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Study on the matrix effect in the determination of selected pharmaceutical residues in seawater by solid-phase extraction and ultra-high-performance liquid chromatography–electrospray ionization low-energy collision-induced dissociation tandem mass spectrometry

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ABSTRACT

Matrix effect is a major problem when trace level pharmaceuticals in seawater were analyzed using solid-phase extraction (SPE) combined with high-performance liquid chromatography–electrospray ionization tandem mass spectrometry (HPLC–ESI–MS–MS). Therefore, efforts should be devoted to diminish matrix effect as much as possible. The present study investigates the matrix effect during the analysis of selected pharmaceutical residues (naproxen, ibuprofen, diclofenac and gemfibrozil) in seawater samples with ultra-high-performance liquid chromatography (UHPLC)–ESI low-energy collision-induced dissociation (CID) MS–MS. Solutions to reduce matrix effect were studied through optimization of SPE procedure and the employment of isotope-labeled analogues. Results showed that 30 mL of deionized water can efficiently diminish matrix effect and satisfactory absolute mean recoveries ranging from 73.5% to 120.5% were obtained in the optimized SPE condition. Isotope-labeled analogues employed as surrogates were found to be efficient to further compensate for matrix effect, with the relative mean recoveries ranging from 85.5% to 110.5%. The optimized method has been successfully applied for the analysis of target pharmaceutical residues in different seawater samples.

1. Introduction

In recent years, pharmaceuticals, an important group of emerging contaminants in the environment, have attracted worldwide attention [1–19]. Pharmaceuticals, usually used in human and veterinary, can enter the aquatic environment as parent compounds, metabolites or conjugates of both. After passing the wastewater treatment plant, in which they might undergo transformation, they are not fully degraded [12]. Although the toxicological effects of pharmaceuticals in the environment to the human and organisms are not well understood until now, it is possible that continuously low doses of pharmaceuticals in surface water can lead to subtle changes in organisms, even these effects can become obvious over long periods of time [20]. Therefore, it is necessary to identify and monitor the occurrence of these pharmaceuticals in various environmental waters.

For the determination of trace level pharmaceuticals, most of analytical methods based on gas chromatography–mass spectrometry (GC–MS) require derivatization prior to instrument analysis [1]. In the past decade, high-performance liquid chromatography (HPLC) combined with electrospray ionization tandem mass spectrometry (ESI–MS–MS) has been used for the determination of polar pharmaceuticals in the environment samples because of its high selectivity and sensitivity [1–4,6–9,12,14–19,21–28]. Recently, an improved HPLC technology named ultra-high-performance liquid chromatography (UHPLC) has been introduced to reduce analysis time, increase sensitivity and separation efficiency [2,5,6,8,15,25]. During UHPLC analysis, due to better resolution and more sharp peaks provided, co-extracted interferences will be reduced during ionization, therefore, matrix effect could be lower, or even eliminated [14].

Because pharmaceuticals in the aquatic environment are often in low concentrations (ng/L–μg/L), sample preparation is usually needed to improve detection sensitivity. The most commonly used sample preparation method is solid-phase extraction (SPE) [9,17,18,26–28] since it allows both sample extraction and cleanup to be conducted at the same time [1]. Sorbents packed in SPE cartridges include non-polar phase, ion-exchange phase and polymeric phase, etc. [1]. Among the cartridges, Waters Oasis HLB (Hydrophilic-Lipophilic Balanced) has been the cartridge of choice for the extraction of both polar and non-polar pharmaceutical compounds [1].

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Matrix effect, which means that the matrix co-extracted with the analytes can cause signal suppression or enhancement during ESI ionization, has been extensively reported in the LC–ESI–MS–MS analysis [1–3,11–19,21–24,26–31]. It was found that matrix effect could result in poor analytical accuracy and reproducibility [12,13]. In the determination of organic compounds in seawater with LC–ESI–MS–MS, matrix effect resulting from high salinity of these samples as well as co-extracted organic contaminants was obvious [24]. Therefore, it is important to eliminate this problem to obtain reliable analytical results. There is no study reported on the matrix effect during the analysis of pharmaceuticals in seawater using SPE combined with LC–ESI–MS–MS.

Normally, many calibration methods such as matrix-matched calibration [30], standard addition [9,16,31] can be employed to compensate for the matrix effect. In addition, optimization of chromatographic separation allows the analytes not to co-elute with interference compounds in the LC analysis [1,12]. Thirdly, splitting the LC-eluent flow before entering the mass spectrometer may help to minimize the matrix effect [1,27,29]. It is also helpful to compensate for the matrix effect by diluting the final extract, which leads to fewer matrix compounds injected into the analysis system [18,19]. Although these operation strategies mentioned above have been proved to be efficient in reducing matrix effect, none of them can eliminate it completely. Thus, efforts such as extensive cleanup procedure during extraction should be performed.

The aim of the present work is to investigate and diminish the matrix effect in the analysis of pharmaceuticals in seawater samples using SPE coupled with UHPLC–ESI low-energy collision-induced dissociation (CID) MS–MS. Naproxen, ibuprofen, diclofenac, gemfibrozil were used as model compounds since they have been identified as high priority pharmaceuticals by the Global Water Research Coalition [32]. Firstly, different steps (including pH value of water sample, drying time and different types of eluting solution) to improve SPE extraction efficiency were investigated. In addition, both dilution factor and washing solution volume during SPE procedure were studied in details when matrix effect was evaluated in seawater analysis. Isotope-labeled analogues utilized as surrogates were also examined. Finally, the matrix effect in different seawater samples was studied.

2. Experimental

2.1. Standards and reagents

Naproxen, ibuprofen, diclofenac, gemfibrozil were supplied by Aldrich (Milwaukee, WI, USA) and their chemical structures were shown in supplementary materials (Fig. S1). Surrogates, isotope-labeled standards including naproxen-d_3, diclofenac-d_4, gemfibrozil-d_6 and ibuprofen-d_3 were purchased from ISOTEC (Miamisburg, OH, USA). HPLC-grade methanol (MeOH) was from TEDIA (Fairfield, OH, USA). HPLC-grade acetonitrile (ACN) was provided by Fisher (Loughborough, UK). Acetic acid (HAc), ammonium acetate (NH_4Ac), hydrogen chloride (HCl) and formic acid (FA) were purchased from Fluka (Buchs, Switzerland). Deionized water (resistance >18.2 MΩ/cm; TOC <2 μg/L) was produced on a USF Maxima (Vivendi Water, UK) water-purification system.

Stock solutions (1 mg/mL of each analyte and its isotope-labeled standard) were prepared in methanol separately. A mixture of working standards containing each compound at 10 μg/mL was prepared by diluting the stock solution in methanol. A mixture of surrogate standards (10 μg/mL) was also prepared in methanol. All the standard solutions were stored at −20 °C.

2.2. Sampling and solid-phase extraction

All seawater samples were collected in amber bottles from Marina Bay and stored at 4 °C after collection. They were filtered through a 0.45-μm Nylon membrane (Millipore, Billerica, MA, USA) prior to extraction. The conductivity of the water samples was detected by Mettler Toledo conductivity meter (Columbus, OH, USA).

During SPE procedure, Oasis HLB cartridge (6 mL, 150 mg) from Waters (Milford, MA, USA) was employed. For recovery test of deionized water, 10 ng of each pharmaceutical and its surrogate were spiked in triplicate into 1 L of water. For recovery test of seawater sample, a mixture of surrogate standards (10 ng of each surrogate included), a mixture of pharmaceutical/surrogate standards (10 ng of each compound included) were spiked in triplicate into 1 L of water sample, respectively. Conditioning of the cartridges was conducted with 5 mL of MeOH followed by 5 mL of deionized water. After loading of 1 L water sample at 10 mL/min (in which pH value was adjusted to 2.0 with concentrated HCl) with AutoTrace SPE workstation (Caliper, Hopkinton, MA, USA) and subsequent washing with 30 mL of deionized water, the cartridge was dried for 10 min under nitrogen flow. The cartridge was then eluted with 18 mL of MeOH. The extracts were then evaporated to 0.7 mL with TurboVap II concentration workstation (Caliper, Hopkinton, MA, USA) under nitrogen flow, reconstituted with 0.1% FA (in methanol) to a final volume of 1.0 mL. All reconstituted extracts were filtrated through 0.2-μm Nylon membrane (Millipore, Billerica, MA, USA). The conductivity of reconstituted extracts from seawater was determined by Horiba B-173 conductivity meter (Kyoto, Japan) with a flat sensor.

2.3. UHPLC–ESI low-energy CID MS–MS analysis

The LC separation was carried out using a Waters Acquity UHPLC system (Milford, MA, USA) equipped with an Acquity BEH C18 (50 mm × 2.1 mm i.d., 1.7-μm) column (Milford, MA, USA) via a binary mobile phase at a flow rate of 0.5 mL/min. The optimized separation conditions were as follows: solvent (A) 0.1%NH_4Ac/HAc; solvent (B) ACN/MeOH (1:1). The gradient mobile phase programme was: 0–0.2 min, 90%A; 0.2–1.2 min, 90 → 1%A; 1.2–3 min, 1%A; 3–3.1 min, 1 → 90%A; 3.1–5 min, 90%A. The injection volume was 10 μL.

The tandem MS analyses were performed on a Waters Quattro Premier XE triple-quadruple mass spectrometer with an electrospray ionization source. The analyses were conducted in negative ionization mode via multiple reaction monitoring (MRM). The source parameters were set as follows: 0.53 kV of capillary voltage, 0.8 V of lens voltage, 120 °C of source temperature, 400 °C of desolvation temperature, 16 L/h of cone gas flow rate, and 900 L/h of desolvation gas flow rate. In addition, a dwell time of 0.02 s and an interscan delay time of 0.01 s were used.

2.4. Evaluation of matrix effect and recovery

In our experiments, absolute recovery is defined as the ratio of MS–MS peak area of extract (B, concentration found) versus that in the pure solvent (A, concentration spiked). Relative recovery is calculated as the ratio of the absolute recovery of target compound to that of its isotope-labeled surrogate.

To assess the matrix effect, method described by Matuszewski et al. [33] was employed. The matrix effect (ME) was calculated as follows [13]:

$$\mathrm{ME}(\%) = \frac{B}{A}100$$

Table 1
UHPLC–ESI low-energy CID MS–MS parameters for the analysis of target pharmaceuticals and related surrogates by MRM in negative ion mode.

Compound	pK_a	RT (min)	CV/CE[a]	MRM1 (quantification)	CV/CE[a]	MRM2 (confirmation)
Naproxen	4.2	1.29	14/15	228.8 → 170.0	14/6	228.8 → 185.0
Naproxen-d_3		1.29	16/15	232.0 → 173.0	16/7	232.0 → 188.0
Ibuprofen	4.5	1.46	18/6	204.8 → 161.0	-	-
Ibuprofen-d_3		1.46	18/8	208.0 → 164.0	-	-
Diclofenac	4.0	1.36	18/20	293.7 → 214.0	18/12	293.7 → 250.0
Diclofenac-d_4		1.36	19/20	297.8 → 217.0	19/11	297.8 → 254.0
Gemfibrozil	4.7	1.55	17/16	248.9 → 121.0	17/10	248.9 → 127.0
Gemfibrozil-d_6		1.55	23/15	255.0 → 121.2	23/12	255.0 → 133.0

[a] CV, cone voltage; CE, collision energy.

It is obvious that the definition of ME is similar to that of absolute recovery. Signal enhancement is observed when an ME value is greater than 100%. The suppression of signal is observed when the ME value is lesser than 100%.

3. Results and discussion

3.1. UHPLC–ESI low-energy CID MS–MS analysis

With gradient eluting described in the experiment section, a good chromatographic separation of the target pharmaceuticals and isotope-labeled surrogates was achieved within 2 min, as demonstrated in supplementary materials (Fig. S2). The optimization of ESI low-energy CID MS–MS parameters was carried out by infusion of 10 μg/mL of each individual pharmaceutical and isotope-labeled surrogate prepared in MeOH. The optimized ESI low-energy CID MS–MS conditions were shown in Table 1. All the precursor ions in ESI negative ion mode were deprotonated molecular ions $[M-H]^-$. The most intensive transition from each precursor ion was chosen for quantification (MRM1). A less sensitive secondary product ion (MRM2) was selected for confirmation. In the case of ibuprofen and ibuprofen-d_3, no secondary transition was observed (Table 1). The related fragmentation schemes of target compounds were demonstrated in supplementary materials (Fig. S3).

3.2. Solid-phase extraction procedure and matrix effect

In SPE procedure, cartridge is primarily important in the extraction of target compounds from water samples [9,15,17]. In this study, Waters Oasis HLB cartridge was used since this cartridge generated the best absolute recoveries for most of pharmaceuticals [9,15,17]. The SPE parameters affecting recovery of target compounds such as pH of water sample, drying time, and eluting solution were investigated. In addition, both dilution factor of water sample and the volume of deionized water as cleanup solution were studied in details when matrix effect of seawater samples was evaluated.

3.2.1. pH value of water sample

The pH value of water sample plays an important role in the SPE extraction efficiency. It was found that pH 2.0 gave the highest absolute recovery for acidic target compounds while Waters Oasis HLB cartridge was employed [2]. This can be explained by the relationship between pH value of water sample and speciation of weakly acidic analytes. When the pH value of water sample is lower than the analytes' pK_a (naproxen, 4.2; ibuprofen, 4.5; diclofenac, 4.0; gemfibrozil, 4.7), the analytes are completely deionized and therefore exist as neutral molecules, which may result in increasing extraction efficiency of the target compounds if only the non-dissociated form binds strongly to the SPE cartridges. Oasis HLB cartridge containing hydrophilic *N*-vinylpyrrolidone and lipophilic divinylbenzene monomers, mainly provides reversed-phase retention. Accordingly, water sample at pH 2.0 was chosen for further experiments.

3.2.2. Optimization of drying time

Generally, cartridge was dried by nitrogen stream to remove excess of water before elution. Under a certain nitrogen flow, the drying time may affect the extraction efficiency of target compounds from SPE cartridge. Thus, when nitrogen stream flow rate was 10 mL/min, the effect of different drying time periods (from 5 min to 20 min) on the absolute recovery was studied. As shown in Fig. 1, for diclofenac, gemfibrozil and ibuprofen, the extraction efficiency increased when the drying time increased from 5 min to 10 min, however it decreased with further increase in drying time from 10 min to 20 min. For naproxen, the trend exhibited was similar when drying time changed from 5 min to 10 min. However, the extraction efficiency was enhanced with further increase of drying time from 10 min to 20 min. On the basis of the observations above, drying time of 10 min was selected.

3.2.3. Eluting solution

The absolute recovery of the target compounds by SPE is highly dependent on the polarity of eluting solvent as well as the pH character. It was reported that MeOH as eluting solvent provided good absolute recovery for target pharmaceuticals [5,9]. The possible reason is that polar target compounds can be easily eluted by relatively high polarity of MeOH. The pH value of eluting solution should not be greater than 7.0. The possible reason is that, when alkalized eluting solution is used, the target acidic compounds with pK_a ranging from 4.0 to 4.7 are ionized, thus making it difficult to elute from cartridge by MeOH. Therefore, 18 mL of MeOH was used as eluting solvent.

3.2.4. Matrix effect and optimization of dilution factor as well as washing solution volume

Matrix effect is obvious in seawater analysis due to the high salinity of these samples, which affects not only the sorption effi-

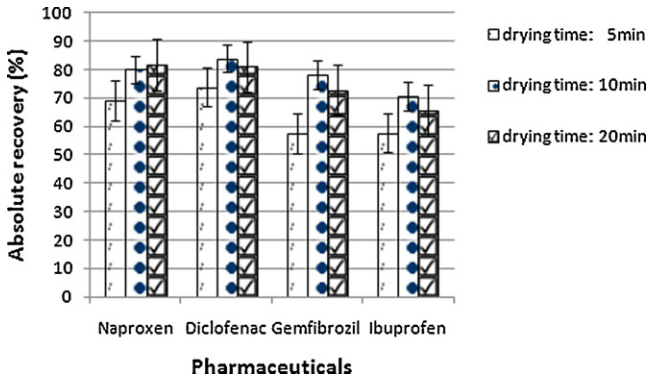

Fig. 1. The effect of drying time on the absolute recovery of target pharmaceuticals during SPE procedure, nitrogen stream flow rate: 10 mL/min.

Table 2
The assignment of experiments with different washing solution volume as well as dilution factor along with conductivity of extracts, absolute recovery of target pharmaceuticals ($n = 3$; spiking level = 10 ng/L).

Experiment no.	Washing solution volume (mL)	Dilution factor	Conductivity of extract (ms/cm)	Absolute recovery (%)			
				Naproxen	Diclofenac	Gemfibrozil	Ibuprofen
1-1	5	10	0.15	71.8	58.2	71.8	69.5
1-2	5	5	0.21	72.7	47.6	62.4	69.1
1-3	5	2	0.33	78.4	41.5	52.0	70.7
1-4	5	1	0.55	73.8	39.9	65.9	79.9
2-1	10	10	0.075	72.8	59.9	71.4	69.7
2-2	10	5	0.089	80.2	62.2	69.6	71.2
2-3	10	2	0.099	78.9	71.1	56.6	79.1
2-4	10	1	0.104	69.8	72.6	53.9	75.9
3-1	20	10	0.055	86.5	74.3	79.3	72.7
3-2	20	5	0.063	90.7	73.5	77.0	74.2
3-3	20	2	0.074	99.9	75.5	74.7	89.9
3-4	20	1	0.097	98.7	92.8	71.7	87.4
4-1	30	10	0.045	104.3	79.4	77.4	77.6
4-2	30	5	0.052	98.7	81.3	83.8	74.2
4-3	30	2	0.056	107.0	90.5	83.6	82.4
4-4	30	1	0.065	111.3	82.0	83.2	90.2

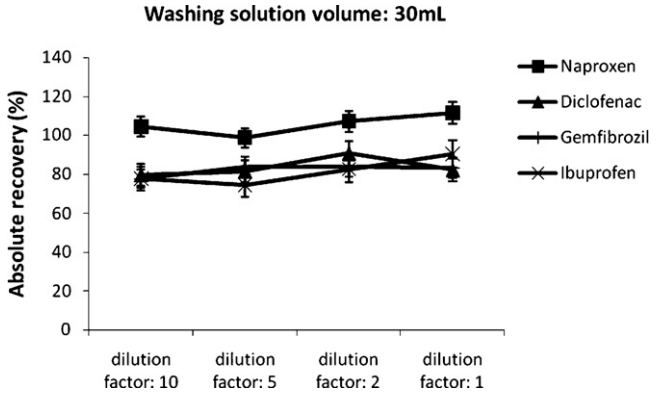

Fig. 2. The effect of dilution factor on the absolute recovery of target pharmaceuticals from seawater samples during SPE procedure.

ciency of SPE cartridges but also the ionization efficiency of ESI [2,24]. Therefore, it is of critical importance to optimize the SPE procedure (diluting the seawater sample with deionized water as well as using deionized water to wash SPE cartridge) to eliminate the matrix effect resulting from high salinity. Seawater sample (conductivity: 43.7 ms/cm) was used for the optimization study. The other SPE conditions were: 2 as pH value of water sample; 10 min as drying time; 18 mL of MeOH as eluting solution. The assignments of experiments and results were illustrated in Table 2. The washing solution volume studied was in the range of 5–30 mL. The dilution factor ranged from 1 to 10. It is clear from Table 2 that the absolute recovery of target compounds increased with the decrease of conductivity of extracts, which confirmed that the salinity of the extracts usually leads to the signal suppression in the ESI procedure [24]. The relationships between absolute recovery of target compounds and dilution factor were evaluated. The results were shown in Fig. 2. It is observed that the absolute recovery of some compounds was enhanced with the decrease in dilution factor, however, the absolute recovery of other compounds increased with the enhancement in dilution factor. The possible reason is the compromise between the increased SPE extraction efficiency with the increase of salt concentration in water sample (salt-out effect) [17], and the increased ion suppression of ESI with the increase of salt concentration in water sample [2]. The relationships between the absolute recovery and washing solution volume were also investigated. As depicted in Table 2, absolute recovery of all four target compounds improved with the increase in washing solution volume from 5 mL to 30 mL. Good absolute recoveries (between 75% and 112%) were obtained for all analytes at a washing solution volume of 30 mL regardless the change of dilution factor from 1 to 10. The possible reason is that 30 mL of washing solution could completely remove the salts retained in the SPE cartridge. It is obvious that the volume of deionized water as washing solution played a key role in eliminating matrix effect from seawater samples analysis when SPE combined with UHPLC–ESI low-energy CID MS–MS was employed. On the basis of the above study, 30 mL of deionized water was used as washing solution and no dilution of water sample was carried out in the optimized experiment conditions.

3.3. The use of isotope-labeled surrogates

The employment of isotope-labeled analogues can effectively compensate for the matrix effect in SPE procedure and LC–ESI–MS–MS analysis because they are chemically and structurally similar to their target analytes but differ in molecular mass [13]. In SPE procedure, isotope-labeled analogues can be extracted to the same extent as the target compounds, as they have the almost same chemical and physical properties. During LC–ESI–MS–MS, there is no doubt that ionization of the target compounds will be suppressed or enhanced to the same extent as the isotope-labeled analogues, since isotope-labeled analogues should have the same

Table 3
Overall recoveries of target pharmaceuticals in different seawater matrixes before and after correction with isotope-labeled surrogates ($n = 3$).

Compound	Mean recovery (RSD)[a]	
	Before correction	After correction
Seawater 1 (conductivity: 18.42 ms/cm)		
Naproxen	73.5 (5.6%)	100.6 (8.2%)
Diclofenac	83.2 (9.2%)	93.1 (5.6%)
Gemfibrozil	75.1 (10.5%)	89.2 (11.0%)
Ibuprofen	87.4 (8.9%)	90.2 (8.3%)
Seawater 2 (conductivity: 43.7 ms/cm)		
Naproxen	120.5 (11.2%)	91.2 (12.5%)
Diclofenac	81.5 (7.6%)	92.8 (7.8%)
Gemfibrozil	80.2 (9.3%)	85.5 (8.4%)
Ibuprofen	79.4 (12.3%)	85.6 (9.9%)
Seawater 3 (conductivity: 34.5 ms/cm)		
Naproxen	113.6 (9.2%)	89.2 (8.8%)
Diclofenac	88.2 (8.5%)	86.0 (8.5%)
Gemfibrozil	75.9 (7.3%)	110.5 (8.9%)
Ibuprofen	90.2 (6.6%)	86.5 (6.5%)

[a] Spiked concentration (10 ng/L).

Table 4
Concentrations of target pharmaceuticals in different seawater samples.

Sample	Naproxen (ng/L)	Diclofenac (ng/L)	Gemfibrozil (ng/L)	Ibuprofen (ng/L)
Location 1	21	4	4	47
Location 2	19	19	4	41
Location 3	13	12	1	46
Location 4	25	19	5	68
Location 5	30	38	9	94
Location 6	26	28	2	121

chromatographic retention time and ionization characteristics as target compounds [13]. Therefore, isotope-labeled analogues (see Fig. S2 and Table 1) were used as surrogates in this study under the optimized SPE conditions. The absolute recovery (recovery before correction) and relative recovery (recovery after correction) were investigated in three seawater matrixes with different conductivities, and the results are given in Table 3. It is clear that satisfactory relative mean recovery was in the range of 85.5–110.5% with relative standard deviations (RSDs) smaller than 12.5%. Compared with the absolute recoveries ranging from 73.5% to 120.5%, the relative recoveries generated from the use of isotope-labeled analogues can almost eliminate the matrix effect from seawater samples.

3.4. Method detection limit (MDL)

The MDL of target compounds in seawater was 0.95 ng/L for naproxen, 0.93 ng/L for diclofenac, 0.4 ng/L for gemfibrozil and 1.0 ng/L for ibuprofen, respectively.

3.5. Seawater samples

The developed method was applied for the analysis of selected pharmaceutical residues in estuarial seawater samples. As shown in Table 4, all four pharmaceuticals were detected. The concentration of naproxen in six seawater samples was determined to be from 13 ng/L to 30 ng/L. The concentrations of diclofenac and gemfibrozil were in the range of 4–38 ng/L and 1–9 ng/L, respectively. For ibuprofen, the concentration ranged from 41 ng/L to 121 ng/L. Among the pharmaceuticals detected, ibuprofen was found at the highest concentration while gemfibrozil was found at the lowest concentration. It is obvious that the developed method has been successfully applied in the determination of selected pharmaceuticals in seawater.

4. Conclusions

In the present study, the matrix effect in the analysis of selected pharmaceutical residues from seawater samples using SPE and UHPLC–ESI low-energy CID MS–MS were investigated in details. Several steps have been employed to diminish matrix effect. Firstly, during SPE procedure, many parameters affecting absolute recovery of pharmaceuticals including pH value of water samples, drying time, and eluting solution were optimized. It was found that 10 min as drying time while 2 as pH value of water samples and 18 mL of MeOH as eluting solution, gave the best absolute recovery. In the analysis of seawater samples, the optimization of dilution factor as well as washing solution volume was also studied to eliminate the matrix effect. Results indicated that deionized water as washing solution played a key factor to remove the seawater matrix effect. With 30 mL of deionized water as washing solution, satisfactory absolute recoveries ranging from 73.5% to 120.5% could be obtained in the seawater sample analysis without dilution with deionized water. Finally, the employment of isotope-labeled analogues can greatly further compensate for matrix effect with relative recovery from 85.5% to 110.5%. The optimized method has been successfully applied for the analysis of target pharmaceutical residues in different seawater samples.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.chroma.2009.12.074.

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