Journal of Chromatography A, 1218 (2011) 603–618

Contents lists available at ScienceDirect

Journal of Chromatography A

journal homepage: www.elsevier.com/locate/chroma

Review

Current approaches to trace analysis of pharmaceuticals and personal care products in the environment

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ARTICLE INFO

Article history:
Available online 23 October 2010

Keywords:
Pharmaceuticals
Personal care products
Environmental analysis
Review

ABSTRACT

A large number of xenobiotics including pharmaceuticals and personal care products are continuously released into the environment. Effluents from sewage treatment plants are well known to be the major source for introduction of pharmaceuticals and personal care products into the aquatic system. In recent years, reliable methods have been established for residue analysis of these pollutants down to low ng/L levels. In this review, the different approaches to their trace determination are reviewed with special attention being paid to sample preparation procedures, state-of-the-art high-performance separation methods hyphenated with mass spectrometry, and immunochemical methods.

Contents

1. Introduction

Nowadays it is a well-accepted fact that the use of a large number of xenobiotics in various areas of our modern life inevitably also leads to the release of them into the environment and their occurrence in water or soil. The public might get the impression that in recent years the situation has become dramatically worse, since a range of xenobiotics has been detected in the environment for the first time. This impression is certainly wrong, because many of the compounds nowadays reported to be present in water or soil may have been there already for decades, but went unnoticed till recent years due to the lack of analytical methods exhibiting sufficiently low detection limits. As a consequence of the tremendous progress in analytical techniques for trace analysis it is not surprising that a

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doi:10.1016/j.chroma.2010.10.040

still increasing number of xenobiotics can be detected and quantitatively measured in environmental samples. In various cases it may still be an open question whether they act as contaminants with or without ecological consequences. In any case, an evaluation of the impact of xenobiotics on the environment requires the availability of reliable data so that there is a demand for adequate new analytical methods that can be the basis for extensive monitoring programs.

In recent years, major attention has been paid to the presence of pharmaceuticals and substances used in personal care products (PPCPs) in the aquatic environment. It is an obvious fact that these compounds are released into municipal sewage systems, and it is also well-known that – depending on their chemical structure – many of them can even survive the passage through sewage treatment plants, which have been identified as the most important sources for introduction of PPCPs into surface water systems. Various PPCPs may also show a strong tendency to sorption in sewage sludge, which is used to some extent for agricultural purposes so that another way of introduction into soil and eventually into water is established. Besides this path, pharmaceuticals employed in veterinary medicine may be transported into soil via manure, or may find a direct way into the aquatic system when used in fish farms.

One of the first papers published on pharmaceuticals in sewage treatment plant effluents was published already in 1977 by Hignite and Azarnoff [1], who found clofibric acid (a metabolite of a widely used hypolipidemic drug) as well as salicylic acid (a metabolite of aspirin) at low ppb levels in this type of samples. Somewhat surprisingly, at that time the paper did not trigger a lot of additional research within the scientific community of analytical chemists working in the field of environmental sciences. Only in 1990 this topic started to attract major attention when in the course of pesticide residue analysis of drinking water and ground water in Germany an unknown compound turned up that had an analogous structure as phenoxyalkanoic acid herbicides. It was identified as clofibric acid and it soon became evident that this compound is a widespread contaminant in water samples at concentration levels similar to pesticides [2,3]. During the following years the field of PPCPs in the environment virtually exploded, and data about a wide range of pharmaceuticals belonging to quite different chemical classes became available from all over the world [4–17]. It is interesting to know that a paper published by Kolpin et al. [18] reporting the first nationwide reconnaissance of the occurrence of pharmaceuticals, hormones, and other organic wastewater contaminants (OWCs) in water resources of the U.S.A. received almost 1700 citation up to now. This clearly demonstrates the importance of this topic for the scientific community. The significant progress of research in this area is also underlined by the existence of monographs dealing with sources, fate, effects and risks of pharmaceuticals [19–22].

Fast progress in the development of analytical methods for pharmaceuticals in the aqueous environment was possible due to extensive existing expertise in pesticide residue analysis, although at the beginning of residue analysis of PCCPs GC–MS techniques still dominated which were less suited for several classes of PCCPs. Nevertheless, various sample pretreatment strategies that had been successfully applied to trace analysis of pesticides could be directly used for residues of pharmaceuticals. Therefore, methods had been soon available to start monitoring programs, such as a comprehensive study in Germany undertaken by the "Bund/Länderausschuss für Chemikaliensicherheit (BLAC)" (the final report released in 2003 can be found on the web [23]). Although this fact might lead to the impression that residue analysis of pharmaceuticals in environmental samples has become a routine issue quite a while ago, this is not fully true. Research work done in recent years has resulted in refined methods for various different classes of PPCPs, in new multimethods, and in lower detection limits as well as simpler sample preparation procedures due to significantly improved mass spectrometers (especially various types of tandem mass spectrometers) used as detectors for chromatographic separations.

Nowadays it is assumed that the concentrations generally found in surface water in the low ng/L range do not necessarily represent a serious threat to drinking water quality. On the other hand, the impact of the constant presence of low concentrations of PPCPs on the ecosystem is not yet fully clear. Especially the introduction of antibiotics into the environment has raised some concern regarding the development of bacteria resistant to antibiotics, and has lead to major research on this issue (see for example the reviews in [24,25]. In recent years, various other classes of PPCPs have been studied with respect to ecotoxicity, but ecotoxicological aspects are beyond the scope of this review paper and are not discussed in detail.

A current guideline on the environmental risk assessment of medicinal products for human use released by the European Medicines Agency states that environmental fate and effect analysis must be performed if the predicted environmental concentration in surface water is higher than 10 ng/L. This guideline clearly indicates that the levels of pharmaceuticals nowadays found in the aquatic environment due to the progress in sophisticated analytical instrumentation may indeed be relevant with respect to possible impacts on the ecosystems. In this context reliable analytical data are of utmost importance to do a proper environmental risk assessment. This justifies the still ongoing flow of publications dealing with further method development for trace analysis of PPCPs.

The present paper provides an overview on the various approaches used for determination of PPCPs in environmental samples and in samples from sewage treatment plants. It is certainly not intended to give a comprehensive compilation of papers published up to now in the literature, because various in-depth reviews dealing with single aspects of PPCPs have already been published in recent years. Instead, the paper gives a balanced overview on strategies and procedures useful for trace analysis of PPCPs, and points out the current trends in this field.

2. Pharmaceuticals in water samples

2.1. Sampling and passive samplers

Sampling procedures for residue analysis of pharmaceuticals in the aquatic environment are in most cases the same as those used for monitoring any other organic pollutants and generally consist in the periodic collection of grab samples. Obviously, the results from such approaches reflect the concentrations at the specific time of sampling but cannot take into account fluctuations with time and therefore cannot always yield information about the average loads of contaminants. An alternative is the use of passive samplers which may be deployed over periods of days to weeks so that time-weighted average (TWA) concentrations can be obtained [26].

A passive sampler optimized for sampling of pharmaceuticals from water is the Polar Organic Chemical Integrative Sampler (POCIS) developed by Petty et al. [27]. Basically, this device consists of a solid-phase extraction sorbent (most often Oasis HLB, a polymer frequently used for solid-phase extraction of pharmaceuticals, see Section 2.2.1) within two thin polyethersulfone membranes in a sandwich-type set-up. After deploying the sampler to the water for a defined time, the analytes are extracted from the sorbent by a suitable solvent and analyzed by chromatography or other analytical techniques. Assuming that the sorbent does not approach the equilibrium with the water, the amount m_s of analyte in the sorbent will depend on the time-weighted average concentration c_w of the analyte in the water, on the deployment time t, and on the sampling rate R which corresponds to the volume of water cleared

of analyte per unit of exposure time:

$$m = c_w R t \quad (1)$$

The POCIS device has been used successfully for sampling of a range of pharmaceuticals, illicit drugs, and personal care products [28–32]. According to Eq. (1), the values of the sampling rates R must be known for the different analytes in order to be able to perform quantitative analysis. Often R is determined by calibration under laboratory conditions, although it must be clear that they are influenced by changes in water temperature or salinity [33].

The use of the POCIS device is obviously not just a sampling step but also includes some sort of sample preparation similar to other sorptive extraction procedures used in the laboratory for grab samples (see Section 2.2.2).

2.2. Sample preparation and preconcentration

Many procedures published in the existing literature for trace analysis of pharmaceuticals in water samples suggest a filtration of the sample prior to the preconcentration procedure. Surprisingly, not much attention has been paid to residues of pharmaceuticals bound to suspended particulate material in water samples (obviously, filtration of the sample leads to the loss of this fraction for the subsequent analysis). Himmelsbach et al. [34] have done some investigations on this topic and have collected suspended particulate material from river water by deploying a sedimentation sampler for a period of several days. Afterwards, the particulate material was extracted and analyzed for traces of pharmaceuticals. To a small extent, hydrophobic compounds like mefenamic acid were indeed found to be bound to suspended material at μg/kg levels. The practice of filtering samples may be problematic when estimating mass loadings and removal efficiencies of pharmaceuticals in wastewater treatment plants based on data from filtered samples. This issue has most recently been put to discussion by Deo and Halden [35,36].

2.2.1. Sample preconcentration by solid-phase extraction

Pharmaceuticals of reasonable hydrophobicity can easily be preconcentrated by SPE using any reversed-phase material such as alkyl-modified silica or poly(styrene-divinylbenzene). Proper adjustment of sample pH may be necessary to avoid deprotonation of acidic compounds or protonation of basic compounds and to enhance extraction efficiency of the analytes. Unfortunately, a range of pharmaceuticals that may turn up in environmental samples have quite polar properties and may become difficult to be enriched on traditional reversed-phase materials like alkyl-modified silica. In this case, mixed-mode materials exhibiting both hydrophobic and ion-exchange properties have become a valuable alternative. In recent years, new polymeric sorbents that improve the retention of polar compounds by novel functional groups in the polymeric structure (resulting in a hydrophilic–hydrophobic balance material) are getting more and more popular. Some of these new materials have turned out to be well suited for multiclass analysis of pharmaceuticals in water samples even without adjusting the pH of the sample. Nowadays, one of the most widely used sorbent is a copolymer of divinylbenzene and vinylpyrrolidone, which has been commercialized under the trade name Oasis HLB by Waters. It has become the prime sorbent for multiresidue methods of pharmaceuticals and can be considered as first choice in this application area. Not surprisingly, this type of SPE material has recently been adopted for EPA Method 1694 [37] which deals with residue analysis of more than 70 pharmaceuticals in environmental samples. Although Oasis HLB or the mixed mode sorbents based on Oasis HLB and containing ion-exchange groups (such as Oasis MCX and Oasis WCX containing strong and weak cation exchange groups, and Oasis MAX and WAX containing strong and weak anion exchange groups) represent the state-of-the-art for SPE of pharmaceuticals in water sample, there may be a few other hydrophilic–hydrophobic balance polymeric materials exhibiting similar properties, such as the Strata-X (a polydivinylbenzene resin containing piperidone groups) manufactured by Phenomenex [38,39], or other materials with proprietary chemistry for improving the universal performance of the sorbent.

It would be beyond the scope of this review to try to give a comprehensive compilation of SPE extraction procedures described so far for pharmaceuticals in water samples. Therefore, only a selection of recently published multiclass methods that can be used for simultaneous preconcentration of pharmaceuticals with different chemical structures is summarized in Table 1.

Despite the publication of various multiclass SPE procedures in the recent literature, it is just fair to mention that there are still various classes of pharmaceuticals that cannot be enriched in a completely satisfactory way, even when using latest SPE materials. As a typical example iodinated X-ray contrast media can be mentioned, that may yield recoveries of far less than 100% due to their polar properties (see [53] for a review). Therefore, some efforts have been made in such cases to avoid SPE and to do a direct injection of the sample. This could be accomplished for iodinated X-ray contrast media using highly sensitive inductively coupled plasma MS as detector after HPLC [54], but even advanced electrospray-ionization MS technologies enabled the direct analysis without preconcentration [55]. It may become a general trend in the future to widen the use of direct injection methods and to fully avoid time- and labour-intensive preconcentration procedures.

The deficiencies of traditional reversed phase SPE materials with respect to preconcentration of polar analytes have repeatedly triggered research on novel sorbent. In this context one should mention the development of hypercrosslinked polymers with partly hydrophilic character [56,57] that have been claimed to outperform other polymeric sorbents commonly used.

The problem of poor recovery of polar analytes during SPE on reversed-phase materials may be overcome by sorbents functioning on the base of molecular recognition. Such materials are certainly not attractive for multiclass analysis, but may provide the advantage that analytes can be extracted from very complex matrices with a minimum of co-extracted matrix components. Especially molecularly imprinted polymers (MIPs) have been used for a few applications, since their synthesis and the tailoring to certain analytes is relatively easy. Table 2 lists MIPs so far used for SPE enrichment of pharmaceuticals from water samples and summarizes the conditions for sample loading and elution.

SPE of pharmaceuticals is generally done in an off-line mode prior to the chromatographic analysis step. Nevertheless, the technique is well-suited of procedures coupled on-line with an HPLC system, which allows a high degree of automation. In the simplest case, the SPE cartridge can be installed in the injection valve instead of the injection loop and the preconcentrated analytes are directly eluted onto the analytical column. A disadvantage with respect to unattended operation is the fact that the SPE cartridge may get contaminated by matrix components during prolonged use and thereby may even suffer from decreased retention efficiency. Therefore, fully automated SPE procedures with single-use cartridges have been realized using commercially available instrumentation such as the Symbiosis™ system manufactured by Spark. This robotic system employs disposable extraction cartridges that are placed online with the chromatographic system after the preconcentration step (for a recent review on on-line SPE see [65]). Trenholm at al. [66] have used automated on-line SPE for pharmaceuticals in water samples and have compared the performance

Table 1
Generic SPE procedures for pharmaceuticals in water samples.

Analyte	Matrix	SPE material	Sample volume	Enrichment factor	Reference
29 pharmaceutical compounds including analgesics and anti-inflammatories, lipid regulating agents, cholesterol lowering statin agents, psychiatric drugs, anti-ulcer agents, histamine H2 receptor antagonist, antibiotics, and β-blockers	River water, waste water	Oasis HLB	100–500 mL	100–500	[40]
16 pharmaceuticals including anti-epileptics, anti-inflammatories, analgesics, antidepressants, β-blockers, antibiotics, and an anti-ulcer drug	Hospital waste water	Oasis HLB	100 mL	50	[41]
20 pharmaceuticals including analgesics and anti-inflammatories, lipid regulators, psychiatric drugs, anti-histaminics, anti-ulcer agent, antibiotics and β-blockers	Surface water, waste water	Oasis HLB	100–500 mL	100–500	[42]
54 analytes including analgesic, anti-inflammatories, antibiotics, antiepileptics, beta-adrenoceptor blocking drugs, lipid regulating agents, etc.; personal care products (sunscreen agents, preservatives, disinfectant/antiseptics); illicit drugs (amphetamine, cocaine, benzoylecgonine)	Surface water, waste water (acidified)	Oasis MCX	250–1000 mL	500–2000	[43]
38 pharmaceuticals and 10 of their metabolites, 6 pesticides, and 2 disinfectants	Waste water	Oasis HLB	200 mL	100	[44]
18 pharmaceuticals including lipid lowering agents, analgesics, anti-inflammatories, anticoagulants, antipyretics, cytostatics, antiepileptics, antidepressants, tranquilizers	Waste water, water from water recycling plants	Strata X	250–500 mL	500–1000	[39]
48 pharmaceuticals and 6 metabolites	Waste water, surface water	Oasis MCX	500 mL	1000	[45]
20 acidic, neutral and basic pharmaceuticals	Waste water, surface water	Oasis HLB	100 mL	100	[46]
7 pharmaceuticals belonging to six different pharmacological classes	Estuarine water	Oasis HLB	2000 mL	5000	[47]
15 basic, neutral and acidic pharmaceuticals	Waste water (acidified)	Oasis MCX and MAX in series	25–50 mL	50–100	[48]
53 analytes including analgesics, anti-inflammatories, lipid regulators, β-blockers, antiepileptics, psychiatrics, bronchodilatadors, acidic herbicides, UV filters, insect repellents, organophosphorous flame retardants, and a bactericide	Tap water, surface water, waste water	Oasis HLB	200–500 mL	200–500	[49]
35 analytes including pharmaceuticals, pesticides, perfluorinated compounds, benzotriazoles, hormones, and endocrine disrupters	Surface water	Oasis HLB	400 mL	800	[50]
59 selected organic compounds, including pharmaceuticals, antibiotics, pesticides, perfluorinated acids, benzotriazoles, hormones, alkylphenolics, caffeine, diethyltoluamide, and triclosan	Ground water	Oasis HLB	950	1900	[51]
70 EPA priority pharmaceuticals	Drinking water, surface water, waste water	Oasis HLB	200	400	[52]

with conventional off-line SPE. It was demonstrated that the on-line approach benefits from smaller sample volumes, smaller volumes of organic solvents for elution, shorter analysis time, and less costs, whereby detection limits of off-line and on-line SPE were quite similar.

A quite novel approach to on-line SPE with renewable sorbents has been described by Quintana et al. [67] exploiting the bead injection concept. The technique includes the automated packing of small amounts of sorbent (<5 mg) into a microdevice and the automated withdrawal after single use. Its potential has been

Table 2
Applications of MIPs for SPE enrichment of pharmaceuticals from water samples.

Analyte	MIP material	Sample loading	Elution	Reference
β-Blockers	25 mg commercially available MIP4SPE™–β-blockers	25 mL, neutral pH	2 × 1 mL methanol containing 10% acetic acid, 2 × 1 mL methanol	[58]
Diclofenac	100 mg poly(2-vinylpyridine-ethylene glycol dimethacrylate)	200 mL, no pH adjustment	3 mL dichloromethane/acetonitrile (94:6, v/v)	[59]
Carbamazepine	200 mg poly(methacrylic acid-divinylbenzene)	100 mL, adjusted to pH 11	5 mL methanol	[60]
Fluoroquinolones	150 mg poly(metacrylamide-ethylene glycol dimethacrylate)	100 mL adjusted to pH 7.5	1 mL methanol containing 1% trifluoroacetic acid	[61]
Non-steroidal anti-inflammatory drugs, clofibric acid	25 mg commercially available SupelMIP-NSAIDs	25 mL adjusted to pH 3	2 × 0.9 mL acetone/methanol (20:80) containing 1% acetic acid	[62]
Antiepileptics (cyclobarbital, phenobarbital, amobarbital and phenytoin)	Poly(4-vinylpyridine-ethylene glycol dimethacrylate) packed into pretreatment column coupled on-line with HPLC	50 mL, no pH adjustment	Backflush using 2 mM ammonium acetate–acetonitrile (60:40, v/v)	[63]
Antidepressants	25 mg SupelMIP™ antidepressant	25–200 mL, neutral pH	4 × 1 mL methanol containing 10% acetic acid	[64]

investigated for PPCPs in surface water and waste water samples [67,68].

2.2.2. Sample preconcentration by sorptive extraction

Sorptive extraction is based on establishing a single partitioning equilibrium of analytes between the aqueous sample and a solid sorbent. It includes solid-phase microextraction (SPME), stir-bar sorptive extraction (SBSE), and several related variants. Originally, these techniques were based on polydimethylsiloxane (PDMS) as material for trapping trace analytes from a water sample, but some alternative sorptive materials have recently become commercially available for SPME, such as polyacrylates, copolymers of PDMS with divinylbenzene, copolymers of polyethylene glycol with divinylbenzene, and mixtures of carbon-based materials with PDMS or divinylbenzene.

When a partition equilibrium of the analytes between the aqueous phase and the sorbent is established, the amount of an analyte in the sorbent can be easily calculated by using the law of conservation of mass and expressed in the following way [69]:

$$n = \frac{K_e V_e V_s c_s^{\circ}}{K_e V_e + V_s} \quad (2)$$

n is the amount of analyte in the sorbent after establishing the partition equilibrium, V_e is the volume of the sorbent, V_s is the volume of the sample, $c_s{}^{\circ}$ is the original concentration of the analyte in the sample, and K_e is the partition coefficient.

Eq. (2) does not take into account possible additional partition equilibria of analytes between the aqueous phase and suspended particles or dissolved organic materials. On the other hand, for high sample volumes the concentrations of the analytes in the aqueous phase remain practically unchanged during sorptive extraction so that any interactions of analytes with suspended particles or dissolved organic material are not disturbed. Thereby, a selective determination of the concentration of the free analyte in the sample becomes possible.

In SPME, the sorbent is present as a coating on a fiber so that the volume of sorbent is quite small. This may lead to problems with the sensitivity of the technique. In case of SBSE, a stir bar coated with the sorbent (commercialized under the trade name Twister by Gerstel), or the sorbent in the form of a rod is used, resulting in a much higher volume of the extraction phase. Although this increased volume has often been claimed the reason for better sensitivity of SBSE, it should be taken into account that the diffusion of analytes within the sorbent may be quite slow so that only the outer layer of the sorbent contributes significantly to the extraction efficiency. Therefore, the increased sensitivity of SBSE in comparison with SPME may be primarily due to the larger surface rather than to the increased volume of the sorbent. Although SBSE generally leads to lower detection limits than SPME, it has to be taken into account that up to now the only commercially available material for SBSE is polydimethylsiloxane (PDMS), whereas fiber coatings for SPME include additional materials as mentioned above besides PDMS. Therefore, SPME may perform better for polar analytes than stir bars coated with PDMS. Nevertheless, SBSE still seems to be the preferred option for residue analysis of PPCPs, so that in the following discussion only SBSE procedures will be included.

A few papers have been published on SBSE followed by liquid desorption using an organic solvent prior to GC with large volume injection (see for example [70]) or prior to HPLC (see Section 5 for applications in the area of personal care products). From the practical point of view, a more attractive approach is the thermal desorption of the analytes in combination with GC. The most widely used sorbent compatible with thermodesorption GC is PDMS, as it is sufficiently stable under the conditions of thermodesorption (and the only material commercially available for SBSE). Besides the problem of poor extraction efficiency for less hydrophobic pharmaceuticals, many of them are not suited for GC analysis. A way around this problem with polar and/or thermally labile analytes may be the use of derivatization, which can be done in the sample prior to the SBSE step or on the sorbent after the extraction. The former approach requires derivatization reagents that are compatible with aqueous conditions. Among water-compatible reagents, alkylchloroformates are attractive reagents for phenols, amines or carboxylic acids and could be successfully employed for determination of the antidepressant fluoxetine in surface water down to the mid pg/L range [71] or to acidic drugs like naproxen and ketoprofen [72]. Kawaguchi et al. used derivatization with acetic acid anhydride prior to extraction for trace determination of the synthetic estrogen 17α-ethinylestradiol [73]. Derivatization after the extraction may be carried out conveniently during the thermodesorption step by addition of a small amount of derivatization reagent such as a silylation reagent into the thermodesorption tube. This approach may be attractive to achieve volatile derivatives for the GC step but does not overcome the problem of poor recovery of the extraction step if the non-derivatized analyte is too polar. Therefore, the approach may be less suited for multi-residue analysis of pharmaceuticals.

2.2.3. Sample preconcentration by liquid–liquid extraction

The importance of traditional liquid–liquid extraction procedures is quite limited in currently used methods for residue analysis of PPCPs. Nevertheless, some liquid-phase microextraction techniques such as membrane-supported liquid–liquid extraction [74] do have a potential for preconcentration of PPCPs from water samples. Pedersen-Bjergaard and coworkers reported the extraction of basic antidepressants from 1.1 L sample (pH adjusted to alkaline conditions) through approximately 50 μL of dihexyl ether immobilized in the pores of a porous hollow fiber into 20 μL of an acidic aqueous acceptor solution, thereby achieving a 25,000-fold preconcentration of the analytes [75,76]. In an analogous way, Ramos et al. [77] were able to extracted acidic pharmaceuticals from acidified waste waters through diethyl ether into an alkaline aqueous acceptor solution. The low volume of extraction solvent required in liquid-phase microextraction reduces the hazards of organic solvents used in traditional liquid–liquid extraction and allows high preconcentration factors. Despite these advantages, the importance of the technique in comparison with solid-phase extraction is still somewhat limited.

2.3. HPLC–MS procedures

The increasing availability of columns packed with sub 2 μm particles together with improved hardware allowing the operation at considerably higher pressures than traditional instrumentation has led to significantly improved separations of PPCPs in complex matrices. Although it has been demonstrated that HPLC with diode array UV absorbance and fluorescence detection may be a low-cost technology suited in some cases for pharmaceuticals in surface and waste water (see for example [78,79]), the hyphenation with MS detection is state-of-the-art and out of question for trace analysis of PPCPs. Single quadrupole (Q) instruments were used when trace analysis of PPCPs began to attract increased interest, soon followed by time-of-flight (TOF) instruments. These may often still be fully sufficient for real samples, but more sophisticated MS analyzers allowing MS^2 detection such as triple quadrupole (QqQ) instruments, combinations of Q and TOF (QqTOF), and combinations of Q and a linear ion trap (QqLIT) have been reported for PPCPS in a wide range of environmental samples and waste water. MS^2 techniques realized by instruments like QqQ provide a high certainty in peak identification due to the possibility of multiple reaction monitoring (MRM). Single ion traps may also be attractive for reliable identification of analytes at trace levels in complex matrices due to the possibility of multiple ion–ion tran-

sitions (MS^n), but the number of applications to PPCPs seems to be lower than that of QqQ. Within recent years, MS detection for HPLC has undergone significant improvements regarding sensitivity and resolution. Therefore, detection limits that can be achieved for PPCPs in real samples may strongly depend on the amount of money one wants to spend for highly sophisticated instrumentation. It can be expected that this trend will remain the same within the next few years, and novel high-resolution MS instruments like the Orbitrap can be expected to play an increasing role in the future. The ongoing improvements in the performance of MS detectors after HPLC separation will also have a significant impact on the sample pretreatment/preconcentration procedures that may become considerably simpler and less time-consuming than nowadays.

Electrospray ionization is by far the most commonly used ionization technique for trace analysis of PPCPs in environmental samples. Unfortunately, it is prone to ionization suppression due to matrix components coeluting with the analytes. This may lead to significant loss of sensitivity and – even more important – would make quantitation less reliable if external standards prepared in pure solvents would be used. Various isotopically labeled pharmaceuticals have become available in recent years which can be used as internal standards to compensate matrix effects. Alternatively, standard addition methods can be applied, although this approach would increase the total time of the analysis procedure considerably.

To illustrate the state-of-the-art of HPLC–MS, Fig. 1 shows the chromatogram of a real river water sample after SPE, demonstrating the presence of pharmaceuticals like ibuprofen, diclofenac, bezafibrate, or naproxen at similar levels as pesticides such as mecoprop, 2,4-D, or bentazone [50]. Fig. 2 shows a real effluent wastewater sample containing various antibiotics [80]. Appropriate HPLC–MS conditions for multi-class analysis of traces of pharmaceuticals can be found in the references given in Table 1.

2.4. GC–MS procedures

In recent years, the main focus in pharmaceutical residues analysis had been put on development of multi-methods based on HPLC. In this case, GC methods seem to be less attractive as they are limited to classes of compounds that are volatile enough to be transferred directly into the gas phase or can easily be derivatized to volatile species without any by-products. On the other hand, one has to take into account that matrix effects may be less serious for ionization modes like electron impact (EI) or chemical ionization (CI) typically used for MS hyphenated with GC than for ionization modes like electrospray ionization (ESI) used for HPLC–MS. As a consequence, detection limits may even be lower for GC–MS than for HPLC–MS. It is therefore quite obvious, that GC procedures may be robust routine methods for certain classes of pharmaceuticals and should not necessarily be replaced by HPLC in all cases.

A typical application area where GC–MS might be the method of choice is the trace determination of acidic non-steroidal anti-inflammatory drugs like diclofenac, ibuprofen, naproxen, ketoprofen, mefenamic acid, or salicylates. The carboxylic acid group of these analytes may be derivatized by pentafluorobenzyl bromide [81,82], which not only enhances the volatility but also allows a highly sensitive and selective detection by negative CI-MS [83] Some work has been reported on the use of diazomethane for derivatization of this class of compounds, but due to its toxicity it is not fully suited for routine analysis. Alternatively, silylating reagents like N-methyl-N-(trimethylsilyl)trifloroacetamide (MSTFA) or N-methyl-N-tert-butyldimethylsilyl)trifluoroacetamide (MTBSTFA) have been suggested for non-steroidal anti-inflammatory drugs [84–86].

Silylating reagents are also suited for derivatization of compounds containing hydroxyl groups so that a wider range of analytes can be included within one run. Lee et al. demonstrated the use of MTBSTFA for various phenolic and acidic pharmaceuticals [87]. Also phenazone-type drugs have been derivatized by silylation [88]. Togola and Budzinski [89] have reported the use of MSTFA for determination of 18 analytes comprising anti-inflammatories, antidepressants and hypolipidic drugs. Derivatization by silylation is also quite common for synthetic estrogens (see for example [90]) although careful selection of the reagent and the reaction conditions is necessary to avoid side-reactions [91].

The role of derivatization reaction for SBSE followed by GC has already been discussed in Section 2.2.2. Regarding the trends in instrumentation of MS detection coupled to GC, the same aspects as for HPLC–MS (see above) are relevant.

2.5. Capillary electrophoresis procedures

Capillary electrophoresis (CE) is generally less sensitive than HPLC procedures so that it is not recommended as first choice for residue analysis of PPCPs in the environment. Nevertheless, it may be an interesting alternative because its separation selectivity can be orthogonal to that of HPLC, and one should consider this technique in cases when results from HPLC should be confirmed by a second independent method.

Similar to the situation in HPLC, the potential of CE is highest when used in combination with MS detection. Ahrer et al. [92,93] were among the first to demonstrate the suitability of CE–MS (using a single quadrupole) for residue analysis of various inflammatory drugs and lipid regulators for surface waters samples, and reported detection limits in the low ng/L range. These low detection limits could only be achieved by a 10,000-fold preconcentration using a combination of SPE and LLE procedures. A similar method was developed by Marcia et al. for several acidic drugs [94]. Using more advanced MS instrumentation such as TOF, reasonable detection limits could be achieved by Himmelsbach et al. [95] for a range of antidepressants in surface water and STP effluents after preconcentration by a factor of 1000 using SPE.

Instead of off-line SPE, in-line SPE procedures have been investigated for preconcentration of pharmaceuticals from water samples. Monolithic SPE materials within the fused silica separation capillaries for analysis of antidepressants [96] or a microcartridge packed with the sorbent and placed within the capillary for naproxen [97] have been reported. Such approaches may simplify the whole sample pre-treatment and separation steps, but they are still less common for routine work.

The disadvantages of less sensitivity of CE in comparison with HPLC methods can be partly compensated by exploiting various on-capillary preconcentration and focusing possibilities. Nowadays there are various well-known approaches to inject relatively large volumes of samples into the capillary and to focus the analytes into narrow bands prior to separation. Marcia et al. have demonstrated trace analysis of some anti-inflammatory drugs by techniques like large-volume sample stacking using the electroosmotic flow pump (LVSEP) and LVSEP with anion-selective exhaustive injection (LVSEP-ASEI) in capillary zone electrophoresis (CZE) [98,99], as well as stacking with reverse migrating pseudostationary phase (SRMP), stacking with reverse migrating micelles–anion selective exhaustive injection (SRMM–ASEI), and field-enhanced sample injection with reverse migrating micelles (FESI–RMM) in micellar electrokinetic chromatography (MEKC) [100,101]. These techniques decreased the detection limits down to the low μg/L range, so that an additional off-line SPE step would allow to analyze real samples in the ng/L range.

More recently, Dawod et al. have applied another on-capillary preconcentration technique called electrokinetic supercharging

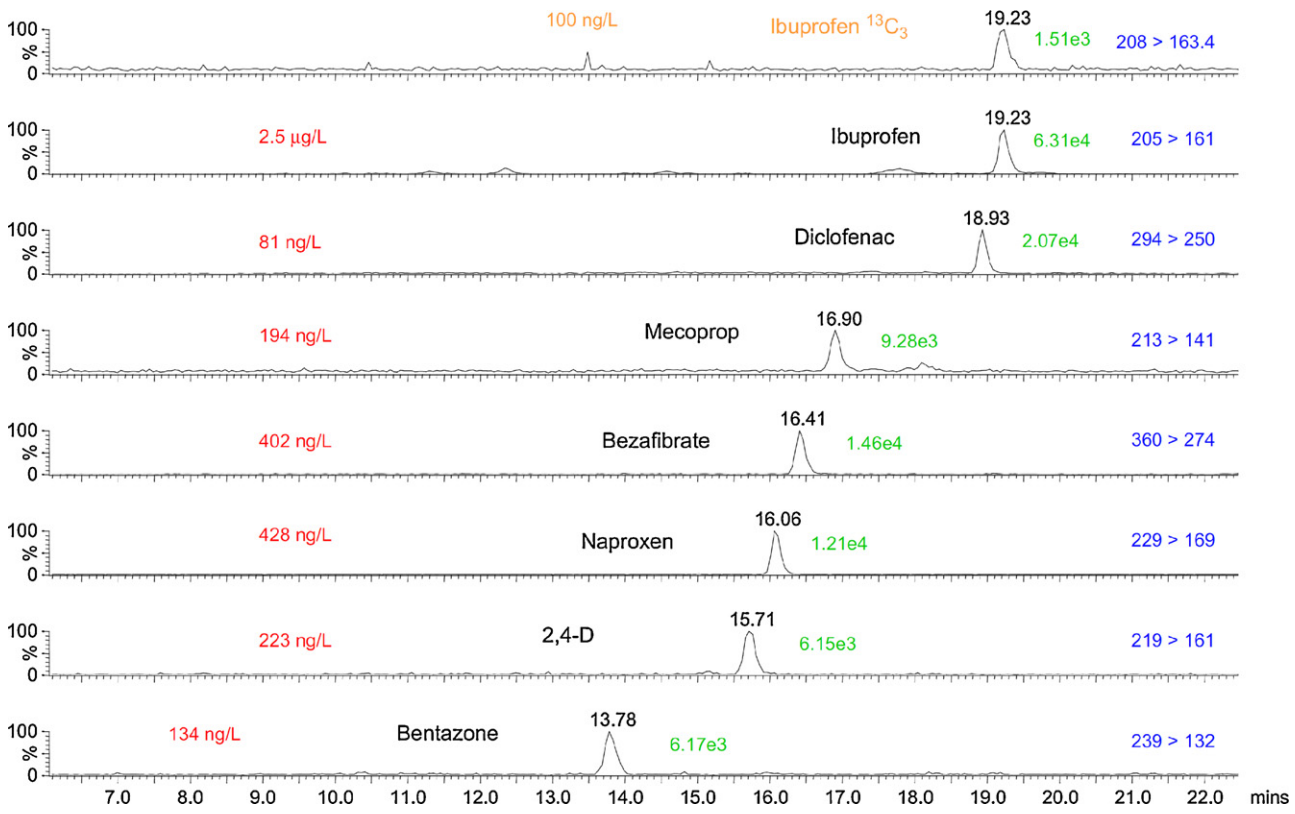

Fig. 1. HPLC–MS/MS chromatogram of a river water sample after preconcentration by SPE.
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(EKS), which is a combination of electrokinetic injection under field amplified conditions (field-amplified sample injection, FASI) and transient isotachophoresis (tITP) [102], and they have improved this technique by applying a hydrodynamic counterflow during the injection (CF-EKS) [103]. Detection limits for anti-inflammatory drugs after CZE separation were in the ng/L range, although the detection limits deteriorated to some extent when waste water samples were analyzed. Therefore, the combination of a simple off-line SPE extraction and CF-EKS may be the method of choice. Fig. 3 shows an electropherogram of a mixture of non-steroidal anti-inflammatory drugs at a concentration of 1 ppb without prior preconcentration. In this case, simple UV absorbance detection has been used, and the coupling with MS might be a promising tool for further decreasing the detection limits.

2.6. Immunochemical methods

Immunoanalytical techniques may be promising for trace analysis of organic pollutants in the environment, since they require only little sample preparation, exhibit high sensitivity, and may be less expensive in comparison with instrumental analysis based on chromatography and mass spectrometry. They are also easily automated so that high throughput analysis becomes feasible. Employing the binding properties of an antibody to the analyte (representing the antigen), various screening methods for residues of pharmaceuticals can be realized.

Immunoassays have been used for quite a while in environmental analysis for detection of pesticides, but they are still quite rare for pharmaceuticals in the aquatic environment. This is not necessarily due to a lack of suitable antibodies available so far. Immunoanalytical test kits for various pharmaceuticals are commercial available, but these kits are mostly optimized for biological samples like blood and urine, or for food. Their possible applicability to environmental samples has been investigated only in few cases.

Obviously, the selectivity of the antibody used in an immunoassay makes it unsuited for simultaneous determination of analytes belonging to different chemical classes. In this context it might be attractive to select a certain drug as a marker that is practically always present in water samples if residues of pharmaceuticals are present. This would allow to quantify just one analyte and thereby to get information about the extent of contamination by pharmaceuticals in the environment. A marker might be diclofenac, a nonsteroidal anti-inflammatory drug that is most frequently present in the water cycle. An immunoassay has been developed for diclofenac with a working range from 20 to 400 ng/L, and reasonable correlation has been demonstrated with GC–MS ($r = 0.70$, slope = 0.90) [104].

Immunoassays originally developed for measurement of some antibiotics in food have been modified for environmental water samples [105–107]. SPE may be a good way to preconcentrate water samples prior to the immunoassay to decrease detection limits if necessary.

Table 3 summarizes immunoassays reported so far for determination of pharmaceuticals water samples. Recently, Martinez et al. [115] developed a microfluidic immunoassay for ethinylestradiol in river water samples yielding a detection limit of 0.32 ng/L that may replace the traditional format of an immunoassay.

As mentioned above, fully automated immunosensor systems can be designed that may serve for routine analysis of real sample. Gauglitz and coworkers [116] have developed a flow-through instrumentation suited for monitoring of pharmaceuticals, hormones, endocrine disrupting chemicals and pesticides in water. The sample is mixed with an appropriate antibody that is labeled with a fluorescent tag and injected into the flow-through cell that is coated with analyte molecules. The competition of analyte molecules in

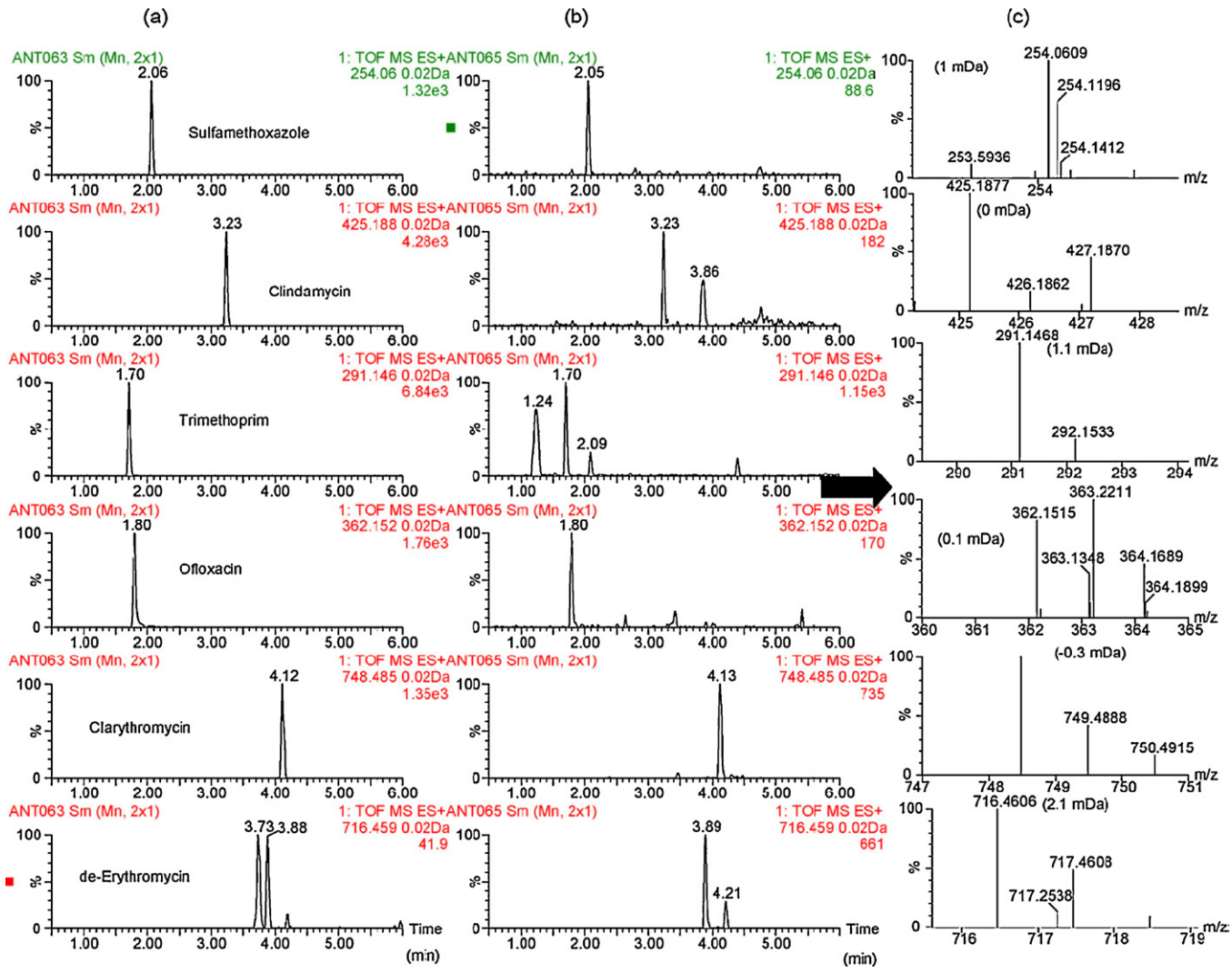

Fig. 2. HPLC–TOF-MS chromatograms of (a) a reference standard, and (b) an effluent wastewater sample containing the antibiotics clarythromycin, ofloxacin, trimethoprim, clindamycin and sulfamethoxazole; (c) TOF-MS spectra of the real sample.
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the sample and immobilized in the cell for the antibody leads to a sample-dependent amount of antibody getting bound to the cell surface, where it is excited by a laser and emits fluorescence light.

MIPs have also been investigated for use in immuno-type assays as an alternative to antibodies. Although molecular-imprinted sorbent based assays have been reported for pharmaceuticals in aqueous samples (see for example [117]), the possible application to environmental water samples are still a matter of future research.

3. Pharmaceuticals in sewage sludge and soil

As mentioned in Section 1, sewage sludge may be used as fertilizer for agricultural purposes so that residues of pharmaceuticals

Table 3
Immunoassays for pharmaceuticals in the environment.

Analyte (matrix)	Sample preparation	Detection limits	Reference
Diclofenac (surface water, waste water)	None	6 ng/L	[104]
Oxytetracycline (surface water, sediment extracts)	None	1 μg/L	[105]
Tetracycline, sulphonamides (surface water, waste water)	SPE	50 ng/L	[106]
Tetracycline (surface water, ground water)	Dilution with buffer 1:1	50 ng/L	[107]
Tylosine (surface water, ground water)	Dilution with buffer 1:1	100 ng/L	[107]
Ethinylestradiol (surface water, waste water)	None	0.2 ng/L	[108]
Ethinylestradiol (surface water, waste water)	SPE	0.01 ng/L	[109]
Indomethacin (drinking water, surface water, waste water)	None	10 ng/L	[110]
Levonorgestrel (waste water)	SPE	70 ng/L (without SPE) 0.7 ng/L (with SPE)	[111]
Sulfonamides	None	40 ng/L	[112]
Carbamazepine	None	24 ng/L	[113]
Monensin (surface water, soil extract)	Dilution	1.5 μg/L	[114]

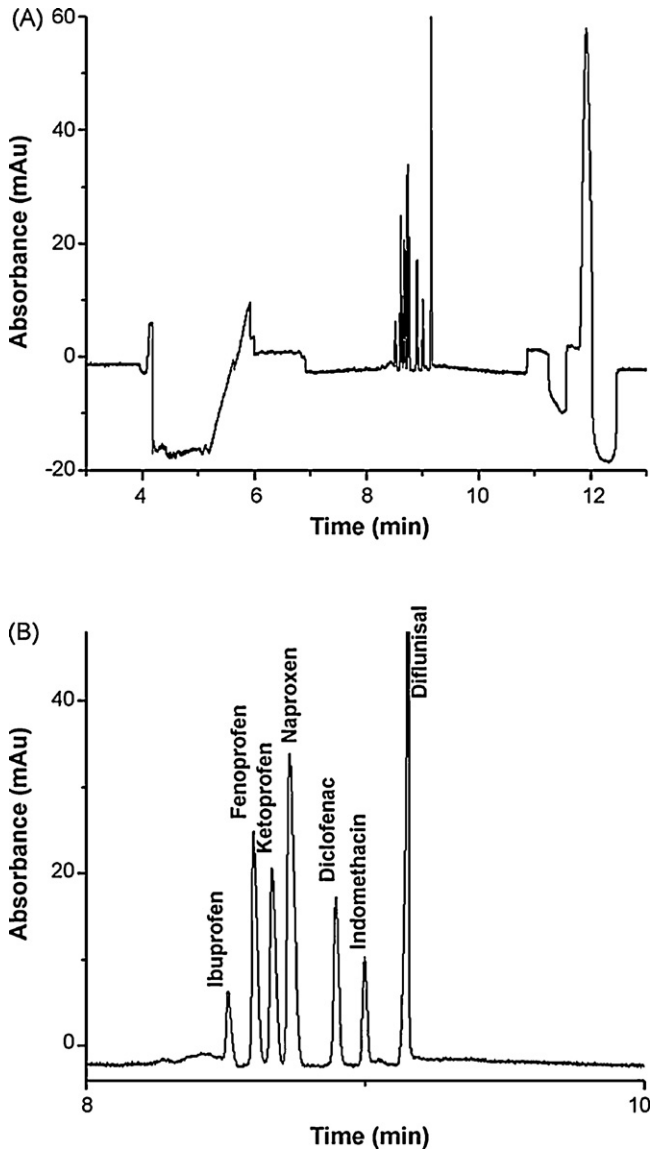

Fig. 3. Capillary zone electrophoretic separation of pharmaceuticals after CF-EKS injection at a concentration of a 1 ppb; (A) full injection and (B) close up of analyte separation; detection, UV at 214 nm.
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may be transferred into soil. Therefore, a lot of work has been dedicated to the determination of residues in sewage sludge and soil samples. Furthermore, surface water contaminated by pharmaceuticals may also lead to the build-up of residues in sediment, which is another solid matrix where the monitoring of pharmaceuticals may be important.

The final analysis step based on HPLC or GC hyphenated with MS is similar to that mentioned above for water samples and does not need further discussion. The major difference is associated with the sample preparation/extraction step. Extraction of pharmaceuticals from solid samples has been done by conventional Soxhlet extraction (which has become less attractive due to the time- and solvent-consuming procedure), microwave assisted extracted (MAE) [118], ultrasonic extraction (USE), or pressurized liquid extraction (PLE) [119,120]. Among these, USE and PLE seem be the most widely used techniques (see references in Tables 4 and 5). The sampling of a sediment sample (as well as other types of solid samples) may result in a solid sample as well as a liquid phase, so that separation by filtration or centrifugation may be necessary. Subsequently, the solid sample may undergo air-drying, drying by heating, or freeze-drying followed by grinding and sieving. Surprisingly, little attention has been paid to the fact, that the filtration or centrifugation step does not necessarily lead to a complete separation of the solid and the liquid phase, and a considerable amount of water may still be in the solid sample used for the drying step. Therefore, the final analysis will quantify both the amount of analyte adsorbed to the solid sample and the amount of analyte dissolved in the aqueous phase still present in the solid sample after filtration or centrifugation. In many procedures reported so far, such a possible systematic error has been neglected although it may be unclear in some cases whether this is justified or not. Extracts obtained by USE or PSE generally require additional clean-up by solid-phase extraction.

USE is attractive because the equipment necessary is widely available and the extraction can be done with a reasonably small volume of solvent (typically 0.1–2 g sample treated with 5–25 mL of solvent) within an extraction time between 10 and 60 min. Table 4 lists typical procedures based on USE. The addition of complexing agents to the extraction solvent may be necessary for compounds like tetracycline antibiotics which form strong complexes with multivalent metal ions. Besides USE, PSE has become a well-established technique and has proven its advantages for pharmaceuticals in solid samples due to high extraction efficiency within a short time, low consumption of solvent, and the possibility of automation. It uses high pressure and temperature (below the critical point of the solvent) for sample amounts typically between 0.5 and 5 g. The sample is often mixed with an inert material to increase the exposure surface area of the sample. For this purpose, sand, aluminium oxide, diatomaceous earth, or Hydromatrix (a commercially available proprietary material) are commonly used. Recent PLE procedures reported for multi-residue analysis are listed in Table 5.

4. Illicit drugs in water and sewage sludge

Considering the knowledge acquired over the years about pharmaceuticals in the environment, it was quite straightforward to speculate that even illicit drugs may be present at trace levels in environmental water samples and sewage sludge. The first papers that proved these speculations were published by Jones-Lepp et al. [28], Zuccato et al. [134], Castiglioni et al. [135], and Kaleta et al. [136] around 2005 demonstrating the presence of compounds like cocaine, amphetamines, morphine, cannabinoids, and methadone. Methods applied to the trace determination of these analytes were optimized and refined during the following years and are based on similar approaches as mentioned for residue analysis of pharmaceuticals, mainly solid-phase extraction followed by HPLC with mass spectrometric detection. Alternatively, GC–MS has been described for various illicit drugs in water after SPE and conversion of the analytes into the corresponding trimethylsilyl derivatives [137]. As mentioned above, Oasis HLB or a mixed mode material like Oasis MCX are efficient sorbents for pharmaceuticals and have also been used extensively for illicit drugs (a comparison of various reversed phase and mixed-mode SPE materials has been done recently for extraction of cocain and metabolites, amphetamine-like compounds, cannabinoids, and opiates from water samples [138]). Furthermore, a molecularly imprinted polymer for amphetamine drugs has been investigated which rendered cleaner extracts than Oasis sorbents [139]. It has been suggested to use the data from analyses of waste waters from sewage treatment plants to estimate the consumption of illicit drugs at both a local and national scale. Results from measurements in Belgium [140,141], in Spain [142–144], in Ireland [145], in Italy [146], and in cities in the United Kingdom, in Switzerland, and in Italy [147] indeed allowed

Table 4
Typical ultrasonic extraction procedures for pharmaceuticals in sludge, soil and sediment.

Analytes	Sample	Solvent for extraction and subsequent clean-up procedures	Reference
Antiphlogistics, lipid regulators, cytostatic agents, carbamazepine, diazepam	Sludge	USE (2× methanol, 2× acetone), SPE	[121]
Fluoroquinolones	Sludge, sediment	USE (methanol/water 30/70), SPE	[122]
Six acidic pharmaceuticals	Sludge	USE (2× methanol, 2× acetone), SPE	[123]
Antibiotics, carbamazepine, triclosan	Sludge	USE (methanol/0.1 M acetic acid/5% EDTA 2:1:1), SPE	[124]
66 pharmaceuticals and personal care products	Sludge	USE (methanol/water 1/9, pH 11)	[125]
16 pharmaceuticals of different classes	Sludge, compost, sediment	USE (2× methanol, 1× acetone), SPE	[126]

a confirmation of estimates done through other studies. A critical review on illicit drug consumption estimates derived from waste water analysis has most recently been prepared by van Nuijs et al. [148]. One should keep in mind that a certain percentage of these drugs and their metabolites may also originate from therapeutic use so that the estimates for consumption of illicit drugs may be somewhat too high.

Table 6 lists various procedures that are suited for analyzing a range of structurally different illicit drugs and some metabolites. A special review on analytical methods for amphetamine and methamphetamine in surface water, waste water and biosolids has recently been prepared by Boles and Wells [154], whereas a more comprehensive review covering the literature up to the end of 2007 has been prepared by Castiglioni et al. [155]. A representative chromatogram demonstrating the performance of HPLC–MS for detecting drugs in waste water is given in Fig. 4.

5. Personal care products

The range of different classes of chemicals released from personal care products into the environment may even be wider than in the case of pharmaceuticals. In recent years, the research has focused on the following types of ingredients from personal care products:

- UV filters.
- Insect repellents.
- Synthetic musk fragrances.
- Antimicrobials and preservatives.

Generally the strategies for analyzing residues of these compounds in environmental samples are quite the same as those described for pharmaceuticals. Therefore, no additional discussion of the details of the techniques seems to be necessary within the scope of this review. Instead, only a short overview on some papers published recently will be given to get a full picture about PPCPs.

5.1. UV filter

UV-absorbing compounds (UV filters) are common ingredients in sunscreens, skin creams, lipsticks, and other personal care products. Regarding organic UV filters, there are 27 compounds approved in the European Union, including benzophenones, p-aminobenzoic acid and derivatives, salicylates, cinnamates, camphor derivatives, triazines, benzotriazoles, benzimidazole derivatives, dibenzoyl methane derivatives, and compounds like octocrylene and benzylidene malonate polysiloxane. Some of these are volatile enough to be analyzed by GC, and due to their hydrophobicity they can easily be extracted from aqueous samples by sorptive extraction. Therefore, SBSE combined with TDS/GC–MS has become an attractive tool for simple screening of environmental samples [71,156,157]. To improve the compatibility of UV filters with GC, derivatization by silylation directly on the sorbent after extraction has been investigated [158]. This approach has been done in the format of SPME so that the detection limits were not as low as they would be in case of SBSE. UV filters together with two antimicrobial agents have also been extracted and preconcentrated by SBSE with subsequent liquid desorption and HPLC analysis [159].

Alternatively, SPE has been used for extraction/preconcentration prior to GC since the beginning of systematic investigations of UV filters in the environment (see for example [160]). Most recently, this approach has been miniaturized using microextraction by packed sorbent (MEPS), which allows a fully automated sample preparation for UV filters (and some polycyclic musk compounds) and required a sample volume of only 800 μL with an eluent volume of 50 μL which was completely used for large-volume injection GC–MS [161].

For multiclass determination of UV filter including non-volatile analytes, SPE followed by HPLC and MS detection is still the preferred technique, as has been shown by Rodil et al. [162] who used Oasis HLB and added an ion-pairing reagent to improve the extraction efficiency for UV filters containing a sulfonic acid group. Instead of electrospray ionization, also photoionization is applicable for MS

Table 5
Recent procedures for pressurized liquid extraction of pharmaceuticals in sludge, soil and sediment.

Analytes	Sample	Dispersion agent	Extraction condition	Reference
27 pharmaceuticals	Biosolid enriched soil, digested sludge	Sea sand	Methanol/water (1:1), 60 °C, 1500 psi, followed by SPE	[127]
10 pharmaceuticals	Sewage sludge	Aluminium oxide	50 mM phosphoric acid/methanol (1:1), 100 °C, 100 bar	[128]
11 antibiotics	Sewage sludge	Aluminium oxide	Water(pH 3)/methanol (1:1), 80 °C, 100 bar	[129]
Natural and synthetic estrogens	Sewage sludge	Aluminium oxide	Methanol/acetone (1:1), and water(pH 7)/methanol (1:1), 75 °C, 100 bar	[130]
31 pharmaceuticals	Sewage sludge	Hydromatrix	Methanol/water (1:2), 100 °C, 1500 psi, followed by SPE	[131]
43 pharmaceuticals	Sewage sludge, sediment	Hydromatrix	Methanol/water (1:2), 100 °C, 1500 psi, followed by SPE	[132]
66 pharmaceuticals and personal care products	Sewage sludge		Water (pH 2), methanol (pH 4)	[125]
Phosphodiesterase type V inhibitors	Sewage sludge	Aluminium oxide	Methanol, 100 °C, 140 bar	[133]

Table 6
Procedures for illicit drugs in water and waste water.

Analytes	Sample matrix	Sample pretreatment (sample volume used/pre-concentration factor)	Chromatographic method	Limits of quantification	Reference
Amphetamine and related compounds, cocaine, benzoylecgonine, LSD, ketamine, phencyclidine, fentanyl	Surface water, waste water	SPE on Oasis HLB (100 mL/200)	Reversed phase HPLC–triple quadrupole MS	<5 ng/L	[149,144]
Amphetamine and related compounds, cocaine and metabolites, methadone, ketamine, norketamine, LSD and metabolite, phencyclidine	Waste water	None	Reversed phase HPLC–triple quadrupole MS using large volume injection (1800 μL)	2.5–10 ng/L	[150]
Amphetamine and related compounds, cocaine and metabolites, ephedrine, heroin, morphine and metabolites, LSD and metabolites, cannabinoids	Surface water, waste water	On-line SPE on Oasis HLB or PLRPs (5 mL)	Reversed phase HPLC–quadrupole/linear ion trap MS	0.7–6 ng/L	[142]
Opiates and metabolites, cannabinoids and metabolite	Waste water, surface water, drinking water	SPE on Oasis HPLC (200 mL/400)	Reversed phase HPLC–triple quadrupole MS	0.3–25 ng/L (waste water) 0.4–12.5 ng/L (surface water)	[143]
Cocaine and metabolites, amphetamines and related compounds, 6-monoacetyl-morphine, methadone and metabolite	Waste water	SPE on Oasis MCX (50 mL adjusted to pH 2/250)	Hydrophilic interaction HPLC–triple quadrupole MS	1–2 ng/L	[151]
Amphetamines and related compounds, cocaine and metabolites, cannabis metabolite	Surface water, waste water	SPE on Oasis MCX (50 mL adjusted to pH 2/50)	Reversed phase HPLC–triple quadrupole MS	10–300 ng/L (surface water), 100–800 ng/L (effluent waste water), 0.15–4 μg/L (influent waste water)	[152]
Cocaine and metabolites, amphetamines and related compounds, opiates and metabolites, cannabis metabolite	Surface water	SPE on Oasis MCX (250 mL adjusted to pH 2/1250)	Reversed phase HPLC–triple quadrupole MS	0.1–1.2 ng/L	[153]
Cocaine and metabolites, amphetamines and related compounds, cannabinoids, opiates	Surface water, waste water	SPE on Oasis HLB (100–500 mL adjusted to pH 8.5/500–2500)	GC–ion trap MS	2–60 ng/L	[137]
Cocaine and metabolites, amphetamines and related compounds, cannabinoids, opiates	Surface water	SPE on Oasis HLB (250 mL/250)	Reversed phase HPLC–triple quadrupole MS	0.03–5.1 ng/L	[138]

detection [163] and was found less susceptible to ion suppression than ESI when real samples were injected.

Some efforts have been made recently to avoid any chromatographic separation step and to analyze UV filters preconcentrated by SBSE directly on the stir bar by novel MS techniques. For this purpose, direct analysis in real-time (DART) MS has been investigated which is suitable for the detection of chemicals on surfaces without any other sample preparation step. The ionization is achieved by interactions of long-lived electronic or vibronic excited-state species of a helium gas with the analyte and the atmospheric gases. Using a polydimethylsiloxane-coated stir bar for extraction, DART-MS was able to detect several UV filters with detection limits lower at about 40 ng/L [164]. Fig. 5 shows a typical mass spectrum obtained for a real surface water sample using a TOF mass analyzer. A disadvantage of DART-MS is the fact that quantification of analytes is problematic so that the technique yields just semiquantitative results (which may be sufficient for screening purposes).

UV filters in sludge or sediment samples have been analyzed successfully by pressurized liquid extraction followed by HPLC–MS [165] or by GC–MS after derivatization by silylation [166], which represents a considerably more attractive approach than traditional solid–liquid extraction using large volumes of solvents [167]. An interesting alternative has been presented by Rodil et al. [168] for sludge and sediment samples using pressurized membrane-assisted liquid extraction. A non-porous low-density membrane bag was used and filled with 0.5 g of sample and 1 mL of extraction solvent. Subsequently, the membrane bags were extracted under pressure and elevated temperature. Due to the membrane, extraction and some clean-up were combined in a single step.

Results from several studies indicate that some UV-filters display estrogenic activity [169]. The occurrence of some lipophilic UV-filters in fish has been known for quite a while, but only recently methods for simultaneous determination of polar and lipophilic UV filters in fish have been reported by Zenker et al. [170,171]. Mid-polar and lipophilic UV filters were extracted from homogenized tissue by a mixture of ethyl acetate, n-heptane, and water, followed by clean-up by reversed-phase HPLC. The fraction containing mid-polar UV filters was analyzed by HPLC–MS, whereas the fraction containing lipophilic UV filters was analyzed by GC–MS. Polar and mid-polar UV filters were extracted by a mixture of methanol and acetonitrile, followed by HPLC–MS analysis.

5.2. Insect repellents

The main target analytes belonging to the group of insect repellents analyzed in environmental samples have been N,N-diethyl-m-toluamide (DEET) and 1-piperidinecarboxylic acid 2-(2-hydroxylethyl) 1-methylpropyl ester (Bayrepel). Similar to the situation in residue analysis of UV filters, SBSE coupled to TD-GC–MS has turned out to be a feasible technique for trace analysis

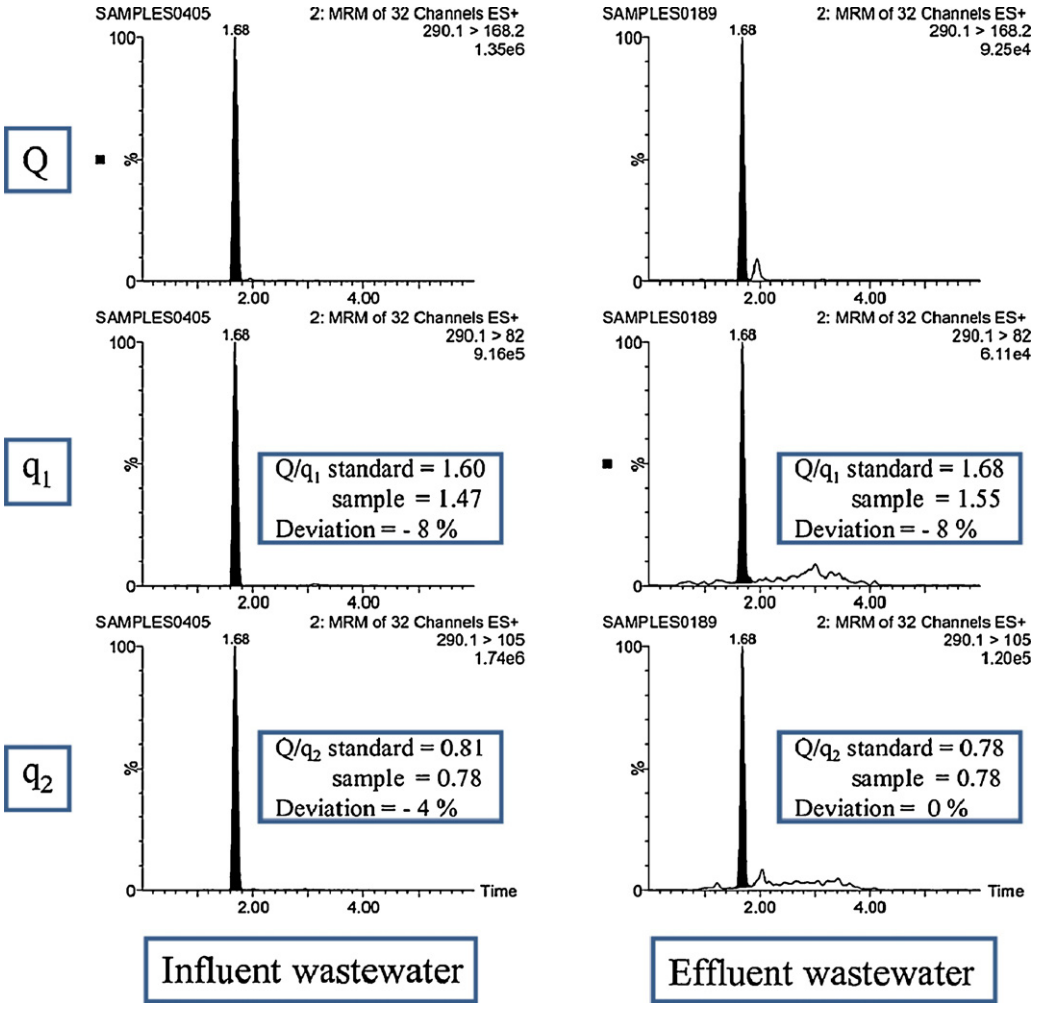

Fig. 4. HPLC–MS/MS chromatograms corresponding to benzoylecgonine (a metabolite of cocaine) in influent (4140 ng/L) and effluent (60 ng/L) 24-h composite wastewater. (Q) Quantification transition; (q_1) and (q_2) confirmation transition.
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down to the low ng/L range [172] which may complement earlier methods based on SPE procedures (see for example [173]).

5.3. Antimicrobials and preservatives

Triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol) is a common antimicrobial that has often been used in personal care products such as soaps, deodorants, or tooth pastes. SPE followed by GC–MS has widely been employed for monitoring triclosan (as well as its metabolite methyl-triclosan) in water or waste water samples (see for example [174]). Besides GC of the underivatized analyte, various derivatization procedures (such as silylation of the hydroxy group) have been suggested to improve the GC performance of triclosan and related compounds, or the use of HPLC methods has been recommended (a review on such procedures can be found in [175]).

Triclosan has also been successfully analyzed by an immunoassay [174,176] without sample preparation, yielding detection limits around 15 ng/L.

Further common preservatives used in personal care products include triclocarban (3-(4-chlorophenyl)-1-(3,4-dichlorophenyl)urea) and p-hydroxybenzoic esters (parabens), mostly methyl- and propylparaben. Since parabens have weak estrogenic activity, they have been included in surveys on xenoestrogens in the environment. Therefore, methods that can analyze parabens together with other endocrine disrupting compounds in surface water and waste water have attracted some interest. Such analyses can be done by HPLC–MS after SPE using Oasis HLB with detection limits between 1 and 2 ng/L for parabens [177], or by GC–MS methods after SPE on Oasis MAX and conversion into pentafluoropropionyl derivatives yielding detection limits at

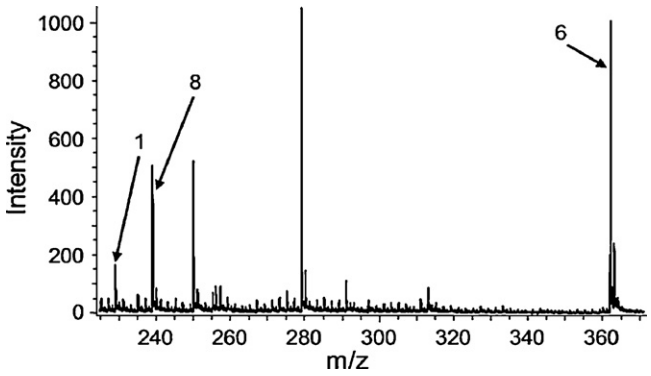

Fig. 5. DART mass spectrum using a TOF-MS of UV filters in a lake water sample enriched by sorptive extraction on a stir bar. 1 = benzophenone-3, 2 = octocrylene, and 3 = benzyl cinnamate. Analyte concentrations between 40 and 1400 ng/L.
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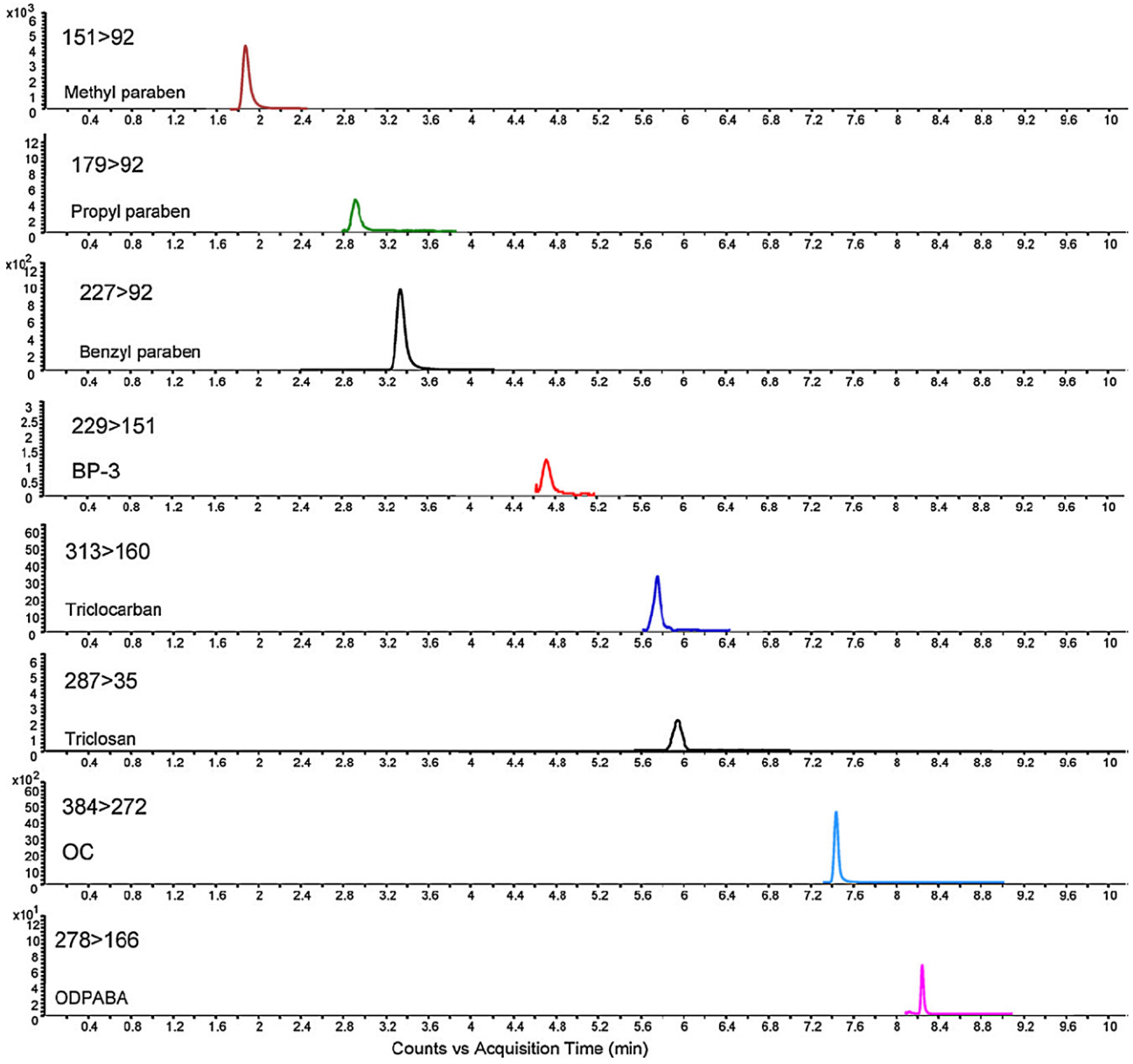

Fig. 6. HPLC–MS/MS chromatogram of a sewage sludge sample containing UV filters, antimicrobials, and parabens after pressurized liquid extraction. The UV filters include BP-3 (benzophenone-3), OC (octocrylene), and ODPABA (octyldimethyl-p-aminobenzoic acid). Analyte concentrations are between 6 and 1800 μg/kg. Reprinted from [165] with permission from Elsevier.

about 10 ng/L [178]. A simultaneous determination of parabens, triclosan, and triclocarban in water samples has been reported by SPE with Oasis HLB and HPLC–MS/MS, yielding detection limits at the sub-ng/L level [179]. As an alternative to Oasis HLB, MIPs for parabens have been synthesized and tested with surface water samples which allowed cleaner chromatograms than in case of non-selective sorbents [180].

Parabens have also been analyzed in water samples by non-aqueous CE and UV detection using a combination of off-line SPE and on-capillary large volume sample stacking [181], although this technique cannot yet cope with HPLC–MS regarding selectivity and sensitivity.

5.4. Synthetic musk fragrances

There are three major groups of synthetic musk fragrances, namely aromatic nitro musk compounds, polycyclic musk compounds, and macrocyclic musk compounds. They are frequently used to scent various personal care products and have been detected in the environment already in the 1980s. Up to now, primarily compounds belonging to the chemical groups of nitro-aromatic musks and polycyclic musks have been investigated with respect to their occurrence in water, waste water, sludge, or sediment. Not surprisingly, these analytes are fully compatible with GC. This may explain the fact that their presence in environmental matrices has been known for quite a while, as reliable GC–MS instrumentation was much earlier available than HPLC–MS instrumentation necessary for other classes of pollutants. In so far, well-established GC–MS methods are nowadays available for routine monitoring.

Sample preparation and preconcentration by SPE is a commonly employed approach for synthetic musk fragrances in water samples so that no further discussion seems to be necessary within the present review. Due to their volatility, musks compounds can also be preconcentrated by headspace SPME, followed by GC–MS. Fibers coated with PDMS-poly(divinylbenzene) or carboxene-PDMS have

been reported as best choice [182]. More recently, microwave-assisted headspace SPME was used for extraction of water samples as well as sewage sludge and sediment samples [183,184] with detection limits at sub-ng/L and sub-ng/g levels respectively. Besides SPME, SBSE followed by liquid desorption and large-volume injection GC has been suggested as an alternative to SPE [185]. As these synthetic musk fragrances may be quite hydrophobic, they may tend to adsorb to suspended particles in waste water samples and may get lost if samples are filtered prior to SPE. Therefore, routine monitoring of surface water and sewage water is often still done by liquid–liquid extraction without filtration of the sample in order to measure the total of adsorbed and dissolved analytes [186]. A recent review dealing with the analysis of musk fragrances in environmental samples can be found in [187]. This review also addresses the analysis of musk fragrances in biota samples. It is well known that hydrophobic musk fragrances lead to bioaccumulation in fish. This fact has been documented various times within the last two decades so that no further discussion seems to be necessary within this review.

5.5. Multimethods for personal care products

Current trends for personal care products clearly indicate the growing importance of multimethods for chemically different classes of personal care products and – if possible – together with other traditional or emerging pollutants such as pesticides, endocrine disrupting compounds, flame retardants, perfluorinated compounds and pharmaceuticals. It is quite clear that such multimethods may require some compromises when selecting the conditions for extraction, preconcentration, and chromatographic analysis. Some of these multimethods have already been mentioned in the part on pharmaceuticals, such as the work of Loos et al. [50,51]. Cuderman and Heath [188] developed a GC–MS method for UV filter and antimicrobials based on SPE on Strata-X and derivatization by silylation in environmental water samples. GC–MS was also used by Guitar and Readman for a range of pharmaceuticals, endocrine-disrupting compounds and triclosan in water samples after enrichment on Oasis HLB and silylation [189]. HPLC hyphenated with triple quadrupole MS after SPE preconcentration on Oasis HLB for sewage samples and Bond Elut Plexa for river water has been employed for 11 UV filters preservatives, and antimicrobials by Pedrouzo et al. [190]. Kasprzyk-Hordern et al. demonstrated the simultaneous determination of 56 analytes in river water including pharmaceuticals, illicit drugs, UV filter, parabens, and antimicrobials by SPE on Oasis MCX and HPLC with triple quadrupole MS [10]. Rodil et al. [49] used SPE on Oasis HLB and HPLC with triple quadrupole MS for determination of 53 analytes such as pharmaceuticals, herbicides, insect repellents, triclosan, UV filters, and organophosphorous flame retardants in water samples. The applicability of atmospheric pressure chemical ionization MS as an alternative to electrospray ionization MS has been investigated for a range of antimicrobials, UV filters and benzothiazoles [191]. Besides the intact compounds, degradation products of personal care products are attracting increasing attention, and analytical methods have been reviewed recently [192]. Multimethods for parabens, UV filter, and antimicrobials have also been developed for sewage sludge [165] after pressurized liquid extraction and HPLC with triple quadrupole MS. A typical chromatogram is shown in Fig. 6.

As mentioned above for UV filters and musk compounds, the presence of different components of personal care products in fish has become a matter of increased interest in environmental sciences. Therefore, multi-methods for structurally different personal care products are of increasing importance. Recently, screening methods have been developed for simultaneous determination of selected UV filters, synthetic musks, alkylphenols, triclosan, and DEET in fish [193]. This procedure included extraction of tissue by acetone, sample clean-up on a silica gel column and by gel-permeation chromatography, derivatization with MSTFA, and GC–MS with MS detection.

6. Conclusions

Within the last few years significantly improved MS technologies have become commercially available which are nowadays routinely used in detectors for high-performance chromatographic separation techniques and make detection limits possible that were completely out of reach two decades ago. At the same time, the reliability of procedures used for trace analysis of PPCPs has been critically checked and interlaboratory exercises have been performed, such as for non-steroidal anti-inflammatory drugs in fresh water and waste water [194,195], or for estrogenic compounds (including the synthetic estrogen 17α-ethinylestradiol) in tap water, river water, and sewage treatment plants influents and effluents [196].

We are facing the problem of having abundant data about traces of xenobiotics in the environment without final conclusions about their (eco)toxicological relevance. Cooperations between analytical chemists and toxicologists will remain an important issue for the future. There will also be a need to improve monitoring strategies. For this purpose the development of analytical methods that require less sophisticated and less expensive instruments than used nowadays will become an important aspect.

In the future increased attention will have to be paid to metabolites generated in the organisms and released into the environment as well as to metabolites generated in the environment itself by biodegradation, photolytic or oxidation reactions. New sample preparation procedures may be necessary to allow the quantitative analysis of metabolites in the environment so that there is enough room for additional innovative approaches. Another important field may be the analysis of pharmaceuticals in aquatic organisms (in addition to personal care products mentioned above). A pilot study on the occurrence of PPCPs in fish has recently been carried out in the United States [197] (just to mention one example), and it can be expected that an increasing number of similar studies will follow in the near future.

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