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Simultaneous liquid–liquid extraction and dispersive solid-phase extraction as a sample preparation method to determine acidic contaminants in river water by gas chromatography/mass spectrometry

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ABSTRACT

A sample preparation procedure that combines a liquid–liquid extraction (LLE) with a dispersive solid-phase extraction (DSPE) has been devised to determine residues of four phenoxyacid herbicides, two aminopolycarboxylic acids and five acidic anti-inflammatory drugs in small volumes of river water samples. Two aliquots of acetone (3 and 0.5 mL) were used to extract the analytes from a 10 mL water sample at pH 2 containing 5 mg of octadecylsilane (ODS) sorbent and NaCl at a 5.5 M concentration. Acetone was isolated by the salting-out effect, collected, evaporated and the extract was treated with BF_3/methanol to obtain the methyl esters of the analytes and determine them by GC with mass spectrometric detection. Recoveries were comprised between 82% and 114% with relative standard deviations about 5–15% ($n=5$) within a concentration range about 0.03–44 μg L^{-1}. The amount of ODS added to sample resulted to be a significant factor in the recovery for most of the analytes as deduced from an experimental design; the sample pH was not a so critical factor. A robustness study of the proposed sample preparation was carried out as defined by Youden and Steiner and an estimation of the uncertainties of the measured concentrations was made following the EURACHEM/CITAC guidelines, too.

1. Introduction

Numerous chemical compounds synthesized by the man reach the environmental compartments. Many of them are ubiquitous and persistent, in such a way that the constant exposure to these pollutants can cause damage to human health and wildlife. Among the environmental pollutants there are some compounds with acidic properties such as non-steroidal anti-inflammatory drugs (NSAIDs), phenoxyacid herbicides and aminopolycarboxylic acids used with household or industrial purposes.

The isolation of acidic anti-inflammatory drugs from natural waters, and aqueous extracts from sediments and soils, is commonly made by solid-phase extraction after acidifying the sample, mainly on Oasis HLB cartridges [1–8] although some authors prefer the use of ODS cartridges [9–11]. Polymeric sorbents, either mixed-ion exchange [12,13] or reversed phases [14], have also been assayed. Alternatively, stir bar sorptive extractions on polyurethane, polydimethylsiloxane and lichrosorb RP-8 [15,16] have been considered, too.

As regards the determination of these drugs in the extracts HPLC and GC can be used for this kind of drugs. In HPLC, electrospray ionization mass spectrometry is the detection technique most applied to identify and quantify the analytes [4–6,8,12]; a fluorescent detection has also been carried out [3]. In GC, various silylating reagents have been used to convert the acidic drugs in GC-amenable compounds, which are mainly analyzed by mass spectrometric detectors [7,9,10,11,13]. Other derivatization reagents can be used in order to achieve a pentafluorobenzylation or methylation of these analytes previously to the GC analysis [1,2,14].

The sample preparation for the analysis of aminopolycarboxylic acids such as EDTA and NTA in waters can be performed by solid-phase extraction on strong anion-exchange or activated charcoal cartridges [17–20]. However, as a consequence of the high water solubility of the aminopolycarboxylic acids and their metal chelating character, many authors have restricted the sample preparation to a simple evaporation of a large volume of water sample and posterior dissolution of the residue in a small volume [21–29]. The determination in the extracts is usually made by HPLC with UV or

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electrospray mass spectrometry detection after complexing the EDTA and NTA with Fe(III) [17,18,21–24,30,31]; the corresponding alkyl esters can also be determined by gas chromatography with different detectors [20,25–27,32].

In the same way, the extraction and clean-up of acidic herbicides, mainly phenoxyacids and bentazone, from water samples or aqueous extracts from solid samples is nowadays based on solid-phase extractions. The stationary phase of the cartridges is almost always ODS [33–39], but manuscripts with other alternative packings such as styrene-divinylbenzene [40], Isolute env+ [41], Envi-chrom P [42] and Oasis HLB [43] have been published. Obviously, mass spectrometry is the most selective detection technique and the reached sensitivities are high, therefore mass spectrometry is coupled to HPLC [38,39,41–43] and GC to analyze the herbicides in extracts. In this latter case pentafluorobenzyl bromide is a common derivatization reagent [36,37,40] although there are other options [34]. Acidic herbicides can be determined by micellar electrokinetic capillary chromatography [35], too.

In the last decades, LLE of water samples with non-miscible organic solvents has been relegated in favour of SPE which allows to handle easier a big amount of samples. Moreover, the solubility of compounds of medium polarity in solvents such as chloroform and dichloromethane is limited; more polar solvents could be appropriate for the solubilization of this type of compounds, pesticides and drugs among them [44,45]. The application of polar and water-miscible organic solvents to the determination of analytes in water samples by LLE is possible turning to the salting-out effect.

Salting-out LLE uses water-miscible organic solvents as the extractants. Phase-separation from an aqueous sample is achieved in presence of a high concentration of salts. The salting-out effect is very used in the analysis of drugs and biologically active compounds from plasma, urine and other biological fluids in combination with acetonitrile as solvent; ammonium formate, magnesium sulphate, ammonium acetate, sodium chloride and zinc sulphate are salts used to accomplish the phase-separation and control the sample pH [46–51]. The use of acetonitrile in combination with ammonium sulphate or sodium chloride has also been applied to the extraction of pesticides in water [52], benzalkonium chloride in pharmaceutical solutions [53], sulphonamides in water, urine and honey [54] and colorants in food [55]. Furthermore, warfarin has been extracted from urine by using acetone and sodium chloride [56] and some antioxidants have been isolated from extracts of *Camellia oleifera* seeds by using isopropanol and sodium chloride [57].

On the other hand, in the last years, the dispersive solid-phase extraction (DSPE) has become popular as a clean-up procedure applied to sample extracts in an organic solvent, regardless of it use in the QuEChERS (Quick, Easy, Chip, Effective, Rugged, Safe) methods developed by Anastassiades et al. [58]. In this way, extracts, mainly in acetonitrile, with pesticides of different physico-chemical characteristics obtained from agricultural and livestock products such as grains, vegetables, fruits and milk have been subject to DSPE with sorbents such as primary secondary amine (PSA), graphitized carbon black, ODS, aluminium oxide and even carbon nanotubes, or mixtures of them [59–69]. In addition, DSPE has been used to clean-up extracts in the analysis of antibiotics in kidney [70] and polybrominated diphenyl ethers in sediments, biological fluids and plastic bottles [71–73]. Unlike the above-mentioned references, the sorbent added in DSPE can be used to retain the target-analytes. This was the case in the determination of pesticides in cereal-based baby foods by using carbon nanotubes [74], tetracyclines in water and milk with PSA as sorbent [75] and quinolones in swine muscle with PSA, too [76].

Within this context, this manuscript shows the usefulness of the LLE with a water-miscible and medium polarity solvent in order to extract 11 acidic pollutants from river water samples; the acidic pollutants represent three families of chemical compounds: five NSAIDs, four phenoxyacid herbicices and two aminopolycarboxylic acids. To this aim, acetone, which is in principle more suitable than other non water-miscible solvents, has been assayed as the extractant to solubilizate the analytes; the separation of the phases is achieved by increasing the ionic strength with the addition of NaCl (salting-out effect).

Moreover, a DSPE procedure with ODS has been used as clean-up in this work, but unlike the commonly published manuscripts the LLE and DSPE have not been carried out in successive steps but in a only step. On the other hand, the sample and reagent amounts used in the analysis are relatively low to decrease the economic cost and improve the sample handling. The robustness of the proposed method and the uncertainty of the measured analyte concentration have been evaluated, too.

2. Experimental

2.1. Material and reagents

The analytical standards were obtained from Sigma Aldrich (St. Louis, MO, USA) and Dr. Ehrenstorfer (Augsburg, Germany): (2,4-dichlorophenoxy)acetic acid sodium salt monohydrate (24D), mecoprop (MEC), diclofop (DFOP), haloxyfop (HAL), ethylenediaminetetraacetic acid (EDTA), nitrilotriacetic acid (NTA), ibuprofen (IBU), ketoprofen (KETO), diflunisal (DIF), diclofenac sodium salt (DFEN) and indomethacin (INDO). The minimum purity of the standards was of 98%. Individual stock solutions at a concentration close to 500 mg L^{-1} were prepared in water whose pH was adjusted to 10 with the help of a pH-meter and a NaOH solution. An analyte mixture was then prepared in a 25 mL volumetric flask, by pipetting 2 mL of each stock solution and diluting to volume with water. Subsequent dilutions of the mixture were made with water.

Residue analysis-grade chloroform, acetone and methanol were supplied by Scharlab (Barcelona, Spain). Calcium and magnesium analytical standards, in 1000 mg L^{-1} solution, were supplied by Panreac (Barcelona, Spain). Ultrapure water was obtained from a Milli-Q plus apparatus (Millipore, Milford, MA, USA) and boron trifluoride in methanol at a concentration of 20% was obtained from Merck (Darmstadt, Germany). For dispersive SPE, octadecylsilane (ODS) was purchased from Sigma Aldrich; ODS mean particle size, mean pore diameter and specific surface area were 45 μm, 6 nm and 475 m^2 g^{-1}, respectively. Analysis-grade sodium chloride, sodium hydroxide and concentrated sulphuric acid (95%, density 1.84 g mL^{-1}) were supplied by Panreac and Helium gas (99.9999% minimum purity) for chromatography by Carburos Metálicos (Barcelona, Spain). A Hewlett–Packard (Little Falls Site, Wilmington, DE, USA) 8453 ultraviolet–visible spectrometer was used to obtain some spectra by using 1.0 cm quartz cells. Water samples were collected from the river Pisuerga, in the urban area of the city of Valladolid.

2.2. Sample preparation

A volume of 10 mL of river water sample, previously filtered through a 0.45 μm pore-size cellulose nitrate disk, was placed in a 15 mL screw-cap glass tube. An amount of 3.2 g of NaCl was added to sample and dissolved by shaking in an ultrasonic bath to achieve a 5.5 M NaCl concentration. Then, 25 μL of a 1:5 dilution of concentrated sulphuric acid (to achieve a pH of 2), 3 mL of acetone and 5.0 mg of ODS were added to the tube. This was closed and the mixture was then mechanically shaken for 10 s, and after separation of the phases the upper organic layer was

collected with a pipette and placed in a 2 mL Eppendorf tube. The phase separation can be accelerated by centrifugation.

After that, 0.5 mL of acetone were added to the aqueous phase and the mixture was shaken again by 10 s. The organic phase was collected after decantation and combined with the previous one contained in the Eppendorf tube. Acetone was evaporated in a vacuum centrifuge evaporator heated at 45 °C, then 0.3 mL of methanol and 0.3 mL of BF_3 in methanol were added. The tube was closed and shaken for 5 s. Methylation was carried out at 90 °C for 70 min. It was allowed to cool at room temperature and 0.1 mL of chloroform and 1 mL of water were added. After manual shaking and decantation to isolate the phases the extract in chloroform was ready for injection in GC.

2.3. Preparation of the calibration curve

Calibration was made with extracts of ultrapure water spiked with increasing amounts of the analytes. Ultrapure water (100 mL) was spiked with a known volume, comprised between 0.2 and 1.0 mL, of a mixture of the analytes in suitable concentration to achieve final concentrations in the low $\mu g\ L^{-1}$ range. The pH of the 100 mL solution was adjusted to 2 with sulphuric acid and NaCl was dissolved up to a concentration of 5.5 M.

Then, the procedure to prepare the calibration standards was similar to that above-described for samples: aliquots of 10 mL of pH and ionic strength-adjusted water were extracted twice with acetone, acetone was evaporated and the analytes methylated. Calibration graphs with seven concentration levels were constructed from extracted ion mass chromatograms, by measuring peak heights.

2.4. Gas chromatography with mass spectrometric detection

A Hewlett–Packard 6890 gas chromatograph coupled to a Hewlett–Packard 5973 mass spectrometer was used to determine the methyl ester derivatives in the extracts, working in electron impact mode. The chromatograph was fitted with a 30 m × 0.25 mm × 0.25 μm (5% phenylmethylpolysiloxane) column from Agilent Technologies (Little Falls Site, Wilmington, DE, USA). The oven temperature was kept at 50 °C for 1 min and programmed at 30 °C min^{-1} to 180 °C, then programmed at 5 °C min^{-1} to 320 °C, held there for 2 min. The carrier gas (helium) flow was kept constant at 1 mL min^{-1}. Splitless injection (2 μL) was performed with an HP7673 automatic sampler at an injection port temperature of 250 °C; the purge valve was on at 1 min; the transfer line temperature was 320 °C. The MS temperatures were as follows: ion source 230 °C, quadrupole 150 °C. Electron multiplier voltage was maintained at 306 V above autotune value. Quantitation was performed by the most abundant ion of each compound, which was selected as target ion. Two qualifier ions were used to confirm the peak identification. Table 1 shows the retention times and m/z ratios recorded in selected ion monitoring (SIM) mode. Indomethacin was hydrolyzed during the derivatization reaction and determined as 3-chlorobenzoic acid methyl ester.

2.5. Experimental designs

The statistical computer package "Statgraphics Plus for Windows, version 5.0" (Manugustics Inc., Rockville, MD, USA), was used to outline an experimental design. After previous experimentation, two types of experimental designs have been used in this work to study and select the extraction conditions. A fractional factorial design was carried out to screen some parameters of the sample preparation procedure (pH, NaCl and ODS amounts, acetone/water ratio, shaking time for the extraction) and evaluate their influence in the peak height of each analyte, and a response surface design was applied to select the value of two selected parameters (pH and ODS amount). The effect of each factor was tested by an analysis of variance at the 5% significance level. The order of the experiments was randomized.

Table 1
Retention times and monitored ions in SIM mode. Relative abundances are shown in parentheses.

SIM group (min)	Retention time (min)	Compound	Target ion (m/z)	Qualifier ions (m/z)
4.60	5.81	INDO	139 (100)	111 (67), 170 (64)
6.50	7.42	NTA	174 (100)	146 (52), 233 (18)
	7.60	IBU	161 (100)	177 (33), 220 (26)
	7.70	MEC	169 (100)	228 (99), 142 (85)
8.10	8.43	24D	199 (100)	234 (65), 175 (60)
10.00	11.14	DIF	232 (100)	264 (67), 175 (38)
13.00	14.51	HAL	316 (100)	288 (97), 375 (84)
	14.87	EDTA	174 (100)	289 (30), 348 (17)
	14.94	KETO	209 (100)	105 (61), 268 (37)
15.80	16.22	DFEN	214 (100)	309 (43), 311 (32)
17.80	18.76	DFOP	340 (100)	253 (82), 342 (65)

Table 2
Experimental design matrix to screen five factors in the extraction procedure.

Experiment	pH	ODS mass (mg)	NaCl concentration (M)	Acetone/water ratio (v/v)	Shaking time (s)
1	1	50	4.9	0.5	60
2	1	5	5.9	0.5	60
3	5	50	4.9	0.2	60
4	5	5	5.9	0.5	10
5	5	5	4.9	0.2	10
6	5	5	4.9	0.5	60
7	5	50	5.9	0.2	10
8	1	50	4.9	0.2	10
9	5	50	5.9	0.5	60
10	3	27.5	5.4	0.35	35
11	5	5	5.9	0.2	60
12	1	50	5.9	0.5	10
13	3	27.5	5.4	0.35	35
14	1	5	4.9	0.2	60
15	1	5	4.9	0.5	10
16	1	50	5.9	0.2	60
17	3	27.5	5.4	0.35	35
18	1	5	5.9	0.2	10
19	5	50	4.9	0.5	10

3. Results and discussion

3.1. Factorial fractional design

The potential influence of five factors in the extraction step was studied: the sample pH, the ionic strength controlled by the NaCl concentration, the amount of sorbent added to sample, the shaking time and the ratio between the sample volume (10 mL) and the volume of acetone used in the first extraction: 2 or 5 mL which correspond to acetone/water ratios of 0.2 and 0.5, respectively. So, it was planned a 2^{5-1} screening design with three central points, which allows to study the effects of 5 factors in 19 experiments, Table 2 shows the experimental domain. As regards the selection of the NaCl concentration range it is interesting to point out that a minimum NaCl concentration, 4.8 M, was required to achieve a phase separation between water and acetone. The peak heights of each analyte recorded in the target

Table 3
Significant factors ($p < 0.05$) found in the factorial fractional design and *R*-squared statistic of the model for each analyte.

	R^2 (%)	ODS mass *p*-Value	ODS–pH interaction *p*-Value
INDO	96	0.046	–
NTA	96	–	0.049
IBU	98	0.008	–
MEC	88	0.004	0.046
24D	92	0.032	–
DIF	94	0.047	–
HAL	92	0.049	–
EDTA	92	–	0.037
KETO	89	–	–
DFEN	94	0.049	–
DFOP	85	–	–

–: Non-significant difference.

ion chromatograms were considered as response variables. Experiments were made with ultrapure water spiked with the analytes of the middle concentration level considered in the below explained recovery studies (close to 1 μg L^{-1}).

Table 3 resumes the results. The *R*-squared statistics indicate that the models could explain at least an 85% of the variability of the response. After analysis of variance, the ODS amount added to sample resulted to be the most influential factor, they were found significant differences ($p < 0.05$) in 7 out of 11 studied compounds; the responses of NTA, EDTA, KETO and DFOP were not statistically different when 5 or 50 mg of ODS were added. As sorbent amount increased so do the sorption of the analytes, decreasing the peak heights as it can be seen in Fig. 1, where main effect plots for MEC and DIF are shown as a representative example.

Significant differences in the extraction of the acidic compounds were not observed when the shaking time, acetone/water ratio, NaCl concentration and sample pH were modified. In principle, the assayed pH range was sufficiently large to observe notable differences in the peak heights according to the acid dissociation constants of the analytes; the explanation of this apparently contradictory fact was attributed to the partial miscibility of acetone (very slightly dissociant solvent and without acid-base properties) in water which could entail a decrease in the acidity of the analytes, favouring its presence as non-ionized molecules. On the other hand, the interaction between pH and ODS amount (pH–ODS interaction) was significant for the amino-polycarboxylic acids NTA and EDTA, and MEC.

3.2. Central composite design

The pH–ODS interaction was found to be statistically significant for 3 analytes after the screening design. Because of that, a peak height response surface was obtained by a central composite design with two factors: the sample pH and the sorbent amount. The study was expanded to the other compounds, too. A 2^2+star design with three central points, involving 11 experiments, was applied. Table 4 shows the experimental domain. The acetone volume used in the first extraction of the 10 mL water sample, the NaCl concentration and the shaking time were fixed in 3 mL, 5.5 M and 10 s, respectively.

Table 5 shows the regression coefficients of the estimated response models, these parameters are in agreement with those shown in Eq. (1), where the values of the variables are specified in their original units. In terms of *R*-squared, the fittings of the models to explain the variation of peak height were relatively

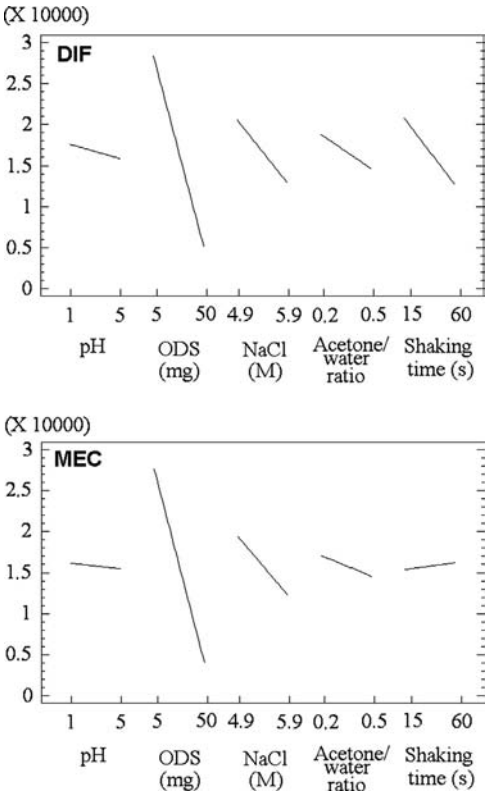

Fig. 1. Main effect plots obtained in the factorial fractional design for DIF and MEC.

Table 4
Response surface design matrix.

	ODS mass (mg)	pH
Low level	5	1
High level	50	6
Central point	27.5	3.5
Experiments	ODS mass (mg)	pH
1	59	3.5
2	27.5	3.5
3	5	1
4	27.5	3.5
5	27.5	0.5
6	27.5	3.5
7	27.5	7
8	50	6
9	50	1
10	0	3.5
11	5	6

acceptable with values higher than 54%.

$$Peak\ height = A + B\,pH + C\,mg_{ODS} + D\,pH^2 + E\,pH\,mg_{ODS} + F\,mg_{ODS}^2 \quad (1)$$

As happened for the factorial design, the main effects of the variable ODS amount were those for which the differences were significant ($p < 0.05$) in many cases. As it can be seen in Table 5, the influence of the ODS amount was not significant for NTA, EDTA, KETO and DFEN. The behavior of the three first compounds was similar to that already mentioned in the previous design but it differed for DFEN. On the contrary, the ODS amount did not affect significantly the extraction of DFOP in the previous study. On the

Table 5
R-squared statistics, coefficients of the built statistical models and *p*-values of the significant effects (ODS, pH–ODS interaction, pH^2) in the response surface design.

	ODS	Other Significant effects		Coefficients of the models					
	p-Value	*p*-Value	R^2 (%)	*A*	*B*	*C*	*D*	*E*	*F*
INDO	0.030	–	73	225157	33586	4589.3	1677.8	422.16	21.096
NTA	–	pH–ODS ($p=0.036$)	77	312174	19112	5416.6	13493	2315.1	92.279
IBU	0.027	–	75	527731	43087	683.08	529.38	604.82	125.34
MEC	0.043	–	62	92783	10264	2272.9	901.89	94.676	18.073
24D	0.035	–	65	93317	3699.9	2190.9	139.23	112.57	13.303
DIF	0.002	–	89	32382	1003.1	23.034	39.929	59.547	3.9583
HAL	0.036	–	65	47698	5122.2	488.31	590.47	7.7733	0.26764
EDTA	–	pH^2 ($p=0.033$)	75	1160.3	771.50	7.1880	178.66	16.982	0.98928
KETO	–	–	61	114986	6284.4	1771.8	1450.5	491.10	11.145
DFEN	–	–	54	30212	4883.4	159.86	579.58	7.4356	0.05829
DFOP	0.004	–	89	34959	1469.6	679.69	740.32	96.716	0.43393

–: Non-significant difference.

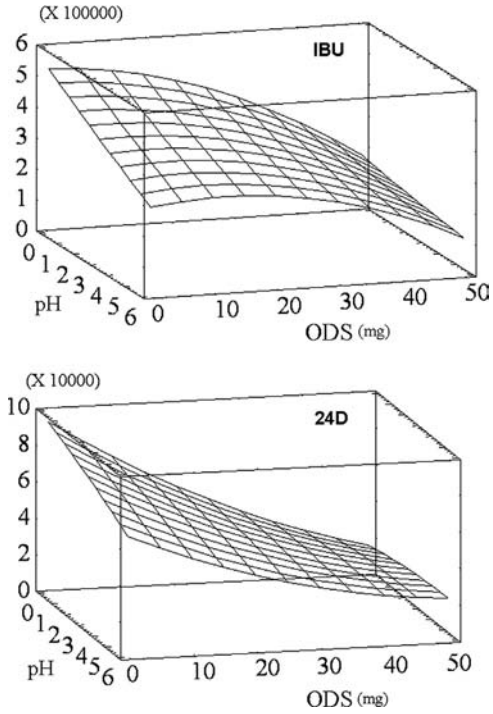

Fig. 2. Estimated response surface for the peak height of 24D and IBU as a function of pH and ODS amount.

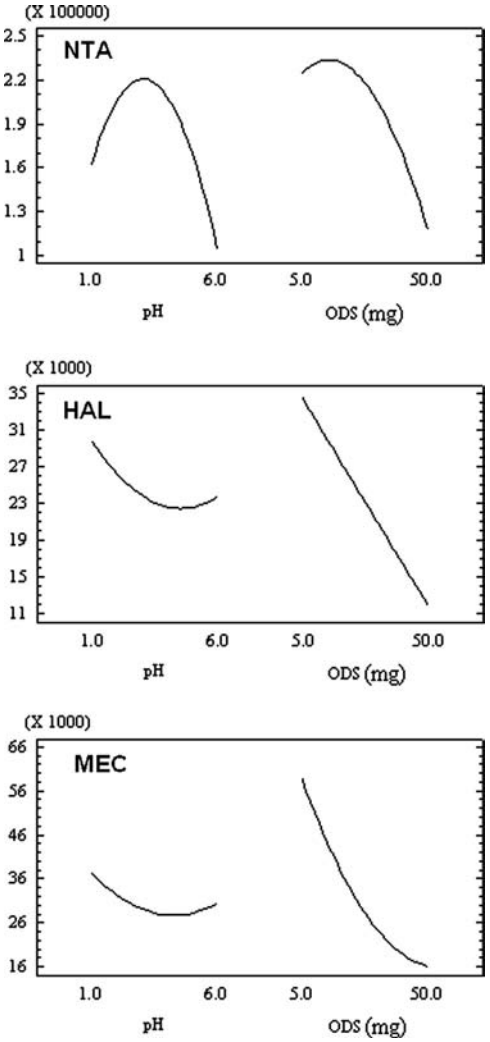

Fig. 3. Main effects plots obtained in the response surface design for NTA, HAL and MEC.

other hand, they were observed other two significant differences in the case of the pH–ODS effect for NTA and the quadratic effect, pH^2, for EDTA.

The response surface graphs and main effect plots (see Figs. 2 and 3) revealed that the peak heights of the analytes, except for the aminopolycarboxylic acids, decreased gradually in a greater or lesser extent when the ODS amount increased while the pH modified slightly the peak heights. In this way, an amount of 5 mg of ODS and a pH-value of 2 were selected as suitable to carry out the extraction of the analytes.

3.3. *Linearity of the calibration graphs, limits of detection and quantification*

Spiked ultrapure water extracts were used to prepare calibration graphs. Table 6 shows the concentration ranges and the parameters of the linear regression for the compounds. The fittings of the linear regressions had a coefficient of determination R^2 of, at least, 0.96. ANOVAs were done to verify the linearity of the fitting ($n=2$), the experimental *F*-values of the compounds were lower than the critical *F*-value which indicated there was not lack of fit.

Limits of detection and quantification were estimated on the basis of chromatograms of river water samples spiked at very low concentrations, according to a signal-to-noise ratio of 3 and 10,

Table 6
Calibration intervals, parameters of the linear fitting, and ANOVA results to test the lack of fit after a calibration with extracts of spiked ultrapure water. Experimental detection and quantification limits.

	Detection limit (ng L^{-1})	Quantification limit (μg L^{-1})	Calibration range (μg L^{-1})	Slope	Intercept	Coefficient of determination, R^2	Lack of fit, experimental F-value[a]
INDO	8	0.04	0.04–18.2	84766	−21411	0.975	0.18
NTA	20	0.16	0.16–79.7	103424	5537	0.987	0.57
IBU	7	0.04	0.04–18.2	183366	−48643	0.962	0.06
MEC	10	0.03	0.03–16.6	27564	−6156	0.998	0.13
24D	12	0.03	0.03–15.4	25491	3475	0.996	0.03
DIF	6	0.04	0.04–19.8	17905	−4750	0.998	0.16
HAL	8	0.04	0.04–18.2	21265	−7103	0.998	0.003
EDTA	40	0.15	0.15–76.8	6613	2495	0.967	0.27
KETO	12	0.04	0.04–19.2	100749	−71402	0.992	0.03
DFEN	10	0.03	0.03–17.0	12142	−7834	0.982	0.08
DFOP	7	0.04	0.04–19.2	25798	−18103	0.993	0.08

[a] Critical F-value to test the lack of fit: 3.97.

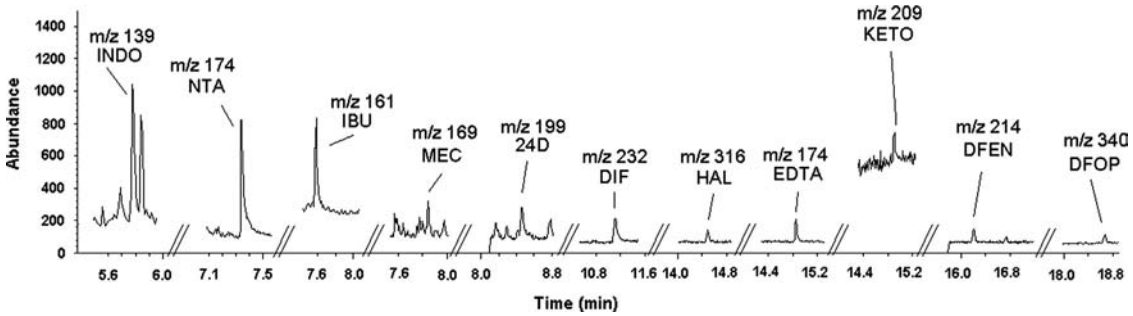

Fig. 4. Chromatogram obtained by the proposed procedure for a river water sample spiked with the analytes at very low concentrations.

Table 7
Recoveries (Rec, in percentage) and precisions (RSD, relative standard deviations) obtained by the proposed method at three concentration levels ($n=5$).

	Concentration (μg L^{-1})	Rec	RSD	Concentration (μg L^{-1})	Rec	RSD	Concentration (μg L^{-1})	Rec	RSD
INDO	0.04	93	9	0.7	100	5	11.4	101	5
NTA	0.16	102	10	3.2	109	6	43.7	96	4
IBU	0.04	96	15	0.7	98	6	2.3	103	11
MEC	0.03	100	8	0.7	106	7	9.1	102	9
24D	0.03	96	16	0.6	106	4	9.2	106	12
DIF	0.04	100	6	0.8	104	11	12.9	102	9
HAL	0.04	103	5	0.7	99	9	9.2	102	8
EDTA	0.15	82	15	3.1	93	7	42.1	97	9
KETO	0.04	114	11	0.8	101	7	2.5	101	8
DFEN	0.03	89	11	0.7	102	5	8.8	105	9
DFOP	0.04	108	5	0.8	100	9	11.3	103	9

respectively, and they are shown in Table 6, too. Fig. 4 shows an extract chromatogram in which the analytes were present at low concentrations.

3.4. Recovery and precision

Table 7 shows the recoveries and repeatabilities obtained on spiked river waters at three concentration levels, one of them close to the corresponding limits of quantification of the analytes. Recoveries did not vary substantially for the assayed concentrations, they ranged between 82% and 114%, 93% and 109%, and 96% and 109% for the low, middle and high concentration levels, respectively. Repeatabilities, expressed as RSD, were not higher than 16%, they were comprised between 9% and 16% for the low concentration level and between 4% and 12% for the other two levels ($n=5$).

In my knowledge, there is not any validation criterion applicable to the studied compounds in river water to assess the recoveries, precisions or other analytical characteristics. However, if the SANCO/12495/2011 guideline [77] is accepted as reference it could be ascertained that the mean recoveries and precisions achieved by the described method are suitable to purpose. The SANCO guideline stipulates mean recoveries within the range 70–120% with RSDs lesser or equal to 20%.

3.5. Influence of the matrix

Calcium and magnesium ions are naturally-present at relatively high concentrations in superficial waters. They are prone to form complexes with organic compounds containing carboxylic acid groups, mainly at alkaline and neutral pHs. The proposed extraction procedure for acidic compounds is carried out at pH 2, however, the potential influence of these ions has been considered.

Table 8 shows the mean peak heights obtained in the extraction of the analytes from ultrapure water spiked with the analytes at

Table 8
Mean peak heights obtained in the analysis of river waters with different COD values, ultrapure water, and ultrapure water spiked with calcium and magnesium ($n=5$).

	COD		Calcium		Magnesium	
	River water, 4.4 mg L^{-1}	River water, 38.5 mg L^{-1}	Ultrapure water	Spiked ultrapure water, 100 mg L^{-1}	Ultrapure water	Spiked ultrapure water, 20 mg L^{-1}
INDO	50303	49562	45395	45718	47293	45177
NTA	782413	807445	773617	789963	789241	794521
IBU	217596	225314	220213	227865	227986	226515
MEC	23730	24343	22403	22472	22448	23083
24D	24045	25544	23248	23523	24109	23498
DIF	38334	34041	30409	32944	32937	35458
HAL	10593	10276	10593	10700	10588	9263
EDTA	20569	25760	19411	20058	20052	19688
KETO	38451	42680	36119	36095	36061	32938
DFEN	11352	10801	11352	11383	11346	10606
DFOP	11209	12497	9825	10355	11030	9750

the middle concentration level after the addition, or not, of calcium and magnesium ions at concentrations close to those generally found in river waters: 100 and 20 mg L^{-1}, respectively.

An independent samples *t*-test was used to compare the means of the two samples differing in the metal content, after checking the homogeneity of the variances. Calculated *t*-values were lower than the critical *t*-values ($p=0.05$). So, it can be deduced that there are not any statistical differences in the mean peak heights, which indicates that the presence of the two ions does not modify the extraction of the analytes.

In the same way, it was studied if the increase of organic matter in the water sample affected to the extraction. The content of organic matter was estimated through the chemical oxygen demand (COD). Two water samples whose COD-values differed in about 9-fold were spiked with the analytes to carry out the sample preparation. After an independent samples *t*-test it was deduced that there was not statistical difference ($p=0.05$) between the peak heights of the analytes in the samples (see Table 8).

On the other hand, the addition of 5 mg of ODS sorbent as a clean-up way did not modify substantially the sample extract chromatograms in comparison with those obtained without the addition of sorbent. The efficacy of the clean-up was ascertained when ultraviolet–visible spectra of the extracts in acetone were recorded. Fig. 5 shows that the absorbance at different wavelengths was lower when the addition of ODS was taken into account in the sample preparation.

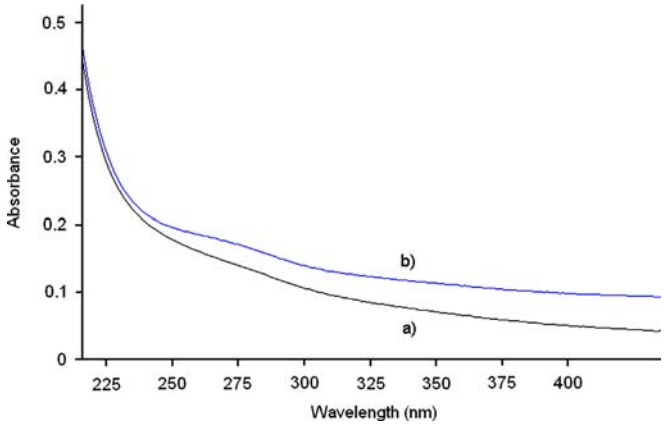

Fig. 5. Molecular absorption spectra of two river water extracts in acetone: (a) with ODS sorbent and (b) without ODS sorbent.

3.6. Robustness

The robustness of a method is an estimation of its capacity to remain unaffected when small variations are deliberately introduced in the analytical parameters and it has been evaluated according to Youden and Steiner's robustness test [78] at the middle concentration level of the analytes. Seven variables that could affect the robustness were identified: pH of the sample, ODS amount, volume of acetone in the first extraction, NaCl amount, derivatization temperature and the volumes of methanol and BF_3 in methanol added in the derivatization.

The robustness test involves eight experiments in which the values of the analytical variables are slightly modified above and below the corresponding nominal value. Table 9 shows the nominal, high and low values, and the experiments carried out. The peak heights of the analytes in each experiment were recorded. To evaluate the effect of each variable for each analyte, the mean of the four peak heights corresponding to low levels was subtracted from the mean of the four peak heights obtained at high levels. Then, the absolute difference value of the means was compared with the standard deviation (s) of the eight results according to Eq. (2), following the criterion used in reference [79].

$$\left|\overline{Peak\ height}_{high\ value} - \overline{Peak\ height}_{low\ value}\right| > s \times \sqrt{2} \Rightarrow \text{the variable is significant} \quad (2)$$

If the value of the difference is higher than the standard deviation multiplied by square root of the variable has a significant effect and the method is sensitive to changes in the variable concerned. Table 9 shows the results: absolute difference values and the standard deviation criterion. As it can be seen there were not significant effects for the studied variables when slight modifications were introduced. So, the procedure can be considered as robust.

In any case, the absolute difference value gives an idea of the influence of each variable in the precision of the method. It can be deduced from the data that the acetone volume and derivatization reaction temperature are two factors to watch in the routine analysis of many of the analytes.

3.7. Uncertainty

The EURACHEM/CITAC guide [80] has been followed to determine the expanded uncertainty associated to the measurement of an analyte concentration. This strategy splits the analytical process in single steps, estimating the contribution of each one to the total uncertainty of the result. The value of the analyte concentration in sample ($C_{analyte}$) depends on two parameters, see Eq. (3): the concentration of analyte obtained from the linear fitting ($C_{extract}$)

Table 9
Experimental design, analytical variables and values to test the robustness of the method. Absolute differences between the experiments with high and low values, and standard deviation criterion to identify significant effects.

Variables:	pH	ODS mass (mg)	Acetone volume (mL)	NaCl mass (g)	Derivatization reaction temperature (°C)	MeOH volume (mL)	BF_3/MeOH volume (mL)
Nominal value	2.0	5.0	3.0	3.2	90	0.30	0.30
High value (+)	2.2	5.1	3.1	3.1	93	0.32	0.32
Low value (−)	1.8	4.9	2.9	3.3	87	0.28	0.28
Experiment 1	+	+	+	+	+	+	+
Experiment 2	+	+	−	+	−	−	−
Experiment 3	+	−	+	−	+	−	−
Experiment 4	+	−	−	−	−	+	+
Experiment 5	−	+	+	−	−	+	−
Experiment 6	−	+	−	−	+	−	+
Experiment 7	−	−	+	+	−	−	+
Experiment 8	−	−	−	+	+	+	−
INDO 0.7 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=3540						
Absolute difference	413	1145	3041	1894	2886	503	580
NTA 3.2 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=60752						
Absolute difference	7371	5484	34867	36950	59625	13168	8070
IBU 0.7 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=7582						
Absolute difference	5479	3409	5850	786	4404	650	2075
MEC 0.7 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=1322						
Absolute difference	159	288	898	566	1269	433	162
24D 0.6 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=1286						
Absolute difference	75	715	862	688	1068	65	147
DIF 0.8 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=940						
Absolute difference	560	496	675	466	559	33	12
HAL 0.7 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=290						
Absolute difference	144	148	192	104	235	25	43
EDTA 3.1 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=573						
Absolute difference	286	348	252	439	298	49	155
KETO 0.8 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=1224						
Absolute difference	703	358	863	526	979	6	148
DFEN 0.7 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=338						
Absolute difference	157	195	260	121	222	81	8
DFOP 0.8 μg L^{-1}	Standard deviation of the eight results × $\sqrt{2}$=360						
Absolute difference	194	207	228	178	241	63	26

and a recovery factor (F), in percentage, to include the uncertainty of the method bias in the estimation.

$$C_{analyte} = C_{extract}\frac{100}{F} \tag{3}$$

The expression to calculate the combined relative standard uncertainty is shown in Eq. (4). This expression also contains other sources of uncertainty: the repeatability of the analytical method (u_{rep}) which is estimated as a whole, and the uncertainty of the concentration of the calibration standards (u_{std}). The uncertainties associated to the measurement of a volume do not appear explicitly in this case.

$$\frac{u(C_{analyte})}{C_{analyte}} = \sqrt{\left(\frac{u(C_{extract})}{C_{extract}}\right)^2 + \left(\frac{u(F)}{F}\right)^2 + u^2{}_{rep} + u^2{}_{std}} \tag{4}$$

The systematic component, or bias, of the uncertainty was estimated on the basis of the recoveries obtained in the in-house validation. The term $u(F)$ was calculated from the RSD of the recoveries and the number of experiments (n=5).

Standard uncertainty associated with the linear least square fitting, $u(C_{extract})$, was calculated using some regression parameters, such as the residual standard deviation of the fitting and the slope of the linear calibration graph, besides the peak heights and concentrations of the standards and the number of readings of the response, and its value, for each sample (one in this work).

The uncertainty associated with the repeatability of the analytical procedure, u_{rep}, was estimated from eight concentrations of analyte found in the in-house validation. These concentrations were grouped in pairs and considered as four sample duplicates. Then, u_{rep} was calculated from the standard deviation of the normalized concentration differences (the difference divided by the mean of the two corresponding samples).

Finally, it is necessary to estimate the uncertainty of the concentration of the calibration standards, u_{std}. First at all, the standard uncertainty of the stock solution concentration was calculated from the weighted mass of analyte, the prepared solution volume and the purity of the standard declared by the manufacturer. Here, it is convenient to state that the purity of the standards used in this work was not certified. After that, a mixture of the individual stock solutions and subsequent dilutions were required: the uncertainty of each calibration standard was obtained by applying the corresponding propagation formulas, in which the uncertainties of the flask and pipette volumes and stock solution concentration have influence. Then, the mean of the uncertainties of the seven calibration standards was calculated for each analyte, and u_{std} was estimated as the quotient of this mean value and the mean concentration of the calibration standards.

The volume measurements are subjected to three main influences as regards the uncertainty: the calibration of the material quoted by the manufacturer (assuming a triangular distribution), the difference between the temperature of the solution/flask and the temperature at which the volume was calibrated, and the repeatability in filling the flask/pipette to the mark. The uncertainty arisen from the laboratory temperature variation (2 °C) was calculated from the coefficient of volume expansion for water and assuming a rectangular distribution; the volume expansion of the glass volumetric material is negligible against the former. On the other hand, the repeatability in filling the flask/pipette to the mark

Table 10
Uncertainty, and contributions, in the determination of the acidic analytes by the proposed method at three concentration levels.

	Spiking level ($\mu g\ L^{-1}$)	$u(C_{extract})/C_{extract}$	$u(F)/F$	u_{rep}	u_{std}	$u(C_{analyte})$ ($\mu g\ L^{-1}$)	$u_{expanded}$ ($\mu g\ L^{-1}$)	$u_{expanded}$ (%)[a]
INDO	11.4	0.088	0.022	0.081	0.051	1.5	3.0	26
INDO	0.7	1.712	0.022	0.075	0.051	1.3	2.5	357
INDO	0.04	31.50	0.004	0.151	0.051	1.4	2.7	6750
NTA	43.7	0.092	0.019	0.084	0.072	6.5	13	30
NTA	3.2	1.239	0.025	0.100	0.072	3.6	7.3	228
NTA	0.16	24.94	0.044	0.137	0.072	3.9	7.8	4875
IBU	2.3	0.668	0.048	0.099	0.074	1.5	3.0	130
IBU	0.7	2.132	0.027	0.126	0.074	1.6	3.2	457
IBU	0.04	39.25	0.070	0.204	0.074	1.6	3.3	8250
MEC	9.1	0.033	0.039	0.088	0.074	0.91	1.8	20
MEC	0.7	0.0437	0.030	0.078	0.074	0.28	0.56	80
MEC	0.03	9.853	0.036	0.066	0.074	0.30	0.60	2000
24D	9.2	0.049	0.051	0.101	0.074	1.2	2.5	27
24D	0.6	0.711	0.017	0.041	0.074	0.41	0.82	137
24D	0.03	14.58	0.075	0.210	0.074	0.46	0.91	3033
DIF	12.9	0.027	0.039	0.129	0.073	2.0	4.0	31
DIF	0.8	0.419	0.047	0.075	0.073	0.33	0.66	83
DIF	0.04	8.363	0.027	0.097	0.073	0.33	0.66	1650
HAL	9.2	0.034	0.035	0.100	0.074	1.2	2.4	26
HAL	0.7	0.422	0.041	0.065	0.074	0.32	0.64	91
HAL	0.04	7.675	0.022	0.066	0.074	0.30	0.60	1500
EDTA	42.1	0.148	0.041	0.115	0.072	9.1	18	43
EDTA	3.1	1.996	0.034	0.031	0.072	6.6	13	419
EDTA	0.15	41.253	0.082	0.139	0.072	7.6	15	10000
KETO	2.5	0.288	0.035	0.105	0.074	0.79	1.6	64
KETO	0.8	0.952	0.031	0.071	0.074	0.73	1.5	188
KETO	0.04	18.35	0.043	0.153	0.074	0.64	1.3	3250
DFEN	8.8	0.112	0.038	0.112	0.077	1.55	3.0	34
DFEN	0.7	1.425	0.022	0.060	0.077	0.95	1.9	271
DFEN	0.03	32.65	0.055	0.174	0.077	1.1	2.2	7333
DFOP	11.3	0.064	0.039	0.074	0.073	1.4	2.8	25
DFOP	0.8	0.901	0.040	0.056	0.073	0.70	1.4	175
DFOP	0.04	17.52	0.021	0.139	0.073	0.65	1.3	3250

[a] In percentage with respect to the measured concentration.

was estimated as the standard deviation of a series of ten fill and weigh experiments with ultrapure water.

As regards the mass measurements to prepare the stock solutions there are two main contributions: the balance linearity (0.20 mg, rectangular distribution), whose contribution must be counted twice (tare and sample weight) and the weighing repeatability, which was also calculated as the standard deviation of a series of 10 weights.

Once all the contributions to the uncertainty were known, they were introduced in Eq. (4) to calculate the combined relative standard uncertainty, and from this latter, the combined standard uncertainty $u(C_{analyte})$ associated to the analyte concentration. Now, a coverage factor $K=2$ was used to calculate the expanded uncertainty ($u_{expanded}$) by multiplying the coverage factor by the combined standard uncertainty.

Table 10 shows the values of the different contributions to the uncertainty, the combined standard uncertainties, $u(C_{analyte})$, the expanded uncertainties, $u_{expanded}$, and the expanded uncertainty expressed as percentage in relation to the concentration of the analytes at the three assayed concentration levels. The uncertainty percentages were directly related to the concentration level. At the high concentration level (about 10 $\mu g\ L^{-1}$ or higher amounts, in general terms) the values of uncertainty, in percentage, were about 25–43% compared with the calculated concentrations, except for IBU and KETO in whose cases they were about 130% and 64%, respectively. At the middle concentration level (in the order of 1 $\mu g\ L^{-1}$), the percentages of uncertainty were comprised between 80% (MEC) and 457% (IBU) while at the low level (lower than 0.05 $\mu g\ L^{-1}$ for most of the compounds) the percentages were higher than 1000% as it can be seen in Table 10. It is obvious that at this low concentration level close to the quantification limit of the analytes the analytical method could be classified as a semiquantitative method rather than as quantitative method.

As it was previously mentioned IBU and KETO are the analytes whose uncertainty is most notable at the highest assayed concentration. This fact can be attributed to the correlation observed between the uncertainty and the concentration level. The concentrations of IBU and KETO were the lowest from those considered at the high spiking level.In order to decrease the uncertainty of the measured concentrations it is important to know those steps of the analytical method in which it could be possible to act. As it can be seen in Table 10 the contribution of the interpolated concentration to the uncertainty was the most relevant influence, mainly at low concentration levels. So, the adjustment of the linear fitting within a concentration range similar to that concentration in sample could help to decrease the uncertainty.

4. Conclusions

A method to determine acidic contaminants in river water samples at trace level has been developed. The sample preparation involves the use of small sample and reagent volumes. Acetone is a valid solvent to separate the analytes from water samples. Matrix effects derived from the organic matter, calcium and magnesium amount have not been observed.

Recoveries are close to 100% with relative standard deviations equal or lower than 16%. The aminopolycarboxylic acids have limits of detection higher than the other analytes. The combined standard uncertainties of the measured concentrations depend mainly on the uncertainties of the interpolated concentrations.

The expanded uncertainty, expressed as percentage in relation to the measured concentration, decreases as this concentration increases. At concentrations close to the quantification limits the uncertainty percentages reach values of 1000%.

It could be inferred from the findings that the simultaneous liquid–liquid extraction and dispersive solid-phase extraction could be applied to the determination of other acidic organic compounds soluble in acetone.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.talanta.2013.07.052.

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