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Review

Recent Trends in Solid-Phase Microextraction for the Monitoring of Drugs of Abuse in Wastewater

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Abstract

Wastewater analysis plays a central role in monitoring patterns of drug use within specific populations. It provides objective and real-time estimates of consumption, with minimal ethical concerns. In the current European context, drugs of abuse continue to be detected in wastewater, with varying incidences across countries. Their monitoring enables the prioritisation of public health and legal interventions by healthcare professionals and drug monitoring agencies. Therefore, the development and implementation of efficient methodologies for monitoring drugs of abuse in wastewater samples is of critical importance. This systematic review aims to explore the use of miniaturised sample extraction techniques based on solid-phase microextraction for the determination of drugs of abuse in wastewater. In fact, the extraction procedure must be fast, effective, and selective in order to retain the analytes of interest. Miniaturised techniques have thus emerged as promising alternatives to conventional methods. Magnetic solid-phase extraction (MSPE) and molecularly imprinted polymers (MIPs) represent the most widely applied solid-phase microextraction techniques in recent years for the analysis of drugs of abuse in wastewater. Looking ahead, future perspectives include the development of eco-friendly workflows, automated and time-efficient techniques, increasingly selective sorbents, and robust analytical methods.

Keywords: solid-phase microextraction; SPME; MSPE; MIPs; drugs of abuse; illicit drugs; wastewater; GC-MS; LC-MS/MS

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1. Introduction

Wastewater can reflect the lifestyle and public health of a specific population, as it represents the excretions of thousands of individuals [1,2]. When a substance enters the human body, it may be excreted either in its unchanged form or as metabolites, entering the wastewater system via urine, faeces, sweat, and/or saliva [1,3,4]. In addition, substances may be directly discharged into the sewage system through illegal dumping from clandestine laboratories, industry, and hospitals [5–7]. As such, wastewater analysis plays a central role in monitoring the presence of various substances, including drugs of abuse, pharmaceutical residues, personal care products, alcohol, and certain pathogens [8].

Wastewater analysis was initially introduced to evaluate environmental contamination by therapeutic substances and to assess the effectiveness of wastewater treatment plants

in removing these compounds [9]. Over time, and particularly in recent years, it has been widely used to estimate drug consumption [8,10]. This approach, known as wastewater-based epidemiology (WBE), is a promising tool for understanding substance use at the community level through the chemical analysis of biomarkers present in sewage [1,10,11]. WBE has emerged as a valuable supplement to traditional drug surveys, which are often costly and potentially unreliable [12]. It provides more objective and near real-time consumption estimates, while raising fewer ethical concerns [12,13]. Data obtained through WBE typically relate to the total quantity of each drug consumed within a given population. It is often expressed in doses per day or per week per 1000 people, depending on the number of users and frequency of use [14]. By identifying drug use patterns, healthcare professionals and support organisations can target harm reduction strategies more effectively. Additionally, drug monitoring agencies can prioritise interventions and contribute to global knowledge on drug consumption trends [8,15].

According to the European Union Drugs Agency (EUDA), the most recent wastewater analysis report revealed that, in nearly all European cities where wastewater was analysed, the targeted drugs of abuse were detected. Since 2010, a Europe-wide network has been established to standardise wastewater analysis methodologies and coordinate studies at the international level through the definition of unified protocols [16]. This network, known as the Sewage analysis CORe group—Europe (SCORE), promotes the use of WBE to improve public health and sustainability through research, development, and annual monitoring campaigns [17]. It had its first intervention in 2011 by evaluating wastewaters from 19 European cities and it was the first study ever carried out in different regions within the context of illicit drug use in Europe [17,18]. Its first campaign took place in 2011, analysing wastewater from 19 European cities—the first study of its kind addressing regional variation in illicit drug use across Europe [17,18]. The most recent campaign covered 128 cities in 26 countries, including EU member states, Norway, and Turkey, and followed the protocol proposed by van Nuijs et al. [16,19]. It revealed both geographical and temporal variability in illicit drug use across the study area. Wastewater samples were analysed for urinary biomarkers of amphetamine, methamphetamine, ketamine, and 3,4-methylenedioxymethamphetamine (MDMA), as well as for urinary metabolites of cannabis and cocaine, namely 11-nor-9-carboxy-delta9-tetrahydrocannabinol (THC-COOH) and benzoylecgonine (BE), respectively. The highest levels of amphetamine were found in northern and eastern Europe, while methamphetamine concentrations remained lower and were historically centred in Czechia and Slovakia. Ketamine and MDMA were detected mainly in central European cities, whereas THC-COOH was most prevalent in western Europe. BE levels indicated that cocaine use remained highest in southern and western Europe, particularly in Belgium, the Netherlands, and Spain [16].

A common problem in wastewater analysis is the intrinsic instability of certain compounds in these matrices, which is a key issue to be assessed in the monitoring drugs of abuse and their metabolites. As so, it can be used to determine the errors associated with the possible degradation of these substances in sewage, improving the reliability of the retroactive calculation of population consumption [20,21]. The stability approach may be subject to two types of uncertainty, as degradation of analytes can occur both on the way from the place of excretion to the wastewater treatment plant and between sample collection and analysis in the laboratory [22]. To minimise pre-analytical losses from the moment the sample is collected, several alternatives can be used to prolong the integrity of the analytes, such as immediate cooling, acidification of the sample, light control and freezing. In fact, most classic drugs of abuse remain stable in wastewater at a pH of 7.5, showing negligible levels of degradation and formation over a period of at least 72 h at 4 °C and 12 h at 20 °C [20,22]. When acidifying a wastewater sample to a pH of 2, both classic

drugs and new psychoactive substances (NPS) show improved storage stability, with the exception of heroin, 6-acetylmorphine (6-AM), cocaine and delta9-tetrahydrocannabinol (THC), which have low storage and in-sewage stability [21,23,24]. Moreover, other techniques may be used, such as storing samples in the absence of light, and for long-term storage of wastewater samples, freeze/thaw cycles are frequently used, as freezing keeps most analytes stable for multiple analyses [22,25]. In general, and under normal conditions, opiates such as morphine, codeine and 6-AM, as well as cocaine and BE, are the least stable compounds within the classic drugs of abuse, while amphetamines cannabinoids exhibit relatively stable behaviour [23,25].

In terms of legislation, the European Urban Wastewater Treatment Directive has been in place since 1991, contributing significantly to the improvement of the quality of rivers, lakes, and seas [26]. Its revised version (Directive 2024/3019), which entered into force at the beginning of 2025, represents a major step forward in addressing remaining sources of pollution and new challenges in wastewater management. In particular, it requires the implementation of advanced "quaternary" treatment to ensure the removal of at least 80% of selected pharmaceutical residues and other micropollutants, introduces extended producer responsibility to involve the pharmaceutical and cosmetics industries in financing these treatment upgrades, and establishes a phased compliance schedule with full implementation expected by 2045 [27]. Furthermore, Directive 2000/60/EC established a comprehensive framework for the protection and improvement of water quality through the progressive reduction in emissions of hazardous substances to water, as well as their systematic monitoring [28]. In line with this directive, Directive 2009/90/EC was introduced, setting out technical specifications for chemical analysis and water status monitoring, which, together with the EN ISO/IEC 17025 standard [29], serve as key references for competent monitoring of substances in wastewater [30]. In addition, in 2016 the SCORE group published ethical research guidelines for WBE studies, outlining the main potential ethical risks and proposing strategies to mitigate them [31].

Beyond the importance of city participation in WBE studies, the development and implementation of increasingly innovative and practical analytical methods is essential for detecting drugs of abuse at trace levels in wastewater. The main challenge lies in the diverse chemical properties of the substances of interest and the complexity of the wastewater matrix, which hinders the development of multi-analyte methods [32–34]. An ideal extraction method should enable efficient separation of target compounds while being simple, cost-effective, rapid, compatible with analytical instrumentation, and environmentally sustainable [35,36]. Solid-phase extraction (SPE) remains the most widely used sample preparation technique in wastewater analysis [34]. Most published studies employ offline SPE, in which extraction and analysis are conducted separately [15,37–43]. However, on-line SPE has emerged as an alternative, offering savings in time, sample volume, and solvent usage [44]. A growing number of publications highlight the advantages of on-line SPE in recent years [44–48]. Regardless of the chosen approach, the selection of an appropriate sorbent is crucial, as it must consider the chemical structure and properties of the target analytes [34,39,49]. Commonly used sorbents in wastewater analysis include normal phase, non-polar, reversed-phase, and mixed-mode materials with both reversed-phase and ion-exchange properties [50].

Currently, laboratories and industries are increasingly concerned with minimising the environmental impact of analytical techniques, which has driven the development of eco-friendly methodologies. Advances in this field have led to significant reductions in both sample volume and the use of organic solvents [51–53]. Emerging techniques focus on green chemistry principles and often involve miniaturised extraction methodologies [52]. Microextraction techniques enable rapid sampling in small volumes, high levels of au-

tomation and performance, and compatibility with on-line analytical systems [53]. These techniques are generally classified into two categories: liquid-phase microextraction (LPME) and solid-phase microextraction, which differ in the nature of the extractive phase and the mechanism by which analytes are retained [51,53,54]. While LPME involves the selective partitioning of analytes between the sample and a liquid phase, solid-phase microextraction relies on the adsorption or absorption of analytes onto a solid sorbent or film [52,55]. Several recent studies have investigated the application of these microextraction techniques for detecting drugs of abuse in wastewater samples [56,57].

This systematic review focuses on miniaturised sample preparation techniques based on solid-phase microextraction for the determination of drugs of abuse in wastewater. It provides a concise overview of the various solid-phase microextraction methodologies and their applications in WBE, highlighting the advantages and limitations of each approach for drug detection. Furthermore, extraction and analytical conditions are presented, compared, and critically evaluated. The discussion underscores the growing relevance of solid-phase microextraction in environmental analysis and emphasises the need for innovative, efficient, and sustainable strategies to monitor illicit drug consumption.

2. Materials and Methods

A systematic literature search was conducted on 29 May 2025 using two electronic databases: Web of Science and PubMed. The search terms included combinations of "illicit drugs" or "drugs of abuse" with "wastewater" or "sewage", along with various expressions related to solid-phase microextraction techniques, such as: "solid-phase microextraction" or "SPME", "fibre solid-phase microextraction" or "fibre SPME", "micro solid-phase extraction" or "micro SPE", "in-tube solid-phase microextraction" or "in-tube SPME", "microextraction by packed sorbent" or "MEPS", "thin film microextraction" or "TFME", "stir bar sorptive extraction" or "SBSE", "magnetic solid-phase extraction" or "MSPE", "molecularly imprinted polymers" or "MIPs", and "molecularly imprinted solid-phase extraction" or "MISPE".

To ensure a comprehensive review, publications from 2000 to the present were considered. Articles focusing exclusively on the analysis of pharmaceuticals or legal drugs in wastewater were excluded. Additionally, although some of the techniques investigated may be more commonly applied to other sample matrices, all types of wastewaters were included in the scope of this systematic review. Figure 1 clearly shows the methodology used in conducting the systematic research in the selected databases.

The articles identified and included in this review present a contemporary temporal distribution, highlighting the growing relevance of miniaturised solid-phase extraction techniques for monitoring drugs of abuse in wastewater. Contrary to what might have been expected from the literature search, magnetic solid-phase extraction (MSPE) and molecularly imprinted polymers (MIPs) emerged as the most widely used techniques within the scope of this systematic review. Furthermore, no published studies involving microextraction by packed sorbent (MEPS) or stir bar sorptive extraction (SBSE) were identified. Of the three articles retrieved on fibre solid-phase microextraction (fibre SPME), only two were deemed relevant and were classified as direct immersion solid-phase microextraction (DI-SPME).

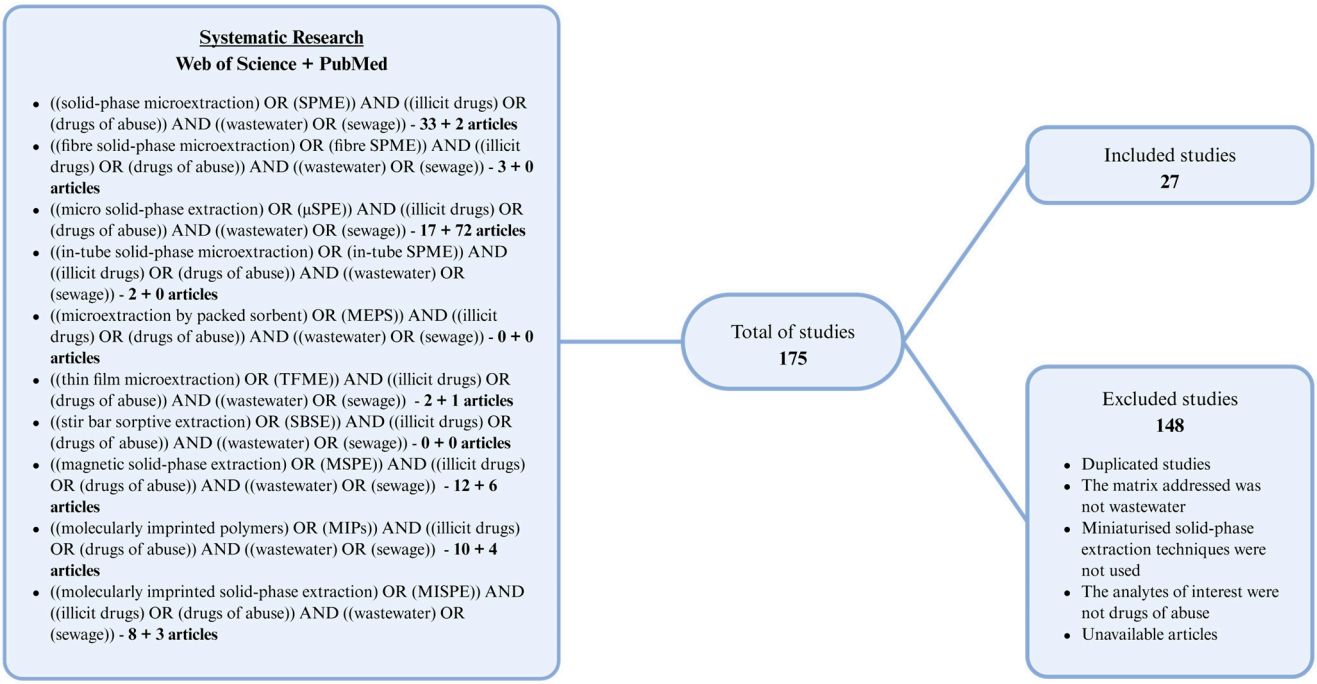

Figure 1. Diagram of the systematic research methodology conducted in Web of Science and PubMed, showing the number of articles retrieved for each set of search terms in both databases, the relevant studies included in this review, and those excluded, together with their exclusion criteria.

3. Solid-Phase Microextraction Techniques

Solid-phase microextraction techniques are modern sample preparation procedures that combine extraction, pre-concentration, and sample clean-up in a single step [58,59]. The growing number of studies describing various solid-phase microextraction workflows—particularly in environmental samples—highlights their relevance to the advancement of analytical sciences [60]. These techniques can be broadly classified into static equilibrium and dynamic flow microextraction methods [55]. The most extensively described technique in the literature is traditional solid-phase microextraction (SPME). In the context of analysing drugs of abuse in wastewater, SPME has been successfully applied in various formats, including in-tube solid-phase microextraction, micro solid-phase extraction, thin-film microextraction, solid-phase dynamic extraction, magnetic solid-phase extraction, and molecularly imprinted solid-phase extraction. This section summarises the key principles of each technique and illustrates their application to wastewater analysis of drugs of abuse.

3.1. Solid-Phase Microextraction

SPME was developed in 1990 by Arthur and Pawliszyn [61]. It is a solvent-free or solvent-minimised extraction technique in which analytes are extracted from the sample matrix using an extractive phase supported on a solid device [61]. This solid support typically consists of a fused silica fibre coated with a stationary phase that interacts with the sample to establish an equilibrium distribution of the analytes, thereby retaining [55,60,62]. The method allows for analyte separation and concentration and is compatible with automation and online coupling to analytical instruments [60,63]. There are three conventional approaches to SPME:

- Direct immersion (DI-SPME): The fibre is immersed directly in the sample, requiring agitation to enhance extraction efficiency [55,62].

- Headspace SPME (HS-SPME): The fibre is exposed to the gas phase above the sample, protecting it from matrix interferences and enabling derivatisation before, during, or after extraction [62,64].
- Membrane-protected SPME: Similarly to DI-SPME, but the fibre is encased in a selective membrane to block interfering substances [62].

SPME has been applied in fields such as food safety, clinical chemistry, pharmaceuticals, forensics, and environmental analysis [54,63,65]. For environmental applications, particularly wastewater analysis, it has been used in various formats to detect drugs of abuse.

Racamonde et al. explored direct SPME for different analytes in two separate studies [66,67]. In the first, they developed a method for determining cannabinoids, testing different fibre coatings and selecting divinylbenzene-carboxene-poly(dimethylsiloxane) (DVB–CAR–PDMS) as the most effective. Optimisation of time, volume, and temperature was followed by a headspace derivatisation step using N-methyl-N-(trimethylsilyl) trifluoroacetamide (MSTFA) and gas chromatography-mass spectrometry (GC–MS) detection [66]. In the second study, they developed a method for amphetamine-type stimulants using a PDMS–DVB coating. This required a higher sample volume compared to the method of cannabinoids. On-fibre derivatisation was unsuccessful due to the polarity of the analytes. Instead, they added isobutyl chloroformate (iBCF) and dipotassium monohydrogen phosphate directly to the raw sample to catalyse the derivatisation [67].

Thin-film microextraction (TFME) is a solid-phase microextraction technique that employs a membrane with a large surface area, increasing the volume of the extractive phase and enhancing sensitivity without altering sampling time [54,68,69]. Three studies have applied TFME to the analysis of drugs of abuse in wastewater. Chen et al. [70] developed a TFME method using a synthesised DVB–PDMS membrane, prepared by dip-coating a PDMS thin film with DVB particles. The method, validated for methamphetamine, ketamine, and methaqualone, was solvent-free and employed thermal desorption coupled with GC–MS.

A related development is the coated blade SPME technique [71,72], which uses a stainless-steel blade coated with sorbent material. Hu et al. [71] introduced a rapid screening method for multiple drugs of abuse using a blade coated with $Ti_3C_2T_x$ nanosheets modified with Cu-TCPP/$Ti_3C_2T_x$ and embedded in a polyacrylonitrile (PAN) binder. The material's high hydrophilicity facilitated the extraction of polar compounds.

Zhou et al. [72] developed SPME blades coated with a mixture of sorbents (HLB, HLB-WCX, HLB-WAX) and PAN. This approach improved extraction efficiency for a broad range of analytes (non-polar, polar, positively and negatively charged), making it more comprehensive than Hu's. Moreover, Hu et al. [71] also implemented coated blade spray–mass spectrometry (CBS–MS), an ambient MS technique. After desorption, high voltage was applied to the blade, generating electrospray ionisation (ESI) and allowing direct MS signal collection. This method is fast, practical, and suitable for high-throughput screening.

SPME also includes dynamic flow techniques, such as in-tube SPME (IT-SPME) and solid-phase dynamic extraction (SPDE). In IT-SPME, capillary tubes are used for extraction, while SPDE employs syringe needles coated internally. In both methods, extraction occurs as the sample flows through the sorbent [73]. Zhao et al. developed both IT-SPME and SPDE methods for detecting amphetamine-type stimulants in sewage samples [74,75]. The IT-SPME method used a synthesised carboxyl-functionalised organic–inorganic hybrid monolithic column (TMOS-co-CES) within a fused silica capillary. Its efficiency was first validated through computational simulation and then under lab conditions [74]. The SPDE method involved a hybrid monolithic column (HMC) coated inside the needle. Three versions were tested—amine-HMC, amine and thiol-HMC, and thiol-

HMC—the latter showing the best adsorption performance [75]. Although both methods achieved comparable detection limits, the IT-SPME required larger sample and elution volumes [74,75].

All the aforementioned SPME techniques and their applications to the analysis of drugs of abuse in wastewater are summarised in Table 1, as well as its illustration for better visualisation in Figure 2.

Table 1. Applications of SPME techniques for the determination of drugs of abuse in wastewater samples.

Sample (mL)	Analytes	Mode	Properties	Conditions	Instrument	LOD	Recovery	References
Wastewater (10)	THC THC-COOH	DI-SPME	DVB-CAR-PDMS fibre	Extraction: 60 min at 60 °C Derivatization with 50 µL of MSTFA (headspace for 10 min at 40 °C) Desorption: 3 min at 250 °C	GC-MS	1.0 and 2.5 ng/L	104 and 112%	[66]
Wastewater (100)	Amphetamine Methamphetamine MDA MDMA MDEA	DI-SPME	PDMS-DVB fibre	Extraction: 40 min at 60 °C Desorption: 3 min at 250 °C	GC-MS	0.4–2 ng/L	98–111%	[67]
Wastewater (19)	Methamphetamine Ketamine	TFME	DVB-PDMS membrane	Extraction: sample was stirred at 200 rpm for 120 min at room temperature Desorption: initially at 50 °C, ramped to 250 °C (700 °C/min) and held for 5 min Preconditioning: 15 min in 1.5 mL of methanol/water (50:50, *v*/*v*)	TDU-GC-MS	5.5 and 2.0 ng/L	95–111%	[70]
Wastewater (1.5)	Amphetamine Methamphetamine Codeine Heroin Morphine Fentanyl	Coated Blade SPME	Cu-TCPP/$Ti_3C_2T_x$ blades	Extraction: 20 min Wash: 5 s in 1.5 mL of Milli-Q water Desorption: 8 µL of MeOH:water (95:5, *v*/*v*) + 0.1% FA and MS analysis after 18 s	CBS-MS/MS	1.5–9.0 ng/L	70.7–115.6%	[71]
Environmental water (1.5)	Amphetamine BE Cocaine Codeine Fentanyl Heroin LSD MDMA Methamphetamine Morphine	Coated Blade SPME	HLB + HLB-WCX + HLB-WAX with a PAN binder blades	Preconditioning: 30 min in 1.5 mL of MeOH:water (50:50, *v*/*v*) Extraction: 30 min Wash: 5 s in 1.5 mL of Milli-Q water Desorption: 10 min in 300 µL of 10 mM NH_4Ac + ACN:MeOH:water (3:3:4, *v*/*v*/*v*)	LC-HRMS and LC-MS/MS	0.002–0.020 ng/mL	67.4–134.2%	[72]

Table 1. *Cont.*

Sample (mL)	Analytes	Mode	Properties	Conditions	Instrument	LOD	Recovery	References
Sewage (2.0)	Amphetamine Methamphetamine Cathinone Methcathinone MDA MDMA MDEA	IT-SPME	TMOS-*co*-CES hybrid monolithic column sorbent	Wash: 150 µL of water Elution: 200 µL of 0.1% FA + MeOH (1:1, *v*/*v*) Extraction flow rate: 150 µL/min	UHPLC-QTRAP MS/MS	0.01–0.02 ng/mL	86.1–114%	[74]
Sewage (1.5)	Amphetamine Methamphetamine Cathinone Methcathinone MDA MDMA MDEA	SPDE	Thiol hybrid monolithic column sorbent	Wash: 150 µL of water Elution: 150 µL of 0.1% FA + MeOH (1:1, *v*/*v*) Extraction flow rate: 150 µL/min	UHPLC-QTRAP MS/MS	0.01–0.02 ng/mL	85.4–114%	[75]

Legend: ACN: acetonitrile; BE: benzoylecgonine; CAR: carboxen; CBS-MS/MS: coated blade spray coupled to tandem mass spectrometry; CES: carboxyethylsilanetriol sodium salt; DI-SPME: direct immersion solid-phase microextraction; DVB: divinylbenzene; FA: formic acid; GC-MS: gas chromatography coupled to mass spectrometry; HLB: hydrophobic/lipophilic balanced; IT-SPME: in-tube solid-phase microextraction; LC-HRMS: liquid chromatography coupled to high resolution mass spectrometry; LC-MS/MS: liquid chromatography coupled to tandem mass spectrometry; LOD: limit of detection; LSD: lysergic acid diethylamide; MDA: 3,4-methylenedioxyamphetamine; MDEA: 3,4-methylenedioxyethylamphetamine; MDMA: 3,4-methylenedioxymethamphetamine; MeOH: methanol; MSTFA: N-methyl-N-(trimethylsilyl)trifluoroacetamide; PAN: polyacrylonitrile; PDMS: poly(dimethylsiloxane); SPDE: solid-phase dynamic extraction; SPME: solid-phase microextraction; TCPP: 4,4′,4′,4′-(Porphine-5,10,15,20-tetrayl) tetrakis (benzoic acid); TDU: thermal desorption unit; TFME: thin-film microextraction; THC: Δ9-tetrahydrocannabinol; THC-COOH: 11-nor-9-carboxy-Δ9-tetrahydrocannabinol; TMOS: tetramethoxysilane; UHPLC: ultra-high-performance liquid chromatography; WAX: weak anionic exchange; WCX: weak cationic exchange.

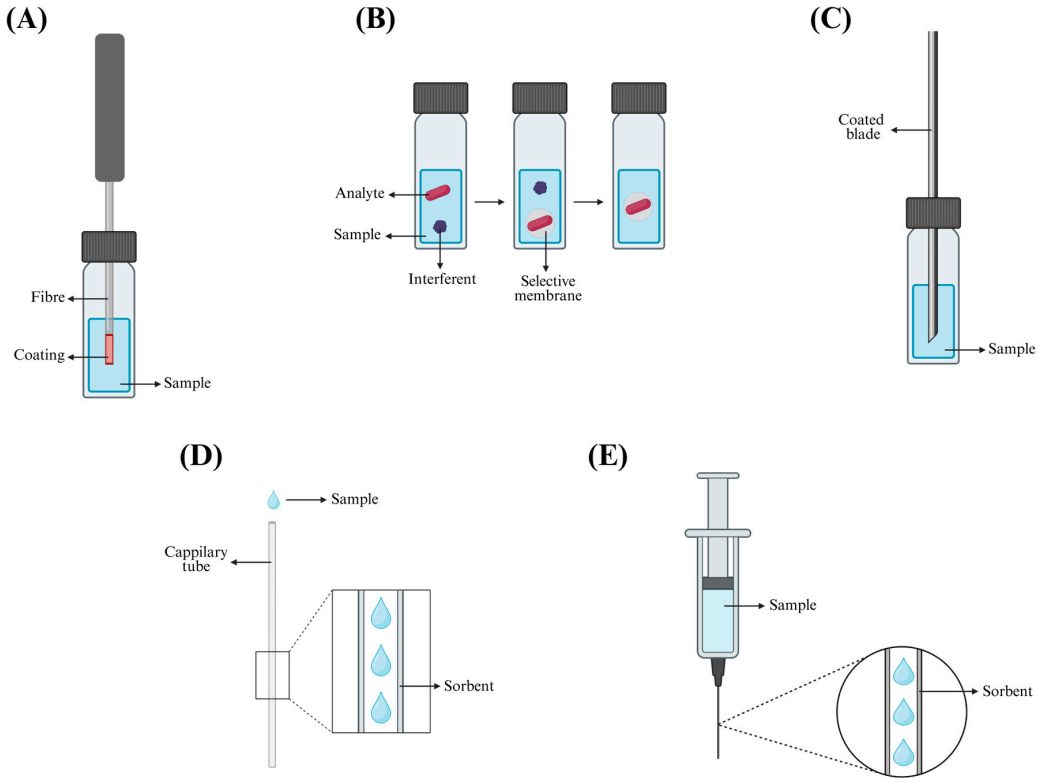

Figure 2. SPME techniques applied to the determination of drugs of abuse in wastewaters: (**A**) DI-SPME; (**B**) TFME; (**C**) Coated Blade SPME; (**D**) IT-SPME; (**E**) SPDE.

3.2. Micro Solid-Phase Extraction

Micro-SPE (μSPE) is a miniaturised version of conventional SPE, characterised by moderate processing time and reduced sorbent consumption [76,77]. Similarly to SPME, μSPE aims to efficiently extract analytes from a wide variety of sample matrices; however, the two are conceptually distinct [76]. The μSPE technique (Figure 3) typically employs small extraction devices—such as porous membrane bags—filled with minimal quantities of sorbent, thereby reducing matrix effects commonly observed in traditional SPE [78]. Its design focuses on reducing the size of the extraction device, the amount of sorbent, the operational time, and the use of organic solvents.

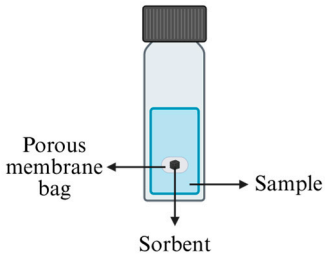

Figure 3. Schematic representation of μSPE technique.

The advantages of μSPE—namely its simplicity, enhanced sensitivity and specificity, and compatibility with analytical instrumentation—justify its increasing implementation, despite certain limitations. These include the fragility of the extraction fibres, a limited range of available stationary phases, and the possibility of carry-over effects [52,79,80].

This miniaturised technique has already been applied to wastewater analysis. Baz-Lomba et al. [81] proposed an offline μSPE method using a 96-well HLB μElution plate with a 30 μm particle size for the simultaneous determination of 13 drugs in influent wastewater samples. The HLB sorbent enabled effective extraction of analytes with diverse physicochemical properties. In addition, a post-loop mixing–large volume injection (PLM-LVI) configuration was implemented in the liquid chromatography coupled to mass spectrometry (LC-MS/MS). It significantly reduced sample preparation time while increasing method sensitivity by enabling the injection of large sample volumes.

In a more recent study, Muñoz-Bartual et al. [57] developed and validated a μSPE method for the LC-MS/MS determination of pharmaceuticals and illicit drugs, including NPS. The researchers synthesised a porous monolith of poly(methacrylic acid-co-ethylene glycol dimethacrylate) and immobilised it onto a nylon membrane within a commercial syringe filter. This monolithic-coated syringe filter approach proved to be efficient for extracting a broad range of compounds when compared to a conventional SPE method. However, a laser-assisted monolithic photopolymerisation step was required to activate the sorbent material. The validated method demonstrated a simple, one-step μSPE protocol with relatively low detection limits across a wide array of substances, although it required relatively large sample volumes.

The methodological conditions and key features of both μSPE applications are summarised in Table 2.

Table 2. Applications of μSPE techniques for the determination of drugs of abuse in wastewater samples.

Sample (mL)	Analytes	μSPE Properties	Conditions	Instrument	LOD	Recovery	References
Wastewater (5)	Amphetamine Methamphetamine MDMA Cocaine BE Cocaethylene	HLB μElution plates, 30 μm	Conditioning: 1 mL of MeOH and 1 mL of ultrapure water Washing: 1 mL of ultrapure water Vacuum drying for 15 min Elution: 50 μL of 1% NH_4OH in MeOH, 100 μL of MeOH and 50 μL of 1% FA in MeOH (200 μL extract)	PLM-LVI-UHPLC-MS/MS	1.0–6.3 ng/L *	92–110%	[81]
Wastewater (25)	Amphetamine Methamphetamine 2-Fluoroamphetamine 2-Fluoromethamphetamine Fenproporex Methylone 6-AM 3-MeO-PCE Deschloroketamine MDMA Butylone Ketamine α-PVP Pentylone PCP Cocaine Fenethylline α-PHP LSD Fentanyl 3-MeO-PCP	poly(MAA-co-EGDMA) monolith immobilised on a nylon membrane	Conditioning: 2 mL of MeOH (0.1% FA) and 2 mL deionised water Washing: 2 mL of deionised water Vacuum drying for 5 min Elution: 200 μL of MeOH (0.1% FA)	LC-MS/MS	4–19 ng/L	88–119%	[57]

Legend: 3-MeO-PCP: 3-methoxyphencyclidine; 3-MeO-PCE: 3-methoxyeticyclidine; 6-AM: 6-acetylmorphine; α-PHP: α-pyrrolidinohexanophenone; α-PVP: α-pyrrolidinopentiophenone; BE: benzoylecgonine; EGDMA: ethylene glycol dimethacrylate; FA: formic acid; HLB: hydrophobic/lipophilic balanced; LC-MS/MS: liquid chromatography coupled to tandem mass spectrometry; LOD: limit of detection; LSD: lysergic acid diethylamide; LVI: large volume injection; MAA: methacrylic acid; MDMA: 3,4-methylenedioxymethamphetamine; MeOH: methanol; PLM: post-loop mixing injection; UHPLC-MS/MS: ultra-high-performance liquid chromatography coupled to tandem mass spectrometry; * limit of quantification.

3.3. Magnetic Solid-Phase Extraction

The MSPE was developed by Šafaříková and Šafařík in 1999, and is based on the use of magnetic or magnetisable adsorbents [82]. In this technique, magnetic nanoparticles are dispersed into a liquid sample and incubated for an optimised period, allowing adsorption of target analytes and subsequent equilibrium. The magnetic sorbent–analyte complex is then separated from the sample using a magnetic field. Alternative separation methods, such as centrifugation or filtration, are less commonly applied [83]. Following an optional washing step to remove residual contaminants, an appropriate elution solvent is used to desorb the retained analytes for instrumental analysis [83,84]. MSPE offers advantages over conventional SPE, such as eliminating issues related to sorbent packing, high backpressures, and clogging [85]. Consequently, a wide variety of magnetic materials and MSPE protocols have been developed and reported in the literature [83,84]. Figure 4 illustrates the commonly used MSPE methodology.

In recent years, the application of MSPE for detecting drugs of abuse in wastewater has gained increasing attention. To the best of our knowledge, Zhang et al. [86] conducted the first study, in 2022, applying MSPE to extract drugs of abuse from wastewater, followed by detection via GC–MS. In that study, a magnetic sorbent derived from pomelo peel biochar was synthesised and applied to retain morphine-like opioids via π–π interactions and

hydrogen bonding. The validated method achieved low detection limits, demonstrating the technique's analytical potential.

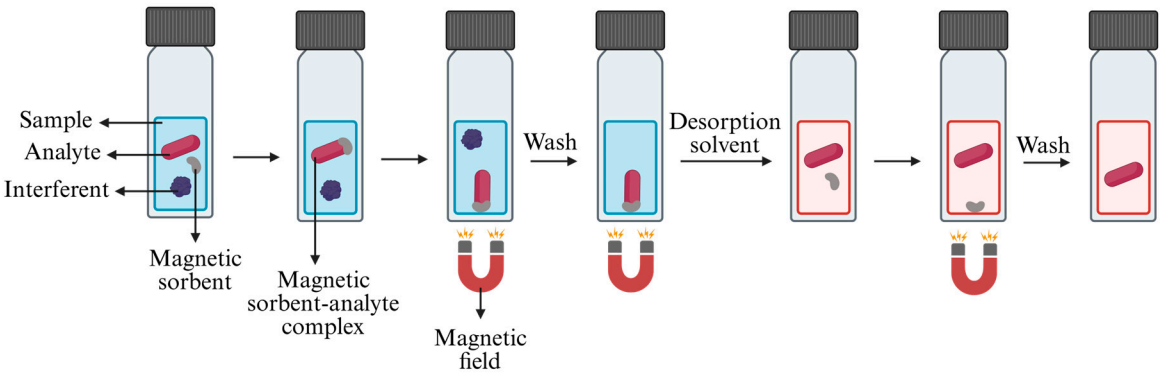

Figure 4. Schematic representation of MSPE technique.

Numerous magnetic sorbents have been described in the literature. Among them, magnetite (Fe_3O_4) is the most frequently used due to its strong magnetic responsiveness and easy surface modification. Other commonly employed materials include polydopamine (PDA) and DVB. PDA provides an ideal surface that enhances the hydrophilicity and stability of the magnetic particles [87] and exhibits strong affinity for amphetamine-type stimulants through π–π interactions and hydrogen bonding [88]. Conversely, DVB can act as both a sorbent and a cross-linking agent and is particularly effective for extracting hydrophobic compounds via Van der Waals forces and π–π interactions [89–91]. Although most MSPE methods report low detection limits, they often require large volumes of wastewater, depending on the analytical instrumentation used. Notable recent developments include studies by Chen et al. [87], Li et al. [90], and Cao et al. [92], who developed sensitive and robust MSPE protocols for the determination of synthetic cannabinoids, each employing different adsorbents and experimental conditions.

Of particular interest, Cao et al. [92] validated a modified MSPE method using a graphene oxide–ferrosoferric oxide (GO–Fe_3O_4) composite, combined with an ionic liquid to form mixed hemimicelles, offering enhanced extraction efficiency. This approach contrasts with conventional MSPE methods, which typically rely on magnetic adsorbents alone.

The methodological parameters and conditions used in the published MSPE studies are summarised in Table 3.

Table 3. MSPE methodologies applied to the determination of drugs of abuse in wastewater samples.

Sample (mL)	Analytes	Magnetic Sorbent	MSPE Conditions	Instrument	LOD	Recovery	References
Wastewater (20)	Morphine Codeine 6-AM	Magnetic pomelo peel-derived biochar	15 mg of adsorbent; Mixing for 14 min at 200 rpm; External magnet and supernatant decanted; 200 µL of MeOH and vortex for 4 min at 14,000 rpm; 0.22-µm membrane filtering.	LC-MS	0.006–0.010 µg/L	71.6–84.4%	[86]

Table 3. *Cont.*

Sample (mL)	Analytes	Magnetic Sorbent	MSPE Conditions	Instrument	LOD	Recovery	References
Wastewater (50)	Amphetamine Methamphetamine Methcathinone MDMA MDA	Fe_3O_4@nSiO_2@mSiO_2 @PDA	50 mg of adsorbent; Mixing in 5 M NaOH solution for 15 min at room temperature in a PET bottle; External magnet and supernatant discarding; 5 mL of washing solution and vortex for 30 s; External magnet and supernatant discarding; 5 mL of desorption solution (95% ACN and 5% FA, *v*/*v*) and vortex for 3 min; Extracts drying at 50 °C under N_2; Reconstitution with 100 µL water (0.1% FA).	UHPLC-MS/MS	0.5–2.5 ng/L	95.1–106.6%	[88]
Wastewater (100)	Amphetamine Codeine Morphine Ketamine Methamphetamine Cocaine 6-AM MDMA BE Norketamine MDA	NP-COF@Mag-PS/DVB/GMA	30 mg of adsorbent; Mixing for 5 min; Magnetic field for 30 s; 2 mL of washing solution: MeOH:water (1:9, *v*/*v*); 1.5 mL of desorption solution: 95% MeOH:Ammonia (95:5, *v*/*v*); Extracts drying; Reconstitution with 1 mL mobile phase (water with 0.1% FA).	LC-MS/MS	0.12–1.47 ng/L	81.6–106%	[93]
Wastewater (100)	5 F-EDMB-PINACA FUB-APINACA MDMB-4en-PINACA MDMB-FUBINACA PB-22 THC-COOH	Fe_3O_4@PDA@poly (MAA-co-EGDMA)	Prior filtration using a glass fibre filter membrane; pH adjustment to 2 by hydrochloric acid or sodium hydroxide in a PET bottle; Mixing for 10 min; External magnet and supernatant discarding; Elution with 200 µL of ACN and vortex for 1 min; Magnetic separation, centrifugation and mix with equal volume of deionised water.	UHPLC-MS/MS	0.1–1.0 ng/L *	64.01–124.0%	[87]
Wastewater (200)	Morphine 6-AM MDMA MDA Ketamine Norketamine Methamphetamine Amphetamine 4-Methylcathinone Methcathinone Cocaine BE Cotinine Codeine PMMA 4-ANPP Norfentayl NAFN Fentanyl	Fe_3O_4 @poly(ST/DVB/MA-COOH)	50 mg of sorbent; Adsorption for 1 min; External magnet and supernatant discarding; Washing with 3 mL of ACN and vortex for 30 s; Elution with 4 mL of 4% TFA/MeOH and N_2 drying at room temperature; Reconstitution with 200 µL of 0.2% HCOOH/MeOH and filtration with 0.22 µm organic phase membrane.	UHPLC-MS/MS	0.03–0.67 ng/L	93.4–118.0%	[89]

Table 3. *Cont.*

Sample (mL)	Analytes	Magnetic Sorbent	MSPE Conditions	Instrument	LOD	Recovery	References
Wastewater (100)	Amphetamine Methamphetamine Methcathinone MDMA	DES/ZIF-MGO	5 mg of adsorbent; Mixing for 30 min at 180 rpm; External magnet and supernatant discarding; Elution with 5 mL of MeOH:Ammonia (95:5, *v*/*v*) and mixing for 10 min; Magnetic separation and N_2 drying at 50 °C; Reconstitution with 100 µL of mobile phase (2 mmol/L ammonium format with 0.1% FA) and filtration with 0.22 µm micropore membrane.	UHPLC-MS/MS	0.02–1.55 µg/L	92.1–100.9%	[94]
Wastewater (50)	Amphetamine Methamphetamine 6-AM Morphine Ketamine Norketamine Cocaine BE MDA MDMA Cathinone Methcathinone Fentanyl	Fe_3O_4@SiO_2-MA@PLS	20 mg of adsorbent; Sonication for 1 min and vortex for 10 min at room temperature; External magnet for 60 s and supernatant discarding; Elution with 3 mL of ACN by ultrasonic washing for 5 min and N_2 drying at 60 °C; Reconstitution with 200 µL of MeOH:Water (2:8, *v*/*v*) and filtration through 0.22 µm filter membrane.	MS system	1–2 ng/mL *	44–100%	[95]
Wastewater (0.99)	Methamphetamine Amphetamine MDMA MDA Morphine 6-AM Codeine Cocaine BE Ketamine Norketamine	Fe_3O_4@PDA	10 mg of adsorbent; Sonication of the adsorbent with 1 mL of MeOH for 5 min; MeOH discarding by magnetic separation; Sample introduction and vortex for 4 min at 1400 rpm; Magnetic rack and supernatant discarding; Washing with 1 mL of deionised water, vortexing for 2 min at 1400 rpm and supernatant discarding; Elution with 1 mL of MeOH:ACN (1:1, *v*/*v*) and vortex for 2 min at 1400 rpm; Drying under a N_2 flow at 50 °C, reconstitution with 500 µL of deionised water and filtration through a PTFE membrane.	UHPLC-MS/MS	2–5 ng/L	27.81–98.29%	[96]
Wastewater (100)	Amphetamine Methamphetamine MDMA Methcathinone Mephedrone	DZMBC	Samples previous filtration with a 0.22 µm aqueous membrane; 5 mg of adsorbent; Mixing for 40 min at 25 °C under 155 rpm; External magnet and supernatant discarding; Desorption with 3 mL with MeOH (1% FA) for 20 min; Drying under N_2 at 60 °C, reconstitution with 0.5 mL of ultrapure water and filtration through 0.22 µm film.	UHPLC-MS/MS	1.0–4.75 ng/L	96.2–106.1%	[97]

Table 3. *Cont.*

Sample (mL)	Analytes	Magnetic Sorbent	MSPE Conditions	Instrument	LOD	Recovery	References
Wastewater (50)	MDMB-FUBINACA 4CN-CUMYL-BUTINACA 5F-MDMB-PICA MDMB-4en-PINACA ADB-4en-PINACA 5F-EMB-PICA AMB-FUBINACA ADB-BUTINACA 4F-MDMB-BUTICA	Fe_3O_4@PDA@poly(DVB-co-NVP)	pH adjustment to 9 by sodium hydroxide; 10 mg of adsorbent; Ultra-sound assisted extraction for 15 min; External magnet and supernatant discarding; Elution with 1 mL of 1% ammonia MeOH for 1 min; Drying under N_2 and reconstitution with 100 µL mobile phase (0.1% FA aqueous solution) and centrifugation at 15,000 rpm for 5 min.	UHPLC-MS/MS	0.01–1.0 ng/L *	69.63–107.38%	[90]
Wastewater (300)	5F-BZO-POXIZID Ethylphehethyl-FUBINCA BIM-018 4CN-CUMYL-BUTCZCA CH-FUBIATA CUMYL-NBMICA JWH-019 RCS-4 ACHMINACA BZO-HEXOXIZID BIM-2201 JWH-249 JWH-307 MDMB-CHMCZCA AFUB7AICA JWH-370 AB-001 JWH-030	GO-Fe_3O_4 with an ionic liquid (ILs-GO-Fe_3O_4)	Samples previous filtration with a 1.2 µm glass filter membrane; 20 mg of adsorbent with 1 mL of ionic liquid solution (20 mg/mL); Ultrasonication for 20 s and mechanical mixing for 30 min; External magnet while stirring and supernatant discarding; Elution with 5 mL of ACN by vortexing for 5 min and magnetic separation; Drying under N_2 and reconstitution with 100 µL of mobile phase (0.1% FA in water).	UHPLC-MS/MS	10 pg/L	72.6–97.8%	[92]
Wastewater (200)	THC CBD CBN THC-COOH	Fe_3O_4@poly (GMA/DVB-WAX)	pH adjustment to 7; 30 mg of adsorbent; 5 min of extraction; External magnet and supernatant discarding; Washing with 3 mL of 5% MeOH/Water and vortex for 30 s; Elution with 4 mL of 8% HCOOH/MeOH and drying under N_2; Reconstitution with 200 µL of 0.2% HCOOH/MeOH and filtration through a 0.22 µm hydrophilic syringe filter.	UHPLC-MS/MS	0.17–0.33 ng/L	69.4–94.0%	[98]

Legend: 4-ANPP: 4-aminophenyl-N-phenethylpiperidine; 6-AM: 6-acetylmorphine; ACN: acetonitrile; BE: benzoylecgonine; CBD: cannabidiol; CBN: cannabinol; COF: covalent organic frameworks; DES: deep eutectic solvent; DVB: divinylbenzene; DZMBC: DES-ZIF-magnetic shrimp shell biochar; EGDMA: ethylene glycol dimethacrylate; FA: formic acid; GMA: glycidyl methacrylate; GO: graphene oxide; ILs: ionic liquids; LC-MS: liquid chromatography coupled to mass spectrometry; LC-MS/MS: liquid chromatography coupled to tandem mass spectrometry; LOD: limit of detection; MA: methacrylate; MAA: methacrylic acid; MDA: 3,4-methylenedioxyamphetamine; MDMA: 3,4-methylenedioxymethamphetamine; MeOH: methanol; MGO: magnetic graphene oxide; NAFN: noracetylfentanyl; NP-nano petal-shape; NVP: N-vinylpyrrolidone; PDA: polydopamine; PET: polyethylene terephthalate; PMMA: p-methoxymethamphetamine; PTFE: polytetrafluoroethylene; PS: polystyrene; ST: styrene; TFA: trifluoroacetate; THC: Δ9-tetrahydrocannabinol; THC-COOH: 11-nor-9-carboxy-Δ9-tetrahydrocannabinol; UHPLC-MS/MS: ultra-high-performance liquid chromatography coupled to tandem mass spectrometry; WAX: weak anionic exchange; ZIF: zeolitic imidazolate framework; * LOQ: limit of quantification.

3.4. Molecularly Imprinted Polymers

The MIPs are synthetic polymers designed to exhibit high selectivity for a target analyte or structurally related compounds. Their growing popularity is attributed to their

reliability, chemical and thermal stability, low-cost and straightforward preparation, and broad affinity for various substances [78,99].

MIPs are synthesised through the polymerisation of functional monomers in the presence of a template molecule, which interacts via covalent or non-covalent bonds, using a cross-linking agent [54,78]. Once the polymer is formed, the template is removed—typically via chemical reaction or solvent extraction—leaving behind specific binding sites that are complementary in shape, size, and chemical functionality to the target analyte. These binding sites enable selective reuptake of the analyte, effectively mimicking the specificity of antibody–antigen systems [99,100].

In recent years, MIPs have been widely used in SPE as selective sorbent materials. This advanced application is commonly referred to as molecularly imprinted solid-phase extraction (MISPE) [101,102]. MISPE can be considered a miniaturised version of SPE, where a small quantity of MIP is packed into cartridges, and conventional SPE steps are followed thereafter (Figure 5) [78].

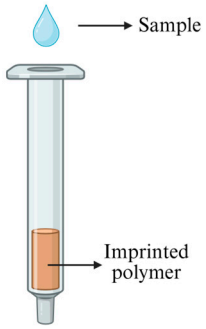

Figure 5. Illustration of MISPE technique.

MISPE has been successfully applied to the extraction of several illicit substances from various matrices, including wastewater. González-Mariño et al. [103] developed a method for the extraction of amphetamine-type stimulants using commercial MIPs specifically designed for this class of compounds. These were compared with conventional sorbents such as HLB and MCX. The MIPs outperformed the traditional sorbents in terms of selectivity, accuracy, reduced matrix effects, and lower limits of detection.

Similarly, Xiong et al. [104] described a MISPE method for amphetamines using N-methylphenethylamine-imprinted polymers (MPEA-MIPs) and smaller sample volumes. The authors compared the extraction efficiencies of three different MIPs—synthesised with dopamine, N-methylethanamine, and MPEA—as well as non-imprinted polymers (NIPs). MPEA-MIPs exhibited superior binding capacities for the target analytes.

On another front, Sorribes-Soriano et al. [105] developed a stir cake sorptive extraction (SCSE) technique using polytetrafluoroethylene (PTFE) discs embedded with monolithic MIP cakes. MIPs were synthesised using ecgonine methyl ester (EME) as the template and methacrylic acid (MAA) as the monomer, exhibiting high specificity for EME in wastewater samples. Both ion mobility spectrometry (IMS) and LC-MS/MS were employed for detection, achieving limits of 13 ng/L and 75 ng/L, respectively.

A further example is provided by El-Akaad et al. [106], who developed a MISPE protocol for the detection of 4-methyl-5-phenylpyrimidine (4M5PP)—a synthetic by-product of amphetamine prepared via the Leuckart method. MIPs were synthesised using MAA and 2-vinylpyridine (2-VP) as functional monomers on a gold electrode surface. A simplified extraction procedure, combined with an electrochemical sensor, enabled efficient detection of the target compound.

The methodologies and conditions applied in these MIP-based approaches are summarised in Table 4.

Table 4. Applications of MIP-based techniques for the extraction and determination of drugs of abuse in wastewater samples.

Sample (mL)	Analytes	MIP Sorbent	Conditions	Instrument	LOD	Recovery	References
Wastewater (50)	Amphetamine Methamphetamine MDA MDMA MDEA	Commercial amphetamine class-selective MIP (25 mg)	Conditioning: 1 mL of MeOH and 1 mL of pH 8 Milli-Q water; Washing: 1 mL of pH 8 Milli-Q water, 1 mL of ACN/Water (6:4, *v*/*v*) and 1 mL of ACN (1% AA) in duplicate; Elution: 1 mL of MeOH (1% FA) in duplicate Drying under N_2; Reconstitution: 100 µL of MeOH/Water (1:1, *v*/*v*) with 2% of NH_3.	LC-MS/MS	0.5–2.7 ng/L	91.6–113.9%	[103]
Wastewater (100)	Cocaine BE	Scopolamine MIP with TFMAA (200 mg)	Conditioning: 3 mL of MeOH and 3 mL of water; Elution: 4 mL of MeOH/Ammonia (19:1, *v*/*v*); Drying under vacuum; Reconstitution with mobile phase (0.1% AA in deionised water).	HPLC-TOF-MS	N.P.	83.6 and 72.1%	[107]
Wastewater (200)	EME	PTFE discs containing EME MIP with MAA	MIP-disc conditioning with 200 mL of deionised water for 5 min with magnetic stirrer mixing; Samples pH adjustment to 10 by 10 mL of carbonate buffer 0.1 M; MIP-disc introduction and mixing for 30 min; Washing: 50 mL deionised water for 1 min and drying with paper tissue; Elution: submerging the MIP-disk in 5 mL of MeOH (1% AA) for 30 min.	IMS and UHPLC-MS/MS	75 and 13 ng/L	100%	[105]
Wastewater (500)	4M5PP	4M5PP MIP with MAA and 2-VP on a gold electrode surface	Sample filtration through 0.22 µm filter membrane;	Electrochemical Sensor	80µM	93.3–101%	[106]
Wastewater (10)	Cathinone Methcathinone Mephedrone Methylone Ethylone MDPV	DMIP (200 mg)	Conditioning: 3 mL of MeOH and 3 mL of deionised water; Washing: 3 mL of deionised water; Drying under negative pressure; Rising with 3 mL of ACN and elution with 6 mL of MeOH (1% FA); Extracts drying with rotary evaporator and reconstitution with 500 µL of MeOH/water (50:50, *v*/*v*); Filtration through 0.22 µm membrane.	HPLC-MS/MS	0.002–0.1 ng/mL	84.1–97.7%	[108]
Wastewater (10)	Amphetamine Methamphetamine MDMA	MPEA-MIPs (50 mg)	Conditioning: 500 µL of 25 mM citrate buffer/ACN (50/50, *v*/*v*) Washing: 500 µL of ACN/Distilled water (3:7, *v*/*v*); Elution: 400 µL of a solution with 15% AA, 35% water and 50% MeOH; 50 µL of MeOH was added to 50 µL of the extract.	LC-MS/MS	0.05–0.29 µg/L	96–97%	[104]

Legend: 2-VP: 2-vinylpyridine; 4M5PP: 4-methyl-5-phenylpyrimidine; AA: acetic acid; ACN: acetonitrile; BE: benzoylecgonine; DMIP: dummy molecularly imprinted polymers; EME: ecgonine methyl ester; FA: formic acid; HPLC-MS/MS: high-performance liquid chromatography couples to tandem mass spectrometry; HPLC-TOF-MS: high-performance liquid chromatography coupled to time of fly mass spectrometry; IMS: ion mobility spectrometry; LC-MS/MS: liquid chromatography coupled to tandem mass spectrometry; LOD: limit of detection; MAA: methacrylic acid; MDA: 3,4-methylenedioxyamphetamine; MDEA: 3,4-methylenedioxyethylamphetamine; MDMA: 3,4-methylenedioxymethamphetamine; MeOH: methanol; MIPs: molecularly imprinted polymers; MPEA: N-methylphenylethylamine; N.P.: not provided; PTFE: polytetrafluoroethylene; TFMAA: 2-(trifluoromethyl) acrylic acid; UHPLC-MS/MS: ultra-high-performance liquid chromatography coupled to tandem mass spectrometry.

4. Comparative Overview of Solid-Phase Microextraction Techniques and Their Integration into WBE

To provide a clearer understanding of the practical aspects of each technique discussed, Table 5 presents a comparative overview of the most commonly used solid-phase microextraction methods for monitoring drugs of abuse in wastewater. This summary includes key operational parameters such as extraction time, solvent consumption, cost per sample, and

material reusability, and highlights the main advantages and limitations of each approach. By outlining these factors, the table supports informed decision-making in both research and routine monitoring contexts.

Table 5. Comparative table of solid-phase microextraction techniques for drug monitoring in wastewater.

Technique	Extraction Time	Solvent Consumption	Cost per Sample	Reusability	Advantages and Limitations
SPME	30–60 min	None/Minimal	Low	Moderate (typically reusable for up to ~100 uses depending on matrix complexity and handling conditions)	Solvent-free; easy automation Limited for highly polar compounds
TFME	20–40 min	None	Low	High	High sensitivity; large surface area Less robust; specialised setup
µSPE	10–30 min	Low	Low	Low	Simple, fast, LC-MS/MS compatible Limited reuse; polymer activation needed
MSPE	10–20 min	Minimal	Moderate	High	High selectivity; nanomaterials adaptable Nanoparticle synthesis complexity
MIPs	30–60 min	Low	Moderate	High	Highly selective; reusable Polymer synthesis and validation time

WBE has emerged as a valuable approach to assess community-level drug use patterns by analysing specific biomarkers in sewage [16]. The reliability of this approach depends not only on accurate analytical quantification but also on the effectiveness and reproducibility of the preceding sample preparation methods [34]. In this context, miniaturised solid-phase extraction techniques play a pivotal role by enabling the efficient pre-concentration and purification of target analytes prior to instrumental analysis [52].

Microextraction techniques such as SPME, TFME, µSPE, MSPE, and MIPs have increasingly demonstrated their utility in WBE workflows. Their high selectivity and sensitivity enable the detection of drugs of abuse at trace levels, which is crucial for calculating per capita consumption based on the concentrations detected in wastewater [38,78]. Since these estimates are often used to inform public health policies and drug prevention strategies, any bias or inaccuracy in extraction efficiency can significantly affect the epidemiological interpretation of the data [19].

Moreover, the integration of these microextraction techniques into standardised protocols enhances data comparability across geographic regions and temporal scales [16]. Initiatives such as the SCORE network have underscored the importance of harmonising sampling and analytical procedures to ensure coherent surveillance across Europe [16,17]. In this light, the use of reproducible and eco-friendly extraction methods that minimise matrix effects and improve analyte recovery becomes essential for maintaining the scientific integrity of WBE.

Additionally, automation and miniaturisation contribute to the feasibility of high-throughput analyses, which are often necessary when dealing with large monitoring campaigns. The reduction in solvent consumption and sample volume aligns with green

analytical chemistry principles, further supporting the integration of these methods in sustainable monitoring frameworks [51,55].

Future perspectives in WBE should include the validation of microextraction techniques not only in terms of analytical performance, but also regarding their impact on epidemiological indicators such as prevalence, incidence, and consumption trends. Strengthening the interface between analytical chemistry and public health surveillance will further enhance the role of WBE as a robust tool for drug monitoring strategies at both national and international levels.

5. Conclusions and Future Perspectives

The growing use and diversification of drugs of abuse worldwide is a cause for concern, driven by the expanding illicit markets and ease of access, which contribute to significant social and public health issues. This scenario underscores the critical importance of developing analytical methodologies capable of identifying and quantifying a wide range of substances, particularly in complex matrices such as wastewater.

Both traditional drugs of abuse, which remain the most widely consumed, and emerging NPS have been effectively monitored through WBE. This approach offers valuable insights into patterns of drug consumption across populations, enabling the prioritisation of health and legal interventions. For these efforts to be successful, analytical methods must demonstrate robustness, sensitivity, and selectivity, ensuring the reliability and efficiency of the monitoring process. Therefore, the extraction step prior to instrumental analysis must be rapid, effective, and selective in order to recover target analytes using practical and scalable methodologies.

In recent years, miniaturised extraction techniques have emerged as promising alternatives to conventional approaches, such as SPE and LLE, which are progressively falling out of favour. Several solid-phase microextraction-based techniques have been applied to the analysis of drugs of abuse in wastewater, including SPME, TFME, IT-SPME, SPDE, μSPE, MSPE, and MIPs. These methods differ in format, sorbent type, and extraction conditions, offering flexibility and adaptability to specific analytical needs.

Among the techniques reviewed, MSPE- and MIP-based methods stand out as the most commonly applied in the recent literature. Their appeal lies in the use of highly selective sorbents or polymers tailored for specific analytes or groups of substances—whether classical drugs or NPS. The exponential rise in the use of MIPs within solid-phase microextraction frameworks is largely attributable to their affordability, as their synthesis is relatively simple and cost-effective.

Looking ahead, the development and implementation of eco-friendly workflows will remain a key priority. These include the use of smaller volumes of organic solvents and the advancement of automated, time-efficient techniques. Future extraction methods are expected to rely on increasingly selective sorbents capable of targeting a broader spectrum of analytes, complemented by robust and sensitive analytical instrumentation that can detect trace levels of substances in small volumes of wastewater.

Enhancing both extraction and analytical methodologies in the field of wastewater analysis will significantly improve our ability to monitor community drug consumption. This, in turn, will contribute to a better understanding of drug use patterns and support the design of evidence-based strategies for public health protection and drug policy implementation by competent authorities.

Moreover, there remains a promising but underexplored opportunity to expand the use of other solid-phase microextraction techniques that have not yet been widely applied to the analysis of drugs of abuse in wastewater. Techniques such as fabric-phase sorptive extraction (FPSE), monolithic in-tip extraction, and electrospun nanofibre-based sorbents

offer unique characteristics such as enhanced surface area, rapid kinetics, and integration with portable or on-site analytical platforms. In fact, FPSE represents an excellent alternative, as the fabric phase can be introduced directly into the wastewater sample, where it absorbs the analytes of interest. Owing to its low solvent consumption, it constitutes an ideal technique for both on-site and off-site sample treatment in the determination of drugs of abuse in wastewater. Monolithic in-tip extraction, in addition to requiring minimal solvent, also offers the possibility of on-site and automated extraction of analytes from liquid samples, as effective adsorption and desorption can be performed both portably and automatically, making it a highly suitable technique for wastewater analysis. Moreover, the application of electrospun nanofibre-based sorbents in sample preparation techniques currently represents a significant gap in the monitoring of drugs of abuse in wastewater. Given their small sorbent mass and high extraction efficiency, ultrafine fibres can be integrated into several miniaturised solid-phase extraction techniques, thereby enhancing the recovery of analytes of interest from diverse matrices.

Although these methods have shown success in other fields, including food and clinical analysis, their potential for WBE remains largely untapped. Exploring these innovative methodologies could further enhance analytical sensitivity, operational simplicity, and eco-efficiency in future drug monitoring strategies.

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