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Short communication

Application of hollow fiber-based liquid-phase microextraction (HF-LPME) for the determination of acidic pharmaceuticals in wastewaters

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ABSTRACT

The presence of pharmaceuticals in the environment is a very important problem that requires analytical solutions. The wide variety of matrices and, usually, the low pharmaceuticals levels in the environmental samples requires high sensitive and selective analytical procedures. Wastewaters are one of the more important sources of environmental pollutants but they are very complex matrices that need clean-up procedures prior the analysis. Hollow fiber-based liquid-phase microextraction (HF-LPME) is a relatively new technique used in analytical chemistry for sample pre-treatment that offers high selectivity and sensitivity compared to most traditional extraction techniques. The low organic solvent consumption derived from the use of HF-LPME is according to the current trends to a “Green Chemistry”, and Analytical Chemistry should follow these environmental good practices. This paper describes an extraction method using a polypropylene membrane supporting dihexyl ether (three-phase hollow fiber-based liquid-phase microextraction (HF-LPME)) for the direct analysis of three pharmaceuticals (salicylic acid (SAC), ibuprofen (IBU) and diclofenac (DIC)) in raw and treated wastewaters followed by a HPLC/MS-MS determination using a highly packed Pursuit® XRs Ultra 2.8 μm C18 column that allows high resolution using low flow-rates and, simultaneously, short retention times. Detection limits were 20, 100 and 300 ng L^{-1} for salicylic acid, diclofenac and ibuprofen, respectively.

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1. Introduction

Pharmaceutical products are a broad and diverse group of chemicals developed and used to produce specific biological effects in humans and animals health care or livestock farming. The growing worldwide consumption of pharmaceuticals and their proved occurrence in the environment has become an important issue in recent years, and in the last decade, the focus of environmental research has been extended from more classical environmental pollutants as PCBs, PAHs or pesticides to pharmaceuticals and personal care products; pharmaceuticals are, in some way, dangerous because they have been designed to be biologically active. The amount of human pharmaceuticals reaching the environment depends on the consumption amount, and excretion rate via faeces and urine. Effluents of wastewater treatment plants (WWTPs) are considered the principal source of drugs in the aquatic environment. A smaller contribution to the presence of pharmaceuticals in the environment is due to the disposal of outdated medicines down household drains [1] and to the pharmaceutical industry waste [2,3].

Raw and treated wastewater are complex matrices that difficult their analysis. Several extraction procedures have been applied to wastewaters and recent results have been reviewed for molecular imprinted polymers [4,5] or stir bar sorptive extraction [6]. However, solid-phase extraction (SPE), using several sorbent types has been the preferred sample preparation technique to extract pharmaceuticals from environmental waters [7–9]; although the sorbents usually show poor selectivity and this will constitute a problem when a selective extraction from complex matrices must be performed. Additionally, SPE involves intensive sample handling and needs several time consuming steps. Liquid–liquid extraction (LLE) is a classical and common technique used for preconcentration and cleanup prior to chromatographic or electrophoretic analysis that requires large organic solvent consumption. It is also tedious and analyte-loss is frequent due to multi-stage operations that cannot be neglected. Liquid-phase microextraction (LPME), based on a droplet of water-immiscible organic solvent hanging at the end of a microsyringe needle (single drop microextraction, SDME) [10,11], is a simple, inexpensive, fast, effective and virtually solvent-free sample pre-treatment technique. However, SDME is not very robust, and the droplets may

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be lost from the needle tip of the microsyringe during extraction.

Audunsson [12] introduced an alternative concept for LPME that was developed by Thordarson et al. [13] and Pedersen-Bjergaard and Rasmussen [14] based on the use of single, low-cost, disposable, porous, hollow fibers made of polypropylene. In this concept, the analytes of interest are extracted from aqueous samples, through a thin layer of organic solvent (several microlitres) immobilized within the pores of a porous hollow fiber, and into an acceptor solution inside the lumen of the hollow fiber. In hollow fiber liquid-phase microextraction (HF-LPME), the organic phase is protected by the fiber, and it appears that the hollow fiber decelerates the process of organic solvent dissolution into the bulk solution. The disposable nature of the hollow fiber totally eliminates the possibility of sample carryover and ensures reproducibility. In addition, the small pore size prevents large molecules and particles present in the donor solution from entering the accepting phase and, at the same time, most macromolecules do not enter the hollow fiber because they are not soluble in the organic phase present in the pores, thus yielding very clean extracts. Several reviews that focus on basic extraction principles, technical setup, recovery, enrichment, extraction speed, selectivity, applications and future trends in hollow fiber-based LPME have been reported [15–18].

There are two modes used: two-phase HF-LPME and three-phase HF-LPME. In two-phase HF-LPME, the analytes are extracted by passive diffusion from the sample into the hydrophobic organic solvent supported by the fiber, and in three-phase HF-LPME the analytes are extracted through an organic solvent immobilized in the pores of the fiber and further into a new aqueous phase in the lumen of the fiber.

Compared with LLE and SPE, HF-LPME gives, at least, a comparable and satisfactory sensitivity and in many cases better enrichment for the analytes; the consumption of solvent is significantly reduced by up to several hundred or several thousand times. The LPME technique is simple, fast, and inexpensive. Due to the small volume of the extracting solvent, the extracted samples do not require further concentration prior to analysis and thus total analysis time considerably decreases in comparison to traditional LLE procedures. Additional advantages of LPME also make the technique attractive. Since, LPME tolerates a wide pH range; it can be used in applications that would not be suitable for solid-phase extraction (SPE) or solid-phase microextraction (SPME). Sample carryover can be avoided because the hollow fibers are enough cheap to be single-used and disposed. It has been demonstrated that HF-LPME is very useful for the extraction of acidic drugs and, in some cases their metabolites, from biological matrices and from environmental samples with a simultaneous cleanup and preconcentration of the extracts [19–30]. This extraction technique has been used for the analysis of ibuprofen using HPLC [23–25], gas chromatography [26,27], capillary electrophoresis (CE) [28,29] and FIA with chemiluminescence detection [30]. Diclofenac [23,25] and salicylic acid [25] have been also analyzed using HPLC previous HF-LPME treatment.

The aim of this work was to develop of an alternative extraction method for pharmaceuticals applicable to wastewaters which avoid some analytical problems that usually overcomes with SPE technique when mass spectrometry is used as detection system coupled to HPLC: important matrix and ionic suppression effects. The simplicity of the HF-LPME could be an interesting way to obtain enough sensitivity due to the low levels of these drugs in wastewaters. Likewise, the consumption of organic solvents can be reduced to several microliters using HF-LPME in contrast to SPE procedures.

In this work, a HPLC/MS–MS method combined with prior HF-LPME was developed for the determination of three widely used drugs: salicylic acid (2-hydroxy-benzoic acid) (SAC), the hydrolysis product of the well known acetylsalicylic acid (2-(acetyloxy)-benzoic acid) and two non-steroidal anti-inflammatory drugs widely used, diclofenac (2-[(2,6-dichlorophenyl)amino]-benzeneacetic acid) (DIC) and ibuprofen ((R,S)-2-(4-isobutylphenyl)-propionic acid) (IBU); the method was applied to their determination in wastewater. The HF-LPME provides very clean extracts that can be directly injected into the chromatographic system allowing excellent baselines. Additionally, HF-LPME also provides sample preconcentration that enhances the applicability of the proposed method.

2. Experimental

2.1. Chemicals and reagents

All chemicals were of analytical-reagent grade or better. All solutions and dilutions were prepared with ultrapure water form a Milli-Q Plus water purification system (Millipore, Billerica, MA, USA). SAC, DIC, IBU, dihexyl ether and 1-octanol were purchased from Fluka-Sigma–Aldrich (Madrid, Spain) and the rest of products were obtained from Merck (Darmstadt, Germany).

Aqueous working solutions of SAC, DIC and IBU were daily prepared by adequate dilutions from aqueous 200 μg mL^{-1} stock solutions. Q3/2 Accurel KM polypropylene hollow fiber (600 μm i.d., 200 μm wall thickness and 0.2 μm pore size) was purchased from Membrana (Wuppertal, Germany).

2.2. Chromatographic conditions

The chromatographic separation was performed at 20 °C using a LaChrom® Elite VWR-Hitachi (Barcelona, Spain) with a quaternary L-2130 pump. The injector was a Rheodyne manual injection valve Model 7725i, fitted with a 20-μL sample loop. Separations were carried out using a Pursuit® XRs Ultra 2.8 μm C18 (100 × 2.0 mm i.d.) (Varian Inc., Palo Alto, CA, USA) preceded by a guard column Kromasil® 100 Å, C18, 5 μm, (15 × 4.6 mm i.d.) (Scharlab S.L., Barcelona, Spain).

The mobile phase consisted of 0.1% formic acid (pH 2.6) (component A) and methanol (component B) at a flow rate of 0.2 mL min^{-1}. An initial 20% component A was used in isocratic mode for 3 min and then a linear elution gradient was programmed from 20% to 0% A for another 7 min. Three minutes were waited between injections which allowed re-equilibration of the column to the initial conditions.

2.3. Mass spectrometry detection

For the MS/MS detection an API 2000 triple quadrupole mass spectrometer (Applied Biosystems/MDS SCIEX, Ontario, Canada) equipped with a Turbo HS-602 source housing was used. Nitrogen was used as collision gas at 4 psi. The ion source and curtain gases were set at 30 psi in both cases. The electrospray voltage was −4500 V. Acquisition was performed in selected reaction monitoring (SRM) mode and the protonated molecular ion of each compound was chosen as precursor ion. Sciex Analyst 4.0 software was used for data acquisition and handling. The optimisation of MS parameters (declustering potential, entrance potential, for precursor ions and collision energy, and collision cell exit potential for product ions) was performed by flow injection analysis for each compound. Table 1 shows the values of the parameters optimised and the SRM transitions selected. Quantitative analysis was performed using external calibration.

2.4. Supported liquid membrane preparation and extraction procedure

Hollow fibers were cut into 27 cm pieces, washed with acetone in an ultrasonic bath and dried. The fiber was soaked with dihexyl

Table 1
Optimised parameters for the MS/MS analysis of the selected compounds.

Compound	Precursor ion (m/z)	Product ion (m/z)	Declustering potential (v)	Entrance potential (v)	Collision energy (eV)	Collision cell exit potential (v)
SAC	137	92.9	−45	−7	−25	−10
DIC	294.2	250	−50	−9	−16	−15
IBU	205.2	161.1	−45	−9	−12	−15

Table 2
Efficiency and selectivity chromatographic parameters for the proposed HPLC procedure.

	t_R (min)	RSD-t_R (%)	$W_{1/2}$ (min)	T	N	K'	α	R_s
SAC	2.25	0.021	0.1273	1.39	1731	130	3.01	10.37
DIC	4.76	0.003	0.1583	1.29	5009	258	1.91	2.64
IBU	5.41	0.007	0.1321	1.18	9292	282	1.17	2.64
Critical values		<1%		<1.5		>2		>1.5

t_R, retention time; RSD-t_R, relative standard deviation for retention time; N, number of theoretical plates; T, asymmetry factor; $W_{1/2}$, peak half-width; K', capacity factor; α, selectivity factor; R_s, peak resolution.

ether during 5 s to impregnate the pores and rinsed with water on the outside by placing it into an ultrasonic bath for 30 s in order to remove the excess of organic solvent. The lumen of the prepared fiber piece was filled with 50 μL of acceptor phase (pH 12.5 aqueous solution) using a HPLC syringe. Both open ends of the fiber were closed by means of a hot soldering tool and adhesive tape. During extraction the membrane portion that contains the acceptor phase was immersed in the 50 mL sample solution (pH 2) contained into a 50 mL glass beaker. The sample was stirred for 15 min by means of a magnetic stirrer (ANS-00/1 Science Basic Solutions (Rubí, Barcelona, SPAIN) at 300 rpm. After extraction, the fiber was taken out, one of the ends was cut and the acceptor phase was extracted using a HPLC syringe and injected into the HPLC system.

2.5. Preparation of wastewater samples

Samples were obtained from "Guadalquivir"-ALJARAFESA Wastewater Treatment Plant (WWTP) which is located in Palomares del Río, Seville, Spain. The plant essentially receives urban wastewaters. The capacity of this WWTP is 100,000 inhabitants and the discharged flow is 12,433,313 m^3/year (2008 data).

Grab samples of the influent (raw water, WWR), after the primary sedimentation tank (WW1), after the aeration tank (WW2) and the effluent (treated water after anaerobic digestion, WWT) were collected in 13th May 2009. All samples were filtered through a GDU1 glass fibre filter bed (10–1 μm) (Whatman, Mainstone, UK) and through Pall Nylaflo™ nylon membrane filter 0.45 μm (Pall Corporation, Ann Arbor, MI, USA) and adjusted to pH 2 with HCl. Filtered samples were stored in the dark at 4 °C prior to HF-LPME extraction.

3. Results and discussion

3.1. Chromatographic conditions

Looking for a fast and high resolution separation a Pursuit® XRs Ultra (2.8 μm) was selected as working column. This column is a highly packed HPLC column that allows high resolution separations using low flow-rates compatible with MS detection coupled to conventional HPLC equipment. The selected column provides good resolution and good peak symmetry.

The mobile phase consisted of 0.1% formic acid and methanol. Different gradient elution conditions were tested searching for the shortest time of analysis without sacrificing peak shape. The gradient elution program described in Section 2.2, was the best option in terms of time of analysis, shape of the peaks and reproducibility.

The efficiency and selectivity chromatographic parameters of the proposed procedure are shown in Table 2. As it can be seen, all resolutions are above the critical value >1.5, and peaks show good symmetry.

3.2. Optimization and evaluation of experimental conditions for HF-LPME extraction

Optimal experimental conditions for the HF-LPME extraction are fully described in our previous paper [25] where aqueous HCl solutions within 1–4 pH range were tested as donor, NaOH aqueous solutions with pH values between 8 and 13 were assayed as acceptor phase and stirring times between 5 and 30 min at 300 rpm were also tested. Optimum values of pH 2 (donor phase), pH 12.5 (acceptor phase) and 15 min of stirring time (300 rpm) were fixed. As in our previous paper [25], a full factorial design [31,32] for three factors and two levels involving eight experiments (2^3) has been used to determine the effect and importance of the mentioned variables on the final result.

Table 3 shows the equations obtained from the experimental data and the calculated t-values for each of the factors and analytes where b_1, b_2 and b_3 are the donor pH, acceptor pH and stirring time, respectively.

As it can be seen, the main factor is the acceptor pH for all the analytes. For DIC and IBU, an increase in the acceptor pH leads to better results in the extraction, while in the case of SAC leads to a decrease in the signal; so this pH value is a critical parameter. The donor pH value is less critical than the acceptor pH, as could be expected considering the extraction procedure and the involved chemical processes. Again, SAC behaviour is the opposite respect DIC and IBU. Time seems to be the less critical factor and always with a positive effect on the extraction procedure.

From the results obtained it is possible to consider the acceptor pH as a critical factor that must be carefully controlled, while with respect to donor pH and time, the extraction procedure can be considered a robust extraction procedure.

3.3. Linearity, sensitivity and precision for HF-LPME extraction

Linearity of the response function was studied from external calibration. A 10-point (in triplicate) calibration curve was constructed using a least-square linear regression analysis of standards mixtures of the analytes at different concentrations. Using the selected HF-LPME conditions, aqueous pH 2 solutions with different SAC, DIC and IBU concentrations were submitted to the liquid microextraction procedure and analyzed according to the described HPLC procedure. Peak areas of SAC, DIC and IBU were proportional

Table 3
Results from the full factorial design.

		t calculated		
		Donor pH	Acceptor pH	Stirring time
SAC	$Y = 2.1358 - 0.1612b_1 + 1.8433b_2 + 0.0018b_3$	1.4733	4.8216	0.2935
DIC	$Y = 1.0735 + 0.2851b_1 - 1.6885b_2 + 0.0523b_3$	2.6285	0.7685	0.0081
IBU	$Y = 1.3766 + 0.4845b_1 - 1.7768b_2 + 0.0036b_3$	1.1523	4.6582	0.3623

Critical value for t ($P = 0.05$, $n = 4$) 2.78.

Table 4
HPLC calibration parameters and instrumental detection limits (ILOD) for the analytes.

	Regression coef. (r^2)	Linearity (%)	Linear range (μg L^{-1})	ILOD (μg L^{-1})
SAC	0.9993	99.32	0.5–300	0.3
DIC	0.9993	98.34	1–300	0.5
IBU	0.9999	99.37	5–300	1.0

Table 5
HF-LPME/HPLC calibration parameters and method detection limit (MLOD) for the analytes.

	Regression coef. (r^2)	Linearity (%)	Linear range (μg L^{-1})	MLOD (μg L^{-1})
SAC	0.9998	99.81	0.1–50	0.02
DIC	0.9989	99.57	0.25–50	0.10
IBU	0.9994	99.68	0.50–50	0.30

to concentrations in the donor phase. A linear relationship was obtained with correlation coefficients $r \geq 0.999$ (figures depicted in Tables 3 and 5) and the calibration curves obtained showed no changes over the course of one month.

Detection and quantitation limits were calculated as the minimum concentration of an analyte giving peaks whose signal-to-noise ratios are 3 and 10, respectively. Instrumental limits (ILOD and ILOQ) are listed in Table 4 and method limits (MLOD and MLOQ) are listed in Table 5. As it can be seen in tables method limits are lower than instrumental limits due to the preconcentration suffered by the analytes during the extraction procedure.

To evaluate the repeatability and the intermediate precision, spiked samples (validation standards) at three concentrations levels 0.25, 10 and 30 μg mL^{-1} of SAC and 0.5, 10 and 30 μg mL^{-1} of DIC and IBU in triplicate were subjected to the entire analytical procedure and measured in one single day and one day per week during two months, respectively. Intermediate precision was performed using the prediction of actual concentrations from the validation standards selected for the analytical assay in the $m \times p \times n$ design (m = analytical levels, p = days and n = replications). From the corresponding ANOVA, the intermediate precision was computed [33]. The repeatability, expressed as relative standard deviation, was in the range 1.1–1.6%. Intermediate precision also expressed as relative standard deviation, was in the range 1.5–2.1%.

3.4. Wastewater analysis using HF-LPME

3.4.1. Recovery assays on spiked wastewater

Recovery assays were performed on the four different wastewater samples at three concentration levels 0.25, 10 and 30 μg L^{-1} for SAC and 1, 10 and 30 μg L^{-1} for DIC and IBU; results obtained are shown in Table 6. As it can be seen, extraction effectiveness for the analyzed substances are unrelated to the type of wastewater, remaining practically constants (about 100% SAC, 71% DIC and 52% IBU). The decrease in the recoveries of DIC and IBU can be due to the high surfactant concentrations in the wastewaters, even after their depuration, which modifies the behaviour of the supported liquid membrane on the polypropylene fiber. This behaviour seems to be more pronounced when the polarity of the extracted substances decreases. The behaviour modification has been checked in our laboratory with several experiments testing the effect of the addition of several surfactants to standards (even at low concentrations). Despite the fact that DIC and IBU recovery decreases, the excellent clean-up obtained implies a great advantage over other sample treatment procedures which justifies the HF-LPME extraction.

Fig. 1 shows representative chromatograms obtained from spiked (5 μg L^{-1} of SAC, DIC and IBU) wastewater samples (raw, WWR and treated, WWT); as it can be seen, both chromatograms show excellent baselines and well-defined peaks corresponding only to the spiked substances, similar chromatograms were obtained for WW1 and WW2 spiked samples. This fact demonstrates that HF-LPME is an adequate clean-up procedure for wastewater samples. Chromatograms from wastewaters without SAC, DIC and IBU show horizontal baselines without peaks.

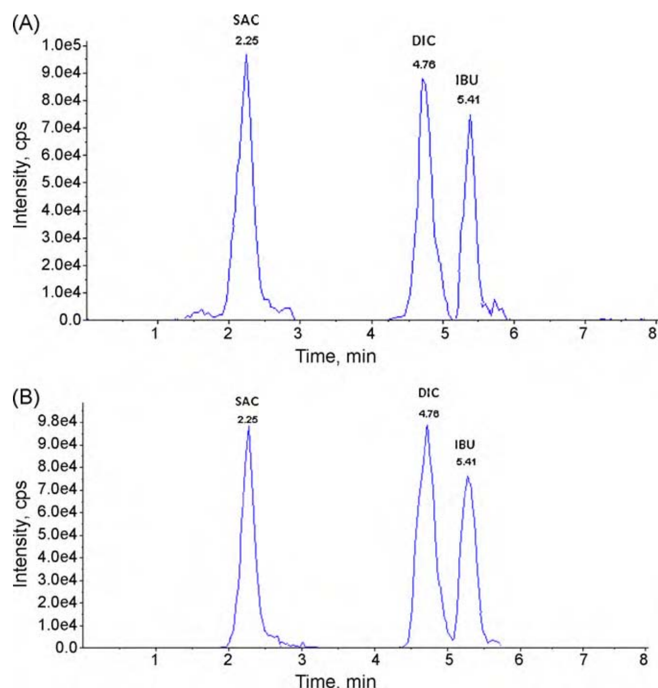

Fig. 1. Representative HPLC/MS–MS chromatograms for extracted raw (A) and treated (B) spiked wastewaters. (5 μg L^{-1} of SAC, DIC and IBU).

Table 6
HF-LPME/HPLC/MS–MS recoveries (average of three determinations ± standard deviation) from spiked wastewaters.

Wastewater	Spiked level ($\mu g L^{-1}$)	SAC	DIC	IBU
WWR	1 (0.25*)	100.3 ± 0.3	71.0 ± 0.7	53.0 ± 1.8
	10	99.3 ± 0.4	70.8 ± 0.9	50.0 ± 1.5
	30	100.1 ± 0.5	72.2 ± 0.6	52.8 ± 1.2
WW1	1 (0.25*)	100.3 ± 0.7	70.8 ± 1.2	50.9 ± 1.1
	10	99.0 ± 0.6	72.9 ± 1.0	51.3 ± 0.9
	30	100.2 ± 0.8	71.9 ± 0.8	50.4 ± 0.9
WW2	1 (0.25*)	99.3 ± 0.2	71.3 ± 0.8	52.8 ± 1.6
	10	99.8 ± 0.1	72.1 ± 0.3	50.9 ± 1.2
	30	100.3 ± 0.5	71.8 ± 0.6	52.1 ± 0.8
WWT	1 (0.25*)	99.8 ± 0.1	71.5 ± 0.9	52.6 ± 1.0
	10	100.0 ± 0.4	72.7 ± 1.0	51.8 ± 0.5
	30	99.6 ± 0.5	71.9 ± 0.8	52.0 ± 1.2

* Spiked level for SAC.

Table 7
Concentration ($\mu g L^{-1}$) of the pharmaceuticals in the analyzed wastewater samples.

Compound	WWR	WW1	WW2	WWT
SAC	*	*	–	–
DIC	*	–	–	–
IBU	0.65	*	*	–

–, Bellow method detection limits.
*, MLOD < Concentration < MLOQ.

3.4.2. Analysis of real samples

The results from the application of the proposed HF-LPME procedure to the wastewater samples are shown in Table 7; as it can be seen, only raw wastewater (WWR) sample showed IBU levels that allows its determination; in this sample, SAC and DIC were only detected. In the other wastewater samples only SAC and/or IBU were detected.

These results obtained are according to several bibliographic data [34–37], and the high ibuprofen levels reflect its large consumption.

4. Conclusions

Wastewater samples are complex matrices that require previous clean-up procedures like SPE that are the most frequently used nowadays. SPE requires several conditioning and elution steps which sometimes traduce in low precision values. Besides, wastewaters extracts obtained by SPE usually produce important matrix effects and ionic suppression when MS detection is used.

This study presents a rapid hollow fiber-based liquid-phase microextraction (HF-LPME) method combined with an HPLC–MS/MS determination using a highly packed chromatographic column that allows a simple, low-cost, fast, accurate, sensitive and selective methodology for the determination of salicylic acid, ibuprofen and diclofenac in wastewater samples. The proposed extraction procedure has a very low (several μLs) organic solvent consumption. The excellent clean-up obtained implies a great advantage over other sample treatment procedures.

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