



# A rapid synergistic cloud point extraction for nine alkylphenols in water using high performance liquid chromatography and fluorescence detection

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## ABSTRACT

A rapid synergistic cloud point extraction for nine alkylphenols coupled with high performance liquid chromatography and fluorescence detection was developed. The non-ionic surfactant polyethylene glycol 6000 (PEG 6000) was selected as the extractant. Acetonitrile was used as a reagent and synergistic reagent with Na<sub>2</sub>SO<sub>4</sub> to lower the cloud point temperature of extractant to room temperature. These two reagents allowed a cloudy solution to form without heating. The affecting factors were optimized by multiple response optimization with a Box-Behnken design and the desirability function. The optimum conditions found were PEG 6000, 4% (*m/v*); acetonitrile, 1.5 mL; Na<sub>2</sub>SO<sub>4</sub>, 0.6 mol L<sup>-1</sup>; no pH adjustment or bathing and dilution; centrifugation for 3 min at 3500 rpm and less 8 min for the throughout sample pretreatment procedure. The extraction efficiencies of the nine alkylphenols ranged from 91.4% to 99.5%. These values varied by less than 2.78% from those predicted by the multiple response optimization model. Good linearity ( $r > 0.994$ ) was obtained in the ranges of 0.6–200 μg L<sup>-1</sup> for eight alkylphenols and 1.8–600 μg L<sup>-1</sup> for nonylphenol. Simultaneously, the method showed low limit of detection (0.17–0.39 μg L<sup>-1</sup>) and excellent repeatability at 50 μg L<sup>-1</sup> for eight alkylphenols and 150 μg L<sup>-1</sup> for nonylphenol (Intraday and Interday of RSD <4.98%,  $n = 6$ ). The proposed method was successfully applied to determination of the nine alkylphenols in environmental water samples with good recoveries (95.2–106%) and precision values (RSD <5.51%, spiked two levels of 10 and 100 μL of mixed standard, respectively).

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## 1. Introduction

Sample preparation is a critical and essential step in the overall analytical process, especially for analyzing trace components in complex matrices. Various techniques such as hollow fiber liquid phase microextraction [1], solid-phase extraction [2], solid-phase microextraction [3], magnetic solid-phase extraction [4], vortex-assisted liquid-liquid microextraction [5], in situ ionic liquid-dispersive liquid-liquid microextraction [6], dispersive liquid-liquid microextraction [7,8], single drop microextraction [9], and cloud point extraction (CPE) [10] have been reported in the literature. Among these methods, CPE is an advanced and promising pretreatment method that is relatively cost effective and environmentally friendly, and it has been widely used and attracted increasing attention in recent years [11,12]. In principle, CPE uses a nonionic surfactant that can generate cloud point phenomenon and

form micelles to extract the analyte into the surfactant-rich phase. Clouding occurs when the concentration of the nonionic surfactant is higher than its critical micelle concentration and the temperature of the solution exceeds the cloud point temperature (CPT). However, CPE is a laborious procedure that usually involves heating, incubation, separation, cooling, and dilution steps [13].

To improve and simplify traditional CPE, some improved CPE methods have been established, such as ultrasound-assisted CPE [14], microwave-assisted CPE [15], mixed-surfactant CPE [16], and ion-pair CPE [17]. Unfortunately, these methods only accelerate the heating step, and the other steps are just as long as in traditional CPE. Another improved method, rapid synergistic cloud point extraction (RS-CPE), was proposed by Wen et al. in 2011 [13]. In RS-CPE, octanol works as a cloud point reagent of the surfactant and synergistic reagent for extraction, and directly decreases the CPT of the surfactant to room temperature. Therefore, the sample pretreatment time is reduced because no heating, incubation, or cooling steps are required. As a simple and fast method, RS-CPE has been applied to the extraction of various metals and drugs and has proven to be an effective alternative pretreatment method

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[18–20]. However, the surfactant-rich phase obtained from RS-CPE requires dilution before analysis because it is composed of the viscous surfactant and octanol. Solving the issue of the high viscosity of the surfactant-rich phase without requiring the extra dilution step would simplify the sample preparation procedure and provide a good preconcentration factor.

Acetonitrile (ACN) has been used extensively as an extractant in various sample pretreatment methods, such as salting-assisted liquid–liquid extraction [21] and the QuEChERS method [22], because of its good solubility and suitable polarity. ACN is less harmful than the solvents employed in conventional liquid–liquid extraction, such as chloroform, and is more favorable from a green chemistry perspective [23]. Furthermore, ACN can affect the aggregation behavior of the surfactant because it changes the hydrophobicity of the solvent [24]. In combination with a salt, ACN could decrease the CPT and assist with extraction of the analyte. ACN has not been used in any CPE approach to decrease the CPT. In addition, the low viscosity of ACN will directly dilute the surfactant-rich phase to solve the issue with high viscosity mentioned above. Therefore, ACN is an excellent choice for substitution of octanol in RS-CPE.

In recent years, alkylphenols (APs) have attracted increasing attention from researchers because of their wide-spread application in the manufacturing industry, agriculture, and domestic consumables, and their high toxicities [25]. APs have been found in various matrices, including water. They are considered to be endocrine disrupting chemicals, and nonylphenol (NP) and octylphenol (OP) have been listed as priority pollutants by the US Environmental Protection Agency. Therefore, it is important to have a sensitive, accurate, and reliable analytical method for simultaneous determination of APs in water.

Development of such a method is a challenging task because the molecular structures of APs only differ in the lengths of their alkyl chains, and most APs have alkyl-chain isomers. To date, two main analytical techniques, gas chromatography (GC) and high-performance liquid chromatography (HPLC) have been widely used for determination of trace APs [26,27]. APs usually need to be derivatized for GC because of their low volatility. This step prolongs the sample preparation and can lead to sample loss. In this regard, HPLC is superior to GC. Moreover, ACN is compatible with HPLC and is commonly used as a mobile phase. Although HPLC has high selectivity and sensitivity for APs, the direct determination of trace APs either with complicated matrices or trace-level concentrations is still problematic [28].

The aim of this study was to develop a RS-CPE technique, using ACN as a novel cloud point reagent and synergistic reagent, coupled to HPLC with fluorescence detection for simultaneous quantification of nine APs. The APs, 4-*n*-propylphenol (4-*n*-Prop), 4-*tert*-butylphenol (4-*t*-BP), 4-*n*-amylphenol (4-*n*-AP), 4-*n*-hexylphenol (4-*n*-Hexp), 4-*t*-OP, 4-*n*-heptylphenol (4-*n*-HepP), NP, 4-*n*-OP, and 4-*n*-NP were selected as target analytes because they have not been included in many simultaneous quantifications and have not been extracted using RS-CPE. Multiple response optimization based on the Box–Behnken design with the desirability function was used to investigate and optimize the factors affecting the extraction. The analytical performance and application of the method to environmental water samples were investigated.

## 2. Material and methods

### 2.1. Chemicals and materials

Analytical standards of 4-*n*-Prop, 4-*t*-BP, 4-*n*-AP, 4-*t*-OP, 4-*n*-HepP, NP, 4-*n*-OP, and 4-*n*-NP were purchased from Dr. Ehrenstorfer (Augsburg, Germany). 4-*n*-Hexp and PEG 6000 were obtained

from Sigma-Aldrich (St. Louis, MO). Ultrapure water (resistivity 18.2 mΩ cm<sup>-1</sup>) was prepared using a Millipore water purification system (Milli-Q, Billerica, MA) and used in all experiments. ACN (chromatographic grade) was obtained from Guangzhou Chemical Reagent Factory (Guangdong, China). Sodium sulfate (analytical grade) was purchased from Jiangsu Qiangsheng Chemical Reagent Co. Ltd. (Jiangsu, China). Before HPLC analysis, all solvents and solutions were filtered through a membrane (pore size 0.45 μm). All other reagents were analytical grade or above.

A stock solution (1.0 mg mL<sup>-1</sup>) of each analyte was prepared by dissolving the corresponding standard compound in ACN. The stock solutions were stored at 4 °C. A working standard solution mixture was prepared each week by diluting and mixing the stock standard solutions of the nine APs with ACN to obtain the required concentrations.

### 2.2. Instrumentation

A Shimadzu LC-20A HPLC system (Kyoto, Japan) equipped with an automatic sampler and RF-10AXL fluorescence detector (Shimadzu) was used for detecting the nine APs. A Shim-pack VP-ODS C18 column (250 mm × 4.6 mm, 4.6 ± 0.3 μm, Shimadzu) was applied to separate the analytes. Phase separation was achieved with a centrifuge (TG12Y, Hunan Xiangli Scientific Instrument Co. Ltd., Hunan, China). The pH values were measured by a PHS-3C precision pH meter (Shanghai Hongyi Instrument Co. Ltd., Shanghai, China). A roller incubator (QB-228, Kylin-Bell Lab Instrument Co. Ltd., Haimen, China) was used to shake the samples. A F-2500 fluorescence spectrophotometer (Hitachi High-Technologies Corporation, Tokyo, Japan) was used to scan the optimum wavelength for each AP. A U-3010 ultraviolet spectrophotometer (Hitachi High-Technologies Corporation, Tokyo, Japan) was used to measure the transmittance in different temperatures for calculating CPT.

Design-Expert software (Version 8.0, Stat-Ease Inc., Minneapolis, MN) was used for processing the data.

### 2.3. Sample preparation

Three river water samples were collected from the Guangzhou River (Guangdong, China), two industrial waste water samples were obtained from Guangzhou industries (Guangdong, China), and a tap water sample was collected from our laboratory (Guangdong, China). To remove suspended impurities and avoid potential physicochemical transformation, all of the water samples were filtered through 0.45 μm membranes and adjusted pH values to acidic range before storage in the refrigerator at 4 °C [29].

### 2.4. RS-CPE procedure

An aliquot of the working solution containing the target analytes (50 μg L<sup>-1</sup> for eight APs and 150 μg L<sup>-1</sup> for NP used in the optimization) or 6.0 mL water sample was mixed with 2.0 mL of a 20% (mass fraction) solution of PEG 6000, 0.85 g of Na<sub>2</sub>SO<sub>4</sub> (final concentration of Na<sub>2</sub>SO<sub>4</sub> = 0.6 mol L<sup>-1</sup>), and 1.5 mL of ACN in a 10.0 mL conical centrifuge tube. The ultrapure water was used to make the total volume of sample solution to 10.0 mL. Then, the tube was vigorously shaken in the roller incubator for 5 min until the solution became turbid. Next, centrifugation at 3500 rpm for 3 min was used to achieve separation into two pellucid phases. The volume of the upper surfactant-rich phase obtained was 2.00 ± 0.05 mL. The surfactant-rich phase was directly filtered through a nylon membrane (pore size 0.45 μm) and injected into the HPLC system for the analysis of APs. The extraction procedure is shown in Fig. 1.

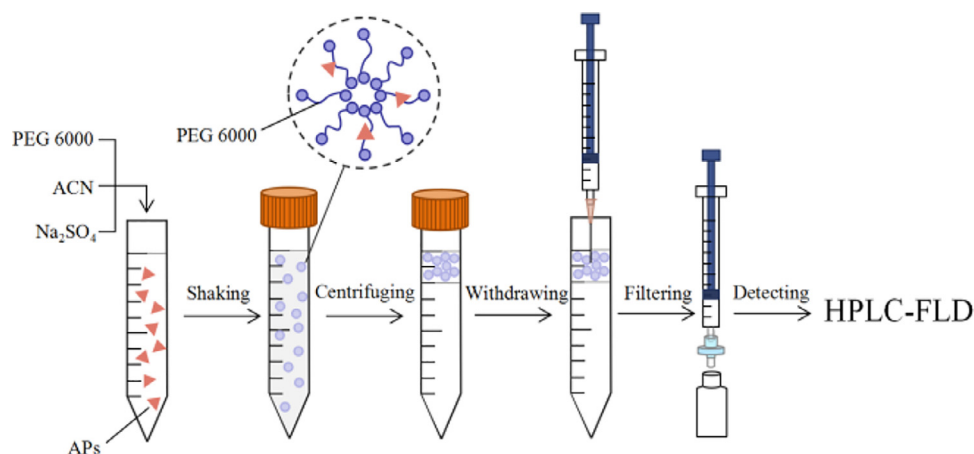


Fig. 1. The rapid synergistic cloud point extraction procedure.

## 2.5. The measurement of CPT

According to reference [30], the CPT was defined as the intercept of the tangent of a transmittance-temperature curve at the onset of turbidity (Fig. S1). Therefore, the transmittance was measured after 5 min stabilization at different temperatures using UV-vis spectrometry at 480 nm. And temperature program increases by 0.5 °C each time.

## 2.6. Chromatographic analysis

HPLC was carried out using a mixture of ACN and ultrapure water as the mobile phase. For the gradient elution, the proportion of ACN was increased linearly from 65% to 85% (0–30 min), then decreased to 65% within 1 min, and the column was re-equilibrated for 9 min. The column temperature was 30 °C and the injection volume was 10.0  $\mu$ L. The mobile phase flow rate was 1.0 mL min<sup>-1</sup>. The optimum wavelengths for excitation and emission were set at 225 nm and 305 nm, respectively.

## 2.7. Calculation

The enrichment factor (EF) was defined as the ratio of slope of calibration with and without RS-CPE. The extraction efficiency (EE) was calculated as the percentage of analyte amount extracted into the surfactant-rich phase [31].

## 2.8. Experimental design

A Box-Behnken design (BBD) was used as the experimental design. The PEG 6000 mass fraction concentration ( $x_1$ ), ACN volume ( $x_2$ ), and Na<sub>2</sub>SO<sub>4</sub> concentration ( $x_3$ ) were chosen as independent factors, and the EEs of nine APs were selected as response variables in the study. The design included 17 experiments with five central points and each factor was studied at three levels (Table S1). A mathematical second-order polynomial model was applied to identify all possible interactions of selected factors using regression analysis. The significance of each factor was analyzed statistically by analysis of variance with a probability ( $p$ ) of 0.05. The desirability function was used to optimize multiple responses.

## 3. Results and discussion

### 3.1. Selection of experimental variables

Before the multiple response optimization, the effects of the surfactant, pH, revulsant and synergistic reagent, and salt on the EEs of nine APs were investigated using a univariate design.

### 3.1.1. Effect of the surfactant

The surfactant is a key reagent in the RS-CPE procedure. In our previous work [10], the two linear chain non-ionic surfactants, Tergitol 15-S-7 and PEG 6000 were screened as extractants, while Triton X-114 commonly used in CPE or RS-CPE would bring interference due to a benzene ring in its molecule. The CPTs of Tergitol 15-S-7 and PEG 6000 are approximately 37 and 100 °C, respectively. Considering that high CPT easily led to the loss of volatile compound, Tergitol 15-S-7 was employed as the extractant in the determination of 12 phenolic compounds for traditional CPE. However, PEG 6000 also is cheap, environmentally friendly, and easily biodegradable, which has high capability to dissolve significant amounts of APs without fluorescence signal in the selected wavelength region. Therefore, no extra operation was required to solve the signal interference problem by using PEG 6000, which may reduce the sample pretreatment time and increase the repeatability of method. Unluckily, PEG 6000 was used infrequently in CPE in light of its high CPT. It is well known that RS-CPE can be implemented at ambient temperatures by using the revulsant and synergistic reagent. Therefore, PEG 6000 is a good candidate in RS-CPE. Furthermore, PEG 6000 includes two hydrophilic polar head groups at its both ends, while both Triton X-114 and Tergitol 15-S-7 are consisted of a hydrophilic and hydrophobic head on their outside. Their structures are listed in Fig. S2. PEG 6000 has a good solubility and forms self-assembled vesicles which provide large interfaces for extraction of APs in aqueous solution [32, 33]. Then phase separation occurred as a result of an increase of the hydrophobicity due to the self-assembly with the assistance of salt and ACN [34,35]. Consequently, APs may be extracted into surfactant-rich phase mainly through hydrophobic interaction in the presence of micelles. In addition, PEG 6000 may form H-bond with the APs (the OH group in PEG 6000 works as a H-bond donor, while the OH group in the APs is considered as a H-bond acceptor or vice versa) and further assist with extraction [36]. Based on the above reasons, PEG 6000 was selected for further development of the RS-CPE method.

### 3.1.2. Effect of the pH

The sample pH also plays a crucial role in the RS-CPE process. In this study, we investigated pH values between 2.0 and 12.0. No significant changes in the EEs of the nine APs were observed with changes in pH 2.0–9.0 (Fig. S3). The EEs were in decline above pH 9.0, and they dramatically decreased to 56.0–89.6% at 12.0. This phenomenon can be explained by the existing chemical forms of APs in different pH. All of the selected APs are weak acids and their pKa values are around 10.0. According to the distribution coefficient ( $\delta$ ), below pH 9.0 ( $\delta_{HA} > 0.9$ ), hydrophobic neutral species

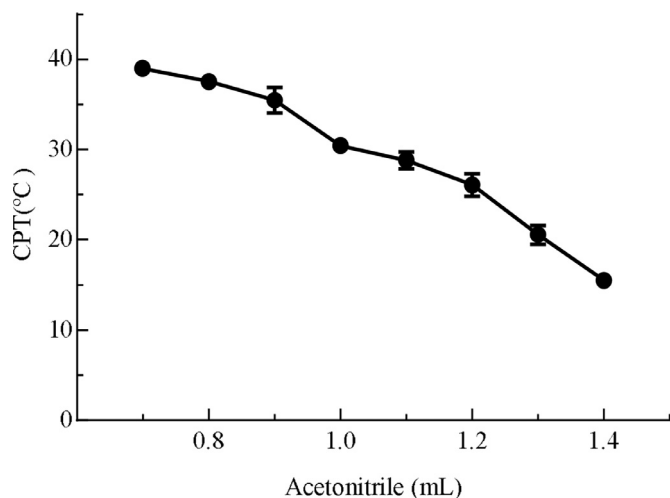


Fig. 2. The effect of ACN on CPT with  $0.5 \text{ mol L}^{-1} \text{ Na}_2\text{SO}_4$ .

of the APs were the dominant chemical forms which could be extracted into surfactant-rich phase. The ionic chemical form of an analyte normally does not interact or bind as strongly as its neutral chemical form with a nonionic surfactant [37]. The pH value of PEG 6000 tested by our laboratory was 6.0. Therefore, the pH of the solution obtained after mixing of the target analytes and PEG 6000 was in the acidic range. This meant that the APs remained as neutral species. Compared the EEs obtained without buffer solution with those adjusted pH (2.0–9.0), changes were not remarkable. Therefore, a buffer solution was not required to control the pH during the RS-CPE process.

### 3.1.3. Effect of the revulsant and synergistic reagent

To select a novel and good candidate as the revulsant and synergistic reagent, methanol, ethanol, and ACN were evaluated for further simplifying the procedure of RS-CPE. In combination with  $0.5 \text{ mol L}^{-1} \text{ Na}_2\text{SO}_4$ , methanol could not reduce the CPT to room temperature and no turbidity was observed, while a large volume of surfactant-rich phase (3.0 mL) was formed by adding 3.0 mL ethanol. Conversely, the CPT decreased with the increased volume of ACN in combination with  $0.5 \text{ mol L}^{-1} \text{ Na}_2\text{SO}_4$ , and was lowered to  $15^\circ\text{C}$  by applying 1.4 mL ACN (Fig. 2). What's more, a smaller volume of surfactant-rich phase (1.5 mL) was produced in comparison of ethanol. Especially, it needs to be mentioned that the ACN has low viscosity and can directly reduce the viscosity of the surfactant-rich phase. Thus, the proposed RS-CPE cut off four main laborious steps (heating, incubation, cooling and dilution) including in traditional CPE or the proposed RS-CPE, and only needed few minutes for the whole procedure. In addition, ACN was used as a mobile phase in this study, and would be more compatible with HPLC than ethanol. Hence, ACN was used in subsequent experiments.

### 3.1.4. Effect of the salt

Usually, addition of an appropriate electrolyte can change the CPT of a non-ionic surfactant and facilitate phase separation because of salting-in and salting-out effects. Different salts have different effects on CPE system [38]. Three commonly used salts ( $\text{NaCl}$ ,  $\text{Na}_2\text{CO}_3$ , and  $\text{Na}_2\text{SO}_4$ ) were investigated in this study. With the assistant of 1.5 mL ACN,  $0.5 \text{ mol L}^{-1} \text{ Na}_2\text{CO}_3$ , or  $\text{Na}_2\text{SO}_4$  could effectively and quickly reduce the CPT of PEG 6000 to room temperature, but  $2.5 \text{ mol L}^{-1} \text{ NaCl}$  was needed to produce turbidity. Furthermore, among these salts,  $\text{Na}_2\text{SO}_4$  obtained the highest EEs (Fig. 3). These results could be attributed to the charge density, anion effect and pH of salt solution. The singly charged  $\text{Cl}^-$  has

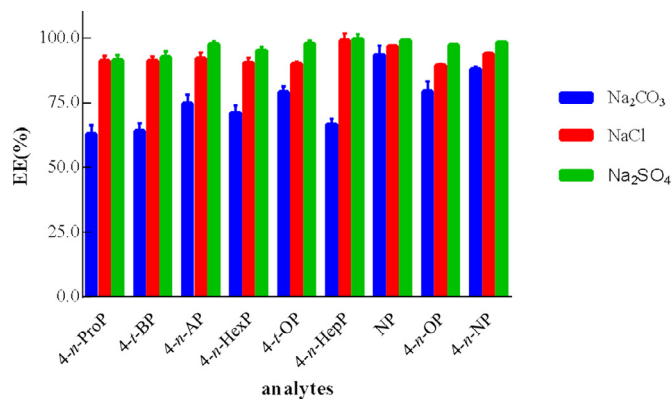


Fig. 3. The effect of salts on the extraction efficiencies of nine alkylphenols. The amount of salt used is  $0.5 \text{ mol L}^{-1} \text{ Na}_2\text{CO}_3$ ,  $0.5 \text{ mol L}^{-1} \text{ Na}_2\text{SO}_4$  and  $2.5 \text{ mol L}^{-1} \text{ NaCl}$ . Reaction conditions: 4% (mass fraction) PEG 6000 and 1.5 mL of acetonitrile.

lower charge density and weaker interaction with water molecules than multiply charged  $\text{CO}_3^{2-}$  or  $\text{SO}_4^{2-}$ . Following the Hofmeister series ( $\text{SO}_4^{2-} \approx \text{CO}_3^{2-} > \text{Cl}^-$ ),  $\text{CO}_3^{2-}$  and  $\text{SO}_4^{2-}$  have strong salting-out effects leading to the increasing aggregation number of micelle and the efficient phase separation [39]. Therefore, both  $\text{Na}_2\text{CO}_3$  and  $\text{Na}_2\text{SO}_4$  were capable to bring cloudy phenomenon faster at relatively lower concentration. However,  $\text{Na}_2\text{SO}_4$  and  $\text{NaCl}$  are neutral salts, while  $\text{Na}_2\text{CO}_3$  is a weak acid salt. The  $\text{pK}_{a1}$  and  $\text{pK}_{a2}$  of  $\text{CO}_3^{2-}$  are 6.38, 10.25, respectively. The pH value of  $0.6 \text{ mol L}^{-1} \text{ Na}_2\text{CO}_3$  solution is around 12.0. Hence, addition of the same  $\text{Na}_2\text{CO}_3$  amount significantly altered the pH of the no buffer solution, which hindered extraction of the APs because they were ionized and became more hydrophilic. Therefore,  $\text{Na}_2\text{SO}_4$  was selected for subsequent experiments.

## 3.2. Box-Behnken design model and analysis of variance

### 3.2.1. Analysis of the model

The effects of the  $x_1$ ,  $x_2$ , and  $x_3$  on the EEs of the nine APs were further optimized using a BBD. All of the  $R^2$  were greater than 0.991 and the associated  $p$ -values were less than 0.0001 (Table 1). The results indicated that the fitted models were significant and could explain more than 99.1% of the variation. All of the differences between the adjusted and predicted  $R^2$  were within 0.1, implying that good statistical models were obtained. The lack of fit values were insignificant ( $p > 0.05$ ), which was further evidence that the quadratic models were reliable. The final quadratic equations in terms of actual factors are given in Table S2. All the  $p$ -values of the quadratic model terms were lower than 0.01, which meant that the linear terms ( $x_1$ ,  $x_2$ , and  $x_3$ ), interaction terms ( $x_1 \times 2$ ,  $x_1 \times 3$ , and  $x_2 \times 3$ ) and quadratic terms ( $x_1^2$ ,  $x_2^2$ , and  $x_3^2$ ) were significant for the EEs of APs.

### 3.2.2. Analysis of response surfaces

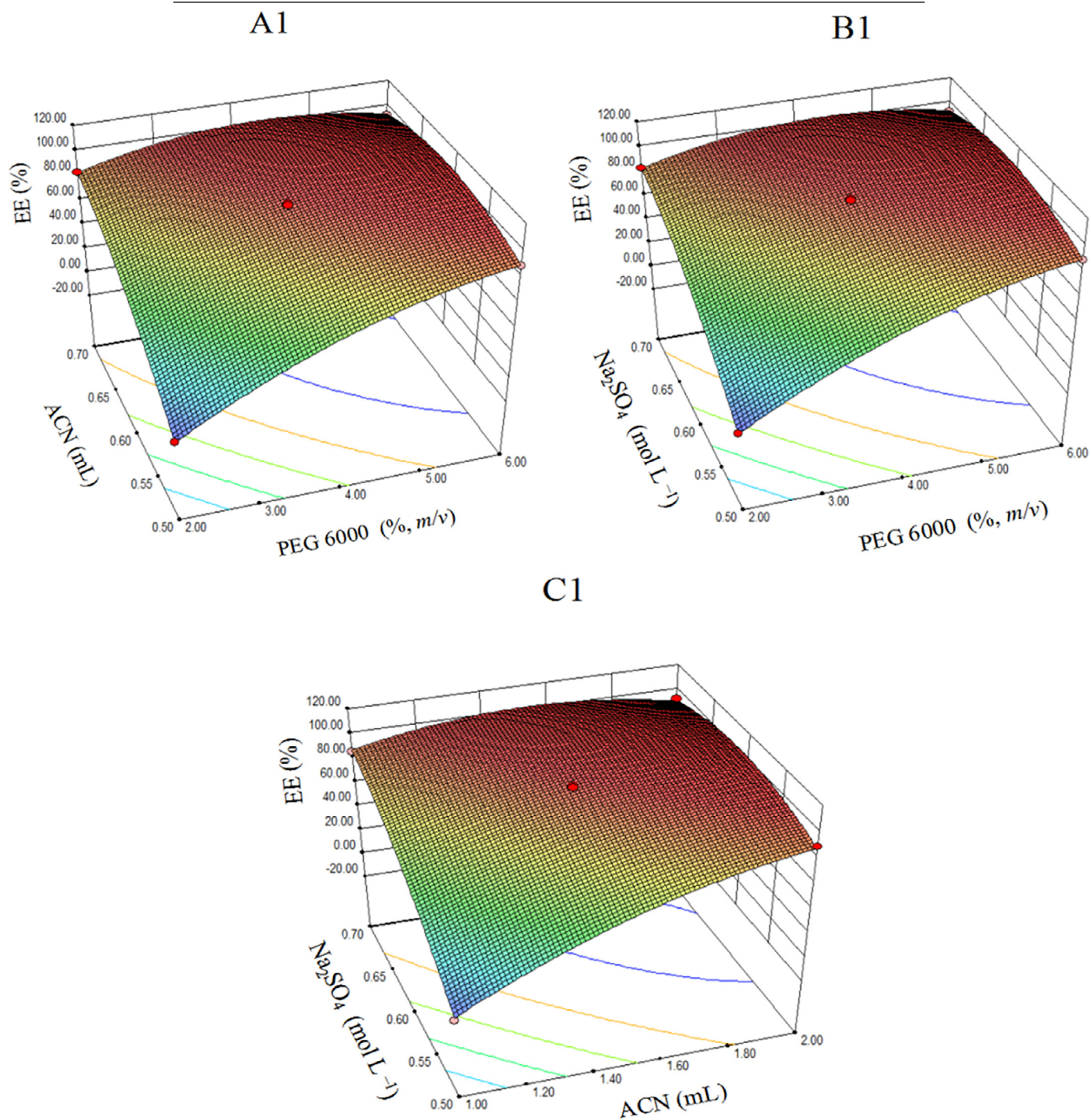
Three-dimensional response surface plots were obtained using Design-Expert for observing the effect of two independent variables at a time, while keeping the other variable at the central level (Fig. 4). The nine APs showed similar trends for changes in the EEs (Fig. S4). Below, 4-n-Prop is used as an example to discuss the results.

There were clear maxima in the response surface plots, indicating that the optimum condition was within the studied range. The mass fraction of PEG 6000 was clearly a significant factor (Fig. 4A<sub>1</sub> and 4B<sub>1</sub>). At the 2.0% mass fraction of PEG 6000, the EE was very low because there was not sufficient surfactant to quantitatively extract analytes from the aqueous solution. Therefore, the EE increased with increases in the PEG 6000 mass fraction. The



**Table 1**  
Adequacy of the model for the alkylphenols.

Analytes	Model		$R^2$	$R^2_{adj}$	$R^2_{pred}$	Lack of Fit	
	F value	p-value				F value	p-value
4- <i>n</i> -ProP	356	<0.0001	0.998	0.995	0.978	1.95	0.264
4- <i>t</i> -BP	462	<0.0001	0.998	0.996	0.981	2.79	0.174
4- <i>n</i> -AP	425	<0.0001	0.998	0.996	0.984	1.25	0.403
4- <i>n</i> -HexP	615	<0.0001	0.999	0.997	0.986	2.57	0.192
4- <i>t</i> -OP	237	<0.0001	0.997	0.992	0.969	1.57	0.328
4- <i>n</i> -HepP	475	<0.0001	0.998	0.996	0.988	0.850	0.535
NP	290	<0.0001	0.997	0.994	0.973	1.85	0.279
4- <i>n</i> -OP	136	<0.0001	0.994	0.987	0.943	1.90	0.270
4- <i>n</i> -NP	87.0	<0.0001	0.991	0.980	0.881	6.10	0.060



**Fig. 4.** Response surface plots for the effects of (A) PEG 6000 (% mass fraction)/ ACN (mL), (B) PEG 6000 (% mass fraction)/ Na<sub>2</sub>SO<sub>4</sub> (mol L<sup>-1</sup>), and (C) ACN (mL)/ Na<sub>2</sub>SO<sub>4</sub> (mol L<sup>-1</sup>) on the extraction efficiencies of 4-*n*-propylphenol.

**Table 2**  
Analytical performance for the alkylphenols.

Analytes	Range ( $\mu\text{g L}^{-1}$ )	Regression equation $A = (a \pm SD) C \pm (b \pm SD)$	$r$	LOD ( $\mu\text{g L}^{-1}$ )	LOQ ( $\mu\text{g L}^{-1}$ )	RSD <sup>a</sup> (%)		RSD <sup>b</sup> (%)	
						Intra-day	Inter-day	Intra-day	Inter-day
4- <i>n</i> -Pr oP	0.6–200	$A = (44,645 + 758.5) C - (3062.5 + 298.2)$	0.999	0.17	0.56	4.91	4.64	1.55	2.66
4- <i>t</i> -BP	0.6–200	$A = (42,956 + 347.5) C - (3540.7 + 352.2)$	0.999	0.18	0.61	4.37	4.80	1.72	2.33
4- <i>n</i> -AP	0.6–200	$A = (41,298 + 523.5) C - (1084.2 + 87.70)$	0.999	0.19	0.62	2.35	4.33	1.80	2.79
4- <i>n</i> -HexP	0.6–200	$A = (41,029 + 862.5) C + (59,189 + 775.3)$	0.994	0.18	0.60	3.35	3.70	3.10	2.46
4- <i>t</i> -OP	0.6–200	$A = (36,155 + 527.5) C - (1529.5 + 177.7)$	0.999	0.20	0.67	4.98	4.18	2.78	3.12
4- <i>n</i> -HepP	0.6–200	$A = (36,455 + 567.5) C + (121,763 + 483.5)$	0.998	0.20	0.68	2.67	4.33	2.91	1.55
NP	1.8–600	$A = (19,162 + 864.0) C - (3112.7 + 297.1)$	0.997	0.39	1.30	2.10	2.81	2.17	2.37
4- <i>n</i> -OP	0.6–200	$A = (40,554 + 460.5) C - (14,232 + 537.9)$	0.998	0.19	0.63	3.45	4.50	2.24	3.47
4- <i>n</i> -NP	0.6–200	$A = (33,534 + 561.0) C - (14,635 + 492.7)$	0.998	0.20	0.68	4.21	4.68	3.44	3.45

<sup>a</sup>  $1 \mu\text{g L}^{-1}$  for eight APs,  $3 \mu\text{g L}^{-1}$  for NP.

<sup>b</sup>  $50 \mu\text{g L}^{-1}$  for eight APs,  $150 \mu\text{g L}^{-1}$  for NP,  $n = 6$ .

EE improved as the volume of ACN rose, too (Fig. 4A<sub>1</sub> and 4C<sub>1</sub>). The optimum PEG 6000 mass fraction was 4% and the optimum ACN volume was 1.5 mL, while the volume of surfactant-rich phase was 2.00 ( $\pm 0.05$ ) mL. With the PEG 6000 and ACN adding, the surfactant-rich phase volume increased. Therefore, when the mass fraction of PEG 6000 and the volume of ACN were above the optimum values, the preconcentration factor decreased, and the EE did not increase any further. At the optimum values of ACN and PEG 6000, as the concentration of Na<sub>2</sub>SO<sub>4</sub> increased, the EE also increased (Fig. 4B<sub>1</sub> and 4C<sub>1</sub>). These results showed there were interactions among the three factors.

In this study, despite ACN is infinitely miscible with water, water-ACN mixtures exhibit microheterogeneity at the molecular level, in which the solution was considered to separate into the hydrophobic regions of ACN and hydrophilic regions of water [40]. Furthermore, ACN has a low solubility in a saline solution and can form two clear layers after phase separation due to salting-out effect [41]. Therefore, ACN may be dissolved in the hydrophobic micelles and adsorbed at the micelles surface facilitating the micellar aggregation and the depression in the cloud point [39,42]. Consequently, ACN in combination with salt can lower the CPT of PEG 6000 to ambient temperature. Furthermore, ACN has good solvability for analytes [43]. When it separated from water, ACN also extracted most of APs into micelles and could be synergetic for the extraction. We also observed that phase separation or clouding couldn't occur in the absent of any kind of reagents among PEG 6000, Na<sub>2</sub>SO<sub>4</sub> and ACN in the room temperature. This might be interpreted that once forming the micelle, it would enhance the salting-out effect in return. As a result, using less reagent could obtain a good extraction effect. Therefore, it was necessary to determine the best compromise using the desirability function.

### 3.3. Optimization using the desirability function and confirmation experiments

The final quadratic equations given in Table S2 also revealed that three factors simultaneously affected the EEs of nine APs. Therefore, a multiple response optimization was performed to find out the optimal point as a compromise for the EEs of nine APs using the desirability function approach. Table S3 shows the details of the optimization procedure. The EEs of the nine APs were of equal importance and the goal was to obtain the maximum re-

sponse. As a result, the optimum values were 4.03% PEG 6000, 1.54 mL of ACN, and  $0.60 \text{ mol L}^{-1}$  Na<sub>2</sub>SO<sub>4</sub>. Under these conditions, the predicted EEs of the nine APs ranged from 93.8 to 102%. For simplicity, the PEG 6000 mass fraction was adjusted to 4.0% in the verification test. Consequently, the experimental EEs for nine APs ranged from 91.4 to 99.5%, which varied by less than 2.78% from the predicted values.

### 3.4. Analytical performance

After the multiple response optimization, the analytical characteristics of RS-CPE including the linearity range, correlation coefficient ( $r$ ), limit of detection (LOD), limit of quantification (LOQ) and precision were investigated (Table 2). The weighted linear calibration curves were established by plotting the measured peak areas ( $A$ ) versus the concentrations of APs ( $C$ , weighting factor  $1/C$ ). The linear ranges of the calibration curves were between 0.6 and  $200 \mu\text{g L}^{-1}$  for eight APs and  $1.8\text{--}600 \mu\text{g L}^{-1}$  for NP with excellent linearity ( $r > 0.994$ ). High calibration curve slopes were obtained in this study, which illustrated the sensitivity of the method for nine APs. The LODs and LOQs were calculated at signal-to-noise ratios of 3 and 10, respectively. The range for the LODs was  $0.17\text{--}0.39 \mu\text{g L}^{-1}$ , and the LOQs ranged from  $0.56$  to  $1.30 \mu\text{g L}^{-1}$ . The precision of the method was evaluated using relative standard deviations (RSDs) obtained by spiking six replicates of ultrapure water with the mixed standard ( $1$  and  $50 \mu\text{g L}^{-1}$  for eight APs,  $3$  and  $150 \mu\text{g L}^{-1}$  for NP). The intra- and inter-day precisions ranged from  $1.55\text{--}4.98\%$ , which indicated the method has acceptable precision. Overall, the proposed method for determination of the nine APs has good analytical characteristics. In addition, the calibration curves obtained by HPLC-FLD without RS-CPE were provided in the supplementary (Table S4), which were used to calculate the EEs of nine APs. Under the optimum conditions, the EEs of the nine APs were  $91.4\text{--}99.5\%$ , which highlighted the good extraction performance of the RS-CPE method.

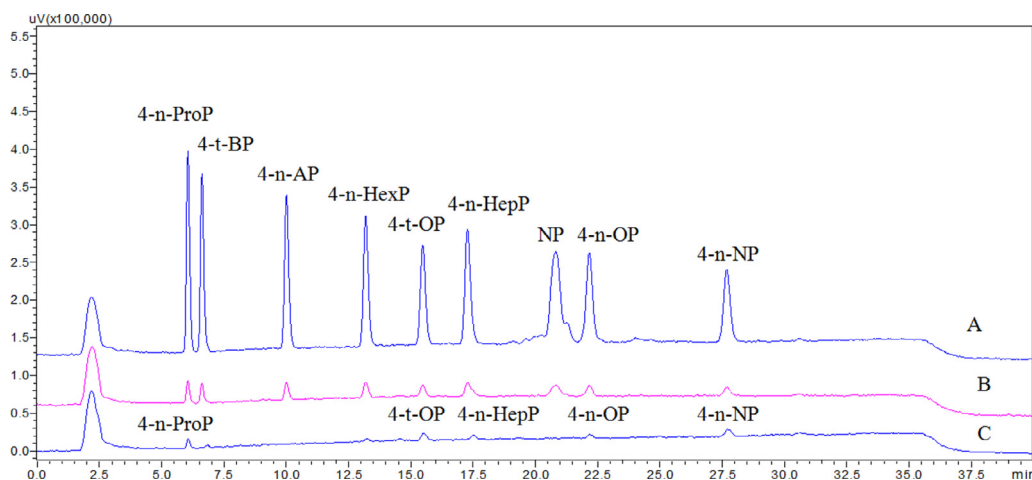
### 3.5. Application

The applicability and reliability of the method for real samples were investigated using six environmental water samples (Table 3). No APs were found in sample 4 collected from our laboratory tap water. Several target analytes such as 4-*n*-Hexp and 4-*n*-HepP were detected in sample 1 to sample 3 obtained from river water in

**Table 3**  
Analysis of water samples and recoveries.

Analytes	Add ( $\mu\text{g L}^{-1}$ )	Recoveries (%) $\pm$ SD (n = 3)					
		Sample1	Sample2	Sample3	Sample4	Sample5	Sample6
4-n-ProP	0	< LOD	< LOD	< LOD	< LOD	< LOD	0.680* $\pm$ 0.01
	5	105 $\pm$ 2	101 $\pm$ 1	101 $\pm$ 1	104 $\pm$ 3	103 $\pm$ 3	105 $\pm$ 2
	50	96.3 $\pm$ 0.1	102 $\pm$ 0.9	101 $\pm$ 0.2	99.7 $\pm$ 1	102 $\pm$ 1	101 $\pm$ 1
4-t-BP	0	< LOD	< LOD	< LOD	< LOD	2.42* $\pm$ 0.07	< LOD
	5	105 $\pm$ 5	105 $\pm$ 2	105 $\pm$ 0.08	103 $\pm$ 2	102 $\pm$ 3	98.7 $\pm$ 1
	50	95.3 $\pm$ 0.3	101 $\pm$ 1	101 $\pm$ 0.5	98.0 $\pm$ 2	102 $\pm$ 0.9	102 $\pm$ 0.6
4-n-AP	0	< LOD	< LOD	< LOD	< LOD	1.24* $\pm$ 0.002	< LOD
	5	103 $\pm$ 0.5	102 $\pm$ 0.9	104 $\pm$ 0.5	101 $\pm$ 2	96.4 $\pm$ 3	95.6 $\pm$ 3
	50	96.6 $\pm$ 0.8	101 $\pm$ 0.1	104 $\pm$ 0.2	97.2 $\pm$ 0.6	102 $\pm$ 0.9	100 $\pm$ 1
4-n-HexP	0	3.46* $\pm$ 0.01	< LOD	< LOD	< LOD	< LOD	< LOD
	5	100 $\pm$ 3	101 $\pm$ 0.5	102 $\pm$ 0.7	101 $\pm$ 2	98.6 $\pm$ 1	101 $\pm$ 2
	50	98.7 $\pm$ 0.7	101 $\pm$ 1	104 $\pm$ 2	101 $\pm$ 2	103 $\pm$ 2	99.2 $\pm$ 1
4-t-OP	0	< LOD	< LOD	< LOD	< LOD	< LOD	0.722* $\pm$ 0.01
	5	104 $\pm$ 4	103 $\pm$ 2	104 $\pm$ 0.9	102 $\pm$ 0.5	102 $\pm$ 0.4	99.4 $\pm$ 0.4
	50	98.1 $\pm$ 0.5	103 $\pm$ 0.1	102 $\pm$ 0.2	101 $\pm$ 2	102 $\pm$ 0.7	98.9 $\pm$ 0.3
4-n-HepP	0	< LOD	2.56* $\pm$ 0.03	4.60* $\pm$ 0.02	< LOD	< LOD	2.45* $\pm$ 0.02
	5	99.4 $\pm$ 1	103 $\pm$ 3	103 $\pm$ 1	101 $\pm$ 2	103 $\pm$ 4	101 $\pm$ 2
	50	99.9 $\pm$ 3	104 $\pm$ 0.4	103 $\pm$ 0.07	102 $\pm$ 2	100 $\pm$ 1	95.6 $\pm$ 1
NP	0	< LOD	< LOD	< LOD	< LOD	4.38* $\pm$ 0.1	< LOD
	15	101 $\pm$ 0.2	102 $\pm$ 0.4	104 $\pm$ 1	103 $\pm$ 0.5	105 $\pm$ 4	101 $\pm$ 3
	150	102 $\pm$ 1	103 $\pm$ 0.08	102 $\pm$ 0.06	101 $\pm$ 2	100 $\pm$ 1	97.0 $\pm$ 0.6
4-n-OP	0	< LOD	< LOD	< LOD	< LOD	< LOD	1.36* $\pm$ 0.02
	5	103 $\pm$ 1	105 $\pm$ 3	106 $\pm$ 2	101 $\pm$ 1	105 $\pm$ 2	101 $\pm$ 3
	50	97.0 $\pm$ 0.6	102 $\pm$ 0.04	103 $\pm$ 1	100 $\pm$ 2	103 $\pm$ 0.6	100 $\pm$ 0.8
4-n-NP	0	< LOD	< LOD	< LOD	< LOD	< LOD	5.25* $\pm$ 0.1
	5	104 $\pm$ 0.6	106 $\pm$ 6	101 $\pm$ 3	102 $\pm$ 2	100 $\pm$ 1	103 $\pm$ 3
	50	102 $\pm$ 2	106 $\pm$ 0.07	104 $\pm$ 3	103 $\pm$ 1	105 $\pm$ 3	103 $\pm$ 1

\* means the blank sample concentration ( $\mu\text{g L}^{-1}$ ).



**Fig. 5.** Typical chromatograms of water samples after rapid synergistic cloud point extraction. blank water sample (C), water sample spiked with  $5 \mu\text{g L}^{-1}$  for eight APs and  $15 \mu\text{g L}^{-1}$  for NP of the mixed standard (B), and water sample spiked with  $50 \mu\text{g L}^{-1}$  for eight APs and  $150 \mu\text{g L}^{-1}$  for NP of the mixed standard (A). The detection wavelength was  $\lambda_{\text{ex}} = 225 \text{ nm}$  and  $\lambda_{\text{em}} = 305 \text{ nm}$ .

the range of  $2.56\text{--}4.60 \mu\text{g L}^{-1}$ , while 4-n-prop, 4-t-BP, 4-n-HepP, 4-n-NP were detected in sample 5 and sample 6 obtained from industrial waste water in the range of  $0.68\text{--}5.25 \mu\text{g L}^{-1}$ . Some researchers also had found APs at various concentration in effluents and river. Kyoung-Woong Kim et al. found 4-n-Hexp, 4-t-BP, 4-t-OP, 4-n-HepP, 4-n-OP, and NP at the concentration of  $29.0\text{--}399 \mu\text{g L}^{-1}$  in the treatment effluents and river waters, Korea [44]. Ru Chen et al. found NP at the concentration of  $0.81\text{--}3.36 \mu\text{g L}^{-1}$  in the runoff outlets of the Pearl River Delta, while OP was detected in  $0.09\text{--}0.58 \mu\text{g L}^{-1}$  [45]. In this study, the recoveries of the spiked concentrations (5 and  $50 \mu\text{g L}^{-1}$  for eight APs, 15 and  $150 \mu\text{g L}^{-1}$  for NP) of mixed standard in water samples ranged from 95.2 to 106% (RSD < 5.51%). Example chromatograms of an industrial waste water sample before and after spiking are shown in Fig. 5. No large interfering peaks were detected around the retention times of the

target compounds, which was evidence that the sample matrix did not greatly affect the RS-CPE results.

### 3.6. Comparison of RS-CPE-HPLC-FLD with other methods

Table 4 shows comparisons among the analytical parameters of the developed method and previous methods [46–48]. Compared with previous methods for the extraction of APs, the advantages of the developed method were (i) quick and simple operation, the proposed method required less time (8 min for the whole sample pretreatment) than other methods. Furthermore, the reagents used in this method are commercial, cheap and available. Inversely, some methods (e.g. MSPE) need special extracted materials that usually spend several hours for preparation; (ii) high extraction efficiency and high sensitivity, the EEs of nine APs were higher than



**Table 4**

Comparison of the introduced method with other extraction techniques used for the determination of APs.

Methods	Analytes	Matrix	Consumingtime	LODs ( $\mu\text{g L}^{-1}$ )	EEs/EFs	Refs.
HF-LPME-UHPLC-MS	4- <i>t</i> -OP, NP	water	30 min	–	48.0%/800	[1]
SPME-HPLC-DAD	4- <i>t</i> -OP, 4- <i>n</i> -OP, 4- <i>n</i> -NP	water	>15 min	0.5–3.3	–	[3]
MSPE-LC-MS/MS	NP, OP	water	>10 min	1.5	–	[4]
VALLME-HPLD-FLD	NP, OP	water	6 min	0.01–0.07	–	[5]
IL-DLLME-HPLC-UV	4- <i>t</i> -BP, 4- <i>t</i> -OP, NP, OP	seawater, Industrial effluent	9 min	0.8–4.8	12.9–91.7/140–989	[6]
MSPE-DLLME-HPLC	4- <i>t</i> -OP, NP	water	>20 min	0.010	–	[7]
MSPE-GC-MS	4- <i>t</i> -BP, 4- <i>n</i> -AP	baby food	>30 min	0.02–0.08	16.3–79.7%/49–239	[27]
	4- <i>n</i> -HexP, 4- <i>t</i> -OP, 4- <i>n</i> -OP, NP					
CPE-HPLC-UV	4- <i>n</i> -ProP, 4- <i>t</i> -BP, 4- <i>t</i> -OP, 4- <i>n</i> -NP	seawater	>40 min	0.28–1.17	–/42.7	[46]
SPE-HPLD-FLD	NP, OP	soft drink	50 min	0.1	–	[47]
SDME/DLLME-HPLC-UV	4- <i>t</i> -BP, NP, OP	seawater	10–60 min	0.2–1.6	85.5–119/44–275	[48]
RS-CPE-HPLC-FLD	4- <i>n</i> -ProP, 4- <i>t</i> -BP, 4- <i>n</i> -AP, 4- <i>n</i> -HexP, 4- <i>t</i> -OP, 4- <i>n</i> -HepP, NP, 4- <i>n</i> -OP, 4- <i>n</i> -NP	water	8 min	0.18–0.42	>93.4%/4.7–5.0	this work

HF-LPME: hollow fiber liquid phase microextraction; MSPE: magnetic solid phase extraction; SPME: solid-phase microextraction; VALLME : vortex-assisted liquid–liquid microextraction; DLLME: dispersive liquid–liquid microextraction.

91.4%. Although it got a low enrichment factor because of its high critical micelle concentration (1.8% mass fraction), its LODs were still better than or similar to other methods e.g. SPME-HPLC-DAD, LPME-HPLC-FLD. To increase enrichment factor, maybe other non-ionic surfactants with lower critical micelle concentration and CPT should be selected. Then, less volume of ACN will be needed, and subsequently smaller volume of the surfactant-rich phase could be obtained. Future research will be focused on selecting an alternative surfactant in an attempt to improve their enrichment factor.

#### 4. Conclusions

In this paper, RS-CPE using the nonionic surfactant PEG 6000 as the extractant,  $\text{Na}_2\text{SO}_4$  as a salting-out reagent, and ACN as a reagent and synergistic reagent was developed for simultaneous extraction and preconcentration of nine APs from water samples. The high CPT of PEG 6000 was directly reduced to ambient temperature at the presence of ACN and salt. Owing to the assistance of ACN, high efficiencies are achieved for nine APs. The proposed method is simple, sensitive, time-saving, economical and environment friendly. At the same time, it shows great potential in the extraction of APs from environmental samples.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Supplementary materials

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