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Determination of pharmaceutical residues in waters by solid-phase extraction and large-volume on-line derivatization with gas chromatography–mass spectrometry

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Abstract

This work presents a modified method to analyze selected pharmaceutical residues (clofibric acid, ibuprofen, carbamazepine, naproxen, ketoprofen and diclofenac) in water samples. Various solid-phase extraction cartridges were investigated. The newly developed Oasis HLB (polystyrene-divinylbenzene-*N*-vinyl pyrrolidone terpolymer) solid-phase extraction (SPE) cartridge provides the optimal sample extraction results. The analytes were then identified and quantitatively determined by gas chromatography–mass spectrometry (GC–MS) via on-line derivatization in the injection-port using a large-volume (10 μl) sample injection with tetrabutylammonium (TBA) salts. This injection-port derivatization technique provides sensitivity, fast and reproducible results for pharmaceutical residues analysis. Mass spectra of butylated derivatives and tentative fragmentation profiles are proposed. Molecular ions and some characteristic ions were used as the quantitation ions to obtain maximum detection sensitivity and specificity. The quantitation limits of these compounds ranged from 1.0 to 8.0 ng/l in 500 ml tap water samples. Recovery of these residues in spiked various water samples ranged from 50 to 108% while RSD ranged from 1 to 10%. The selected analytes were detected in concentrations of 30 to 420 ng/l in wastewater treatment plant effluent and river water samples.

Keywords: Pharmaceuticals; Large-volume injection; GC-MS; SPE; Water samples

1. Introduction

Currently, society is highly concerned about the potential risk to human life and wildlife associated with exposure to bioactive substances and pharmaceutical residues, some of which compounds may be carcinogenic, mutagenic and reproductive toxic (often called CMR toxic) [1–5]. The rapid rise in the use of pharmaceutical products is a newly environmental problem, so in 1999, the European Science Foundation held the "Pharmaceuticals in the Environment" workshop to begin to explore this issue deeply [6]. Unlike pesticides and many industrial chemicals, most drugs are discharged into the environment continuously by domestic or industrial sewage systems and surface runoff. Such bioactive substances and their metabolites are ubiquitous and persistently occur in, and undergo bioconcentration from, surface water. Many of these residues have been detected in wastewater, surface water, groundwater and even in drinking water samples [7–25]. Although the concentration of these residues in the aquatic environment is too low to pose a very acute risk, it is unknown whether other receptors in non-target organisms are sensitive to individual residues, or the combination of drugs that share a common mechanism of action exhibits synergistic effects [5,6]. It is necessary to develop a sensitive and convenient analytical technique to study the occurrence and fate of these residues in the aquatic environment. Fig. 1 shows structures of four frequently used analgesic/anti-inflammatory drugs (ibuprofen, naproxen, ketoprofen and diclofenac), one antiepileptic (carbamazepine) and one lipid regulator (clofibric

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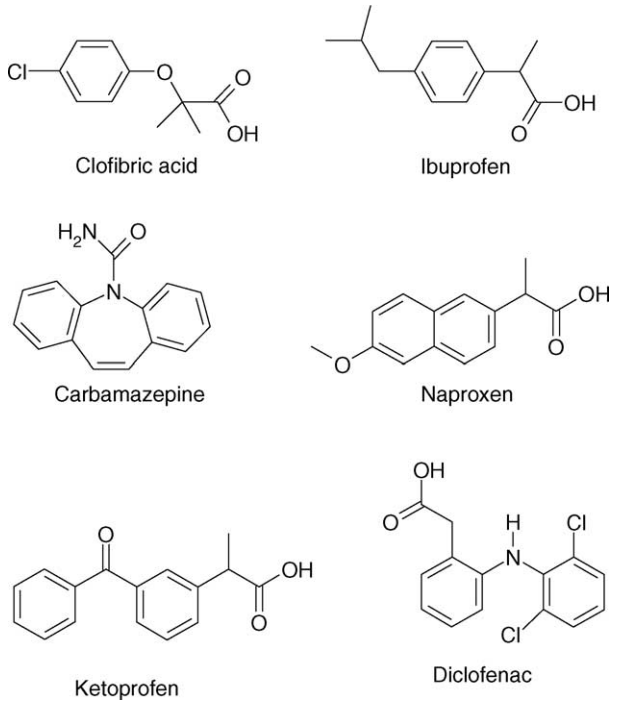

Fig. 1. Structures of the selected acidic and neutral pharmaceuticals.

acid) employed in method development and evaluation in this study.

Various solid-phase extraction (SPE) methods combined with GC–MS and GC–MS–MS [8,9,18–21] or LC–MS techniques with electrospray ionization (LC–ESI–MS) and LC–MS–MS [7,14–17,22–25] have been developed as identification and quantitation methods. In order to enable high resolution GC as the determination step for acidic pharmaceutical residues (i.e., clofibric acid, ibuprofen, naproxen, ketoprofen and diclofenac), derivatization must be performed to increase the volatility of analytes and improve chromatographic separation. Diazomethane is the most commonly used derivatization compound for acidic pharmaceuticals analysis [8,9,18,19]. However, the toxicity, carcinogenicity and explosiveness of this agent, are such that alternative procedures must be considered. Injection-port derivatization with ion-pair reagents has been reported to be a rapid and simple alternative to conventional derivatization methods for aliphatic, aromatic acids and sulfonic acids [21,26–29]. Moreover, the large-volume sample injection (LVI) with GC is attractive for improving the detection sensitivity, and preventing the discrimination inside the syringe needle and injector liner from the injection of a small volume of sample. Mol et al. reviewed and evaluated the technique of inserting glass wool into injector liners with large dimensions, and referred to this method of sample introduction as “solvent-split injection” [30]. Amirav et al. developed a direct sample introduction device that enables solid materials to be directly sampled into a GC [31,32]. This device is commercially available as “ChromatoProbe” from Varian. The device works by requiring a micro-vial that contains the sample to be placed into the GC injection-port. For liquid sample, it is placed in the micro-vial, and the technique can be performed just like an LVI techniques. The micro-vial can be used as a small reactor for on-line injection-port derivatization. This procedure has been successfully developed in our laboratory and used to determine LAS, carboxylate surfactant metabolites, chlorophenoxy acid herbicides and naphthalenesulfonic acids in water samples [33–37]. The procedure was initiated by reacting carboxylic acid with tetraalkylammonium salts (i.e., tetrabutylammonium hydrogen sulfate, $N(Bu)_4^+HSO_4^-$) to form carboxylate ion pairs [$RCOO^-N(Bu)_4^+$] in solution. Upon introduction to a high temperature (i.e., above 280 °C) GC injection-port, the carboxylic acid groups were transformed to their corresponding butyl esters [RCOOBu].

This work presents a modified method for rapidly and quantitatively determining the pharmaceutical residues in aqueous samples. The recovery efficiency of the SPE methods was evaluated using various sorbents, and sensitivity and precision were determined after the optimization of the on-line derivatization approach using selected drugs (Fig. 1) as trial analytes in various water samples.

2. Experimental

2.1. Chemicals and reagents

Unless stated otherwise, all high purity chemicals and solvents were purchased from Aldrich (Milwaukee, WI, USA), Tedia (Fairfield, OH, USA) and Merck (Darmstadt, Germany), and were used without further purification. Reagent grade tetrabutylammonium hydrogen sulfate (TBA-HSO_4) was purchased from TCI (Tokyo Chemical Industry, Tokyo, Japan). Clofibric acid, ibuprofen, carbamazepine, naproxen, ketoprofen and diclofenac were purchased from Aldrich-Sigma (Milwaukee, WI, USA). [$^2H_{12}$]Chrysene (as an internal standard) was purchased from ChemServices (West Chester, PA, USA). Stock solutions of each drug (1000 μg/ml) were prepared in methanol. Mixtures of the drugs for working standard preparation and sample fortification were also prepared in methanol. All stock solutions and mixtures were stored at −10 °C in the dark.

2.2. Sample collection

Tap water samples were directly collected in our laboratory in National Central University. Groundwater samples were collected from a groundwater monitoring well in National Central University. River water samples were collected from Fu-Hsing River, which received a large percentage of untreated municipal and agricultural wastewater near the Hsin-Chu electronic industrial parks. The river samples were collected at a 0.5-m depth from mid-stream using pre-rinsed glass bottles. Wastewater treatment plant

(WWTP) effluents were collected from An-Ping community in Tainan. This WWTP consists of mechanical clarification, biological treatment, and flocculation filtration; population equivalent 380,000. All samples were collected in duplicate (500 ml/each) and shipped to the laboratory in ice-packed containers. Upon arrival, the samples were immediately adjusted to pH 2–3 by adding concentrated HCl to depress microbial degradation, and then stored at −10 °C until analysis.

2.3. Sample extraction

Water samples were preconcentrated with RP-C_{18} (Supelclean ENVI-18 SPE, 3 ml, 0.5 g, surface area 500 m^2/g, Supelco, Bellefonte, PA, USA), PS-DVB (polystyrene-divinylbenzene, LiChrolut EN) polymeric sorbent (3 ml, 0.2 g, surface area 1200 m^2/g, Merck), or Oasis HLB (3 ml, 60 mg, surface area 810 m^2/g, Waters, Milford, MA, USA) SPE cartridges. For optimal procedure of RP-C_{18} SPE, each cartridge was pre-conditioned with 3 ml of eluting solution, methanol, and then rinsed by deionized water on an SPE manifold (VacMaster, IT Sorbent Technology, Cambridge, UK). Water sample 500 ml (pH 5) was passed through the cartridge at a flow rate of about 5–10 ml/min via a siphon tube with the aid of a vacuum. When the extraction was completed, the cartridge was washed with 1 ml 10% methanolic solution, and subsequently air-dried under vacuum for 5 min. The drug residues were then eluted from the cartridge by two eluting solutions: Condition I, 8 ml of acetone–ethyl acetate (1:1, v/v); or Condition II, 8 ml of acetone–ethyl acetate (2:1, v/v). For optimal procedure of LiChrolut EN SPE, each cartridge was pre-conditioned with 3 ml of eluting solution, and then rinsed by deionized water. Water sample 500 ml was passed through the cartridge at a flow rate of about 5–10 ml/min. When the extraction was completed, the cartridge was washed with 1 ml deionized water, and subsequently air-dried under vacuum for 5 min. The drug residues were then eluted from the cartridge by 5 ml of acetone–methanol (3:2, v/v).

For optimal extraction (see Section 3.3), a Waters Oasis HLB SPE sorbent was applied to quantitatively extract pharmaceutical residues from the water samples, which has been reported by Öllers et al. [9] and was used with modifications. Before extraction, each HLB cartridge was pre-conditioned with 3 ml of methanol, and then rinsed by 3 ml of deionized water on an SPE manifold. Water sample 500 ml (pH 5) was passed through the HLB-cartridge at a flow rate of about 4–6 ml/min. When the extraction was completed, the cartridge was washed with 1 ml 5% methanolic solution, and subsequently air-dried under vacuum for at least 15 min. The drug residues were then eluted from the cartridge with 2 ml of methanol eluent.

All the extracts from three types of SPE were completely evaporated to dryness by a stream of nitrogen. The residues were then redissolved in 100 μl of chloroform with internal standard and 10 mM TBA-HSO_4, and made ready for GC–MS analysis.

2.4. GC–MS analysis

A Varian 3400CX gas chromatograph directly connected to a Saturn 2000 ion-trap mass spectrometry (Varian, Walnut Creek, CA, USA) was used in the analysis of the sample extracts. A ChromatoProbe and a temperature-programmed injector (Varian) were used to introduce a large-volume sample and on-line derivatization approach, as described elsewhere [34–37]. A DB-5MS capillary column (30 m × 0.25 mm i.d., 0.25 μm film, from J&W, USA) connected to 2 m of deactivated fused-silica per-column (as retention gap), was used. The temperature of the injector was held at 80 °C for 1 min to evaporate the solvent, then rapidly heated to 290 °C, and held for another 23 min. After the injector temperature had reached 290 °C, the GC temperature program began as follows: 70 °C for 4 min, followed by a 10 °C/min ramp to 300 °C, and hold for 4 min. The conditions of ion-trap MS system can be found elsewhere [36,37]. The transfer line to the mass spectrometer was set at 280 °C.

Saturn revision 5.2 software was used for full-scan electron ionization (EI) data acquisition, and acquired under the following conditions: mass range 50–500 *m/z*, scan time 1 s, solvent delay 15 min, manifold temperature 80 °C, emission current 10 μA (70 eV), multiplier voltage 1950 V, automatic gain control (AGC) target 20,000.

3. Results and discussion

3.1. Evaluation of ion-pair reagents and injector-port conditions

According to our previous experience with ion-pair reagents, TBA-HSO_4 was the best reagent for on-line derivatization because characteristic ions of butylated acidic pharmaceuticals (see Section 3.2) produced the highest average peak areas and quantitative results. No retention effect either for TBA salt or sample was observed since the disposable micro-vial was used for sample introduction and no glass wool was inserted into the inlet glass liner. Among the four TBA concentrations (5, 10, 15 and 20 mM), 10 mM was selected because it produced the highest average peak areas of the butylated acidic pharmaceuticals. Details on how to evaluate the conditions of the injection-port can be found elsewhere [34]. This work employed a sample volume of 10 μl and an injection temperature of 290 °C following the injector-temperature program as described in Section 2.

3.2. GC–MS of butylated derivatives

Fig. 2 depicts the full-scan EI mass spectra and tentative fragmentation patterns for the butylated acidic pharmaceuticals by TBA-HSO_4 and carbamazepine. The butylated analytes showed some common fragmentation pathways. Either the molecular ions $[M]^+$ or the $[M–COOC_4H_9]^+$ (i.e., $[M–101]^+$) ions were the base peaks of butylated clofibric

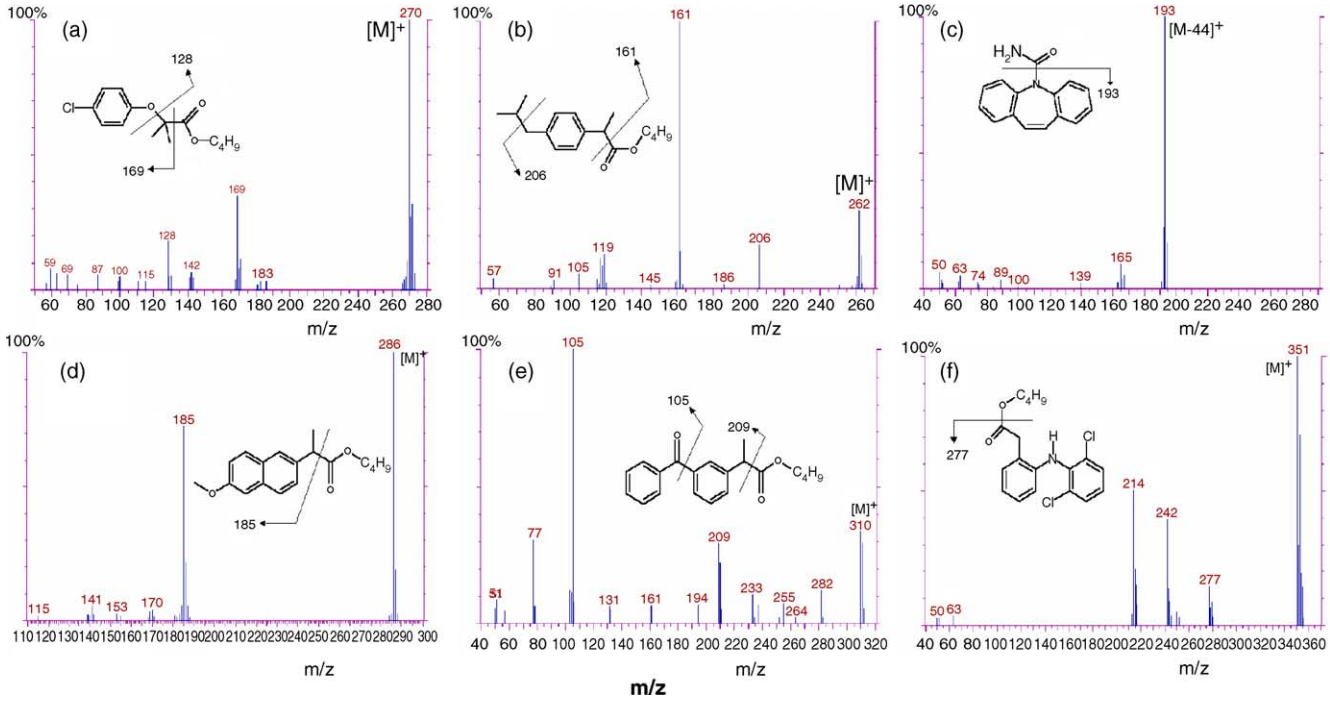

Fig. 2. The profiles of EI mass spectra and tentative fragmentation of the butylated derivatives of the selected acidic pharmaceutical and carbamazepine: (a) clofibric acid, (b) ibuprofen, (c) carbamazepine, (d) naproxen, (e) ketoprofen and (f) diclofenac.

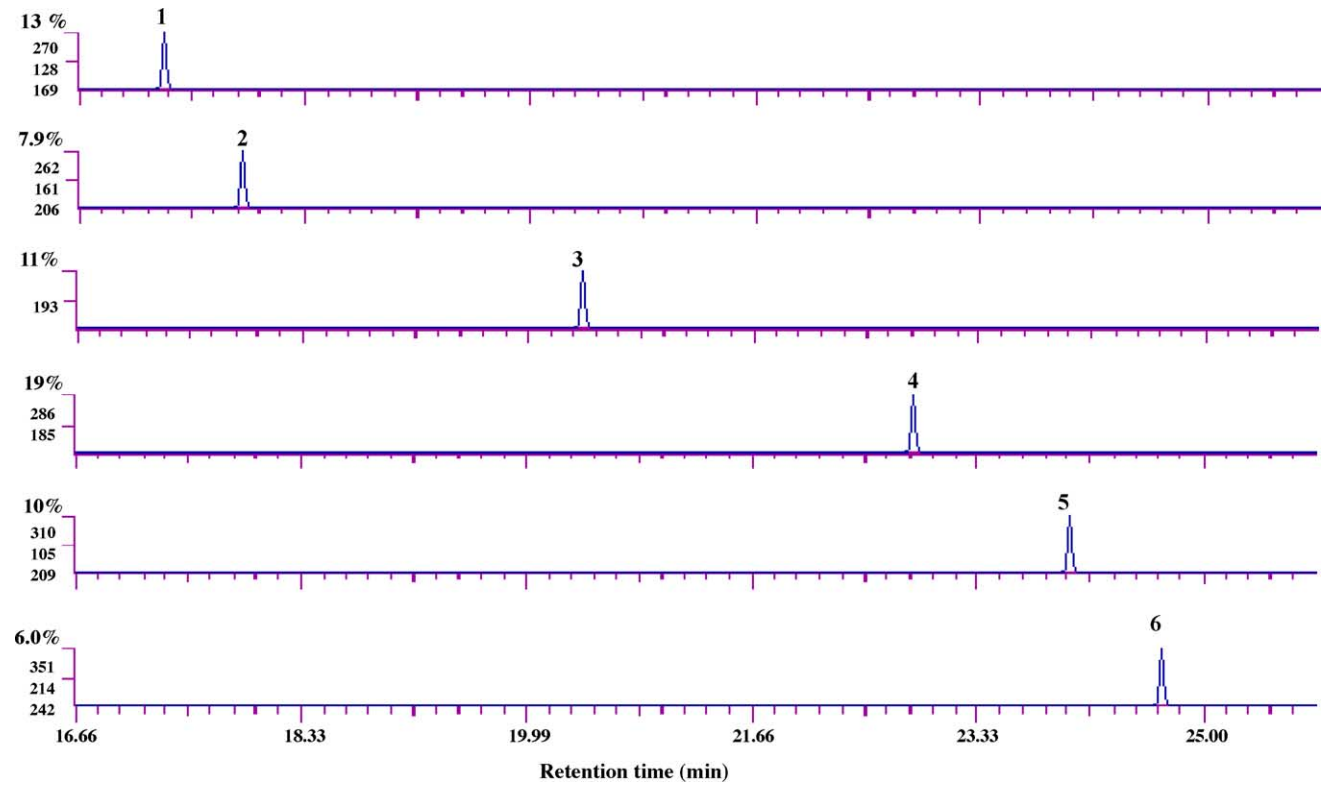

Fig. 3. The extracted mass chromatograms of butylated acidic pharmaceutical residues and carbamazepine from a spiked river water sample: peak (1) clofibric acid, (2) ibuprofen, (3) carbamazepine, (4) naproxen, (5) ketoprofen and (6) diclofenac.

Table 1
Detection characteristics, linearity and quantitation limits of butylated derivatives of the selected pharmaceuticals

Compound	Quantitation ions (*m/z*)	Linearity[a] (r^2)	Quantitation limit (ng/l)
Clofibric acid	270 + 128 + 169	0.995	2.0
Ibuprofen	161 + 262 + 206	0.997	2.0
Carbamazepine	193	0.999	8.0
Naproxen	185 + 185	0.999	1.0
Ketoprofen	105 + 310 + 209	0.999	2.0
Diclofenac	351 + 214 + 242	0.995	2.0

[a] Linearity described by linear correlation coefficients for concentration range (6-level): 0.1–10 ng/μl.

acid, ibuprofen, naproxen, and diclofenac, therefore, to be used as the quantitation ions to obtain maximum detection sensitivity and specificity. The characteristic ion at *m/z* 128 of butylated clofibric acid represented the chlorophenol fragment ion (Fig. 2a). For butylated ketoprofen (Fig. 2e), the base ion was found at *m/z* 105, presumable further loss of ethylbenzene from $[M–COOC_4H_9]^+$ (i.e., *m/z* 209) ion. The characteristic ions of butylated diclofenac (Fig. 2f) were observed at *m/z* 277 (presumable loss of HOC_4H_9), *m/z* 242 (further loss of Cl) and *m/z* 214 (further loss of CO). For the neutral drug carbamazepine (Fig. 2c, was not derivatized by TBA-HSO_4), the base ion of *m/z* 193 ($[M–44]^+$) was observed due to the loss of $CONH_2$. Fig. 3 displays the extracted mass chromatograms of butylated acidic pharmaceutical residues and carbamazepine from a spiked river water sample. The procedures used herein indicate that on-line derivatization by TBA-HSO_4 reagent is an effective and robust technique of positively identifying and reliably determining pharmaceutical residues in aqueous samples.

3.3. Method validation and applications

Table 1 presents an overview of the quantitation ions, linearity and quantitation limits for these butylated derivatives and carbamazepine. The quantitation limits of these analytes were ranged from 1.0 to 8.0 ng/l in 500 ml tap water samples, defined at a signal to noise ratio (S/N) ≥10. The quantitation of these analytes was calculated from the six-level calibration curve (or average response factor) covering the range 0.1–10 ng/μl, each divided by the fixed concentration of internal standard ($[^2H_{12}]$chrysene) [36,37]. The calibration curves were linear with coefficients of determination $r^2 \geq 0.995$. The curve covered a range equivalent to the concentration of the analytes in final extract.

Various SPE sorbents were investigated to determine the optimal sample extraction procedures. The effectiveness of hydrophobic SPE cartridges (RP-C_{18} and PS-DVB) for extracting acidic and neutral pharmaceuticals from spiked deionized water samples was evaluated initially, since they are widely available and inexpensive. However, preliminary experiments revealed that hydrophobic-based SPE cartridges did not efficiently extract acidic pharmaceuticals from spiked water samples (Table 2), the best recoveries ranged from 25 to 70%, except in the case of neutral pharmaceutical carbamazepine (the recovery of which exceeded 95%). These results might be explained by the bad "wet-ability" of such cartridges toward polar or hydrophilic analytes [9,38], or by the shorter drying time associated with these hydrophobic-based SPE cartridges [39]. High rates of recovery were obtained using the newly developed Oasis HLB-SPE cartridge with hydrophilic and lipophilic balance characteristics, which provides the excellent wetting properties of the hydrophilic *N*-vinylpyrrolidine monomer [38,39]. The recoveries of these analytes from spiked deionized water samples ranged from 77 to 102% while RSDs ranged from 1 to 10% (Table 2). A breakthrough for the extraction of 500 ml of a spiked water sample was made using tandem cartridges, and no significant amounts of analytes (<2%) were detected in the eluate from the second cartridge. These findings indicate that the best conditions for the simultaneous extracting of acidic and neutral pharmaceutical residues from water samples were achieved using HLB-SPE cartridges by adjusting the pH of the water sample to 5.0 and by drying the cartridge in air for longer time before eluting the analytes. To determine the efficiency and precision of the method, the recovery from HLB-SPE was further evaluated using three replicate analyses with various volumes of real water samples from various sources, each spiked to yield final concentrations of analytes from 40 to 500 ng/l as shown in Table 3. The average recovery of these pharmaceuticals from the spiked real water samples ranged from 50 to 108%, whereas RSD ranged from 4 to 10%. Car-

Table 2
Recoveries (%) of selected pharmaceuticals obtained by different sorbents from the spiked deionized water samples ($n = 4$)

	Recovery, % (RSD)			
Compound	RP-C_{18} (Condition I)	RP-C_{18} (Condition II)	LiChrolut EN	Oasis-HLB
Clofibric acid	52[a] (10)[b]	70 (9)	40 (10)	95 (1)
Ibuprofen	35 (20)	41 (18)	25 (8)	77 (5)
Carbamazepine	109 (15)	107 (11)	95 (10)	93 (6)
Naproxen	46 (8)	67 (10)	46 (9)	91 (10)
Ketoprofen	64 (8)	82 (10)	28 (20)	102 (6)
Diclofenac	27 (15)	56 (9)	30 (9)	92 (2)

Condition I: eluted with 8 ml of acetone–ethyl acetate (1:1, v/v). Condition II: eluted with 8 ml of acetone–ethyl acetate (2:1, v/v).
[a] Average of four results of the spiked recoveries.
[b] The relative standard deviations (RSD%) are given in parentheses.

Table 3
Concentrations (ng/l) of the selected pharmaceutical residues in various water samples and their spiked recoveries

Sample	Clofibric acid	Ibuprofen	Carbamazepine	Npproxen	Ketoprofen	Diclofenac
Tap water[a] ($n = 3$)						
Background concentration (ng/l)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Spike recovery (%)	88[b] (7)[c]	77 (9)	103 (5)	96 (8)	50 (6)	80 (9)
Groundwater[d] ($n = 3$)						
Background concentration (ng/l)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Spiked recovery (%)	80 (9)	87 (12)	99 (7)	100 (10)	59 (5)	81 (9)
Fu-Hsing River[e] ($n = 3$)						
Background concentration (ng/l)	n.d.	n.d.	n.d.	30	n.d.	n.d.
Spiked recovery (%)	74 (7)	54 (7)	108 (10)	72 (9)	77 (7)	63 (4)
WWTP effluent[f] ($n = 3$)						
Background concentration (ng/l)	n.d.	30	420	170	n.d.	n.d.
Spiked recovery (%)	70 (3)	50 (9)	79 (2)	52 (9)	83 (2)	54 (7)

[a] Tap water 500 ml, spiked to yield final concentration for each analyte 40 ng/l.
[b] Average of three results of the spiked recoveries.
[c] The RSDs (%) are given in parentheses.
[d] Groundwater 200 ml, spiked to yield final concentration for each analyte 50 ng/l.
[e] Fu-Hsing River water 100 ml, spiked to yield final concentration for each analyte 200 ng/l.
[f] WWTP effluent 50 ml, spiked to yield final concentration for each analyte 500 ng/l.

bamazepine and naproxen were detected in WWTP effluent samples in concentrations of 420 and 170 ng/l, respectively (Table 3). The results reveal that the method is appropriate for analyzing pharmaceutical residues in environmental samples.

4. Conclusion

The analytical procedures developed herein demonstrate that HLB-SPE and injection-port derivatization using a large-volume sample introduction device with TBA salts, is a rapid and quantitative method for the trace determination of pharmaceutical residues in aqueous samples. The method significantly reduces the solvent waste and simplifies the sample preparation requirements, typically avoiding derivatization with hazardous reagents in current use. The method can be used as a rapid screening tool to yield detailed information on the sources, behavior and fate of the widely used pharmaceutical residues in both surface water and groundwater, and to understand the effect of pharmaceutical residues in untreated wastewater that is directly discharged into the aquatic environment.

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