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# Multi-residue analytical methods for the determination of pesticides and PPCPs in water by LC-MS/MS: a review

**Review Article**

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**Abstract:** Residues of pesticides, pharmaceutical and personal care products (PPCPs) are contaminants of world-wide concern. Consequently, there is a growing need to develop reliable analytical methods, which enable rapid, sensitive and selective determination of these pollutants in environmental samples, at trace levels. In this paper, a review of the liquid chromatography–tandem mass spectrometry (LC–MS/MS) based methods for the determination of pesticides and PPCPs in the environment is presented. Advanced aspects of current LC–MS/MS methodology, including sample preparation and matrix effects, are discussed.

**Keywords:** *Environmental waters • Pesticides • PPCPs • Tandem mass spectrometry • Sample preparation*



## 1. Introduction

Water is one of the essential resources for life and its multiple uses are indispensable for a series of activities, such as agriculture, generation of energy, public and industrial supply, among others. However, the developmental models adopted by humankind have not taken into account the risks to the environment. The 20th century introduced more than 100 000 chemicals that are still being used in our everyday life, either in households, industries or agriculture. These chemicals were introduced without realizing the consequences on the environment, and directly or indirectly for human health [1,2].

Labeled as emerging organic contaminants, pharmaceuticals and personal care products (PPCPs) have caused widespread concern due to their extensive use.

The determination of PPCPs in the environment has also drawn much due interest to the fact that many of these substances are frequently found in effluents from Wastewater Treatment Plants (WWTPs) and natural waters, in concentrations that range from μg $L^{-1}$ to ng $L^{-1}$. Another important aspect is that these chemicals have been produced on a large scale worldwide, have been used in a wide range of applications, and have become indispensable to our modern society [3], but there is limited knowledge about their unintended effects on the environment.

The extensive use of pesticides in world-wide agricultural practice has led to contamination of water resources, which is a challenge for the preservation and sustainability of the environment. After applications to the field, pesticides undergo different types of degradation pathways. Depending on their mode of action and physico-chemical properties they are distributed into environmental compartments, which may cause contamination of environmental waters [4,5].

National governments introduced residue limits and guideline levels for pesticide residues in water looking for the minimization of the contamination of ground and surface waters. Initially, the main attention was given to drinking water, but values have also been proposed for environmental waters, effluent waters, irrigation waters and livestock drinking waters. The contamination of ground water is of concern because it may be used as drinking water and may act as a source of contamination for surface waters [6].

The maximum residue limits (MRLs) for pesticides and its terminology have different meanings in different

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systems, and the values differ a lot. For example, guideline value (GV) in World Health Organization (WHO) means a value calculated from a toxicology parameter, whereas in Australia, a GV is at or about the analytical limit of determination or a maximum level that might occur if good practices are followed [6]. In the European Union, water intended for human consumption must meet minimum specified requirements, including a maximum level for each pesticide of 0.1 μg $L^{-1}$ and a maximum of 0.5 μg $L^{-1}$ for total pesticides, except for aldrin, dieldrin, heptachlor, and heptachlor epoxide, which are each limited to maximum levels of 0.03 μg $L^{-1}$ [7]. In Brazil, the MRLs were established for some pesticides and the values vary from 0.03 to 500 μg $L^{-1}$ [8].

As stated earlier, European regulations on the quality of water intended for human consumption have fixed quality limits of concentration for some substances, including polycyclic aromatic hydrocarbons (PAHs), pesticides and residues of food-contact materials. Nevertheless, occurrence in groundwater and drinking waters of some other unregulated substances have also been reported in the literature, including pharmaceuticals and personal-care products (*e.g.* carbamazepine, caffeine and sulfamethoxazole), endocrine-disrupting compounds (*e.g.* nonylphenol) and flame retardants) [9]. The US Food and Drug Administration (USFDA) have regulated pharmaceuticals in the environment in the USA since 1977 under the auspices of the National Environmental Policy Act of 1969. Regulation occurs through the environmental review process for New Drug Applications submitted to the FDA. USEPA has not set a national primary drinking-water regulation (NPDWR) for PPCPs. USEPA does not believe that there is sufficient information to warrant regulation of PPCPs at this time [10]. Other countries are considering how pharmaceuticals might be regulated. In Brazil, the decree n° 379 of 2011 [8] establish the procedures and responsibilities for the control and surveillance of potable water and it does not include the monitoring of waste PPCPs.

Efficient, fast and sensitive analytical methods are needed to address the occurrence, distribution and final destination of PPCPs and pesticides in the environment. Their relatively low concentration together with their interaction with complex environmental matrices makes their analysis difficult.

Before the introduction of atmospheric pressure ionization, determinations of PPCPs and mainly pesticides were performed by high performance liquid chromatography coupled to ultraviolet detection (HPLC–UV) and gas chromatography (GC) coupled to flame ionization detection (GC–FID), electron capture detection (GC–ECD) and mass spectrometry (GC–MS). Nowadays, liquid-chromatography coupled to mass spectrometry (LC–MS) has largely replaced GC and HPLC methods, especially LC–tandem mass spectrometry (LC–MS/MS) and ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) which provides additional selectivity and sensitivity. Although mass spectrometry techniques enables increasing sensitivity, a sample preparation technique which allows the analyte preconcentration is almost always necessary to reach limits of detection low enough to determine the trace levels at which emerging contaminants are present in the environmental waters [11]. The sample preparation is an important step for the determination of trace compounds, thus, there is considerable interest in developing methods for extracting and isolating components from complex environmental matrices.

Several analytical methods of the measurement of PPCPs and pesticides in environmental waters have been published lately. A general view of LC–MS and LC-MS/MS methods developed for the determination of regularly used PPCPs and pesticides in environmental waters samples is given in Table 1.

This review covers the development and application of the LC-MS and LC-MS/MS to environmental water samples and highlights the sample preparation used within these techniques over the period from 2005 to September 2011. Abstract searches were carried out using Web of Science and Scopus, and in many cases, full papers were analyzed.

## 2. Sample preparation

### 2.1 Solid-phase extraction (SPE)

First introduced in the mid-1970s, it became commercially available in 1978. Now SPE cartridges and disks are available from many suppliers [12]. Conventional SPE is generally performed by passing aqueous samples through a solid sorbent in which the pollutants will be retained. Afterwards, they are eluted from the sorbent with an appropriate organic solvent [13].

SPE is undoubtedly the preferred technique for sample preparation of water samples in combination with LC-MS, since it provides a convenient, cost-effective alternative to liquid-liquid extraction (LLE) and has been shown to be valuable for extracting, concentrating, and cleaning-up molecules with a wide range of physicochemical properties. Most of the recent papers found during the revision (Table 1) employed SPE as sample preparation; it remains the most popular means of extraction and concentration for PPCP and

pesticide extraction. The last trends in the application of SPE for the extraction of pesticides in waters samples and subsequently determination with LC-MS or LC-MS/MS have been reviewed here.

### 2.1.1 SPE cartridges

One of the greatest difficulties in developing a multi-residue method is finding the appropriate sorbent and extraction conditions that produce an acceptable recovery for most analytes [14]. Therefore, this area also continues to change as new sorbents that offer improved recoveries for polar analytes are manufactured and dual-phase media are being used to capture a broader range of analytes within a single extraction [15]. In many of the analytical methods described in the literature, the target compounds are determined simultaneously in a multi-residue method. This simultaneous analysis of several groups of compounds generally requires care in the selection of experimental conditions, which, in some cases, means that the best performance will not be obtained for each compound.

The most common retention mechanisms in SPE are based on van der Waals forces (non-polar interactions), hydrogen bonding, dipole-dipole forces (polar interactions) and cation-anion interactions (ionic interactions). Hydrophobic interaction occurs when the solid sorbent is highly non-polar. The most common non-polar sorbent is octadecyl-bonded silica (C18-silica). Bonded-phase silica materials are the dominant sorbents used in SPE. In part, this is a carryover from liquid chromatography where the use of octadecylsilane silicas (ODS) is well established. It should be recognized that the sorptive properties of silicas vary with the percentage of carbon in the bonded phase and whether the sorbents are end-bonded phase and whether the sorbents are end-capped [16,17].

Although bonded-phase silica sorbents are generally considered to be satisfactory for use in SPE, the percentage recovery of analytes is frequently lower than with polymeric sorbents. Polymeric materials, have been widely used. Polymer-based sorbents are styrene/divivinylbenzene materials. It is used for retaining hydrophobic compounds which contain some hydrophilic functionality, especially aromatics. A copolymer of divinylbenzene and N-vinylpyrrolidone (Oasis HLB from Waters) is the most employed, and the presence of both hydrophilic and lipophilic moieties supposedly make this a balanced sorbent. It is capable of extracting acidic, basic and neutral compounds of varying polarities. Its ability to extract relatively small polar compounds effectively may be explained in part by the ability of the amide group to act as a hydrogen acceptor [16,17].

As shown in Table 1, Waters Oasis HLB (Hydrophilic-Lipophilic Balanced) cartridge has been the cartridge of choice for the preconcentration of both polar and non-polar compounds using the same extraction conditions, a pre-requisite for multi-residue analysis of different PPCPs [18]. Several papers reported on the evaluation of a number of stationary phases for SPE of the selected pharmaceuticals, however, in some cases, reaching opposite conclusions with respect to the best sorbent material for the extraction of the same group of pharmaceutical compounds. For example, for acidic non-steroidal anti-inflammatory drugs some authors indicated that C18 silica sorbents yield superior results than the polymeric ones, while other reported higher recoveries by the polymeric Oasis HLB cartridges [19].

Recently, mixed-mode polymeric sorbents have enabled highly selective extraction for acid and basic compounds. These new sorbents provide the dual modes of retention (ion exchange and reversed phase) and are very useful because the interactions among the analytes and the sorbent allow exhaustive clean-up. The most commonly used mixed-mode polymeric sorbents for extracting PCPs are cationic [*e.g.* Oasis MCX (strong cationic-exchange/reversed)] because of its effectiveness at extracting the basic compounds. It is known that Oasis MCX is more selective than Oasis HLB, and capable of sorpting fewer matrix components, which results in higher SPE recoveries or lower ion suppression in the ESI source [20,21].

Kasprzyk-Hordern *et al*. [22] developed a new multi-residue method for the determination of 25 acidic/neutral PPCPs in surface water with the use of UHPLC–MS/MS. The SPE method was optimized in several preliminary experiments involving some variables, such as the type of adsorbent. Oasis MCX (60 mg) and HLB (60 mg) were found to give the best recoveries for most PPCPs and therefore they were used for further analysis. One liter of acidified and filtered water sample was passed through the cartridge. The average recovery (R%) was between 9.4 to 133.9% with relative standard deviation (RSD) lower than 18.3%. The limits of quantification of the method (LOQs) were at low ng $L^{-1}$ levels and ranged from 0.3 to 30 ng $L^{-1}$.

Some studies have reported the use of other sorbents. Kuster *et al*. [23] investigated the presence of 21 emerging contaminants, including PPCPs and pesticides, of various chemical groups found in river waters in Spain. Chemical analyses were performed by means of on-line or off-line SPE followed by LC- MS/MS with electrospray (ESI) ionization. In off-line SPE water samples (250 mL river and drinking water, 50 mL effluent wastewater) were loaded onto SPE

**Table 1.** Overview of representative LC-MS methods for quantitative determination of PPCPs and pesticides in environmental samples.

| Matrix | Analytes | Sample preparation | LC-MS characteristics | | | LOQ LOD (ng $L^{-1}$) | R (%) | Matrix effect compensation | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | Analytical column | Mobile-phase constituents | Ionization and detection | | | | |
| **PPCPs** | | | | | | | | | |
| **Surface water** | PPCPs | SPE- MCX and HLB cartriges | C18 100×2.1 mm i.d., 3.5 $\mu$m | 20 mM ammonium acetate (pH 6.5) and acetonitrile | LC–ESI-MS/MS | LOQ: 5.52 - 150.15 | 62.1 - 125.4 | Internal standard | [99] |
| **Surface water** | Antibiotics | SPE - HLB cartridges | C18 100×2.1 mm i.d., 1.7 $\mu$m | ultrapure water and acetonitrile, both solvents with 0.01% formic acid | UHPLC-ESI-MS/MS | LOQ: 10 | 70-120 | n.e.[a] | [81] |
| **Surface sea water** | Antibiotics | SPE - HLB cartridges | C18 2.1×50 mm i.d., 5 $\mu$m | 0.01% formic acid in water and methanol | LC–ESI-MS/MS | LOQ: 2-13 | 71-100 | External standard calibration | [82] |
| **Surface water** | Antibiotics | SPE - HLB cartridges | C18 250×4.6 mm i.d., 5 $\mu$m | 0.1% aqueous trifluoracetic acid and acetonitrile | LC–ESI-MS | LOD: 600–8100 LOQ: 2000–24000 | >80 | External standard calibration | [84] |
| **Drinking water, surface water, effluent water.** | Estrogens Progestogens PPCPs Pesticides | on-line SPE cartridges: estrogens and progestogens: PLRP-s Pesticides: Hysphere Resin GP PPCPs: C18 | C18 125×2 mm i.d., 5 $\mu$m | acetonitrile and methanol | LC-ESI-MS/MS | LOD: 850-30000 | 30-108 | External standard calibration | [23] |
| **Surface water, ground water** | Antibiotics | SPE - HLB cartridges | C18 100×2.1 mm, 3 $\mu$m | acetonitrile, methanol and water with 0.3% formic acid | LC-ESI-MS/MS | LOD: 30- 190 LOQ: 100- 650 | 71-119 | Internal standard | [83] |
| **Surface water** | Antibiotics Neutral pesticides Acidic pesticides | SPE on-line-HLB cartridges | C18 125×2mm i.d., 5 $\mu$m ODS 3 CP, 125×2 mm i.d., 3 $\mu$m | water, formic acid, ammonia acetate and methanol | LC-ESI-MS/MS | LOD: 0.5 -5 LOQ: 1-10 | 85-112 | Isotope labelled standard | [48] |
| **Surface water** | Analgesics/anti-inflammatories Lipid regulators Diuretics Pesticides Disinfectants | SPE - HLB cartridges | C18 250×3.0 mm i.d., 5 $\mu$m | acetonitrile and water (pH 8 with ammonium hydroxide) | LC–ESI-MS/MS QqLIT | LOQ: 100 -10000 | 75-120 | Matrix-matched calibration | [92] |
| **Surface water** | Pharmaceuticals Hormones Personal care products Flame retardant | SPE - HLB cartridges | C12 250×4.6 mm i.d., 4 $\mu$m | 0.1% formic acid (v/v) in water and methanol | LC-MS/MS ESI and APCI | LOD: 1.0-10 | 68-112 | n.e. | [100] |
| **Influent and Effluent Wastewater** | Neutral pharmaceuticals | SPE - HLB cartridges | C18 150×3 mm i.d., 4 $\mu$m | 10 mM ammonium acetate and acetonitrile | LC-APCI-MS/MS QTrap | ------ | 85-130 | Isotope labelled standard | [85] |
| **Surface water** | Histamine receptor antagonists Psychoactive stimulant Antiepileptics Antihypertensive Non-steroidal anti-inflammatory Analgesic and antipyretic Lipid regulator Antibiotics Antibacterial Skin care ingredients Metabolites | SPE - HLB cartridges and Strata-X cartridges | C18 150×4.6 mm i.d., 3 $\mu$m | 0.1% formic acid and acetonitrile | LC-ESI-MS/MS | LOQ: 0.5 to 98 | 51-115 | Standard addition method | [101] |
| **Surface water, sea water, influent and effluent wastewater** | UV sunscreen agents | SPE - HLB cartridges | C18 150× 2.1mm i.d., 3.5 $\mu$m | ultrapure water and methanol, both containing 5 mM of ammonium acetate (pH 6.8) | LC-ESI-MS/MS | LOQ: 300 - 4000 LOD: 7-46 | 63-102 | Standard addition method | [102] |

Continued **Table 1.** Overview of representative LC-MS methods for quantitative determination of PPCPs and pesticides in environmental samples.

| Matrix | Analytes | Sample preparation | LC-MS characteristics | | | LOQ LOD (ng $L^{-1}$) | R (%) | Matrix effect compensation | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | Analytical column | Mobile-phase constituents | Ionization and detection | | | | |
| **Surface water** | Antibacterial drugs<br>Anti-inflammatory/ Analgesics<br>Antiepileptic drugs<br>Beta-adrenoceptor blocking drugs<br>Lipid regulating agents<br>H2-receptor antagonists<br>Diuretics<br>Triazides<br>Cardiac glicozides<br>Bronchodilators<br>Antidepressants<br>Illicit drugs<br>Personal care products | SPE - MCX cartridges | C18<br>100×1 mm i.d.,<br>1.7 $\mu$m | water, methanol, 0.5% acetic acid and 5 mM ammonium hydroxide | UPLC-ESI-MS/MS | LOD: 0.05-20<br>LOQ: 0.3-30 | 5-144<br>(most between 70-120) | Surrogate/ internal standards | [103] |
| **Surface water** | Antiepileptic drugs<br>Antibacterial drugs<br>Beta-adrenoceptor blocking drugs<br>Non-Opioid Analgesics<br>Opioid analgesics<br>Lipid-regulating agents<br>Bronchodilators<br>Histamine-2 blockers<br>Anti-inflammatory agents<br>Antidepressants<br>Drugs of abuse<br>Calcium channel blockers<br>Angiotensin II antagonists | SPE - MCX cartridges | C18<br>100×1 mm i.d.,<br>1.7 $\mu$m | water, methanol, acetonitrile, acetic acid 0.5% | UPLC–ESI-MS/MS | LOQ: 0.3 to 50 | 0.5-175.9 | Standard addition method | [104] |
| **Surface water** | Antibiotics<br>Anti- Inflammatory/ analgesics<br>Lipid regulating agents<br>Diuretics<br>Triazides<br>H2-receptor antagonists<br>Cardiac glicozideso<br>Angiotensin II antagonists<br>Sunscreen agents<br>Preservatives | SPE - MCX cartridges and HLB cartridges | C18<br>100×1 mm i.d.,<br>1.7 $\mu$m | water, methanol and acetonitrile 0.5% acetic acid, 10 mM TrBA; | UPLC–ESI-MS/MS | LOQ: 0.3- 30 | 8.3-130 | Internal standards calibration | [22] |
| **Surface water, influent and effluent wastewater** | Analgesics/anti-inflammatories<br>Lipid regulators<br>Psychiatric drugs<br>Antiulcer agent<br>Histamine H1 and H2 receptor antagonists<br>Antibiotics<br>ß-Blockers | SPE - HLB cartridges | C18<br>125×2.0 mm i.d.,<br>5 $\mu$m | water and methanol | LC–ESI-MS/MS | LOD<br>Surface :0.5-30<br>Influent :1-60<br>Effluent :2-60<br>LOQ<br>Surface :2-160<br>Influent :3-160<br>Effluent :6-160 | Surface :30-121<br>Influent :30-114<br>Effluent :34-113 | Internal standards calibration | [105] |
| **Surface water, tap water, treated and raw wastewater** | Pharmaceuticals<br>Bactericide<br>Acidic herbicides<br>Insect repellents<br>UV screen filters<br>Organophosphorous flame retardants | SPE - HLB cartridges | C18<br>150×2.1 mm i.d.,<br>3.5 $\mu$m | ultrapure water and methanol, both containing 5 mM of ammonium acetate | LC–ESI-MS/MS | LOD: 0.3 and 30 | Tap: 22-115<br>Surface: 55-146<br>Treated ww : 34-132<br>Raw ww :43-121 | Internal Standards calibration | [106] |

Continued **Table 1.** Overview of representative LC-MS methods for quantitative determination of PPCPs and pesticides in environmental samples.

| Matrix | Analytes | Sample preparation | LC-MS characteristics | | | LOQ LOD (ng $L^{-1}$) | R (%) | Matrix effect compensation | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | Analytical column | Mobile-phase constituents | Ionization and detection | | | | |
| **Surface water** | Pharmaceuticals | SPE - HLB cartridges | C18 75×4.6 mm i.d., 3.5 μm | ultrapure water with 0.1% formic acid, acetonitrile and methanol | LC–ESI-MS/MS | LOD Ultrapure water :1000-214000 Surface water :2000 -715000 LOQ Ultrapure water :1000-288000 Surface water :4000-963000 | 65–103 | Deuterated internal standards | [107] |
| **Surface water, wastewater, drinking water** | Anti-depressants and metabolites | SPE- MCX cartridges | C18 150 x 2.1 mm i.d., 4 mm | Not cited | LC-APCI-MS/ MS Q-Trap | LOD Wastewater: 4000 Surface water: 3000 LOQ Wastewater: 13000 Surface water: 9000 | 6-113 (70-110 for most) | External standard method | [108] |
| **Coastal waters, Sea water** | Antibiotics | SPE - HLB cartridges and MCX cartridges | C18 150×2.1 mm i.d., 3.5 μm | methanol and ultrapure water, both with 0.1% formic acid | LC–ESI-MS/MS | LOQ: 0.13–2.38 | 67-109.3 | Matrix-matched calibration | [25] |
| **Surface and tap water** | Antibacterials Antidepressants Antiepileptics Antihistamines Antineoplastics and immunosuppressants Anxiolytic Bronchodilators Gastrointestinal drugs Local anesthetics Stimulants | SPE - HLB cartridges | C18 250×3.0 mm i.d., 5 μm | acetonitrile and ultrapure water with 0.1% formic acid | LC–ESI-MS/MS Q-Trap | LOD: 0.1–60 | >70 | n.e. | [109] |
| **Reconstituted water (represented lake and river water)** | Lipid-regulator Antiepileptic drug Synthetic hormone Antimicrobial | SPE - ENVI-18 cartridges and HLB cartridges | C8 100×2.1 mm i.d., 3.5 μm | water and methanol | LC-ESI-MS/MS | LOD: 1120 - 4330 LOQ: 3760 - 14420 | 71-91 | Internal standard | [96] |
| **WWTP effluents** | Endocrine Disrupting Compounds Pharmaceuticals and Personal Care Products | SPE - HLB cartridges | C12 250×4.6 mm i.d., 4 μm | 0.1% formic acid (in water and methanol | LC-MS/MS ESI and APCI | LOD: 0.126-5.5 | 72-96 | External standard calibration | [110] |
| **Wastewater Influent and effluent** | Pharmaceuticals | SPE - HLB cartridges | C18 150×4.6 mm i.d., 5 μm | 5 mM ammonium acetate in water and methanol | LC-ESI-MS/MS | LOD: 0.02-0.55 | Influent: 88-106 Effluent: 85-108 Surface: 96-113 Drinking water: 91-116 | Isotopically labeled standards | [111] |
| **Raw and treated wastewaters** | Analgesics/anti-inflammatories | HF-LPME polypropylene membrane supporting dihexyl ether (three-phase hollow fiber-based liquid-phase microextraction (HF-LPME)) | C18 100×2.0 mm i.d., 2.8 μm | 0.1% formic acid (pH 2.6) and methanol | LC-ESI-MS/MS | LOD: 20- 300 | 50-100.3 | External standard calibration | [112] |

Continued **Table 1.** Overview of representative LC-MS methods for quantitative determination of PPCPs and pesticides in environmental samples.

| Matrix | Analytes | Sample preparation | LC-MS characteristics | | | LOQ LOD (ng $L^{-1}$) | R (%) | Matrix effect compensation | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | Analytical column | Mobile-phase constituents | Ionization and detection | | | | |
| **Surface and drinking water** | Pharmaceuticals | SPE - Strata-X cartridges | C18 50×3 mm i.d., 3.5 μm | methanol and water acidified with 0.1% formic acid | LC-APCI-MS/MS | LOD: 53 - 530 LOQ: 160 – 1600 | 76-120 | Matrix-matched calibration | [98] |
| **River and tap water** | Analgesics/anti-inflammatory | DLLME Extrac. solvent: Chloroform dispersing solvent:acetone | C18 50×2.0 mm i.d., 3 μm | ammonium acetate in water and methanol | LC-ESI-MS/MS | LOQ: 0.5 to 10 | 71-85 | No matrix effect observed | [113] |
| **Wastewater and surface water** | Biocides UV-filter Benzothiazoles | SPE - HLB cartridges | C18 150×3 mm i.d., 4 μm | 10 mM ammonium formate pH 3.2 with formic acid, and acetonitrile with 0.1% formic acid | LC–MS/MS ESI and APCI | LOQ ESI: WWT influent: 5-200 effluent: 2.5-100 Surface water: 0.5-20 | ESI: 69-130 APCI: 70-135 | Isotope-labeled surrogate standards, internal standard | [86] |
| **Surface water, influent and effluent wastewater** | Preservatives Antimicrobial agents UV filters | SPE - river water samples - Bond Elut Plexa cartridge sewage samples - HLB cartridges | C18 50×4.6 mm, 1.8 μm | ultrapure water with acetic acid (pH 2.8) and methanol | UHPLC–ESI-MS/MS | River water: LOQ: 3-5 LOD: 1-4 sewage water: LOQ: 5-50 LOD: 3-10 | Influent: 27-89 Effluent: 38-92 river water:46-101 | n.e. | [114] |
| **PESTICIDES** | | | | | | | | | |
| **Agricultural drainage** | 15 pesticides | SPE- Graphitized Carbon Black (GCB) disks | C18 250×4.6 mm i.d., 5 μm | water and methanol, both 1 mM of formic Acid | Screening SALDI/MS Quantification: LC-ESI-MS/MS | LOD: 4 - 280 | 55-86 | Internal standard | [39] |
| **Surface** | 36 compounds (19 pesticides) | SPE – Strata-X | C18 125×2.1 mm i.d., 3 μm | water 1 mM ammonium acetate and methanol | LC-FLD-ESI-MS/MS Qtrap | LOQ: 0.2-9 | 83-105 | | [115] |
| **Wastewaters (WW), treated (TW), surface (SW) and ground Waters (GW)** | 33 compounds (20 pesticides) | SPE – Strata C18 | C18 100×2.0 mm i.d., 3 μm | 10 mM ammonium acetate in water and methanol | LC-ESI-MS/MS QqQ | LOQ: 0.2 - 296 | 50-118 | Standard addition | [31] |
| **Surface and urban wastewater** | 5 pesticides and 6 transformation products | SPE – Oasis HLB | Acquity UPLC HSS T3 column, 100×2.1 mm i.d., 1.8 μm | Water and methanol | UHPLC-ESI-MS/MS QqQ | LOQ: SW: 0.9 - 20 IWW: 6 - 150 EWW: 3 - 58 | SW: 77 - 118 IWW: 70 -121 EWW: 70 - 113 | Isotope-labelled standards | [116] |
| **Facade run-off waters** | 13 biocides | SPE - H2Ophobic DVB cartridges | Synergy polar-RP column 150×2 mm, 4 μm | water and acetonitrile with 0.1% formic acid | LC-APCI-MS/MS QqQ | LOQ: 20 - 200 | 32 - 200 | Labelled internal standards and APCI | [32] |
| **Wastewater** | 14 compounds (1 pesticide) | SPE – Oasis HLB | C18 250×3.0 mm i.d., 5 μm | acetonitrile and water p 8 H HH 8 | LC-MS/MS QqQLIT | LOQ: 3 | 112 | Matrix-matched calibration | [92] |
| **Marine aquaculture** | 29 compounds (15 pesticides and biocides) | POCIS | C18 250×3.0 mm i.d., 5 μm | acetonitrile and water 0.1% formic acid | LC-ESI-MS/MS QqQLIT | LODi: 10 - 1250 | 5 - 98 | Matrix-matched calibration | [65] |
| **wastewater** | 56 compounds (6 pesticides) | SPE – Oasis HLB | C18 250×3.0 mm i.d., 5 μm | acetonitrile and water 0.1% formic acid | LC-MS/MS Qtrap LC-ESI-TOF-MS | LOQ: 0.2 - 7 | 16 - 1120 | Matrix-matched calibration | [117] |
| **Tap water** | 3 compounds | DLLME –carbon tetrachloride and acetonitrile | C18 50×3.0 mm i.d., 3.5 μm | acetonitrile and water both 0.1% formic acid | LC-ESI-MS/MS QqQ | LOQ: 20 | 62.7 - 120 | n.e. | [60] |

Continued **Table 1.** Overview of representative LC-MS methods for quantitative determination of PPCPs and pesticides in environmental samples.

| Matrix | Analytes | Sample preparation | LC-MS characteristics | | | LOQ LOD (ng $L^{-1}$) | R (%) | Matrix effect compensation | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | Analytical column | Mobile-phase constituents | Ionization and detection | | | | |
| **Groundwater** | 4 pesticides | SPE – Strata C18-E | C18 50×3.0 mm i.d., 3.5 $\mu$m | acetonitrile and water both 0.1% formic acid | LC-ESI-MS/MS QqQ | LOQ: 4 - 40 | 67 – 108.9 | n.e. | [118] |
| **River** | 18 pesticides (7 by LC-MS) | SPE- Carbograph 4 | C18 150×3.0 mm i.d., 5 $\mu$m | water and methanol, both containing 0.25% acetic acid | LC-ESI-MS Ion trap | LOD: 6 - 30 | 91 - 116 | No matrix effect observed | [40] |
| **Drinking, surface and wastewater** | 28 pesticides | SPE – Oasis HLB | C18 100×2.1 mm i.d., 3 $\mu$m | methanol and water 5 mM ammonium acetate | LC-ESI-MS/MS QqQ | LOQ: 25 - 50 | 44 - 90 | n.e. | [33] |
| **Surface and drinking** | 18 pesticides and 2 metabolites | SPE – C18 | C18 50×3.0 mm i.d., 3.5 $\mu$m | methanol, acetonitrile 0.1% formic acid and water 0.1% formic acid | LC-ESI-MS/MS QqQ | LOD: 0.4 – 40 | 53.1 – 136.3 | n.e. | [30] |
| **Tap and wastewater** | 31 pesticides | Direct injection | C18 50×4.6 mm i.d., 1.8 $\mu$m | 5 mM ammonium formiate in Water and methanol | LC-ESI-MS/MS QqQ | LOD: 2 - 15 | - | No matrix effect found | [67] |
| **Surface and ground** | 14 pesticides | SPE – Oasis HLB | C18 75×4.6 mm i.d., 3.5 $\mu$m | water, methanol and 10 % acetic acid | LC-ESI-MS/MS Ion trap | LOD: GW: 0.4 – 5.5 SW: 0.5 - 5 | GW: 72 - 129 SW: 73 - 121 | Matrix-matched calibration | [119] |
| **River and sea** | 12 pesticides | SPE – C18 | C18 150×75 mm i.d., 3.5 $\mu$m | water and acetonitrile | Direct-EI-MS Single quadrupole | LOD: 44 - 330 | 66 - 113 | No matrix effect found | [120] |
| **River** | 19 pesticides | SPE- Carbograph | C18 150×75 mm i.d., 3.5 $\mu$m | water and acetonitrile both acidified with 0.1% formic acid | Direct-EI-MS Single quadrupole | LOD: 2 - 52 | 56 – 113 | n.e. | [38] |
| **Tap, leaching and sewage** | 48 pesticides and 19 metabolites | UAE – acetonitrile | C8 150×4.6 mm i.d., 5 $\mu$m | acetonitrile and water with 0.1% HCOOH | LC-ESI-MS/MS QqQ | 50 - 5000 | 74.6 – 111.2 | Matrix-matched calibration | [61] |
| **Drinking and surface** | 14 compounds (3 pesticides and 2 transformation products) | SPE on-line- Strata X | C18 50×2.0 mm i.d., 4 $\mu$m | water, methanol and acetonitrile all with 0.1% formic acid | LC-ESI-MS/MS QqQ | 0.4 - 3 | 60 - 109 | Standard addition | [49] |
| **Groundwater** | 8 pesticides and 3 metabolites | SPE- molecularly imprinted polymer (MIP4SPE Triazine 10) | C18 125×2.0 mm i.d., 5 $\mu$m | water and methanol | LC-ESI-MS/MS QTrap | LOD: tapwater 0.025 – 1.449 Groundwater 0.015 – 2.37 HPLC water 0.017 – 2.183 | 31 - 105 | Internal labeled standard | [36] |
| **Surface** | 31 pesticides | SPE – Oasis HLB | C18 bounded to an ethylene-bridged hybrid substrate 50×1 mm i.d., 1.7 $\mu$m | acetonitrile and water both 0.1% formic acid | UPLC-ESI-MS/MS QqQ | LOD: 1 - 20 | 76.7 – 106.7 | n.e. | [121] |
| **Mineral** | 300 pesticides | Direct sample injection | C18 50×2 mm i.d., 5 $\mu$m | methanol, water and 5mM ammonium formate | LC-ESI-MS/MS QqQ | LOD: 100 - 1000 | between 80 and 120% for 240 compounds | Standard addition | [122] |
| **Rainwater, surface and groundwater** | 1 pesticide | SPE – Strata X | C8 150×2 mm i.d., 5 $\mu$m | methanol and 50 mM heptafluorbutyric acid in water | LC-ESI-MS/MS QqQ | LOD: 3 - 8 | 58-92 | Internal standard | [123] |
| **Surface and groundwater** | 11 pesticides and 15 transformation products | SPE – Oasis HLB | C18 80×2 mm i.d., 5 $\mu$m | 1 mM aqueous formic acid and acetonitrile for acidic and neutral pesticides<br>water and acetonitrile for basic pesticides | LC- MS/MS QqQ QTOF hybrid | LOD: SW: 2 - 25 GW: 2 - 25 | SW: 72 – 110 GW: 70 - 109 | n. e. | [91] |
| **Groundwater and surface** | 3 pesticides | SPE on-line – Oasis HLB | C18 50×2.0 mm, 5 $\mu$m | water 5 mM acetic acid and ammonium acetate pH 4.8 and acetonitrile | LC-ESI-MS/MS QqQ | LOD: 5 | GW: 72 – 116 SW: 84 – 111 | internal labeled standard | [124] |

Continued **Table 1.** Overview of representative LC-MS methods for quantitative determination of PPCPs and pesticides in environmental samples.

| Matrix | Analytes | Sample preparation | LC-MS characteristics | | | LOQ LOD (ng $L^{-1}$) | R (%) | Matrix effect compensation | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | Analytical column | Mobile-phase constituents | Ionization and detection | | | | |
| **River** | 1 pesticide | LLE - dichloromethane | C18 125×4.0 mm i.d., 5 µm | methanol and ammonium acetate 0.01 M | LC-ESI-MS/MS QqQ | LOD: 0.9 | 46.8-56.6 | n.e. | [63] |
| **Groundwater** | 1 pesticide and 5 degradation products | SPE – Oasis HLB | C18 150×3.0 mm i.d., 3.5 µm | acetonitrile and 5 mM acetate ammonium pH 4 | LC-ESI-MS/MS QqQ | LOD: 7-253 | 51 - 110 | n.e. | [125] |
| **River** | 30 pesticides | SPE- Bond elut PPL | C18 50×2 mm i.d., 5 µm | methanol and water with 0.1% formic acid | LC-ESI-MS/MS QqQ | LOQ: 4 - 93 | 23.6 – 114.3 | n.e. | [126] |
| **Natural and treated** | 20 pesticides | SPE on-line - PLRP-s and Hysphere Resin GP | C18 125×2.06 mm i.d., 5 µm | acetonitrile and water | LC-ESI-MS/MS QqQ | LOD: 0.004 – 2.8 | 21 - 111 | n.e. | [57] |
| **River** | 22 pesticides | SPE on-line - PLRP-s and Hysphere Resin GP | C18 125×5.0 mm i.d., 5.0 µm | acetonitrile and water | LC-MS/MS QqQ | | | n.e. | [50] |
| **Drinking, surface and groundwater** | 1 pesticide | Direct injection | C18 100×2.1 mm i.d., 1.8 µm | acetonitrile and water 0.01% formic acid | UPLC-ESI-MS/MS QqQ | LOD: 10 | n.e. | Internal labeled standard | [68] |
| **River** | 21 compounds (5 pesticides) | SPE on-line – PLRP-s (cross linked styrene-Divinylbenzene) | C18 125×2.0 i.d., 5.0 µm | acetonitrile and water | LC-ESI-MS/MS QqQ | LOD: 0.03 – 0.99 | 69 - 108 | n.e. | [23] |
| **Dam ponds (surface)** | 13 pesticides | SPE – Strata X | C18 50×2.1 mm i.d., 1.8 µm | acetonitrile and water 0.0125% acetic acid | LC-ESI-MS/MS Qtrap | LOD: 0.2 – 74.6 | 42 - 125 | - | [127] |
| **Drinking** | 9 pesticides | SPE – Speedisks 18 | C18 150×2.1 mm i.d., 3.5 µm | water and acetonitrile | LC-ESI-MS/MS Single quadrupole | LOD: 10- 23 | 34 - 111 | Found but not corrected | [45] |
| **Mineral and natural waters** | 25 pesticides and 8 metabolites | SPE- Chromabond HR-X<br>Polar Organic Chemical Integrative Sampler (POCIS) | C18 100×2.0 mm i.d., 3 µm | acetonitrile and 5 mM ammonium acetate | HPLC-ESI-MS/MS QqQ | LOD: 20 - 100 | 80 - 120 | Internal labeled standard | [66] |
| **Water samples** | 7 pesticides | SPE – Oasis HLB | C18 150×3.0 mm i.d., 3.5 µm | water and acetonitrile both with 0.1% acetic acid | LC-ESI-MS/MS QqQ | LOD: 100 | Acetochlor Carbofuran Dimethoate, Isoproturon, (63.5 – 108.6) Acephate , Methamidophos (5.3 – 10.9) | Internal standard | [128] |
| **Ground** | 59 compounds (12 pesticides and 4 transformation products) | SPE – Oasis HLB | Hypersil gold column 100×2.1 mm i.d., 3 µm | water and acetonitrile Different modifiers were used in aqueous condition depending on the compounds | LC-ESI-MS/MS QqQ | LOD: 0.2 – 0.5 | | Internal labeled standards | [129] |
| **River** | 34 compounds (10 pesticides) | SPE – Oasis HLB | Hypersil gold column 100×2.1 mm i.d., 3 µm | water and acetonitrile Different modifiers were used in aqueous condition depending on the compounds | LC-ESI-MS/MS QqQ | LOD: 1 | 69 - 75 | Not found | [130] |
| **Surface and tap** | 33 compounds (7 pesticides) | SPE –Oasis HLB | Hypersil gold column 100×2.1 mm i.d., 3 µm | water 0.1% acetic acid and acetonitrile | LC-ESI-MS/MS QqQ | LOD: 0.02 – 0.5 | 69 - 75 | Internal labelled calibration | [131] |
| **River** | 35 compounds (9 pesticides) | SPE- Oasis HLB | Hypersil gold column 100×2.1 mm, 3 µm | water and acetonitrile Different modifiers were used in aqueous condition depending on the compounds | LC-ESI-MS/MS QqQ | LOD: 0.001 | 56 - 72 | Internal labeled standard | [132] |

Continued **Table 1.** Overview of representative LC-MS methods for quantitative determination of PPCPs and pesticides in environmental samples.

| Matrix | Analytes | Sample preparation | LC-MS characteristics | | | LOQ LOD (ng $L^{-1}$) | R (%) | Matrix effect compensation | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | Analytical column | Mobile-phase constituents | Ionization and detection | | | | |
| **Ground and surface water** | 18 pesticides | SPE on-line – PRP1 cartridges (polymeric) | C18 80×2.0 mm i.d., 5 $\mu$m | water and acetonitrile for basic and neutral pesticides<br>acetonitrile and 0.01% formic acid for acidic pesticides | LC-ESI-MS/MS QqQ | LOD: 0.1 - 25 | GW: 56 - 115 SW:25 - 114 | No found | [51] |
| **Surface, drinking, treated wastewater and groundwater** | 37 pesticides | SPE – Oasis HLB | Acquity UPLC HSS T3 100×2.1 mm i.d. 1.8 $\mu$m | water and methanol both 0.1 mM ammonium acetate | UHPLC-ESI-MS/MS QqQ | LOD: 25 | DW: 41 – 134 SW: 36 – 126 GW: 55 – 194 TW: 24 - 120 | isotope labeled standards | [87] |
| **River** | 33 compounds (19 pesticides) | SPE on-line – Oasis HLB | C18 100×2.0 mm, 3 $\mu$m | acetonitrile and water with 0.1% formic acid | LC-ESI-MS/MS QqQ | LOD: 0.0005 | - | n.e. | [52] |
| **Creek, pond, drinking, wll, surface** | 2 pesticides | SPE – Oasis MCX | Phenyl-hexyl 150×4.6 mmi.d., 3 $\mu$m | water 0.1% HCOOC and methanol | LC-ESI-MS/MS | LOD: 0.001 – 0.02 | 66 - 104 | No matrix effect found | [133] |
| **Paddy field water** | 70 pesticides | Direct injection | C8 150×4.5 mmi.d., 5 $\mu$m | acetonitrile and water with 0.1% formic acid | LC-QqLIT-MS/MS | LOD: 4 - 500 | - | No matrix effect was observed | [69] |
| **Groundwater** | 22 pesticides | SPE on-line - PLRPs positive ionization mode Hysphere-Resin GP cartridges | C18 125×2 mm i.d., 5 $\mu$m | acetonitrile and water | LC-ESI-MS/MS | LOD: 0.05 – 3.91 | 75 - 158 | n.e. | [53] |
| **Drinking** | 4 pesticides | SPE – Lichrolut EN – C18 | LichroCart 125-4 Lichrosphere 100 5 $\mu$m | water and methanol, both with 0.01% acetic acid | LC-ESI-MS Single quadrupole | LOD: 10 | 95 - 104 | n.e. | [134] |
| **Drinking** | 21 compounds | Direct aqueous injection (DAI) | Waters Atlantis T3 analytical column (2.1× 150 mm i.d., 5 $\mu$m) | methanol and water 20 M ammonium formate | LC-ESI-MS/MS QqQ | 11 - 1500 | Deionized water (92-107) Tap water (88.4-109) Chlorinated ground water (89.3-112) | Standard calibration curves with preservatives and internal Standards | [70] |
| **Surface and wastewater** | 13 compounds (11 pesticides) | SPE on-line – Strata-X | C18 50×2 mm i.d., - | water and methanol both with 0.1% formic acid | LC-ESI-MS/MS QqQ | LOQ: 5 - 100 | Surface – 71 – 103 Wastewater – 62 - 104 | Isotope labelled surrogate standards | [54] |
| **Drinking** | 8 pesticides | Lyophilization and extraction with acetonitrile | C18 50×4.6 mm i.d., 5 $\mu$m | water 0.1% formic acid and acetonitrile | LC-ESI-MS/MS Q-trap | LOD: 4.9 – 28.7 | 96 - 103 | n.e. | [62] |
| **Surface** | 28 compounds (18 pesticides) | SPE on-line – Oasis HLB | C18 125×2 mm i.d., 5 $\mu$m, neutral pesticides<br>GromSil ODS, 125×2 mm i.d., 3 $\mu$m Acidic pesticides | methanol and water with formic acid | LC-ESI-MS/MS QqQ | LOD: 0.5 - 3 | 95 - 112 | Isotope labelled internal standards | [48] |
| **River and sea** | 1 pesticide | SPE - C18 | C18 150×2.1 mm i.d., 5 $\mu$m | methanol and water with 0.1% formic acid | LC-ESI-MS/MS QqQ | LOD: 6 | 90 - 95 | n.e. | [28] |
| **Pharmaceutical effluent** | 9 compounds (1 pesticide) | SPE - Phenyl | pentafluorophenyl 100×4.6 mm i.d., 5 $\mu$m) | water and acetonitrile both with 2 mM ammonium acetate and 2 mM acetic acid | LC-ESI-MS/MS QqQ | LOQ: 0.05 | 55.8 -108.3 | Standard addition | [34] |
| **waste water, surface water, ground water** | 9 compounds (1 pesticide) | SPE - Phenyl | Pentafluorophenyl 100×4.6 mm i.d., 5 $\mu$m | water and acetonitrile both with 2 mM ammonium acetate and 2 mM acetic acid | LC-ESI-MS/MS QqQ | LOQ: 0.05 | - | Standard addition | [76] |
| **Agricultural waters** | 32 pesticides | SPE – Oasis HLB | C18 150×2 mm i.d., 5 $\mu$m | methanol and water both 0.1% acetic acid | LC-ESI-MS | LOQ: 25 - 50 | 60 – 109.9 | Matrix-matched calibration | [135] |

Continued **Table 1.** Overview of representative LC-MS methods for quantitative determination of PPCPs and pesticides in environmental samples.

| Matrix | Analytes | Sample preparation | LC-MS characteristics | | | LOQ LOD (ng $L^{-1}$) | R (%) | Matrix effect compensation | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | Analytical column | Mobile-phase constituents | Ionization and detection | | | | |
| **Surface and wastewater** | 10 compounds (3 pesticides and 2 metabolites) | SPE on-line - Hypersil GOLD column | Hypersil GOLD column 50×2.1 mm i.d., 3 $\mu$m | methanol and 0.1% formic acid in water | LC-ESI-MS/MS QqQ | LOD: 2 - 17 | SW: 91 – 106 WW: 87 - 104 | Internal standards | [55] |
| **Municipal wastewater treatment plants and surface** | 36 compounds (26 pesticides) | SPE - Oasis-HLB | C18 150×3 mm i.d., 4 $\mu$m | 10 mM ammonium formate pH 3.2 with formic acid acetonitrile with 0.1% formic acid and 0.1% formic acid and acetonitrile | LC-ESI-MS/MS LC-APCI-MS/MS QqQ | 5 - 50 | 84 - 136 | Stable isotope-labeled surrogate standards | [86] |
| **River** | 1 pesticide and 3 transformation products | SPE – oxidized MWCNT | C18 50×2.1 mm i.d., 1.8 $\mu$m | methanol and water pH 4 | HPLC-UV-ES-MS | LOD: 20 - 40 | 85.6 – 101.4 | n.e. | [43] |
| **Source waters** | 2 pesticides | SPE - Oasis WCX | CAPCELL PAK CR 1:4 (2.0×150 mm 5 $\mu$m, SCX:C18 = 1:4) | acetonitrile and water 20 mM acetate ammonium and acetic acid | LC-ESI-MS Single quadrupole | LOD: 14 - 22 | 91 - 118 | Matrix matched-calibration | [77] |

*n.e. – not evaluated*

C18 cartridges (500 mg). Fully automated on-line trace enrichment and analysis of estrogens, progestogens and acidic pesticides in samples, aqueous standards and blanks were performed with an automated on-line SPE sample processor configured for high sample volumes and connected in series with the LC–MS/MS instrument. Extraction of the sample (20 mL) was performed with disposable trace enrichment polymeric cartridges; PLRP-s for estrogens and progestogens and Hysphere Resin GP for pesticides. LODs were 60.85 ng $L^{-1}$ for estrogens, 63.94 ng $L^{-1}$ for progestogens, 630 ng $L^{-1}$ for PPCPs and 60.99 ng $L^{-1}$ for pesticides. The average recovery was between 30 and 108% with RSD lower than 10%.

Yan *et al*. [24] extracted and quantified ten highly potent estrogens by SPE followed by LC-MS. An improved two-step SPE process was employed in this study. C18 cartridge was used for both enrichment of all target estrogens and retention of some non-polar impurities, and then a polar florisil cartridge was subsequently used to separate the estrogens of interest from the polar impurities. After this pretreatment for water samples, the results showed clean chromatograms without interference of matrix effects. The R% was between 70.4 and 106.8% with RSDs varying from 3.4 to 16.7% for river water and between 73.4 and 101.3% with RSD from 1.3 to 17.8% for raw sewage. The LOQ was in the range from 15 to 70 ng $L^{-1}$.

The application of more than one cartridge in series has also gotten attention in recent studies. Guangshui *et al*. [25] developed a method for the rapid detection of 36 antibiotic residues in coastal waters: its consists of SPE and LC-ESI-MS/MS. SPE was carried out using an Oasis HLB cartridge (60 mg) and an Oasis MCX cartridge (60 mg) in series and connected to a SPE manifold. The sample volume was 500 mL. Typical recoveries of the analytes ranged from 67.4 to 109.3% with RSD below 14.6% for all the compounds. The LODs varied from 0.45 pg to 7.97 pg.

Locatelli *et al*. [26] describes the development and application of a method for the determination of antibiotics in Brazilian surface waters. Anion exchange and polymeric SPE cartridges, in series, were employed during the extraction procedures. Anionic-exchange cartridges containing 500 mg Strata SAX were used to remove humic substances, and a polymeric Oasis HLB (500 mg) was used to retain target compounds. The samples (1 L) were loaded at a flow rate of 5 mL $min^{-1}$. LODs varied from 0.13 to 0.76 ng $L^{-1}$. The average recovery was 16.8 and 105%, with RSD lower than 19.1%.

Lacey *et al*. [27] developed an analytical method for simultaneous detection and identification of 20 pharmaceutical compounds from various therapeutic classes using SPE followed by LC–MS/MS. Various sorbents including Strata-X cartridges (200 mg), Supelco C8 (500 mg), Supelco C18 (500 mg), Waters Oasis HLB (200 mg), Varian Focus (20 mg) and Merck LiChrolut-EN (200 mg) were investigated for sample pretreatment and analyte preconcentration. Strata-X yielded the highest average recovery for the analytes under investigation and it was used for further studies. Aliquots of 500 mL of samples were used. LOQ ranged from

0.005 to 2.850 μg $L^{-1}$ in influent samples and from 0.003 to 2.478 μg $L^{-1}$ in effluent samples. The RSDs were lower than 20%.

Several types of SPE sorbents have been found to be suitable for extracting pesticides from water samples. There are sorbents with more selectivity and others that cover a higher range of polarities. Therefore an appropriate balance between selectivity and the ability to retain as many analytes of potential interest as possible is required. For the extraction of pesticides belonging to a higher range of polarity, C18 bonded silicas and styrene/divinyl benzene co-polymers are the most commonly used.

C18 bonded silica has been less applied than polymeric phases for pesticide extraction., Its use is mostly reported for the extraction of few analytes or analytes belonging to the same chemical class. Tsukatani *et al*. [28] developed a simple and selective method for the determination of hexaconazole in river and sea water samples. Samples (200 mL) were extracted in cartridges with 360 mg of C18. The average recovery was 95 and 90% for river and sea water samples, respectively, with RSD lower than 7.3%. The LOD was 6 ng $L^{-1}$.

Famiglini *et al*. [29] employed a method for organochlorine determination based on SPE preconcentration step followed by nanoscale liquid chromatography coupled to a direct-electron ionization direct interface (Direct-EI). Tests were performed in seawater, river water, and ultrapure water samples. Water samples (1 L) were extracted by SPE with C18 cartridges packed with 500 mg. The recovery values of all compounds varied from 66 up to 113% with RSD between 4 and 32%. LODs of the method ranging from 0.044 to 0.33 μg $L^{-1}$ were obtained.

More compounds belonging to several classes were extracted using SPE with C18 in the study developed by Demoliner *et al*. [30]. An analytical method using SPE and LC-ESI-MS/MS for the determination and confirmation of eighteen polar pesticides (herbicides, insecticides and fungicides) and two metabolites in water samples was presented. A volume of 250 mL of surface and drinking water samples was pre-concentrated and extracted by SPE cartridges containing 500 mg of C18. The results showed satisfactory recovery percentages from 70 to 120% for 95% of the compounds, with RSD values lower than 20% for all compounds. The LOD varied between 0.4 and 40.0 ng $L^{-1}$.

The behavior of C18 for the extraction of 33 multi-class pollutants in wastewaters, surface and groundwater, using SPE was evaluated by Baugros *et al*. [31]. Target compounds include, in addition of pesticides, phthalates, alkylphenols and bisphenol A. The recovery rates for the pesticides under study that were determined by LC-MS gave levels ranging from 50 to 118% with RSD below 13%. The authors discussed the difficulties found during the extraction of both polar and apolar compounds. The performances of different SPE materials available in the laboratory were compared, testing cartridges with different sorbents: carbon graphite black, C18, and polymeric. C18 with 500 mg and a sample volume of 300 mL were selected. LODs varied between 0.0002 and 0.0889 μg $L^{-1}$.

Among the most employed cartridges are the polymeric ones, which are being produced with different modification and by many suppliers. Bester and Lamani [32] studied the extraction of biocides of four chemical classes and the fungicide thiocyanatomethylthiobenzothiazole with the determination by LC-MS/MS with atmospheric pressure chemical ionization (APCI). 100 mLsample from facade run-off waters were extracted. Considering that the pKow of the compounds ranges from 1.5 to 4.4, the extraction cartridges containing hydrophobic divinylbenzene, hydrophilic divinylbenzene, polar modified polystyrene-divinylbenzene, styrene divinylbenzene and C18 top layer with 200 mg styrene divinylbenzene lower layer were evaluated. Using the $H_2$Ophobic DVB (200 mg) cartridge all the compounds were well-extracted, except for the most hydrophilic compounds. The recoveries were between 32 and 200% with average RSD lower than 34%. The LOQs varied from 0.02 to 0.2 μg $L^{-1}$.

Twenty eight pesticides from 14 different chemical groups were extracted and quantified in a single procedure, comprising an SPE step and subsequent analysis by LC-MS/MS in a study developed by Carvalho *et al*. [33]. The optimized conditions for 500 mL sample enrichment deal with extraction with polymeric cartridges Oasis HLB (225 mg). Using C18 cartridges, for some of the compounds, namely 2,4 D, MCPA, and bentazone, retention was poor or absent. Changing the sample pH could minimize this problem but would create additional difficulties for the remaining compounds, thus, this option was put aside. Recoveries between 44 and 90% were reached with RSDs lower than 39.1%. The LOQs ranged from 0.025 to 0.05 μg $L^{-1}$.

Cartridges with phenyl sorbents also been used. Van de Steene *et al*. [34] reported the development and validation of a quantitative LC-ESI-MS/MS method for the simultaneous analysis of pharmaceuticals including a pesticide in environmental waters. Wastewater and surface samples (100 mL) were extracted with SPE on a phenyl cartridge (100 mg). Recoveries for all compounds were in the range of 55.8 and 108.3% with RSDs lower than 15%. LODs were in the range of <0.05 and 5 ng $L^{-1}$.

Field researches focusing on the design of selective extraction and clean-up materials, specific for one compound or a family of compounds, have also been found. Molecularly imprinted materials (MIPs) have been developed aiming at high capacity and selectivity. MIPs have proved to be a useful alternative to overcome the drawbacks of traditional SPE sorbents and immunosorbents [35]. Garcia-Galan *et al*. [36] describes the development of a selective and sensitive method for the simultaneous determination of triazines and triazine metabolites in waters, and its further application to natural samples. The method is based on sample extraction and pre-concentration with commercial molecularly imprinted polymer cartridges (MIP4SPE Triazine 10) followed by LC–ESI-MS/MS analysis. LODs achieved were as low as 0.015 ng $L^{-1}$ (groundwater). Method recovery rates were found to be analyte dependent, ranging from 55 to 123% with RSD values between 2 and 4%.

Gros *et al.* [37] describes the development of an analytical methodology to determine eight β-blockers in wastewaters using MIPs as extraction and pre-concentration material, followed by LC-MS and as mass analyzer the quadrupole-linear ion trap (QqLIT). The advantages offered by MIPs, in terms of selectivity and specificity, were compared with the most commonly used polymeric materials. Even though R% with both sorbents were similar, ranging from 50 to 110% for WWTP effluent and from 40 to 110% for WWTP influent, respectively. MIPs provided lower LODs than Oasis HLB, due to their specificity for target analytes and closely related analogues. LODs achieved using MIPs ranged from 0.2 to 6.4 µg $L^{-1}$ for WWTP effluent and from 0.4 to 6.5 µg $L^{-1}$ for WWTP influent. The intra-day precision was given by RSD values between 0.7 and 4.6%.

Graphitized carbon black (GCB), which is produced by heating carbon black to 2700-3000°C in an inert atmosphere, has been used for SPE of pesticides with varying polarities from water [38-40]. A simple platform for combining SPE and surface-assisted laser desorption ionization mass spectrometry (SALDI-MS), using disks prepared by embedding graphitized carbon black (GCB-4) particles in a network of polytetrafluoroethylene (PTFE) is presented by Amini *et al*. [39]. The system provides a convenient approach for rapid SALDI-MS screening of 15 pesticides in aqueous samples (200 mL), which can be followed by robust quantitative by LC-ESI-MS/MS of positive samples. The extraction disks are easily transferred between gaskets where the sample extraction and desorption of selected samples is performed. The recoveries after SALDI-MS were in the range from 55 to 86% with RSDs lower than 9%. The LC-ESI-MS/MS LODs were between 0.004 and 0.28 µg $L^{-1}$.

Another sorbent that has been used since its first report in 1991 are carbon nanotubes (CNTs) which have shown good possibilities for a wide variety of processes and applications. Because of their advantageous characteristics (high adsorption capacity, good thermal stability, wide pH range of application), CNTs have been employed in the extraction techniques such as SPE. There are two structural forms of CNTs exist: single-walled (SWCNTs) and multi-walled (MWCNTs) nanotubes [41,42].

The adsorptive potential of oxidized multi-walled carbon nanotubes (100 mg) for the extraction of mefenacet (MN) and its three photolysis degradation products namely hydroxylbenzothiazole (HBT), N-methylaniline (N-MA) and 2-benzothiazoloxyacetic acid (2-BAA) in water samples (500 mL) was investigated for the first time in the study developed by Yu *et al*. [43]. The determinations were done by LC-UV-ESI-MS. The mean recoveries were between 85.6 and 101.4% and RSDs were between 3.0 and 9.2%. The LODs obtained were between 0.02 and 0.04 µg $L^{-1}$.

### 2.1.2 SPE disks

Alternatively to the extraction cartridge, a membrane disk containing sorbent particles may be used in SPE. The sorbent particles embedded in the disks are smaller than those found in the cartridge. The short sample path and small particle size allow efficient trapping of analytes with a relatively high flow-rate through the sorbent, by comparison with the cartridges. The disks are primarily used to reduce analysis time when handling large volumes of aqueous environmental samples [44]. Li *et al*. [45] employed C18 disks for extraction of seven phenylurea compounds and two related herbicides in drinking water (500 mL). The determinations were carried out by LC-ESI-MS. The obtained method LODs were less than 0.03 µg $L^{-1}$, and the mean recoveries were 74–128% with a RSD of 2.6–8.3% for all compounds under study.

### 2.1.3 SPE on-line

An important feature of a sample preparation technique is to allow the automatization of all parts of analytical methods, through coupling the sample preparation procedure to the separation and detection system [11]. On-line SPE provides an automated way of sample pretreatment with automatic direct analysis of a high number of samples. When compared with off-line SPE, on-line SPE has made possible the development of faster methods. Conditioning, washing and elution steps can be performed automatically and some systems can also permit to extract one sample while another one is being analyzed by LC [46]. Besides, there is the decreasing risk

of contamination of the sample, elimination of analyte losses by evaporation or by degradation, improved precision and accuracy and higher sensitivity.

García-Galán *et al*. [36] presented a study that describes an automated methodology based on an on-line SPE-LC-ESI-MS/MS for the simultaneous analysis of 16 sulfonamides and five of their acetylated metabolites in groundwater. Recovery values employing HLB cartridges ranged from 34.3 to 134.4%. The LOD for all the analytes varied from 0.09 to 11 ng $L^{-1}$. On-line Oasis HLB cartridges were employed for the extraction of the samples (5 mL), as they showed the highest recovery rates in both off-line and on-line SPE.

López-Serna *et al*. [47] describes the development of a fully automated method, based on SPE–LC–MS/MS, for the determination of 74 pharmaceuticals in environmental waters (surface water and groundwater) as well as sewage waters. On-line SPE is performed by passing 2.5 mL of the water sample through a HySphere Resin GP cartridge. According to the authors, the main advantages of the method developed are high sensitivity (in the low ng $L^{-1}$ range), selectivity due the use of tandem mass spectrometry and reliability due the use of 51 surrogates and minimum sample manipulation. Absolute recoveries achieved 70, 73, 61, 42 and 36% for the target compounds in ultrapure water, groundwater, surface water, effluent and influent wastewater, respectively.

SPE on-line has been also performed for the extraction of pesticides from water samples [23,48,49,50-56].

Kampioti *et al*. [57] reports the development of a fully automated method for the multi-analyte determination of twenty pesticides belonging to different classes (triazines, phenylureas, organophosphates, anilines, acidic, propanil, and molinate) in natural and treated waters. The best results were achieved with 20 mL and with the polymeric cartridges. Under these conditions, recoveries higher than 50% were achieved for all compounds except deisopropylatrazine (23%), desethylatrazine (21%) and dimethoate (33%).The method, based on on-line SPE-LC-ESI-MS/MS presented LODs between 0.004 and 2.8 ng $L^{-1}$, RSDs between 2.0 and 12.1%; besides, it is rapid and simple.

## 2.2. Dispersive Liquid-Liquid Extraction

In 2006, Assadi and co-workers reported a rapid and inexpensive microextraction technique named dispersive liquid–liquid microextraction (DLLME). The technique uses µL volumes of extraction solvent along with a few mL of dispersive solvents. A mixture of the extraction and dispersive solvents are injected into an aqueous sample and a cloudy solution is formed, which generates a very high contact area between the aqueous phase and the extraction solvent. The advantages of the DLLME method over conventional solvent extraction methods are simplicity of operation, rapidity, low cost, easier manipulation, fewer of organic extraction solvents, high recovery and enrichment factor, and easier linkage to analytical methods.

Due to the characteristics of the extractor solvents employed in DLLME, it has been used more in combination with GC. In general it is important that the selected extracting organic solvent for DLLME method be compatible with the HPLC mobile phase. However, halogenated hydrocarbons such as chlorobenzene, carbon tetrachloride, chloroform and tetrachloroethylene, usually selected as extracting solvents in DLLME, have not a good chromatographic behavior. For this combination, an extra evaporation step is needed to evaporate them before final analysis. Since water-immiscible solvents are generally used in DLLME, the preferred technique for the analysis of extracts is GC. The versatility of DLLME-GC is seen in relation to the variety of applications in many areas [59], such as multi-residues analytical methods for the determinations of PPCPs and pesticides.

Caldas *et al*. [60] investigated the suitability of the DLLME and LC–ESI-MS/MS for the simultaneous determination of carbofuran, clomazone and tebuconazole in water samples. Under the optimum conditions, the R% ranged from 62.7 to 120.0%. The RSDs varied between 1.9 and 9.1%. The LOQs were 0.02 µg $L^{-1}$. The comparison of DLLME with SPE indicates that DLLME is a simple, fast, and inexpensive method for the determination of pesticides in environmental waters.

## 2.3. Less frequent sample preparation techniques

Currently, the most commonly used technique for extracting PPCPs and pesticides from waters is SPE; however, some studies have reported alternative techniques such as ultrasound assisted extraction, liquid-liquid extraction, passive sampling techniques and direct injection analysis. Some studies are described below.

Ultrasound assisted extraction was employed for the extraction of pesticides. A procedure involving initial single phase extraction of samples (10 mL) with acetonitrile (10 mL) by sonication, followed by liquid–liquid partition aided by “salting out” process using NaCl and determination by LC-MS/MS was developed by Fenoll *et al*. [61]. The method is rapid and sensitive for the simultaneous determination of 48 pesticides and 19 metabolites in waters (tap, leaching and sewage). The most frequent detection limit was 0.05 µg $L^{-1}$. The

average recovery by the LC–MS/MS method obtained for these compounds varied from 74.6 to 111.2% with a RSD between 2.5 and 8.9%.

A lyophilization of the sample after extraction with a solvent followed by LC-ESI-MS/MS is proposed by Sinha *et al*. [62]. In the method, acetonitrile was used directly to extract monocrotofos, imedacloprid, triazofos, ethion, atrazine, propanil, quinolfos and metribuzin from lyophilized samples at neutral pH, which prevented loss of compounds and gave better recovery by comparison with other methods. The method was accurate (96-103%), as it possessed LOD between 4.9 and 51 ng $L^{-1}$. The method employing lyophilization showed to be very sensitive, selective, accurate, simple and cost-effective for the determination of eight commonly used organophosphate pesticides in Indian drinking water samples.

Studies employing the liquid-liquid extraction (LLE) have already been found in the literature. Jacomini *et al*. [63] proposed a LLE for ametryn extraction from waters sample preparation with the determination by LC-ESI-MS/MS. The samples (100 mL) were extracted with 12 mL of dichloromethane. The recoveries were between 46.8 and 56.6% with RSD lower than 6.68%. The LOQ was 20 ng $L^{-1}$.

Throughout the last decade, aquatic passive sampling received increasing attention and a growing number of devices have been presented in the literature, such as the polar organic chemical integrative samplers (POCIS). POCIS have been applied successfully to the screening and the determination of contaminants in various aquatic environments (wastewater effluents, streams, lakes, rivers and coastal waters).

Generally, passive sampling techniques are based on the diffusion of chemicals from a medium to a receiving phase that is separated from the medium by a membrane, basically due to a difference in the chemical potential gradients. The uptake of the analytes depends on several factors such as the properties of both the receiving phase and the membrane, the physicochemical properties of the compounds, and environmental parameters such as temperature, water properties (pH, salinity, *etc.*), water turbulence and flow, biofouling of the membrane, *etc*. [64].

The POCISs enable the estimation of the cumulative aqueous exposure to bioavailable hydrophilic organic chemicals and permit the estimation/determination of the biologically relevant time-weighted average concentrations. The POCIS approach has been used as a screening tool for determining the presence/absence, possible sources and relative amounts of organic compounds at field sites.

Bueno *et al*. [65] assessed the capability to detect trace levels of contaminants in marine environments by means the use of sampler POCIS, by using LC–QqQLIT-MS for the determination of a group of chemicals, including antibiotics, fungicides, herbicides and biocides. Among the 27 compounds selected for this study, recovery values higher than 75% were obtained for most of them. For six compounds, the R% was lower or close to 50%. The instrumental LODs were between 0.01 and 1.50 µg $L^{-1}$.

Lissalde *et al*. [66] proposed an analytical method for determining 33 molecules representing eight pesticide classes in water using LC–ESI-MS/MS. Two techniques of field-sampling and analyte extraction were used: SPE and field exposure of POCIS. For SPE 50 mL water samples in 60 mg polymeric cartridges were used. For POCIS, 5 g of polymeric sorbent and elution with 6 mL solvent were used. The author's comparison concludes that, with POCIS, there is a high pre-concentration of analytes and reduced use of solvents since the extraction step was performed directly in situ. Furthermore, the development of a POCIS-LC–ESI-MS/MS method requires the optimization of a limited number of parameters with respect to SPE methods. For the POCIS, when sampling rates are available, only few adjustments (i.e. dilution of POCIS extracts and internal standard calibration) were necessary to obtain both acceptable accuracy and very low LOQs.

Some studies have reported the direct injection analysis (DIA) of the sample. The authors commented the use of SPE as sample preparation technique, but highlighted that it still is a quite laborious and expensive technique, as many work-up steps are involved and cartridge cost is quite high. Another important disadvantage of SPE is the high amount of co-extractives presented in the final extract, as generally 50- to 750-fold pre-concentration is needed to reach appropriate LODs. With the advance of the technologies involved in LC–MS/MS the instrumental detection limits of LC–MS systems have been improved from nanograms to sub-picograms levels, turning LC/MS–MS an invaluable tool for the detection of polar contaminants in aqueous environmental matrices. Thus, the number of studies employing DIA is increasing [67-70]. They report the development of a multi-residue method for the analysis of 70 pesticides from different chemical classes in paddy fields water by DIA avoiding some of the typical sample treatment steps employed in water analysis. After the water sample filtration, 5 µL sample was injected directly in a liquid chromatograph coupled to a hybrid triple quadrupole-linear ion trap-mass spectrometer (QqLIT).

LODs achieved were in the range from 0.4 to 80 ng $L^{-1}$. An important factor using this approach is the lower matrix effect found. The authors, found more than 20% of signal suppression/enhancement just 9 pesticides.

Modern techniques such as the solid-phase microextraction (SPME) have also been employed a sample-preparation method used for isolating and pre-concentrating organic molecules from gaseous, liquid and solid samples. It is highly sensitive and can be used for polar and non-polar analytes with different types of matrices. The mechanism of SPME is similar to that of SPE because SPME is a miniature version of SPE. The only difference being the volume of sorbent. SPME uses a short piece of a fused-silica fiber coated with a polymeric stationary phase placed on a syringe. During transport, storage and manipulation, the fiber is retracted into the needle of the device. Balakrishnan *et al*. [71] compared SPME with SPE procedures for extracting 10 sulfonamide antibiotics from wastewater in an effort to overcome these matrix effects. Considering the five different fiber assemblies under investigation, the carbowax/divinylbenzene (CW/DVB) fiber produced the optimal response to sulfonamides. SPE was not effective for the determination of sulfasalazine (not detectable after SPE) as opposed to SPME, which extracted all the sulfonamide compounds with efficiency higher than 75%.

Stir bar sorptive extraction (SBSE) deals with a magnetic stir bar coated with liquid phase (polymeric coat). The stir bar is introduced into the aqueous sample. After a time for equilibration the analytes are desorbed thermally or with a solvent. The main factor that determines the extraction efficiency is the partition coefficient of analytes between the phases. In a study developed by Bratkowska *et al.* [72] the preparation of stir bar coated with hydrophilic polymer based on poly(N-vinylpyrrolidone-co-divinylbenzene) for the sorptive extraction of polar pharmaceuticals is described. The developed method was applied in different complex environmental samples, including river, effluent and influent wastewater. The accuracy values for river waters ranging from 50 to 100% for most of the compounds, demonstrating the satisfactory ability of the monolithic material employed to retain both polar and semi-polar compounds.

## 3. LC-MS/MS

The development of liquid chromatography-atmospheric pressure ionization-mass spectrometry in the 1980s, and its broad instrumental implementation in the 1990s increased the analytical capabilities. After its introduction into environmental analysis a lot of progress has been made and a wide variety of compound classes has been determined [73].

LC–MS techniques have been increasingly employed for the determination of pesticides and PPCPs in water samples, especially regarding to the more polar ones, which are readily degradable. The most recent methods rely on the use of the tandem mass spectrometry detection (MS/MS), once its fragmentation pattern is a powerful tool for obtaining confidence in compound identification. In addition, the use of MS/MS detection allows analysis without complete chromatographic separation between the analytes, and therefore shortening of the chromatographic run time [74,75].

Most LC–MS systems rely on API interfaces namely atmospheric pressure chemical ionization (APCI) and electrospray ionization (ESI), but atmospheric pressure photoionization (APPI) and sonic spray ionization are now also being used.

For compounds from moderate to high polarity, ESI constitutes the most important ionization technique in mass spectrometry for the on-line coupling with LC for the analysis for typical environmental contaminants (<1000 Da). APCI is employed in few studies. Bester and Lamani [32] developed a method for the determination of biocides from facade material run-off water employing HPLC-MS/MS with APCI. The use of APCI is highlighted since it is less susceptible to matrix effects than ESI. SPE was used as sample preparation, and recovery rates in the range of 70 and 100% were reached. The LOQ for the compounds of interest ranged from 0.01 to 0.1 μg $L^{-1}$.

Related to the separation, reversed phase is the most employed kind of separation, and C18 is the sorbent most employed, regardless of the compounds to be determined. However, studies with C8, C12, polymeric, phenyl and silica sorbents also have been found. As an example, Van de Steene *et al*. [76] reports the development and validation of a quantitative LC-ESI-MS/MS method for the simultaneous analysis of nine basic pharmaceuticals in environmental waters. The authors have done experiments with a C18 column. But, trying to minimize matrix effects, a more specific pentafluorophenyl (PFP) column was chosen in view of the specific interactions possible between the stationary phase and the analytes. Matrix effects were expected to be less due to less interaction with interferences as compared to the C18-column. Although the matrix effect showed no differences in C18 and PFP column; due to the better separation of the standards achieved on the PFP column, and consequently better peak shape and reproducibility, this column was chosen for further

experiments. In another study, Yu *et al*. [77] developed a LC–MS method for the identification and quantification of chlormequat and mepiquat in water. Usually, C8, C18 or silica-based reversed-phase column was applied with aqueous HFBA (15–20 mM) and methanol or acetonitrile as mobile phases for the analyses of these compounds. To remove the need for the use of the ion-pair reagent, HFBA, which can pollute the MS, the CAPCELL PAK CR 1:4 (SCX:C18 = 1:4) column containing strong cationic exchange resins and C18 was tested in the study. The separation condition was determined as 20 mM ammonium acetate – acetic acid and 80% acetonitrile. The method avoids the MS instrument fouling problem accompanied with the use of ion-pair reagents.

In LC-MS/MS analysis, many factors could affect the detection sensitivity. The chemical and physical properties of the analyte and the composition of the mobile phase are amongst them. Detection sensitivity may also be enhanced *via* introduction of moieties with high proton affinity or electron affinity, which is reached with the mobile phase component modification, improving ionization efficiency [78]. Weak organic acids, such as acetic or formic acid, are often added to the solution when positive-ion ESI is performed. It is commonly accepted that the presence of the acid facilitates protonation of analytes with basic functional groups in positive-ion mode [79]. For the determination of pesticides and PPCPs the pH of the aqueous mobile phase is normally adjusted with formic acid, acetic acid, ammonium formate and ammonium acetate, while the most employed organic mobile phase contains methanol, acetonitrile or a combination of these two solvents.

PPCPs with acid characteristics, such as analgesic and nonesteroidal anti-inflammatory drugs or basic psychiatric drugs or analgesics require adjusting the pH of the mobile phase, where its value depends on the pKa of the compounds [80]. For the determination of antibiotics, the mobile phase is normally acidified with formic acid with concentrations that vary between 0.01 to 0.1% [25,81-83]. Besides, acidification with trifluoracetic acid is also found in the literature [84]. When methods for the determination of neutral pharmaceuticals are developed, ammonium acetate is the modifier most employed [85]. For the determination of a wide range of compounds, ranging from neutral to acids and belonging to different chemical classes, formic acid with ammonia acetate, acetic acid with TrBA and formic acid with ammonia hydroxide are preferred [22,48,86].

Trends in chromatographic analysis of environmental water samples comprises the employment of fast-LC methods using short, narrow bore columns, high mobile phase flow-rates and ultra-high pressures [75]. Moreover, when working with environmental samples monitoring studies are usually required; thus, shortening the analytical run times is an important step.

UHPLC is one of the options that have been used in environmental analysis; in which columns packed with sub-2 µm particles are used, resulting in better chromatographic resolution and increased peak capacity. UHPLC has been used to separate pesticides, as can be seen in the study developed by Marin *et al*. [87]. For the determination of 37 pesticides (herbicides, insecticides and fungicides) in environmental and wastewater an UHPLC-MS/MS with fast-acquisition triple quadrupole mass analyzer was used. The study shows that UHPLC–MS/MS is a rapid, selective and sensitive technique for the determination of multi-class pesticides in environmental and wastewater samples. With a chromatographic run time of 10 min, up to 37 pesticides were satisfactorily quantified at 0.025 µg $L^{-1}$ in different water types, with a previous off-line SPE pre-concentration step.

Recently, the application of UHPLC for the multi-residue analysis of pharmaceuticals in wastewater was presented. UHPLC was applied to the determination of 23 pharmaceuticals, including different classes of analgesic, anti-inflammatory, lipid regulators, psychiatric drugs, anti-ulcer agents, antibiotics and β-blockers, in a time of analysis of less than 10 minutes, using Quadrupole Time-of-flight (QqTOF) analyzer. The analysis of WWTP samples gave LODs ranging from 10 to 500 ng $L^{-1}$ [88].

In a study developed by Tamtam *et al*. [81] the occurrence and final destination of 17 antibiotics (quinolones, sulfonamides, nitroimidazoles and diaminopyrimidines) were investigated by UHPLC-MS/MS in the aqueous in the Seine River inner estuary. The study included SPE using HLB cartridges reached R% for all compounds varying from 70 to 120%.

Increasingly, tandem-MS and multiple reaction monitoring (MRM) are being used with both LC-MS and GC-MS to provide added selectivity and sensitivity [20]. The types of mass spectrometry include triple quadrupole (QqQ), ion trap (IT) and less frequently time-of-flight (TOF). According Wu *et al*. [14] triple quadrupole is the primary choice for PPCPs because of the selectivity and sensitivity, as well as the wide dynamic range. It enables the detection of a high number of analytes, and, in the literature, methods with detection from one to more than 250 pesticides are found. Normally, the analytical characteristics of the LC-QqQ-MS/MS show sensitivity and selectivity, although matrix effects are a drawback of this technology and they have to be carefully considered for correct quantification.

Hernandez *et al*. [89] pointed out some general limitations of QqQ for target screening; for example,

the required selection of the analytes prior to the development of the method (always target analysis); and the need for re-analysis when other compounds are suspected to be present in the sample.

Time of flight detectors has been used due to its power for identification of transformation products. Their intrinsic characteristic of highly accurate mass measurement and sensitivity in full-scan acquisition mode allows the reliable identification of a large number of degradation products in a single chromatographic run. Ferrer and Thurman [90] developed a comprehensive multi-residue method for the chromatographic separation and accurate mass identification of 101 pesticides and their degradation products using LC-TOF-MS. Several classes of compounds belonging to different chemical families (triazines, organophosphorous, carbamates, phenylureas, neonicotinoids, *etc.*) were carefully chosen to cover a wide range of applications in the environmental field. Excellent chromatographic separation was achieved by the use of narrow accurate mass windows (0.05 Da) in a 30 min interval. At least the accurate mass for one main fragment ion for each pesticide was obtained to achieve the minimum of identification points. The methodology was successfully applied to the analysis of vegetables and water samples containing pesticides and their degradation products.

Hybrid systems have also been used, mainly for the identification of non-target and transformation products. Many pesticide transformation products (TPs) can reach environmental waters as a consequence of their normal high polarity, by comparison with similar pesticides. Hernandez *et al*. [91] reports the photodegradation of several pesticides in surface and groundwaters using the high-resolution and exact-mass capabilities of hybrid quadrupole time-of-flight mass spectrometry (QqTOF-MS) hyphenated to LC. Using on-line SPE-LC-MS/MS with a QqQ analyzer, the method reached LODs of 0.025 μg $L^{-1}$, obtaining satisfactory recoveries (70-100%) for all compounds. The study illustrates the extraordinary potential of LC-MS/MS with QqTOF and QqQ analyzers for qualitative/structural and quantitative analysis, respectively, offering analytical chemists one of the most powerful tools available at present to investigate the presence of pesticide TPs in water.

The application of hybrid instruments such as quadrupole-linear ion trap (QqLIT) that permits performing a sensitive quantitative analysis combined with an unequivocal identification and confirmation of target compounds is another approach used to confirm positive findings.

Martinez Bueno *et al*. [92] describe the development of an analytical method by using LC-QqLIT-MS for the determination of a group of chemicals, including antibiotics, fungicides, herbicides and biocides. The triple quadrupole/linear ion trap (QqLIT) is a hybrid system in which the final quadrupole can operate as conventional mass filter or as linear ion trap. The QqLIT-MS/MS system is an effective tool for obtaining excellent qualitative and quantitative results in a single analysis, based on its two most important features, the high selectivity and specificity of triple quadrupole for carrying out the quantification of analytes, and the confirmation criterion that the QqQ offers using the relationship between abundances of transitions selected for identification and quantification (SRM ratios). The instrumental limits of detection varied from 0.01 to 1.50 μg $L^{-1}$.

## 4. Matrix effect

The matrix effect is one of the obstacles of the LC-MS techniques. Reemsta *et al*. [73] highlights that due to the high selectivity and the low chemical noise usually experienced when using LC-API-MS to detect target compounds in water samples it is a fascinating technique, but also misleading.

Even when using LC–MS/MS, which is a highly selective method in selected ion monitoring and in multiple reaction monitoring (MRM) mode, matrix effects (ME) must be taken into account. In these operation modes only the signal of interest is registered, leaving out the information about the occurrence of all the other compounds. This gives the illusion that the other substances that co-elute with the analyte do not interfere with the results. However, the other compounds although invisible in the LC/MS signal, may and very often do interfere [93].

The mechanism and the origin of the matrix effect is not fully understood, but it may originate from the competition between an analyte and the coeluate, undetected matrix components reacting with primary ions formed in the LC-MS/MS interface. Depending on the environment in which the ionization and ion evaporation processes take place, this competition may effectively decrease (ion suppression) or increase (ion enhancement) the efficiency of formation of the desired analyte ions present at the same concentrations in the interface [94]. Ion suppression is often observed particularly for complex environmental samples and biosamples, and suppression may vary depending on the compound and matrix [95].

The number of reported examples of lack of selectivity due to ion suppression or enhancement caused by the sample matrix and interferences are increasing. Therefore, questions about how to develop and validate

reliable and selective LC-MS/MS method are being raised. Once the matrix effect is observed, procedures to compensate this effect should be performed, since the quantitative analysis based on a pure standard solution curve will be not appropriate. The central topic is, what experiments, in addition to the validation data usually provided need to be conducted to confirm LC-MS/MS reliability. Practical, experimental approaches for studying, identifying, and compensate the effect of matrix on the results of quantitative analyses by LC-MS/MS will depend on the analytes and the sample matrix. In general, the strategy to diminish matrix effects should take into account the variability of the matrix within the set of samples to be analyzed (*e.g.* river water, WWTP influent, effluent, sediment extracts, etc) and should be tested for each type of matrix.

In most cases the matrix effect cannot be eliminated. Some operating strategies such as the exhaustive sample clean-up; which may help remove interfering components, but it is time-consuming and runs the risk of losing analytes of interest [18]; better chromatographic separation to avoid analyte coeluting with the matrix components and serial dilution of the final extract so that fewer matrix components will be injected into the analytical are some of the options.

To provide more reliable and accurate analytical results several calibration methods can be implemented. Matrix-matched calibration standards can be used to establish a calibration curve; however, this approach requires the availability of uncontaminated sample matrix to be used to prepare calibration standards and that can be difficult to obtain [95]. Another approach would be to use standard addition, in which the calibration standards are added to the samples to generate a calibration curve for each sample. This process is tedious and impractical when there are a large number of samples. An effective approach to compensating for the matrix effect is the application of internal labelled compounds (ILCs). However, the poor availability and the high cost of ILCs are disadvantages of this approach [18].

An appropriate internal standard (structurally similar unlabeled compound) may compensate, over a limited retention time window, for the signal irreproducibility that leads to erroneous results. However, the matrix effect can strongly depend upon the chromatographic retention time and more than one internal standard may be needed and finding a suitable internal standard for each analyte can be a difficult task [19].

Another cited method consists of the addition of an ILC to each sample prior to analysis to correct for variations in ionization efficiency brought about by interactions with matrix co-eluents. Although widely accepted, this technique is most effective when the co-eluents have an identical effect on both the internal standard and the target analyte(s). In cases where the internal standard interacts with matrix components in a different manner than do the target analytes, the use of this approach would incorporate a non-systematic bias into calculations, resulting in quantification errors [96].

To compensate for matrix effects in LC-MS, isotope dilution methods are also becoming more common. For example, Hao *et al*. [97] used isotope dilution with SPE and LC-MS/MS to measure 51 organic contaminants, including 38 pharmaceuticals and 10 endocrine disruption compounds.

Highly-loaded environmental samples (*e.g*. influent and sludge from WWTPs) present a more severe matrix effect for the target analytes. From the outset, ESI is more susceptible to matrix effect than APCI. Since a majority of the applications of LC-MS and LC-MS/MS analysis of PPCPs use ESI as the ionization technique, it is essential to address this issue when developing and validating analytical methods in environmental matrices [18]. While matrix effects have been relatively well studied for applications of LC-MS/MS instrumentation with electrospray ionization, there have been relatively few studies to evaluate matrix effects when using atmospheric pressure chemical ionization (APCI) as the ion source [85]. Matrix effects was evaluated for 37 selected pesticides in nine waters (two groundwater samples, three surface water, two treated wastewater and two 50-fold diluted raw leachate water) in the study developed by Marin *et al.* [87]. The SPE extracts obtained for each blank sample were spiked with each individual pesticide and the ILCs used. The responses obtained after UHPLC–MS/MS analysis were compared with those of a solvent standard mix at the same level. Signal suppression (ME<100%) was typically observed. Pesticides determined in negative ionization mode presented matrix effects not much significant; while for most pesticides determined in positive ionization mode signal suppression was generally observed for all water types under analysis. The authors conclude that the results found in the study illustrate a heterogeneous behavior when determining multi-class analytes in different environmental water matrices, making rather difficult matrix effect correction. Due to differences existing in environmental waters composition, application of matrix-matched calibration is not reliable; standard additions or additional clean-up steps are time-consuming and involve more sample manipulation and sample dilution although might be a good option it would reduce method sensitivity. The best solution found by the authors was the use of 7 labelled compounds for correction of the matrix effect; showing satisfactory corrections.

The matrix effect for the determination of caffeine, fluoxetine, diclofenac, atenolol and sulfamethoxazole was evaluated in surface and treated waters and it was found to be quite different in both matrices. While in surface water most compounds presented enrichment of the signal, in the treated water signal suppression was found, and for fluoxetine and atenolol the matrix effect was higher than 30% [98].

Van de Steene and Lambert [34] compared matrix effects for LC-MS/MS and UHPLC-MS/MS for nine basic pharmaceuticals in surface waters. Matrix effects were substantial for these drugs with LC-ESI-MS/MS, such that analogue internal standards could not compensate for them and a standard addition approach was necessary. On the other hand, UHPLC provided much lower matrix effects (and sometimes eliminated them) due to better chromatographic resolution and less coelution of matrix compounds. As a result, UHPLC could be used with internal standards to simplify the quantification procedure.

## 5. Trends and conclusions

Several advanced analytical methods have been developed and optimized in recent years for water matrices, aimed at obtaining better precision and sensitivity and accurately quantifying contaminants present at trace concentrations in the aquatic environment.

For the extraction of pesticides and PPCPs from environmental samples, different sample preparation techniques have been employed, with emphasis to SPE, which is a well-established technique used for the extraction of numerous compound classes in water, with high accuracy and precision. Some modifications, such as the automation of SPE and the development of new sorbents have improved the extraction speed and the extraction efficiency. The polymeric sorbent are the most employed for extraction of PPCPs and pesticides. Alternative techniques have been applied more recently due to several advantages that they have over SPE in terms of speed, ease of sample handling and minimum solvent use. However, acceptable accuracy related to compounds belonging to several different classes has not been reached, indicating the need for more studies related to these techniques.

The use of LC-MS for qualitative and quantitative analyses of aqueous samples is growing. The rapid developments in the field of LC-MS/MS have transformed this technique into a key technique for the analysis of PPCPs and pesticides as environmental contaminants. The progress in LC-MS field, mainly for water analysis, is accompanied by a gradual shift in the perception of the tasks of water quality control: from the traditional focus on environmental contaminants of limited polarity that have long been accessible by GC-MS, towards more polar com-pounds that are relevant for the water cycle and, thus, for the potential of water reuse and for which LC-MS is the appropriate tool for analysis [73].

Regarding to the chromatography technique, the fastest trend continues to be the use of UHPLC. In addition to providing narrow peaks and improved chromatographic separations, UHPLC can also dramatically shorten analysis times.

LC-MS/MS with a QqQ detector is still the most employed technique; combined with a good sample preparation, it allows the determination of the compounds in trace levels. Nowadays, hybrid instruments such as QqTOF and QqLIT are expected to be widely applied due to their capabilities in achieving accurate mass measurements and acquiring indispensable qualitative information through full-scan spectra, respectively. However, the application of hybrid systems is still less common since the high cost that makes it unaffordable to most environmental laboratories.

The matrix effect in these kinds of samples has been discussed in many studies and strategies have been employed to compensate this effect. Although it is the most expensive way, the use of isotopically labeled compounds has been increasingly used to allow more accurate quantification in water samples (especially for wastewater, in which matrix effects and ion suppression can be substantial).

Petrovic *et al*. [75] highlight that the key issue is the quality of analytical data that should be tested and confirmed through the performance of inter-laboratory tests and combined with the use of reference materials. With the advance, many approaches to avoid false positives and detected, increasingly, environmental contaminant in ng and pg levels. According to Capdeville *et al*. [9], to prevent false positives, many authors make "blanks" go through analysis in parallel with their samples. In general, they use water free from organic matter and free from the targeted analytes. They are introduced at different moments to the sample treatment, from the sampling to the injection on the analytical instrument, in order to identify the origin of the contamination such as the environment at sampling time, the equipment used for sampling, filtration or extraction.

Degradation products of pesticides and pharmaceutical have become increasingly important and improved analytical techniques are enabling their identification and measurement in environmental

samples. Besides, new studies address their final destination in wastewater and drinking water treatment [20].

However, the main drawback of the conventional approach is target compound monitoring, which is often insufficient to assess the environmental relevance of emerging contaminants. With the increase of the analytical science and the advances in LC-MS/MS techniques, more knowledge about environmental contamination is becoming available, leading to the understanding of the complex behavior of these contaminants in the environment. Cooperation between analytical chemists and toxicologists is needed to answer the question: may low concentrations of xenobiotics still have any impact on living organisms? This paper aims at reviewing the analytical methods used for the analysis of various toxic compounds in water.

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