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REVIEW ARTICLE

Analysis of psychoactive substances and metabolites in sludges, soils, sediments and biota: a review

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Abstract

The use of psychoactive substances, including illegal drugs, drugs of abuse and psychiatric pharmaceuticals, is a major health and environmental issue. In particular, drugs are found in urban sewage and water ecosystems. The analysis of drugs in wastewater is challenging because drugs occur at trace levels in complex organo-mineral media, calling for advanced analytical methods. Here we review recent methods developped to analyze drugs in sludge, sediments, soils and biota. Extraction methods include solid–liquid extraction, sonication, microwave, and quick, easy, cheap, effective, rugged and safe extraction (QuEChERS). We compare and discuss advantages and disadvantages of each analytical step for various sample types.

Keywords Solid matrix · Ultrasonic-assisted extraction · Pressurised liquid extraction · Microwave-assisted extraction · Illicit drugs · Psychoactive compounds

Introduction

The excessive use of psychoactive substances, such as illicit drugs, some kinds of antidepressants or stimulants and certain opioids, is currently a matter of concern because they are potentially addictive. Apart from logical negative social impacts, these compounds are not completely metabolised, as many other pharmaceutical compounds are, and are excreted in their original form or as metabolites, reaching the wastewater treatment plants. Many of them are not fully eliminated or degraded during these processes and are detected in both effluents and receiving waters (Kostich et al. 2014; Yadav et al. 2017). Given their properties, they may harm the ecology of the receiving environment (Petrie et al. 2016). In addition, an increasing consumption trend is noted for many of these compounds and, thus, their entry in the environment would increase. Hence they can be considered pseudo-persistent pollutants (Gualano et al. 2014; United Nations 2020).

The term psychoactive substances refers to a group of substances capable of exerting strong stimulatory and hallucinogenic effects on the central nervous system (Kasprzyk-Hordern et al. 2008), although new psychoactive substances can be central nervous system depressants. Psychoactive substances encompass illicit drugs, which can be natural substances like marihuana or cocaine, substances prepared from natural substances like heroin or synthetic substances, such as amphetamines and most other neuropsychiatric prescription drugs. Of these psychoactive substances, opioids are widely used against severe pain because they are the most effective treatment against it (Zöllner and Stein 2007). Nevertheless, these drugs are addictive, and their abuse can seriously harm physical and mental health. Opioids include natural alkaloids: morphine and codeine, which can be considered drugs of abuse; semisynthetic derivatives of these alkaloids, such as heroin and hydrocodone, which are considered illegal drugs, although hydrocodone is prescribed in several countries; synthetic opioids like methadone and tramadol, which can be taken as drugs of abuse. Cannabinoids present hallucinogenic activity, and these compounds are considered illicit drugs in some countries although in others its use is legalized for medicinal purposes or private consumption. Finally, several pharmaceuticals are neuropsychiatric prescription compounds, such as benzodiazepines

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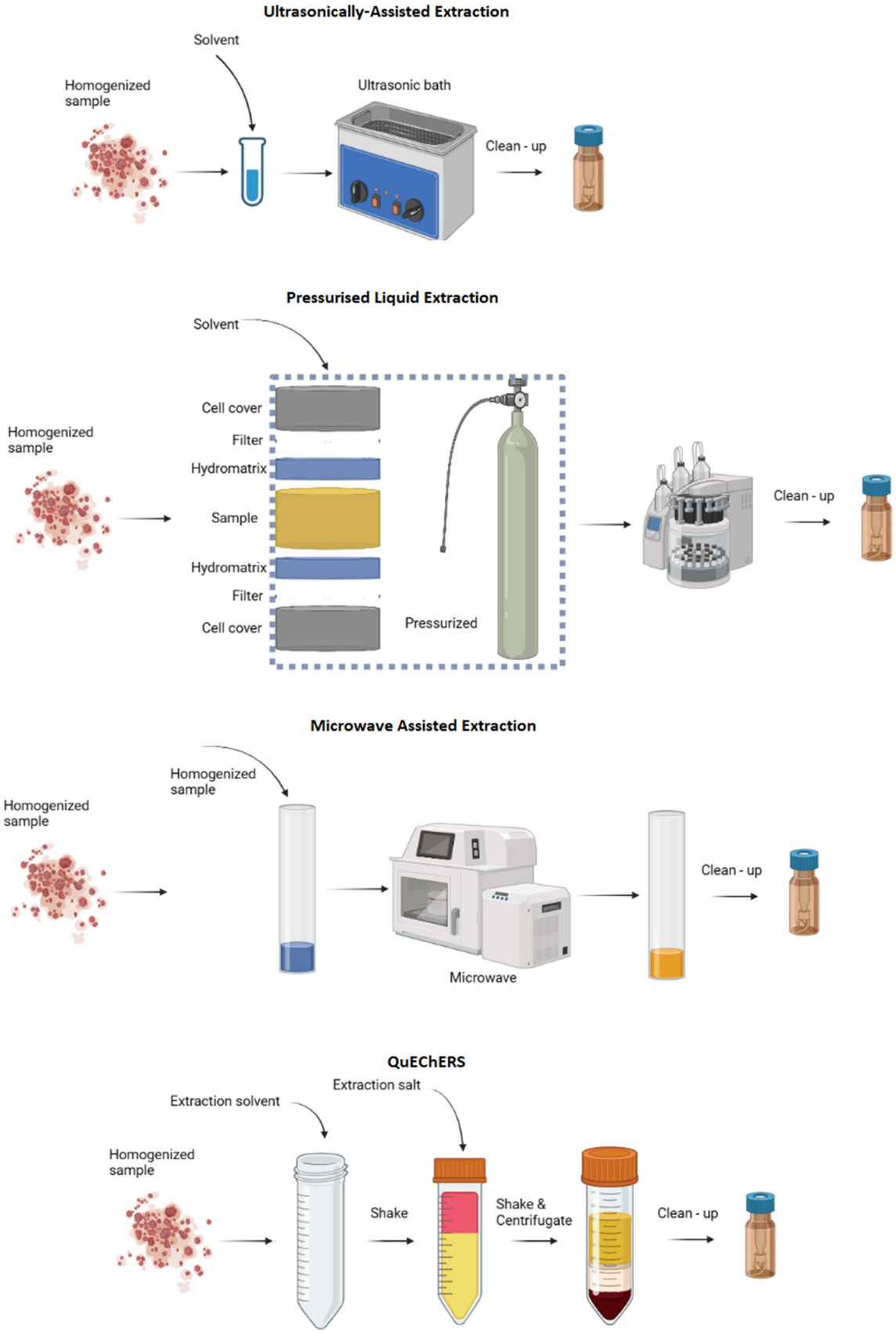
Ultrasonically-Assisted Extraction
Solvent
Homogenized sample
Ultrasonic bath
Clean - up
Pressurised Liquid Extraction
Solvent
Cell cover
Filter
Hydromatrix
Sample
Hydromatrix
Filter
Cell cover
Homogenized sample
Pressurized
Clean - up
Microwave Assisted Extraction
Homogenized sample
Homogenized sample
Microwave
Clean - up
QuEChERS
Extraction solvent
Extraction salt
Homogenized sample
Shake
Shake & Centrifugate
Clean - up

◂**Fig. 1** Extraction procedures for the extraction of analytes from solid phase: ultrasonically assisted extraction, pressurized liquid extraction, microwave assisted extraction and quick, easy, cheap, effective, rugged and safe (QuEChERS) (Created with BioRender.com)

and antidepressants, which are employed mainly to treat mental disorders like anxiety and sleep disorders. However, they also have a very high abuse potential, can generate addiction and can be used as recreational drugs.

The determination of drugs by wastewater analyses can add valuable information to existing surveillance sources (Thomas et al. 2012; Ort et al. 2014). This new approach is called wastewater-based epidemiology, and has been used mainly with illicit drugs or drugs of abuse, determining the types and quantity of consumed illicit drugs (Vitale et al. 2021). The basic wastewater-based epidemiology concept is essentially that after using drugs, their traces eventually reach wastewater. Therefore, their analysis allows data on the types and use of drugs to be calculated. Several organisations, such as the United Nations Office on Drugs and Crime or the European Monitoring Centre for Drugs and Drug Addiction, have performed them, as have many authors, to this end (van Nuijs et al. 2018). The aim of most research works have been to analyse liquid samples (Hernández et al. 2014; Cunha et al. 2017; Yadav et al. 2017; Choi et al. 2018; López-García et al. 2019a; Borden et al. 2020; Hahn et al. 2021; Gent and Paul 2021; Mohan et al. 2021). However, very little attention has been paid to solid matrices (Tomai et al. 2020).

Developing extraction and determination procedures for analytes from environmental solid matrices is a challenging process because small amounts of target compounds must be extracted from the sample material, and also because environmental samples, especially solid matrices, contain many potential interferences. With biota, for instance, protein and lipid content widely range depending on the organism. Accordingly, and unlike liquid samples that are extracted mainly by solid phase extraction (Baker and Kasprzyk-Hordern 2011a; Cunha et al. 2017), many techniques can be applied for solid matrices. For determination purposes, chromatographic techniques coupled to mass spectrometric systems have been confirmed as the best choice from among the available analytical techniques for monitoring illicit substances and their metabolites in solid matrices. Although high-resolution mass spectrometry (HRMS) instruments, such as Time of Flight, are being shown more interest, triple quadrupole still guarantees good and adequate sensitivity.

In this overview, the occurrence and concentration levels of psychoactive drugs with potential addiction and their metabolites in different solid environmental compartments, and their potential impact on ecosystems, are revised. It presents the current methods employed in the trace analysis of psychoactive drugs in solid matrices as sludge, marine or river sediment and biota, in the last 10 years (Figure S1). It focuses on not only parent compounds, but also on their metabolites. Finally, the risk that the measured concentrations of these psychoactive drugs could pose for non-target organisms was estimated, and some critical aspects are evidenced from an environmental point of view.

Extraction techniques

In the last few decades, most studies that have determined the presence of different classes of drugs have been conducted in aqueous samples, where the presence of some target compounds has been detected at up to thousands of nanograms per litre (Campos-Mañas et al. 2018). However, very few studies have focused on solid matrices like biota, sludge, soil, among others, in recent years.

Determining these drugs in solid samples is very challenging due to the growing number of compounds with new chemical structures found on the drug market, and also because of the complexity of the matrix. Indeed, this kind of analyses requires extensive laboratory work. When analysing solid samples, sample preparation is a crucial analysis step to obtain reliable data and to minimise interference owing to matrix effects. Therefore, a sample pretreatment step is required. These pretreatments can include freeze-drying, sieving, grinding and homogenisation to obtain a homogeneous sample before performing extraction. Once samples are pretreated, most extraction techniques consist in the diffusion of the analytes from the solid matrix to the organic solvent. Frequently, a simultaneous or posterior clean-up step is necessary because of the matrix interferences extracted along with analytes. These purification steps were based on reducing the amount of co-eluting substances that are coextracted during the target analyte extraction such as solid phase extraction or gel permeation chromatography.

Figure 1 shows a scheme of the different extractions process, and the Table 1 summarises the extraction process for the different families of drugs in environmental solid matrices. The main purpose of these procedures was to develop a multiresidue method by achieving good extraction efficiencies, recoveries and reproducibility. These extraction techniques range from the most traditional technique, such as solid–liquid extraction, to the most innovative ones, such as Quick, Easy, Cheap, Effective, Rugged and Safe (QuEChERS), which are discussed in this section by focusing on the most recent applications for the extraction of legal and illegal drugs in environmental solid matrices.

Solid: liquid extraction

Solid–liquid extraction is a traditional technique that is still used for its efficiency and simplicity, and because it requires

Table 1 Extraction methods for the determination of target drugs in environmental solid samples: analysed compounds of interest (total number of analytes included in the method by the authors), the matrix from which they were extracted, the technique used for the extraction and determination, and the analytical parameters of the developed methodology

Compounds	Matrix	Method	Recovery (%)	RSD (%)	LOD ($ng \cdot g^{-1}$)	Matrix effect (%)	Reference
METH, COD, COC, MTD, CBZ, DZP (7)	Biota (algae)	Shake + UAE + centrifugation + LC–MS/MS	69.3–110.2	< 12.4	0.06–3.51 (MDL)	−33–6	Helou et al. 2018
DZP, BZP, LPZ, CBZ (25)	Sediments	Shake + UAE + LC–MS/MS	10–125	< 22	1–3	−30–30	Radović et al. 2015
CBZ, ECMZ, DHCMZ, TCMZ, OCBZ, CIT, DMCIT, CNZ, METH, OZP, STL, NSTL, TMD, VFX, ODV (74)	Biota	SLE (centrifugation) + LC-HRMS	20–200	< 38	0.02–19 (LOQ)	−1167–86	Grabicova et al. 2018
MOR, COD, COC, CBZ, DZP (20)	Sediments	SLE (vortex) + stir-disc SPE + LC–MS/MS	35–111	< 20	0.02–3.1	−51–68	Tomai et al. 2020
CBZ, CIT, NFXT (36)	Biota (mussel)	SLE + LC–MS/MS	26—163	< 19	< 1 (MDL)	4–417	Bayen et al. 2015
APPZ, DAPPZ, QTP, NQTP, LPZ, ALPZ, OH-ALPZ, DZP, OZP, NDZ, CBZ, VFX, BPP, STL, NSTL, CIT, DMCIT (27)	Sludge	Vortex + UAE + clean-up SPE + LC–MS/MS (Based on (Yu et al. 2011))	50—132	< 21	0.1—20		Subedi et al. 2013
COC, BE, NCOC, COCET, MOR, M3G, M6G, MTD, EDDP, AMP, METH, MDA, MDMA, MDEA, COT (18)	Sludge suspended particulate matter	Vortex + UAE + clean-up SPE + LC–MS/MS (Same as (Subedi et al. 2013))	74—128	< 22	0.1—1		Subedi and Kannan 2014
LPZ, ALPZ, DZP, OZP, NDZ, CBZ, VFX, BPP, STL, CIT, APPZ, QTP, DAPPZ, OH-ALPZ NSTL, DMCIT (27)	Sludge suspended particulate matter	Vortex + UAE + clean-up SPE + LC–MS/MS (Same as (Subedi and Kannan 2014))	51–122 (sludge) 53–130 (suspended particulate matter)		0.1–1		Subedi and Kannan 2015
CBZ (16)	Biota (mussel) Sediments	Mollusks (same as (Bayen et al. 2015)) Sediments: SLE (vortex) + LC–MS/MS	47–130 (sediments)	< 50 (sediments)	0.007–1.7 (MDL)	−82–383 (sediments)	Bayen et al. 2016
BZP, LPZ, DZP, CBZ (56)	Sediments	Same as (Radović et al. 2015)	4–106	< 20	0.03–8.8		Matić Bujagić et al. 2019

Table 1 (continued)

Compounds	Matrix	Method	Recovery (%)	RSD (%)	LOD ($ng \cdot g^{-1}$)	Matrix effect (%)	Reference
BE, MDMA, MEP, DVFX, NFENT, MEPH, CBZ, COC, VFX, FENT, FXT (31)	suspended particulate matter Sediments	UAE + clean up SPE + LC-HRMS	27–102	< 19	0.3–3.7 (MDL)	−168–177	Comtois-Marotte et al. 2017
CBZ, TZP, DZP, FXT, (29)	Biota (amphipod)	UAE + clean-up SPE + LC/MS/MS	41–89	< 11 (intraday)	1–13	−56–−9	Miller et al. 2015
ALPZ, BE, CBZ, ECMZ, CIT, COC, COT, DZP, KET, LPZ, NIC, MDMA, MEP, METH, METCAT, NDZ, OZP, TZP, TMD (107)	Biota (amphipod)	UAE + clean-up SPE + LC/MS/MS	26–100	< 18 (intraday) < 24 (interday)	0.1–25.2	−82–59	Miller et al. 2019
ALPZ, COD, LPZ, TMD (92)	Sediments Soil Biota (plants)	UAE + clean-up SPE + LC/MS/MS	16–89 (sediments) 15–91 (soil) 14–112 (plants)	< 33 (sediments) < 23 (soil) < 34 (plants)	0.02–0.9 (LOQ)		Picó et al. 2020
CBZ, DHCMZ (19)	Sludge Sediments	UAE + clean-up SPE + LC–MS/MS	65–126 (sludge) 63–108 (sediments)	< 15	0.1–3 (sludge) 0.02–0.5 (sediments)		Yu et al. 2011
AMP, METH, EPHED, ETONE, MEPHEN, MEP, METONE, MDMA, MDA, bk-MMBDB, NAPH, PMA, 4-AcO-DIPT, BUF, TFMPP, PPP, α-PVP, MDPP, 4-MePPP, 4'-MePHP, MPBP, 3-MeO-PCP, 4-MeO-PCP, KET, COC, COCET, ECME, COD, HRN, MTD, MOR, ETAMINE, EPH, EDDP, 2C-B, mCPP, MDPV, MDEA, MDBD, 4'-MePHP, 6-MAM	Sediments Sludge Suspended particulate matter	UAE + clean-up SPE + LC–MS/MS	14–109 (sediments) 19–97 (sludge) 25–94 (Suspended particulate matter)	< 20 / < 21 (sediments)	0.04–1.32 (sediments)	41–225 (sediments)	Álvarez-Ruiz et al. 2015

Table 1 (continued)

Compounds	Matrix	Method	Recovery (%)	RSD (%)	LOD ($ng \cdot g^{-1}$)	Matrix effect (%)	Reference
OH-ALPZ, ALPZ, AMP, BE, BPP, CBZ, CIT, COC, COCET, COD, DZP, DMCIT, EDDP, LPZ, MTD, METH, MDA, MDEA, MDMA, MOR, NCOC, NDZ, NSTL, OXY, OZP, STL, VFX (56)	Sludge	UAE + clean-up SPE + LC–MS/MS (Same as (Subedi and Kannan 2014))	36–106		0.1–20		Subedi et al. 2015
CBZ, DZP (9)	Sediments	UAE + LC–MS/MS	87–94	Reproducibility > 90	0.1		Beretta et al. 2014
TMD, MOR, 6-MAM, HRN, MTD, EDDP, COD, OXY, BNOR, COC, BE, ECME, MDMA, MDEA, MDA, METH, AMP, THC-COOH, LSD, OH-LSD, ALPZ, BZP, CDP, CLB, DZP, NDZP, FNZP, 7AFZP, LPZ, NZP, MDZ, OZP, TZP, PB, PTB, CPZ, CZPN, NCZPN, OZPN, RPN, ORPN, FENT, LID, NFENT, TP, KET, NKET,, NTP, ATP, CMP, IPM, DXP, MZP, OHMZP, CIT, FXT, PRX, STL, NSTL, VFX, EPH, NEPH (148)	Sludge	UAE + LC–MS/MS	16–126	< 20	0.6–19.9 (MDL)	−92–90	Gago-Ferrero et al. 2015
OHMZP, ATP, CBZ, CIT,CZPN, NEPH, FXT, LPZ, MZP, NCZPN NSTL, OZP, PRX, STL, TMD, VFX, COD, MDA, MTD (50)	Sludge	UAE + LC–MS/MS (Based on (Gago-Ferrero et al. 2015)	19–126	< 20	0.9–14.3 (MDL)	−92–38	Thomaidi et al. 2016
COD, CBZ, ALPZ, DZP, THC, THC-COOH (47)	Biota (fish) Soil Sediments	UAE + SPE + LC–MS/MS	41–104 (fish) 31–88 (soil) 40–95 (sediments)	< 30 (fish) < 24 (soil) < 21 (sediments)	5–30 (fish) 10–50 (soil) 2–40 (sediments) (LOQ)	−40–5 (fish) −60–55 (soil) −45–45 (sediments)	Carmona et al. 2017
COC, BE	Sediment Biota (mussel)	UAE + SPE + LC–MS/MS	49–109	< 5	0.43–1.15		Fontes et al. 2021

Table 1 (continued)

Compounds	Matrix	Method	Recovery (%)	RSD (%)	LOD ($ng \cdot g^{-1}$)	Matrix effect (%)	Reference
ALPZ, ATP, AMP, BE, CBZ, COC, COD, COT, DZP, FXT, HCOD, MPB, NFXT, OXY, PRX, PPPH, STL (108)	Sediments Biota (mussel)	UAE + SPE + LC–MS/MS	20.9–509 (sediments) 20.9–449 (mussel)	< 39.7 (sediments)	0.133–2410 (sediments) 0.0285–669 (mussel)		Klosterhaus et al. 2013
DZP, LPZ, PZP, OZP, ALPZ, NDZ, BZP, TZP, CDP, CNZ, FZP, NZP, FNZP, CLB, MDZ, CZPN, EZM, 6-CPQ, 2-ACB, 5-CNB	Sludge	UAE + SPE + LC–MS/MS	48.5–162	< 2.85	0.014–0.274 (MDL)	90.8–175	Lei et al. 2021
AMP, BE, METH (13)	Suspended particulate matter	UAE + SPE + LC–MS/MS	45.2–96.4		5.24–27.8 (ng/L)		Wilkinson et al. 2017
METH, AMP, BE, (13)	Sediment Biota (amphipod, biofilm and plant)	UAE + SPE + LC–MS/MS	76 (sediments) 62–81 (biota)				Wilkinson et al. 2018
MOR, COD, MDMA, METH, BE	Sludge	UAE + SPE + LC–MS/MS	93—116		0.4–19.3		Yadav et al. 2019
AMP, METH, METCAT, MDA, MDMA, NKET, KET, BE, COD, COC, MTD, HRN	Biota (fish)	UAE + SPE + LC–MS/MS	60—127	< 11 (intraday) < 12 (interday)	0.005–0.025	−19–83	Yin et al. 2019
BZP, CBZ, CPZ, COD, DZP, KET, LPZ, MTD, MDZ, OZP, OCBZ, STL, TZP, VFX (47)	Biota (fish)	UAE + SPE + LC-ToF–MS	40–196	< 22 (intraday) < 25 (interday)	0.1–3.6	−87–84	Peña-Herrera et al. 2020
FXT, NFXT, CIT, CMCIT, PRX, STL, NSTL	Biota (mussel)	UAE + SPE + LC–MS/MS	69–102	< 6.66 (intraday) < 10.06 (interday)	0.55–1.13 (MDL)	98.59–102.33	Silva et al. 2017

Table 1 (continued)

Compounds	Matrix	Method	Recovery (%)	RSD (%)	LOD ($ng \cdot g^{-1}$)	Matrix effect (%)	Reference
COC, BE, NBECG, NCOC, COCET, AECGME, ECGO, AMP, METH, METCAT, BZP, TFMPP, MDA, MDMA, MDEA, MDBD, BDB, MESCA, LSD, O–H-LSD, HRN, 6-ACMOR, COD, NCOD, OXY, OXYM, MOR, NORMOR, DHC, BNOR, NORBNOR, MTD, EDDP, EMDP, FENT, NFENT, TMD, NTMD, TZP, DZP, NDZ, NZP, 7-ATZP, OZP, CDP, DSP, ATP, NTP, FXT, NFXT, VFX, PCP, KET, NKET, MAQ, EPH, NEPH, PPPH, NPPPH	Soil Suspended particulate matter	PLE + clean-up SPE + LC–MS/MS	11–85 (soil) 4–106 (Suspended particulate matter)	< 37 (intraday) < 52 (interday) (soil)	0.01–1.31 (soil) 0.02–4.07 (Suspended particulate matter) (MDL)	−212–42 (soil) −363–97 (Suspended particulate matter)	Baker and Kasprzyk-Hordern 2011b
COC, BE, COCET, AMP, METH, MDMA, EPH, MOR, HRN, 6-ACMOR, MTD, EDDP, LSD, OH-LSD, THC, OH-THC, CBD, CBN, ALPZ, DZP	Sediments	PLE + clean-up SPE + LC–MS/MS	15–77	< 15	0.01–2.3	−40—4.7	López-García et al. 2021
COC, BE, COCET, EPH, AMP, METH, MDMA, MOR, 6-ACMOR, HRN, METH, EDDP, ALPZ, DZP, LSD, OH-LSD, THC, CBD, CBN, OH-THC	Sludge	PLE + clean-up SPE + LC–MS/MS	5—63	< 14	0.1–6.4	−89—26	Mastroianni et al. 2013
CBZ, COD, DZP (17)	Sediments Soil	PLE + clean-up SPE + LC–MS/MS	66–110 (sediments) 62–119 (soil) (relative)	< 13 (sediments) < 12 (soil)	0.2–6.8 (sediments) 0.1–5.3 (soil)		Vazquez-Roig et al. 2012
VFX, ODV, CBZ, ECMZ, HCMZ, CIT, ALPZ (23)	Biota (bivalves)	PLE + clean-up SPE + LC–MS/MS	31–115	< 12.2 (intraday) < 20.7 (interday)	0.01–0.06 (MDL)	−89—12	Alvarez-Muñoz et al. 2015
CBZ, CIT, DZP, ECMZ, HCMZ, LPZ, STL, VFX, COD (20)	Biota (fish)	PLE + GPC + LC–MS/MS	19.3–107.8	< 21	0.03–0.5	−24.8–54.3	Huerta et al. 2013
NIC, COD, DHC, 6-ACMOR, COC, BE, EDDP, MTD, MOR, THC-COOH	Sludge	PLE + LC–MS/MS	44–95 (relative)	< 14 (intraday) < 20 (interday)	0.5–10	−95—15	Arbeláez et al. 2014

Table 1 (continued)

Compounds	Matrix	Method	Recovery (%)	RSD (%)	LOD ($ng \cdot g^{-1}$)	Matrix effect (%)	Reference
AMP, BE, COC, METH, CBZ, CIT, FXT (13)	Sediments Sludge	PLE + LC–MS/MS	30–734 (sediments) 8–461 (sludge)	< 61 (sediments) < 89 (sludge)	1–10 (sediments) 2–20 (sludge)	−7–77 (sediments) -39–110 (sludge)	Langford et al. 2011
MTD, EDDP, ALPZ, LPZ, DZP, CBD, CBN, COC, BE, COCET, EPH, AMP, METH, MDMA, MOR, HRN, 6-ACMOR, LSD, OH-LSD, THC, OH-THC, THC-COOH	Airborne particulate matter	PLE + LC–MS/MS (same as (Postigo et al. 2009))	14–69	< 15	0.1–26 ($pg \cdot m^{-3}$)	−89–0	Mastroianni et al. 2015
MOR, 6-ACMOR, M3G, COC, BE, AMP, MDMA, METH, THC-COOH, OH-THC, MTD, EDDP, COD	Sludge Suspended particulate matter	PLE + SPE + LC–MS/MS	3–92 (Suspended particulate matter)	< 28 (Suspended particulate matter)	0.1–3.5 (Suspended particulate matter) (MQL)	41–145 (Suspended particulate matter)	Senta et al. 2013
EPH, PSE, NEPH, KET, NKET, VFX, DVFX, CIT, DMCIT, CBZ, ECMZ, DHCBZ, TZP, MOR, DHMOR, MTD, MZP EDDP, COD, NCOD, DHC, TMD, NDMTMD, ODMTMD, AMP, METH, MDMA, MDA, COC, BE, AECGME, COCET, MDPV, HRN, 6-ACMOR (81)	Biota (plants)	MAE + clean up SPE + LC–MS/MS	2.4–45.1	< 16.2 (intraday) < 14.8 (interday)	0.02–12.71 (MDL)	−93–−10	Petrie et al. 2017
AMP, METH, MDMA, MDA, VFX, ODV, CIT, DMCIT, EPH, NEPH, PSE, TMD (18)	Sludge	MAE + clean-up SPE + chiral LC–MS/MS	0.2–97.5	< 45.1 (intraday) < 72.3 (interday)	0.03–80.03 (MDL)		Evans et al. 2015
KET, NKET, VFX, NDV, FXT, NFXT, STL, MZP, CIT, DMCIT, CBZ, ECMZ, DHCBZ, TZP, MOR, DHMOR, NORMOR, MTD, EDDP, COD, NCOD, DHC, TMD, NDMTMD, ODMTMD, AMP, METH, MDMA, MDA, COC, BE, AECGME, COCET, MEP, MDPV, HRN, 6-ACMOR (90)	Sludge	MAE + clean-up SPE + LC–MS/MS	0.3–45.6	< 8.7 (intraday) < 13.9 (interday)	0.03–4.81 (MDL)	−88.6–−27.5	Petrie et al. 2016
BUF, 4-MeO-PCP (23)	Biota (mussels)	QuEChERS + dSPE + LC–MS/MS	37–99	< 4 (intraday) < 26 (interday)	0.65–10 (LOQ)	−68–−20	Álvarez-Ruiz et al. 2021

Table 1 (continued)

Compounds	Matrix	Method	Recovery (%)	RSD (%)	LOD ($ng \cdot g^{-1}$)	Matrix effect (%)	Reference
COC, BE, COCET, AMP, METH, MDMA, MOR, 6-ACMOR, MTD, EDDP, KET, LSD, THC, OH-THC, THC-COOH, AH-7921, MEP, MDPV, EPH, ALPZ, OH-ALPZ, MDZ, OH-MDZ, LRMZ, DZP, OZP, TZP, CIT, FXT, STL, VFX, ZOPD, CPZ, HXZ	Biota (mussels)	QuEChERS + LC–MS/MS	2–101	< 20	0.1–10	−90–60	López-García et al. 2019b
NNDDODV, NODDV, ODV, NDV, NNDDV, VFX	Biota (mussels)	QuEChERS + LC–MS/MS	55–88	< 14 (intraday) < 6 (interday)	0.1–0.3	−31–19	Martínez Bueno et al. 2014
CIT	Biota (fish)	Direct injection—LDTD-APCI-HRPS	97—108	< 5 (intraday)	0.39	−80	Borik et al. 2020

*Drugs abbreviations: *2-ACB* 2-amino-5- chlorobenzophenone; *2C-B* 4- bromo-2,5-dimethoxyphenethylamine; *3-MeO-PCP* 3-methoxyphencyclidine; *4'-MePPP* 4'-methyl-α-pyrrolidinohexanophenone; *4-AcO-DIPT* 4-acetoxy-N,N-diisopropyltryptamine; *4-FMeCAT* 4-fluoromethcathinone; *4-MeEtCA* 4-methylethcathinone; *4-MeO-PCP* 4-methoxyphencyclidine; *4'-MePHP* 4-methyl-α-pyrrolidinohexaphenone; *4-MePPP* 4-methyl- α-pyrrolidinopropiophenone; *5-CMB* 5-chloro-2-(methylamino)benzo- phenome; *6-ACMOR* 6-acetylmorphine; *6-ACOD* 6-acetylcodeine; *6-CPQ* 6-chloro-4-phenyl-2(1H)-quinazolinone; *6-MAM* 6-monoacetylmorphine; *7AFZP* 7-amine-flunitrazepam; *7-ATZP* 7-aminonitrazepam; *AECGME* Anhydroecgonine methylester; *AH-7921* 3,4-dichloro-N-[[1-(dimethylamino)cyclohexyl]methyl]benzamide; *ALPZ* Alprazolam, *AMP* Amphetamine; *APPZ* Aripiprazole; *APR* Azaperone; *ATP* Amitriptyline; *AZP* Azaperol; *BE* Benzoylecgonine; *bk-MMBDB* Dibuthylone; *BNOR* Buprenorphine; *BPP* Bupropion hydrochloride; *BTL* Barbital; *BUF* Bufotenine; *BUTONE* Butylone; *BZP* Benzylpiperazine; *BZP* Bromazepam; *CBD* Cannabidiol; *CBN* Cannabinol; *CBZ* Carbamazepine; *CDP* Chlordiazepoxide; *CIT* Citalopram; *CLB* Clobazam; *CMP* Clomipramine; *CNZ* Clonazepam; *COC* Cocaine; *COCET* Cocaethylene; *COD* Codeine; *COT* Cotinine; *CPZ* Chlorpromazine; *CZPN* Clozapine; *DAPPZ* Dehydro-aripiprazole; *DHC* Dihydrocodeine; *DHCBZ* 10,11-Dihydro-10-hydroxycarbamazepine; *DHCMZ* Dihydrocarbamazepine; *DHMOR* Dihydromorphine; *DMCIT* Desmethylcitalopram; *DSP* Dosulepin; *DVFX* Desvenlafaxine; *DXP* Doxepin; *DZP* Diazepam; *ECGO* Ecgonidine; *ECME* Ecgoninemethylester; *ECMZ* 10,11-epoxycarbamazepine; *EDDP* 2-ethylidene-1,5-dimethyl-3,3- diphenylpyrrolidine; *EMDP* 2-ethyl-5-methyl-3,3-diphenyl-1-pyrroline; *EPH* Ephedrine; *EPHED* Ephedrone; *ETAMINE* Ethylamphetamine; *ETONE* Ethylone; *EtS*Ethyl sulfate; *EZM* Estazolam; *FENT* Fentanyl; *FNZP* Flunitrazepam; *FXT* Fluoxetine; *FZP* Flurazepam; *HCMZ* 2-hydroxycarbamazepine; *HCOD*Hydrocodone; *HRN* Heroin; *HXZ* Hydroxyzine; *IPM* Imipramine; *KET* Ketamine; *LID* Lidocaine; *LPZ* Lorazepam; *LRMZ* Lormetazepam; *LSD* Lysergic acid diethylamide; *M3G* Morphine-3-β-D-glucuronide; *M6G* Morphine-6-β-D-glucuronide; *MAQ* Methaqualone; *mCPP*1-(3-chlorophenil)piperazine; *MDA* 3, 4-methylendioxyamphetamine; *MDBD* N-Methyl-1-(3,4-methylenedioxy- phenyl)-2-butanamine; *MDEA* 3,4-methylenedioxy-N-ethylamphetamine; *MDMA* 3,4-methylenedioxymethamphetamine; *MDPP* 3,4-methylendioxy-α-pyrrolidinopropiophenone; *MDPV* Methylenedioxypyrovalerone; *MDZ* Midazolam; *MEP* Mephedrone; *MEPH* Methylephedrine; *MEPHEN* Methylphenidate; *MESCA* Mescaline; *METCAT* Methcathinone; *METH* Methamphetamine; *METHONE* Methedrone; *METONE* Methylone; *MOR* Morphine; *MPB* Meprobamate; *MPBP* 4'-methyl- α- pyrroli- dinobutiophenone; *MTD* Methadone; *MZP* Mirtazapine; *NAPH* Naphyrone; *NBECG* Norbenzoylecgonine; *N-CAT* N-ethylcathinone; *NCOC* Norcocaine; *NCOD* Norcodeine; *NCZPN* Norclozapine; *NDMTMD* N-desmethyltramadol; *NDV* N-desmethylvenlafaxine; *NDZ* Nordiazepam; *NEPH* Norephedrine; *NFENT* Norfentanyl; *NFXT* Norfluoxetine; *NIC* Nicotine; *NKET* Norketamine; *NNDDODV*N,N—didesmethyl—O – desmethylvenlafaxine; *NNDDV* N,N-didesmethylvenlafaxine; *NODDV* N,O-didesmethylvenlafaxine; *NORBNOR* Norbuprenorphine; *NORMOR* Normorphine; *NPPPH* Norpropoxyphene; *NQTP* Norquetiapine; *NSTL* Norsertraline; *NTMD* Nortramadol; *NTP* Nortriptyline; *NZP* Nitrazepam; *OCBZ* Oxcarbazepine; *ODMTMD* O-desmethyltramadol; *ODV* O- desmethylvenlafaxine; *OH-ALPZ* A-hydroxy-ALPZ; *OH-LSD* 2-oxo-3-hydroxy-LSD; *OH-MDZ* A-hydroxy-MIDZ; *OHMZP* 8-OH mirtazapine; *OH-THC* 11-hydroxy-Δ9-THC; *ORPN* 9-OH-risperidone; *OXY* Oxycodone; *OXYM* Oxymorphone; *OZP* Oxazepam; *OZPN* Olanzapine; *PCP* Phencyclidine; *PMA* P-methoxyamphetamine; *PNB* Phenobarbital; *PPP* A-pyrrolidinopropiophenone; *PPPH* Propoxyphene; *PRX* Paroxetine; *PSE* Pseudoephedrine; *PTB* Pentobarbital; *PZP* Prazepam; *QTP* Quetiapine; *RPN* Risperidone; *SCB* Secobarbital; *STL* Sertraline; *TCMZ* Trans-10,11-dihydro-10,11-dihydroxycarbamazepine; *TFMPP* 1-(3-trifluoromethylphenyl)piperazin; *THC* Tetrahidrocannabinol; *THC-COOH* 11-Nor-9-carboxy-Δ9-tetrahidrocannabinol; *TMD* Tramadol; *TPT* Thiopental; *TZP* Temazepam; *VFX* Venlafaxine; *ZOPD* Zolpidem, *α-PVP* α-pyrrolidinopentiophenone

*Techniques abbreviations: *UAE* Ultrasonically assisted extraction; *LC–MS/MS* Liquid chromatography tandem mass spectrometry; *SLE* Solid–liquid extraction; *LC-HRMS* Liquid chromatography with high resolution mass spectrometry; *SPE* Solid phase extraction; *PLE* Pressurized liquid extraction; *MAE* Microwave assisted extraction; *QuEChERS* Quick, Easy, Cheap, Effective, Rugged and Safe extraction, *dSPE* Dispersive solid phase extraction; *LDTD-APCI-HRPS* Laser diode thermal desorption with atmospheric pressure chemical ionization and high-resolution product scan

no expensive equipment. This technique is based on the distribution of the chemical of interest between the solid matrix and the organic solvent. Solid–liquid extraction efficiency depends mainly on the affinity of the analyte for the solvent. Common organic solvents, such as methanol or acetonitrile, or a mixture with another solvent like isopropanol, have been used to extract neuropsychiatric pharmaceutical compounds like carbamazepine or diazepam, and drugs of abuse like codeine or morphine, to obtain a multiresidue method that covers a wide range of polarities with recoveries ranging from 35 to 130% (Grabicova et al. 2018). In addition, some additives like ethylenediaminetetraacetic acid (EDTA) buffer or formic acid were added to improve the extraction of some compounds (Liu et al. 2009), since slightly acidic pH favours extraction of basic drugs, such as carbamazepine, benzoylecgonine, venlafaxine or codeine that have a pKa higher than (Liu et al. 2009). Regarding the amount of sample, a wide range of values has been found in the bibliography from 500 mg for more complex matrix like high lipid content matrices such as hepatic tissues, with a high percentage of co-eluting substances to 5 g (Bayen et al. 2015; Tomai et al. 2020).

Another key parameter for solid–liquid extraction is extraction time, which normally ranges from 10 to 30 min. Bayen et al. 2016 and Grabicova et al. 2018 extracted several pharmaceutical products, including psychiatric drugs (carbamazepine or norfluoxetine), from biota samples for 30 min and 10 min, respectively (Bayen et al. 2016; Grabicova et al. 2018). Their recoveries were acceptable, higher than 60%, and extraction was carried out by applying some stirring during extraction.

Lastly, another parameter normally tested in solid–liquid extraction is the number of extraction cycles. This parameter can vary between one single step to three or more to obtain appropriate results, with a corresponding increase in time and the amount of organic solvent, which is one of the inconveniences of this technique. However, most of the latest published solid–liquid extraction studies for drug extractions were based on a single extraction step (Bayen et al. 2015; Grabicova et al. 2018). Solid–liquid extraction usually requires a later centrifugation step, and even an additional clean-up step for complex matrices, using, for instance, traditional solid phase extraction or stir-disc solid phase extraction with reverse phase cartridges (Tomai et al. 2020). However, other authors did not perform this purification step, especially for multiresidue methods, due to the wide range of chemicals with different physicochemical properties that were analysed at the same time (Bayen et al. 2015; Grabicova et al. 2018).

This technique has been successfully used for extracting psychoactive pharmaceutical compounds and drugs of abuse in biotic samples, such as fish tissues or bivalves (Bayen et al. 2015; Grabicova et al. 2018), and in abiotic matrices like soil and sediment samples with good recoveries, generally higher than 40%.

Ultrasonically-assisted extraction

Most methods based on solid–liquid extraction and published in the last decade incorporate sonication to allow better solvent penetration in the matrix sample and, thus, apply ultrasonic-assisted extraction (Carmona et al. 2017; Tomai et al. 2020). In this case, extraction was carried out in an ultrasonic bath in which small vacuum bubbles are generated in the solvent to favour extraction (Fig. 1). Like solid–liquid extraction, extraction efficiency varied for each employed matrix and solvent. The amount of sample varied from a few milligrams to 1 or 2 g. The extraction of a larger amount of sample also increased the number of matrix interferences, especially in complex matrices like biota or sludge (Senta et al. 2013; Beretta et al. 2014; Miller et al. 2015; Peña-Herrera et al. 2020). Because of this, most of the methods that employed sonication included a later clean-up step.

It should be noted that all the published studies based on ultrasonic-assisted extraction for drugs extraction required samples to be previously dried in an air dryer or a freeze dryer to obtain better extraction recoveries. This is probably due to a higher solvent diffusion rate (Herrero et al. 2012).

Given its simplicity, because no sophisticated equipment is required, ultrasonic-assisted extraction has been widely used for the extraction of legal and illegal drugs in different environmental solid matrices with recoveries ranging from 14 to 196% (see Table 1). Nevertheless, the main disadvantage of this technique was the same as that for solid–liquid extraction: employing large volumes of organic solvents.

A study published by Álvarez-Ruiz et al., developed the extraction of 41 drugs of abuse and their metabolites in three environmental solid matrices like sediment, sewage sludge and particulate matter, by ultrasonic-assisted extraction with methanol in combination with a buffer solution, followed by a clean-up step (Álvarez-Ruiz et al. 2015). Recoveries were higher than 50% for most analysed compounds; for instance, benzoylecgonine obtained recoveries of 106, 75 and 77% for sediment, sludge and suspended particulate matter, respectively. With biota samples, a research work of Fontes et al., extracted illicit drugs like cocaine and benzoylecgonine from mussels by ultrasonic-assisted extraction with acetonitrile and a buffer solution (Fontes et al. 2021). Others authors like Miller et al. used a smaller amount of sample, 20 mg, to extract illicit drugs, such as methamphetamine, MDMA, among other compounds, from freshwater invertebrates with recoveries of up to 64% and 65%, respectively (Miller et al. 2019).

In another work, Yadav et al., analysed the removal of several compounds, including drugs of abuse like morphine and codeine, in sludge and biosolids by ultrasonic-assisted

extraction with methanol and acetic acid in combination with solid phase extraction (Yadav et al. 2019). They obtained recoveries ranged between 93 and 116%. With psychiatric drugs, Picó et al., assessed the presence of selected drugs, such as alprazolam and lorazepam, among different emerging contaminants in sediment, soil and plants with recoveries of up to 112% (Picó et al. 2020). Carbamazepine, another of the most widely studied psychiatric drugs, has been extracted in several solid matrices by ultrasonic-assisted extraction in up to 12 studies in recent years with recoveries of 76% in sludge, 62% in particulate matter and 117% in mussel and sediment (Klosterhaus et al. 2013; Gago-Ferrero et al. 2015; Comtois-Marotte et al. 2017).

Pressurised liquid extraction

Pressurised liquid extraction is still one of the most applied methodologies to extract organic compounds from solid samples. This extraction method needs special equipment because it works at high pressure and temperature to improve extraction (Fig. 1). Similarly, to other extraction techniques, solid samples must be dried and homogenised before extraction.

Some parameters that influence extraction efficiency are temperature, extraction cycles, amount of sample and organic solvents. High temperatures have widely demonstrated the extraction of more matrix interferences, and the degradation of the target analysis in some cases. In fact this may be the case of drugs whose optimised temperature for pressurised liquid extraction was lower than 100 °C (Mastroianni et al. 2013, 2015; Álvarez-Ruiz et al. 2015; López-García et al. 2021). Polar organic solvents, such as methanol or methanol–water mixtures, were more efficient than non-polar solvents for psychiatric or illegal drugs when considering the polarity of many of them. In some cases, the use of acidified solvents could improve the extraction of selected compounds like opioids and amphetamine-type drugs (Langford et al. 2011; Baker and Kasprzyk-Hordern 2011a; Senta et al. 2013).

In sample quantity and extraction cycle terms, most research works about the extraction of legal and illegal drugs have used less than 5 g mixed with a dispersant, such as inert material like diatomaceous earth or quartz sand, and a maximum of three extraction cycles to obtain satisfactory recoveries (Vazquez-Roig et al. 2012; Huerta et al. 2013; Mastroianni et al. 2013; Arbeláez et al. 2014).

After extraction, a clean-up step was also required. Some published works included a simultaneous in-cell clean-up step by adding activated sorbent (e.g., alumina or florisil) to do away with interferences from pressurised liquid extraction extracts. However, this occurred in most studies as a subsequent step by gel permeation chromatography or solid phase extraction with a single solid phase extraction cartridge (e.g., Oasis HLB or Evolute ABN as polymeric cartridges), or a combination with gel permeation chromatography (Huerta et al. 2013; Mastroianni et al. 2013; Alvarez-Muñoz et al. 2015; López-García et al. 2021). For example, Huerta et al. used a combination of two clean-up steps for psychiatric drugs extraction in fish muscle tissues (Oasis HLB and gel permeation chromatography) with recoveries of 88.7% for diazepam, 74.8% for carbamazepine and 126.4% for venlafaxine (Huerta et al. 2013).

Of the most recent studies to focus on drugs extraction with pressurised liquid extraction, Alvarez-Muñoz et al. and Huerta et al., extracted such compounds from biota samples (fish and bivalves) with recoveries of up to 72 and 108%, respectively (Alvarez-Muñoz et al. 2015; Huerta et al. 2018). Furthermore, the extraction of sediment and soil samples has also been optimised with pressurised liquid extraction for opioids and morphine derivatives, amphetamines, among others (Langford et al. 2011; Baker and Kasprzyk-Hordern 2011a; Vazquez-Roig et al. 2012). By way of example, Vazquez-Roig et al. reported recoveries ranging between 99 and 110% for carbamazepine, codeine and diazepam in soil and sediment samples (Vazquez-Roig et al. 2012).

Some authors have determined the presence of illicit drugs in not only the wastewater dissolved phase, but also in suspended particulate matter by detecting up to 34.5% of 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) of the wastewater concentration in suspended particulate matter (Baker and Kasprzyk-Hordern 2011a). Along the same lines, Senta et al., found an average contribution in suspended particulate matter of between 1 and 28% of the wastewater concentration for several drugs, which reveals the importance of also analysing suspended particulate matter (Senta et al. 2013).

Microwave-assisted extraction

The microwave-assisted extraction technique has been widely applied to analyse organic compounds since 1995 (Lopez-Avila et al. 1995). In this case, the extraction of compounds from the matrix is improved by increasing the energy of molecules due to microwaves. The main parameters that are often optimised for microwave-assisted extraction are temperature, sample mass and solvent composition (Fig. 1). As in the above-mentioned techniques, a later clean-up step after microwave-assisted extraction is recommended.

Only a few works have applied microwave-assisted extraction for the extraction of different families of drugs. Evans et al., used a mix of methanol–water, which was heated to 120 °C for 30 min to extract up to 30 compounds, including pharmaceuticals and illicit drugs, from sludge, which suggests that higher temperature values degrade some chemicals (Evans et al. 2015). Petrie et al., developed a multiresidue method, also for sludge, by employing a similar mixture

for extraction, methanol–water, but at pH 2 and heating to 110 °C (Petrie et al. 2016). Up to 63 emerging pollutants were extracted under these conditions. The same authors have applied the microwave-assisted extraction process for the extraction of micropollutants, such as illicit drugs or psychiatric drugs (up to 81 compounds) in macrophytes, including some metabolites (i.e., 3, 4-methylendioxyamphetamine, benzoylecgonine) (Petrie et al. 2017). In this case, extraction was carried out at a relatively low temperature (50 °C) with similar recoveries, up to 45%, as those reported in a previous work (Petrie et al. 2016).

Quick, easy, cheap, effective, rugged and safe extraction

Ever since quick, easy, cheap, effective, rugged and safe (QuEChERS) extraction was employed for the extraction of pesticides for the first time almost 20 years ago (Anastassiades et al. 2003), the use of this technique has considerably grown, even in different matrices than those for which it was designed. A wide range of compounds can be extracted given the good results obtained and their easy implementation because no expensive materials or instruments are involved. It has been satisfactorily applied for environmental, biological and food analysis, and has reduced the amount of organic solvent employed (Santana-Mayor et al. 2019). The QuEChERS procedure consists of liquid–liquid partition favoured by adding different salts like Na_2SO_4, $MgSO_4$ and buffering salts to adjust pH, for example, citrate salts (Fig. 1). The composition of extraction salts or solvent volumes and ratios are the parameters that are normally modified to adapt to each type of compound family and the studied matrices.

According to the available literature on drugs extraction in biota samples, the most widely used solvents for QuEChERS are acetonitrile and water-acetonitrile mixtures, a mixture of salts to improve separation, mainly $MgSO_4$, NaCl, Na_2SO_4 or citrate salt. The amount of sample ranges from 1 to 10 g of homogenised sample. One of the parameters to affect analyte extraction is pH, especially in pH-dependent compounds.

This technique includes a solid–liquid extraction step and a clean-up step by means of dispersive solid-phase extraction (dSPE). For dSPE, the common sorbents used are primary secondary amine, to remove fatty acids and sugars, C_{18} and Zsep +, to remove lipids, and $MgSO_4$, to remove water waste.

Methodologies that applied QuEChERS to extract illicit drugs from environmental matrices are still scarce. Recently, some works based on the extraction of biota samples, mainly mussels, have been published. Overall, the recovery of drugs by this technique ranged from 37% to 142.5% in biota samples. Ávarez-Ruiz et al. tested different QuEChERS, acid, standard and miniaturised, and two solid phase extraction procedures to removal phospholipids to optimise the extraction of several groups of organic pollutants, including illicit drugs (bufotenine and 4-methoxyphencyclidine) in mussels (Álvarez-Ruiz et al. 2021). López-García et al. developed a QuEChERS procedure to determine 35 psychoactive substances in fresh mussel samples with good relative recoveries ranging from 77 to 118% (López-García et al. 2019b). Marínez-Bueno et al. also applied this technique to extract venlafaxine and its metabolites in marine mussels collected from the Mediterranean Sea in south east France (Martínez Bueno et al. 2014) with recoveries ranging between 55 and 70%. It was observed that some compounds in QuEChERS multiresidue methods were not recovered properly. This behaviour could be attributed to the difference in their physico-chemical properties. As example, tetrahydrocannabinol has a high log K_{ow}, close to 6 (PubChem), compared to other illegal drugs, such as cocaine, with a log K_{ow} of 2.3 (PubChem), or α-hydroxy-alprazolam with a log K_{ow} of 2.2 (PubChem). For instance, Lopez-Garcia et al. obtained absolute recoveries for cannabinoids lower than 30% and for cocaine and α-hydroxy-alprazolam higher than 50% (López-García et al. 2019b).

Others

The interest in determining emerging organic compounds, such as psychiatric drugs, in all kind of matrices leads innovative isolation techniques being constantly developed, many of which are based on short sample preparation and analysis times. Such is the case of coupling laser diode thermal desorption, followed by mass spectrometry, which is a direct sample introduction technique whose main advantages include easy sample preparation and a small sample volume. This technique has been tested with satisfactory results achieving recoveries between 97 and 108%, with limits of detection of 0.39 $ng \cdot g^{-1}$ for citalopram determination in, approximately, 0.05 g of fish brain tissue samples (Borik et al. 2020).

Determination

According to the latest published works, liquid chromatography is the predominating separation technique used for the determination of several groups of drugs in solid matrices, mainly due to the wide polarity range that it covers (Table 1). The mobile phases commonly employed for drugs separation are methanol or acetonitrile and H_2O, which contain additives like formic acid, normally at concentrations lower than 0.5%, and a buffer like ammonium formate, to maintain pH at below 4 and to improve posterior compounds ionisation. The column flow used to separate substances can vary

between 100 µL·min^{-1} and 600 µL·min^{-1} (Alvarez-Muñoz et al. 2015; Evans et al. 2015). Regarding the volume of sample injected into liquid chromatography instruments, the published studies indicate a range between 5 µL and 50 µL depending on each instrument's limitations (Arbeláez et al. 2014; Carmona et al. 2017).

The separation of the drugs will be largely controlled by the molecules physico-chemical properties and their polarities. The specific equilibrium constant octanol–water distribution (K_{OW}) describes the distribution of a compound between mobile phase and the column. In the case of psychoactive substances, log K_{OW} values range, for instance, from 1.76 for more polar compounds, such as the well-known amphetamine (PubChem), to less polar compounds such as tetrahydrocannabinol (log K_{OW} = 6) (PubChem). The pattern of separation followed by the compounds during the chromatographic separation step of the sample depends largely on their polarities. Those compounds with highest polarities shown weaker retention in traditional reverse phase C_{18} columns, and are eluted earlier, while less polar compounds are eluted later. The method aim is to utilize the polarity to achieve maximum separation in a single run within a reasonably short analysis time. The target compounds can be well separated by changing the polarity of the mobile phase during the instrumental analysis step.

Regarding the detection technique, mass spectrometry in tandem (MS/MS) is considered one of the most selective detectors. When coupled to an liquid chromatography system (LC–MS/MS), it allows the determination of dozens of target analytes in a single run (Buchberger 2011). Selective reaction monitoring or multiple reaction monitoring present high sensitivity and selectivity, which are especially relevant when the target matrix is complex. In the last decade, LC–MS/MS has been used in several solid matrices, such as sludge, biota, soil, suspended particulate matter (Jakimska et al. 2014) (Table 1).

However, to couple a liquid chromatography system to a MS/MS, it is necessary to use an ionisation source before the mass spectrometry system, and electrospray ionization is the commonest ionisation source in this field. With electrospray ionization, it is possible to ionise most molecules, but it is also its drawback because this ionisation source is very sensitive to interferences. The matrix effect is not completely understood, but is believed to come from the competition of co-eluted interferences and target analytes. Hence the more complex a matrix is, the stronger this effect is. These interferences can lead to signal enlargement or suppression, which directly affects the quality of measurements (Matuszewski et al. 2003; Kang et al. 2007; Gosetti et al. 2010). Matrix effect calculations depend on the author. In most cases, a positive value indicates an increase in the signal, whereas a negative value denotes a reduction in the signal, and both because of the matrix. However, setting a value of 100 to indicate no matrix effect is frequent. A lower value would indicate signal suppression and a higher value would denote signal enlargement. As Table 1 shows, wide variations in this parameter regardless of the matrix were observed, which were more pronounced when many analytes are studied (e.g. -212 – 42% (soil) and -363 – 97% (suspended particulate matter) (Baker and Kasprzyk-Hordern 2011b). In most cases, matrix effects remain between -50% and 50%, which is close to the acceptable ranges for matrix effects, 75–125%, according to the "Gesellschaft für Toxikologische und Forensische Chemie" guideline for the validation of analytical methods for forensic-toxicological analyses (Peters et al. 2009). Nevertheless, the range was in concordance with the European Union guidelines recommended for other organic compounds such as pesticides in complex matrix where the matrix effect can range between -50% and 50% (SANTE 2015). For those cases where strong matrix effect was observed the use of stable isotopically labelled and methods matrix matched calibration were frequently performed to compensate matrix effects for complex matrices (Nasiri et al. 2021).

As Table 1 shows, limits of detection varied considerably depending on analytes and the extraction technique, and even with biota samples that had a very complex matrix. Low limits of detection have been obtained in fish using ultrasonic-assisted extraction in the analysis of illicit drugs, and ranged from 0.005 to 0.025 ng·g^{-1} (Yin et al. 2019). Lower limits of detection have been reported when applying solid–liquid extraction with a vortex for pharmaceuticals in mussel, and the method detection limits went from 0.007 to 1.7 ng·g^{-1} (Bayen et al. 2016), while the method detection limits ranged from 0.01 to 0.06 ng·g^{-1} when using pressurised liquid extraction with bivalves (Alvarez-Muñoz et al. 2015). Limits of detection values generally ranged from 0.01 to 10 ng·g^{-1} despite not indicating any technique or matrix that could be superior to others because the results reported by different authors vastly vary. In the last few years, a new analysis that employed mass spectrometry detectors based on HRMS was developed for target and non-target screening analyses (Castro et al. 2021). When working with MS/MS, some interferences could be detected as a false-positive, but this inconvenience is solved in most cases with HRMS because it measures the exact mass (Kaufmann et al. 2010). Additionally this detector, unlike multiple reaction monitoring, works in the full-scan mode, making possible a retrospective analysis of the results (Kaufmann et al. 2010).

In general, limits of detection were slightly higher when using HRMS, but the matrix effect was milder. For instance, carbamazepine has a limit of detection of 1.5 ng·g^{-1} and signal suppression lower than 21% with HRMS (Peña-Herrera et al. 2020), whereas the same compound in MS/MS has a limit of detection of 0.06 ng·g^{-1}, but 30% signal suppression, with both biota (Petrie et al. 2017). Cocaine showed

the same limit of detection in HRMS of 2.1 $ng \cdot g^{-1}$ and signal suppression was 40% (Comtois-Marotte et al. 2017). In MS/MS, the limit of detection was 0.2 $ng \cdot g^{-1}$, but signal suppression was 50% (Tomai et al. 2020).

To date, HRMS detectors have been used only in a few studies about drugs, including illicit drugs and psychoactive compounds, in biota, sediment, sludge and suspended particulate matter samples (Comtois-Marotte et al. 2017; Grabicova et al. 2018). Unfortunately as this technique also applies electrospray ionization, a strong matrix effect has been observed depending on analytes and tissues, and ranged from -168% to 177% (Comtois-Marotte et al. 2017) and from −1,167 to 86% (Grabicova et al. 2018) respectively, among all the studied analytes. Nevertheless, low limit of quantification between 0.02 $ng \cdot g^{-1}$ and 19 $ng \cdot g^{-1}$ (Grabicova et al. 2018), and method detection limit between 0.3 and 3.7 (Comtois-Marotte et al. 2017) for such a big amount of analytes, have been obtained. In addition, HRMS allows a more complete evaluation, since the developed methods can cover a larger number of compounds. Furthermore, it can be used for the study of metabolic changes in drugs due to marine organisms, which are still cases (Miller et al. 2018).

Occurrence

The occurrence of analytes analysed in this review is summarised in this section. The study of sludge and the suspended particulate matter are essential to understand the complete cycle of compounds in wastewater treatment plants. A compound may be detected in the influent, but not in the effluent, and it would not mean that it has been degraded, but may have been adsorbed in sludge (Álvarez-Ruiz et al. 2015). The study of sludge is more necessary when reused in agriculture because the presence of contaminants could limit its use (Mastroianni et al. 2013; Arbeláez et al. 2014), and also because contaminated sludge could even pose a threat to groundwater and terrestrial organisms (Langford et al. 2011). Although drugs are relatively polar compounds, sorption in sludge not only depends on lipophilicity, but solubility, temperature, pH, vapour pressure, soil organic matter content, are also involved (Langford et al. 2011; Gago-Ferrero et al. 2015). Furthermore, some drugs have been demonstrated to remain stable in sludge, such as codeine, morphine or methamphetamine (Yadav et al. 2019). Regarding suspended particulate matter, it should not be assumed that although these drugs are mainly polar compounds, they are only found in the dissolved fraction (Senta et al. 2013). The concentration of drugs might be underestimated when suspended particulate matter is not taken into account (Baker and Kasprzyk-Hordern 2011a; Baker et al. 2012; Comtois-Marotte et al. 2017).

Furthermore, if a substance exists in the effluent from a wastewater treatment plant, it can be deposited in nearby sediment. Therefore, sediment is considered a route of exposure to benthic organisms because high concentrations are usually detected in them (Miller et al. 2021). Consequently, marine organisms can adsorb these compounds because they might be bioavailable to organisms (Evans et al. 2015) and be transferred to them by the food chain to humans (Radović et al. 2015).

For marine or aquatic biota, these contaminants are also hazardous for organisms and, therefore, this issue is currently a prominent one (Huerta et al. 2013). Pharmaceuticals are designed to have biological effects on humans. Nevertheless, adverse biological effects have been proven at environment concentrations to aquatic organisms (Grabicova et al. 2018). By way of example, exposing mussels to cocaine and its by-products increases DNA damage, cytotoxic effects and alterations in lysosomal membrane stability (Binelli et al. 2012; dos Santos Barbosa Ortega et al. 2019), and exposing cocaine's metabolite benzoylecgonine to *Daphnia magna* brought about changes in swimming behaviour and oxidative stress (Parolini et al. 2018). Cocaine at environmental concentrations acted as an endocrine disruptor in silver eels (Gay et al. 2013). After exposing molluscs to cannabis derivatives, an imbalance in antioxidant defence enzymes and increased DNA fragmentation in haemocytes occurred (Parolini et al. 2017). In zebra mussels exposed to a mixture of several widely used illicit drugs: cocaine, benzoylecgonine, amphetamine, morphine and 3,4-methylenedioxymethamphetamine (MDMA), DNA fragmentation and the genotoxic potential markedly increased (Parolini et al. 2016). Fish exposed to carbamazepine, venlafaxine and fluoxetine presented genetic changes associated with development and changes in behaviour (Thomas et al. 2012a). In addition, theirs concentration may increase up the food chain and some marine organisms may present drug concentrations similar to human doses (Richmond et al. 2018).

To study them, we divided the matrices into three categories. The first one was aquatic biota, which includes biological samples, mainly molluscs, fish and crustaceans. The second one is sludge and suspended particulate matter, in which the few studies into suspended particulate matter are included. Finally, one last session is on marine sediment and soil. The concentration shown in the graphs was obtained by calculating the mean of the concentrations detected by the different reviewed authors. The different drugs under study were classified into three groups. In the first place come drugs of abuse, which are mainly certain types of analgesics (opioids) and other compounds that can be misused as recreational substances, and may be accompanied by alcohol intake. For instance, it was found that low doses of morphine increased the consumption of alcohol (Herz 1997). In second place come illegal drugs like marihuana or cocaine, which

mainly involve stimulants and hallucinogens, and are illegal in most countries. Finally come psychiatric drugs like anxiolytics (benzodiazepines) and antidepressants (venlafaxine, fluoxetine, sertraline), which, if not used for the duration and in the manner indicated by a doctor, may not be effective or cause addiction problems.

Aquatic biota

So far, limited studies have been conducted to estimate the occurrence of psychoactive drugs in aquatic organisms. To the best of our knowledge, only 19 papers measured the concentration of target compounds in aquatic biota. One reason for this is that the determination of trace contaminants in biota has been traditionally very challenging, and not only in terms of the analytical selectivity required to reliably separate hundreds of different compounds, but it has to be done quantitatively at trace concentrations. Most studies have been conducted on fish, with studies on mussels and other species, but they are still scarce.

In the drugs of abuse group, although methadone (analgesic) was the most frequently detected compound, its frequency of detection was low, only in 9% of the reviewed papers about aquatic biota, and it also appeared at high concentrations in seaweed samples (Helou et al. 2018). The number of detected illegal substances and drugs of abuse was similar. Of illegal drugs, cocaine and its metabolite benzoylecgonine were highlighted for being more frequently detected, approximately 22% of the reviewed papers about aquatic biota. Cocaine was also stressed for its high concentration in seaweed (Helou et al. 2018). Due to its low frequency of detection, more research should be carried out on the occurrence of drugs of abuse and illegal drugs in aquatic organisms.

The largest number of substances detected in aquatic biota corresponds to psychiatric medications, as seen in Fig. 2. The concentrations of these compounds were usually low and rarely exceed 5 $ng \cdot g^{-1}$, except norfluoxetine and norsertraline in mussel (Silva et al. 2017). It is worth mentioning that the above-mentioned authors measured the parent compound (fluoxetine (antidepressant)) at a lower concentration than its metabolite (norfluoxetine), and sertraline (antidepressant or anxiolytic) was not detected, while its metabolite (norsertraline) was, which highlights the importance of measuring metabolites. Carbamazepine (anticonvulsant) was the most widely detected compound, being present in 61% of the reviewed papers about aquatic biota, followed by citalopram (antidepressant) and venlafaxine (antidepressant). These high detection frequencies may be related to the fact that the use of antidepressants is alarmingly high today (Gould et al. 2021).

In view of these results, the presence of psychoactive drugs in marine biota showed that these organisms are able

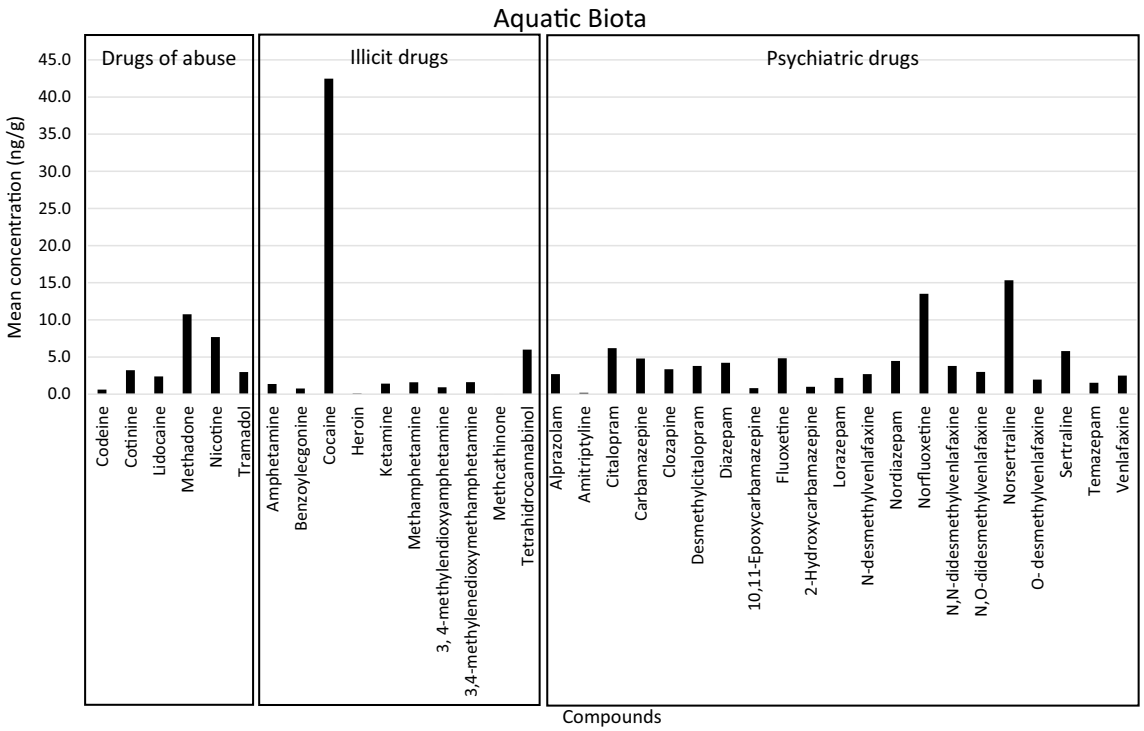

Fig. 2 Mean concentration of the target analytes in aquatic biota obtained from 19 papers

to bioaccumulate these compounds from their surroundings, with the risk that this poses for them.

Sludge and suspended particulate matter

During sewage treatment, drugs are affected by different treatments and may finally be adsorbed in sludge. The distribution and fate of drugs depend on a range of factors, such as their physico-chemical properties, and also on processes like partitioning and degradation in the water and sludge; for instance, cannabinoids are highly hydrophobic and bind to sewage sludge. For this reason, the biggest amount of compounds detected and the highest concentrations measured appeared in sludge, although the number of papers that measured target analytes in this matrix was similar than in aquatic biota, 20 papers. Depending on their characteristics, these compounds may concentrate within a wide range of concentrations. This was why we divide the figure into two, depending on the measured concentration: from 50 $ng{\cdot}g^{-1}$ to 200 $ng{\cdot}g^{-1}$ (Fig. 3a) and from not detected to 50 $ng{\cdot}g^{-1}$ (Fig. 3b). Seventy-seven different analytes were detected, including both parent compounds and metabolites.

With drugs of abuse, derivatives of opioids appear at similar concentrations to those of illicit drugs. Of them, tramadol (analgesic) stands out for its mean measured concentration, up to 63 $ng{\cdot}g^{-1}$, and its frequency, approximately in 30% of the reviewed papers about sludge. Codeine (analgesic) was highlighted for its frequency of detection, approximately 55%, but its mean concentration was lower, 44.5 $ng{\cdot}g^{-1}$. In this group, it was worth stressing the concentration of not only some tramadol derivates, but also of some other metabolites. For instance, methadone (analgesic) was detected at a mean concentration of 24.4 $ng{\cdot}g^{-1}$ in 55% of the reviewed papers, but its metabolite EDDP appeared at a higher concentration, 69 $ng{\cdot}g^{-1}$, but not so frequently, being measured in 45% of the reviewed papers about sludge. In addition, methadone is one of the newly identified chemicals in bio-solids in the 2020–2021 by the Environmental Protection Agency (Environmental Protection Agency 2022). Nortramadol appeared at a mean concentration of 92 $ng{\cdot}g^{-1}$, which was higher than its parent compound tramadol (analgesic), but was also less frequent. In light of these results, metabolites should be studied at least at the same frequency as parent compounds to arrive at conclusions as to which of them appear in the environment at higher concentrations.

Of illicit drugs, cannabis derivatives were the compounds detected at the highest concentrations: 168 $ng{\cdot}g^{-1}$ for cannabidiol, 138 $ng{\cdot}g^{-1}$ for tetrahydrocannabinol and 101 $ng{\cdot}g^{-1}$ for cannabinol (Fig. 3a). This was probably because cannabis was the most produced and used drug in Europe (European Monitoring Centre for Drugs and Drugs Addiction). It is highly hydrophobic and binds to sewage sludge, although its frequency of detection was low, approximately 6%. Cocaine and its metabolite benzoylecgonine were the most detected drugs, being measured in 55% of the reviewed papers about sludge, along with MDMA, being measured in 45% of the reviewed papers. Nevertheless, their concentration was low, 13.6 $ng{\cdot}g^{-1}$, 10.8 $ng{\cdot}g^{-1}$ and 4.9 $ng{\cdot}g^{-1}$, respectively (Fig. 3b). These substantially low concentrations might be due to the high removal percentages of these compounds during wastewater treatment processes.

Psychiatric drugs appeared at the highest concentrations and in larger numbers. Of them, sertraline (antidepressant) was highlighted for its high concentration in the UK, up to 1,138 $ng{\cdot}g^{-1}$ (Petrie et al. 2016), and the USA, up to 1,176 $ng{\cdot}g^{-1}$ (Subedi and Kannan 2015). Other psychiatric drugs with a high measured concentration were citalopram (antidepressant), with a mean concentration of 191 $ng{\cdot}g^{-1}$ and the sertraline (anxiolytic or antidepressant) metabolite, norsertraline, with a mean concentration of 186 $ng{\cdot}g^{-1}$. These compounds also presented a high detection frequency of 50% and 25%, respectively, in the reviewed works (Fig. 3a). Venlafaxine (antidepressant), carbamazepine (anticonvulsant) and citalopram (antidepressant) feature among the most widely detected psychiatric drugs, being present in approximately 40% of the reviewed papers about sludge, with carbamazepine and citalopram measured at a mean concentration over 50 $ng{\cdot}g^{-1}$ (Fig. 3a) and the mean venlafaxine concentration was 44 $ng{\cdot}g^{-1}$ (Fig. 3b).

Particulate matter has been scarcely studied (Baker and Kasprzyk-Hordern 2011b; Baker et al. 2012; Senta et al. 2013; Álvarez-Ruiz et al. 2015), but some studies showed that a significant fraction of drugs ends in this matrix, with a similar trend to sludge and only slight differences. However, the concentration of some opiates, such as tramadol (analgesic) and codeine (analgesic), were higher in suspended particulate matter than in sludge (Baker and Kasprzyk-Hordern 2011b; Álvarez-Ruiz et al. 2015).

The presence of several drugs and their metabolites in sludge and suspended particulate matter reveals their resistance to conventional wastewater treatment. Hence the need to use more advanced methods to remove them.

Sediment and soil

Despite contamination being a major concern, the monitoring and study of different drugs in sediment and soil is still scarce. To the best of our knowledge, only 16 papers measured target analytes in this matrix, with tramadol (analgesic) being the only one detected at high concentrations, with a mean concentration of 25 $ng{\cdot}g^{-1}$, and frequently, being measured in 19% of the reviewed papers about sediment and soil. The results are shown in Fig. 4.

Of illicit drugs, tetrahydrocannabinol was the compound detected at the highest concentration, measuring 210 $ng{\cdot}g^{-1}$ in the Turia River (Spain), probably due

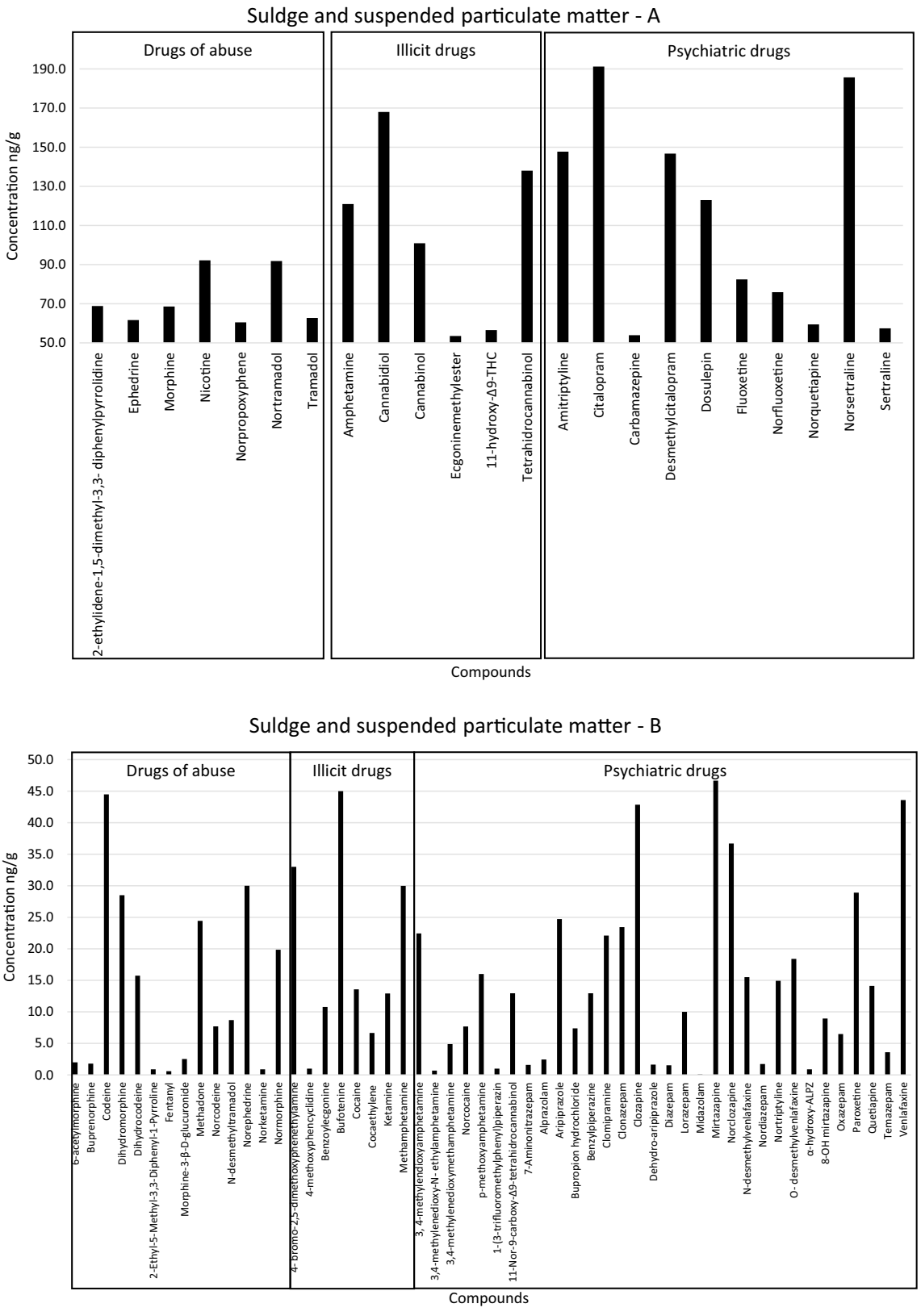

Fig. 3 **a** Mean concentration of target analytes in sludge and suspended particulate matter obtained from 20 papers (concentration range 50–200 ng·g^{-1}). **b** Mean concentration of the target analytes in sludge and suspended particulate matter obtained from 20 papers (concentration range from 0 to 50 ng·g.$^{-1}$)

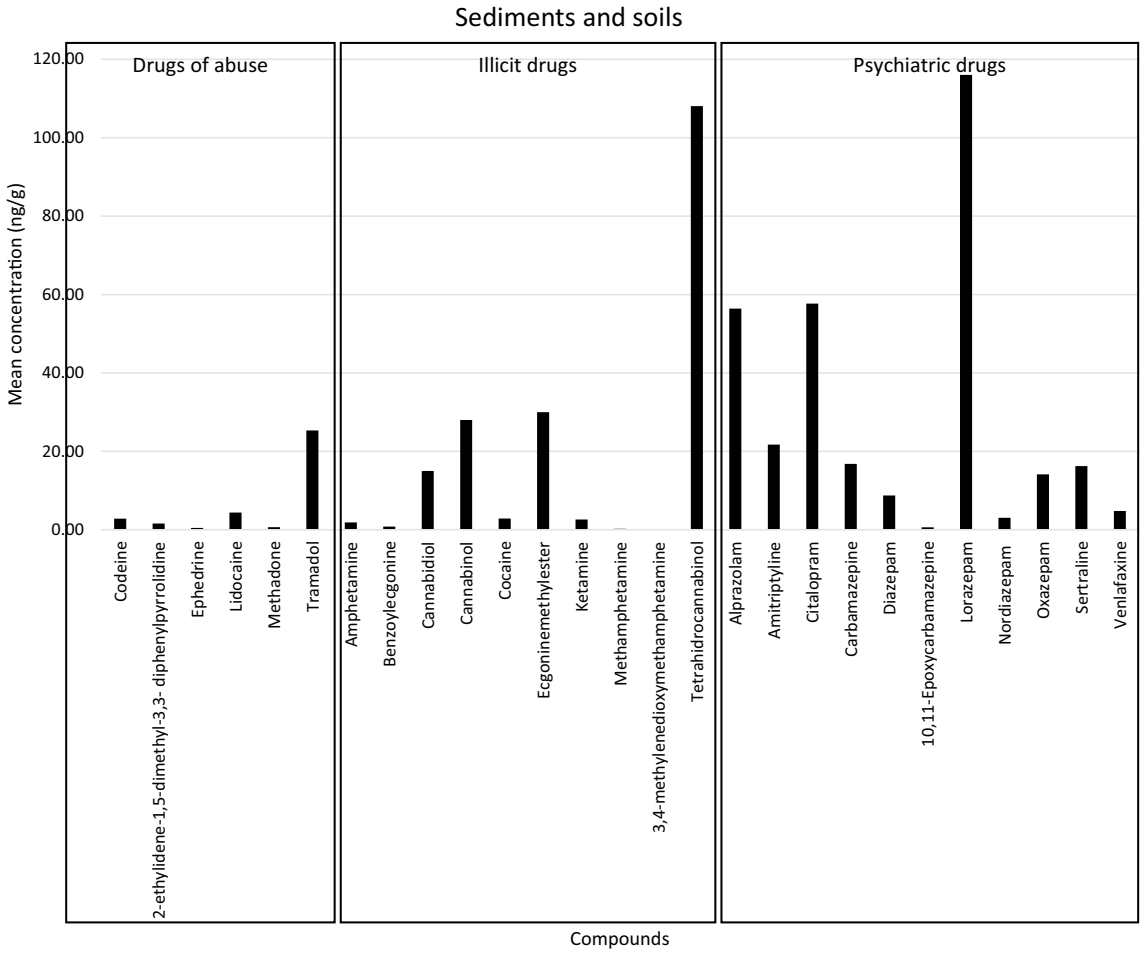

Fig. 4 Mean concentration of the target analytes in sediment and soil obtained from 16 papers

to its high hydrophobicity (log K_{ow} approximately 6 (PubChem)). On the contrary, cocaine and its metabolite benzoylecgonine were the most frequently detected compounds in this matrix, 31% and 19%, respectively, but at low concentrations, only 3 $ng \cdot g^{-1}$ and 1 $ng \cdot g^{-1}$, respectively.

The analysis of the reviewed publications indicates that the number of psychiatric drugs detected in sediment and soil was similar to that of illicit drugs but, as expected, the total amount of detected analytes was smaller than in sludge. Carbamazepine (anticonvulsant) and diazepam (anxiolytic) were the most widely detected psychiatric drugs, being measured in 44% and 38%, respectively, but, as in previous matrices, at a low concentration: 17 $ng \cdot g^{-1}$ and 9 $ng \cdot g^{-1}$, respectively. On the contrary, lorazepam (anxiolytic) was highlighted for its high concentration, above 100 $ng \cdot g^{-1}$. Alprazolam (anxiolytic) and citalopram (antidepressant) were also found at high concentrations, with mean concentrations of 56 $ng \cdot g^{-1}$ and 58 $ng \cdot g^{-1}$, respectively, but in only one work (Miller et al. 2021).

Risk assessment

The potential ecological effects of drugs and their metabolites on the ecosystem are still not exactly known, especially in relation to the potential harmful effect on non-target aquatic systems or their bioconcentration in biota. Information on the ecotoxicity of illicit drugs in the scientific literature is scarce and not systematic.

In order to assess the potential ecotoxicological risks of drugs on the aquatic ecosystem, a risk assessment is used. The risk assessment for each compound was calculated as the quotient between their measured environmental concentration and the predicted non-effect environmental concentration (PNEC) of a substance. PNEC depends on different parameters and varies according to the source, so we decided to use the PNEC values of the Norman List (Norman). Measured environmental concentrations were taken from the previous section in which the mean concentration of the measurement taken by the authors was calculated. The risk assessment was calculated by the following formula:

Table 2 Risk assessment calculated with the mean concentration measured in the reviewed papers and PNEC values obtained from Norman List (green means low risk, yellow means medium risk and red means high risk)

	Mean measured concentration ng·g^{-1}			LOWEST PNEC (µg·kg^{-1}) (Norman)			Risk assessment		
Compounds	Sediments	Fish	Mollusc	Sediment	Fish	Mollusc	Sediment	Fish	Mollusc
Alprazolam	56	6	0.3	2.39	2.14	0.53			
Amphetamine	0.5	2	1	42.28	7.69	1.92			
Amitriptyline	22		0.03	44.25		1.16			
Benzoylecgonine	0.75 ± 0.25			50.71					
Cannabidiol	15			290.76					
Cannabinol	28			1923.44					
Citalopram	58	1.6 ± 0.99	10 ± 4.3	1.42	164.45	41.11			
Carbamazepine	1.5 ± 1	6.8 ± 5.9	3 ± 1	142.56	0.06	0.01			
Cocaine	0.4 ± 0.1	0.01	1	50.71	1.72	0.43			
Codeine	0.4	0.6		69579.89	45.28				
Clozapine			2			9.72			
Desmethylcitalopram		1	7		0.92	0.23			
Diazepam	1.5 ± 1.8	2	0.4	11.58	1.42	0.35			
10,11-epoxycarbamazepine	0.6	0.2	0.3	116.01	0.97	0.24			
EDDP	2			36.98					
Ephedrine	0.5			555.62					
Fluoxetine			5			0.95			
2-hydroxycarbamazepine		0.7			2.22				
Heroin		0.1			1.06				
Ketamine	3	0.07	0.2	65.99	15.38	3.84			
Lidocaine	4		2	83.75		1.58			
Lorazepam	116			7.41					
Methamphetamine	0.3	0.02		73.51	19.62				
4-methylendioxyamphetamine		0.9			0.90				
MDMA	0.2	0.03		610.25	50.19				
Methadone	0.3	0.1		124.79	17.75				
Norfluoxetine			14			8.32			
N,O-didesmethylvenlafaxine			3			2.95			
Oxazepam	14			7.19					
Sertraline	16	9.5 ± 7.5	1.1 ± 0.7	20.18	1.29	0.32			
Tetrahydrocannabinol	6	6		237.19	2.37				
Tramadol	38 ± 30	5	3	256.32	51.50	12.88			
Temazepam			0.7			0.10			
Venlafaxine	5	2.2 ± 2	3.7 ± 0.9	1.29	0.32	0.08			

$$RA = \frac{MEC\left(\frac{ng}{g}\right)}{PNEC\left(\frac{ng}{g}\right)} \quad (1)$$

Calculation of the risk assessment (RA) (MEC = measured environmental concentration; PNEC = predicted non-effect environmental concentration).

If risk assessment is lower than 0.1, there is no risk (green), there is a moderate risk if it is between 0.1 and 1 (yellow) and the risk is high (red) if it exceeds 1. The results are shown in Table 2 for the different studied matrices and for those compounds for which data are available.

As Table 2 shows, the concentrations of the target analytes in sediment do not generally pose a risk. Only psychiatric drugs citalopram, followed by alprazolam, lorazepam, venlafaxine and oxazepam (anxiolytics or antidepressants), posed a high ecotoxicological risk for the aquatic environment. Nevertheless, it should be taken into account that these pharmaceuticals were measured by only one work and, according to the guideline on the environmental risk assessment of medicinal products for human use of the European Medical Agency, a different PNEC should be used in these cases (European Medicines Agency 2018). Drugs of abuse or illicit drugs had a risk assessment lower than 0.1, and did not pose an ecotoxicological risk for the aquatic environment because the PNEC value in sediment is usually high. Nevertheless, it should be noted that for soils, according to the guideline on the environmental risk assessment of medicinal products for human use of the European Medical Agency, if a single compound present risk, a risk to the entire soil compartment is indicated (European Medicines Agency 2018). In addition, in a multi-compartment and cross-species study, it was concluded that sediment is a route of exposure to take into account since the organisms that inhabit it tend to have higher concentrations of pollutants (Miller et al. 2021).

For marine biota, especially fish and molluscs, most measured concentrations presented a high risk for organisms.

Nevertheless, the PNEC values very much depend on the organism, which might explain the results. It is probably for this reason that a risk calculation in biological matrices is lacking and, hence, by means of the Norman List (Norman), we attempted to make a first approximation. In addition, as most of the measured concentrations were taken from only one paper, no comparison of the results was possible. Compared to the previous matrix, psychiatric drugs were highlighted for their risk. Carbamazepine (anticonvulsant) is a widely studied drug in marine biota, and posed a high risk in both fish and molluscs. Antidepressants also stand out because several measured samples presented a high risk in fish and molluscs for venlafaxine and sertraline. Once again, the importance of metabolites stands out; citalopram (antidepressant) was measured on several occasions with no risk for biota, but its metabolite, desmethylcitalopram, posed a high risk for marine biota. The metabolite of venlafaxine, N,O-didesmethylvenlafaxine, and the metabolite of fluoxetine, norfluoxetine, were also measured in molluscs, and they posed a high risk. However, for biological matrices, it was not easy to establish a precise risk assessment. As drugs affect each organism differently, their PNEC value should be independently calculated. Furhtermore, not only the toxicity of the compounds should be studied, but also the possible impact on non-target organisms that compounds such as those studied in this review may have on their behaviour (Ford et al. 2021).

The other studied compounds were measured in a few samples to draw generic conclusions. Nevertheless, it would seem that several illicit drugs like tetrahydrocannabinol posed a high risk for fish and cocaine for molluscs, and 4-methylendioxyamphetamine fell within the limit between a medium and a high risk.

Overall, carbamazepine should be monitored because, in all the samples where it was measured, it posed a medium–high risk with a mean concentration of 1.4 $ng{\cdot}g^{-1}$ and, in accordance with the directive of the European Parliament and of the Council that establishes a framework for community action in the field of water policy, it has been added as a priority pollutant (EUROPEAN COMMISSION 2022a). Furthermore, venlafaxine had a high risk assessment in all matrices justifying its inclusion for the first time in the Watch List (EUROPEAN COMMISSION 2022b).

On the other hand, although many of the compounds studied had a low risk assessment because they did not present toxicity at the concentrations measured, the possible effect that a substance could have on behaviour must be taken into account. For example, antidepressants may affect reproduction of fishes and molluscs, they caused slower predator avoidance behaviours, changes in migration path, decrease in food ingestion, at lower concentration that toxic (Castillo-Zacarías et al. 2021; Shaheen et al. 2022; Salahinejad et al. 2022; Moreira et al. 2022). In that sense, the term "behavioural ecotoxicology" appeared (Peterson et al. 2017), which studies the response and adaptation of the individual and of the population to toxic compounds and is broadly lacking (Ford et al. 2021). Although the measured concentrations of some of the psychoactive substances studied are not toxic, these substances should be monitored because of above-mentioned side effects or because the mixture of substances in the environment could have synergistic effects, since the effects of drug mixtures are greater than the predicted effects for individual drugs (Liess et al. 2020).

Conclusion

This review summarises the available information from 2010 to the present-day about the presence of the main categories of psychoactive drugs with potential addictive effects in environmental solid matrices. The study of solid matrices near or related to wastewater treatment plants is essential to know the true degree of contamination in the environment. Although conventional extraction techniques, such as solid–liquid extraction or ultrasonic-assisted extraction, are still employed, today the trend is to adopt automatic and miniaturised procedures that provide a fast analysis with little organic solvent waste to, thus, move towards greener analytical chemistry. Pressurised liquid extraction, microwave-assisted extraction and QuEChERS offer the advantage of significantly reducing the amounts of organic solvent consumed, amount of sample and time. Regarding the determination technique, liquid chromatography tandem mass spectrometry is a widely accepted technique of choice for the determination of psychoactive compounds and metabolites from environmental matrices. Only a few works have used high-resolution mass spectrometry as a detection system, and, although this technique is characterised for its higher resolution and lower sensitivity, the obtained limit of detections fell within the same range as that of mass spectrometry in tandem. Therefore, we encourage it uses because it offers many other benefits such as the possibility of using libraries for a first screening of the possible compounds present in the samples before quantifying, reduction of the noise due to the accurate mass and possibility of performing more analyses in the future without having to reinject the sample. Moreover, it is capable of detecting not only the parent compound, but also metabolites and transformation products. The study of metabolites or transformation products is fundamental because many compounds can undergo degradation through wastewater treatment plants or be excreted as metabolites.

After reviewing the occurrence, as expected, the highest concentrations appeared in sludge, where 77 drugs were detected, with psychopharmaceuticals standing out. These results confirm that they can indeed be adsorbed in solid matter. Therefore, these matrices should be taken into account when estimating the mass loadings of these compounds in

wastewater treatment plants or when studying the environmental impact of an area to acquire more in-depth information. On the presence of drugs in sediment, although current knowledge of these compounds is still limited, up to 27 drugs were detected, and the concentrations of psychopharmaceuticals like lorazepam and alprazolam, together with tetrahydrocannabinol, were the highest. In marine biota, different frequency or concentration patterns were often observed. The highest concentration was for cocaine, which should be controlled bearing in mind the side effects that this drug causes on marine organisms. However, in the aquatic environment, organisms are exposed to mixtures of a wide variety of drugs and for long times, which should be taken into account because the mixture of compounds can induce toxicity at concentrations at which a single compound shows either no effect or only a mild one. In addition, the risk assessment study of the above-mentioned drugs revealed that the studied drugs might pose a high risk for the aquatic organisms living or feeding on/in sediment, being necessary further research.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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