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Review

Contamination with Pharmaceuticals in Aquatic Environment: Focus on Analytical Methodologies

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Abstract: The growing prevalence of pharmaceutical compounds in the environment raises significant concerns due to their potential impacts on ecological and human health. This present manuscript focuses on the methods used to extract and determine these pharmaceuticals in water samples. It provides a comprehensive analysis of the extraction techniques and analytical approaches employed for the identification and quantification of pharmaceuticals in environmental water. Due to their chemical properties and widespread use, pharmaceuticals persist in the environment and contaminate water bodies, soil, and sediments. The presence of pharmaceuticals in the aquatic environment has been linked to several adverse effects on aquatic organisms, including the disruption of physiological processes and reproductive impairment. Furthermore, pharmaceuticals in the environment can affect human health through food and drinking water contamination and contribute to antibiotic resistance. The analysis of pharmaceutical contaminants in water samples presents several challenges due to the complex matrix and low concentrations of target substances. Various sample preparation techniques and protocols, including solid-phase extraction (more than 76% of the studied literature) and QuEChERS (quick, easy, cheap, effective, rugged, and safe), coupled with liquid chromatography–tandem-mass spectrometry, are commonly used for their determination. These methods offer high sensitivity, selectivity, and efficiency in identifying and quantifying pharmaceuticals in environmental samples. It is, therefore, essential that ongoing research is conducted in order to develop more efficient analytical methods and mitigation strategies to address pharmaceutical contamination in the environmental water effectively. It is also crucial that increased awareness and regulatory measures are put in place in order to minimize the environmental and human health risks associated with pharmaceutical pollutants.

Keywords: pharmaceuticals; environmental samples; analysis; extraction; determination

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1. Introduction

Pharmaceutical substances are indispensable components of contemporary medicine and veterinary practice. They are primarily used to treat and prevent disease in humans and animals, and their beneficial effects on food production and economic prosperity are widely recognized. The growing global population, advances in research, investments in the pharmaceutical industry, and the ubiquitous availability of pharmaceuticals on the global market contribute to a significant increase in drug consumption [1]. According to a report by the Organization for Economic Co-operation and Development (OECD), global antibiotic consumption for livestock is expected to rise by 67% by 2030. Furthermore, drug consumption in industrialized nations such as Germany could rise by up to 67% by 2045 due to demographic changes [2].

Pharmaceuticals do not represent a new group of contaminants; their research in the environment has been dealt with worldwide and for a long time by many development researchers and workers; however, their specific occurrence according to actual medical situations, concentration levels, and variability in effluents is changing.

Although pharmaceuticals are not a novel class of contaminants, their presence in aquatic environments is becoming increasingly prevalent. These substances enter these ecosystems via a number of different pathways, including direct discharge from wastewater treatment plants (WWTPs) [3], agricultural runoff, and the improper disposal of unused medications [4]. The persistence and extensive distribution of these compounds give rise to concerns regarding their potential environmental and health impacts—the full extent of which is yet to be determined.

It is estimated that between 70 and 80 percent of this pollution originates from treated wastewater, while the remaining 20 to 30 percent is attributable to industrial waste [5], the improper disposal of unused or expired medications, and agricultural runoff. The pervasive occurrence of these contaminants underscores the inadequacy of conventional wastewater treatment processes in effectively removing pharmaceutical compounds. Despite numerous endeavors, current wastewater treatment methods frequently prove incapable of degrading or eliminating pharmaceutical substances, their metabolites, and byproducts [6].

Another significant source of contamination is the runoff from livestock farms and aquaculture, which utilize pharmaceuticals such as antibiotics and hormones [7]. The improper disposal of pharmaceuticals from households, hospitals, and healthcare facilities, in addition to landfill leachates, contributes further to the issue [8]. Despite the advent of novel advanced treatment methods, including biological processes and electrocoagulation, their overall efficiency remains constrained [9–11]. On the other hand, the occurrence and concentration of drugs in wastewater depend on the physicochemical properties of the pharmaceutical compounds ($\log K_{ow}$, volatility, etc.), the characteristics of the wastewater influent (i.e., alkalinity and acidity), the sorption of drugs onto suspended particles, and the treatment processes used [8]. Recently, novel treatment methods were introduced for the elimination of pharmaceuticals using advanced materials, such as micromotors and solar evaporation techniques [12,13], and Phoslock TM as a P&N-inactivation agent was also applied [14].

A selection of the most frequently occurring groups of monitored pharmaceutical substances in environmental water samples is shown in Figure 1. The pharmaceuticals that were identified in the aquatic environment belong to a number of different chemical classes. These include non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antiepileptics, β-blockers, steroid estrogens, and psychiatric medications [15–20]. Among the pharmaceuticals most often detected in the aquatic environment include (1) NSAIDs—such pharmaceuticals as ibuprofen, diclofenac, and naproxen are frequently detected due to their extensive use in the treatment of pain, inflammation, and fever [21]. (2) Antibiotics, including penicillin, macrolides, and sulfonamides, are prevalent due to their extensive application in human and veterinary medicine. Antibiotics are often detected in water due to their incomplete metabolism and disposal through agricultural runoff, improper waste management, and excretion from treated animals [22,23]. (3) Antiepileptic drugs and drugs for the treatment of mental disorders (antipsychotics) are a group of substances that do not contain a carboxyl group in their structure and are separable in a reverse-phase system. Such analytes can show a weak basic character due to the presence of the NH2 group or nitrogen in the cycle, such as carbamazepine or 10,11-epoxycarbamazepine (a drug for the treatment of mental disorders), diazepam [24], and others. Antiepileptics like carbamazepine, known for their persistence in wastewater treatment processes, are often used as indicators of pharmaceutical contamination [25,26].

The group of steroid estrogens are hormonal drugs, which include estrogens (hormonal contraceptives). With uncontrolled entry from the environment into living organisms, they can act as endocrine disruptors, i.e., disrupt the proper functioning of the organism. The structure of these compounds is formed by a phenolic core and possibly several hydroxyl groups. Estrogens are divided into natural (17-β-estradiol, estrone, estriol) and synthetic (17-α-ethinylestradiol, mestranol) types, and both types are lipophilic substances [27,28].

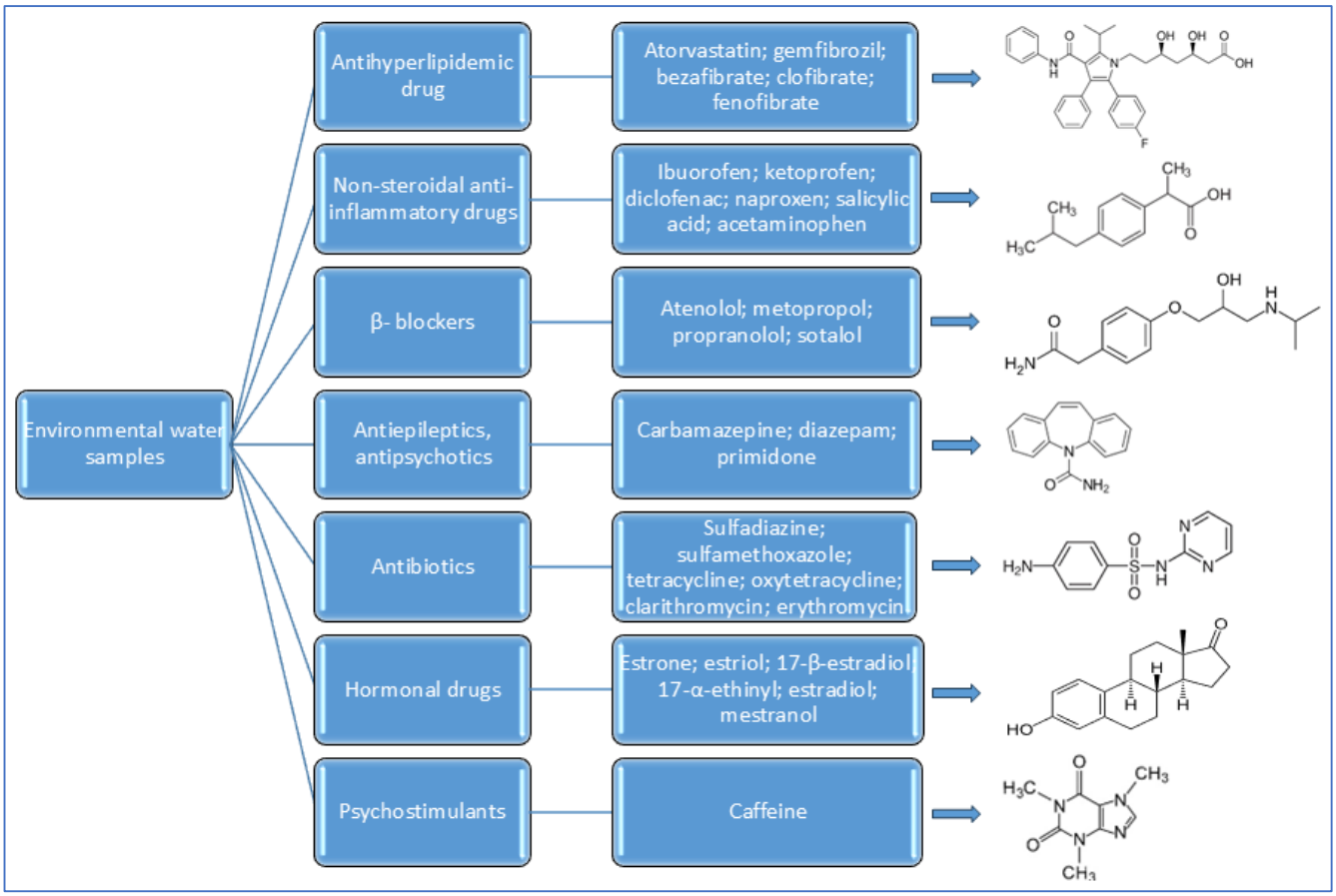


Figure 1. The most commonly detected pharmaceuticals in water samples and their chemical structures of the first representant in the group.

The concentrations of pharmaceuticals in the environment typically range from nanograms to micrograms per liter (ng/L to μg/L) [8,29], with over 600 pharmaceutical compounds detected globally [30]. The low levels of pharmaceuticals in the environment, combined with the complex nature of water matrices, present a significant challenge to their detection. Solid-phase extraction (SPE) is a commonly employed sample preparation technique due to its capacity to extract analytes by sorption onto a solid material from large volumes of water samples and subsequently elute them with a minimal volume of organic solvent, thereby achieving the preconcentration of target compounds [31]. Combining SPE, which preconcentrates the analytes and eliminates the interferents from environmental samples, with liquid chromatography separation and tandem-mass spectrometric detection (LC–MS/MS) provides a highly efficient analytical method for trace and ultra-trace analyses of pharmaceutical pollutants in environmental samples with high selectivity and sensitivity [32].

The physicochemical properties of pharmaceuticals exhibit considerable variation, which in turn affects their behavior in the environment. Lipophilic compounds tend to sorb onto particulate matter, whereas hydrophilic substances exhibit a greater propensity to disperse in aqueous solutions [4]. NSAIDs are persistent in the environment, where they can cause oxidative stress and reproductive harm to aquatic species. For example, diclofenac has been associated with cardiovascular damage in fish [33,34].

Considering antibiotics, such compounds contribute to the development of antibiotic resistance, which represents a significant environmental and public health concern. The exposure of organisms to sub-lethal concentrations of antibiotics in the environment has been demonstrated to promote the development and spread of antibiotic-resistant genes (ARGs) [35].

Meanwhile, steroid estrogens and the use of these hormonal drugs in contraception have been linked to endocrine disruption in aquatic organisms, which can result in reproductive abnormalities and population declines [36].

Antiepileptic and psychiatric medications, such as pharmaceutical agents carbamazepine and fluoxetine, have been demonstrated to exert an influence on the behavior of aquatic species while also causing neurotoxicity [37].

The toxic effects of these pharmaceuticals are not limited to the effects of individual compounds [38]. The combined effects of pharmaceuticals with other environmental contaminants can be additive or synergistic, leading to an exacerbation of the harm they cause to aquatic life.

Pharmaceuticals in the environment rarely exist in isolation. Instead, they form complex mixtures, which include active parent compounds, metabolites, and degradation products. These mixtures pose a greater risk than individual compounds, as they may interact with one another, leading to enhanced toxicity. Consequently, ecotoxicological studies are increasingly focusing on these combined effects, though assessing and managing such risks remains challenging [38].

The presence of pharmaceutical mixtures in aquatic environments gives rise to a number of significant regulatory and treatment challenges. The current wastewater treatment plants are not equipped to fully remove these complex compounds, which have the potential to exert long-lasting effects on ecosystems and human health [3,6].

This manuscript aims to raise awareness about pharmaceuticals' widespread presence and risks in the environment, emphasizing the need for improved monitoring, detection, and extraction methods for these contaminants in water samples. One of the main focuses of this manuscript is to address the challenges and complexities involved in accurately identifying and quantifying pharmaceuticals in environmental waters. Therefore, this manuscript highlights the importance of developing advanced analytical techniques, including optimized extraction modes, preconcentration procedures, and more sensitive detection methods such as high-performance liquid chromatography (HPLC), gas chromatography–mass spectrometry (GC–MS), liquid chromatography–mass spectrometry (LC–MS), and solid-phase extraction (SPE). These techniques are essential for identifying pharmaceuticals at low concentrations and ensuring that their presence and risks are accurately assessed.

2. Methodology

The main focus of this manuscript is to provide a review of the sample preparation and determination techniques used for pharmaceutical analysis in water samples. Table 1 contains a review of the publications for determining pharmaceuticals in water samples. A systematic literature search was conducted across multiple databases, including Web of Science, PubMed, ScienceDirect, and Google Scholar, to ensure a comprehensive and up-to-date review. The search was performed using a combination of key terms such as "pharmaceuticals in aquatic environment", "pharmaceutical contamination in water", "pharmaceutical occurrence in water bodies", "environmental impacts of pharmaceuticals", "analytical methodologies for pharmaceutical detection", and "sample preparation techniques for water analysis". The literature search was restricted to peer-reviewed articles, reviews, and relevant reports published between 2010 and 2023 to ensure that the review incorporates the most relevant findings and technological advances. The extracted data were synthesized to provide a comprehensive overview of the current knowledge on pharmaceutical contamination in water bodies. The studies were compared to identify common trends, methodologies, and findings, and critical insights were drawn.

Table 1. Overview of extraction techniques and analytical methods for the determination of selected pharmaceuticals in different types of water.

Sample	Analyte	Extraction Method	Instrumentation	Separation Conditions	LOD µg/L	Real Samples Finding µg/L	Ref.
Drinking water	NPS (15) Illegal drugs (3) Antidepressants (2)	SPE Strata-X-Drug B cartridge (60 mg/6 mL) Conditioning with 2 mL MeOH equilibration with 2 mL of 0.1 M HCl volume samples 200 mL acidified with 0.1 M HCl (pH = 2) washing with 0.1 M HCl elution 15% isopropanol/85% ethyl acetate and 2× 10% NH_4OH/20% isopropanol/70% ethyl acetate evaporation and reconstitution with 0.1 mL LC–MS solvent (0.5% formic acid/5% acetonitrile/94.5% water)	LC–MS	A: 0.5% formic acid in water B: 0.5% formic acid in ACN	0.00001–0.0011	-	[39]
Drainage water	Antibiotics (25)	DLLME 5 mL samples 20% (*w*/*v*) NaCl pH = 7.6 685 µL/1250 µL ACN Vortex 30 min Centrifuge 4000 rpm 10 min Evaporate the solvent with N_2 and dissolve in 150 µL of mobile phase	UHPLC–DAD	A: 0.3% CH_3COOH in water B: ACN	0.35–10.5	-	[40]
Groundwater	NSAIDs (6) Antibiotics (6)	DLLME	UPLC–ESI–MS/MS	A: 0.1% formic acid B: ACN	0.006–0.091		[19]
Hospital wastewater	Antibiotics (3) Pharmaceuticals (13)	SPE Oasis HLB cartridge (500 mg/6 cm^3) pre-conditioning with MeOH and pure water volume of samples 200 mL (pH = 8 NH_4OH) evaporation under vacuum elution MeOH	LC–MS/MS	A: 5 mM CH_3COONH_4 B: ACN	0.02–0.59	0.63–3.29	[41]

Table 1. *Cont.*

Sample	Analyte	Extraction Method	Instrumentation	Separation Conditions	LOD µg/L	Real Samples Finding µg/L	Ref.
Municipal and hospital wastewater	Pharmaceuticals (58) Antibiotics (16) Pesticides (33)	QuEChERS d-SPE ACN:MeOH (85:15, *v*/*v*) vortex citric acid monohydrate trisodium citrate dihydrate vortex centrifuge supernatant 5 mL Z-Sep vortex centrifuge evaporation of 150 µL extract using N_2 reconstitution to 150 µL H_2O:ACN (90:10, *v*/*v*)	LC–QqLIT–MS/MS	A: 0.1% HCOOH in Milli-Q water B: MeOH	0.002–0.2	0.005–0.677	[42]
Municipal and hospital wastewater	Pharmaceuticals and personal care products (138)	SPE Oasis HLB cartridges (200 mg/cm^3) Conditioning with Mili-Q water and MeOH sample with 5% Na2EDTA with a final concentration of 0.1% elution (×2) MeOH evaporation with N_2 and reconstitution to 0.5 mL with MeOH	LC–MS/MS	A: 5 mM NH_4COOH in Mili-Q water B: 5 mM NH_4COOH in MeOH	0.0002–0.00506	<LOD–81.491	[43]
River water	Anticonvulsants (1) Pacemakers (1) Muscle relaxants (1) Antiretroviral medicines (1) Antidepressants (1)	MASE-MIP (50 mg) Sample volume 18 mL 5 g NaCl mixing extraction time 60 min 1 mL $CHCl_3$ (acceptor solvent) MeOH (eluent)	LC–q-TOF/MS	A: 0.1% HCOOH in deionized water B: 0.1% HCOOH in ACN	0.09–0.20	0.31–2.48	[44]

Table 1. *Cont.*

Sample	Analyte	Extraction Method	Instrumentation	Separation Conditions	LOD µg/L	Real Samples Finding µg/L	Ref.
River water	Antiretroviral drugs (1) Antipyretics (1) Antibiotics (3) NSAIDs (1) Antiparasitics (1)	SPE Strata cartridges (200 mg/6 mL) Conditioning with MeOH elution 50% and 30% MeOH/distilled water sample volume 300 mL isolation 0.5% formic acid/MeOH evaporation reconstitution to 1 mL in 0.5% buffered MeOH concentration with compressed air and reconstitution in 1 mL of acidified MeOH	LC–MS/MS	A: 0.1% HCOOH in water B: 0.1% HCOOH in ACN	0.0439–0.0219	Up to 398.98	[45]
River water	Antibiotics (1) Anticonvulsants (1)	SPE 1 L samples 25 mg AC-PPS/AC-SBG Conditioning with 10 mL of ultrapure water Elution 5 mL + 5 mL acetone	HPLC–UV HPLC–FLD	A: 1% CH3COOH in water B: ACN	Carbamazepine 0.69 Sulfamethoxazole 0.015	-	[7]
Surface water	Antihistamine (4)	SPE Oasis HLB (500 mg) conditioning with distilled water volume 100 mL of equimolar mixture of samples (pH = 6.8) washing with distilled water elution with MeOH	LC–MS/MS	A: 0.1% HCOOH in water B: MeOH	5.3×10^{-8} mol/L–7.8×10^{-8} mol/L	-	[46]
Wastewater	Anticonvulsants (1) Antidepressants (2) Antibiotics (2) Stimulators (1)	Online SPE RAM-BSA column (664.5 mg Luna C18) conditioning with MeOH elution with 0.05 mmol/L phosphate (pH = 6) elution 1.0 mg/mL BSA elution with ultrapure water and 25% (*v*/*v*) glutaraldehyde solution washing with 1 mg/mL sodium borohydride solution conditioning with ultrapure water	LC–MS/MS	A: 0.1% HCOOH ultrapure water B: 0.1% HCOOH in ACN C: ultrapure water	0.01–3	<9.60	[47]

Table 1. *Cont.*

Sample	Analyte	Extraction Method	Instrumentation	Separation Conditions	LOD µg/L	Real Samples Finding µg/L	Ref.
Wastewater	Antibiotics (3) Anticonvulsants (1) Antidiabetic drugs (1) Gastroprotectors (1)	SPE OASIS HLB cartridges (200 mg/6 mL) conditioning with MeOH and deionized water sample volume 20 mL washing with deionized water elution (×2) MeOH filtration 0.2 µm PTFE	LC–MS/MS	A: water without additives B: 0.1% HCOOH in water C: ACN	0.0001–0.5114	0.00811–4.9859	[48]
Wastewater	Pharmaceuticals and personal care products (13)	SPE Oasis HLB cartridge (60 mg/3 cm^3) conditioning with MeOH and Mili-Q water sample volume 30 mL elution MeOH adjunction of 300 µL Mili-Q waters evaporation with N_2 to 1.0 mL vortex	UHPLC–Q–Orbitrap–MS	A: 0.1% CH3COOH in water B: ACN	0.01–0.61	-	[49]
Wastewater	Anticonvulsants (1)	D-µ-SPE 40 mg MIL to 10 mL samples with 300 ug/L 10% NaCl *w*/*v* mixing 700 rpm pH 2.8 desorption 500 µL with ACN ultrasound 45 min	HPLC–DAD	A: ACN B: deionized water C: 50 mM phosphate buffer solution with pH 3.5	Carbamazepine 0.51	-	[50]

3. Determination of Pharmaceuticals in Environmental Samples

One of the current challenges associated with the analysis of pharmaceutical contaminants in waters, such as wastewater from treatment plants and surface waters, is the complexity of the sample matrix. Analytes are often present in trace amounts along with other organic, inorganic, and/or biological interferents. Therefore, highly sensitive and selective analytical methods are used to reliably detect, identify, and quantify the target analytes. The developed analytical method for the trace to ultra-trace level analyses consists of sampling, sample preparation (i.e., isolation of the target analytes from the matrix), and analyte separation and detection [32].

3.1. Sample Preparation Techniques

Sample preparation is the first step of the analytical method and is crucial for the accurate and correct determination of analytes.

Suitable pretreatment methods are selected for different analytes in various environmental samples based on the physicochemical properties of the substances. In complex environmental matrices, analytes are converted into forms that can be easily extracted and purified. The result of sample preparation is the reduction of matrix interferences and the concentration of the analyte [51]. SPE has gradually replaced the traditionally used liquid–liquid extraction (LLE) method for the sample treatment, used to isolate organic compounds from the aqueous matrix into the organic layer. SPE is suitable for many types of environmental samples, allows for the analysis of the sample as a whole, and can also be automatized, ultimately enabling the processing of a large number of samples in a set time [10].

3.1.1. Solid-Phase Extraction (SPE)

SPE was developed in the 1970s [51] and is the most used extraction technique for the isolation of pharmaceuticals from environmental samples (Table 1). The mechanism employed in the extraction procedure is somewhat similar to that of liquid chromatography but occurs in several steps. The first step is to condition the sorbent by washing it to maximize analyte sorption by increasing the effective surface area. In the next step, the sample is applied to the sorbent, with the sorbent capacity depending on the sorbent type. For example, the sorbent capacity based on SiO_2 is 5 to 10% of its weight. Higher sorbent loading can lead to inefficient extraction. The third step involves washing out interferents, substances that did not bind to the sorbent or have significantly lower interactions with the sorbent than the analyte–sorbent interactions. The wash solution is a solvent that selectively removes unwanted components while not disrupting the analyte–sorbent bond. Several reagents or their mixtures may be used to achieve the desired sample purity. In the final step, the analytes are eluted from the sorbent surface. The eluent has a greater elution strength than the wash solution. The result is an analyte concentration by reducing the volume relative to the sample volume applied to the SPE device [32].

By using columns with various types of sorbents and selecting suitable eluents, a degree of analyte preconcentration sufficient for further determination by various detection techniques can be achieved. Depending on the analyte properties, silica-based composites, polymeric materials, organic–inorganic hybrid materials, natural sorbents, and carbon-based materials have been successfully used [7]. Some commonly used SPE sorbents include C8, aluminum oxide, C18, and silica [51]. Oasis HLB is widely used as an SPE sorbent because it can extract a wide range of pharmaceuticals from different types of water [52]. Oasis HLB columns with various particle sizes are capable of extracting both polar and non-polar compounds over a wide pH range due to their chemical compositions (a combination of lipophilic divinylbenzene and hydrophilic N-vinylpyrrolidone polymers) [53]. Strata-X is a surface-modified styrene-divinylbenzene polymer that, similar to Oasis HLB, can retain a wide range of analytes through hydrophilic and hydrophobic interactions. It is almost a universal sorbent for acidic, basic, and neutral analytes [54].

Although SPE is predominantly used offline, online coupling is also possible using column switching. Online SPE allows the automation of the analytical procedure, resulting in increased process efficiency, reduced sample handling, and prevention of cross-contamination [55].

The online SPE technique represents an automated continuous solid-phase extraction method, most often in a SPE–LC–MS/MS chromatographic system. In this type of solid-phase extraction, the same types of sorbents are used for the SPE columns in the "offline" system. Most often, conventional non-polar sorbents (C18 or C8 bound to a carrier, such as silica gel), whose sorption uses hydrophobic interactions, van der Waals interactions between the hydrophobic part of the analyte and the hydrophobic part of the sorbent are the most popular. The first analytes that were extracted in the online SPE system were pesticides in water, and later, the application was also developed for pharmaceuticals [24]. An essential advantage of online SPE compared to the classic "offline" SPE is the timesaving and elimination of manual operations from preparation to elution of the analytes since all sub-operations of SPE take place in a closed system (within high-performance liquid chromatographic (HPLC) and ultra-high-performance liquid chromatographic (UHPLC) systems), thereby eliminating losses of the target analytes. Idder et al. [24] developed and validated a multi-residue method for the determination of 40 pharmaceutical substances, where online SPE preconcentration was chosen as the sample preparation technique. For the extraction of surface water and drinking water samples, they used the SPE columns Strata-X (20 mm × 2 mm, 25 µm) for the analytes subsequently detected in positive ionization mode by the LC–MS/MS. A volume of 1 mL of surface water sample was satisfactory for analysis. The recoveries achieved by online SPE preparation (compared to direct injection of the sample, without preconcentration and with an injection volume of 20 µL) for most monitored analytes were in the range of 90–120%, with the exception of the acetaminophen and trimethoprim analytes, where they reached recoveries in the range of 70–80%. They verified and confirmed that the usability of the selected online SPE columns was up to 400 injections without changing the sensitivity, accuracy, or repeatability of the method.

Camilleri et al. [56] used online SPE for the preparation of surface water samples for the determination of 37 multi-residual xenobiotics (medicinal substances, pesticides, steroid hormones, UV filters, alkylphenols, and other contaminants). A volume of 2.5 mL of a portion of the sample (acidified with formic acid, pH = 1.6) and Oasis HLB SPE columns (20 × 2.1 mm, 5 µm) were used. Developing the method, the authors optimized the sample volume for online SPE, the SPE sorbent type, composition, and volume elution solvents, as well as the step of cleaning the sorbent after the elution of the analytes from the SPE column. By choosing online SPEs, they appear to significantly achieve low limits of determination at ultra-trace concentration levels (within the limit of quantification (LOQ) range from 0.1 ng/L to 10 ng/L). Other advantages of this are the eliminated sample handling, low solvent consumption, time aspect, and cost of analysis. The recoveries achieved by the online SPE preparation were in the range of 85–110% for all determined analytes.

Axel et al. [26] proposed an analytical method for the determination of 17 antibiotics in surface water samples. A combination of an online SPE system with LC–ESI–MS/MS was proposed. The target analytes were selected according to the recommendation of the Finnish Medicines Agency (FIMEA) and were the anticonvulsant carbamazepine and the antibiotics sulfadiazine, sulfamethoxazole, clarithromycin, oxytetracycline, tetracycline, trimethoprim, and others. The online SPE columns used PLRP-S with the parameters 2.1 × 12.5 mm and 15–20 µm and a composition of macroporous polystyrene and divinylbenzene. Axel et al. [26] tested the addition of different additives (formic acid, acetic acid, and ammonium formate) in the elution process after online SPE extraction. They found that a 0.1% addition of formic acid increased the sensitivity of the method in the positive ionization mode for the monitored analytes the most. They also tested the extraction volume of the sample and finally used a 1.8 mL portion of the surface water sample. The method showed satisfactory linearity (with determination coefficients of 0.989–0.999) in the tested range, and the achieved LOQ values were 1 to 50 ng/L.

Alternative Sorption Materials

In recent years, new extraction materials such as carbon nanotubes (CNTs), magnetic nanoparticles, magnetic cellulose nanoparticles, graphene, metal–organic frameworks (MOFs), restricted access material (RAM), and molecularly imprinted polymers (MIPs) have come to the forefront (Figure 2) [56].

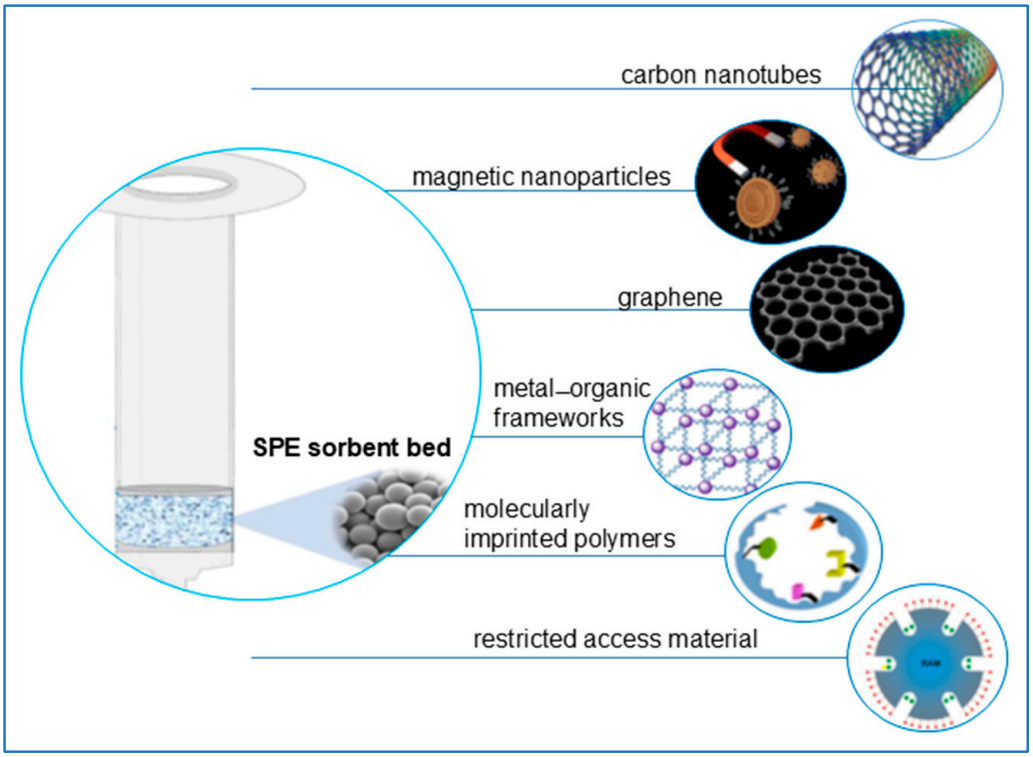


Figure 2. Advanced types of SPE sorbents used for the isolation of pharmaceuticals from water samples.

Among the various SPE sorbents, MIPs are capable of selectively extracting one molecule or a group of analytes by utilizing their unique properties, such as functional groups, molecular shapes, and sizes. MIPs represent a specific type of sorbent that offers a highly selective retention mechanism to the extracted molecule of the target analyte or a group of structurally similar compounds [57]. This approach reduces the matrix effect and allows analysis using cost-effective analytical equipment such as liquid chromatography with a diode array detector. MIPs demonstrate increased selectivity toward target analytes and also allow for reuse [31]. However, in samples with a high matrix effect, MIPs tend to lose their recognition abilities after a few extractions. Using a porous membrane as a protective shell is a simple approach to prevent matrix interferents from accessing the sorbent. The combination known as membrane-assisted solvent extraction with molecularly imprinted polymers (MASE–MIP) is very advantageous, combining the membrane's separation ability (filtering high-molecular-weight interfering compounds and solid particles) with the high selectivity of MIPs. Khulu et al. used MASE–MIP to extract pharmaceuticals from river water, achieving limits of detection (LODs) of 0.09–0.2 ng/mL [44]. Martinez-Sena et al. [58] applied MIPs to the selective extraction of NSAIDs (ibuprofen, ketoprofen, diclofenac, and naproxen) from environmental and biological samples. Sample preparation using MIPs consisted of sorbent conditioning (1 mL of acetonitrile, 1 mL of methanol, and 1 mL of 10 mM ammonium formate), application of 1 mL of the sample, washing of the interfering components from MIPs (1 mL of deionized water and 1 mL of 40% (v/v) acetonitrile in water), and NSAID elution (1 mL of methanol). The extract was finally filtered with a 0.22 µm polytetrafluoroethylene (PTFE) filter and analyzed by HPLC with a diode array detector (DAD) and LC–MS/MS. The achieved MIP extraction recoveries for biological samples ranged from 102 to 113%.

Magnetic SPE represents a new type of SPE technique, which is based on the use of magnetic or magnetically modified sorbents [48,49]. Magnetic nanoparticles offer high extraction yields in a short time and with minimal adverse impact on the environment. Nanoparticles show advantageous properties: they are stable, do not undergo oxidation, do not agglomerate (without the formation of agglomerates), and are easily separated by an external magnet after extraction, making them reusable. They can be modified with functional groups of inorganic or organic molecules such as polymers with intrinsic conductivity, MIPs, etc. [58].

With the current development of nanotechnology, the synthesis of nanomolecules with a precisely defined structure and size, which can function as building blocks of nanotechnological processes, is being promoted in synthetic chemistry. Dendrimers (2–20 nm) are synthetic macromolecules, highly branched with a defined globular structure. In the surface part, dendrimers have multiple functional groups. Magnetic dendrimer polyamidoamine (PAMAM), a new type of sorbent for the extraction of NSAIDs in environmental water samples, was applied by Alinezhad et al. [48]. Magnetic PAMAM (Fe_3O_4@PAMAM) combines magnetic nanoparticles (Fe_3O_4) with a commercially available PAMAM dendrimer. The advantages are properties such as an excellent extraction capacity, structural homogeneity, high internal porosity, controlled composition, integrity, and biocompatibility [59]. Another nano-sorbent for magnetic SPE—a composite of Fe_3O_4/graphene—has been used for the extraction of cytostatic pharmaceuticals used in chemotherapy and applied to wastewater analysis [60].

Abujaber et al. [61] proposed magnetic cellulose nanoparticles as an equivalent of the classic SPE sorbents for the extraction of pharmaceuticals (paracetamol, ibuprofen, naproxen, and diclofenac) in water. Magnetic nanoparticles show a negative charge on the surface, thus giving room for a type of retention mechanism, such as electrostatic interactions. Such "magnetic SPE material" is suitable for the extraction of inorganic as well as organic analytes. In addition, the microcrystalline cellulose base of the nanoparticles is a non-toxic and renewable polymer. The nanoparticles were covered with a layer of ionic liquid (1-butyl-3-methylimidazolium hexafluorophosphate). A water sample (acidified, pH 1.5) was added to the vial along with magnetic nanoparticles coated with a layer of ionic liquid (vortex, 5 min). After extraction, the nanoparticles were separated from the solution with the help of a magnet, and the desorption of the target analytes took place using 250 µL of 0.5 M phosphate buffer (ultrasound, 10 min). The achieved extraction yields were in the range of 85–116% [61].

As a basis for magnetic nanoparticles, modified sporopollenin was invented [62]. Sporopollenin is a natural biopolymer isolated from the outer cell wall of Lycopodium clavatum spores. They bound/immobilized magnetite (Fe_3O_4) to the surface structure of sporopollenin and subsequently substituted the hydroxyl functional group with silica gel derivatives (3-cyanopropyltriethoxysilane, tetraethylorthosilicate) in order to ensure and increase the extraction yield of pharmaceuticals (ketoprofen, diclofenac, ibuprofen, and mefenamic acid) from surface and wastewater samples. Abd Wahib et al. [62] reported that the synthesized sporopollenin sorption material can be used up to seven times in the sorption–desorption cycle without changing the response of the target analytes analyzed by the HPLC–UV method [62].

Marasco et al. first described an automated method that allows the direct injection of wastewater samples for the simultaneous determination of six pharmaceuticals using RAM for online sample preparation. A laboratory-made RAM column with bovine serum albumin (RAM-BSA) was prepared for this purpose. In this case, RAM functions as a precolumn responsible for analyte preconcentration and extraction, with a switching valve connecting it to the analytical column. RAM carriers enable the separation of analytes based on a combination of size exclusion and conventional hydrophobic or ion-exchange interactions, allowing small molecules to pass through while restricting the macromolecules from accessing the extraction phase. Compared to traditional SPE sorbents, RAM sorbents offer many advantages, including a long lifespan, high separation efficiency, reduced

analyte loss, low organic waste production, and low overall analysis costs. Marasco et al. achieved LODs of 0.01–3 µg/L using this method [47].

An interesting alternative sorbent for SPE sorbents is carbon nanotubes (CNT), formed by single-walled carbon nanotubes or several layers of graphite (multi-walled carbon nanotubes), with a diameter of several nm and several µm long, rolled into a cylinder shape [63]. They find application in microextractions in the environmental analysis of waters.

Abujaber et al. [64] replaced the rod used for adsorptive microextraction—BAµE with a CNT rod covered with multiple layers of carbon material. A CNT rod (15 mm length × 2 mm inner diameter × 3 mm outer diameter) was inserted into a 25 mL portion of the sample (pH 5.5) and stirred for 3 h (1000 rpm) at room temperature. The extraction was followed by desorption in 100 µL of methanol (ultrasound, 30 min). LOQ values of 80 ng/L for all monitored pharmaceuticals in this type of microextraction were achieved [64].

3.1.2. QuEChERS

An alternative, less explored strategy for determining pharmaceuticals in environmental samples is the use of extraction methods based on QuEChERS (quick, easy, cheap, effective, rugged, and safe) (Table 1). This method is commonly used as a preliminary preparation of solid samples in the multi-residue analysis of polar and non-polar pesticides. The QuEChERS method is based on solid–liquid extraction with an organic solvent, followed by liquid–liquid partitioning using a suitable salt mixture. Dispersive solid-phase extraction (d-SPE) is usually used for the clean-up [42]. Acetonitrile is used as the extraction solvent, and interfering compounds contained in the extract are removed in the clean-up step [65].

Due to its high versatility, the QuEChERS method has recently been successfully used to extract 19 pharmaceuticals and personal care products in surface and wastewater using acetate buffer and achieved LODs of 0.001–0.167 ng/mL [66]. Martínez-Piernas et al. performed wastewater analysis based on the QuEChERS extraction procedure for more than 100 contaminants, including compounds with various physicochemical properties such as pharmaceuticals, antibiotics, and pesticides [42].

3.1.3. Microextraction Techniques

Microextraction techniques are highly favored in current analytical practice due to miniaturization and the possibility of automation or the use of small volumes of extraction solvents. The advantage of microextraction techniques is also the elimination of the risk of sample contamination in the sample pretreatment process [67].

Liquid microextraction using hollow fiber (HF–LPME) represents a microextraction technique based on extraction in the pores of the hollow fiber walls. The pores are filled with an organic solvent. Due to the porosity, the target analytes of the sample have a large contact area with the extraction agent, making the extraction process efficient.

Saleh et al. [17] introduced HF–LPME as a purification and preconcentration technique for monitoring selected pharmaceuticals (ketoprofen, diclofenac, ibuprofen, and naproxen) in treated sewage sludge samples. HF–LPME was also applied to the microextraction of other pharmaceuticals, such as benzodiazepines [68,69], sulfonamides in water, etc. [68,70]. Hydrophobic polymer (polypropylene) hollow fiber represents a carrier with an applied liquid phase (e.g., ammonium carbonate 0.1 M, organic solvents), which is immobilized in the fiber. The fiber used by Saleh et al. [17] for HF–LPME was with the following parameters: 25 µL volume, 10 cm U-shaped, 600 µm I.D., 200 µm fiber wall thickness, and 0.2 µm pore size. The fiber was immersed in the sample, resp. to 100 mL of pressurized hot water extract (PHWE), and the HF–LPME microextraction lasted 120 min with constant stirring with a magnetic stirrer. The resulting 10 µL of fiber extract was analyzed directly by LC–ESI–MS/MS. This preparation of the samples achieved a significant elimination of the effect of suppressing or increasing the resulting signal during electrospray ionization,

and the use of organic solvents of a small volume (a few µL of di-n-hexyl ether) was also an advantage [17].

Guan et al. [19] used dispersive liquid–liquid microextraction (DLLME) to isolate pharmaceuticals from water. DLLME is a technique using a three-component extraction system and is based on the dispersion of the solvent in the sample [71]. Guan et al. monitored six pharmaceuticals from the NSAID group (e.g., ketoprofen, naproxen, sulindac, piroxicam, mefenamic acid, and tolfenamic acid) and six antibiotics (tinidazole, cefuroxime-axetil, ciprofloxacin, sulfamethoxazole, sulfadiazine, and chloramphenicol). Surface water samples after collection were filtered (0.45 µm nylon filter). A 5 mL portion of the sample was used for the extraction, which was subsequently acidified (HCl 0.1 mol/L, pH 4), and a mixture of solvents, such as methanol/acetonitrile (1200 µL, 1:1, *v*/*v*) and dichloromethane, was added as a dispersion solvent (800 µL of dichloromethane, vortex for 60 s, ultrasound for 10 min). The phases were separated by centrifugation (4000 rpm, 10 min). The supernatant was separated with a microsyringe and the residual sediment phase was evaporated with a stream of N_2. The residue was reconstituted with a mixture of acetonitrile/water (1:1, *v*/*v*), while 5 µL of the filtered extract was analyzed by the UPLC–ESI–MS/MS method. The method was applied to real samples of surface water analysis and achieved LODs of 0.006–0.091 ng/mL, thus ranking among the works of authors who achieved significantly low values of LODs [19].

Bar adsorptive microextraction (BAµE) was proposed for the microextraction of pharmaceuticals from water samples. BAµE represents a type of extraction technique for the determination of ultra-trace polar and non-polar analytes in water samples. Moreover, the combination of BAµE and microfluidic desorption provides a "green chemistry" technique compared to the traditional extraction methods [67]. BAµE was applied to the analysis of pharmaceuticals, e.g., ketoprofen, diclofenac, mefenamic acid [58], or sulfonamide antibiotics [24,68].

The extraction of pharmaceuticals by BAµE—diclofenac, ketoprofen, gemfibrozil, and mefenamic acid with multi-walled carbon nanotubes (5–20 µm length, 30 ± 15 nm film layer, 95% purity) used as the sorption material was proposed, and LOQs lower than 0.35 µg/L were achieved [64].

Abd Wahib et al. [62] selected the dispersive-micro-solid-phase extraction (d-µ-SPE) technique for the extraction of pharmaceuticals from the NSAID group (ketoprofen, diclofenac, ibuprofen, and mefenamic acid). Surface water and drinking water samples were filtered and acidified (HCl; 0.1 M) after collection. For d-µ-SPE extraction, an amount of 40 mg of derivatized sporopollenin sorbent and 15 mL of a water sample (vortex, 5 min) were applied. After separating the sample solution and modified sporopollenin, 250 µL of isopropanol was used for the desorption of the analytes from the sorbent (ultrasound, 5 min). This technique, in combination with LC–MS/MS, achieved LODs in the range of 220–510 ng/L [62].

Stir bar sorptive extraction (SBSE) represents a type of microextraction technique based on the sorption of analytes, most often on a layer of polydimethylsiloxane (PDMS) applied to a magnetic stirrer. Tanwar et al. [70] used the SBSE technique with a commercially available type of PDMS sorbent to analyze NSAIDs in surface water samples. PDMS is suitable for the extraction of non-polar and semi-polar substances from various matrices and is a relatively widespread and used type of sorbent for SBSE [67,71]. SBSE sorbents such as polyacrylate (PA), polyethylene glycol (EG), or polyethylene glycol-modified silicone (EG-SIL) are suitle for the extraction of polar analytes, and they find application in the extraction of pharmaceutical substances, e.g., in wastewater [71]. The resulting extraction conditions—40 mL of the sample, pH 2, extraction time of 3 h (500 rpm), desorption time, and elution solvent volume of acetonitrile being 800 µL (ultrasound 40 min)—provided satisfactory LOD values for diclofenac 11 ng/L, mefenamic acid 7.5 ng/L, and ibuprofen 8 ng/L, as well as for ketoprofen 60 ng/L and naproxen 71 ng/L using the EG-SIL sorbent, which was more suitable for the monitored analytes with a polar character [71].

Aparicio et al. [72] compared the use of SBSE sorbents—EG-SIL and PDMS—for the extraction of pharmaceuticals (diclofenac, bezafibrate, ethinylestradiol, estrone, ibuprofen, ketoprofen, gemfibrozil, etc.) in surface waters. Compared to the PDMS sorbent, the highest recoveries were achieved with the EG-SIL type sorbent, which was more favorable for analytes with both polar and non-polar character. The LOD values ranged from 5.6 to 23 ng/L for pharmaceuticals in surface waters [72].

Manzo et al. [73] used sorption microextraction with the MIP phase immobilized on rotating disks (RDSE) to isolate pharmaceuticals (diclofenac and mefenamic acid) from wastewater. The methods developed for the synthesis of the MIP fibers for solid-phase microextractions or MIP stir rods for SBSE are relatively simple and robust, and therefore, their use and applications in analytical laboratories can be foreseen in the coming years. RDSE represents an alternative to microextractions or purification techniques. RDSE offers a large extraction surface, and rotating disks can be stirred at higher speeds than stirring bars in SBSE extraction, during which they can be damaged [73]. Higher rotational speeds in RDSE help and facilitate mass transfer to the sorption surface. Manzo et al. used Teflon rotating disks (diameter 1.5 cm) that were inserted into vials with the prepared MIP phase (3000 rpm, 60 min, laboratory temperature). After extraction, the disk was transferred to a vial with 10 mL of methanol, where the target analytes were desorbed (2000 rpm, 5 min), and the extract was evaporated to dryness under a stream of nitrogen and reconstituted with ethyl acetate to a volume of 0.5 mL. The extract was derivatized because they used gas chromatography–mass spectrometry (GC–MS) for the analysis. The achieved RDSE recoveries with the synthesized MIP phase were from 99 to 100% for diclofenac and mefenamic acid with an RSD of less than 6%. The LOQ for the pharmaceuticals reached 220 ng/L for diclofenac and 200 ng/L for mefenamic acid in wastewater [73].

3.2. Instrumental Separation and Detection Technique

Purified and concentrated extracts containing pharmaceuticals are further analyzed using instrumental analytical techniques such as HPLC and, less commonly, gas chromatography (GC). The main requirement for the analysis of molecules using GC is high volatility. Most pharmaceutical pollutants are not sufficiently volatile and are not directly compatible with GC. However, several examples of pharmaceutical derivatization have been recorded, allowing for their analysis using GC–MS. Some examples of derivatizing agents used for the analysis of pharmaceuticals in environmental samples by GC–MS include pentafluorobenzyl bromide, methyl chloromethane, methanol/boron trifluoride (BF3), and tetrabutylammonium salts. The main advantage of GC–MS is that the ionization techniques, such as electron ionization (EI) or chemical ionization (CI), are less affected by the sample matrix compared to the ionization techniques used in LC–MS [32]. HPLC and the more advanced UHPLC–MS/MS with ultra-high-performance rapid flow rates and MS detection are alternative methods offering several advantages, including fast separation, absence of the need for derivatization, good sample stability, and small sample size [74].

Reverse-phase HPLC is widely used for multicomponent analysis with C18-based chromatographic columns. The typical column size parameters are as follows: (i) a length ranging from 10–25 cm, (ii) an internal diameter of 2.1–4.6 mm, and (iii) a particle size of 3–5 mm [75]. Most LC–MS/MS applications use electrospray ionization (ESI), which is generally compatible with lower mobile phase flow rates, from 0.1 to 0.5 mL/min. Due to these low flow rates, LC columns with narrow diameters (i.e., 2–3 mm) are more popular compared to the conventional analytical columns with a diameter of 4.6 mm. Narrower diameter columns also provide high separation efficiency and sensitivity and are less susceptible to matrix effects. Acidic and neutral pharmaceuticals are typically analyzed using columns longer than 15 cm [76].

Gradient elution represents the most common strategy for separating multiple classes of pharmaceuticals. Organic solvents such as acetonitrile and methanol are commonly used as mobile phases. Mobile phase modifiers, buffers, and acids are often used to achieve effective analyte retention in the column and improve MS detection sensitivity.

Common modifiers include ammonium acetate, ammonium formate, tri-n-butylamine (TNBA), formic acid, and acetic acid [75,77]. Typical salt concentrations range from 2 to 20 mM, as higher concentrations have been observed to reduce signal intensity [56,75].

Among the detection techniques, MS and MS/MS are the most commonly used. Spectrophotometric detection in the ultraviolet–visible (UV–VIS) region is used less frequently. MS is often employed due to its high specificity and sensitivity. The triple-quadrupole (QqQ) mass analyzer is frequently used in combination with LC and has become the standard for many pharmaceuticals in various environmental samples. The QqQ mass analyzer uses multiple reaction monitoring (MRM) modes to achieve high selectivity and provide very low LODs [51]. The identification and quantification of pharmaceutical residues are also performed using high-resolution MS techniques such as time-of-flight (TOF) MS and quadrupole time-of-flight (Q-TOF) MS [74].

The most frequently detected pharmaceuticals in surface and wastewater are antibiotics, analgesics, beta-blockers, and estrogens. LODs are generally in the range of ng/L to µg/L [77]. The detected concentrations range from a few ng/L to 100 µg/L [75]. However, LC–MS/MS analysis can be affected by matrix effects (i.e., co-eluting components), which influence the ionization efficiency of target analytes and reduce method sensitivity and reproducibility [78]. These effects are most frequently observed in complex matrices such as sewage, wastewater, and solid samples [75].

Togunde et al. used the QuEChERS procedure to extract drugs from wastewater samples, reporting that the matrix effects are more pronounced in ESI than atmospheric pressure chemical ionization (APCI) [78]. Matrix effects can also be minimized or eliminated using HRMS. When using LC with HRMS, Q-TOF and Q-Orbitrap are used. Q-Orbitrap is more advantageous for the identification of unknown analytes due to its higher resolving power, mass accuracy, and long-term stability [77]. Recent studies show that coupling the Q-Orbitrap to the LC with online SPE provides the simultaneous determination of polar and non-polar contaminants. Thus, the wide-scope screening of pharmaceuticals in water samples is possible, although concentrations may be higher compared to the conventional method due to the lack of certified standards in HRMS libraries. However, the quantitative results of target analytes obtained by LC–MS/MS and LC–HRMS are comparable [77,78].

Many studies have documented the occurrence of pharmaceuticals and their transformation products in effluents, surface waters, groundwater, and drinking water [79]. Antibiotics such as sulfonamides, penicillin, tetracyclines, and macrolides are some of the most frequently detected pharmaceuticals in aquatic environments. Diclofenac and ibuprofen, among NSAIDs, are the most commonly detected in wastewater effluents [80]. Psychiatric drugs such as fluoxetine and carbamazepine are often detected in surface waters and effluents. To improve the understanding of the occurrence of pharmaceuticals in surface waters, various pharmaceutical residues in river water from different locations around the world were analyzed. The overall frequency of detection was 63.1% for all pharmaceuticals, including NSAIDs, antibiotics, psychiatric drugs, and β-blockers. The detection frequencies for diclofenac, carbamazepine, and propranolol were 75.5%, 45.4%, and 40.5%, respectively. Among the antibiotics analyzed, the frequency of detection was highest for erythromycin and trimethoprim, at 57.5% and 51.4%, respectively. The antibiotics trimethoprim and ciprofloxacin, the NSAID diclofenac, the psychiatric drug carbamazepine, and the β-blocker propranolol were among the most frequently detected contaminants worldwide [79].

Pharmaceutical pollution in the aquatic environment has become a global issue, and there is a continuous effort to improve methods for the detection, identification, and quantification of these contaminants. Advanced sample preparation techniques, along with sophisticated analytical instruments such as UHPLC–MS/MS, have significantly enhanced our capability to monitor these pollutants, contributing to a better understanding of their occurrence, distribution, and potential risks. It is crucial to continue developing more efficient, sensitive, and selective analytical methods to accurately assess the presence and

impact of pharmaceuticals in the environment and to devise strategies to mitigate their harmful effects.

An overview of the analytical methods for pharmaceutical detection in environmental samples is given in Table 1.

4. Conclusions and Future Remarks

The presence of pharmaceutical compounds in the environment represents a complex and multifaceted issue with significant implications for ecosystems and human health. The key constraints include the ongoing release of pharmaceuticals from wastewater, improper disposal, and agricultural activities, which contribute to their accumulation and slow degradation. The adverse effects on aquatic life, such as physiological disruptions and antibiotic resistance, highlight the need for effective regulatory measures and sustainable practices. This manuscript has highlighted the widespread occurrence of pharmaceuticals in various environmental compartments, the adverse effects they pose to living organisms, and the methodologies used for their detection and quantification.

Analytical techniques such as SPE and LC–MS/MS play a crucial role in the detection and quantification of pharmaceuticals in environmental samples. These methods offer high sensitivity, selectivity, and efficiency, enabling researchers to identify complex mixtures of pharmaceuticals at trace levels.

Future research should focus on refining these methods, implementing stricter regulations, and fostering interdisciplinary collaboration. Greater attention is needed in developing advanced degradation technologies, improving wastewater treatment processes, and promoting responsible pharmaceutical use and disposal practices. These efforts are essential for mitigating environmental and health risks and ensuring the protection of ecosystems and public health.

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