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Determination of acidic drugs in sewage water by gas chromatography–mass spectrometry as *tert*.-butyldimethylsilyl derivatives

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Abstract

A procedure is described for the determination of five acidic non-steroidal anti-inflammatory pharmaceuticals (ibuprofen, naproxen, ketoprofen, tolfenamic acid and diclofenac) in sewage water. The analytical method involves the concentration of water samples using a solid-phase extraction polymeric sorbent, functionalized with *N*-vinylpyrrolidone. Analytes were eluted with ethyl acetate, derivatized using *N*-methyl-*N*-(*tert*.-butyldimethylsilyl)trifluoroacetamide (MTBSTFA) and analyzed by GC–MS. Influence of time, temperature and volume of MTBSTFA in the yield of the derivatization step were studied in detail using a factorial central composite design. Quantification limits of the analytical procedure for 500 ml of sewage water ranged from 20 to 50 ng/l. Recoveries from 90 to 115% were found for sewage water samples spiked with the studied compounds at the low ng/ml level. Results obtained for real samples show the presence of ibuprofen and naproxen in both influent and effluent of a sewage water treatment plant.

Keywords: Water analysis; Derivatization, GC; Non-steroidal anti-inflammatory drugs

1. Introduction

In the last few years there has been a growing interest in the role of different groups of pharmaceutical compounds such as anti-inflammatories, lipid regulators, psychiatric and antiepileptic drugs in the aquatic environment. In developed countries, annual prescriptions of some of these compounds can achieve several hundreds of tons [1]. Human excretion of the original drugs (as free or conjugated species) and of their metabolites have caused their presence in the influent of sewage treatment plants. Furthermore, a number of studies have shown that some acidic pharmaceutical compounds are not totally eliminated in sewage treatment plants, therefore, they can reach surface and groundwaters [1–3]. Concentrations of anti-inflammatory pharmaceuticals such as diclofenac and ibuprofen in the range of several hundreds of ng/l have been found in different European rivers [1,4–6]. Obviously, these levels are much lower than those used in medical applications, and their possible ecotoxicological effects are still unknown [3,6]; however, these compounds must be classified as environmentally relevant.

Quantitative evaluation of the fate of NSAI drugs (NSAIDs)in the aquatic environment, proper risk assessment and improvement of the efficiency of sewage treatment plants need sensitive and reliable

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analytical methods. Generally, procedures used for the analysis of acidic pharmaceuticals, such as NSAIDs, in aqueous samples are based on an enrichment step followed by the chromatographic determination of the analytes, usually with mass spectrometric detection. Sample pre-concentration is normally performed using solid-phase extraction after pH adjustment to 2–3. Reversed-phase sorbents such as C_{18} [7], polymeric materials (e.g. LiChrolut EN) [8] and also functionalized polymers such as the Oasis HLB sorbent [5] (polydivinylbenzene-co-*N*-vinylpyrrolidone) are currently used. Typically, 500 ml of sample are concentrated in case of wastewater, and up to 1000 ml for river and groundwater.

Regarding the determination step, recently HPLC–MS has been successfully employed in the analysis of acidic drugs in water samples [6,9]. However, GC–MS is by far the most often used technique; probably, because of the widespread and availability of GC–MS systems in environmental laboratories, and also because of possible problems related with signal suppression in HPLC–MS, when extracts from real samples are analyzed. Gas chromatographic separations of NSAIDs can be performed only after derivatization of the native compounds to less polar species. The carboxylic group of these drugs can be converted into their methyl ester derivative using diazomethane [4,5,7]. The yield of the reaction is usually excellent; however, because of some drawbacks of the process such as the high toxicity of diazomethane, its low stability and the need to be generated in situ, some alternatives to their use have been proposed in the literature. Zwiener et al. [8] described an on-line method which allows the methylation of several NSAIDs in the hot injector of a gas chromatograph using trimethylsulfonium hydroxide. Sacher et al. [10] derivatized several acidic drugs containing carboxylic groups using a solution of pentafluorobenzyl bromide in cyclohexane; the reaction was performed at 100 °C for 2 h after dryness evaporation of the sample extract. Several silylation reagents have been widely used as alternatives to diazomethane for the derivatization of pesticides and drugs, containing phenolic, carboxylic or amide groups in environmental and biological samples, respectively [11–14]; however, only one publication reports the use of bis(trimethylsilyl)trifluoroacetamide (BSTFA), for the analysis of NSAIDs in organic extracts of water samples [15].

The aim of this paper was the optimization of a GC–MS method for the analysis of NSAIDs in sewage water, based on their derivatization using a commercial silylation reagent, which serves as alternative to the use of diazomethane. *N*-Methyl-*N*-(*tert*.-butyldimethylsilyl)trifluoroacetamide (MTBSTFA) was preferred to trimethylsilyl derivatization because of the greater thermal and hydrolytic stability of the *tert*.-butyldimethylsilyl derivatives, added to their higher molecular mass that improves chromatographic separation and MS detection [16]. The previous solid-phase extraction (SPE) step was carried out using Oasis HLB cartridges, which exhibit both hydrophilic and lipophilic retention characteristics. Elution of analytes from the sorbent material was performed with solvents compatible with their further silylation, thus evaporation of the extract to dryness was not necessary. Influence of experimental parameters such as time, temperature and volume of MTBSTFA in the efficiency of the derivatization reaction were also evaluated using an experimental design. This study was performed with extracts of spiked real sewage water samples. In this way, matrix influence on the derivatization step was taken into account. The developed method was applied to the analysis of NSAIDs in 24 h composite water samples taken in the inlet and the outlet streams of a sewage treatment plant.

2. Experimental

2.1. Reagents

HPLC-grade methanol and ethyl acetate were supplied by Merck (Darmstadt, Germany). Pesticide grade *n*-hexane was also purchased from Merck. PCB-30 (2,4,6-trichlorobiphenyl) was obtained from Dr Ehrensdorfer (Augsburg, Germany); ibuprofen, naproxen, ketoprofen, tolfenamic acid, diclofenac and meclofenamic acid were purchased from Aldrich (Milwaukee, WI, USA). MTBSTFA was also obtained from Aldrich in 1 ml ampoules. Individual stock solutions of NSAIDs were prepared in methanol. Diluted standards and mixtures of acidic drugs were prepared in both methanol (when used to spike water samples) and ethyl acetate (when used as calibration solutions, after been converted into their *tert*.-butyldimethylsilyl derivatives). Standards of

PCB-30 were prepared in *n*-hexane and then diluted in ethyl acetate.

SPE cartridges containing 60 mg of the Oasis HLB were obtained from Waters (Milford, MA, USA) and used as received.

2.2. Samples

Spiked and non-spiked sewage and Milli-Q water samples were used in this paper. Sewage samples were taken in a plant equipped with primary and biological treatments. The plant receives urban and industrial wastewater from a city of 100 000 inhabitants and also from a hospital complex which gives medical assistance to approximately 500 000 persons. Influent and effluent sewage water was used to optimize the analytical procedure. Samples were filtrated immediately after being received using glass or cellulose filters (pore size 5 μm), and stored refrigerated at 4 °C for a maximum of 72 h before the enrichment step.

2.3. Solid-phase extraction

Water samples were allowed to reach room temperature, adjusted at pH 2–2.5 with 0.1 N HCl, and spiked with 50 μl of a meclofenamic acid solution in methanol (21.6 μg/ml). This compound was used as internal surrogate through the analytical process. Normally, 500 ml of filtered sewage water and up to 2000 ml of Milli-Q water samples were used in the SPE studies. Samples were forced to pass through the SPE cartridge (approx. at 15 ml/min) that had been sequentially preconditioned with ethyl acetate, methanol and Milli-Q water adjusted to pH 2.5 (3 ml of each one). Cartridges were then dried with a stream of nitrogen for 30 min and eluted with 2 ml of ethyl acetate.

2.4. Derivatization

Acidic NSAIDs were derivatized in a 1.5 ml GC autosampler vial with MTBSTFA. For optimal conditions 800 μl of a solution of these compounds in ethyl acetate (extract from the SPE cartridge or calibration standards containing increasing amounts of the analytes and a fixed concentration of the surrogate) were mixed with 200 μl of MTBSTFA. Vials were then capped and placed in a GC oven at 60 °C for 1 h. After that, they were cold down to room temperature and stored at −20 °C until being analyzed.

2.5. Equipment

Derivatized drugs were determined by GC–MS. The system consisted of a Varian Star 3400 CX gas chromatograph (Walnut Creek, CA, USA) equipped with a split–splitless injector and connected to an ion-trap mass spectrometer (Varian Saturn 4). Separations were carried out using a BP5 type capillary column (30 m×0.25 mm I.D., d_f: 0.25 μm) purchased from Varian. Helium (99.999%) was used as carrier gas at a constant head pressure of 8 p.s.i. (1 p.s.i.=6894.76 Pa). Injections were performed in the splitless mode (purge time 1 min), and the injection volume was 1 μl.

The GC oven was programmed as follows: 1 min at 50 °C, first ramp at 10 °C/min to 180 °C (held for 7 min), second ramp at 10 °C/min to 230 °C (held for 25 min), third ramp at 20 °C/min to 250 °C (held for 5 min). The GC–MS interface and the ion trap temperature were set at 250 °C. Mass spectra were obtained in the electron impact mode (70 eV). Two segment of mass acquisition were set: from m/z 100 to m/z 330 between 10 and 25 min, and from m/z 140 to m/z 420 for the rest of the chromatogram. Retention times and ratio m/z used for quantitative purposes were those given in Table 1.

2.6. Quantification

Recoveries of the analytical procedure for spiked Milli-Q and sewage samples and concentrations of acidic drugs in real polluted samples, were determined using meclofenamic acid as internal standard throughout the whole analytical procedure. Calibra-

Table 1
Retention times and m/z ratio of the derivatized pharmaceuticals

Compound	Retention time (min)	m/z for quantification
Ibuprofen	20.47	263
Naproxen	30.04	287
Ketoprofen	33.59	311
Tolfenamic acid	36.28	318+320
Diclofenac	36.94	352+354+356
Meclofenamic acid	41.01	352+354+356

tion curves were built plotting the ratio: analyte peak area/meclofenamic peak area versus the analyte concentration.

3. Results and discussion

3.1. Derivatization reaction

Normally, the weakest point of GC methods applied to the analysis of acidic compounds is the derivatization step, therefore in this study it was optimized in detail:

3.1.1. Choice of solvent

The solvent used to carry out the conversion of the acidic drugs into their *tert*.-butyldimethylsilyl derivatives was selected on the basis of two criteria: first its compatibility with the derivatization reaction and second its capacity to elute the acidic compounds retained on the SPE cartridge. Recently, it has been proved that acetonitrile and ethyl acetate are favourable solvents to carry out the silylation of several endocrine-disrupting chemicals (containing phenolic and carboxylic groups) with MTBSTFA [13]. The choice between them was made in function of their elution strength. When acetonitrile was used at least three fractions of 1 ml were necessary to recover the NSAIDs previously retained on an Oasis cartridge. For ethyl acetate, only two fractions were necessary. Therefore, the latter was chosen as elution solvent.

3.1.2. Time, temperature and volume of MTBSTFA

Influence of these parameters on the yield of the derivatization was studied using a central composite ($\alpha = 1.682$) design type 2^3 plus star with four central points (Table 2). Experimental domain points for the three factors were selected according to derivatization conditions available in the literature for compounds containing phenolic or carboxylic groups in their molecules [11–14]. Experiments were performed not using standards in ethyl acetate, but with a pool of SPE extracts corresponding to a sample of sewage water (influent). This sample was processed as follows: 5 l of water were passed through glass fibre filters, adjusted to pH 2.5–3, spiked with the studied compounds at the level of 4–5 ng/ml (depending on each specie), and divided into fractions of 500 ml. Each fraction was concentrated using a SPE cartridge, eluted with ethyl acetate and organic extracts mixed. Aliquots of 730 μl of this combined extract were placed in a vial, spiked with

Table 2
Design matrix and chromatographic responses obtained for the studied compounds

Exp. no.	Order	Time (h)	Factors		Response: peak area/PCB-30 peak area					
			T (°C)	Vol. MTBSTFA (μl)	Ibuprofen	Naproxen	Ketoprofen	Tolfenamic acid	Diclofenac	Meclofenamic acid
1	11	1	45	60	24.8	28.9	10.8	17.7	12.0	14.8
2	12	3	45	60	27.2	33.0	13.6	22.2	15.3	19.4
3	13	1	85	60	24.8	32.0	14.2	22.2	15.6	13.2
4	7	3	85	60	25.0	27.5	10.8	16.7	10.8	14.5
5	16	1	45	200	28.0	34.8	16.8	26.1	18.6	23.6
6	2	3	45	200	28.2	34.8	16.8	26.6	19.0	20.1
7	10	1	85	200	32.4	32.9	16.5	27.0	20.4	21.9
8	6	3	85	200	24.7	32.2	15.4	23.5	16.8	13.9
9	5	0.3	65	130	33.2	35.6	19.3	29.7	22.5	22.8
10	15	3.7	65	130	32.4	33.7	13.3	21.0	14.2	16.9
11	3	2	31	130	24.9	31.6	14.5	23.6	17.0	18.2
12	14	2	99	130	27.5	33.3	14.9	22.8	15.9	19.9
13	17	2	65	12	26.4	27.7	10.6	16.4	10.7	12.6
14	4	2	65	248	29.7	36.7	19.6	30.9	22.9	24.4
15	9	2	65	130	26.4	31.0	12.1	18.2	12.5	11.8
16	8	2	65	130	26.9	33.5	13.0	19.8	13.9	13.7
17	1	2	65	130	27.1	37.2	17.8	20.2	19.7	14.2
18	18	2	65	130	30.3	34.4	18.3	28.3	21.2	28.1

the corresponding volume of MTBSTFA (Table 2) and made up to 1 ml with ethyl acetate. Then, 40 μl of a PCB-30 standard solution (5 μg/ml in ethyl acetate) were also added to each vial in order to compensate possible volume variations during the derivatization step and also to correct variations in the response of the GC–MS instrument from injection to injection. Each vial was capped and placed in an oven according to conditions (time and temperature) given in Table 2. Corrected responses (peak area/PCB 30 peak area) for each drug and experimental condition are also shown in Table 2. Data were statistically evaluated using the software packages Statgraphics Plus (Manugistics) and Nemrod for Windows 95 (LPRAI, University of Marseille III, Marseille).

As shown in Table 3, results of the central composite design were similar for the six investigated compounds. In general, time and specially temperature affected in a minor extension to the yield of the derivatization step. More concretely, the effect of temperature was positive for ibuprofen and negative for the rest of compounds. The reaction time always showed a negative effect on the yield of the process. However, both factors were not statistically relevant. Conversely, the volume of MTBSTFA showed a positive and statistically significant effect on the yield of the derivatization for naproxen, ketoprofen, tolfenamic acid and diclofenac. In case of ibuprofen and meclofenamic acid, it was again the most important factor with standardized effects very close to the statistically significance bound (2.31). Quadratic terms and first order interactions affected in minor extension to the derivatization reaction (results not shown).

Table 3
Standardized values for the main effects of time, temperature and volume of MTBSTFA in the efficiency of the derivatization reaction

Compound	Main effects		
	Time (min)	Temperature (°C)	Volume MTBSTFA
Ibuprofen	−0.83	0.39	2.27
Naproxen	−0.51	−0.48	3.40*
Ketoprofen	−1.32	−0.05	3.48*
Tolfenamic acid	−1.52	−0.39	3.94*
Diclofenac	−1.68	−0.31	3.71*
Meclofenamic acid	−0.63	−0.41	1.78

* Statistically significant factors at the 95% confidence level.

To complete the statistical evaluation of results given in Table 2 and in order to obtain the optimal derivatization conditions for all compounds considered in this study a total desirability function was used [17–19]. This function was a measure of overall quality and provided a convenient means by which to compare several responses and to select the optimum with the most desirable properties. All responses were transformed into a dimensionless desirability scale (d_i). The scale of the desirability function ranges between $d = 0$, for a completely undesirable response, to $d = 1$ for a fully desired response.

The responses for ibuprofen, naproxen, ketoprofen, tolfenamic acid, diclofenac and meclofenamic acid were transformed into an appropriate desirability scale d_1, d_2, . . . ,d_6, respectively, having regard to the fact that all responses had to be maximised. Then, the global desirability is calculated as: $D = (d_1 d \ldots d_m)^{1/m}$ and graphically mapped over the experimental domain. Partial and global desirability functions have presented values of 100%.

Examination of the various contour plots of the global desirability (D) surface will give a reliable picture of the effect of the considered experimental factors in the yield of the derivatization for all compounds. As shown in Fig. 1, an extensive zone of acceptable derivatization conditions is defined. The regions in grey correspond to null values for desirability where level factors are not suitable to be chosen. Predicted conditions to obtain the optimum yield in the derivatization step, for all considered compounds, were found near the boundary of the experimental domain in the neighbourhood of volume of MTBSTFA $V = 200$ μl, temperature $T = 60$ °C and reaction time $t = 1$ h (indicated by arrows in Fig. 1).

Therefore, in further experiments the derivatization reaction was carried out using the above conditions and 800 μl of sample extract or of calibration solutions. MS spectra for two of the studied compounds (naproxen and tolfenamic acid) are shown in Fig. 2. For both, and also for the rest of compounds, the base peak corresponded to the loss of the *tert*.-butyl group in the derivatized compounds (m/z [M-57]$^+$). Tolfenamic acid, diclofenac and me-

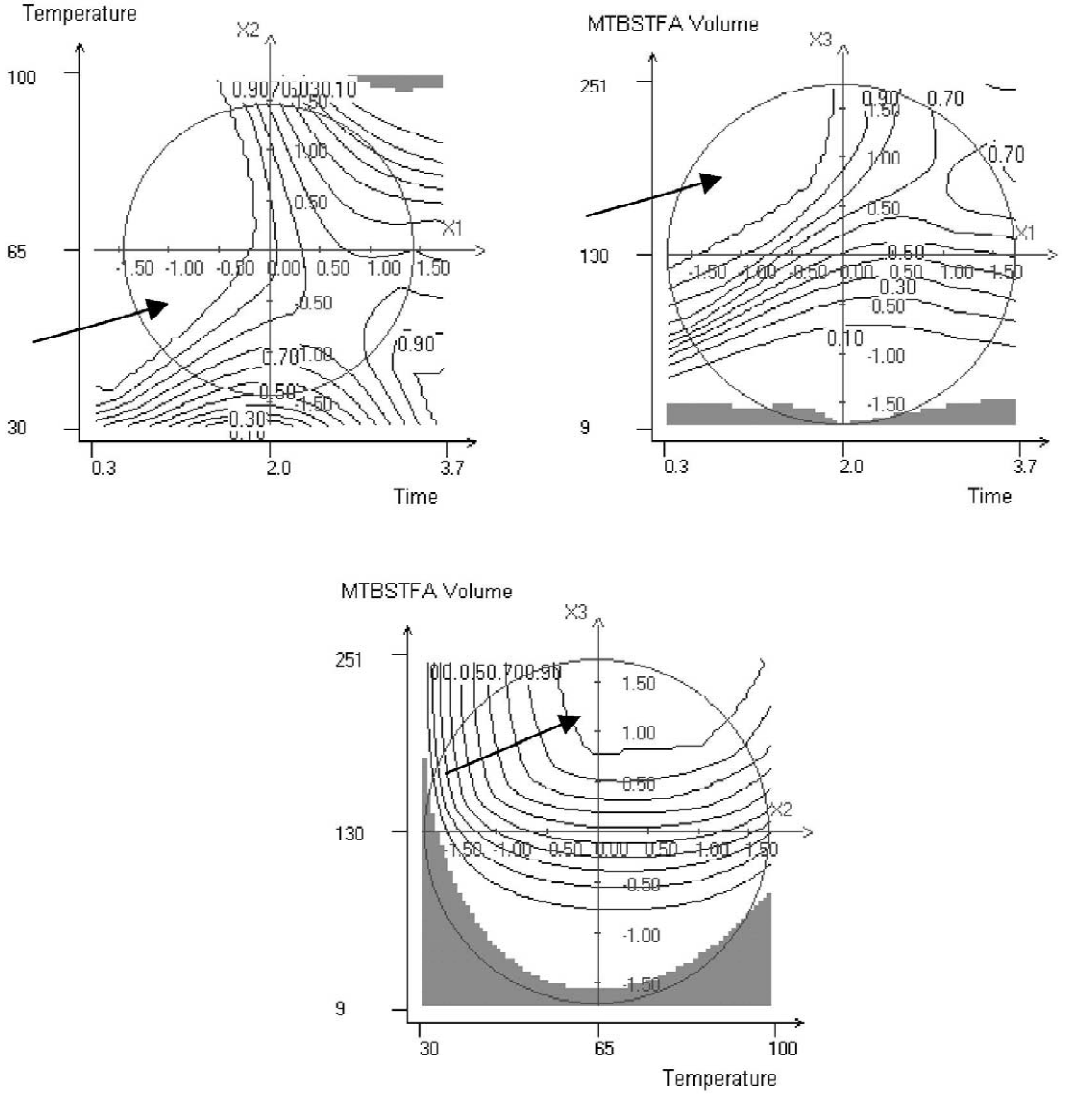

Fig. 1. Two-dimensional projections of the global desirability plot as function of the experimental factors: time, temperature and volume of MTBSTFA.

clofenamic acid have in their structure not only the carboxylic moiety but also an amine group that hypothetically could react with MTBSTFA; however, no evidences from the derivatization of the secondary amine were noticed in the corresponding MS spectra. Probably this secondary amine group, which besides have chlorine or methyl groups in ortho position, was not available or hindered to silylation. These findings were in good agreement with the difficulties reported by Schoene et al. [11] to derivatize secondary amines with MTBSTFA.

3.2. Linearity

The linearity of the analytical method was tested with standard mixtures (previously derivatized under the optimized conditions) containing meclofenamic as internal standard (430 ng/ml), and increased

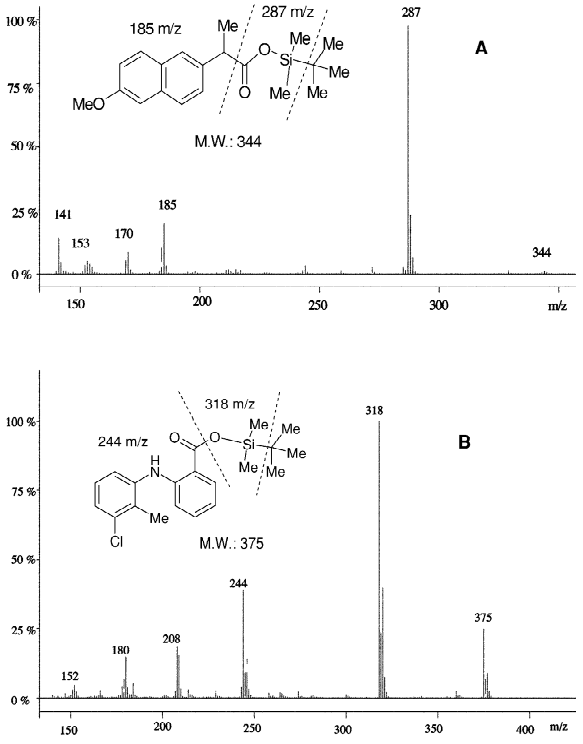

Fig. 2. MS spectra for naproxen and tolfenamic acid as their *tert.*-butyldimethylsilyl derivatives.

concentrations of the rest of acidic drugs, at seven levels, between 10 and 1000 ng/ml. Correlation coefficients higher than 0.995 were obtained for all compounds. Relative standard deviations (RSDs) for consecutive injections of a standard, containing ca. 100 ng/ml of each compound, ranged from 1 to 6%. Instrumental quantification limits from 2 to 5 ng/ml were obtained for a signal-to-noise ratio of 10 (Table 4). Even when standards containing up to 1000 ng/ml of the studied compounds were injected traces of the underivatized species were not detected, therefore it was assumed that the yield of the reaction was higher than 95%.

3.3. Performance of the analytical method

Breakthrough of the SPE sorbent was first investigated using spiked Milli-Q water samples (≈10 ng/ml for each drug) from 500 up to 2000 ml. Samples were forced to pass through two cartridges sequentially connected. After finishing enrichment step they were disconnected and processed separately. Even for samples of 2000 ml, peak areas for naproxen, ketoprofen, diclofenac and meclofenamic acid in the extract from the second cartridge, were less than 1% of those in the extract from the first one. Ibuprofen and tolfenamic acid were not detected in the eluate from the second cartridge. Then breakthrough assays were repeated using spiked sewage water (5-μm filtered effluent). In these experiments the first solid-phase extraction cartridge was completely blocked for water volumes higher than 1500 ml. For this sample volume breakthrough of the cartridge for the selected analytes was not detected.

Sewage water samples need to be filtered previously to solid-phase extraction. Obviously apart form suspended matter, filters will also remove analytes associated to particles; however, the fraction of analytes dissolved in the sample should not be modified during filtration. To verify this assumption, 500 ml Milli-Q water samples with a spike of NSAIDs (only ibuprofen, diclofenac and meclofenamic acid were used in this study) were concentrated with and without being passed through glass fibre filters (5 μm pore size). Significant differences ($P = 0.05$) were not found between responses for these compounds in filtered and not

Table 4
Linearity, repeatability and instrumental quantification limits (QL) of the analytical procedure (without solid-phase extraction)

Compound	Correlation coefficient (R^2)	Repeatability ($n = 5$; RSD, %)	QL ($S/N = 10$) (ng/ml)
Ibuprofen	0.998	5.8	2
Naproxen	0.999	2.1	2
Ketoprofen	0.995	5.1	5
Tolfenamic acid	0.999	0.7	3
Diclofenac	0.997	4.2	5

Table 5
Peak areas for ibuprofen, diclofenac and meclofenamic acid in spiked Milli-Q water (500 ml samples spiked at the 2 ng/ml level) with and without filtration

Compound	Filtered		Not filtered	
	Mean ($n=3$)	RSD (%)	Mean ($n=3$)	RSD (%)
Ibuprofen	42 821	9.0	41 554	4.2
Diclofenac	15 083	10.5	13 054	3.4
Meclofenamic acid	40 420	6.3	41 306	6.6

filtered samples (Table 5). This behaviour is in agreement with the hydrophilic nature of acidic NSAIDs. Similar results were obtained using cellulose filters (data not shown). In further experiments sewage water samples were filtered first through cellulose paper and then through glass fibre filters with a pore size of 5 μm.

Recoveries of the analytical procedure for 500 ml samples of Milli-Q and sewage water (effluent) are given in Table 6. The spiked level was 2 ng/ml for each compound including the surrogate. In case of sewage water, spiked and non-spiked samples (only meclofenamic acid was added to the last) were concentrated and values in the non-spiked water subtracted to evaluate the yield of the solid-phase extraction step. Quantitative recoveries were obtained for both Milli-Q and sewage samples (Table 6). These results are similar to those previously reported by Öllers et al. [5] using the same SPE sorbent followed by diazomethane derivatization; however, in this reference cartridges were eluted with 6 ml of an acetone–ethyl acetate mixture, versus only 2 ml of ethyl acetate in the present work.

Quantification limits are also given in Table 6. They were estimated from the instrumental quantification limits (Table 4), and the pre-concentration factor achieved in the solid-phase extraction of 500 ml samples. In case of sewage water these values were multiplied by a factor of two to compensate for a noisier baseline in the GC–MS chromatograms. As up to 1500–2000 ml of water samples could be concentrated without appreciable breakthrough of the SPE cartridges, theoretically better quantification limits could be obtained just increasing the sample volume. This approach could be valid for river and groundwater but not for sewage water: in this case, even if breakthrough problems were not detected up to 1500 ml samples, an increase in the water volume will lead to extremely long SPE enrichment steps and thus it is not advisable.

3.4. Analysis of waste water

The developed procedure was applied to the analysis of influent and effluent (in each point, samples were taken automatically every hour for a period of 24 h and combined before being analyzed) from a sewage treatment plant. Two series of samples were taken, the first one in October 2001 and the second one in January 2002. In both cases only

Table 6
Recoveries and quantification limits of the analytical procedure

Compound	Recoveries for 500 ml samples (%)[a] (spiked level 2 ng/ml)		QL ($S/N=10$, ng/l)	
	Milli-Q water ($n=3$)	Sewage water ($n=3$)	Milli-Q water	Sewage water
Ibuprofen	98.9±14.0	90.0±13.4	10	20
Naproxen	102.6±7.2	88.3±7.5	10	20
Ketoprofen	94.5±9.1	117.8±8.2	25	50
Tolfenamic acid	100.5±7.8	94.8±4.9	15	30
Diclofenac	101.3±6.0	105.0±2.8	25	50

[a] Mean value±RSD.

ibuprofen and naproxen were found. A chromatogram of an effluent sample is shown in Fig. 3. Table 7 presents the obtained concentrations. As influent and effluent samples were taken with a temporal difference of 48 h (which correspond to the residence time of the sewage water in the treatment plant), data in Table 7 allowed us to obtain a preliminary estimation of the efficiency of the treatment plant. Removal percentages around 65 and 45% were obtained for ibuprofen and naproxen, respectively.

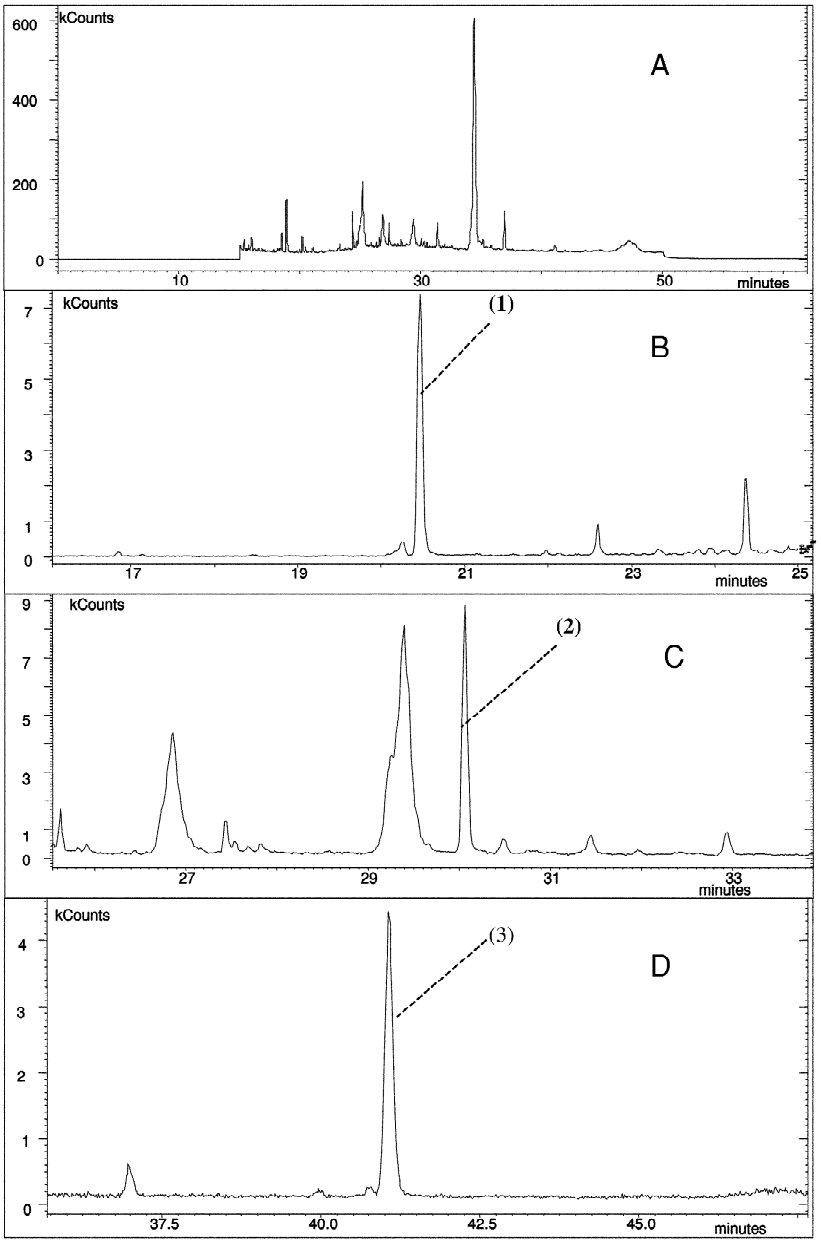

Fig. 3. GC–MS chromatograms for a sample of sewage water (effluent). (A) Total ion current signal, (B) plot at 263 m/z, (C) plot at 287 m/z, (D) plot at 352 + 354 + 356 m/z. Compounds: ibuprofen (1), naproxen (2) and meclofenamic acid (3).

Table 7
Levels of ibuprofen and naproxen in the influent and effluent of a sewage treatment plant ($n=3$ replicates for each sampling data and point)

Compound	Influent (ng/ml)[a]	Effluent (ng/ml)[a]	Sampling month
Ibuprofen	2.81±0.15	0.91±0.05	October 2001
	5.77±0.43	2.10±0.06	January 2002
Naproxen	3.50±0.18	1.87±0.11	October 2001
	4.50±0.36	2.56±0.23	January 2002

[a] Mean value±standard deviation.

Obviously, these results should be confirmed in a long term and more systematic study which is outside of the scope of this paper.

4. Conclusions

An analytical procedure for the determination of five NSAIDs in water samples by GC–MS was developed. The use of MTBSTFA to silylate the studied acidic compounds was a valuable alternative to other derivatization procedures based mainly in the use of diazomethane. The method was applied to the analysis of sewage water samples and it could be extended to cleaner samples such as surface and pre-potable water due to the large breakthrough volume of the SPE sorbent. Analysis of non spiked sewage samples demonstrated the presence of ibuprofen and naproxen at relative high levels. The persistence of both species in the plant effluent indicates the need of improving sample treatments to avoid the contamination of the aquatic environment.

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