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Determination of drug residues in water by the combination of liquid chromatography or capillary electrophoresis with electrospray mass spectrometry

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Abstract

Methods for the determination of drug residues in water have been developed based on the combination of liquid chromatography (LC) or capillary electrophoresis (CE) with mass spectrometry (MS). For HPLC–MS two types of interfaces (pneumatically assisted electrospray ionization interface or an atmospheric pressure chemical ionization interface, respectively) were employed and compared in terms of detection limits. 2 m*M* Ammonium acetate at pH 5.5 and a methanol gradient was used for the HPLC–MS allowing the separation of a number of drugs such as paracetamol, clofibric acid, penicillin V, naproxen, bezafibrate, carbamazepine, diclofenac, ibuprofen and mefenamic acid. A 20 m*M* ammonium acetate solution, pH 5.1 was employed for the separation of clofibric acid, naproxen, bezafibrate, diclofenac, ibuprofen and mefenamic acid by CE–MS. Sample pretreatment was performed by solid-phase extraction (SPE) for HPLC–MS or by a combination of liquid–liquid extraction and SPE for CE–MS. The applicability of both the HPLC–MS and CE–MS method was demonstrated for several river water samples. © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

Besides other micropollutants, drug residues have become a noteworthy contamination factor in surface water during recent years. The excretion of drugs and their metabolites together with improper waste disposal have led to considerable concentrations of various compounds. Even the processing of communal waste water in sewage treatment plants cannot avoid the entry of drugs into surface water because of the high stability of some drug compounds or their metabolites against biological degradation. Finally, these compounds may even enter groundwater as well as drinking water produced from groundwater as recent studies have shown [1–13].

Up to now, drug residue analysis in surface water has mainly been carried out by gas chromatography, usually in combination with mass spectrometric detection, which often requires derivatization [1–10]; only little work has been done on the analysis of these compounds by high-performance liquid chro-

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matography–mass spectrometry (HPLC–MS) [8,9,11–13] and to our knowledge no work on capillary electrophoresis (CE)–MS has been published in this context. Taking into account the acidic or basic properties of a number of drugs, LC and CE in combination with electrospray ionization (ESI) MS or atmospheric pressure chemical ionization (APCI) MS seem to be very suitable for the determination of a number of compounds which are shown in Table 1; the selection of drugs to be analyzed was made in accordance with the total amount sold and the stability against metabolization and degradation. Some of them show either an acidic site (carboxylic group or phenol), a basic site (amide) or both, which makes protonation or deprotonation and hence the detection by MS possible.

Apart from the analytical separation technique, water samples have to be pretreated in order to get rid of matrix components and to enrich the analytes; the usual way to accomplish this aim is to perform a solid-phase extraction (SPE) step employing suitable stationary phases (reversed-phase materials) and conditions. In contrast to drinking water, which contains only little organic carbon [dissolved organic carbon (DOC) about 2 mg/l] surface water often carries a high amount of organic carbon (DOC up to 20 mg/l for the rivers investigated in the present work) in the form of humic acids or similar compounds, making the sample pretreatment more difficult especially when high enrichment factors are aspired.

The aim of the present work was the optimization of sample pretreatment procedures for surface water and a comparison of ESI and APCI interfaces for the combination of LC and MS; furthermore, the applicability of CE–MS as an alternative to HPLC–MS for the determination of drug residues should be demonstrated.

2. Experimental

2.1. Instrumentation and conditions

The liquid chromatographic separations were performed on a HP 1100 HPLC system equipped with a HP 1050 autosampler (Agilent, Palo Alto, CA, USA) employing a YMC ODS-AM column 250×2 mm (YMC, Kyoto, Japan). Using a flow-rate of 150 μl/min the optimized mobile phase was a ternary gradient of a 20 m*M* ammonium acetate solution adjusted to pH 5.5 with 1 *M* acetic acid (A), methanol (B) and water (C) in the following form: 0 min: A–B–C (10:15:75); 3 min: A–B–C (10:15:75); 10 min: A–B–C (10:50:40); 20 min: A–B–C (10:90:0).

A Crystal 310 CE instrument (Thermo CE, Franklin, MA, USA) was employed for CE–MS experiments. Fused-silica capillaries of 50 μm I.D. were obtained from Polymicro Technologies (Phoenix, AZ, USA); new capillaries with a length of 70 cm were conditioned by flushing with 0.1 *M* NaOH followed by water (each for 10 min). Finally, the conditioning procedures were completed by flushing with the CE carrier electrolyte consisting of 20 m*M* ammonium acetate, pH 5.1 for 5 min; prior to each run the capillary was flushed with carrier electrolyte for 3 min.

MS detection was performed on a quadrupole system HP 5989B (Agilent) equipped with a radiofrequency-only hexapole (Analytica of Branford, Branford, CT, USA) using either a pneumatically assisted electrospray ionization interface HP 59987A (Agilent) or an APCI interface (Analytica of Branford) for the combination with the LC instrument. A CE probe was used for CE–MS experiments. The sheath liquid for CE–MS consisted of 2-propanol–water (80:20, v/v) containing 0.1% (v/v) acetic acid for the positive detection mode or 0.1% (v/v) triethylamine for the negative mode and was delivered by a syringe pump (Model 22; Harvard Apparatus, South Natick, MA, USA) at a flow-rate of 4 μl/min. The drying gas flow-rate was 7 l/min for HPLC–MS (nitrogen 5.0 at a temperature of 300°C) and 1.4 l/min for CE–MS (at 150°C). The nebulizing gas (nitrogen 5.0) was kept at a pressure of 550 kPa for HPLC–MS; for CE–MS no spraying gas was applied.

2.2. Chemicals

Ammonium acetate, acetic acid, methanol, 2-propanol and triethylamine were purchased from Merck (Darmstadt, Germany), methyl *tert*.-butyl ether (MTBE) from Fluka (Buchs, Switzerland) and hexane was obtained from Baker (Deventer, The Netherlands). Drug standard materials were purchased from

Table 1
Structures and m/z values of the investigated drugs

Compound	Structure	m/z (positive mode)	m/z (negative mode)
Paracetamol		152.1	150.1
Clofibric acid		–	213.0
Penicillin V		351.1	349.1
Naproxen		231.1	229.1
Bezafibrate		362.1	360.1
Carbamazepine		237.1	–
Diclofenac sodium		296.0	294.0
Ibuprofen		–	205.1
Mefenamic acid		242.1	240.1

Sigma–Aldrich (St. Louis, MO, USA). High-purity water was prepared by a Milli-Q water purification system (Millipore, Milford, MA, USA).

2.3. Pretreatment and enrichment of water samples

For the optimization of the SPE procedure (choice

of stationary phase, pH of the sample) a sample volume of 100 ml together with 100 mg of stationary phase was employed, whereas the analysis of real samples by HPLC–MS was performed using a sample volume of 500 ml and 500 mg stationary phase.

Using the optimized SPE procedure, the samples were brought to pH 2 with concentrated hydrochloric acid and passed through an SPE cartridge (6 ml) packed with 500 mg Bondesil ODS 40 μm (Varian, Palo Alto, CA, USA) conditioned with acetone, methanol and water, pH 2 (one cartridge volume each). The flow-rate was adjusted to approximately 10 ml/min. After the cartridges had been allowed to dry for 30 min, the drugs were eluted using an overall volume of 2 ml methanol. The extract was brought to dryness in a nitrogen stream (purity 4.6) and finally redissolved in 50 μl methanol and diluted with 300 μl water which was then used for injection (100 μl injection volume).

All glassware in contact with either the water sample or the extract was silanized by flushing with a 10% (v/v) solution of dimethyldichlorosilane in toluene, followed by flushing with pure toluene (twice) and methanol (twice). The glass equipment was then placed in a dryer for 3 h at 160°C.

For the determination of drug residues by CE–MS the water samples were pretreated by liquid–liquid extraction prior to SPE. A 500-ml volume of water sample was brought to pH 2 with concentrated hydrochloric acid; after the addition of 50 g sodium sulfate the sample was extracted twice with 25 ml of a mixture of hexane–MTBE (1:1, v/v). The organic phase was re-extracted twice with 50 ml 2 m*M* sodium hydroxide solution, brought to pH 2 with hydrochloric acid and diluted to 250 ml with water, pH 2. The SPE was carried out similar to the procedure described for the HPLC–MS measurements except that the residue was redissolved in 50 μl of a mixture of methanol–carrier electrolyte (80:20, v/v) prior to injection (5 kPa, 0.3 min).

3. Results and discussion

3.1. Optimization of the SPE

Some major problems associated with the SPE of the drugs had to be faced: the SPE conditions had to meet the requirement of a quantitative adsorption to the stationary phase and furthermore the elution and the redissolution may depend on the solubility of the analytes which is rather poor for some of them (especially for mefenamic acid, diclofenac and ibuprofen). Adsorption to glassware during the SPE may also negatively affect the recoveries. In preliminary experiments various stationary phases were investigated for SPE; recoveries were determined with 100 ml standard solutions brought to pH 2 containing 4 μg/l of each drug employing 100 mg cartridges. Among five investigated stationary phases, Bondesil ODS offered the best average recoveries (60%) for the selected analytes and was therefore chosen for further optimization of the SPE, whereas LiChrolut RP 18 (30%), LiChrolut EN (56%), Oasis HLB (47%) and Bond-Elut C_{18}-OH (46%) were excluded from further investigations. The data indicate that among C_{18} silica sorbents an end-capped material with a high percent carbon content yields superior results; the reasons for the lower recoveries obtained with the polymeric sorbents LiChrolut EN and Oasis HLB is not yet fully clear.

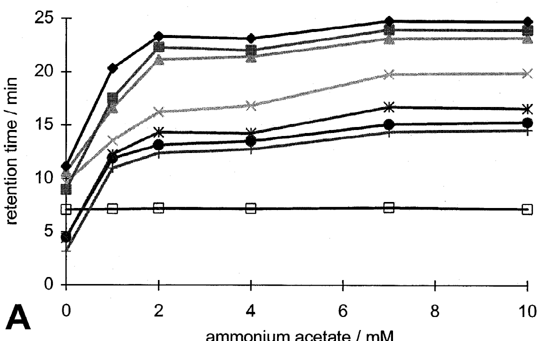
The influence of the sample pH was checked for pH 2, pH 5.5 and pH 8.5 resulting in best recoveries for pH 2 for all analytes. To further improve the recoveries, the redissolution of the analytes after blowing off the solvent of the SPE was facilitated using an organic solvent like methanol first (50 μl) to take up the residue and then diluting the solution with 300 μl water prior to injection.

Another precaution leading to a remarkable improvement of the overall extraction efficiencies was the silanization with dimethyldichlorosilane of the glassware getting in contact with either the water sample or the extract. Finally, after consideration of all the factors influencing the extraction, the following recoveries (and the standard deviations given in parentheses) were obtained for the drugs under investigation using a 500-ml sample volume (and 500 mg of stationary phase): clofibric acid 96.3% (1.2), penicillin V 53.3% (13.3), naproxen 95.7% (0.8), bezafibrate 97.1 (1.0), carbamazepine 98.0% (0.1), diclofenac 83.5% (2.1), ibuprofen 90.2% (1.7), mefenamic acid 43.1% (2.4); paracetamol could not be preconcentrated because of breakthrough in the SPE procedure.

3.2. HPLC–MS determination of drug residues in surface water

In order to obtain reproducible retention times the use of a buffer in the eluent was inevitable, well knowing that electrolytes usually lower the signal intensities due to suppressing effects in the MS interface. In general the employment of electrolytes is limited to volatile compounds such as ammonium formate or acetate, although previous studies showed that also non-volatile organic salts do not necessarily result in a contamination of the MS [14]. Nevertheless, ammonium acetate was preferred in this case because its suppressing effect on the signal is low; additionally, it is well suited as a buffer compound at pH 5.5 which was found as the optimum pH for the separation of paracetamol, clofibric acid, penicillin V, naproxen, bezafibrate, carbamazepine, diclofenac, ibuprofen and mefenamic acid. Concentration of ammonium acetate higher than 2 m*M* in the mobile phase hardly affected the retention times but below 2 m*M* a strong influence could be observed resulting even in a change of the retention order as can be seen in Fig. 1A. An explanation for this behavior may be the low buffering capacity leading to unstable retention times of the mainly acidic analytes. For a robust method a concentration not lower than 2 m*M* seemed to be reasonable but on the other hand an increase in concentration led to a decrease in signal intensity (except for ibuprofen which showed broadened and therefore lower peaks below 2 m*M*) as it is often observed with ESI-MS (see Fig. 1B). As a compromise, a concentration of 2 m*M* ammonium acetate was chosen for all the following experiments.

MS detection was investigated both with an ESI and an APCI interface. These are complementary techniques in HPLC–MS, each showing characteristic features. The fragmentation patterns can be quite different in APCI-MS compared to ESI-MS as was found for naproxen with molecular mass of 230 as an example; using the ESI interface a strong fragmentation due to decarboxylation was observed leading to signals at m/z 185 in both the positive and negative detection mode. Additionally, a fragment with m/z 170 could be detected in the negative ESI mode. In the positive APCI mode only the fragment at m/z 185 was detected at a low intensity but the dominating signal was the ammonium adduct of naproxen at



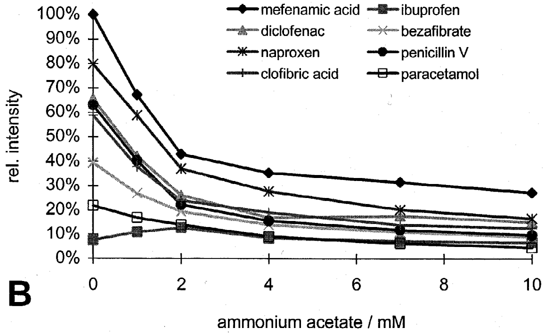


Fig. 1. Influence of the ammonium acetate concentration in the mobile phase on the retention times (A) and the signal intensity (B) of selected drugs in HPLC combined with negative ESI-MS.

m/z 248. By collisionally induced dissociation (CID) experiments, which are performed by increasing the extraction voltage (in the employed instrument also called capillary exit voltage) of the ESI or APCI interface, the fragmentation could be enforced; this technique represents an additional tool to increase the selectivity of ESI (APCI) mass spectrometry by detecting one or two fragments besides the molecular ion in the selected ion monitoring (SIM) mode.

Using either ESI or APCI the detection limits were determined for a signal-to-noise ratio of 3. The results are given in Table 2 for the injected standard solutions. As can be seen, best detection limits were obtained with the ESI interface in the positive ion mode (all below 1 μg/l) except for clofibric acid and ibuprofen which could only be detected in the negative ion mode because of their highly acidic nature, lacking basic sites in the molecule. This rule does not hold for naproxen, apparently also lacking a basic site; nevertheless, this compound could be detected at a m/z value of 231 corresponding to the

Table 2
Comparison of the detection limits for selected drugs using either an ESI or an APCI interface in both the negative and positive detection modes (for signal-to-noise ratios of 3, in μg/l for an injection volume of 100 μl)

Compound	Detection limit (μg/l)			
	ESI negative	ESI positive	APCI negative	APCI positive
Paracetamol	3.7	0.27	20.0	1.5
Clofibric acid	1.0	–	1.1	–
Penicillin V	1.3	0.85	16.6	12.5
Naproxen	2.3	0.65	3.5	7.0
Bezafibrate	0.7	0.24	1.8	2.3
Carbamazepine	–	0.05	–	0.4
Diclofenac	0.4	0.29	0.6	3.6
Ibuprofen	0.8	–	2.2	–
Mefenamic acid	0.2	0.14	0.2	0.3

protonated molecule. On the other hand, carbamazepine which is the most basic compound among the selected drugs, cannot be detected in the negative ion mode but yields an excellent detection limit (0.05 μg/l) in the positive ESI mode. Generally, it holds that the ESI interface is more efficient for the drugs under investigation compared to the APCI interface resulting in a higher sensitivity. Table 3 gives the linearity data and detection limits for water samples using the detection mode which offers the optimum detection limit. For the analysis of real surface water samples the ESI interface was chosen in the positive ion mode (except for clofibric acid and ibuprofen which were detected in the negative ESI mode). A standard chromatogram is shown in Fig. 2, acquired in the SIM mode at the m/z value of the molecular ions.

A volume of 500 ml water sample was treated as

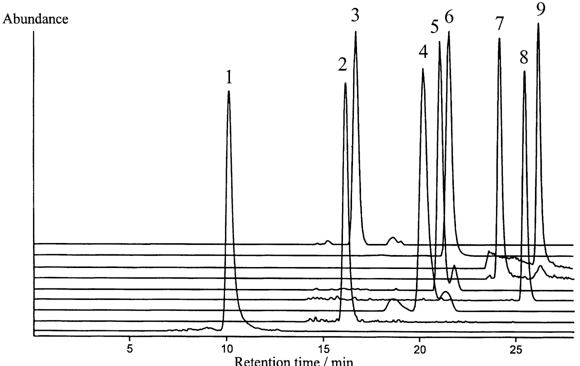


Fig. 2. Extracted ion chromatogram of a standard mixture. Column: YMC ODS AM (250×2 mm). Mobile phase: 2 m*M* ammonium acetate, pH 5.5, methanol gradient. Injection volume: 100 μl. Peaks: 1 = paracetamol, 2 = clofibric acid, 3 = penicillin V, 4 = naproxen, 5 = bezafibrate, 6 = carbamazepine, 7 = diclofenac, 8 = ibuprofen, 9 = mefenamic acid (20 μg/l each).

Table 3
Linearity data and detection limits for selected drugs analyzed by HPLC–MS (corresponding to the MS detection mode offering the best detection limits)

Compound	Mode	Linear range (μg/l)	Correlation coefficient	Detection limit (injected concentration) (μg/l)	Detection limit in sample (ng/l)
Paracetamol	ESI positive	0.3–850	0.9999	0.3	–[a]
Clofibric acid	ESI negative	1.0–600	0.9999	1.0	0.7
Penicillin V	ESI positive	0.9–500	0.9995	0.9	1.1
Naproxen	ESI positive	0.7–750	1.0000	0.7	0.5
Bezafibrate	ESI positive	0.2–650	0.9999	0.2	0.2
Carbamazepine	ESI positive	0.05–500	0.9997	0.05	0.04
Diclofenac	ESI positive	0.3–750	1.0000	0.3	0.3
Ibuprofen	ESI negative	0.8–450	0.9996	0.8	0.6
Mefenamic acid	ESI positive	0.1–500	1.0000	0.1	0.2

[a] Paracetamol could not be extracted by the present SPE method.

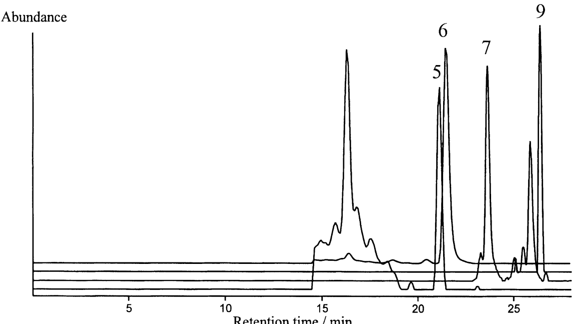


Fig. 3. Extracted ion chromatogram of a real sample after preconcentration by SPE. Conditions and peak assignment as in Fig. 2. Approximate concentrations between 1.8 and 23 ng/l.

described in the Experimental section. The concentrated extract was transferred into an autosampler vial and injected twice using an injection volume of 100 μl. Additionally, one run was acquired using a capillary exit voltage of 170 V for a CID experiment to ensure a correct peak assignment; in this case, the following fragment ions were used: *m/z* 160 for penicillin, *m/z* 185 and 170 for naproxen, *m/z* 192 for carbamazepine, *m/z* 250 and 215 for diclofenac, *m/z* 224 for mefenamic acid. In the case of clofibric acid and bezfibrate the ^{37}Cl isotope was used to confirm the identity (this was also done for diclofenac in addition to the CID run). Iboprofen did not yield a fragment ion and does not contain an isotope suited for confirmation, so that peak assignment could only be done by its retention time. A chromatogram of a real sample is shown in Fig. 3. In four analyzed samples some drugs could be found at a concentration between 1.6 and 133 ng/l; each sample was analyzed twice, the averaged results of the analysis are given in Table 4. Components of the matrix eluted well before the analytes (visualized by UV detection prior to the MS detection) so that they do not affect the ionization efficiency of the ESI interface. This absence of interferences of the matrix on the ionization was also checked for a typical river sample by standard addition experiments.

3.3. CE–MS determination of drug residues in surface water

For the CE–MS analysis the carrier electrolyte had to be optimized with respect to both separation selectivity and compatibility with the MS interface. The analytes were limited to those that showed pK_a values allowing the deprotonation and hence the separation under typical pH conditions used in CE–MS. Furthermore, the efforts for sample pretreatment had to be extended because of a higher enrichment factor necessary for CE–MS compared to HPLC–MS.

Ammonium acetate at a concentration of 20 m*M* was generally employed as the carrier electrolyte; the pH was adjusted with 1 *M* acetic acid in a range between 4 and 6.6 in order to optimize the separation of the drugs. Fig. 4 shows the dependence of the mobilities on the pH; the analytes may be divided into two groups: one group (consisting of ibuprofen, naproxen, diclofenac and mefenamic acid) showing a strong increase of the mobility with the pH and a second group (bezafibrate, penicillin V, clofibric acid) showing only little influence of the pH on the mobilities. This behavior can be attributed to the different pK_a values of the investigated drugs: Those belonging to the first group exhibit pK_a values between 4.2 and 4.6 [15] while the drugs of the second group show pK_a values between 2.8 (penicillin V [16]) and approximately 3.3 (clofibric acid and bezafibrate, in analogy to chlorophenoxyacetic acid [17]). As a result the drugs of the first group undergo increasing deprotonation with increasing pH whereas

Table 4
Results of drug residues analysis by HPLC–MS in samples from rivers in Upper Austria (in ng/l)

Compound	Content (ng/l)			
	"Feldaist 4/I"	"Trattnach 2"	"Gusen 4/I"	"Grünbach"
Bezafibrate	12.5	1.8	8.2	1.6
Carbamazepine	67.9	23.0	133.1	26.4
Diclofenac	19.7	20.0	15.8	35.5
Mefenamic acid	10.9	10.3	13.6	<0.4

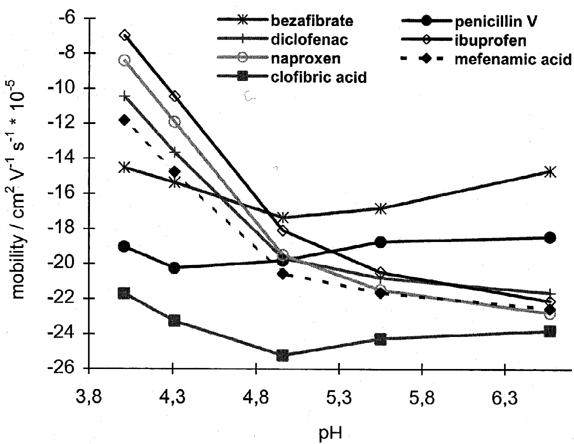


Fig. 4. Dependence of the mobilities of the selected drugs on the pH. Carrier electrolyte: 20 m*M* ammonium acetate, pH adjusted with 1 *M* acetic acid. Voltage: 20 kV. Injection: 5 kPa, 0.3 min.

those of the second group are deprotonated in the whole pH range investigated, which results in roughly constant mobilities. As can be seen from Fig. 4 the separation of the analytes would be best at a pH of 4, but at such a low pH clofibric acid reaches the MS only after 42 min due to its high electrophoretic mobility directed against the electroosmotic flow (EOF). In order to keep the run time below 20 min, a pH of 5.1 was chosen (resulting in a somewhat lower resolution between the analytes). With MS as a very selective detector, peak overlapping is not a real problem as long as the overlapping analytes have different m/z values and there is no interference with matrix components; these requirements were fulfilled in the present case and therefore a carrier electrolyte containing 20 m*M* ammonium acetate adjusted to pH 5.1 with acetic acid was used for the determination of the detection limits which were between 27 and 93 μg/l (see Table 5) for standard solutions without the pretreatment procedure necessary for real water samples.

Because of the poorer detection limits of CE–MS compared to HPLC–MS a higher enrichment factor was necessary for the determination of drug residues in surface water by CE–MS. Using a sample volume of 500 ml, the eluate of the SPE procedure can be brought to dryness and redissolved in 50 μl methanol–carrier electrolyte (80:20, v/v), thus giving an enrichment factor of 10 000. The problem of such a rather high preconcentration was the fact that matrix components of the sample were also strongly enriched which resulted in electropherograms not suited for quantitation by CE–MS due to serious disturbance of the peak shapes (the electrospray ionization itself was not affected). As a way around the problem, a sample clean-up by liquid–liquid extraction (LLE) prior to the SPE was investigated. The extraction was performed using a mixture of MTBE and hexane as the extraction solvent after the water sample had been acidified with hydrochloric acid (see Experimental section). The organic phase was re-extracted with a 2 m*M* sodium hydroxide solution which was then brought to pH 2 and diluted to 250 ml with Milli-Q water, pH 2. This dilution step was necessary in order to lower the percentage of organic solvent being dissolved in the aqueous phase which otherwise would lower the extraction efficiencies due to an undesirably high elution strength in the SPE procedure.

Table 5
Detection limits for selected drugs analyzed by CE–MS in both the negative and positive detection modes

Compound	Detection limit (injected concentration) (μg/l)	
	ESI positive	ESI negative
Clofibric acid	–	60
Penicillin V	59	134
Naproxen	18	93
Bezafibrate	33	27
Diclofenac	33	66
Ibuprofen	–	47
Mefenamic acid	25	27

Employing this combination of LLE and SPE, a sample pretreatment procedure was developed allowing the enrichment of the water sample by a factor of 10 000 and the compatibility with CE as well. The detection limits were between 4.8 and 19 ng/l except for mefenamic acid and penicillin V which could not be extracted by the described procedure. In general, the recoveries of the other analytes were between 63 and 80%, unfortunately with rather high standard deviations (between 16 and 30%). Nevertheless, the analysis of several real samples demonstrated the applicability of CE–MS as a complementary technique to HPLC–MS. The results given in Table 6 were obtained by external calibration (standard matrix was Milli-Q water) and for one sample the peaks

Table 6
Results of drug residues analysis by CE–MS in samples from rivers in Upper Austria (in ng/l)

Compound	Content (ng/l)				
	"Feldaist 3"	"Feldaist 4/II"	"Gusen 2"	"Gusen 3"	"Gusen 4/II"
Bezafibrate	4.8	20.1	20.4	<4.8	10.5
Naproxen	<13	<13	<13	<13	38.2
Diclofenac	28.3	392.1	163.5	85.0	161.4
Clofibric acid	24.8	43.5	24.4	19.3	41.8

were also confirmed by standard addition. There was no significant difference between the results obtained by external standards and by standard addition. The samples "Feldaist 4/II" and "Gusen 4/II" were taken at the some places as "Feldaist 4/I" and "Gusen 4/I" (analyzed by HPLC–MS) but at different times of the year which is the reason for differences in the results obtained by HPLC–MS and CE–MS.

4. Conclusions

HPLC–MS is a powerful technique for the determination of drug residues in water offering both a high selectivity and good detection limits between 0.05 and 1 μg/l in the solution injected; with a sample pretreatment procedure based on SPE before the LC separation, detection limits in the sample of about 1 ng/l and below can be achieved. The applicability of the technique could be demonstrated for the analysis of several river water samples; concentrations between approximately 2 and 130 ng/l of bezafibrate, carbamazepine, diclofenac and mefenamic acid were found. These data are similar to the concentrations found in other rivers in Europe; obviously, traces of pharmaceutical drugs are ubiquitous in the aquatic environment. It is unlikely that the concentrations present in surface waters may have acute toxic affects on aquatic organisms. Nevertheless, the monitoring of drug residues is certainly an issue for the future in order to avoid possible residues in water systems used for drinking water supply; regardless of any toxicity, the presence of drug residues in drinking water should be completely avoided.

CE–MS proved to be a useful alternative to HPLC–MS, although the sample pretreatment had to be expanded by an LLE prior to the SPE. Because of rather high standard deviations of the recoveries due to the combination of three extraction steps, a method based on standard addition is recommended for quantitation. As expected the detection limits for the CE–MS method are poorer than the detection limits obtained by HPLC–MS namely between 27 and 93 μg/l for standard injections which resulted in detection limits in the samples between 4.8 and 19 ng/l; Nevertheless, CE–MS may be a useful technique for the confirmation of questionable results obtained by HPLC–MS.

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