12	90 ± 19	80 ± 9	71 ± 17	118 ± 15	120 ± 10
Ethylparaben	92 ± 9	78 ± 18	74 ± 8	103 ± 10	82 ± 18	70 ± 16	120 ± 10	105 ± 13	108 ± 10
Propylparaben	109 ± 13	75 ± 19	66 ± 5	115 ± 18	90 ± 12	63 ± 10	120 ± 6	85 ± 14	96 ± 9
Butylparaben	77 ± 2	72 ± 1	63 ± 8	109 ± 13	96 ± 14	64 ± 7	110 ± 12	73 ± 19	95 ± 9
Bisphenol A	126 ± 12	89 ± 13	64 ± 1	77 ± 16	85 ± 9	91 ± 12	116 ± 10	76 ± 14	113 ± 5
Benzophenone	92 ± 13	79 ± 9	80 ± 12	80 ± 9	104 ± 14	96 ± 8	82 ± 15	116 ± 18	120 ± 9
Triclocarban	88 ± 10	115 ± 15	85 ± 10	72 ± 1	101 ± 17	112 ± 6	69 ± 16	75 ± 18	105 ± 6

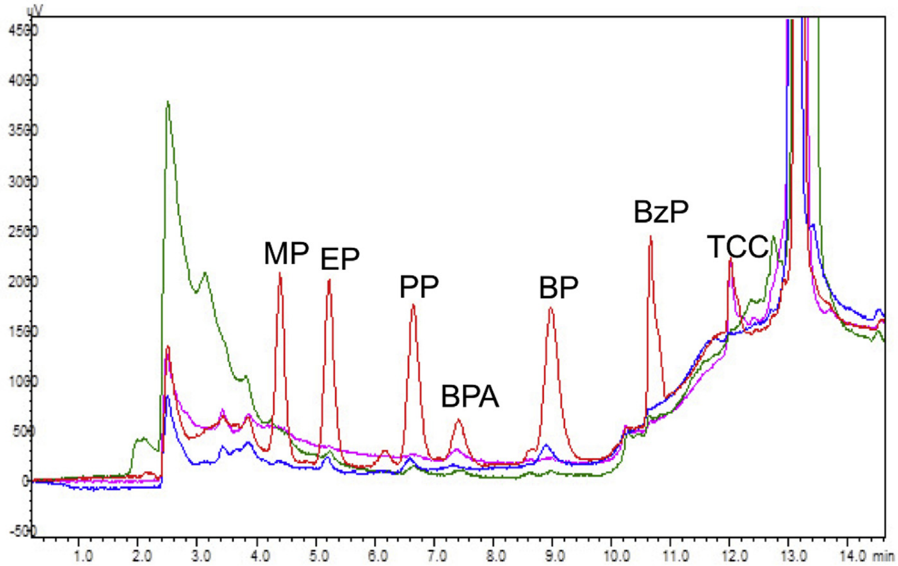

Fig. 4. Chromatograms obtained by HPLC-DAD (265 nm) for the blank of lake water sample (blue line), blank of stream water sample (green line), blank of swamp water sample (pink line) and lake water sample spiked with 50 μg L^{-1} of each analyte (red line) using the Pa-SDME/MIL-based procedure under optimized extraction conditions. Analytes: MP, methylparaben; EP, ethylparaben; PP, propylparaben; BPA, bisphenol A; BP, butylparaben; BzP, benzophenone and TCC, triclocarban. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Analytical features of the proposed methodology compared to previously reported studies in the literature.

Sample preparation technique	Separation/ detection technique	Analytes	Extraction phase	Sample preparation time per sample	LOD (μg L^{-1})	Sample volume	Desorption/ Dilution	Reference
SADBME[1]	HPLC-DAD	MP and BPA	$[N^+_{8,8,8,1}][FeCl_4^-]$	15 min	1.05[a] and 10.8[e]	30 mL	30 μL of ACN:water (3:1)	[33]
HS-SDME and DLLME	HPLC-DAD	BzP	$[P^+_{6,6,6,14}]_2[MnCl_4^{2-}]$	60 min	1.0	6 mL	20 μL of ACN	[31]
MSPE[2]	HPLC-UV	TCC	Fe_3O_4@MMIPs[4]	35 min	0.40	15 mL	Without solvent desorption	[46]
DMSPE[3]	GC–MS	MP, EP, PP and BP	Fe_3O_4@MWCNT[5]	24 min	1.44[a], 0.75[b], 0.15[c] and 0.15[d]	10 mL	3 mL of ethyl acetate	[47]
Pa-SDME	HPLC-DAD	MP, EP, PP, BP, BPA, BzP and TCC	$[P^+_{6,6,6,14}]_2[MnCl_4^{2-}]$	0.94 min	1.5[a-f] and 3[g]	1.5 mL	20 μL of ACN	This study

Analytes: methylparaben[a], ethylparaben[b], propylparaben[c], butylparaben[d], bisphenol A[e], benzophenone[f], e triclocarban[g].
[1] Stirring-assisted drop-breakup microextraction.
[2] Magnetic solid phase extraction.
[3] Dispersive magnetic solid phase extraction.
[4] Magnetic mesoporous molecularly imprinted polymers.
[5] Magnetic multi-walled carbon nanotube composite.

4. Conclusions

In this study, an environmentally-friendly and high-throughput 96-well plate Pa-SDME/MIL approach based on the extraction properties of the $[P^+_{6,6,6,14}]_2[MnCl_4^{2-}]$ MIL was proposed for the first time. Using this optimized and straightforward methodology, the analytes MP, EP, PP, BP, BPA, BzP and TCC were successfully extracted/determined in aqueous samples. This configuration provides a considerable enhancement of conventional SDME, particularly in the analysis throughput, compared to previously reported studies when MILs have been applied as extraction solvent. Moreover, the magnetic-based extraction solvent exhibited good stability in comparison with other typical solvents employed for conventional SDME applications. In summary, formidable advantages of the proposed method consist of small amount of sample required (which is of particular interest for environmental investigations), simple workflow, suitability of full automation and high-throughput sample preparation that, in the end of the extraction time of 90 min, enabled the efficient extraction of the analytes with a sample throughput lower than 1 min per sample. In a near future, this novel Pa-SDME approach can be adapted to a fully *96 Concept* Autosampler, which can reduce the human errors and the significantly increase the precision of the technique. The main limitation of this Pa-SDME approach is the need for magnetic extraction phases, such as magnetic ionic liquids.

Conflict of interest

The authors declare no conflict of interest or competing financial interest.

Acknowledgments

The authors are grateful to the Brazilian Government Agency Conselho Nacional de Desenvolvimento Científico e Tecnológioco (CNPq), Fundação de Amparo à Pesquisa do Estado de Santa Catarina (FAPESC) and to Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). These abovementioned funding agencies made this research possible.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aca.2019.02.013.

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