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Determination of estrogens and estrogen mimics by solid-phase extraction with liquid chromatography-tandem mass spectrometry

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ABSTRACT

An analytical method has been developed and validated for the determination of six estrogens and estrogen mimics, namely estriol (E3), bisphenol A (BPA), 17β-estradiol (E2), estrone (E1), ethynyl estradiol (EE2) and dienestrol (DIE), with frequent occurrence in the natural environment. Solid phase extraction coupled with liquid chromatography tandem mass spectrometry (SPE-LC-MS/MS) using electrospray ionization (ESI) in a negative mode was applied to concentration, identification, and quantification of estrogens and estrogen mimics. The SPE conditions were optimized as the selection of C18 as cartridges and MeOH as an eluent, and the control of solution pH at 9.0. The method was validated by satisfactory recoveries (80–130%) and intra-day and inter-day precision (<18.4%, as relative standard deviation), and excellent linearity for calibration curves ($R^2 > 0.996$). The limits of detection (LODs) for six target estrogenic compounds ranged between 2.5 and 19.2 ng/L. The effects of matrix background on the determination were evaluated in terms of LODs, LOQs, analyte recovery, and slopes of calibration curves in five different water matrices. Matrix effects by tap water were negligible. However, both matrix suppression and enhancement (i.e., E3, E1, DIE) were observed in surface water and wastewater. The positive correlation between LODs and TOC in various water matrices indicated the negative effect of organic pollutants on the method sensitivity. The sum of target estrogenic compounds in environmental samples were within 17–9462 ng/L.

1. Introduction

Endocrine disrupting chemicals (EDCs) are a category of exogenous substances that interfere with synthesis, excretion and activities of hormones in organisms [1]. EDCs, as natural and anthropogenic persistent chemicals, include pesticides, heavy metals, hormones, etc. [2]. Among hormones, estrogens have attracted increasing attention due to their wide variety, high reactivity, high frequency of occurrence, and considerable concentrations in the aquatic environment [3,4]. According to their origination, estrogens can be divided into natural (e.g., estrone (E1), 17β-estradiol (E2), estriol (E3)) and synthetic compounds (e.g., ethynyl estradiol (EE2) and diethylstilbestrol (DES)). Furthermore, some chemical additives used in plastics industry, like bisphenol A (BPA), can act as estrogen mimics [5]. They are widely used for human and veterinary therapy [6], and as growth promoters for livestock [7]. Abundant natural estrogens are released via feces and urine by humans and animals [8]. For example, the concentrations of E2 in swine urine and feces were 71.6 μg/L and 18.4 μg/kg, respectively [9]. Considerable amounts of E2 and E1 have remained in manure even after 16 days of incubation [10]. In addition, the synthetic estrogens such as EE2 were reported to persist longer than natural ones in the environment [11]. The conventional municipal wastewater treatment process seems insufficient for the removal of estrogenic contaminants [12,13], which partially contributes to the frequent presence of them with ng/L and even μg/L levels in surface water [14–19]. Chronic exposure to estrogens and estrogen mimics at even trace ng/L levels can destroy

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reproductive organism function of humans and wildlife [20], resulting in health risks and environmental issues. The development of a sensitive analytical method for determination of estrogens and estrogen mimics is indispensable for the effective control of estrogenic contaminants.

Liquid chromatography (LC) and gas chromatography (GC) coupled with mass spectrometry (MS) techniques have been widely used for the determination of trace contaminants in environmental samples [21–23]. GC-based methods for the determination of compounds with high polarity and low volatility always require a complicated derivatization process which is time and labor consuming [24]. This weakness has led to the wide use of LC-MS considering the simple pretreatment process, fast detection, high sensitivity, and separation efficiency [21,25,26]. Estrogenic compounds with limited functional groups for ionization lead to a weak response signal to MS, particularly for samples with trace amounts [27]. Therefore, pretreatment processes such as extraction, cleanup and concentration prior to the sample loading to LC-MS are essential to improve the method sensitivity. Solid phase extraction (SPE) is the most widely used pretreatment method due to the fast process and high extraction efficiency of a wide range of organic compounds from various samples [28]. The optimization of the SPE procedure should contribute to better extraction efficiency and therefore enhance detection sensitivity [29].

Although a handful of studies have reported the detection of estrogens and estrogen mimics by LC-MS coupled with SPE [30,31], most of them were conducted under deionized water or environmental samples with simple and/or single matrix. However, the uncertainty of using such methods for the determination of estrogens and estrogen mimics in various and complicated environmental water matrices is often unavailable. How and to what extent the method accuracy and sensitivity is affected by matrix background has yet to be systematically investigated. The objective of this study was to develop a sensitive and reliable SPE-LC-MS/MS method for the determination of six estrogens and estrogen mimics, namely E3, BPA, E2, E1, EE2 and DIE. The conditions for LC-MS/MS and SPE were optimized to enhance the chromatographic signal intensity and improve the accuracy of qualitative and quantitative analysis. The analytical method was validated by extraction efficiency, precision, recovery, linearity of calibration curves, limit of detection (LOD), and limit of quantification (LOQ). The matrix effect on determination was systematically assessed in four environmental samples with diverse characteristics (i.e., tap and surface water, and raw and treated swine wastewater), which will provide an appropriate quantification strategy in order to obtain accurate and robust results for each matrix. The occurrence of target estrogenic compounds was assessed through a regional survey of samples from Jinze reservoir, rivers, and swine and municipal wastewater treatment plant in Shanghai (China), which will demonstrate the applicability of the method to a wide variety of environmental samples.

2. Materials and methods

2.1. Chemicals and reagents

Six estrogenic standards including E3, BPA, E2, E1, EE2 and DIE have a purity of $\geq$ 98%, with some property parameters presented in Supporting Information S1. Four isotope-based internal standards including bisphenol A-d16 (BPA-d16), 17β-estradiol-d3 (E2-d3), ethynyl estradiol-d4 (EE2-d4) and diethylstilbestrol-d8 (DES-d8) have been used. Considering that E1, E2 and E3 have the similar tetracyclic molecular structure, i.e., one phenol group, two cyclohexane groups and one cyclopentane group, and are only different in the functional groups, positions and stereochemical arrangements of C16 and C17 on the D-ring, E2-d3 was chosen as their common isotope-based internal standard [32–34]. LC-MS grade Methanol (MeOH) and acetonitrile (ACN) were used as the organic mobile phases. Ammonium hydroxide (NH_4OH) was used for the inorganic mobile phase modifications. Sodium hydroxide and sulfuric acid (1 M) were used for sample pH adjustment. Ethyl acetate (EtAC) and Na_2-EDTA were used during the extraction of targeted compounds. The purity and supplier information of these chemicals has been listed in Supporting Information S2. A mixture of 1000 mg/L of each estrogenic compound was prepared with MeOH as the stock solution. The internal standards were mixed as a concentration of 1 mg/L with MeOH as the stock solution. The standard samples with a concentration range of 16–800 ng/L were prepared by diluting the stock solution with deionized water. The calibration ranges were 16–800 ng/L for tap water, 8–400 ng/L for surface water, and 80–4000 ng/L for wastewater, respectively. The varied calibration ranges were a result of different dilution ratios for different matrices (Section 2.3).

2.2. Samples collection and preparation

To validate the method and investigate the effect of water matrices, five types of water samples have been collected, namely, deionized water (DIW), tap water (TW) in the campus, surface water (SW) in Jinze reservoir (Shanghai), and the influent and effluent of wastewater (IW and EW) in an onsite swine wastewater treatment plant (Jinshan district, Shanghai). The characteristics of five water types have been summarized in Supporting Information S3. Some additional water samples, including river water (RW), and the influent and effluent of a wastewater treatment plant (IWTP and EWTP) in the campus, have been collected for survey purpose. The environmental samples were collected by amber glass bottles, stored at 4 °C, and analyzed within one week. DIW and TW were freshly collected before analysis. The collected samples were filtered by 0.47 μm glass fiber filters to remove particles and suspended solids to eliminate their potential interferences. The sample pH was adjusted to 9.0 by 1 M NaOH [35]. Na_2-EDTA was added to the samples to reach a concentration of 0.0014 M to shield Ca^{2+} and Mg^{2+}, since these cations may form chelates with targeted compounds [36]. The internal standards were added to reach a concentration of 400 ng/L for DIW and TW, 200 ng/L for SW, 2000 ng/L for IW and EW, respectively.

2.3. Analytical methods

The SPE cartridges were preconditioned successively with 5 mL MeOH, 5 mL EtAC, and 5 mL ultrapure water (pH 9.0). The samples were loaded on the cartridge at a flow rate of 2 mL/min by a mechanical pump (SHB-III). The loading volume was 250 mL for DIW and TW, and 500 mL for SW, IW, and EW. We need to point out that a dilution ratio of 10 was performed for IW and EW, in order to improve extraction efficiency by extending contact time between targeted compounds and SPE cartridges. After extraction, SPE cartridges were rinsed with 10 mL ultrapure water (pH 9.0) and air-dried under a negative pressure of 1.0 MPa for 30 min. The second round of cleaning process for SPE cartridges was performed by rinsing with 5 mL ultrapure water (pH 9.0) and 5 mL MeOH (5%, v/v) at a flow rate of 1 mL/min, followed by 30 mins' air-drying (1.0 MPa). The SPE cartridges were then eluted with 10 mL MeOH (0.1 MPa) into a glass tube. The eluent was evaporated to reach dryness by a gentle stream of nitrogen gas at 35 °C. The extracts in glass tubes were dissolved by 1 mL MeOH via an ultrasonic cleaner (KQ-100 V, 40 KHz) working for 10 min. The enriched sample was filtered by a 0.22 μm Teflon filter (ANPEL, Shanghai, China) and transferred to a 2 mL amber glass vial. The flow chart of analysis procedure of these estrogenic compounds has been shown in Supporting Information S4.

In order to optimize the SPE process, C18 (CNW® HC-C18, 500 mg, 6 mL) and HLB (hydrophilic-lipophilic balance, CNW® Poly-Sery HLB, 500 mg, 6 mL, Millford, MA) have been compared since these two SPE cartridges were widely used in separation and determination of estrogens and pharmaceuticals [22,37,38]. The different eluents, namely, EtAC, MeOH, MeOH: EtAC = 1:1, MeOH: EtAC = 3:1, and MeOH: water = 1:1, have been attempted considering the potential influence of hydrophobic/hydrophilic interaction between elution phases and analytes on extraction efficiency [39,40]. Solution pH was varied from 3.0 to 11.0 considering that the different ratio between neutral and ionic forms

of estrogenic compounds under different pHs may affect their extraction efficiency as well [35,41].

The samples were analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS, LCMS-8050, Shimadzu, Japan) using electrospray ionization (ESI) in a negative mode coupled with a Shimadzu-pack GISS C18 column (2.1 × 100 mm, 1.9 μm). The 5 μL sample was injected by an autosampler (SIL-30AC) with a mixture of solution A (0.075‰ NH_4OH) as inorganic mobile phase and B (MeOH/ACN, 1:1, v/v) as organic mobile phases at a flow rate of 0.4 mL/min. NH_4OH as a mobile phase additive under ESI negative mode can improve the sensitivity of MS detection, which is commonly used in the reported methods [34,42,43]. The relatively low concentration of 0.075‰ for NH_4OH was applied considering that excessive alkali can cause a long-term damage to the instrument. The mobile phase gradient program took for 10 min as follow: maintained 35% B for 1.5 min, linearly increased to 75% B in 5 min, linearly increased to 95% B in 0.1 min and maintained for 1.4 min, and reduced back to 35% B in 0.1 min and maintained for 1.9 min. The temperature of column, desolvation line and heat block was kept at 40, 250, and 400 °C, respectively. The mass spectrometry was operated under multiple reaction monitoring (MRM) and electron ionization (EI) mode. The MRM parameters were optimized by infusing each analyte at a concentration of 100 μg/L into the mass spectrometer. Argon was used as collision gas. Nitrogen was used as nebulizing gas at a flow rate of 3 L/min and heating and drying gas at a flow rate of 10 L/min.

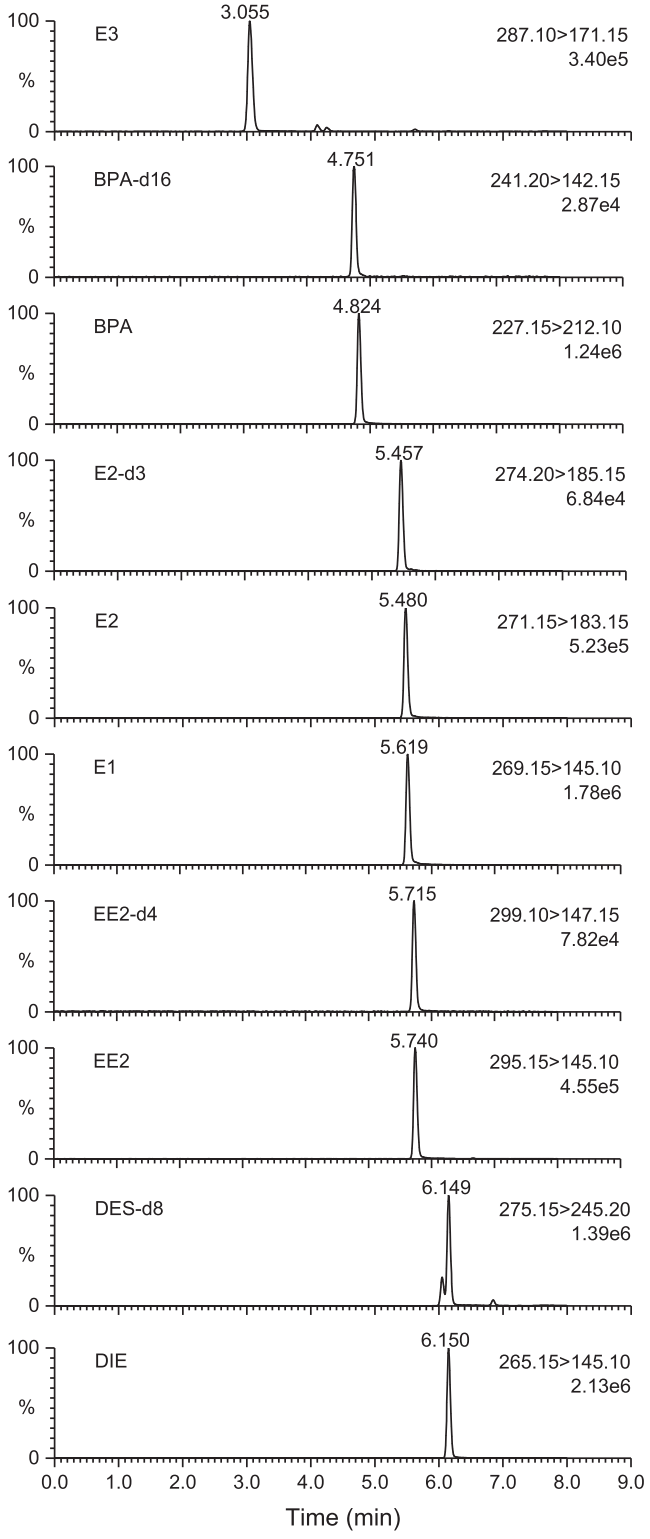

Fig. 1. Chromatogram of a mixture standard with a concentration level of 900 μg/L of each compound by LC-MS/MS.

Method validation was performed in terms of linearity of calibration curves, LOD, LOQ, extraction efficiency, precision (intra-day and inter-day precision) and recovery [32]. The calibration curves and linearity were based on six calibration levels. LOD and LOQ were determined as a concentration which would yield a signal-to-noise (S/N) ratio of greater than or equal to three and ten, respectively. The RSD and recovery were determined at three concentration levels (CL1, CL2 and CL3), i.e., 10 μg/L, 50 μg/L and 200 μg/L after different enrichment factor (250 times for DIW and TW, 500 times for SW, and 50 times for IW and EW), which was designed in order to acquire lower LOD for different water matrices [44]. Intra-day precision was evaluated by relative standard deviation (RSD) with triplicate of each calibration level in the same day (n = 3). Inter-day precision was evaluated by RSD with triplicate of each calibration level in four consecutive days (n = 12). The recovery to evaluate the matrix effect during the entire sample preparation procedure was obtained by spiking a known amount of analytes to the matrix background (Eq. (1)) according to EPA method 539 [45],

$$R = \frac{A - B}{C} * 100\% \quad (1)$$

where R represented the recovery of each analyte. A and B were measured concentrations in the fortified and unfortified sample, respectively (ng/L). C was the fortified concentration (ng/L).

The RSD of the replicate analyses within ±20% and the recovery for each analyte ranged from 70 to 130% are accepted levels for method validation according to EPA method 539 [45].

2.4. Water characterization

Total organic carbon (TOC) was determined by a TOC analyzer (liquid TOC, Elementar, Germany). Total nitrogen (TN) and total phosphorus (TP) were determined by HACH colorimetry (DR3900, HACH, America). NH_4^+, NO_2^- and NO_3^- were determined by UV–Vis spectrophotometry based on HJ 535-2009, GB7493-1987, and HJ/T 346-2007, respectively. Conductivity was determined by a digital conductivity meter (Myron L's Ultrameter II 4P).

3. Results and discussion

3.1. Optimization of LC-MS/MS conditions

The current LC program provided satisfactory chromatographic separation of targeted compounds and internal standards within a running time of 6.5 min (Fig. 1). All analytes were analyzed using ESI negative mode, considering that the deprotonated molecules of these compounds during negative ion electrospray were more abundant than the corresponding protonated molecules in a positive ion mode [46]. In addition, according to the molecular structures of these analytes

Table 1
Multiple reaction monitoring for estrogen determination by LC-MS/MS.[a]

Compounds	Abbreviation	Retention time (min)	Precursor ions (*m/z*)	Product ions[b] (*m/z*)	Q1 energy (V)	Collision energy (eV)	Q3 energy (V)
	Target compounds						
Estriol	E3	3.055	287 $[M-H]^-$	171 $[M-C_6H_{12}O_2]^-$	30.0	35.0	18.0
				145 $[M-C_8H_{14}O_2]^-$	14.0	41.0	15.0
Bisphenol A	BPA	4.824	227 $[M-H]^-$	212 $[M-CH_3]^-$	26.0	18.0	14.0
				133 $[M-C_6H_6O]^-$	27.0	23.0	26.0
17β-estradiol	E2	5.480	271 $[M-H]^-$	183 $[M-C_5H_{12}O]^-$	13.0	39.0	20.0
				239 $[M-OH-CH_3]^-$	13.0	38.0	25.0
Estrone	E1	5.619	269 $[M-H]^-$	145 $[M-C_8H_{12}O]^-$	29.0	37.0	15.0
				159 $[M-C_7H_{10}O]^-$	13.0	35.0	18.0
Ethynyl estradiol	EE2	5.740	295 $[M-H]^-$	145 $[M-C_{10}H_{14}O]^-$	14.0	41.0	15.0
				159 $[M-C_9H_{12}O]^-$	14.0	34.0	16.0
Dienestrol	DIE	6.150	265 $[M-H]^-$	93 $[M-C_{12}H_{12}O]^-$	13.0	27.0	10.0
				235 $[M-CH_2O]^-$	30.0	26.0	26.0
	Internal standards						
Bisphenol A-d16	BPA-d16	4.751	241	142	26.0	26.0	15.0
				97	26.0	26.0	10.0
17β-estradiol-d3	E2-d3	5.457	274	185	13.0	38.0	19.0
				145	30.0	39.0	25.0
Ethynyl estradiol-d4	EE2-d4	5.715	299	147	15.0	39.0	15.0
				187	14.0	36.0	19.0
Diethylstilbestrol-d8	DES-d8	6.149	275	245	13.0	29.0	17.0
				259	13.0	25.0	18.0

Note:
[a] The MRM parameters were optimized by infusing each analyte into mass spectrometer at a concentration of 100 μg/L.
[b] The product ions were selected based on their most intense signal during the optimization of Q3 energy. Their element structures were proposed based on mass and charge balance as a general rule.

containing hydroxyl groups, the negative ionization mode compared to the positive one gives the better S/N radio for estrogen analysis. The deprotonated molecules $[M-H]^-$ for all compounds were selected as precursor ions in the first quadrupole of mass spectrometer (Q1). The third quadrupole (Q3) was scanned to determine the two characteristic product ions which were generated by collision energy (CE). The product ions were selected based on their most intense signal during the optimization of Q3 energy. Their element structures were proposed based on mass and charge balance as a general rule. For example, the loss of a methyl group and a phenol group from BPA generated the product ions of $[M-CH_3]^-$ (*m/z* 212) and $[M-C_6H_6O]^-$ (*m/z* 133), respectively, which was consistent with a previous study [37]. The abundant presence of a product ion of *m/z* 145 for E3, E1 and EE2 was in agreement with a previous study [47], which was proposed to be a dihydronaphthalenic structure. The MRM parameters including retention time, precursor and product ions, Q1 and Q3 energy, and CE were summarized in Table 1. The chromatogram of a mixture standard with a concentration level of 900 μg/L of each compound by LC-MS/MS was shown in Fig. 1.

3.2. Optimization of SPE conditions

An efficient sample enrichment technique is necessary, since it contributes to high extraction efficiency of analytes and thereafter a high detection sensitivity. Therefore, the selection of SPE cartridges and eluents and the control of solution pH have been discussed considering their potentially great influence on the extraction efficiency (reflected by peak area [48,49]) of analytes. MeOH (5%, v/v), a commonly used washing solution, was selected to achieve the effective removal of interfering substances from the complicated water matrices and to retain the analytes of interest on the sorbent [50,51].

3.2.1. Effect of SPE cartridges

Two commonly used commercial SPE cartridges, i.e., C18 (alkyl-bonded silica [52]) and HLB (hydrophilic-lipophilic balanced polymers [52]), have been compared in terms of extraction efficiency, since different sorbent materials may have different interaction strength with analytes [52–54]. C18 had the better extraction efficiency than HLB for most analytes except for DIE, which was reflected by the larger peak area of precursor ions (increased by 31% in average, $P < 0.05$, ANOVA, Fig. 2a). The lower extraction efficiency of E3, BPA and E2 by HLB cartridges has been documented elsewhere [22,53]. Compared with HLB, C18 cartridges are more suitable for the extraction of compounds with relatively weak polarity based on hydrophobic interaction mechanism. Therefore, C18 cartridges have preferential retention for weak polar substances, e.g., estrogenic compounds with high logKow ranging

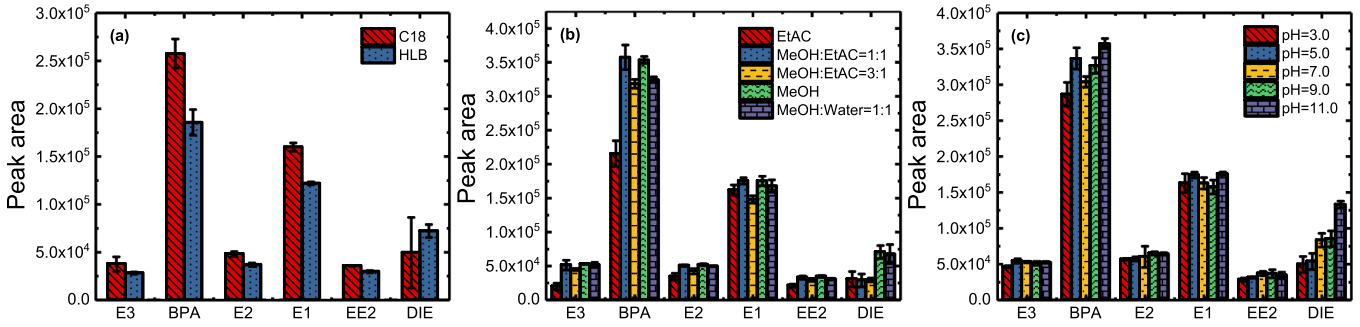

Fig. 2. Effect of SPE cartridges (a), eluents (b), and solution pH (c) on chromatographic signal intensity of estrogens. A mixture of 40 ng/L of each compound was prepared in DIW. The error bars were based on three independent experiments.

Table 2
LODs, LOQs and linearity for targeted estrogenic compounds in five different water matrices.[a]

	LOD (ng/L)					LOQ (ng/L)					Linearity (R^2)[b]				
	DIW	TW	SW	IW	EW	DIW	TW	SW	IW	EW	DIW	TW	SW	IW	EW
E3	19.2	22.3	38.5	433	503	64.1	74.2	128.3	1443	1675	0.9992	0.9941	0.9998	0.9952	0.9999
BPA	13.4	11.0	21.4	274	176	44.8	36.5	71.4	913	586	0.9987	0.9993	0.9998	0.9992	0.9992
E2	14.0	11.55	76.6	235	150	46.7	38.5	266.3	784	500	0.9979	0.9985	0.9982	0.9994	0.9989
E1	2.5	3.0	6.7	103	45	8.3	10.1	22.3	342	150	0.9980	0.9982	0.9975	0.9973	0.9999
EE2	10.5	10.2	59.6	366	168	35.0	33.9	198.6	1220	560	0.9996	0.9992	0.9997	0.9992	0.9992
DIE	4.8	3.7	6.4	61	74	16.1	12.4	21.4	202	246	0.9966	0.9975	0.9993	0.9997	0.9987

Notes:
[a] LOD and LOQ mean limit of detection and limit of quantification, respectively.
[b] The linearity of calibration curves was obtained based on six calibration levels.

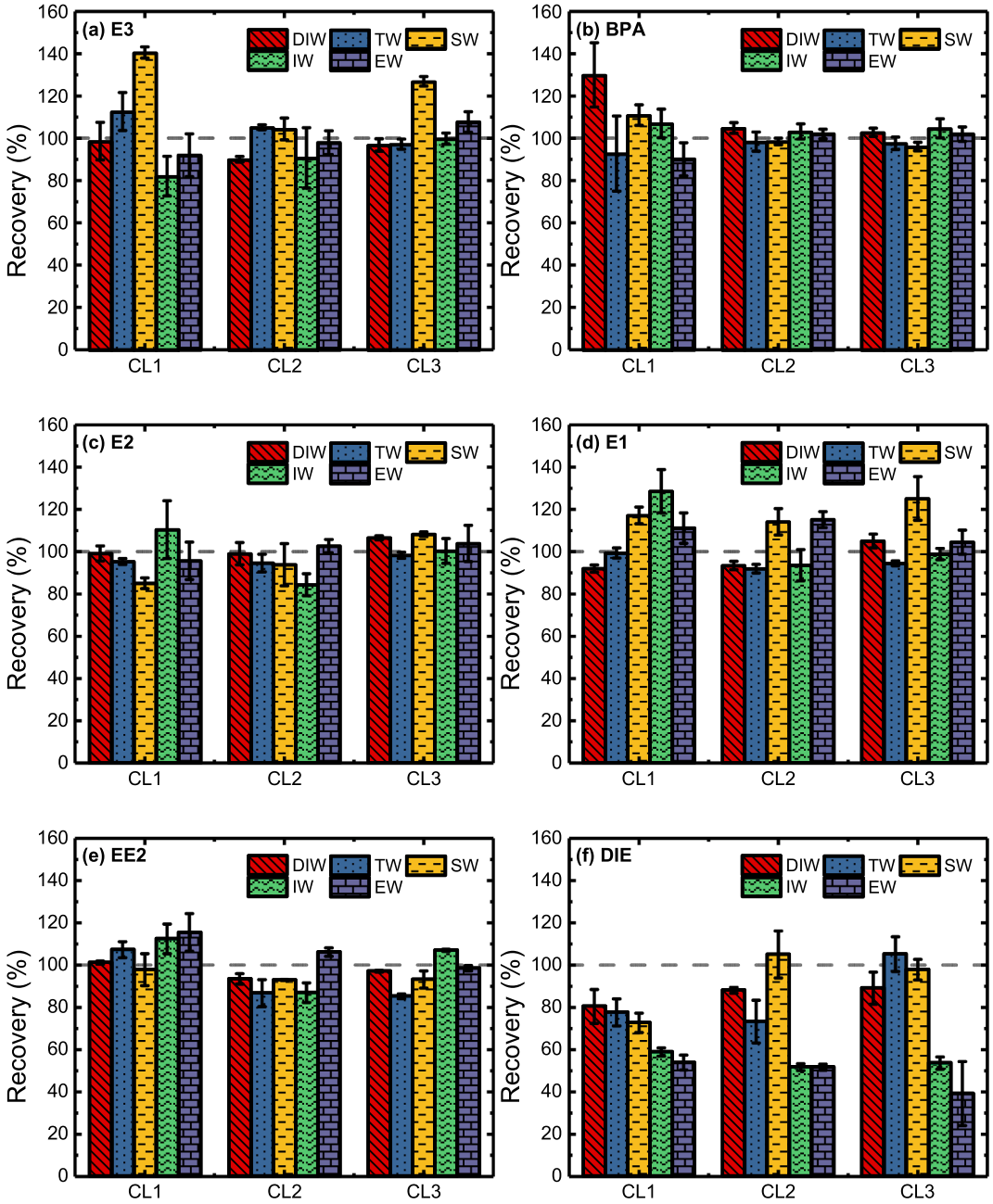

Fig. 3. Effect of water matrices on analyte recovery. The spiked concentrations at three levels (CL1, CL2 and CL3), i.e., 10 μg/L, 50 μg/L and 200 μg/L after different enrichment factor (250 times for DIW and TW, 500 times for SW, and 50 times for IW and EW). The error bars were based on three independent experiments.

from 2.81 to 5.32 (Supporting Information S1). Therefore, C18 cartridges were used in subsequent experiments.

3.2.2. Effect of eluents

Fig. 2b shows the effect of eluents on the extraction efficiency of analytes. The polarity of pure solvents follows the decreasing order of water > MeOH > EtAC, therefore the polarity of five eluents follows the decreasing order of MeOH: water (1:1) > MeOH > MeOH: EtAC (3:1) > MeOH: EtAC (1:1) > EtAC. EtAC generally showed the least extraction efficiency compared to other eluents, reflected by its corresponding smallest peak area. For example, the extraction amount (reflected by peak area) by pure EtAC was only 38–44% for E3 and 60–68% for BPA compared to those by other eluents ($P < 0.05$). MeOH and the mixture of MeOH and EtAC (1:1, v/v) achieved higher extraction efficiency for all analytes with DIE as an exception, in comparison to other eluents. The addition of water to MeOH (1:1, v/v) did not significantly affect extraction efficiency ($P > 0.05$) compared to pure MeOH due to the weak polarity and low water-solubility of targeted compounds, but greatly increased evaporation time (240 v.s. 120 min). MeOH was therefore selected as the optimum eluent for extraction of targeted compounds.

3.2.3. Effect of solution pH

The pH-dependent distribution of compounds as ionic and neutral forms may affect its interaction with cartridges and eluents, and therefore extraction efficiency as well. Fig. 2c shows that the peak area of DIE and BPA generally increase with the increase of pH values. The changes for other compounds were not obvious. The targeted compounds equipped with phenolic hydroxyl have a tendency to deprotonate to form negatively charged ions. For example, the increase of pH from 3.0 to 11.0 increased the ionic DIE from 3×10^{-6}% to 76% (calculated based on its pKa values of 10.50, Supporting Information S1), which resulted in a more than doubled amount of DIE extraction, reflected by the increase of peak area. The target estrogenic compounds under pH 11.0 resulted in a substantial formation of negative ions, contributing to enhanced adsorption by C18 cartridges via the additional electrostatic interaction [52], therefore increased extraction efficiency. Meanwhile, by taking cost into dual consideration (higher pH indicates more alkali addition), samples were adjusted to pH 9.0 since extraction efficiency under this condition was still relatively high. The optimum pH of 9.0 was selected for diethylstilbestrol, hexestrol, and DIE determination as well [35].

3.3. Method validation

Under the optimized pretreatment and instrument conditions, linearity, LOD, LOQ, intra-day and inter-day precision, and recovery for targeted analytes in DIW were determined. The calibration curves based on six calibration levels (Supporting Information S5) showed excellent linearity, reflected by correlation coefficients R^2 higher than 0.996 (Table 2). The *P*-values for lack-of-fit tests were higher than 0.05, which means that the calibration curves fitted well (Supporting Information S6). The LODs and LOQs for six target estrogenic compounds were 2.5–19.2 ng/L and 8.3–64.1 ng/L, respectively. The RSDs to evaluate intra-day precision (repeatability) were less than 15.2%, within the acceptability criterion of ≤20% (Supporting Information S7). The samples with higher concentrations had higher repeatability, reflected by an average RSD of 6.4%, 2.5%, and 2.2% for samples with three concentration levels (CL1, CL2 and CL3). The RSDs to evaluate inter-day precision (reproducibility) were 2.7%-18.4% (Supporting Information S8). The recoveries (to evaluate the matrix effect during the entire sample preparation procedure) for six target estrogenic compounds in DIW ranged from 80% to 130% (Fig. 3), within the recovery criterion of 70–130% stipulated by U.S. EPA [55]. The relative mean error of replicates revealed the good accuracy (Supporting Information S9).

The co-existence of some substances such as humic acids, natural organic matters and other contaminants in environmental samples may affect extraction efficiency and ionization efficiency through signal enhancement or suppression [56]. The method validation was first evaluated by the recovery of analytes in five different water matrices (Fig. 3). The recoveries for BPA, E2, E1 and EE2 ranged between 84% and 128%. For E3, only SW samples spiked with 20 ng/L showed a recovery beyond the range of 70–130%, demonstrating that the samples with relatively low concentration may increase the determination uncertainty. For DIE, 72–105% of spiked analytes were recovered for TW and SW samples, while only 39–59% for wastewater samples. It indicates that wastewater matrix may play a negative role on DIE extraction and/or ionization, probably due to competitive extraction and ionization between DIE and other organic impurities [57]. The raised chromatogram baseline by contaminants in the sample matrix masked the peaks of analytes (data not shown), which may lead to the underestimation as well [57]. The RSDs to reflect intra-day and inter-day precision for environmental samples were 2.9–8.2% and 5.8–14.2% respectively (Supporting Information S7 and S8).

The presence of matrix components can influence signal intensity of analytes by using LC-MS/MS, therefore the traditional post-extraction approach was used to evaluate the matrix effect [48]. In addition, a direct comparison of slopes for calibration curves (area ratio divided by concentration) was also regularly used [58,59]. The calibration curves for four environmental samples showed excellent linearity with correlation coefficients R^2 higher than 0.994 (Table 2). The slopes of TW, SW, IW, and EW samples were obtained by the standard addition method and were normalized by that of DIW samples (Supporting Information S10). For TW samples, the normalized slopes for six target estrogenic compounds were between 0.9 and 1.1 within the tolerable range of 0.8–1.2 [59], indicating its negligible matrix effect on estrogen determination. The relatively low slopes of 0.68 in IW and 0.73 in EW for DIE indicated an intense suppression effect by water matrices. The relatively high slopes of E3 and E1 in some environmental samples (>1.2) may be a result of signal overlap by other ion fragments, leading to signal enhancement [60]. The LODs for TW samples were comparable to that for DIW samples (Table 2). The LODs for SW samples (6.4–76.6 ng/L) were 1.3–5.7 times higher than that for DIW samples. The LODs for wastewater samples were orders of magnitude higher (45 to 503 ng/L) than that for DIW samples, indicating the negative influence of wastewater matrices on detection sensitivity. By correlating TOC with LODs, we found that the lower sensitivity (reflected by the higher LODs) of analytes was corresponding to the higher organic contaminant concentration in water matrices (Fig. 4), indicating the negative effect of organic pollutants on the method sensitivity. The degree of influence by TOC differed from one compound to another.

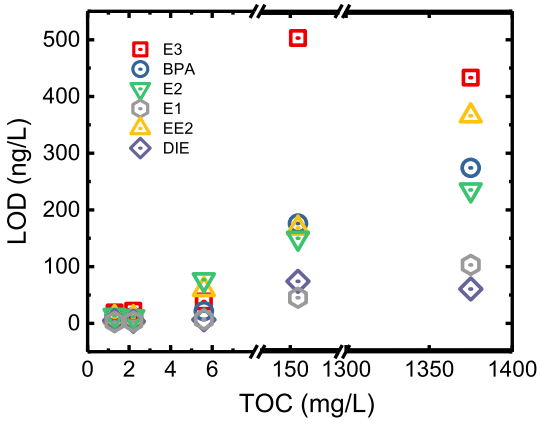

Fig. 4. Effect of TOC in five different matrices on LODs of target estrogenic compounds.

Table 3
Concentrations of target estrogenic compounds in environmental samples.[a]

	Concentration (ng/L)								
	TW	SW	RW	IWTP	EWTP	IW (Winter)	EW (Winter)	IW(Summer)	EW (Summer)
E3	N.D.	N.D.	N.D.	26 ± 4[b]	N.D.	2499 ± 164	N.D.	2880 ± 420	N.D.
BPA	17 ± 1	38 ± 1	78 ± 1	526 ± 2	375 ± 6	502 ± 195	266 ± 84	1264 ± 4	408 ± 10
E2	N.D.	N.D.	N.D.	N.D.	N.D.	244 ± 6	N.D.	128 ± 8[b]	N.D.
E1	N.D.	N.D.	31 ± 2	37 ± 7	4 ± 1[b]	3453 ± 282	N.D.	5190 ± 595	69 ± 4
EE2	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.
DIE	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

Notes:
[a] Mean ± Standard Deviation, n = 2. N.D. means not detectable.
[b] The chromatographic peak was observed although the obtained concentration was less than LOD.

3.4. Determination of estrogens and estrogen mimics in environmental samples

The optimized analytical method was used for the determination of estrogens and estrogen mimics in environmental samples (Table 3). EE2 and DIE in all environmental samples were below LODs, which is similar to previous observations by other researchers [32,42]. On the contrary, BPA was detectable in all samples, with concentrations of 17, 38, 78, 526, 375, 502–1264, and 266–408 ng/L in TW, SW, RW, IWTP, EWTP, IW, and EW, respectively. The removal efficiency of BPA was 47–68% by swine wastewater treatment and only 29% by domestic wastewater treatment. Other researchers have documented the presence of BPA at 4.2–141 ng/L and 19–68 ng/L in surface water [61,62], and 345–6030 ng/L and 116–696 ng/L in the influent and effluent of wastewater [63]. E1, E2, and E3 mainly appeared in wastewater samples. E1 and E3 in the municipal wastewater influent were two orders of magnitude lower than those in swine wastewater influent (37 vs. 3453–5190 ng/L, 26 vs. 2499–2880 ng/L). E1, E2, and E3 in IW samples collected in winter were 3.5, 0.2, and 2.5 μg/L, respectively, and were not detectable in EW samples, which indicates that these estrogenic compounds were effectively removed by the onsite swine wastewater treatment. The total concentrations of six estrogens and estrogen mimics were 17, 38, 109, 589, 379, 6698–9462, and 266–477 ng/L for TW, SW, RW, IWTP, EWTP, IW, and EW, respectively. The overall removal efficiency of these estrogenic compounds reached 95% by onsite swine wastewater treatment, while only 36% by domestic wastewater treatment.

4. Conclusions

A sensitive and reliable SPE-LC-MS/MS method was established for the determination of six estrogens and estrogen mimics in different water matrices. The optimized SPE conditions included the selection of C18 as cartridges and MeOH as an eluent, and the control of solution pH at 9.0 by taking extraction efficiency and operation time into consideration. The LODs for six target estrogenic compounds in DIW ranged between 2.5 and 19.2 ng/L, a sensitivity at environmentally relevant concentrations. The method was validated by recovery, intra-day and RSD precision, and linearity of calibration curves. Matrix effects on estrogen determination by TW were negligible, while both matrix suppression and enhancement for some target analytes occurred in surface water and wastewater samples, reflected by LODs, LOQs, analyte recovery, and slopes of calibration curves. The sum of six estrogens and estrogen mimics in TW, SW, RW, IWTP, EWTP, IW, and EW reached 17, 38, 109, 589, 379, 6698–9462, and 266–477 ng/L, respectively.

CRediT authorship contribution statement

Yejin Li: Conceptualization, Methodology, Validation, Data curation, Writing - original draft. **Linyan Yang:** Writing - review & editing, Visualization. **Huajun Zhen:** Formal analysis. **Xueming Chen:** Supervision. **Mei Sheng:** Supervision. **Kai Li:** Software. **Weibo Xue:** Investigation. **Huihui Zhao:** Investigation, Validation. **Shujuan Meng:** Project administration. **Guomin Cao:** Resources, Funding acquisition.

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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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jchromb.2021.122559.

References

[1] C. Yang, G. Song, W. Lim, Effects of endocrine disrupting chemicals in pigs, Environ. Pollut. 263 (2020), 114505, https://doi.org/10.1016/j.envpol.2020.114505.
[2] H.R. Andersen, A.M. Andersson, S.F. Arnold, H. Autrup, M. Barfoed, N. A. Beresford, P. Bjerregaard, L.B. Christiansen, B. Gissel, R. Hummel, E. B. Jørgensen, B. Korsgaard, R. Le Guevel, H. Leffers, J. McLachlan, A. Møller, J. B. Nielsen, N. Olea, A. Oles-Karasko, F. Pakdel, K.L. Pedersen, P. Perez, N. E. Skakkebœk, C. Sonnenschein, A.M. Soto, J.P. Sumpter, S.M. Thorpe, P. Grandjean, Comparison of short-term estrogenicity tests for identification of hormone-disrupting chemicals, Environ. Health Perspect. 107 (1999) 89–108, https://doi.org/10.2307/3434476.
[3] R.P. Schwarzenbach, B.I. Escher, K. Fenner, T.B. Hofstetter, C.A. Johnson, U. Von Gunten, B. Wehrli, The challenge of micropollutants in aquatic systems, Science 313 (2006) 1072–1077. http://doi.org/10.1126/science.1127291.
[4] F.L.P. Gabriel, E.J. Routledge, A. Heidlberger, D. Rentsch, K. Guenther, W. Giger, J. P. Sumpter, H.P.E. Kohler, Isomer-specific degradation and endocrine disrupting activity of nonylphenols, Environ. Sci. Technol. 42 (2008) 6399–6408, https://doi.org/10.1021/es800577a.
[5] H. Adamusova, Z. Bosakova, P. Coufal, V. Pacakova, Analysis of estrogens and estrogen mimics in edible matrices – a review, J. Sep. Sci. 37 (2014) 885–905, https://doi.org/10.1002/jssc.201301234.
[6] G.M. Solomon, T. Schettler, Environment and health: 6 Endocrine disruption and potential human health implications, CMAJ 163 (2000) 1471–1476.
[7] M. Gonzalez Ronquillo, J.C. Angeles Hernandez, Antibiotic and synthetic growth promoters in animal diets: review of impact and analytical methods, Food Control 72 (2017) 255–267, https://doi.org/10.1016/j.foodcont.2016.03.001.
[8] G. D'Ascenzo, A. Di Corcia, A. Gentili, R. Mancini, R. Mastropasqua, M. Nazzari, R. Samperi, Fate of natural estrogen conjugates in municipal sewage transport and treatment facilities, Sci. Total Environ. 302 (2003) 199–209, https://doi.org/10.1016/S0048-9697(02)00342-X.
[9] H. Zhang, J. Shi, X. Liu, X. Zhan, J. Dang, T. Bo, Occurrence of free estrogens, conjugated estrogens, and bisphenol A in fresh livestock excreta and their removal by composting in North China, Environ. Sci. Pollut. Res. Int. 21 (2014) 9939–9947, https://doi.org/10.1007/s11356-014-3002-9.

[10] Y. He, T. Wang, F. Sun, L. Wang, R. Ji, Effects of veterinary antibiotics on the fate and persistence of 17B-estradiol in swine manure, J. Hazard. Mater. 375 (2019) 198–205, https://doi.org/10.1016/j.jhazmat.2019.04.080.
[11] E. Diamanti-Kandarakis, J.P. Bourguignon, L.C. Giudice, R. Hauser, G.S. Prins, A. M. Soto, R.T. Zoeller, A.C. Gore, Endocrine-disrupting chemicals: an Endocrine Society scientific statement, Endocr. Rev. 30 (2009) 293–342, https://doi.org/10.1210/er.2009-0002.
[12] B. Huang, X. Li, W. Sun, D. Ren, X. Li, X. Li, Y. Liu, Q. Li, X. Pan, Occurrence, removal, and fate of progestogens, androgens, estrogens, and phenols in six sewage treatment plants around Dianchi Lake in China, Environ. Sci. Pollut. Res. Int. 21 (2014) 12898–12908, https://doi.org/10.1007/s11356-014-3236-6.
[13] G.P. Pessoa, N.C. de Souza, C.B. Vidal, J.A. Alves, P.I. Firmino, R.F. Nascimento, A. B. dos Santos, Occurrence and removal of estrogens in Brazilian wastewater treatment plants, Sci. Total Environ. 490 (2014) 288–295, https://doi.org/10.1016/j.scitotenv.2014.05.008.
[14] S. He, D. Dong, C. Sun, X. Zhang, L. Zhang, X. Hua, Z. Guo, Contaminants of emerging concern in a freeze-thaw river during the spring flood, Sci. Total Environ. 670 (2019) 576–584, https://doi.org/10.1016/j.scitotenv.2019.03.256.
[15] L.J. Zhou, B.B. Zhang, Y.G. Zhao, Q.L. Wu, Occurrence, spatiotemporal distribution, and ecological risks of steroids in a large shallow Chinese lake, Lake Taihu, Sci. Total Environ. 557–558 (2016) 68–79, https://doi.org/10.1016/j.scitotenv.2016.03.059.
[16] L. Wang, G.G. Ying, F. Chen, L.J. Zhang, J.L. Zhao, H.J. Lai, Z.F. Chen, R. Tao, Monitoring of selected estrogenic compounds and estrogenic activity in surface water and sediment of the Yellow River in China using combined chemical and biological tools, Environ. Pollut. 165 (2012) 241–249, https://doi.org/10.1016/j.envpol.2011.10.005.
[17] J. Gong, Y. Ran, D.Y. Chen, Y. Yang, Occurrence of endocrine-disrupting chemicals in riverine sediments from the Pearl River Delta, China, Mar. Pollut. Bull. 63 (2011) 556–563, https://doi.org/10.1016/j.marpolbul.2011.01.026.
[18] P. Labadie, A.B. Cundy, K. Stone, M. Andrews, S. Valbonesi, E.M. Hill, Evidence for the migration of steroidal estrogens through river bed sediments, Environ. Sci. Technol. 41 (2007) 4299–4304, https://doi.org/10.1021/es063062j.
[19] H.C. Zhang, X.J. Yu, W.C. Yang, J.F. Peng, T. Xu, D.Q. Yin, X.L. Hu, MCX based solid phase extraction combined with liquid chromatography tandem mass spectrometry for the simultaneous determination of 31 endocrine-disrupting compounds in surface water of Shanghai, J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 879 (2011) 2998–3004, https://doi.org/10.1016/j.jchromb.2011.08.036.
[20] R.J. Williams, A.C. Johnson, J.J.L. Smith, R. Kanda, Steroid estrogens profiles along river stretches arising from sewage treatment works discharges, Environ. Sci. Technol. 37 (2003) 1744–1750, https://doi.org/10.1021/es0202107.
[21] V. Pacáková, L. Loukotková, Z. Bosáková, K. Štulík, Analysis for estrogens as environmental pollutants - a review, J. Sep. Sci. 32 (2009) 867–882, https://doi.org/10.1002/jssc.200800673.
[22] E. Bizkarguenaga, O. Ros, A. Iparraguirre, P. Navarro, A. Vallejo, A. Usobiaga, O. Zuloaga, Solid-phase extraction combined with large volume injection-programmable temperature vaporization-gas chromatography-mass spectrometry for the multiresidue determination of priority and emerging organic pollutants in wastewater, J. Chromatogr. A 1247 (2012) 104–117, https://doi.org/10.1016/j.chroma.2012.05.022.
[23] H. Nakata, K. Kannan, P.D. Jones, J.P. Giesy, Determination of fluoroquinolone antibiotics in wastewater effluents by liquid chromatography-mass spectrometry and fluorescence detection, Chemosphere 58 (2005) 759–766, https://doi.org/10.1016/j.chemosphere.2004.08.097.
[24] T.Y. Fang, S.M. Praveena, C. deBurbure, A.Z. Aris, S.N.S. Ismail, I. Rasdi, Analytical techniques for steroid estrogens in water samples – a review, Chemosphere, 165 (2016) 358–368. http://doi.org/10.1016/j.chemosphere.2016.09.051.
[25] M. Zheng, L. Wang, Y. Bi, F. Liu, Improved method for analyzing the degradation of estrogens in water by solid-phase extraction coupled with ultra performance liquid chromatography-ultraviolet detection, J. Environ. Sci. 23 (2011) 693–698, https://doi.org/10.1016/s1001-0742(10)60439-1.
[26] R.D. Briciu, A. Kot-Wasik, J. Namiesnik, Analytical challenges and recent advances in the determination of estrogens in water environments, J. Chromatogr. Sci. 47 (2009) 127–139, https://doi.org/10.1093/chromsci/47.2.127.
[27] N. Denver, S. Khan, I. Stasinopoulos, C. Church, N.Z.M. Homer, M.R. MacLean, R. Andrew, Derivatization enhances analysis of estrogens and their bioactive metabolites in human plasma by liquid chromatography tandem mass spectrometry, Anal. Chim. Acta 1054 (2019) 84–94, https://doi.org/10.1016/j.aca.2018.12.023.
[28] A. Andrade-Eiroa, M. Canle, V. Leroy-Cancellieri, V. Cerdà, Solid-phase extraction of organic compounds: A critical review. part ii, TrAC Trends, Analyt. Chem. 80 (2016) 655–667, https://doi.org/10.1016/j.trac.2015.08.014.
[29] J.A. Erustes, A. Andrade-Eiroa, A. Cladera, R. Forteza, V. Cerdà, Fast sequential injection determination of benzo[A]pyrene using variable angle fluorescence with on-line solid-phase extraction, Analyst 126 (2001) 451–456, https://doi.org/10.1039/b010129j.
[30] L. Mandaric, E. Diamantini, E. Stella, K. Cano-Paoli, J. Valle-Sistac, D. Molins-Delgado, A. Bellin, G. Chiogna, B. Majone, M.S. Diaz-Cruz, S. Sabater, D. Barcelo, M. Petrovic, Contamination sources and distribution patterns of pharmaceuticals and personal care products in Alpine rivers strongly affected by tourism, Sci. Total Environ. 590–591 (2017) 484–494, https://doi.org/10.1016/j.scitotenv.2017.02.185.
[31] A.C. Naldi, P.B. Fayad, M. Prevost, S. Sauve, Analysis of steroid hormones and their conjugated forms in water and urine by on-line solid-phase extraction coupled to liquid chromatography tandem mass spectrometry, Chem. Cent. J. 10 (2016) 30, https://doi.org/10.1186/s13065-016-0174-z.
[32] K. Goeury, S. Vo Duy, G. Munoz, M. Prevost, S. Sauve, Analysis of Environmental Protection Agency priority endocrine disruptor hormones and bisphenol A in tap, surface and wastewater by online concentration liquid chromatography tandem mass spectrometry, J. Chromatogr. A 1591 (2019) 87–98, https://doi.org/10.1016/j.chroma.2019.01.016.
[33] A. Hibberd, K. Maskaoui, Z. Zhang, J.L. Zhou, An improved method for the simultaneous analysis of phenolic and steroidal estrogens in water and sediment, Talanta 77 (2009) 1315–1321, https://doi.org/10.1016/j.talanta.2008.09.006.
[34] T.F.T. Omar, A.Z. Aris, F.M. Yusoff, S. Mustafa, An improved SPE-LC-MS/MS method for multiclass endocrine disrupting compound determination in tropical estuarine sediments, Talanta 173 (2017) 51–59, https://doi.org/10.1016/j.talanta.2017.05.064.
[35] W.Y. Hu, X.J. Kang, C. Zhang, J. Yang, R. Ling, E.H. Liu, P. Li, Packed-fiber solid-phase extraction coupled with high performance liquid chromatography-tandem mass spectrometry for determination of diethylstilbestrol, hexestrol, and dienestrol residues in milk products, J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 957 (2014) 7–13, https://doi.org/10.1016/j.jchromb.2014.02.036.
[36] Z. Yu, F. Jin, J. Hu, X. Zhang, J. Sun, M. Yang, An improved method for analyzing chlormequat and mepiquat in source waters by solid-phase extraction and liquid chromatography-mass spectrometry, Anal. Chim. Acta 678 (2010) 90–95, https://doi.org/10.1016/j.aca.2010.08.006.
[37] A. Moid AlAmmari, M. Rizwan Khan, A. Aqel, Trace identification of endocrine-disrupting bisphenol A in drinking water by solid-phase extraction and ultra-performance liquid chromatography-tandem mass spectrometry, J. King Saud Univ. Sci. 32 (2020) 1634–1640, https://doi.org/10.1016/j.jksus.2019.12.022.
[38] J.Y. Pailler, A. Krein, L. Pfister, L. Hoffmann, C. Guignard, Solid phase extraction coupled to liquid chromatography-tandem mass spectrometry analysis of sulfonamides, tetracyclines, analgesics and hormones in surface water and wastewater in Luxembourg, Sci. Total Environ. 407 (2009) 4736–4743, https://doi.org/10.1016/j.scitotenv.2009.04.042.
[39] N. Migowska, M. Caban, P. Stepnowski, J. Kumirska, Simultaneous analysis of non-steroidal anti-inflammatory drugs and estrogenic hormones in water and wastewater samples using gas chromatography-mass spectrometry and gas chromatography with electron capture detection, Sci. Total Environ. 441 (2012) 77–88, https://doi.org/10.1016/j.scitotenv.2012.09.043.
[40] A. Prieto, A. Vallejo, O. Zuloaga, A. Paschke, B. Sellergen, E. Schillinger, S. Schrader, M. Moder, Selective determination of estrogenic compounds in water by microextraction by packed sorbents and a molecularly imprinted polymer coupled with large volume injection-in-port-derivatization gas chromatography-mass spectrometry, Anal. Chim. Acta 703 (2011) 41–51, https://doi.org/10.1016/j.aca.2011.07.007.
[41] R. Liu, J.L. Zhou, A. Wilding, Simultaneous determination of endocrine disrupting phenolic compounds and steroids in water by solid-phase extraction-gas chromatography-mass spectrometry, J. Chromatogr. A 1022 (2004) 179–189, https://doi.org/10.1016/j.chroma.2003.09.035.
[42] A. Iparraguirre, P. Navarro, R. Rodil, A. Prieto, M. Olivares, N. Etxebarria, O. Zuloaga, Matrix effect during the membrane-assisted solvent extraction coupled to liquid chromatography tandem mass spectrometry for the determination of a variety of endocrine disrupting compounds in wastewater, J. Chromatogr. A 1356 (2014) 163–170, https://doi.org/10.1016/j.chroma.2014.06.051.
[43] K. He, A. Timm, L. Blaney, Simultaneous determination of UV-filters and estrogens in aquatic invertebrates by modified quick, easy, cheap, effective, rugged, and safe extraction and liquid chromatography tandem mass spectrometry, J. Chromatogr. A 1509 (2017) 91–101, https://doi.org/10.1016/j.chroma.2017.06.039.
[44] M. Pedrouzo, F. Borrull, E. Pocurull, R.M. Marce, Estrogens and their conjugates: determination in water samples by solid-phase extraction and liquid chromatography-tandem mass spectrometry, Talanta 78 (2009) 1327–1331, https://doi.org/10.1016/j.talanta.2009.02.005.
[45] Environment Protection Agency US, Method 539: Determination of Hormones in Drinking Water by Solid Phase Extraction (SPE) and Liquid Chromatography Electrospray Ionization Tandem Mass Spectrometry (LC-ESI-MS/MS). http://water.epa.gov/drink/, 2010.
[46] Y. Sun, C. Gu, X. Liu, W. Liang, P. Yao, J.L. Bolton, R.B. van Breemen, Ultrafiltration tandem mass spectrometry of estrogens for characterization of structure and affinity for human estrogen receptors, J. Am. Soc. Mass. Spectrom. 16 (2005) 271–279, https://doi.org/10.1016/j.jasms.2004.11.002.
[47] M.a.J. Lopez de Alda, S. Díaz-Cruz, M. Petrovic, D. Barceló, Liquid chromatography–(tandem) mass spectrometry of selected emerging pollutants (steroid sex hormones, drugs and alkylphenolic surfactants) in the aquatic environment, J. Chromatogr. A 1000 (2003) 503–526. http://doi.org/10.1016/s0021-9673(03)00509-0.
[48] B.K. Matuszewski, M.L. Constanzer, C.M. Chavez-Eng, Strategies for the assessment of matrix effect in quantitative bioanalytical methods based on HPLC-MS/MS, Anal. Chem. 75 (2003) 3019–3030, https://doi.org/10.1021/ac020361s.
[49] Y. Wang, S. Jin, Q. Wang, G. Lu, J. Jiang, D. Zhu, Zeolitic imidazolate framework-8 as sorbent of micro-solid-phase extraction to determine estrogens in environmental water samples, J. Chromatogr. A 1291 (2013) 27–32, https://doi.org/10.1016/j.chroma.2013.03.032.
[50] G.N.V. Satyanarayana, J. Du, A. Asati, A.K. Pandey, A. Kumar, M.T. Sharma, M.K. R. Mudiam, Estimation of measurement uncertainty for the quantitative analysis of pharmaceutical residues in river water using solid-phase extraction coupled with injector port silylation-gas chromatography-tandem mass spectrometry, Microchem. J. 159 (2020), 105560, https://doi.org/10.1016/j.microc.2020.105560.

[51] J. Tso, D.S. Aga, A systematic investigation to optimize simultaneous extraction and liquid chromatography tandem mass spectrometry analysis of estrogens and their conjugated metabolites in milk, J. Chromatogr. A 1217 (2010) 4784–4795, https://doi.org/10.1016/j.chroma.2010.05.024.
[52] A.I. Schafer, I. Akanyeti, A.J. Semiao, Micropollutant sorption to membrane polymers: a review of mechanisms for estrogens, Adv. Colloid Interface Sci. 164 (2011) 100–117, https://doi.org/10.1016/j.cis.2010.09.006.
[53] F. Guo, Q. Liu, G.B. Qu, S.J. Song, J.T. Sun, J.B. Shi, G.B. Jiang, Simultaneous determination of five estrogens and four androgens in water samples by online solid-phase extraction coupled with high-performance liquid chromatography-tandem mass spectrometry, J. Chromatogr. A 1281 (2013) 9–18, https://doi.org/10.1016/j.chroma.2013.01.044.
[54] W. Yan, Y. Li, L. Zhao, J.M. Lin, Determination of estrogens and bisphenol A in bovine milk by automated on-line C30 solid-phase extraction coupled with high-performance liquid chromatography-mass spectrometry, J. Chromatogr. A 1216 (2009) 7539–7545, https://doi.org/10.1016/j.chroma.2009.05.002.
[55] H.H. Wu, N.Y. Gao, R.F. Wan, L.S. Le, J.M. Wu, Effect and kinetics of haloacetic acids degradation by advanced oxidation processes, J. Harbin Inst. Technol. 39 (2007) 1974–1978.
[56] P. Charisiadis, K.C. Makris, A sensitive and fast method for trihalomethanes in urine using gas chromatography-triple quadrupole mass spectrometry, J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 947–948 (2014) 17–22, https://doi.org/10.1016/j.jchromb.2013.11.060.
[57] M.J. Gomez, M. Petrovic, A.R. Fernandez-Alba, D. Barcelo, Determination of pharmaceuticals of various therapeutic classes by solid-phase extraction and liquid chromatography-tandem mass spectrometry analysis in hospital effluent wastewaters, J. Chromatogr. A 1114 (2006) 224–233, https://doi.org/10.1016/j.chroma.2006.02.038.
[58] A.G. Frenich, R. Romero-Gonzalez, M.L. Gomez-Perez, J.L. Vidal, Multi-mycotoxin analysis in eggs using a QuEChERS-based extraction procedure and ultra-high-pressure liquid chromatography coupled to triple quadrupole mass spectrometry, J. Chromatogr. A 1218 (2011) 4349–4356, https://doi.org/10.1016/j.chroma.2011.05.005.
[59] E.S. Emidio, C.P. da Silva, M.R. de Marchi, Determination of estrogenic mycotoxins in environmental water samples by low-toxicity dispersive liquid-liquid microextraction and liquid chromatography-tandem mass spectrometry, J. Chromatogr. A 1391 (2015) 1–8, https://doi.org/10.1016/j.chroma.2015.02.067.
[60] H. Trufelli, P. Palma, G. Famiglini, A. Cappiello, An overview of matrix effects in liquid chromatography-mass spectrometry, Mass Spectrom. Rev. 30 (2011) 491–509, https://doi.org/10.1016/j.watres.2016.07.059.
[61] H. Jin, L. Zhu, Occurrence and partitioning of bisphenol analogues in water and sediment from Liaohe River Basin and Taihu Lake, China, Water Res. 103 (2016) 343–351, https://doi.org/10.1016/j.watres.2016.07.059.
[62] Y. Liu, S. Zhang, N. Song, R. Guo, M. Chen, D. Mai, Z. Yan, Z. Han, J. Chen, Occurrence, distribution and sources of bisphenol analogues in a shallow Chinese freshwater lake (Taihu Lake): implications for ecological and human health risk, Sci. Total Environ. 599–600 (2017) 1090–1098, https://doi.org/10.1016/j.scitotenv.2017.05.069.
[63] Q. Sun, Y. Wang, Y. Li, M. Ashfaq, L. Dai, X. Xie, C.-P. Yu, Fate and mass balance of bisphenol analogues in wastewater treatment plants in Xiamen City, China, Environ. Pollut. 225 (2017) 542–549, https://doi.org/10.1016/j.envpol.2017.03.018.