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Endocrine disrupting compounds (EDCs) in environmental matrices: Review of analytical strategies for pharmaceuticals, estrogenic hormones, and alkylphenol compounds

Tuan Fauzan Tuan Omar [a], Azrilawani Ahmad [b], Ahmad Zaharin Aris [a,c,*], Fatimah Md Yusoff [d]

[a] Department of Environmental Sciences, Faculty of Environmental Studies, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia
[b] School of Marine and Environmental Sciences, Universiti Malaysia Terengganu, 21030 Kuala Terengganu, Terengganu, Malaysia
[c] Laboratory of Halal Science Research, Halal Products Research Institute, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia
[d] Laboratory of Marine Biotechnology, Institute of Bioscience, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

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ABSTRACT

Endocrine disrupting compounds (EDCs) have been widely reported as potential carcinogenic threats to the human population. The release of EDCs to environmental compartments, such as water, sediment, and biota, has been monitored extensively. Considering the typically low levels of EDC concentrations found in environmental samples and the complexity of biota matrices, the main challenge is with the extraction and cleanup of samples, as well as with finding a sensitive enough instrumentation system for analyte detection. This paper presents a review of recent trends in the analysis of EDCs in environmental matrices. The focus of this review is three classes of environmentally important EDCs; namely, pharmaceuticals, estrogenic hormones, and alkylphenol compounds. Discussions about state-of-the-art instrumentation and sample preparation techniques, as well as a review of sample storage and preservation, are highlighted. Overall, the use of LC-MS-MS as an instrumentation technique has increased over the past 15 years.

Contents

Abbreviations: ACN, acetonitrile; APs, alkylphenols; APEs, alkylphenol ethoxylates; ASE, accelerated solvent extractor; DW, drinking water; E1, estrone; E2, 17β-estradiol; EE2, 17α-ethynyl estradiol; EDCs, endocrine disrupting compounds; ESI-MS, electrospray ionization mass spectrometry; GC, gas chromatography; LC, liquid chromatography; LC-MS-MS, liquid chromatography mass spectrometry-mass spectrometry; LOD, limit of detection; MAE, microwave-assisted extraction; MeOH, methanol; MS, mass spectrometry; NP, nonylphenol; NPE1, nonylphenol monoethoxylates; NPE2, nonylphenol diethoxylates; NPE3, nonylphenol triethoxylates; OP, octylphenol; PAHs, polyaromatic hydrocarbons; PCBs, polychlorinated biphenyls; PLE, pressurized liquid extraction; PPCPs, pharmaceuticals and personal care products; QuEChERS, quick-easy-cheap-effective-rugged-safe; SBSE, stir bar sorptive extraction; SPME, solid phase microextraction; SPE, solid phase extraction; STPs, sewage treatment plants; SW, surface water; UAE, ultrasonic-assisted extraction; USEPA, United States Environmental Protection Agency; WWTPs, wastewater treatment plants.

* Corresponding author. Tel: +603 89466764; Fax: +603 89438109.
E-mail address: zaharin@upm.edu.my (A.Z. Aris).

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1. Introduction

Endocrine disrupting compounds (EDCs) have garnered wide attention among the scientific and legislative communities in the past decade because of their widespread presence in the environment and their ability to interfere with hormonal systems. Examples of EDCs include naturally produced compounds, such as natural estrogens, natural androgens, and phytoestrogen, as well as a wide range of industrial chemicals and household products that includes synthetic hormones, polycyclic aromatic hydrocarbons (PAHs), polychlorinated compounds (e.g., PCBs, dioxins, and furans), alkylphenolic compounds, pharmaceuticals, and pesticides. EDCs have been detected in various environmental matrices in concentrations as low as parts per billion (ppb) and parts per trillion (ppt) [1–7]. This low-level detection of various EDC pollutants in complex environmental matrices is possible mainly because of advancements in sample preparation and instrumental techniques that continue to evolve rapidly. These advancements have allowed for an increasing number of research papers reporting on the low-level detection of EDCs over the past 15 years, and with continuous innovation in both sample preparation and instrumental techniques, it is predicted that many more EDC pollutants will be detected in the coming years. This is also in line with the increase in new chemical compounds that have been synthesized in recent years.

Among EDCs, estrogenic hormones are major contributors to estrogenic activity, and their pathways to the environment are mainly through effluent from sewage treatment plants (STPs), wastewater treatment plants (WWTPs), and from livestock activities [8–11]. Raman et al. [9] evaluated the estrogen content in animal waste and concluded that 17α-estradiol, estrone (E1), and 17β-estradiol (E2) were the major estrogen compounds contained in the waste samples collected. Meanwhile, Hutchins et al. [10] analyzed effluent and suspended solid samples from lagoons that were affected by the discharge of animal waste and identified that 17α-estradiol, 17β-estradiol (E2), and estrone (E1) were among the estrogenic hormones present in the analyzed samples. The presence of synthetic estrogens, such as 17α-ethynyl estradiol (EE2), in the aquatic environment has received much attention, as these compounds have been detected in various aquatic compartments (water, sediments, and biota) due to their high bioactivity, ubiquitous nature, toxicity, and persistence in the environment [11]. EE2 is a derivative from the natural hormone, estradiol (E2), which is used commonly in the formulation of contraceptive pills.

In addition to estrogenic hormones, pharmaceuticals and alkylphenolic compounds are groups of EDC pollutants ubiquitously found in environmental matrices [12–14]. Pharmaceutical compounds consist of hundreds of thousands of chemicals intended either for human consumption or as veterinary drugs, and the list grows from year to year as new medicines and formulations are introduced on the market. This will make the monitoring of pharmaceutical compounds a much more demanding task for researchers and regulators. To help laboratories worldwide, in 2007, the United States Environmental Protection Agency (USEPA) published a comprehensive technical method known as Method 1694 that determines the concentrations of over 74 targeted pharmaceuticals compounds in water, sediments, soils, and biosolid samples [15,16]. This technical note is very useful as guidance for analytical chemists in developing reliable methods for the continuous monitoring of environmental samples. The occurrence of pharmaceutical compounds in the environment can be from varying sources, such as water effluent from municipal STPs, water effluent from wastewater treatment plants (WWTPs), and landfill leachate [17–19]. Incomplete removal of pharmaceutical compounds from the effluent discharged from STPs and WWTPs subsequently affects the receiving waters where the compounds are released as environmental organic contaminants. Ternes [17], in a study carried out to monitor the occurrence of drugs in sewage treatment plants and rivers, concluded that more than 80% of 32 pharmaceutical drugs analyzed were detected in STP effluent. Similarly, Kolpin et al. [19] also detected an almost equal percentage of pharmaceuticals, hormones, and organic wastewater contaminants in the water samples analyzed. Meanwhile, a review by Heberer [20] supported both findings by stating that more than 80 pharmaceutical compounds and several drug metabolites have been detected up to the μg/L level in municipal sewage and surface waters located downstream from municipal STPs.

Alkylphenol ethoxylates (APEs) are one of the most widely used classes of surfactants, and are used in domestic detergents, pesticide formulations, and industrial products. The degradation of APEs in wastewater treatment plants or in the environment generates more persistent shorter-chain APEs and alkylphenols (APs), such as nonylphenol (NP), octylphenol (OP), and AP mono- to tri-ethoxylates (NPE1, NPE2, and NPE3) [21]. Nonylphenols and octylphenols are two types of alkylphenol compound commonly detected in environmental matrices, as reported by Wenzel et al. [12], Ferrara et al. [22], Ceśpedes et al. [23], and Nurulnadia et al. [24]. The sources of alkylphenols in the environment are mainly effluent from STPs, industrial waste discharge, and effluent from WWTPs [23,25]. Fig. 1 shows a conceptual diagram of the sources and pathways of pharmaceuticals, estrogenic hormones, and alkylphenol compounds in the ecosystem.

The analytical methods and techniques used to detect and measure EDCs in environmental matrices vary. This is due to the complexity of these matrices and the broad range of EDC pollutants found in environmental samples. Various sample preparation techniques, such as Soxtec [26], pressurized liquid extraction (PLE) [27,28], quick-easy-cheap-effective-rugged-safe (QuEChERS) [7,29], microwave-assisted extraction (MAE) [30–32], ultrasonic-assisted extraction (UAE) [33,34], stir-bar-sorptive extraction (SBSE) [35], solid phase microextraction (SPME) [36], and even classical Soxhlet [1] and liquid-liquid extraction (LLE) [37], have been applied for the extraction of EDCs from the matrices. Whereas for analyte enrichment and sample cleanup, solid phase extraction (SPE) using C18 cartridges is the most dominant technique [27,29]. For the past 15 years, trace analysis determination for EDCs has been dominated by two instrumentation methods – gas chromatography (GC) with various types of detector, such as a flame ionization detector (FID) and an electron capture detector (ECD), and mass spectrometry (MS) [1,3,14], or the liquid chromatography (LC) technique, also with a wide range of detectors, such as a diode array detector (DAD) and fluorescence and MS [38,39]. Each instrumentation method has its own advantages and how they determine EDCs depends on the physical and chemical properties of the compounds to be determined. However, the use of these instrumental techniques has certain limitations such as being unable to achieve required sensitivity and having poor selectivity in some cases. Therefore, a substantial shift was observed when researchers opted for more sophisticated, sensitive, and selective detector systems such as triple quadrupole MS, ion trap MS, time-of-flight MS, and orbitrap MS. LC-MS-MS and GC-MS have been the preferred instrumental techniques for the determination of EDCs, particularly for pharmaceuticals, estrogenic

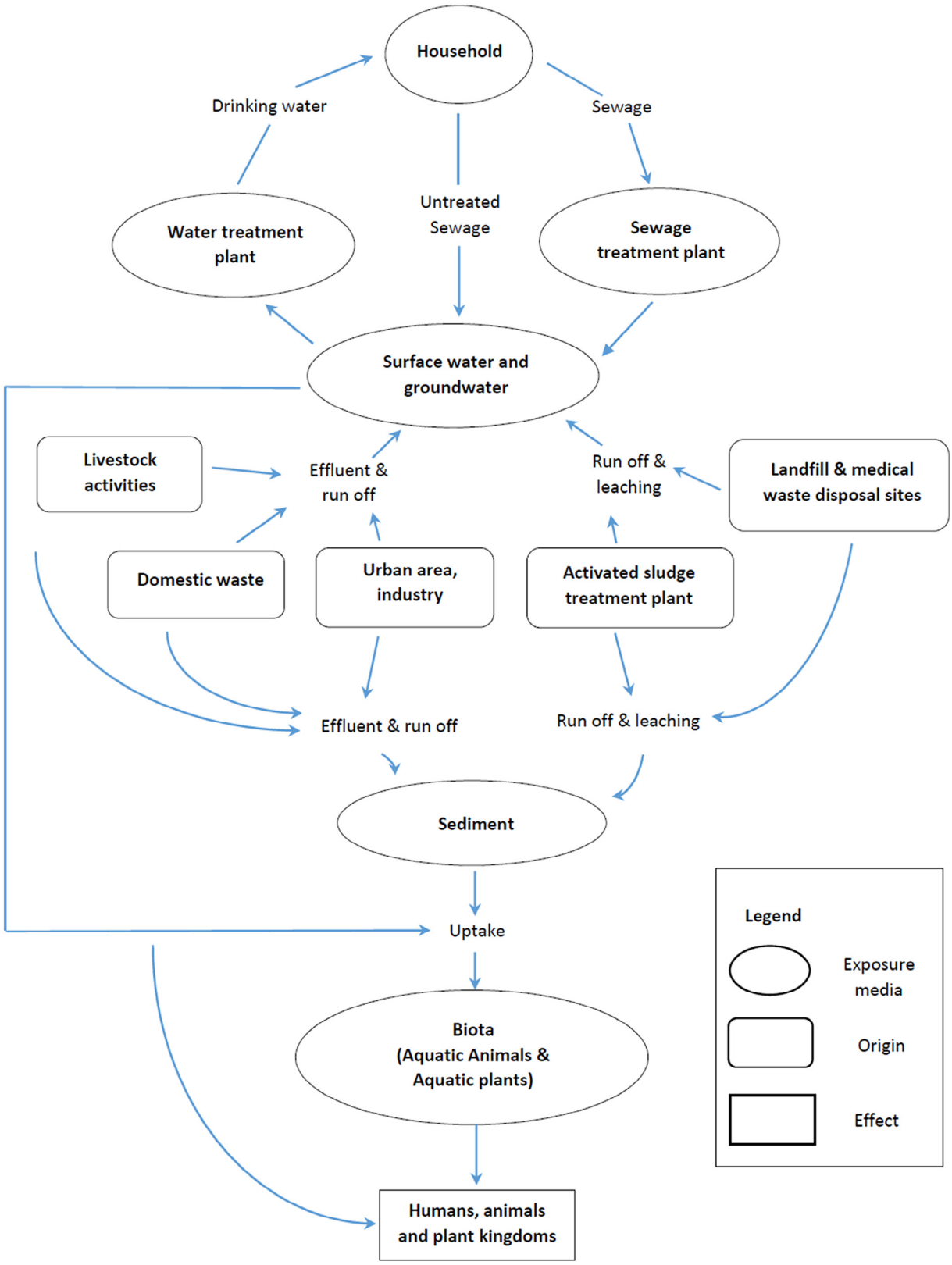

Fig. 1. Sources and pathways of pharmaceuticals, estrogenic hormones and alkylphenol compounds in environmental ecosystem.

hormones, and alkylphenol compounds in environmental matrices as shown in Fig. 2. In addition to the instrumental techniques based on LC and GC, a bioanalytical technique is widely used for environmental applications, as reported by Goda et al. [40], Rodriquez-Mozaz et al. [41], Ahmad and Moore [42], and Zehani et al. [43]. Despite some limitations in its application, this technique is gaining popularity as a fast and rapid assay for the screening of EDCs contamination in environmental samples.

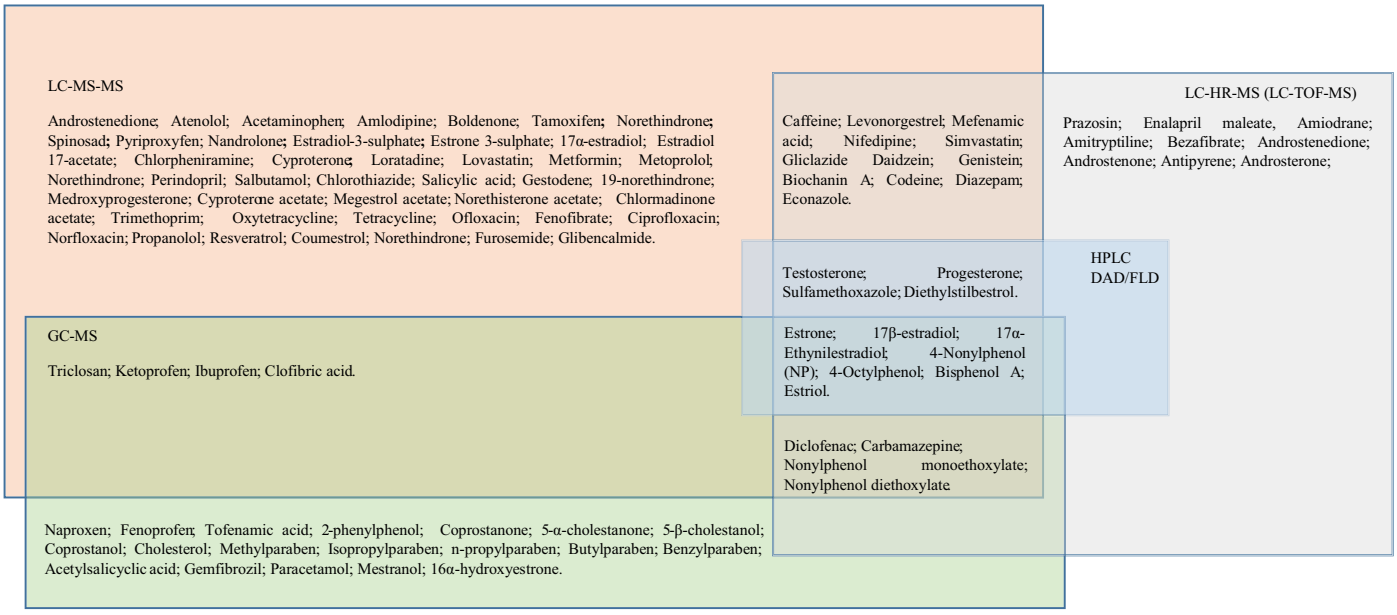

Fig. 2. Pharmaceuticals, estrogenic hormones and alkylphenol compounds analysed using LC-MS-MS, GC-MS, LC-HR-MS (LC-TOF-MS) and HPLC DAD/FLD in the environmental matrices.

This paper presents a review of the previous literature as well as an update on the latest developments in sample preparation and instrumental techniques for the determination of EDCs, with a focus on pharmaceuticals, estrogenic hormones, and alkylphenol compounds in environmental matrices. The application of the bioanalytical technique for the determination of these compounds will also be reviewed. This paper also discusses the sample handling, storage, and preservation techniques as important parameters for ensuring quality and integrity of the results produced. Insight into the parameters that can be manipulated to improve the detection and separation of analytes in the LC-MS-MS and GC-MS techniques will also be highlighted.

2. Sample handling, storage, and preservation

Sample handling, storage, and preservation are among the pertinent aspects of sample management to ensure that the analyte of interest is well preserved and retained in the environmental samples collected. Often, this part of the analysis is taken for granted, and, consequently, will give an inaccurate value for the concentration detected in the ecosystem. Poor sample handling and storage can also lead to data misinterpretation and wrong conclusions being drawn from the results, which may compromise the integrity of the research being carried out. The major factors that affect samples include contamination from the container leaching, sorption of the analyte onto the container surface, oxidation and photochemical decomposition of compounds, and decomposition of compounds due to microorganisms [44]. In addition to these, the inappropriate material for the sampling container can also have a significant effect on the final analytical findings. Therefore, proper sample handling, storage, and preservation are important to minimize any physical, chemical, or biological changes that may take place in the samples from the time of sample collection to the time of sample analysis [45]. Generally, this can be achieved via three approaches: (i) immediately refrigerating the samples at a particular temperature, (ii) choosing an appropriate container, and (iii) adding preserving chemicals to the samples. Complete elimination of factors that affect sample contamination is impossible, but the effects can be minimized by following and adhering to an appropriate procedure. This section highlights the procedures and techniques available for the storage, handling, and preservation of water, sediment, and biota samples for the purpose of analyzing pharmaceuticals, estrogenic hormones, and alkylphenol compounds.

Numerous studies have reported on the storage and preservation techniques for environmental samples collected for analysis of pharmaceuticals, estrogenic hormones, and alkylphenol compounds [46–53]. Each paper reported a different storage and preservation technique, depending on the nature of the samples and the targeted compounds to be analyzed. Baker and Kasprezyk-Horden [46] produced a comprehensive review and critical verification of methodologies commonly used for sample collection, storage, and preparation of aqueous environmental samples for the analysis of pharmaceuticals and illicit drugs using SPE-LC/MS techniques. This comprehensive review covered over 60 analytes including stimulants, opioid and morphine derivatives, benzodiazepines, antidepressants, dissociative anaesthetics, drug precursors, and human urine indicators and their metabolites. A review by Ort et al. [47] described the importance of sample preservation and reported that preservation was mentioned the most in the literature cited. Therefore, the preservation of samples is a key element and should receive the highest consideration in analytical strategies for determining EDCs in aqueous environmental samples.

Togola and Budzinski [48] studied the suitable storage conditions for natural water and WWTP effluent for the determination of pharmaceutical compounds, such as aspirin, caffeine, carbamazepine, diclofenac, ketoprofen, naproxen, ibuprofen, clofibrate, clofibric acid, and gemfibrozil. No significant losses in these compounds occurred during eight days of storage at ambient temperature (20°C), irrespective of the addition of conserving agents. However, Castiglioni et al. [49] made a contrasting observation when the degradation of several compounds – cocaine, norcocaine, cocaethylene, 6-acetylmorphine, and morphine-3β-$_D$-glucurinode – in wastewater samples was analyzed and reported. In this study, the wastewater samples did not have any chemical preservative added. Vanderford et al. [50] conducted a comprehensive and specific study that assessed the proper storage and preservation techniques for 16 PPCPs and 5 steroids in surface water (SW) and drinking water (DW). It was suggested that the SW and DW samples collected in amber glass,

Table 1
Storage and preservation technique for pharmaceuticals, estrogenic hormones and alkylphenol compounds in environmental matrices

Compounds	Matrix	Storage	Preservation	Ref.
16α-hydroxyestradiol; E2; EE2; Testosterone; Estrone; 4-androstene-3,17-dione; Equilin.	Drinking water.	Stored at or below 6°C and protected from light. Samples must not be frozen.	Sodium thiosulfate; 2-mercaptopyridine-1-oxide, sodium salt.	[51]
Atenolol; Carbamazepine; Diazepam; Diclofenac; DEET; Fluoxetine; Gemfibrozil; Ibuprofen; Iopromide; Meprobamate; Naproxen; Phenytoin; Primidone; Sulfamethoxazole; Trimethoprim; E2; EE2; Estrone; Progesterone; Testosterone; TCEP.	Surface and drinking water.	Store at 4°C in amber bottles.	Ascorbic acid; sodium azide.	[50]
Sulfapyridine; Sulfadiazine; Sulfamethazine; Sulfamethoxazole; Trimethoprim; Oxytetracycline; Tetracycline; Chlortetracycline; Doxycycline; Norfloxacin; Ciprofloxacin; Ofloxacin; Lomefloxacin; Enrofloxacin; Oleandomycin; Roxithromycin; Erythromycin.	Sediment.	Freeze dried and sieved through 60 mesh. Stored at 4°C.	Sodium azide.	[54]
E1; E2; 17α-estradiol (α-E2); Estriol (E3); EE2; Estrone-glucuronide (E1-3G); Estrone-sulfate (E1-3S); 17β-estradiol-3-glucuronide (E2-3G); 17β-estradiol-17-glucuronide (E2-17G); 17β-estradiol-3-sulfate (E2-3S); Estriol-3 glucuronide; (E3-3G); Estriol-3-sulfate (E3-3S).	Sediment.	Freeze dried at –30°C.	-	[56]
Clarithromycin; Metronidazole; Propranolol; Sulfamethoxazole; Trimethoprim; Triclosan; Chlortalidone; Amitriptyline; Carbamazepin; Azathioprine; Caffeine; Diltiazen; Flurazepam; Gemfibrozil; Glibenclamide; Ketonazole; Miconazole; Lidocaine; Mebendazole; Eusolex; Nimesulide; Prednisone; Theophyllim; Benzophenone; Methylparaben; Propylparaben.	Sludge.	Freeze dried at –18°C.		[58]
Atenolol;Carazolol; Carbamazepine; Sotalol; Citalopram; Clopidrogel; Codeine; Diazepam; Diclofenac; 10,11 epoxyCBZ; Venflaxine; Hydrochlorothiazide; 2, HydroxyCBZ; Levamisol; Lorazepam; Metropolol; Nadolol; Propanol; Salbutamol; Sertraline.	Fish tissue.	Homogenized using meat grinder and freeze dried.	-	[57]
Nonylphenol; Octylphenol; Nonylphenol polyethoxylates; Octylphenol polyethoxylates.	Mussels.	Homogenized with Polytron homogenizer and freeze dried at –80°C to –20°C.	-	[107]

quenched with ascorbic acid, preserved with sodium azide, and stored at 4°C, could be kept for 28 days without appreciable loss of any of the assessed compounds. However, if the samples were not chemically preserved, they could be stored at 4°C with extraction carried out within 72 hours of sampling. USEPA Method 539 [51], which was developed for the determination of hormones in drinking water, suggests the use of sodium thiosulphate and 2-mercaptopyridine-1-oxide sodium salt as preservative agents, and that samples should be stored at or below 6°C and protected from light. Meanwhile, Method 1694 suggests that biosolid, semisolid, and mixed-phase samples should be freeze-dried to avoid analyte degradation, and that the samples should be extracted within 48 hours of removal from the freezer.

Another technique for preservation, especially for pharmaceutical compounds, that is commonly applied to collected samples, is acidification. González-Marino et al. [52] reported that the acidification of wastewater samples (pH=2) together with the addition of sodium azide as a preservative, gives more stability to several pharmaceutical compounds, such as cocaine, methadone, and cocaethylene. Using the same samples, the stability of pharmaceutical compounds stored in SPE cartridges for a certain period was investigated. In that experimental work, raw wastewater samples were subjected to SPE cleanup immediately, without the addition of chemicals, and were kept at –20°C for different periods (1–3 weeks and 12 weeks). Acceptable stability after 3 months for all targeted compounds was observed and this procedure was adopted as an alternative to avoid the degradation of analytes. Georghe et al. [53] also reported a similar observation when a stability study was carried out for several targeted pharmaceutical compounds in wastewater samples. The pH of the samples was adjusted to 2 and 6 and stored at three different temperatures (–20°C, 4°C, and 20°C) for 5 days. From the study, it was concluded that the samples should be acidified to pH=2 immediately after sampling and stored at –20°C.

Not many studies were found regarding the addition of chemical preservatives for solid and biota matrices. Zhou et al. [54] used sodium azide to preserve sediment samples collected for determination of human and veterinary antibiotics. Meanwhile, Combalbert et al. [55] carried out a comprehensive study on the storage and preservation condition for the determination of steroid hormones in swine manure samples, which implied that the addition of formaldehyde as a preservative agent in swine manure samples intended for steroid hormone analysis should be avoided. The analysis of the hormones was affected by the matrix changes after the addition of formaldehyde. Most of the studies on solid and biota matrices emphasize the use of freeze drying for storage and preservation [37,56–58]. Other than the freeze-drying technique, researchers have used the air-drying technique followed by storage of the samples at 4°C, especially for sludge, sediment, and soil samples [59]. Table 1 summarizes the storage and preservation techniques that can be applied for the determination of pharmaceuticals, estrogenic hormones, and alkylphenol compounds in environmental and biota matrices.

3. Analytical methods for the determination of pharmaceuticals, estrogenic hormones, and alkylphenol compounds in environmental matrices

The environment has been widely exposed to pharmaceuticals, estrogenic hormones, and alkylphenol compounds from various sources and through various pathways. As shown in the conceptual diagram in Fig. 1, the main sources of these contaminants are livestock activities, domestic waste, industrial discharge, activated sludge treatment plants, landfills, and medical waste disposal sites. Runoff, effluent, and leaching are the main pathways for the distribution of these contaminants in surface water, groundwater, and sediment. Consequently, these pollutants will directly affect biota, such as aquatic animals or aquatic plants that live within the vicinity of the contaminated environment. Therefore, analytical determination, using advanced sample treatment and instrumental techniques, is needed to monitor these pollutants in complex environmental matrices at trace levels.

3.1. Optimization of parameters for LC-MS-MS analysis

A review of the literature over the past 15 years shows an increasing trend in the use of the LC-MS-MS and LC high resolution

MS (LC-HR-MS) techniques for the determination of EDCs in environmental matrices [5,7,13,60–64],. These soft ionization techniques are chosen over the GC method because they eliminate the need for derivatization steps, which are required for the GC method. The derivatization procedure is much more tedious, laborious, and time consuming and requires skillful analysts to obtain optimum results. Despite having superior resolving power, the use of LC-HR-MS such as orbitrap MS is still relatively new and most researchers choose LC-MS-MS for routine analysis, as shown in Fig. 2. Moreover, technique improvements are needed for the determination of EDCs using LC-MS-MS especially on the compounds optimization.

The optimization of LC and MS-MS parameters is an important part in the development of a successful method for trace analysis of pharmaceuticals, estrogenic hormones, and alkylphenol compounds. Table 2 describes in detail the LC parameters, such as mobile phase and chromatography column for compound separation, and MS parameters, such as ion source temperature, collision energy, desolvation temperature, and source temperature, that should be optimized to obtain good peak separation and optimum peak intensity. The mobile phase, for example, plays an important role in compound optimization, as described by Sodrė et al. [65], who reported that adding a certain percentage of ammonium hydroxide (NH_4OH) and formic acid ($C_2H_4O_2$) as ionization additives into the mobile phase can increase the peak intensity of compounds in MS detection. Collision energy has also been examined as a way to improve compound ionization. The amount of energy applied to the collision cell has a major influence on the formation of fragmentation in the product ion spectra. The addition of chemical additives, such as ammonium hydroxide (NH_4OH) [65,66], ammonium formate (CH_5NO_2) [7], formic acid (CH_2O_2) [67], tributyl amine ($C_{12}H_{27}N$) [68] and ammonium fluoride (NH_4F) [69], into mobile phase composition to help increase the ionization of compounds has been reported in a number of papers. However, the use of chemical additives has to be evaluated accordingly, as some additives might not be compatible with certain modes of MS. Matějíček [66] reported that the use of 0.1% ammonium hydroxide (NH_4OH) in 2-propanol and 0.1% formic acid (CH_2O_2) in methanol produced the highest intensity peaks for analytes in negative and positive modes, respectively. The analysis was carried out using MS operated under an atmospheric photoionization pressure chemical ionization (APPCI) ion source. In the same study, the signal intensity significantly decreased when ammonium formate and ammonium hydroxide were used in positive mode, whereas formic acid (CH_2O_2), acetic acid ($C_2H_4O_2$), and ammonium formate (CH_5NO_2) negatively influenced ionization efficiency in negative mode. Berlioz-Barbier et al. [7] discovered that the addition of ammonium acetate ($C_2H_7NO_2$) gave the best separation and sensitivity for negatively charged compounds, whereas formic acid (CH_2O_2) allowed for the best peak separation for positively charged compounds. Vazquez-Roig et al. [67] observed excellent sensitivity for pharmaceutical compounds running in positive mode with the addition of 0.1% formic acid (CH_2O_2) in both water and MeOH. However, a problem was encountered for the separation of ibuprofen, clofibric acid, and diclofenac in negative mode, even with the addition of ammonium acetate ($C_2H_7NO_2$) as the mobile phase additive. Separation was finally achieved by using a Luna C18 column with a mixture of ACN/MeOH (60:40) with column preconditioning prior to the next injection of ACN instead of ACN/MeOH (60:40). Kasprzyk-Horden et al. [68] carried out a comprehensive evaluation of the mobile phase composition suitable for the analysis of multiclasses of acidic/neutral pharmaceutical compounds, which include antibiotics, anti-inflammatory/analgesics, lipid-regulating agents, diuretics, triazides, H_2-receptor antagonists, cardiac glicozides, and angiotensin II antagonists. A few chemical additives were added into the mobile phase, and it was found that ammonium hydroxide (NH_4OH) and tributylamine (TrBA, $C_{12}H_{27}N$) were the most effective additives for the analyzed compounds. However, because of the higher sensitivity, better peak shape, and longer retention times, which resulted in better separation for all analytes, TrBA was chosen as the mobile phase additive for the developed method. The study also suggested that the concentration of mobile phase additives should be kept to the minimum, as a high concentration might affect the separation of analytes due to signal suppression in ESI-MS detection.

3.2. Optimization of parameters for GC-MS analysis

Despite the growing number of reported studies using LC-MS-MS as the instrumental technique for detecting pharmaceuticals, estrogenic hormones, and alkylphenol compounds in environmental matrices, a GC-MS is still the instrument of choice for analyzing these classes of compounds. Due to the high capital cost involved, not every laboratory has the privilege of having a LC-MS-MS system. Therefore, GC-MS is an excellent alternative for researchers that can provide comparable sensitivity and selectivity to the LC-MS-MS system. Numerous studies, including those by Shareef et al. [70], Hu et al. [71], and Magi et al. [72], report successful method development for pharmaceuticals, estrogenic hormones, and alkylphenols compounds using GC-MS techniques. Application of a GC-MS technique requires an analyst with hands-on experience and skill in handling samples, as this technique uses an additional step, the derivatization step. Generally, the compounds are derivatized for the following reasons: (i) to bring the analytes to chemical forms that are more compatible with the chromatographic environment; (ii) to create a separation mechanism or to maximize resolution efficiency; (iii) to improve detection or structural elucidation effectiveness, or (iv) to make use of the specific structural features of the analyte for analytical needs [73]. Optimization of the derivatization procedure is important when developing a method for GC-MS analysis. Bowden et al. [74] evaluated the derivatization strategies for the determination of 33 EDCs in one chromatographic analysis and found that the thermal and microwave derivatization methods were effective for comprehensive analysis of EDCs mixtures. The microwave derivatization method provides an efficient and suitable sample preparation method for the GC-MS analysis of estrogenic steroids [75]. Shareef et al. [70] discovered that the reaction conditions and the choice of reagents and/or solvents play an important role in the effectiveness of the derivatization procedure. Two popular types of reagent for derivatization are *N,O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) and *N*-(*tert*-butyldimethylsilyl)-*N*-methyltrifluoroacetamide (MTBSTFA), which generate the formation of trimethylsilyl (TMS) and t-butyldimethylsilyl (TBS) derivatives, respectively. The application of these derivatization reagents has to be assessed accordingly for the developed compounds. Zhang et al. [76] evaluated the stability of silylated steroid hormones and alkylphenol compounds developed for water matrices and suggested the use of a combination of BSTA and pyridine together with the use of hexane as the final solvent in order to generate more stable compounds. Meanwhile, Guitart and Readman [77] chose a combination of MTBSTFA and 1% of *tert*-butyldimethylhydrochlorosilane (TBDMSCI) as a catalyst for the derivatization of multiclass pharmaceuticals, personal care products, phenolic endocrine disruptors, and fecal steroid compounds in environmental water matrices. However, the use of BSTFA and MTBSTFA has to be evaluated carefully, particularly for the analysis of E1 and EE2, as Shareef et al. [78] reported that these two compounds could convert partially to their respective E1 derivatives, leading to an inaccurate interpretation of the results. Therefore, in a separate study, Shareef et al. [70] recommended that derivatization could be best achieved by (i) the formation of disubstituted TBS-TMS-EE2 derivatives or (ii) using TMS reagents in dimethyl formamide solvent. Table 3 shows the sample derivatization reagents for GC-MS analysis of pharmaceuticals, estrogenic hormones, and alkylphenol compounds in various environmental matrices.

Table 2
LC MS parameters, sample treatment and method performances for pharmaceuticals, estrogenic hormones and alkylphenol compounds in environmental matrices.

LC-MS-MS parameters	Matrix/Sample treatment	Compounds	% Recovery	LOD	Ref.
LC = Agilent 1200 LC system (Agilent Technologies) Column: Kinetex XDB C18 (50 mm × 2.1 mm, 1.7 µm) Column oven temperature, °C = 60. Mobile phase : Flow rate = 350 µL/min; Solvent A = 0.1 mM ammonium acetate in water; Solvent B = 0.1% formic acid in water; Solvent C = MeOH. *MS = AB Sciex API 3200 QTRAP Triple quadrupole MS with ESI.* Ionization mode = Negative and Positive; Source temperature, °C = 600 (-, +); Ion spray voltage, kV = -4.5, 5.5; Nebulising gas = nitrogen.	Matrix = sediment. Sample size = 2 grams. Sample treatment = extraction with QUECHERS followed by clean up using dispersive solid phase extraction using PSA/GCB.	Carbamazepine Tamoxifen Triclosan Econazole Ketoprofen Norethindrone Estrone Spinosad Pyriproxyfen Piperonyl butoxide 3,4-dichloroaniline 3-5-di-ter-butylphenol 2,6-di-ter-butylphenol 4-methylbenzylidene champor Bisphenol A	82 76 80 77 37 81 79 80 79 90 80 94 72 80 98	0.5 [b] 2.0 [b] 5.5 [b] 1.5 [b] 20.0 [b] 5.0 [b] 1.5 [b] 1.5 [b] 1.5 [b] 3.5 [b] 4.5 [b] 2.0 [b] 8.0 [b] 12.8 [b] 8.5 [b]	[7]
LC = Ultimate 3000 system (Dionex). Column: Acclaim PA2 (3 µm × 3 mm × 150 mm) (*Thermo Scientific*); Column temperature, °C = 40. Mobile phase : Solvent A = ACN; Solvent B = Water. *MS = Waters Quattro Ultima triple quadrupole MS (Micromass).* Infusion: 500 ng/mL (estrogens); 1 µg/mL (androgens) –5 µL were infused at 10 µL/min using individual standard.	Matrix = river water, WWTPs effluent and influent. Sample volume = 50 mL. Sample treatment = Online SPE. SPE column: IonPac NG1 (10 µm × 4mm × 35 mm, Thermo Scientific).	Estrone Estradiol Estriol Ethynilestradiol Diethylstilbestrol Testosterone Nandrolone Androstenedione Boldenone	101 105 117 103 107 32 65 51 58	0.5 [a] 1.0 [a] 2.0 [a] 0.5 [a] 0.5 [a] 4.0 [a] 3.0 [a] 5.0 [a] 2.0 [a]	[5]
LC = HP 1200 series LC-triple quad QqQ tandem MS (Agilent). Column : Kromasil 100 C18 (25.0 cm × 0.46 cm, 5 µm, Teknokroma, Spain); Column temperature, °C = 35. Mobile phase : Flow rate = 1 mL/min; Solvent A = Water with acetic acid (pH 3.0); Solvent B = ACN. *MS=HP 1200 series LC-triple quad QqQ tandem MS (Agilent).* Ionization mode = Negative; Capillary voltage (kV) = 3.0; Source temperature, °C = 350; Drying gas flow = 12 L/min; Nebulizing, collision, desolvation gas = nitrogen.	Matrix = sewage sludge Sample size = 1 gram Sample treatment = Extraction with ASE 200 accelerated solvent extraction system (Dionex).	Estriol Estradiol-3-sulphate Estrone 3-sulphate 17α-estradiol 17β-estradiol 17α-ethynilestradiol Estrone Diethylstilbestrol Estradiol 17-acetate	84 99 100 83 92 88 88 81 83	26.0 [b] 0.15 [b] 0.15 [b] 150.0 [b] 150.0 [b] 150.0 [b] 11.0 [b] 12.0 [b] 175.0 [b]	[108]
LC = Waters Alliance HPLC System (Waters). Column: ESI (+) Zorbax SB-C18, RRHT (2.1mm × 100mm, 1.8 µm); ESI (-) Zorbax Extend-C18 (2.1 mm × 100mm, 3.5 µm). Mobile phase : ESI (+) Solvent A = 5 % Solvent B in ultrapure water containing 0.1% HFBA, Solvent B = ACN/MeOH (66/34, v/v). Both solvent contain 10 mM ammonium acetate; ESI (-) Solvent A = 5% Solvent B in ultrapure water containing 0.05% TrBA (pH 10.5)Solvent B = ACN/MeOH (66/34, v/v); Flow rate = 0.25 mL/min. *MS = Micromass Quattro Ultima Pt tandem QQQ Mass Spectrometer.* Ionization mode = Positive and Negative; Capillary voltage (kV) = 3.5; Ion source temperature, °C = 80; Desolvation temperature, °C C = 160; Cone gas flow (L h^{-1}) = 50; Desolvation gas flow (L h^{-1}) = 550; Collision gas cell pressure (mbar) = 3.50 × 10^{-3}; Nebulizer gas = nitrogen; Collision gas = Argon.	Matrix = river water, STP effluent. Sample volume = 150 mL (river water), 100 mL STP effleunts. Sample treatment = Offline SPE using HLB Oasis MCX Cartridge (3 cm^3, 60 mg).	Acetaminophen Amlodipine Atenolol Chlorpheniramine Cyproterone Loratadine Lovastatin Metformin Metoprolol Nifedipine Norethindrone Levonorgestrel Perindopril Salbutamol Simvastatin Chlorothiazide Diclofenac 17α-ethynilestradiol Furosemide Glibencalmide Gliclazide Mefenamic acid Salicylic acid	18 63 74 75 87 79 62 43 71 61 87 81 25 49 48 108 68 59 96 81 70 93 89	9.0 [a] 2.0 [a] 14.0 [a] 3.0 [a] 68.0 [a] 3.0 [a] 48.0 [a] 281.0 [a] 67.0 [a] 9.0 [a] 46.0 [a] 31.0 [a] 4.0 [a] 1.0 [a] 140.0 [a] 1.0 [a] 10.0 [a] 32.0 [a] 5.0 [a] 0.25 [a] 1.6 [a] 2.0 [a] 15.0 [a]	[13]
LC = Waters Acquity UPLC. Column: Acquity BEH C18 (50mm × 2.1mm, 1.7 µm). Mobile phase: Solvent A = (methanol, group 1; ACN, group 2); Solvent B = Ultrapure water; Flow rate = 0.1 mL/min. *MS = Waters Quattro Premier triple quadrupole MS (Micromass).* Ionization mode = Negative (G1) and Positive (G2); Capillary voltage (kV) = 3.5 (G1); 3.3 (G2); Extractor voltage = 4V (G1); 3V (G2); Multiplier voltage, V = 650; Ion source temperature, °C = 120; Desolvation temperature, °C = 450; Cone gas flow (L h^{-1}) = 50; Desolvation gas flow (L h^{-1}) = 700; Nebulizer gas = nitrogen; Collision gas = Argon; Collision gas cell pressure (mbar) = 3.00 × 10^{-3} mbar.	Matrix = waste water. Sample volume = 100mL. Sample treatment= ENVI-C18 SPE disk (47mm diameter, 0.6 mm thick).	17β-estradiol Estriol Estrone- 17α-ethynilestradiol 19-norethindrone Gestodene Levonorgestrel Medroxyprogesterone Cyproterone acetate Megestrol acetate Progesterone Norethisterone acetate Chlormadinone acetate 17β-estradiol-3-benzoate Hydroxyprogesterone caproate	95 93 88 89 98 97 86 96 87 88 91 86 93 86 82	0.5 [a] 0.6 [a] 1.0 [a] 1.2 [a] 2.8 [a] 3.4 [a] 0.8 [a] 1.0 [a] 0.9 [a] 0.9 [a] 0.8 [a] 0.8 [a] 1.0 [a] 1.3 [a] 1.8 [a]	[109]

(*continued on next page*)

Table 2 (*continued*)

LC-MS-MS parameters	Matrix/Sample treatment	Compounds	% Recovery	LOD	Ref.
LC = Alliance 2695 HPLC (Waters). Column = ESI (+) Sunfire C18 (4.6 mm × 150 mm, 3.5 µm, Waters); ESI (-) Luna C18 (2) 100 Å (2.0 mm × 150 mm, 3.0 µm, Phenomenex). Mobile phase : Flow rate = 0.2 mL/min; Solvent A = ACN/MeOH (60/40); Solvent B = 10 mM ammonium acetate in water. *MS = Quattro triple Quadrupole (Micromass)* Ionization mode = Negative and Positive; Capillary voltage (kV) = 4.0 (+), 3.2 (-); Extractor voltage (V) = 2.0 (+), 1.0 (-); Multiplier voltage, V = 650; Ion source temperature, °C = 125; Desolvation temperature, °C = 350; Cone gas flow (L h^{-1}) = 50; Desolvation gas flow (L h^{-1}) = 600; Nebulizer gas = nitrogen; Collision gas = Argon; Collision gas cell pressure (mbar) = 2.5×10^{-3}	Matrix = soil, sediment. Sample size = 3 grams. Sample treatment = Extraction using ASE 200 (Dionex) pressurized liquid extraction system. SPE cleaned up was performed using a combination of SAX cartridge (Symta) and Oasis HLB cartridge (Waters).	Oxytetracycline Tetracycline Ofloxacin Fenofibrate Ciprofloxacin Norfloxacin Codeine Trimethoprim Diazepam Metoprolol Propanolol Sulfamethoxazole Carbamazepine Acetaminophen Ibuprofen Clofibric acid Diclofenac	64 70 50 47 55 67 99 93 77 98 71 85 91 72 83 77 39	23.0 [b] 19.0 [b] 6.0 [b] 1.8 [b] 11.0 [b] 17.0 [b] 1.5 [b] 1.2 [b] 2.3 [b] 0.8 [b] 3.7 [b] 0.9 [b] 0.5 [b] 0.5 [b] 3.6 [b] 4.2 [b] 3.7 [b]	[67]
LC = Waters Acquity UPLC. Column 1 (Free estrogens): Acquity BEH C8 (100mm × 2.1mm, 1.7 µm); Column 2 (Conjugated estrogens): Acquity BEH C18 (50mm × 2.1mm, 1.7 µm). Mobile phase : Flow rate = 0.2 mL/min; Solvent A = water; Solvent B = ACN. *MS = Waters Quattro Ultima triple quadrupole MS (Micromass).* Ionization mode = Negative; Spray voltage (kV) = 3.5; Ion source temperature, °C = 120; Desolvation temperature, °C = 350; Cone gas flow (L h^{-1}) = 50; Desolvation gas flow (L h^{-1}) = 800; Collision gas cell pressure (mbar) = 3.50×10^{-3}	Matrix = river water, wastewater. Sample volume = 500 mL (sewage effluent), 600 mL (activated sludge), 800 mL (secondary effluent, 1000 mL (river water). Sample treatment = Oasis HLB Cartridges (200 mg/6cc, 30 µm, Waters) for solid phase extraction with subsequent clean up using Sep-Pak NH_2 cartridge (360 mg, Aminopropyl, 55-105 µm).	Estrone 17β-estradiol Estriol 17α-ethynilestradiol Estrone -3-sulphate sodium salt Estradiol-3-sulpahte sodium salt Estriol-3-sulphate sodium salt Estrone-3-glucuronide sodium salt Estradiol-3-glucuronide sodium salt Estriol-3-glucuronide sodium salt	74 75 102 63 91 101 - 100 - -	0.3 [a] 0.5 [a] 0.5 [a] 0.5 [a] 0.5 [a] 0.2 [a] 0.2 [a] 0.6 [a] 0.6 [a] 0.8 [a]	[83]
LC = Waters Alliance 2690 HPLC System Column : C18 Symmetry column (150 mm × 2.1 mm, 3.5 µm) Mobile phase: Solvent A = Water; Solvent B = ACN. *MS-TOF(Micromass)* Ionization mode = Negative; Capilary voltage (kV) = 2.60; Cone voltage, (V) = 35; Multiplier voltage, (V) = 650; Ion source temperature, °C = 140; Desolvation temperature, °C = 400; Desolvation gas flow (L h^{-1}) = 600; Nebulizing gas flow (L h^{-1}) = 100; Nebulizing, desolvation gas = nitrogen; Collision gas = argon. *MS = Quattro Premier triple quadupole MS (Micromass)* Ionization mode = Negative; Capilary voltage (kV) = 2.70; Extractor voltage, V = 4.0; Multiplier voltage, (V) = 650; Source temperature, °C = 140; Desolvation temperature, °C = 400; Desolvation gas flow (L h^{-1}) = 600; Nebulizing gas flow (L h^{-1}) = 100; Nebulizing, desolvation gas = nitrogen; Collision gas = argon.	Matrix = river sediment. Sample size = 1 gram. Sample treatment = Microwave assisted solvent extraction (MASE) followed by clean up using Strata-X-AW SPE cartridges (200 mg/6 mL, Phenomenex).	Estrone (E1) Estradiol (E2) Ethynilestradiol (EE2)	95 89 92	0.2 [b,c]/0.015 [b,d] 0.4 [b,c]/0.03 [b,d] 0.5 [b,c]/0.04 [b,d]	[110]
LC = Waters Alliance 2690 LC system (Waters). Column : Purospher STAR-RP-18e (125mm × 2mm, 5 µm) Mobile phase: Solvent A = ACN (0.1 % formic acid); Solvent B = Water (0.1% formic acid); Flow rate = 0.2 mL/min. *MS = Quattro triple quadrupole MS with orthogonal electrospray ion source (Micromass).* Ionization mode = Negative and Positive; Capilary voltage (kV) = 3.50; Ion source temperature, °C = 150; Desolvation temperature, °C = 450; Extractor voltage, V = 2 ; Nebulising, desolvation gas = nitrogen; Desolvation gas flow (L h^{-1}) = 550; Nebulizing gas flow (L h^{-1}) = 60; Collision gas = argon; Collision gas pressure (mbar) = 2.58×10^{-3}; RF lens, V = 0.4.	Matrix = river water, waste water. Sample volume = 500 mL. Sample treatment = Offline SPE using LiChrolut RP-18 (Merck).	Estriol-3-sulphate Estriol-16-glucoronide Estradiol-17- glucoronide Estrone 3-glucoronide Estradiol-3-sulphate Estriol Estrone 3-sulphate Estradiol Ethynyl estradiol Estrone Diethylstilbestrol Daidzein Resveratrol Coumestrol Genistein Norethindrone Biochanin A Levonorgestrel Progesterone	14 35 23 25 19 19 28 38 47 59 42 94 13 65 111 81 138 101 108	0.07 [a] 0.56 [a] 0.74 [a] 0.28 [a] 0.15 [a] 1.13 [a] 0.16 [a] 2.27 [a] 7.55 [a] 1.15 [a] 0.92 [a] 0.95 [a] 2.02 [a] 1.72 [a] 2.46 [a] 3.59 [a] 1.73 [a] 1.16 [a] 0.39 [a]	[111]

(*continued on next page*)

Table 2 (*continued*)

LC-MS-MS parameters	Matrix/Sample treatment	Compounds	% Recovery	LOD	Ref.
LC = Varian LC System (Varian). Column : Pursuit XRs Ultra-C18 (50mm × 2mm, 2.8 µm) Mobile phase: Solvent A = Water; Solvent B = MeOH (0.1% acetic acid + 15 mM ammonium acetate); Flow rate = 0.2 mL/min; Column oven temperature, °C = 40. *MS = Varian 320-MS TQ (Varian).* Ionization mode = Negative and Positive; Capilary voltage (kV) = 4.50(+), 3.0(-); Desolvation temperature, °C = 450; Nebulising, drying gas = nitrogen; Desolvation gas pressure (psi) = 30; Nebulizing gas pressure (psi) = 65; Collision gas = argon; Collision gas pressure (mTorr) = 2; Shield voltage, V = 600.	Matrix = wastewater (dissolved and particulate phase). Sample volume = 250 mL (dissolved phase); 0.1~0.2 g (particulate phase). Sample treatment = Dissolved phase: Solid phase extraction clean up using Sep PAK VAC C18 (500 mg, Varian); Particulate phase: Extraction with Ultrasonic Assisted Extraction (UAE).	Bisphenol-A (BPA)	82 [e]/73 [f]	5.7 [a, e]/9.8 [b, f]	[112]
		17β-Estradiol (E2)	91 [e]/81 [f]	3.3 [a, e]/5.1 [b, f]	
		Estrone (E1)	81 [e]/88 [f]	4.0 [a, e]/5.7 [b, f]	
		Estriol (E3)	79 [e]/71 [f]	3.7 [a, e]/6.9 [b, f]	
		17α -Ethynylestradiol (EE2)	79 [e]/76 [f]	2.8 [a, e]/5.0 [b, f]	
		4-Octylphenol (OP)	79 [e]/71 [f]	5.7 [a, e]/9.4 [b, f]	
		Octylphenol monoethoxylate	73 [e]/71 [f]	7.2 [a, e]/12.7 [b, f]	
		Octylphenol diethoxylate	82 [e]/69 [f]	3.7 [a, e]/6.6 [b, f]	
		Octylphenol triethoxylate	85 [e]/87 [f]	2.6 [a, e]/3.8 [b, f]	
		Octylphenol tetraethoxylate	84 [e]/84 [f]	3.9 [a, e]/5.8 [b, f]	
		4-Nonylphenol (NP)	82 [e]/67 [f]	2.7 [a, e]/5.1 [b, f]	
		Nonylphenol monoethoxylate	85 [e]/71 [f]	3.5 [a, e]/6.2 [b, f]	
		Nonylphenol diethoxylate	86 [e]/60 [f]	1.5 [a, e]/3.1 [b, f]	
		Nonylphenol triethoxylate	94 [e]/71 [f]	1.6 [a, e]/2.8 [b, f]	
		Nonylphenol tetraethoxylate	86 [e]/74 [f]	2.0 [a, e]/3.4 [b, f]	

[a] ng/L.
[b] ng/g.
[c] MDL based on TOF-MS detection.
[d] MDL based on MS-MS detection.
[e] Dissolved phase.
[f] Particle phase.

3.3. Analytical methods for aqueous and solid samples

The complexity of environmental matrices has led to the introduction of various extraction procedures. As shown in Table 2, numerous sample extraction procedures have been developed by researchers to extract pharmaceuticals, estrogenic hormones, and alkylphenol compounds from solid and semisolid matrices, such as activated sludge, soil, and sediment. Extraction protocols, such as UAE, MAE, PLE, SPME, and QuECheRS, provide a rapid and fast extraction technique compared to conventional techniques, such as Soxhlet and LLE. The optimization of these protocols is important, particularly when dealing with complex matrices, such as sediments and sludge samples, due to the potential problems that may arise from matrix interferences. Gomes et al. [79] suggested that an assessment of the potential matrix interferences in environmental solid matrices should be undertaken during method development, as the composition may vary considerably between sample types and geographic origin, and thus may affect the method of recovery due to the coextracted compounds. Other aspects that should be considered when developing a method for solid environmental matrices are: (i) the potential for the transformation of analytes during sample preparation and (ii) ion suppression phenomena, particularly when using LC-MS-MS.

3.3.1. Extraction methods

The main goal for the optimization of extraction methods is to reduce the interference to the lowest possible level and eliminate any coextracted compounds to achieve the required accuracy and sensitivity for the compounds being studied. Optimized extraction protocols will allow satisfactory recovery and a low-level of detection limit, which are very important for trace-level analysis.

Numerous studies have reported on the excellent accuracy and sensitivity for the determination of these compounds in environmental solid matrices using various extraction techniques [27,29,33]. Gineys et al. [27] developed a fast and efficient extraction method for the determination of steroid hormones in soils using a pressurized liquid extraction technique utilizing an accelerated solvent extractor (ASE) 200 from Dionex Corporation (Sunnyvale, CA, USA). The combination of elevated temperature and high pressure with small volumes of organic solvent enabled fast and efficient extraction in approximately 15 minutes per sample. This developed method achieved satisfactory recoveries of between 45% and 100% with a range of limit of detection (LOD) for all compounds between 0.09 ng/g and 2.84 ng/g. However, a drawback of this extraction method is that some compounds may degrade due to the application of high temperatures, leading to low recovery for some of the developed compounds [29].

Cerqueira et al. [58] developed a quick and simple extraction method for the determination of 21 pharmaceutical compounds in sludge samples using the QuEChERS technique, and achieved good recoveries, ranging from 50% to 93% and LOD between 0.15 ng/g and 3 ng/g. Anastassiades et al. [80] originally introduced the QuEChERS technique to extract pesticides from vegetables and fruits but application of the technique has been explored for many types of matrix as well as various types of organic pollutant. This technique is based on extraction with ACN followed by liquid-liquid partition and cleanup steps using dispersive solid-phase extraction. Nowadays, it is gaining popularity because it is quick, simple, and less time-consuming. A growing number of researchers have applied this technique over the past three years for the method development of multiclass EDCs [7,29,81]. Salvia et al. [29] optimized the QuEChERS technique for the determination of veterinary antibiotics and steroid hormones in soils and suggested that QuEChERS extraction followed by cleaning with tandem SPE using both SAX and Strata X cartridges was the best combination to obtain better recovery and minimize matrix effects. Good recoveries were obtained of between 60% and 90% and lower matrix effects (lower than –40%) were observed for most of the developed compounds. Berlioz-Barbier et al. [7] evaluated three different combinations of sorbents when optimizing the QuEChERS protocol for multiresidue emerging pollutants in sediment samples. Based on the assessment conducted, the combination of primary secondary amine (PSA) and graphitized carbon black (GCB) as a sorbent for the cleanup reduced the matrix effects for most of the compounds. Satisfactory recoveries of between 37% and 98% were also achieved for the developed compounds, with the LOD ranging from 0.5 ng/g to 20 ng/g. Due to the quick, effective, and ease of use, this technique has enabled researchers to develop multiresidue and multiclass compounds, as

Table 3
Gas Chromatography Mass Spectrometry (GCMS) parameters, sample treatment and method performances for pharmaceuticals, estrogenic hormones, and alkylphenol compounds in environmental matrices.

GC MS parameters	Matrix/sample treatment	Compounds	% Recovery	LOD	Ref.
GC = Agilent 6890 GC (Agilent Technologies, USA) equipped with Agilent PTV inlet. Column: HP-5MS capillary column (30 m × 0.25 mm, 0.25 µm); Carrier gas = helium; Flow rate = 1 mL/min. *MS =5973N Mass Spectrometer (Agilent Technologies).* Ionization mode = electron impact (EI); Inlet temperature, °C = Programmable inlet temperature (50 – 280); MS transfer line temperature, °C = 280; Source temperature, °C = 230; Quadrupole analyser temperature, °C = 150; Injection volume = 1 µL; Injection mode = splitless.	Matrix = seawater. Sample volume = 2000 mL. Sample treatment = Clean up using cyanopropyl (CN) and 2,3-dihydoxypropoxypropyl (DIOL) followed by analyte enrichment using C18 SPE (OASIS HLB, 60 µm, 6 cm3, 500mg, Waters, UK). Derivatization reagent = MTBSTFA with 1% TBDMSCI.	Clofibric acid Ibuprofen Gemfibrozil Fenoprofen Naproxen Triclosan Tofenamic acid Diclofenac 2-phenylphenol 4-tert-octylphenol 4-n-nonylphenol Bisphenol A Coprostanone 5-α-cholestanone 5-β-cholestanol Coprostanol Cholesterol	106 108 116 123 111 88 120 131 75 76 63 91 78 82 56 102 107	6.1 [a] 0.4 [a] 6.4 [a] 2.9 [a] 2.9 [a] 0.5 [a] 0.9 [a] 1.3 [a] 0.2 [a] 0.1 [a] 1.0 [a] 0.7 [a] 5.8 [a] 3.0 [a] 3.9 [a] 19.5 [a] 5.2 [a]	
LC = Agilent 6890 GC coupled to Gerstel thermodesorption system and equipped with PTV inlet (CIS-4). Column: HP-5MS capillary column (30 m × 0.25 mm, 0.25 µm); Carrier gas = helium; Flow rate = 1.2 mL/min; Injection mode = splitless. *MS = HP 5973N quadrupole MS.* Ionization mode = electron impact (EI); Inlet; temperature, °C = Programmable inlet temperature (10 – 280); Desorption temperature, °C = 275.	Matrix = river sediment. Sample volume = 0.5 g. Sample treatment = Samples were directly extracted using stir bas sorptive extraction (SBSE) technique with in situ derivatization. Derivatization reagent =Acetic acid anhydride.	Methylparaben Isopropylparaben n-propylparaben Butylparaben Benzylparaben Triclosan Methyltriclosan	100 106 96 102 95 100 98	1.06 [b] 0.51 [b] 0.74 [b] 0.08 [b] 0.37 [b] 0.18 [b] 0.16 [b]	[59]
GC = Agilent 6890N (Agilent Technologies, USA). Column : HP-5MS (30 m × 0.25 mm, 0.25 µm); Carrier gas = helium; Flow rate = 1.2 mL/min; Injection mode = pulsed splitless; Injection volume = 1 µL *MS = 5975C MSD.* Ionization mode = electron impact (EI); GC-MS interface temperature, °C = 280; Ion source temperature, °C = 230; Quadruple temperature, °C = 150.	Matrix = sludge Sample weight = 1 grams Sample treatment = Ultrasonic extraction followed by cleaned up using Supelclean Envi-carb (500 mg/6 mL, Supelco). Derivatization reagent = MTBSTFA.	Acetylsalicyclic acid Bisphenol A Carbamezapine Clofibric acid Diclofenac Estrone Gemfibrozil Ibuprofen Ketoprofen Naproxen Nonylphenol Octylphenol Paracetamol Triclosan	64 83 67 99 n.a 78 72 87 74 91 73 72 n.a 89	6.0 [b] 1.4 [b] 2.7 [b] 3.9 [b] 11.0 [b] 4.8 [b] 5.0 [b] 2.0 [b] 5.0 [b] 2.2 [b] 2.3 [b] 1.6 [b] 11.0 [b] 2.1 [b]	[34]
GC=GC-2010 (Shimadzu Corporation, Japan). Column: RTX®-PCBs fused silica capillary column (60 m × 0.25 mm, 0.25 I.D µm film thickness; Restek, Pennsylvania, USA); Carrier gas = helium; Carrier gas flow rate = 1.43 mL/min (OP, BPA); 1 mL/min (NP); Injection mode = splitless. *MS=QP 2010 Mass Spectrometer (Shimadzu Corporation, Japan).* Ionization mode = electron impact (EI), 70 eV; Ion source temperature, °C = 230 (OP, BPA), 200 (NP); Interface temperature, °C = 270 (OP, BPA); 290 (NP).	Matrix = river water. Sample volume = 1000 mL. Sample treatment = Extraction using SPE cartridge (C18-E). Derivatization reagent = MSTFA.	Octylphenol (OP) Nonylphenol (NP) Bisphenol A (BPA	72 74 94	1.1[a] 0.3[a] 1.5[a]	[14]
GC=Agilent 6890 GC (Agilent Technologies, USA) equipped with Agilent PTV inlet (G2619A). Column: DB-5MS capillary column (30 m × 0.25 mm, 0.25 µm); Carrier gas = helium. *MS=5973 Mass Spectrometer (Agilent Technologies).* Ionization mode = electron impact (EI); Inlet temperature, °C = Programmable inlet temperature (40 – 350); MS transfer line temperature, °C = 280; Source temperature, °C = 230; Injection volume = 50 µL; Injection mode = multiple injection.	Matrix = water. Sample volume = 1000 mL. Sample treatment = Liquid-liquid extraction using dichloromethane as extraction solvent. Clean -up was performed using C18- AccuBond II SPE cartridges (1000mg, 6 mL).	Estrone 17β-estradiol 17α-Ethynilestradiol	54 68 61	0.12[a] 0.10 [a] 0.11 [a]	[71]
GC=Varian GC 3400 equipped with PTV injector. Column: XTI-5 (30 m × 0.25 mm, 0.25 µm, Restek Pennsylvania, USA); Carrier gas = helium. *MS=Varian Saturn 4D Mass Spectrometer.* Ionization mode = electron impact (EI); MS transfer line temperature, °C = 280; Ion trap temperature, °C = 250; Injection volume = 5 µL; Injection mode = splitless.	Matrix = sludge, sediment. Sample size = 5 grams (sediment); 0.5 grams (sludge) Sample treatment = Sediment: Liquid-liquid extraction with methanol and acetone followed by silica gel clean up. SPE clean-up was performed using RP-C18. Sludge: Liquid-liquid extraction with methanol and acetone followed by Gel Permeation Chromatography (GPC) and silica gel clean up. Derivatization reagent = MSTFA.	Estrone 17β-estradiol Mestranol 17α-ethynilestradiol	119[e]/113[f] 83 [e]/110 [f] 113 [e]/98 [f] 113 [e]/105 [f]	2.0[b,e]/0.2[b,f] 2.0[b,e]/0.2 [b,f] 2.0[b,e]/0.4[b,f] 4.0[b,e]/0.4[b,f]	[37]

(*continued on next page*)

Table 3 (*continued*)

GC MS parameters	Matrix/sample treatment	Compounds	% Recovery	LOD	Ref.
GC=Varian 4000 GC MS system equipped with Varian CP-1079 programmable injector. Column: BPX-5 capillary (30 m × 0.25 mm, 0.25 µm, SGE); Carrier gas = helium. *MS=Varian Saturn 4D Mass Spectrometer.* Ionization mode = electron impact (EI); MS transfer line temperature, °C = 280; Ion trap temperature, °C = 210; Manifold temperature, °C = 80.	Matrix = sewage sludge. Sample size = 0.5 grams. Sample treatment = Extraction using microwave assisted using water as extractant and purification applying modified dispersive solid phase extraction followed by C18-SPE clean up (OASIS HLB, Waters). Derivatization reagent = hexamtehyldisilizane + trifluoroacetic acid and hydroxylamine-HCl in pyridine.	Ibuprofen Naproxen Ketoprofen Diclofenac	85 88 84 84	20.0[b] 15.0 [b] 19.0 [b] 22.0 [b]	[113]
GC=Hewlet Packard 5890 Series II GC. Column: DB5 MS capillary column (60 m × 0.32 mm; 0.25 µm, Supelco); Carrier gas = helium; Flow rate = 0.9 mL/min. *MS=Hewlet Packard HP 5971 MSD.* Ionization mode = electron impact (EI); Inlet temperature, °C = 280; MS transfer line temperature, °C = 280; Source temperature, °C = 180; Injection volume = 1 µL; Injection mode = splitless.	Matrix = waste water, sewage slude. Sample volume = 100 mL (waste water); not mention (sewage sludge). Sample treatment = Waste water: Sample were mixed in ultrasonic bath followed by clean up using Silica bonded C18 (Sep-Pak, 6 mL, 500 mg). Sludge : Extraction using sonication with mixture of MeOH and MilliQ water followed by clean up using C18 cartridges (Sep-Pak, 6 mL, 500 mg). Derivatization reagent = BSTFA+pyridine.	4-n-nonylphenol Nonylphenol monoethoxylate Nonylphenol diethoxylate Bisphenol A Triclosan	31[g]/55[e] 60 [g]/99 [e] 60 [g]/88 [e] 87 [g]/101 [e] 80 [g]/77 [e]	30.0[a]/40.0[b] 340.0 [a]/490.0 [b] 410.0 [a]/960.0 [b] 140.0 [a]/560.0 [b] 130.0 [a]/150.0 [b]	[114]
GC=Trace GC 200 (Thermoquest, CE Instrument). Column: ZB5 capillary column (30 m × 0.25 mm, 0.25 µm); Carrier gas = helium; Flow rate = 1.5 mL/min. *MS=Polaris Q Mass Spectrometer (Thermoquest, CE Instrument).* Ionization mode = electron impact (EI); Inlet temperature, °C = 280; MS transfer line temperature, °C = 280; Source temperature, °C = 250; Injection volume = 1 µL.	Matrix = river sediment. Sample size = 5 grams. Sample treatment = Samples were subjected for microwave assisted extraction followed by silica gel cleaned up. Derivatization reagent = BSTFA (1% TMCS) + pyridine.	4-tert-Octylphenol 4-nonylphenol Bisphenol A Estrone 17β-estradiol 17α-ethynilestradiol 16α-hydroxyestrone	84 92 86 82 96 74 87	0.5[b] 0.5 [b] 1.0 [b] 0.3 [b] 0.3 [b] 0.4 [b] 0.2 [b]	[115]
GC=Agilent 6890N GC (Agilent Technologies, USA. Column: HP-5MS capillary column (30 m × 0.25 mm, 0.25 µm); Carrier gas = helium; Carrier gas flow rate = 1.2 mL/min. *MS=5975 Mass Spectrometer (Agilent Technologies).* Ionization mode = electron impact (EI); Inlet temperature, °C = 250; MS transfer line temperature, °C = 280; Source temperature, °C = 230; Injection volume = 2 µL; Injection mode = splitless.	Matrix = soil. Sample size = 5 grams. Sample treatment = Ultrasonic solvent extraction using acetone and ethyl acetate as extraction solvent. Clean up was performed using HyperSep C18 cartridge (500 mg/6mL, Thermo Electron Corporation). Derivatization reagent = MTBSTFA.	Clofibric acid Ibuprofen 4-tert-octylphenol 4-n-nonylphenol Naproxen Triclosan Ketoprofen Diclofenac-Na Bisphenol A Estrone	64 103 64 74 111 96 89 89 104 78	0.4[b] 0.2 [b] 2.4 [b] 0.4 [b] 0.4 [b] 0.4 [b] 0.4 [b] 1.2 [b] 0.4 [b] 1.2 [b]	[116]
GC=Agilent 7890A GC (Agilent Technologies, USA). Column: HP-5MS capillary column (30 m × 0.25 mm, 0.25 µm); Carrier gas = helium; Carrier gas flow rate = 1.5 mL/min. *MS=5975 Mass Spectrometer (Agilent Technologies).* Ionization mode = electron impact (EI); Inlet temperature, °C = 280; MS transfer line temperature, °C = 280; Source temperature, °C = 230; Quadrupole temperature, °C = 150; Injection mode = splitless.	Matrix = activated sludge (liquid and solid phase). Sample volume = 400 mL (liquid phase); 1 g (solid phase). Sample treatment = Liquid phase: extraction using SPE column (Oasis HLB) followed by clean up by silica cartridge (Sep-Pak). Solid phase: pretreatment with ultrasonic liquid extraction (ULE). Extraction using SPE (Oasis HLB) followed by clan up using neutral Al_2O_3/silica gel column. Derivatization reagent = Liquid phase: pyridine and BSTF; Solid phase: pyridine and BSTFA.	Estrone 17β-estradiol Estriol 17α-ethynilestradiol 4-nonyphenol Bisphenol A	95[c]/80[d] 97[c]/71[d] 115[c]/119[d] 118[c]/91[d] 88[c]/105[d] 103[c]/83[d]	1.2[a,c]/1.5[b,d] 0.8[a,c]/1.2[b,d] 2.3[a,c]/7.1[b,d] 4.0[a,c]/10.0[b,d] 30.3[a,c]/188.7[b,d] 0.2[a,c]/1.3[b,d]	[82]

[a] ng/L.
[b] ng/g.
[c] Liquid phase.
[d] Solid phase.
[e] Sewage sludge.
[f] Sediment.
[g] Wastewater.

described by Peysson and Vulliet [62] when the QuEChERS protocol was developed to determine 136 pharmaceuticals and hormones in sewage sludge samples and by Salvia et al. [81] who developed it for 31 substances in soil samples. Two additional widely used extraction techniques for environmental solid matrices are UAE and MAE. Nie et al. [82] developed an extraction protocol based on UAE for activated sludge samples, with recoveries obtained ranging from 88.4% to 117.8%, and LOD between 0.2 ng/g and 30.3 ng/g. Matějíček [66] established an extraction technique using microwave-assisted extraction for river sediments, which performed excellently, with recoveries for all compounds of between 98.8% and 107.1%, and LOD ranging from 90 pg/g to 250 pg/g.

3.3.2. Cleanup and purification methods

Sample cleanup is an important part of method development during which further purification and enrichment of the analytes takes place. The optimization of this step is pertinent, particularly for liquid and aqueous samples for which extractions for these types of samples are not applied. Liquid samples are basically subjected directly to the cleanup process after undergoing filtration using a membrane filter or glass microfiber filter. Therefore, a rigorous sample cleanup must occur for environmental liquid and aqueous samples to produce clean extracts that are essential for instrumental analysis. The samples cleanup was dominated mostly by solid phase extraction using C18 as the cleanup sorbent. Oasis hydrophobic lipophilic balanced (HLB) cartridge from Waters (Milford, MA, USA) has been a popular choice of C18 cartridge for extraction and analyte enrichment. The use of an Oasis HLB cartridge for various environmental solid and liquid matrices has been described by Nie et al. [82], Kumar et al. [83], Vazquez-Roig et al. [67], and Al-Qaim et al. [63]. The versatility and efficiency of Oasis HLB cartridges are attributed to its hydrophobic lipophilic balance, which has made this sorbent an efficient C18 cartridge for the extraction of analytes covering a wide range of polarities and pH values. This polymeric reversed-phase sorbent also covers a wide range of acidic, basic, and neutral compounds. The Strata X series from Phenomenex (Torrance, CA, USA) is another popular choice of C18 sorbent for these types of compound. Having similar characteristics to Oasis HLB, Vazquez-Roig et al. [67] achieved more than 70% recovery using the Strata X sorbent for some pharmaceutical compounds when both types of cartridge were assessed. A summary of sample treatments and types of SPE cartridge are shown in Table 2.

3.4. Analytical methods for biota samples

Biota is considered an important compartment of the ecosystem, especially in the aquatic environment. The biodiversity of the aquatic environment is dominated largely by aquatic biota, such as phytoplankton, zooplankton, benthos, fish, and plants. The aquatic biota is exposed to various kinds of pollutants because the aquatic ecosystem acts as a sink for many of the chemicals discharged into the environment.

Different parts of the biota have been used as biological indicators for much of the environmental pollution from both organic and inorganic pollutants [84–87]. Torres et al. [88] stated that parts of the aquatic biota, particularly marine microalgae, are promising indicator species for organic pollutants because they are typically the most abundant life form in the aquatic environment and occupy the base of the food chain. Despite gaining popularity as a pollution indicator, this matrix poses a challenge for environmental chemists, especially during laboratory analysis because of the nature of this matrix. Some of the biota matrices consist of high organic and lipid content, and some have a complex structure that makes analytical determination more challenging. Huerta and Barceló [89] addressed this problem in a review of analytical methodologies for the determination of pharmaceutical compounds in biota matrices. The main challenge for analytical development of this type of matrix is how to obtain efficient extraction for all the targeted compounds, which is why few methods have been developed for multiresidue determination. Huerta and Barceló [89] stated that the critical obstacle to overcome is the complexity of this matrix, which is rich in undesirable components and low in analytes concentrations, which are usually present at the trace level. This section highlights the current applications of analytical methodologies for the determination of pharmaceuticals, estrogenic hormones, and alkylphenol compounds in biota matrices as well as the latest and potential techniques that can be applied for analytical determination.

3.4.1. Extraction methods for biota samples

Several previous studies have reported on the analytical determination of these compounds in biota matrices, such as fish, oysters, mussels, crustaceans, and clams [22,30,32,86]. Various sample preparation techniques have been used to extract these samples, whereas instrumental analysis is dominated mainly by LC-MS-MS and GC-MS. Table 4 describes the sample treatments, LC-MS-MS and GC-MS conditions for the analytical determination of pharmaceuticals, estrogenic hormones, and alkylphenol compounds in various biota matrices. As mentioned earlier, the main challenges for the analytical determination of compounds in biota matrices are the complexity of these matrices and the presence of pollutants at trace levels. These factors will make analytical determination much more demanding and good sample preparation from extraction to cleanup should be established before any monitoring study is carried out. Good and efficient sample extraction and cleanup should remove 99% of the lipids from biota extracts without destroying or removing the compounds of interest [90]. A number of sample extraction protocols have been successfully developed, such as QuEChERS, PLE, dynamic microwave-assisted extraction, SPME, and UAE for various biota samples [6,24,29,30,57]. Jakimska et al. [6] developed a PLE combined with QuEChERS technique for determination of 19 multiresidue EDCs consisting mainly of steroid hormones in fish (*Cyprinus carpio*). The accuracy of the method was satisfactory with the percentage of recovery ranging from 29.1% to 125.1%, and the LOD between 0.01 ng/g and 2.88 ng/g. Nurulnadia et al. [24] used UAE to analyze alkylphenol and steroid hormones in a benthic polychaete, *Paraprionospio* sp. The recovery of all compounds analyzed was between 82% and 104.9%, and the LOD was between 0.01 ng/g and 1.0 ng/g. Wang et al. [32] developed an extraction protocol using dynamic microwave-assisted extraction coupled with salting out liquid-liquid extraction for the determination of steroid hormones in fish tissue. Salting out liquid-liquid extraction is a classical homogeneous liquid-liquid extraction method that is very useful for sample cleanup and analyte enrichment. The extraction protocol gave excellent accuracy, with average recoveries ranging from 78.2% to 92.4%, and the LOD between 0.03 ng/g and 0.15 ng/g.

3.4.2. Cleanup and purification methods of biota samples

Similar to the method development for environmental solids and water matrices, the cleanup of biota samples is an important aspect, which is even more crucial when considering the complexity of these matrices. Various techniques have been developed and practiced for the cleanup of samples, such as GPC, SPE, and high performance liquid chromatography fractionation. GPC is a well-established method for the removal of lipids in biological samples. Application of these techniques has been reported in a number of studies [57,91]. Ronan and McHugh [85], Saravanabhavan et al. [92], and Alvarez-Muñoz et al. [93] reported on the use of SPE with C18 cartridges. Cleanup using Florisil has also been reported [94,95]. For the effective removal of interfering lipids, some researchers developed a combination of SPE extraction and cleanup for purification and analyte enrichment. Dévier et al. [30] optimized SPE extraction using a combination of both C18 (EnviChrom-P) and NH_2 (LC-NH_2 Supelclean) cartridges. The recoveries for the whole procedure ranged between 85% and 114%, with the LOD ranging from 0.07 ng/g to 0.38 ng/g. Kaklamanos et al. [96] established a cleanup protocol using an Oasis HLB C18 cartridge followed by additional cleanup with an Amino Supelclean NH_2 cartridge, which had excellent accuracy, with recoveries ranging from 78.7% to 119.4%. A combination of purification steps is also widely implemented, as it can efficiently remove any interfering lipid and organic content in biota matrices. Simon et al. [90] evaluated a three-step purification technique involving dialysis, GPC, followed by fractionation with normal phase HPLC for cleanup and fractionation of multiresidue EDCs in fish samples. The method gave satisfactory recoveries for all compounds,

Table 4
Analytical methods, concentration level and method performances for pharmaceuticals, estrogenic hormones, and alkylphenol compounds in biota matrices

Instrumentation	Study area	Matrix/Sample treatment	Compounds	Recovery, %	LOD (ng g^{-1})	Concentration, (ng g^{-1})	Ref.
GC=HP 6890 GC (Agilent Technologies) Column: HP5-MS (30 m × 0.25 mm, 0.25 µm); Carrier gas = helium; Flow rate = 1 mL/min. *MS=HP 5973 Mass Selective Detector.* Ionization mode = electron impact (EI); MS transfer line temperature, °C = 280; Source temperature, °C = 230; Quadrupole analyser temperature, °C = 150; Injection volume = 2 µL; Injection mode = splitless.	Arcachon Bay (France).	Matrix = Mussels (gland) – *Mytillus edulis trossolus.* Sample size = 1.5 g – 2.5 g. Sample treatment = Extraction using microwave assisted extraction (MAE), clean up by double SPE EnviChrom-P cartridge (PS-DVB, 500 mg) + NH_2 SPE (LC- NH_2, 500 mg). Derivatization reagent = MSTFA/ mercaptoethanol/NH_4I.	Testosterone Androstenedione Dehydroandrostenedione Dehydrotestosterone Estrone 17β-estradiol Progesterone Pregnelone	101 102 85 64 94 114 107 85	0.09 0.10 not determine not determine 0.16 0.07 0.38 0.17	< MDL < MDL < MDL < MDL < MDL < MDL 0.4 – 8.9 0.5-7.6	[30]
HP 6890 GC/MS (Agilent Technologies). Column: Rtx-5 (15 m × 0.25 mm, 0.25 µm; Restek); Carrier gas = helium; Ionization mode = electron impact (EI); Inlet temperature, °C = 300; Source temperature, °C = 280; Injection volume = 1 µL; Injection mode = splitless.	Adriatic Sea (Italy).	Matrix = Crustacean–*Nephrops norvegicus and Squilla mantis*; Fish-*Engraulis enchrascicolus, Scomber scombrus, Mullus barbatus, Merluccius merluccius and Solea vulgaris;* Sample size = 1 – 1.5 g; Sample treatment = Liquid – liquid extraction.	Octylphenol Nonylphenol Octylphenol ethxoylates	94 89 79	0.5 8.1 1.1	0.3 – 4.7 1.7 – 1285.0 0.2 – 21.1	[22]
LC=Agilent 1100 HPLC System Column: Luna C8-2 (250 mm × 4.6mm, 5 µm, Phenomenex, USA). Mobile phase: Flow rate = 0.7 mL/min; Solvent A=ACN; Solvent B=water. *MS=Agilent 1100 MSD-Trap SL (Agilent Technologies, USA).* Ionization mode=Negative and positive; Capillary voltage, V = 3500; Cone voltage, V = 4; Source temperature, °C = 350; Nebulizing and drying gas = Nitrogen; Collision gas cell pressure, psi = 50; Drying gas flow, L/min = 10.	Venice lagoon (Italy).	Matrix = Mussel – *Mytillus galloprovincialis*; Sample size = 5 g; Sample treatment = Extraction using sonication, cleaned up using activated Florisil.	Estriol Estrone 17β-estradiol Nonylphenol Bisphenol A Benzophenone Mestranol 17α-ethynylestradiol Diethylstilbestrol Nonylphenol monoethoxylate-carboxylate	56 44 52 63 40 70 51 48 72 40	5.0 1.5 1.5 - 3.0 - 4.0 3.0 - 0.2	< MDL < MDL < MDL 115.0-240.0 < MDL < MDL < MDL 7.2-38.0 < MDL < MDL	[94]
LC= Waters Acquity UPLC. Column : Acquity BEH C18 (50mm × 2.1mm, 1.7 µm); Column oven temperature, °C = 40; Mobile phase : Flow rate = 0.4 mL/min; Solvent A=MeOH; Solvent B = Water (pH 9, adjusted with ammonia). *MS=5500 QTRAP (Applied Biosystem).* Infusion = 10 µg/L using individual standard; Curtain Gas = 30V; Nitrogen collision gas (CAD) = medium; Source temperature, °C = 600; Ion spray voltage = 5000V to 3000V.	Mediterrnean sea	Matrix = fish (*Cyprinus carpio*). Sample size = 1 grams. Sample treatment = Pressurised Liquid Extraction followed by QuECheRS (Agilent Technologies) clean up.	1H-benzotriazole Caffeine Progesterone Levonorgestrel Tolyltriazole TCEP TBEP TCCP Estrone 17β-estradiol Estriol 17α-ethynilestradiol Estrone-3-sulfate Bisphenol A Triclosan Methylparaben Ethylparaben Propylparaben Benzylparaben	79 73 75 101 67 125 103 104 69 54 91 29 49 109 58 89 98 91 46	0.06 0.14 0.50 0.35 0.15 0.25 0.45 0.09 0.34 2.77 2.88 0.81 0.02 0.01 0.30 0.04 0.05 0.01 0.02	< MDL < MDL < MDL < MDL 10.18 < MDL 38.13 < MDL < MDL < MDL < MDL < MDL < MDL 223.91 1.25 1.68 < MDL < MDL < MDL	[6]
Varian GC/MS system (Saturn 3, Varian Inc., USA). Column: DB-5 (30 m × 0.32 mm, 0.25 µm); Ionization mode = electron impact (EI); GC-MS interface temperature, °C = 280; Ion trap temperature, °C = 225.	Halifax and St. John harbor, Canada.	Matrix = mussels (*Mytilus edulis*). Sample size = 5 grams. Sample treatment = Liquid-liquid extraction followed by cleaned up using C18 solid phase extraction cartridges (ENVI-18, Supelco). Derivatization reagent = BSTFA with 1% trimethylchlorosilane (TMCS).	Diethylstilbestrol Estrone 17β-estradiol 17α-ethynilestradiol	78 87 64 78	0.1 0.1 0.3 1.0	< MDL 0.30 < MDL < MDL	[92]
LC = Agilent 1200 Series. Column: Kinetex C18 (4.6 × 50 mm, 2.1 mm, 2.5 µm); Column oven temperature, °C = 30. Mobile phase = Flow rate = 0.3 mL/min; Solvent A = 0.025% tritehylamine in water; Solvent B = 0.025% triethylamine in 5:95 water/ACN. *MS=3200 Q-TRAP MS (Applied Biosystem)* Ionization mode = negative; Source temperature, °C = 550; Ion spray voltage, V= 4400; Curtain gas pressure, psi = 44.	Dublin and Galway Bay, Ireland.	Matrix = mussel tissue. Sample size = 0.5 grams. Sample treatment = Ultrasonic extraction followed by SPE cleaned up using Oasis HLB (3 mL, 60 mg, Waters).	Estrone 17β-estradiol 17α-ethynilestradiol	88 100 93	0.4 0.9 0.3	< MDL < MDL < MDL	[85]

(*continued on next page*)

Table 4 (*continued*)

Instrumentation	Study area	Matrix/Sample treatment	Compounds	Recovery, %	LOD (ng g^{-1})	Concentration, (ng g^{-1})	Ref.
LC=Agilent Series 1100 HPLC System (Palo Alto, CA, USA). Column: Zorbax Eclipse (150mm × 4.6 mm, 3.5 µm, Agilent); Column oven temperature, °C = 40. Mobile phase: Solvent A = ACN; Solvent B = Water; Flow rate = 0.8 mL/min. *MS=QTRAP MS (Applied Biosystem).* Ionization mode: Positive and negative; Injection volume = 20 µL; Curtain Gas = 30 psi; Nitrogen; collision gas (CAD) = high; Source temperature, °C = 400; Ion spray voltage = 5200V.	Bohai Sea, China.	Matrix = fish tissue. Sample size = 3.0 g. Sample treatment = Dynamic microwave assisted extraction coupled with salting out liquid-liquid extraction.	Estriol Corticosterone 17α-estradiol Estrone 17α-hydroxyprogesterone Medroxyprogesterone 19-nortestosterone Testosterone Progesterone	83 78 80 89 90 92 84 85 89	0.13 0.15 0.12 0.04 0.03 0.05 0.07 0.05 0.06	< MDL 0.57 0.39 < MDL 0.26 < MDL 0.30 0.45 < MDL	[32]
GC = Varian GC equipped with seotum programmable injector. Column: DB5-MS (30 m × 0.25 mm, 0.25 µm); Carrier gas=helium; Flow rate= 1mL/min. *MS = Saturn II Ion Trap MS.* Ionization mode = electron impact (EI); MS transfer line temperature, °C = 280; Manifold temperature, °C = 233; Emission current, µA=17; Injection volume= 1µL.	St. Lawrence River, Montreal, Canada.	Matrix=Mussels (*Elliptio complanata*) Sample size= 50 grams Sample treatment= Microwave assisted digestion followed by liquid-liquid extraction Derivatization reagent = Pentafluorobenzyl bromide (PFBBr) + hexaoxacyclooctadecane (18-crown-6).	4-n-NP 4-t-OP NP_1EO NP_2EO NP_3EO NP_4EO NP_5EO NP_6EO NP_7EO NP_8EO NP_9EO $NP_{10}EO$ $NP_{11}EO$ $NP_{12}EO$ $NP_{13}EO$ $NP_{14}EO$ $NP_{15}EO$ $NP_{16}EO$ NP_1EC OP_1EC	31 26 63 63 24 64 70 91 87 64 81 38 24 50 62 111 59 61 45 53	3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0 3.0	< MDL < MDL < MDL < MDL-2566.0 ND ND 467.0-2896.0 1440.0-9036.0 224.0-2823.0 4061.0-18923.0 < MDL < MDL-641.0 < MDL < MDL < MDL < MDL-1210.0 < MDL-1411.0 < MDL < MDL < MDL	[107]
LC = Waters Acquity UPLC. Column: Acquity HSS T3 (50 mm × 2.1 mm, 1.8 µm) for positive mode; Acquity BEH C18 (50 mm × 2.1 mm, 1.7 µm) for negative mode. Mobile phase = Positive mode = Flow rate: 0.5 mL/min; Solvent A: MeOH; Solvent B: 10mM formic acid/ammonium formate (pH 3.2). Negative mode = Flow rate: 0.6 mL/min; Solvent A: ACN; Solvent B: 5mM ammonium acetate/ammonia (pH=8). Injection volume = 5 µL. *MS = 5500 QTRAP MS (Applied Biosystem)* Positive mode = Curtain gas, psi: 30; Nitrogen collision gas: Medium; Source temperature, °C: 650; Ion spray voltage, V: 5500; Ion sources gas (GS1, GS2), psi: 50, 60). Negative mode = Curtain gas, psi: 30; Nitrogen collision gas: Medium; Source temperature, °C : 650; Ion spray voltage, V : 3500; Ion sources gas (GS1, GS2), psi : 60, 70).	Mediterranean Rivers.	Matrix = fish (homogenate). Sample size = 1 grams. Sample treatment = Pressurized liquid extraction followed by purification using GPC.	Atenolol Carazolol Carbamazepine Citalopram Clopidrogel Codeine Diazepam Diclofenac 10,11 epoxyCBZ Hydrochlorothiazide 2-HydroxyCBZ Levamisol Lorazepam Metropolol Nadolol Propanolol Salbutamol Sertraline Sotalol Venflaxine	47 85 75 59 51 50 89 64 45 67 79 48 42 64 47 74 88 48 126 38	0.10 0.03 0.01 0.05 0.08 0.06 0.08 0.19 0.11 0.17 0.08 0.02 0.42 0.18 0.09 0.18 0.18 0.07 0.16 0.11	< MDL 3.8 17.9 0.8 < MDL < MDL < MDL 8.8 < MDL < MDL < MDL < MDL < MDL < MDL < MDL 4.2 2.6 < MDL < MDL 0.6	[57]
GC = Agilent 7890 (Agilent Technologies, USA). Column: DB5-MS (30 m × 0.25mm, 0.25µm); Carrier gas=helium; Flow rate= 1mL/min; Injector temperature, °C = 280. *MS = Agilent 5975C (Agilent Technologies, USA).* Ionization mode = electron impact (EI); MS interface temperature, °C = 280; Ion source temperature, °C = 233; Injection volume= 1µL; Injection mode = spitless.	Yundang Lagoon, Xiamen, China.	Matrix = short-necked clam (*Ruditapes philippinarum*). Sample size = 1 grams. Sample treatment = Samples were extracted using pressurized liquid extraction followed by purification on GPC column. Derivatization reagent = MSTFA	Octylphenol Nonylphenol Bisphenol A Estrone 17β-estradiol Diethylstilbestrol 17α-ethynylestradiol	70 121 67 74 70 85 64	1.50 1.21 0.50 2.40 2.50 1.00 2.20	271.6 2724.6 181.3 3.1 3.6 11.4 3.4	[86]

which averaged from 35% to 106%. Wenzel et al. [12] developed double cleanup and purification steps using GPC followed by SPE for the analysis of alkylphenol compounds in bream and mussel samples. This method gave excellent recoveries for all compounds, which averaged from 76% to 138%, and the LOD was between 0.2 ng/g and 2.0 ng/g. Tanoue et al. [91] developed triple cleanup steps using a combination of silica gel chromatography and GPC, followed by SPE (Oasis HLB) for the determination of 17 pharmaceutical compounds in biological tissue. Satisfactory accuracy was obtained for the method with percentage recoveries ranging from 48% to 88%.

4. Bioanalytical techniques

Bioanalytical techniques are widely used for environmental applications. Biosensors or bioassays can provide complementary information to the chemical analysis concerning the presence of contaminants in the complex environmental matrices. These analytical devices are able to provide fast and reliable results and are designed mostly for the screening of samples by both regulatory authorities and industry [97]. The regulatory authorities can save on costs when using biosensor devices by screening the samples first before submitting any positive result for further confirmatory chemical analysis. The advantages of the biosensor method are that minimum sample preparation is required, it is simple and user-friendly, direct analysis can be conducted in the field, it requires a small volume of the sample, there is less organic solvent consumption, and it is cost effective. The most common types of biosensor for environmental applications are optical and electrochemical-based, in which the biorecognition elements are usually antibodies, enzymes, receptors, nucleic acids, or whole cells.

The application of this technique for the detection of endocrine disrupting pollutants, particularly for phenols and estrogenic hormone groups in environmental samples, has been reported by a number of researchers [41,98–104]. EDC pollutants, such as bisphenol A, are widely developed compounds, which can be determined using the biosensor approach. Due to bisphenol A's widespread presence in environmental ecosystems, a fast and reliable technique is needed for immediate detection, especially in water matrices. Portaccio et al. [98] developed amperometric biosensor with improved sensitivity and lower detection limit using a thionine-modified carbon paste electrode for the determination of catechol and bisphenol A in water samples. Wu et al. [99] developed a nanographene-based tyrosinase biosensor for the rapid detection of bisphenol A in water, and the performance of the newly developed biosensor was compared systematically with a multiwall carbon nanotube (MWCNT) modified tyrosinase biosensor. Nanographene-based tyrosinase biosensors have significant advantages over multiwall nanotube (MWNT)-based tyrosinase biosensors in terms of response, repeatability, background current, and limit of detection. Zehani et al. [43] developed a simple and highly sensitive electrochemical biosensor for the detection of bisphenol A (BPA) in wastewater by immobilizing tyrosinase onto a diazonium-functionalized boron doped diamond electrode (BDD) modified with multiwalled carbon nanotubes (MWCNTs). The developed electrochemical biosensor had very good reproducibility, selectivity, and stability with a detection limit of 10^{-11} M, which is lower compared to others reported in the literature. Some techniques for detecting estrogenic hormone compounds were developed based on the biosensor approach, as reported by Tschmelak et al. [100], Tschmelak et al. [101], and Tan and Wei [102],. Tschmelak et al. [100,101] developed a biosensor technique for detecting estrone and progesterone, whereas Tan and Wei [102] developed a biosensor for the detection of 17β-estradiol in water samples. Yildrim et al. [103] developed a reusable evanescent wave aptamer-based biosensor for rapid, sensitive, and highly selective detection of 17β-estradiol in wastewater samples. A detection limit of 0.6 ng/mL was achieved for the developed biosensor, and it was used for on-site real time monitoring of 17β-estradiol in wastewater effluents and waterbodies.

Although this technique offers various advantages, it also has drawbacks, as it can be used only for single analyte determination and low biological material stability [97]. Few researchers have reported on the development of biosensors for environmental solids and biota matrices, such as sediment or fish samples, for the detection of pharmaceuticals, estrogenic hormones, and alkylphenol compounds. Many papers reported on the development of bioanalytical devices for application in aqueous environmental samples, such as wastewater, river water, and effluent water [38,102–104]. Therefore, the use of the bioanalytical approach is still limited to certain environmental matrices, and much more effort is required to explore more complex environmental samples, such as sediment and biota matrices.

5. Current trends and future perspective

The development of analytical techniques for EDC pollutants in environmental matrices has been the main challenge for environmental chemists. Due to the complexity of these matrices, considerable attention has been given to sample preparation and detection techniques. Exhaustive extraction and cleanup provide a cleaner extract without compromising the analyte of interest and a selective and sensitive instrument that is capable of analyzing low-levels of compounds are the determining factors for successful method development. A few parameters that can improve analyte detection and compound separation that should be considered during method development are described in Table 5. After a thorough review of past and current literature on the analytical methods for the determination of pharmaceuticals, estrogenic hormones, and alkyphenol compounds in environmental matrices, some prominent trends were observed.

First, an increasing number of studies reported the use of LC-MS-MS as the detection system for analyses. Based on the available and latest literature (Fig. 2), the compounds detected with LC-MS-MS system are far greater in number compared to those detected using GC-MS. This trend is contributed to largely by the advancement in the triple quadrupole technique of the LC-MS-MS system, which can provide more selectivity, specificity, and sensitivity for the developed compounds, which allows for quantification at concentrations of sub-ppb and sub-ppt. Second, an increasing number of researchers reported on the development of multiresidue and multiclass analytical determination in a single analytical run was

Table 5
Important parameters for consideration during method development

Parameter	Function	Notes
Mobile phase	Separation of compound in HPLC DAD/FLD, LC-TOF- MS and LC-MS-MS.	Selection of suitable mobile phase composition will help to improve peak separation of developed compounds.
Chemical additives and buffer	Improve ionization in LC-MS-MS and LC-TOF-MS.	Addition of certain amount of chemical additives such as ammonium hydroxide (NH_4OH), ammonium fluoride ((NH_4F), formic acid or buffer such as ammonium formate will help to favour ionization of compounds in mass spectrometry.
Chromatographic column	Peak separation in HPLC DAD/FLD, LC-MS-MS, LC TOF-MS and GC-MS.	Selection of suitable chromatographic column will provide good peak shape and fast compounds elution.
Derivatization reagent	Improve detection and maximize resolution efficiency	Selection of appropriate chemical derivative such as BSTFA or MSTFA or combination of derivatization chemical (e.g pyridine) will help for the enhancement of analyte detection and maximizing peak separation and resolution in GC MS.
Clean up sorbent	Elimination/reduction of matrix interferences.	Selection of sorbent material such polymeric C18 will help to reduce and eliminate matrix interferences in order to achieve the lowest possible limit of detection.

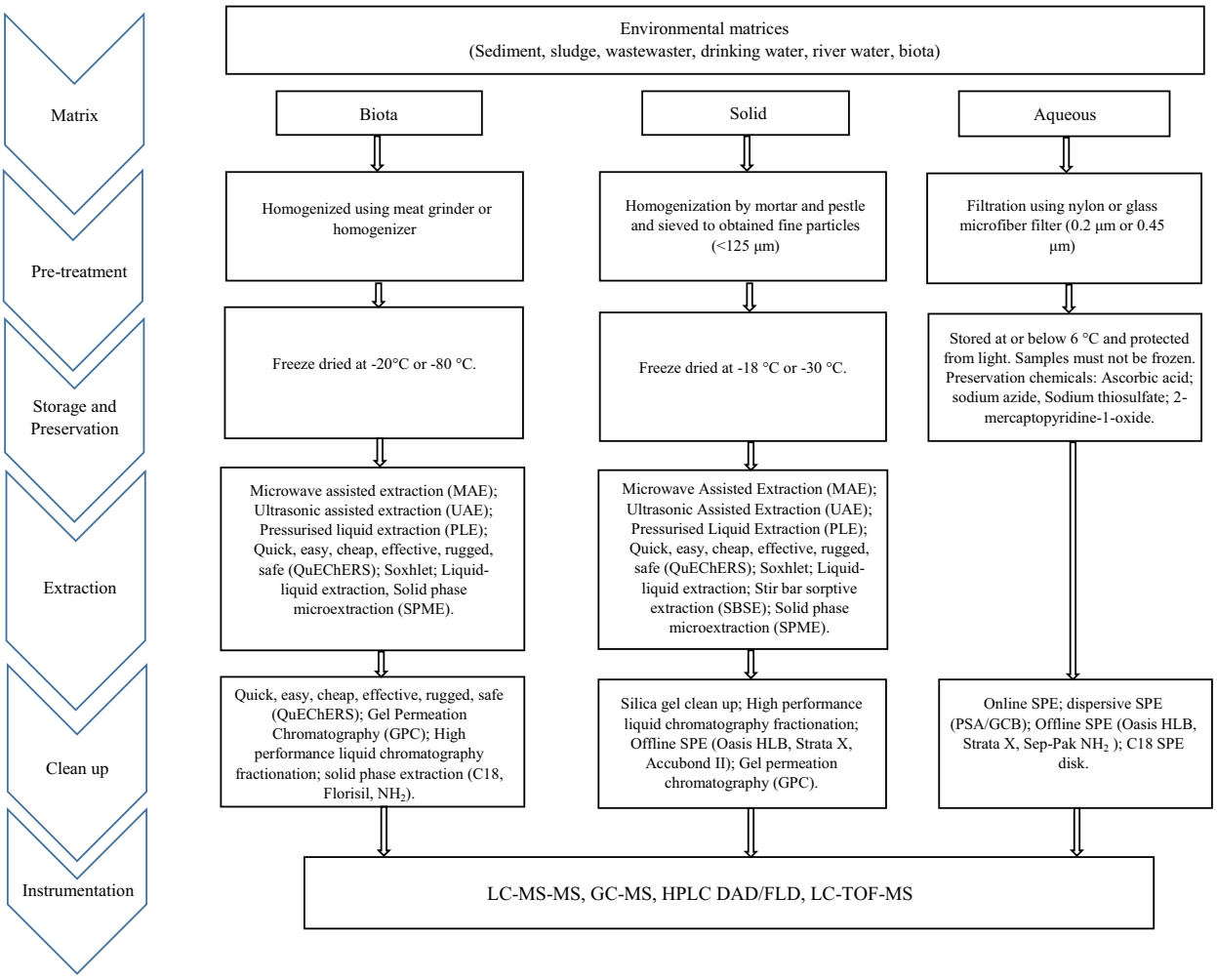

Fig. 3. Overview of analytical strategies for determination of pharmaceuticals, estrogenic hormones and alkylphenol compounds in environmental matrices.

observed, as described by Alvarez-Muñoz et al. [93] and Berlioz-Barbier et al. [105]. These trends are partly due to the innovation in sample extraction and cleanup techniques. The QuEChERS technique, for example, which was developed originally for the determination of pesticide residue in food matrices, has been explored extensively for method development for environmental and biological matrices. Third, an increasing trend was seen in the application of automated and miniaturized sample extraction, which can provide a cleaner extract while using less solvent. PLE, also known as accelerated solvent extraction, and MAE, are widely used automated extraction techniques for solid and biological matrices. Both techniques offer automated operation, high sample throughput, and shorter analysis time, which are important for laboratories that carry out monitoring work. Based on the literature published over the past 15 years, analytical strategies that can be applied to the determination of pharmaceuticals, estrogenic hormones, and alkylphenol compounds are summarized in Fig. 3.

LC-MS-MS operating in multiple reaction monitoring (MRM) mode is well known for its ability to offer selective and sensitive detection of targeted compounds in complex environmental matrices. However, the capability of this technique to screen and identify unknown compounds is relatively low. A significant advancement in the field of analytical instrumentation of note is that researchers have begun to explore full scan accurate mass detection systems, such as LC-TOF-MS for determination of EDCs in environmental matrices [61,62]. The advantage of LC operating at full scan accurate mass is that the analysis can be carried out for an unlimited number of analytes simultaneously. In addition, LC-TOF-MS can also screen for unknown compounds in the complex environmental matrices [106]. However, few published studies report on the application of LC-TOF-MS for the analysis of pharmaceuticals, estrogenic hormones, and alkylphenol compounds. Researchers generally opt for LC-MS-MS, as it provides more sensitivity, giving a lower detection limit compared to LC-TOF-MS. It is believed that, with the comparative advantages of LC-TOF-MS, a combination of both detection systems will provide more accurate quantification, which will be useful for the analysis of complex environmental matrices.

Although it has some limitations, the bioanalytical technique is one analytical approach that offers fast and rapid screening of EDCs in environmental samples. It is gaining popularity because it is easy to use in the field and does not require a high-end detection system. This method can be regarded as a complementary assay to confirmatory chemical analysis. Table 6 shows the SWOT analysis for the comparison of the instrumental and bioanalytical techniques for environmental analysis. The current application of bioanalytical devices is limited to certain environmental matrices. With the introduction of nanotechnology-based material to the development of bioanalytical devices, it is expected that more EDCs will be able to be detected using bioanalytical methods.

Table 6
SWOT analysis for analytical technique comparing both instrumentation and bioanalytical based detection

Analytical technique	Strength	Weakness	Opportunities	Threat
Instrumentation (LC-MS-MS, GC-MS, LC-TOF MS)	Simultaneous determination of multiclass compounds in a single analysis. Accurate quantitation and sensitive determination of compounds in complex environmental matrices.	High capital cost. Required experience and trained analyst to perform the analysis.	Continuous evolution and innovation of mass analyzer technologies will help to achieve lower instrumental detection limit. Introduction of highly accurate mass analyzer such Orbitrap system for environmental application will broaden the scope of environmental research.	Instrumentation breakdown may cause a delay in sample analysis. Running the instrument may require high cost for maintenance in order to keep the instrument in optimum condition.
Bioanalytical (Biosensor, bioassay)	Fast and rapid assay that can be a useful tool for *in situ* and field measurement. No need for tedious and time consuming sample preparation.	Single analyte determination. Some biosensor application may not achieved required sensitivity especially in complex environmental matrices such as biota samples.	Recent progress on nano- based material such as graphene will help to the advancement of detection capabilities of the developed biosensor. Development of biosensor to cover wide range of compounds will help the regulatory authorities to improve their enforcement capabilities.	Results of analysis may not be acceptable for a law proceeding as it will regarded as for screening purposes only. Variation of analytical result may occurred when comparing with chemical analysis.

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