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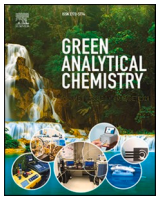

Eutectic solvent mixtures in environmental contaminants analysis: A review on current trends and future perspectives

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ABSTRACT

This review provides an overview of recent advancements in applying eutectic solvents (ES) to extract and quantify a wide range of environmental contaminants, including pharmaceuticals, personal care products, plasticizers, metals, and emerging pollutants. The unique physicochemical properties of ES, such as low volatility, thermal stability, and tunable solvation capabilities, align with green analytical chemistry principles, making them attractive alternatives to conventional organic solvents. In particular, ES-based microextraction techniques have emerged as promising strategies to reduce hazardous solvent consumption and minimize waste. Despite these advantages, specific challenges persist, including insufficient toxicity and biodegradability data, incomplete understanding of their long-term environmental fate, and difficulties in meeting regulatory requirements when using ES as extraction media. By evaluating current practices and pinpointing areas that require further investigation, this review aims to provide a comprehensive overview of the state-of-the-art, guiding future research toward more informed applications of ES in environmental contaminant analysis and fostering the adoption of sustainable microextraction approaches.

1. Introduction

Contaminant analysis is a multidisciplinary field focused on identifying and quantifying unwanted substances such as pollutants, toxins, and chemicals in various matrices like air, water, soil, food, and consumer products [1,2]. These substances may harm human health and the environment, making their detection and monitoring essential. Regulatory agencies, researchers, and industries rely on contaminant analysis to make informed decisions that protect public health and ecological systems.

The continuous introduction of new chemicals and materials presents a substantial challenge in identifying and analyzing emerging contaminants, which may not be covered by existing regulatory frameworks [3]. For instance, the United States (US) Environmental Protection Agency (EPA) tracks approximately 80,000 chemicals in its Substance Registry Services [4,5]. This database is continuously updated to evaluate new potential contaminants. In 2022, the EPA published the fifth Contaminant Candidate List (CCL 5), including 66 individual chemicals, three chemical groups, per- and polyfluoroalkyl substances (PFAS), cyanotoxins, and disinfection byproducts, and 12 microbial contaminants [6]. The CCL 5 serves as a foundation for identifying contaminants that may require future regulation, particularly those posing risks to human health. Comprehensive overviews of global legislation and policies on emerging contaminants are available [7–9].

In environmental contaminant analysis, significant challenges arise from complex sample matrices and the ultra-trace levels at which contaminants are present. While advanced analytical instruments offer high sensitivity and accessibility, the sample preparation step remains critical for accurate detection and quantification [10]. Efficient sample preparation methods are essential to isolate and concentrate analytes, reduce matrix interferences, and enhance the sensitivity and selectivity of measurements. However, these protocols can account for over 75 % of the total analysis time due to their complexity [11]. Additionally, traditional sample preparation techniques, such as liquid-liquid extraction (LLE), solid-liquid extraction (SLE), and solid-phase extraction (SPE), often rely on significant volumes of organic solvents, making this

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step the most environmentally impactful in the analytical process [12].

Global consumption of organic solvents is projected to reach 32.7 million metric tons by 2026 [13]. Although analytical laboratories contribute only a small fraction, the environmental impact is considerable and demands attention. International policies drive a shift towards sustainable alternatives with minimal environmental impact [12]. The European Green Deal, through its Zero Pollution Action Plan and Sustainable Chemicals Strategy, promotes reductions in volatile organic compounds (VOCs) and supports the use of sustainable chemicals, influencing laboratories to adopt greener solvent options [14]. Similarly, the EU's Registration, Evaluation, Authorization, and Restriction of Chemicals regulation requires companies to register chemicals and restricts hazardous solvents, steering laboratories toward safer alternatives [15]. The Stockholm Convention on Persistent Organic Pollutants limits chemicals that persist in the environment, encouraging labs to avoid hazardous solvents and adopt globally recognized safety standards [16]. Collectively, these frameworks support the adoption of alternative solvents in laboratory practices, promoting environmentally friendly and safer operations.

In alignment with these global initiatives, the principles of green chemistry have been embraced in analytical method development [17]. Gałuszka *et al.* (2013) published the 12 principles of green analytical chemistry (GAC), providing guidelines for sustainable practices in analytical chemistry [18]. A decade later, López-Lorente *et al.* (2022) introduced the 10 principles of green sample preparation, further advancing environmentally friendly procedures [19]. Adhering to these principles is crucial for enhancing operator safety and reducing the environmental footprint of analytical processes.

A central theme in green chemistry is the substitution of traditional organic solvents [20–25]. Selecting appropriate solvents is complex, involving compromises dictated by specific application requirements [26]. The trend towards environmentally sustainable alternative solvents in analytical chemistry has evolved notably over the years [27]. Initial enthusiasm for ionic liquids (IL) was tempered by concerns over their toxicity, limited biodegradability, and complex synthesis processes that often yield <100 % [28].

These limitations have shifted scientific attention to eutectic solvents (ES), an emerging class of solvents that offer a more sustainable profile. ES overcome many environmental concerns posed by IL and provide a simpler, cost-effective synthesis aligning with green chemistry principles. Typically composed of natural or non-toxic components like choline chloride (ChCl), sugars, and amino acids, ES have been reported to be less toxic and safer for humans and the environment [29–33]. Their non-volatile nature minimizes exposure risks for laboratory personnel and reduces environmental burdens associated with solvent disposal [34]. Moreover, some ES are biodegradable, breaking down readily in the environment and reducing the risk of long-term pollution [30,32,33].

The term ES (originally introduced as "deep eutectic solvent") was first used by Abbott *et al.* to describe ChCl-urea mixtures exhibiting significantly lower freezing points than their individual components, enabling their use at room temperature [35]. Since then, numerous studies have demonstrated the potential of ES as an extraction media in various applications [34,36,37].

This review aims to provide a comprehensive overview of ES applications in environmental contaminant analysis, focusing on diverse classes of pollutants. By examining ES-based methodologies across a broad spectrum of contaminants, including active pharmaceutical compounds and personal care products ingredients (e.g., antibiotics, estrogens, antidiabetics, parabens), plasticizers like bisphenol-A and phthalates, metals and metalloids, polycyclic aromatic hydrocarbons, and phenols, we highlight the innovative approaches and advancements in this field. Additionally, we explore ES's potential in addressing emerging contaminants such as PFAS and flame retardants. Through this detailed analysis, we aim to illustrate the versatility and limitations of ES in advancing sustainable analytical practices for contaminant monitoring. This review synthesizes current knowledge and identifies gaps and future directions.

2. Theoretical basis of eutectic mixtures

Eutectic mixtures are homogeneous combinations of two or more substances with lower melting points than any of their components. This phenomenon, known as eutectic melting, occurs when substances are mixed in specific proportions, resulting in a mixture that melts at a lower temperature than its pure constituents [38].

ES represent a unique class of eutectic mixtures formed by combining hydrogen bond donors (HBD) and hydrogen bond acceptors (HBA) [36,37]. Described by Abbott *et al.* in 2003, ES typically consist of readily available substances such as metal halides, quaternary ammonium salts, urea, organic acids, or sugars [35,36]. These substances act as either HBD or HBA, facilitating the formation of ES through hydrogen bonding interactions. Despite being described and used for almost 20 years, the first strict definition of ES was provided by Martins *et al.* in 2019, defining them as "a mixture of pure compounds for which the eutectic point temperature is below that of an ideal liquid mixture, presenting significant negative deviation from ideality" [39]. Many researchers have preferred this definition since it clearly sets boundaries between an ideal eutectic and a "deep" eutectic solvent (DES) from a thermodynamic viewpoint [40–42]. For a eutectic mixture to be defined "deep", the solid – liquid phase diagram should be provided to evaluate the deviation from ideality (Fig. 1). Otherwise, the term "eutectic solvent"

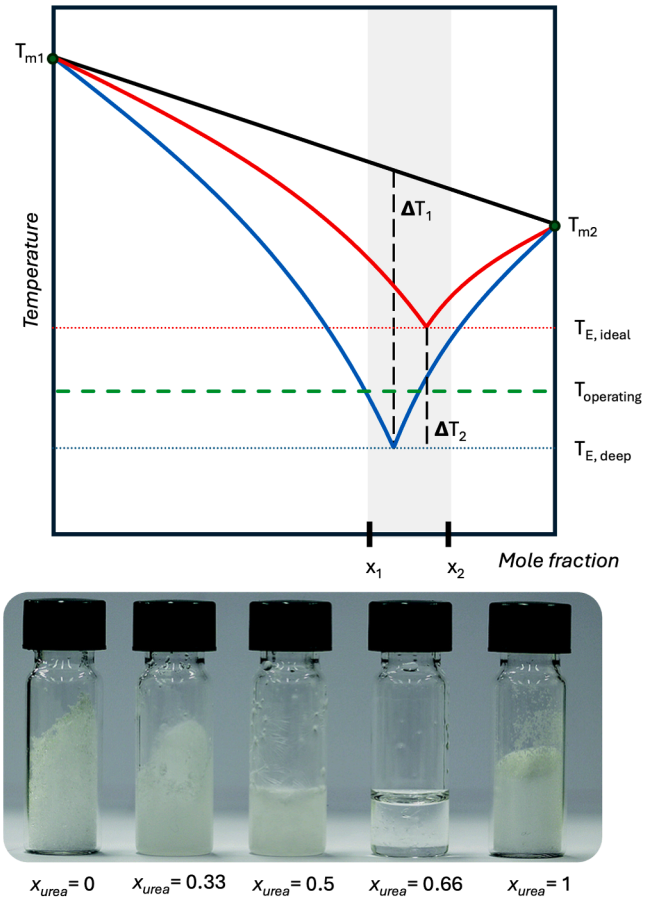

Fig. 1. In the upper part the solid-liquid phase diagram of an eutectic mixture (red line) compared to a deep eutectic mixture (blue line). Modified and reprinted with the permission of Martins *et al.*, 2019 [39]. In the lower part, the appearance of a ChCl - urea mixtures at different mole fractions of urea, from left to right: 0, 0.33, 0.5, 0.66, and 1. Modified and reprinted with the permission of Kollau *et al.*, 2018 [43].

should be preferred [39,41]. Despite this definition, no universally accepted quantitative threshold strictly defines how much a mixture's melting point must deviate from the ideal eutectic prediction to be termed "deep eutectic". To avoid overgeneralization and misclassification, particularly when the complete characterization of the eutectic mixture is not available (e.g., no solid-liquid phase diagram), the term ES will be used as a general term to address all eutectic mixtures that are liquid at room temperature and have been used for the applications discussed [39,41].

From an analytical chemistry perspective, the lower melting point and liquid stability at room temperature make ES particularly suitable for sample extraction and preparation applications.

Depending on the specific HBA and HBD used, ES can exhibit varied viscosity, polarity, and solvation capabilities, making them highly versatile for diverse applications.

The most common classification system divides ES into five primary types.

Type I ES are formed by combining a quaternary ammonium salt, such as ChCl, the HBD, with a metal halide like zinc chloride ($ZnCl_2$), the HBA. These mixtures exhibit eutectic behavior and are particularly useful in electrochemistry and metal processing [44].

Type II ES extend the concept of Type I by incorporating a metal halide hydrate, such as chromium chloride hexahydrate ($CrCl_3{\cdot}6H_2O$). These solvents have been tested for catalysis and separation processes [45,46].

Type III ES are the most common and are formed by combining a quaternary ammonium salt, such as ChCl, with an HBD like urea, glycerol, or ethylene glycol. These ES are widely used due to their ease of preparation and versatility [36,44]. A notable subclass of Type III includes hydrophobic ES, typically formed by combining quaternary ammonium or phosphonium salts with long carbon chains and hydrophobic HBD, such as long-chain fatty acids or alcohols [47,48].

Type IV ES replace the quaternary ammonium salt with a metal chloride hydrate, such as ferric chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), as the HBA. These ES are used in catalytic processes and as alternative solvents for various reactions [49–51].

Type V ES differ from the previous types by comprising entirely non-ionic components. They combine a non-ionic HBD, such as phenol or fatty acids, with a non-ionic HBA, such as sugars or aliphatic hydroxyls [52–54].

While ES are often presented as greener solvents due to their high thermal stability, low volatility, and low vapor pressures, they are also considered less expensive, potentially more biodegradable, and easier to prepare than IL. However, recent research emphasizes caution in generalizing these properties across all ES, as some may exhibit toxicity or environmental persistence similar to traditional solvents [40]. This highlights the importance of thoroughly characterizing each ES for its environmental impact before widespread application.

Given the vast number of possible ES combinations (estimated to be up to one million) not all have been fully characterized. The toxicity and biodegradability of many ES remain under investigation, with limited publications addressing these aspects [55]. Therefore, evaluating each ES individually and using precise terminology is crucial to avoid overgeneralization and misclassification.

3. Eutectic solvents in environmental analysis

Hydrophobic ES were first reported in 2015 by Van Osch *et al.*, who presented ES composed of a quaternary ammonium salt with a long alkyl chain as the HBA and decanoic acid as the HBD [47]. These ionic hydrophobic ES demonstrated the ability to extract acetic, propionic, and butyric acids from water samples. Despite some drawbacks, such as minimal leaching of the quaternary ammonium salt into the aqueous phase and high viscosity, they showed superior extraction efficiency (in the range 30–92 %) compared to the conventional method using trioctylamine (19–74 %). In the same year, only a few months later, Ribeiro *et al.* characterized different non-ionic hydrophobic ES based on menthol as the HBA, being the first to refer to this class of non-ionic hydrophobic eutectic mixtures as solvents [56]. The solvents presented were eutectic menthol mixtures and various natural carboxylic acids such as acetic, pyruvic, lactic, and lauric acid. Their characterization showed lower viscosities (5–100 mPa*s) than ionic hydrophobic ES (173 – 783 mPa*s).

Building on this foundation, the application of hydrophobic ES in water sample analysis has been extensively studied, particularly in conjunction with LLE and its miniaturized variants, such as liquid-liquid microextraction (LLME) and dispersive liquid-liquid microextraction (DLLME) [57,58]. Hydrophobic ES have emerged as good candidates for this purpose due to their simple preparation and high extraction efficiency. Moreover, the physicochemical characteristics of hydrophobic ES are highly tunable by varying the type of HBA, HBD, and their molar ratios. However, as their application expands, an equally important consideration is their environmental impact. The toxicity and biodegradability of ES used in these and future studies are critical considerations. Several studies have examined these aspects. For example, the toxicity and biodegradability of cholinium-based ES have been evaluated [59,60]. It was observed that Type I and Type II cholinium-based ES exhibit higher toxicity toward *Cyprinus carpio* (common carp) compared to Type III cholinium-based ES. However, all tested cholinium-based ES were classified as readily biodegradable based on the results of a closed bottle test [59]. For a more detailed discussion on this topic, readers are encouraged to consult the relevant literature [61–64].

The following sections provide an overview of recent trends in environmental water analysis using ES for the extraction of active pharmaceutical ingredients, metals, plasticizers, polycyclic aromatic hydrocarbons (PAHs), and emerging contaminants. The studies discussed were selected based on their novelty, impact on the field, and analytical performance comparable (or at least promising to become comparable) to traditional methods, meaning their possible use to meet regulatory requirements. Discussed methods are summarized in Table 1. When a comparison with the conventional method was performed in the paper, the performance parameters of the latter were also reported in the Table, but just considering the recovery and precision. LOD was not considered since it is highly dependent on the analytical instrument used, so not relevant for the purpose of discussion of this review.

3.1. Active pharmaceutical compounds and personal care product ingredients

Pharmaceuticals in the environment have emerged as a significant concern due to their ubiquitous presence and potential impacts on aquatic ecosystems and human health [96]. These substances enter the environment through various pathways, including pharmaceutical manufacturing, improper disposal of unused or expired medications, and human and animal excretion. Given their biological activity, even low concentrations (ng/L to μg/L) of pharmaceuticals in water bodies can affect aquatic organisms, leading to ecological consequences and posing risks to human health through the water supply [97].

Like active pharmaceuticals, personal care product ingredients (PCPI) embody a broad class of chemicals utilized in daily life, ranging from cosmetics to hygiene products. The environmental footprint of PCPI, characterized by their continuous discharge into water bodies, underscores the necessity for efficient detection and quantification methods.

In this context, environmental analysis is crucial in monitoring and understanding the distribution, fate, and effects of active pharmaceutical and PCPI residues [98].

3.1.1. Antibiotics

Among pharmaceuticals, antibiotics are considered pseudo-persisting contaminants, and their presence in the environment increases the spread of antibiotic-resistance genes [99,100].

Table 1
Table schematically reporting the analytical methodologies present in the main text.

Sample	Analyte(s)	ES composition (molar ratio)§	Sample preparation technique	Analytical technique	ES-based method			Comparison methods		References
					LOD (ng/L)	Recovery (%)	Precision (RSD %)	Recovery (%)	Precision (RSD %)	
Tap water, surface water, rainwater, lake water, sewage treatment plant outlet water	Triclosan	Triclosan : 2,2,4-trimethyl-1,3-pentanediol	LLME[1]	HPLC-UV	500	76 – 115	< 7	–	–	[65]
Tap water	Ciprofloxacin	ChCl : Malonic acid (1:1)	LLME[1]	Custom-made electrochemical cell	830	71 – 93	–	89–108	0.1–19	[66]
Tap water, pond water	Ofloxacin, Norfloxacin, Ciprofloxacin, Enrofloxacin	Thymol : Heptanoic acid (2:1)	LLME[1]	HPLC-UV	3000	84 – 114	< 8	–	–	[67]
Tap water, feed water, wastewater	Levofloxacin, Ciprofloxacin	Thymol : hexanoic acid (2:1)	LLME[1]	HPLC-UV	18,000–27,000	95 – 111	3.6 – 4.2	97–114	≤ 8.9	[68]
River water	Ofloxacin, Sparfloxacin	ChCl : Ethylene Glycol (2:1) Used as carrier solvent onto GO@Fe_3O_4 composite	LPME[2] based on GO@Fe_3O_4 -DES FF [3]	HPLC-UV	5.8 – 6.3	70 – 122	–	58–108	–	[69]
Tap water, agricultural well water, river water, wastewater	E1, E2, EE2, E3°	Menthol : Camphor-10-sulfonic acid (5:1)	LLME[1]	GC-EI-MS	1–0.2	91 – 109	< 5.7	–	0.92–14	[70]
Tap water, river water	Bisphenol A, Ethynylestradiol, Diethylstilbestrol, Benzophenone, 4-nonylphenol	Octanoic Acid : Nonanoic Acid : Dodecanoic Acid (1:1:1)	DLLME[4]	HPLC-PDA	960 – 230	90 – 104	< 8	–	–	[71]
Wastewater	E1, E2, EE2, E3°	Methol : Octanoic acid 1:1	LLE[5]	HPLC-MS/MS	–	98 - 99	–	–	–	[72]
Wastewater	E1, E2, EE2, E3°	Citric acid monohydrate : 1-octyl-3-methylimidazolium chloride (1:1)	SPE- DLLME[6]	GC–MS	0.05–0.01	90 – 108	1.5 – 3.8	–	0.4–15	[73]
Westwater	Empagliflozin, Metformin, Sitagliptin, Gliclazide, Repaglinide	Thymol : Menthol (1:1) Mixed with curcumin and immobilized on polyvinyl alcohol electro spoon nanofibers to create a custom made sorbent to retain the analytes	QuEChERS syringe based-μSPE[7]	HPLC-PDA	30–90	91 –97	≤ 2.03	80–114	0.41–14.20	[74]
Westwater	Benzophenone UV-filters	Menthol : Decanoi acid (1:1)	LLME[1]	UHPLC-PDA	50	89 – 106	< 9.6	–	–	[75]
Spiked ultrapure water	Parabens (methyl-, ethyl-, propyl-, and butylparaben)	Menthol : Caprilic acid (2:1)	LLME[1]	UV–Vis	–	72 – 98	–	–	–	[76]
Spiked ultrapure water	Methylparaben	Menthol : Decanoic acid (2:1)	LLE[5]	UV–Vis	–	90	–	–	–	[77]
Tap water, well water, river water, mineral water	Bisphenol-A	Thymol : Decanoic acid (1:1)	LLME[1]	HPLC-UV	20	81	2.2 (intra-day) 4.3 (Inter-day)	–	<13	[78]
Wastewater, runoff water, pond water	14 phthalic acid esters bis-(2-ethylhexyl) adipate	Thymol : Menthol (2:1)	LLME[1]	UHPLC-ESI (+)-QqQ-MS	–	70 – 127	< 14	70–127	4–20	[79]
Groundwater, seawater, wastewater	15 phthalates, 5 phthalates metabolites, bis-(2-ethylhexyl) adipate	Menthol : Carvacrol (1:1.78)	LLME[1]	UHPLC-ESI (+)-QqQ-MS	–	61 - 117	< 16.4	–	–	[80]

(*continued on next page*)

Table 1 (*continued*)

Sample	Analyte(s)	ES composition (molar ratio)§	Sample preparation technique	Analytical technique	ES-based method			Comparison methods		References
					LOD (ng/L)	Recovery (%)	Precision (RSD %)	Recovery (%)	Precision (RSD %)	
Tap water	Dimethyl Phthalate, Diethyl Phthalate, Dibutyl Phthalate,	*p*-cresol :Butyl lactate 4:1	DLLME[4]	GC-FID	500 - 2000	76 – 118	< 8.19 (intra-day) < 10.3 (inter-day)	63–118	–	[81]
River water, sea water, waste water	Dimethyl Phthalate, Diethyl Phthalate, Dibutyl Phthalate	ChCl : Ethylene glycol (1:4) Used to desorb analytes from the hollow fiber	HF-SPME[8] Sorbent of the HF was ZIF-8–90@GO[9]	HPLC-UV	26 - 58	90 – 103	< 4.7	–	1.6–13.5	[82]
River water, seawater, spring water	Al^{3+}	ChCl : Phenol (4:1)	LPME[2]	ETAAS	0.0032	97 – 99	3.3	–	0.35–5.85	[83]
Tap water, wastewater	Fluorene, Biphenyl, Phenanthrene, Anthracene, Pyrene, Chrysene, Benzo[a] pyrene	ChCl : Phenol (1:2)	LLME[1]	HPLC-UV	20 - 700	93 – 103	< 4.5	–	–	[84]
Effluents from production of bitumen	21 PHAs	Thymol : Camphor (1:1)	DLLME[4]	GC-EI-qMS	3.9–9.8	90 –99	< 6	61–152	2.0–29.5	[85]
Well water, river water, lake water, lagoon water	Naphthalene, Fluorene, Phenanthrene, Anthracene, Fluoranthene, Pyrene	Tetra-n-butylammonium bromide : Decanoic acid (1:2)	DLLME[4]	HPLC-FLD	0.7 – 6.6	83 – 110	< 7.1	–	0.7–17.4	[86]
Tap water, well water, river water, wastewater	16 PAHs	ChCl : Oxalic acid (1:2)	HSSDME[10]	GC–MS	3–12	94 – 106	< 7.2 (intra-day) < 11.3 (inter-day)	–	–	[87]
Wastewater	4-chlorophenols, 2,4-dichlorophenol, 2,4,6-trichlorophenol	Methyltrioctylammonium chloride : Octanoic acid (1:2)	DLLME[4]	HPLC-UV	30,000–50,000	91 – 93	1.8 - 3.1 %	91–99	1.0–6.1	[88]
Tap water, lake water, wastewater	Phenol, m-cresol, 2,4-dichlorophenol, 2,4,6-trichlorophenol	α-terpineol: Octanoic acid (1:2)	DLLME[4]	HPLC-UV	150–380	82 - 99	< 7.5	90–118	1.5–6.2	[89]
Spiked ultrapure water	Perfluoroheptanoic acid (PFHpA)	Menthol : Acetic acid (1:1)	LLE[5]	UHPLC-ESI (-)-QTOF-MS	–	80 – 90	–	–	–	[90]
River water, well water, wastewaters	7 organophosphate flame retardants	Benzyltriphenylphosphonium bromide : 1-undecanol (1:4)	LLE-SPE[12]	GC–MS/FID	2–23	96 – 104	≤5.7 % (intra-day) ≤8.2 % (inter-day)	27–119	<37	[91]
Tap water, Waste, water River, water Well, water	7 organophosphate flame retardants	Benzyltriphenylphosphonium bromide : 1-undecanol (1:4) Used as coating of the Fe_3O_4 @SiO magnetic particles	DLLME[4] based on Fe_3O_4 @SiO -DES[13]	GC-FID	2–23	97 - 101	2.4 – 5.9 % (repeatability) 4.7–8.5 (reproducibility)	–	–	[92]
Surface water, well water, soil	11 explosive or explosive precursors (including nitroaromatic compounds)	Menthol : Decanoic acid (1:2) Used as coating of the MMT@ Fe_3O_4 magnetic nanoparticles*	DSDME[11] based on MMT@ Fe_3O_4* ferrofluid of magnetic montmorillonite nanoclay	HPLC-PDA	220–910	88 – 104	< 10	–	–	[93]
Tap water, stream water	Multi residue: Parabens, Bisphenols,	Thymol : Camphor (1:1) Used to impregnate the polypropylene membrane of the hollow fiber	Hollow fiber LLE[5]	HPLC-PDA	300 - 6100	64 – 123	1.6 – 18.4 (intra-day)	–	–	[94]

(*continued on next page*)

Table 1 (*continued*)

Sample	Analyte(s)	ES composition (molar ratio)§	Sample preparation technique	Analytical technique	ES-based method			Comparison methods		References
					LOD (ng/L)	Recovery (%)	Precision (RSD %)	Recovery (%)	Precision (RSD %)	
Seawater, wastewater	Estrogens, Antibiotics Multi residue: Phthalates, Bisphenols, Estrogens, Testosterone, Phenols	Fenchol : Acetic acid (1:1 or 2:1)	DLLME[4]	HPLC-UV (for optimization) UHPLC-ESI (±)-QqQ-MS (for validation)	120 - 390	49 – 100	5 – 21–3 (inter-day) < 19	–	–	[95]

[1]LLME: Liquid-Liquid Microextraction;.
[2]LPME: Liquid-Phase Microextraction;.
[3]GO@Fe_3O_4-DES FF: Graphene Oxide@Magnetic Fe_3O_4 Nanoparticles in Deep Eutectic Solvent Ferrofluid;.
[4]DLLME: Dispersive Liquid-Liquid Microextraction;.
[5]LLE: Liquid-Liquid Extraction;.
[6]SPE-DLLME: Solid-Phase Extraction followed by Dispersive Liquid-Liquid Microextraction;.
[7]QuEChERS syringe based-μSPE: Quick, Easy, Cheap, Effective, Rugged, and Safe syringe-based Micro-Solid Phase Extraction;.
[8]HF-SPME: Hollow Fiber Solid-Phase Microextraction;.
[9]ZIF-8–90@GO: Zeolitic Imidazolate Framework-8–90 (ZIF8 and ZIF90) on Graphene Oxide (GO). ZIF8 and ZIF 90 were accommodated on GO and then placed on the hollow fiber cavities;.
[10]HSSDME: Headspace single drop microextraction;.
[11]DSDME: Dispersive Single Drop Microextraction;.
[12]LLE-SPE: Liquid-Liquid Extraction followed by Solid Phase Extraction;.
[13]Fe_3O_4 @SiO -DES: Silica magnetic particles coated with the eutectic solvent composed by benzyltriphenylphosphonium bromide and 1-undecanol (1:4 molar ratio);.
*MMT@Fe_3O_4: a ferrofluid based on Magnetic Montmorillonite Nanoclay;.
§If not specified otherwise the reported ES was used as extraction medium;.
°estrone (E1), 17-β-estradiol (E2), 17-α-ethynyl estradiol (EE2), estriol (E3).

Applications exploiting ES for this class of contaminants are mainly focused on the extraction of fluoroquinolone antibiotics. The core of fluoroquinolones is a quinoline ring system functionalized with different substituents. The amphiphilic nature of these antibiotics makes them favorable candidates to be extracted using ES due to their ability to interact with both hydrophilic and lipophilic functional groups. Fluoroquinolones are an extensively used antibiotic category, recognized for their broad-spectrum efficacy. They are applied in various fields, including animal, agriculture, and aquaculture, as well as in treatments for companion animals and humans. The absorption of fluoroquinolones by organisms is not entirely complete, leading to their excretion through urine and feces either as unaltered drugs or as metabolites. Consequently, this results in their presence in environmental waters and soils [101,102].

It is worth mentioning that in the European Union (EU), among all fluoroquinolones only ciprofloxacin and ofloxacin have been added to the watch list of potential water pollutants under the Water Framework Directive (WFD) [103,104]. Specifically, ciprofloxacin has been on the watch list between 2018 and 2022. However, according to the WFD, the duration of a continuous watch list monitoring period for any individual substance shall not exceed four years, therefore, ciprofloxacin is not considered anymore. According to the European Commission, an analytical method for the quantitation of ciprofloxacin in wastewaters should have had a limit of detection (LOD) of 0.089 μg/L maximum obtained via a sample preparation involving solid phase extraction (SPE) followed by analytical determination via high-performance liquid chromatography coupled to triple quadrupole mass spectrometry (HPLC-QqQ-MS) [104]. In regard to ofloxacin, which entered in the watchlist in 2022, an analytical method should achieve an LOD of 0.026 μg/L using SPE as sample preparation and ultra (U)HPLC-QqQ-MS as detection technique [103].

Hydrophobic eutectic mixtures formed by thymol and hexanoic (or heptanoic) acid have been recently employed for the extraction of ciprofloxacin, ofloxacin, norfloxacin, enrofloxacin, and levofloxacin from environmental water samples [67,68]. The first approach, presented by Li *et al.* exploited the in-situ formation of the hydrophobic ES. The HBA (thymol) and HBD (hexanoic acid) were added separately to the aqueous sample [67]. The test tube was then shaken and incubated at 52 °C for 5 min to promote the formation of the ES (thymol: hexanoic acid 2:1), which, once formed, appeared as a small floating droplet. After the in-situ formation, the test tube was shaken and centrifuged to enable the collection of the ES-enriched phase and its subsequent analysis via reverse phase (RP) HPLC coupled to an ultraviolet detector (UV) (λ=277 nm). The method showed LODs and limits of quantification (LOQs) of 3 μg/L and 9 μg/L, respectively, and recovery in the 84.1 – 113.6 % range.

The following year, in 2021, Ma and Row used a similar ES composed of thymol and hexanoic acid (molar ratio 2:1) to extract levofloxacin and ciprofloxacin [68]. Instead of implementing a classic LLME, the authors exploited the pH-induced transition of the ES of choice. After the addition of 100 μl of ES to the water sample, 100 μL of KOH 6 M were added to dissolve the ES, obtaining a homogenous phase. After manually shaking for 30 s, 100 μL of HCl 6 M were added to break this homogenous state. Tiny droplets of ES, formed after the breakage of the homogeneous state, trapping the analytes. The ES-enriched phase was withdrawn, diluted with methanol (MeOH), and subjected to RP HPLC-UV separation and detection (λ=280 nm). The schematic workflow of the procedure is reported in Fig. 2.

The method gave LODs of 18 ng/mL for levofloxacin and 27 ng/L for ciprofloxacin; and LOQs of 60 μg/L for levofloxacin and 90 μg/L for ciprofloxacin. The method also exhibited the following extraction recoveries: 110.83 % for levofloxacin, and 94.52 % for ciprofloxacin.

A few approaches exploiting Type III ES, have also been developed to extract fluoroquinolones. Interestingly, these approaches achieved better performances in terms of LODs and LOQs compared to the ones discussed previously. In 2018, Gabbana *et al.* implemented a custom-made electrochemical cell for the direct in-situ sample preparation and quantification of ciprofloxacin using an ES composed of ChCl and malonic acid (molar ratio 1:1) [66]. The ES (between 80 and 160 mg) was added to the water sample and thoroughly mixed for 5 min. After this step, a chiller was turned on to cool the solution and allow the decantation of the enriched ES-phase onto the electrode for quantitation. Authors reported recovery rates ranging from 71 % to 93 %, with an LOD of 0.83 μg/L.

Among these works, none achieve the LOQ required by the EU (but this is most probably due to the use of an HPLC coupled to a UV detector instead of triple quadrupole MS), except for the work by Mohammad *et al.*, which by exploiting a ferrofluid functionalized by a type III – ES achieved and LOD of 0.0063 μg/L, in line with the requirements of the EU, just using an HPLC-UV for analysis [69]. The authors developed a ferrofluid combining graphene oxide magnetite (GO@Fe_3O_4) with an ES composed of ChCl and ethylene glycol (1:2). This approach leveraged the magnetic separation capabilities of GO@Fe_3O_4 and the characteristics of the ES for the extraction process. The procedure involved the addition of 20 μL of ferrofluid to a spiked water solution and shaking for

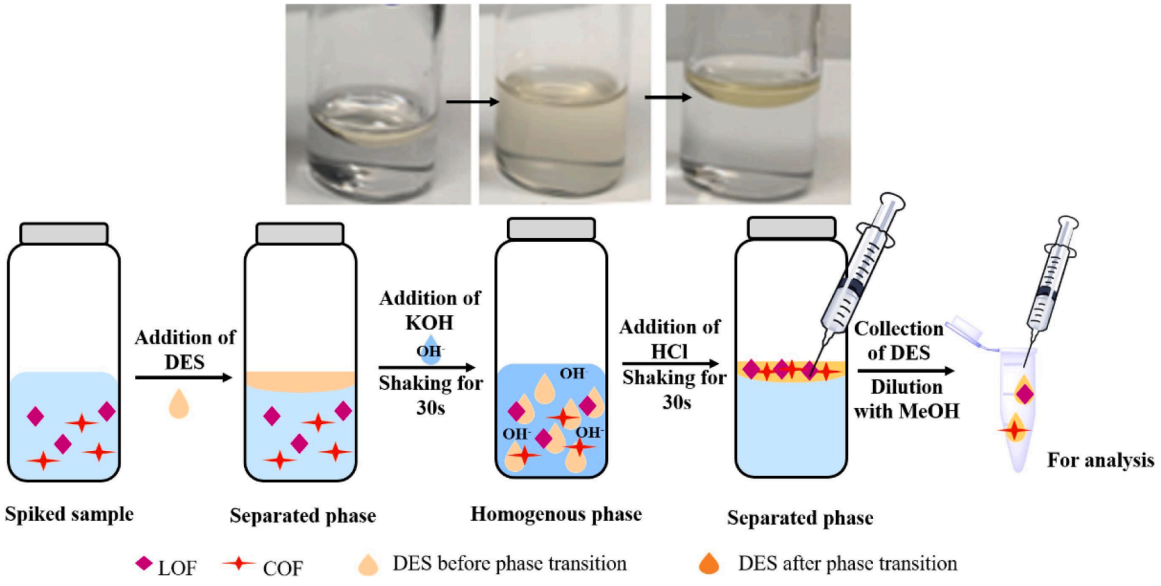

Fig. 2. Schematic workflow of the LLME exploiting a pH-induced ES transition. Reprinted with the permission of Ma *et al.*, 2021 [68].

20 min. The ferrofluid, with adsorbed analytes, was then separated using a magnet, and the supernatant was removed. The analytes were desorbed into a 500 μL MeOH: ammonium solution by ultrasonication for 3 min, separated magnetically, the solution was then filtered (0.22 μm) for RP HPLC-UV analysis (λ=254 nm). The schematic workflow of the procedure is reported in Fig. 3. The optimization of the extraction parameters led to LODs of 0.0063 μg/L for ofloxacin and of 0.0058 μg/L for sparfloxacin; LOQs were 0.0190 μg/L for ofloxacin and 0.0176 μg/L for sparfloxacin. Recovery rates ranged from 70.3 % to 121.5 %.

Another extensively used antibiotic is triclosan, which is a PCPI used a preservative. Triclosan and its degradation byproducts (dioxins and 2, 4-dichlorophenol) have been found in waters, soil, and human breast milk [105,106]. Together with the concern regarding increasing bacterial resistance due to the extensive presence of this antibiotic in the environment, the effect of triclosan on human health as a possible endocrine disruptor is still a matter of debate [107]. However, triclosan was banned from soap products by the Food and Drug Administration (FDA), while still allowed in toothpaste, hand sanitizer, and mouthwash [107]. On the other extent, in the EU the Scientific Committee on Consumer Safety published a final opinion on triclosan in 2022, reporting its safety in some formulations, at the conditions that its concentration is in the range of 0.2–0.3 % (w/w) [108]. This opinion led to the decision present in the Commission Regulation 2024/996 to limit the concentration of triclosan to 0.3 % (w/w) in all personal care products and report the label '*Not to be used for children under 3 years of age*' for toothpaste containing it [109].

A recent study by Du *et al.* reported a method for the quantitative determination of triclosan in environmental water samples, employing an eutectic mixture formed directly between triclosan and 2,2,4-trimethyl-1,3-pentanediol [65]. In this case, triclosan functions as the HBA, while 2,2,4-trimethyl-1,3-pentanediol serves as the HBD. This approach effectively captured triclosan from the sample matrix by exploiting their interaction to form a eutectic mixture. Although the authors referred to this system as a DES, it is more appropriate to consider it simply as a eutectic mixture. This is further reflected by the fact that no fixed proportion between HBA and HBD was provided, given that the triclosan concentration in real samples cannot be known a priori. The reported method achieved a LOD and LOQ of 0.5 and 1.7 μg/L, respectively. Recovery values ranged from 76 % to 115 %, and the precision, expressed as the RSD, was <7 %. In terms of sample preparation, a 5 mL aliquot was first added with NaCl to achieve a 1 M solution. Subsequently, 150 mg of 2,2,4-trimethyl-1,3-pentanediol were added, and the mixture was maintained at 45 °C in a thermostatic bath to ensure the formation of the eutectic system. After cooling the solution to room temperature, the hydrophobic eutectic phase was collected, and 100 μL of MeOH were added to break the eutectic mixture. The resulting methanolic solution was then analyzed by reversed-phase HPLC-UV at 279 nm, the maximum absorption wavelength of triclosan.

3.1.2. *Estrogens*

Estrogens, a class of steroid hormones, have emerged as environmental pollutants due to their endocrine-disrupting capabilities. These compounds enter the environment through various routes, including agricultural runoff, sewage effluent, and industrial waste [110]. The European Commission has proposed annual average Environmental Quality Standards (EQS) of 3.6 ng/L, 0.4 ng/L, and 0.035 ng/L for estrone (E1), 17-β-estradiol (E2), and 17-α-ethynyl estradiol (EE2), respectively. As outlined in the Joint Research Centre technical report, the analytical methods employed by member states must have a LOQ that is equal to or lower than the environmental quality standard for each analyte [111].

Due to their structure, based on a cyclopentane phenanthrene ring, estrogens are highly hydrophobic. Therefore, it is not surprising that their extraction with hydrophobic ES has been evaluated in recent years.

A study by Fattahi *et al.* in 2022 Introduced a LLME method utilizing a pH-switchable ES, formulated from l-menthol and camphor-10-sulfonic acid, for isolating E1, E2, EE2, and estriol (E3) from environmental water samples [70]. This technique exploited the ES's property to undergo a phase transition in response to pH adjustments. To 10 mL aliquot of sample was rapidly injected 50 μL of ES, followed by 80 μL of NaOH (7 M), which was manually shaken for 30 s, obtaining a homogenous solution. A 120 μL of HCl (7 M) was then added to disrupt the homogenous solution formed and favored the separation of the analytes enriched ES. The ES was then collected from the surface without the need for centrifugation. The test tube was subsequently frozen for 2 min to solidify the ES, which was then transferred into a conical glass vial for derivatization prior to gas chromatography – mass spectrometry analysis (GC-MS–). Under optimized conditions, the authors reported LODs

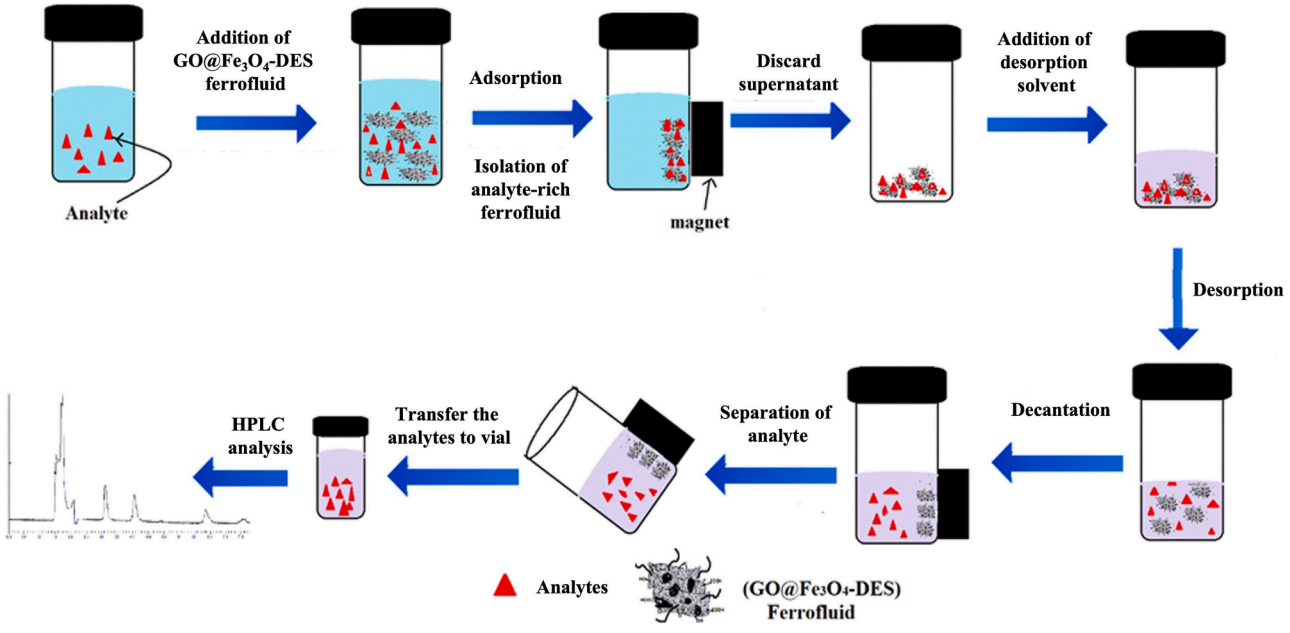

Fig. 3. Schematic workflow of the extraction method for ofloxacin and sparfloxacin. The extraction exploited a GO@Fe_3O_4 ferrofluid functionalized with a ChCl : Ethylene glycol (1:2) ES. Reprinted with the permission of Mohammad *et al.*, 2022 [69].

in the range of 0.2–1.0 ng/L, a linearity range of 0.5–100 ng/L, and recovery rates between 91.0 % and 108.8 % with relative standard deviation (RSD) values below 5.7 %. Similar approaches for estrogen extraction have also been investigated using hydrophobic ES composed of menthol and fatty acids [71,72]. However, none of these approaches, despite using a hydrophobic extraction media and fine tuning of the extraction process, could fulfill the stringent requirements of the EC.

A notable method using an ES-based extraction for estrogens (E1, E2, EE2, and E3) was published by Davoodi *et al.* in 2020 [73]. The authors developed a procedure for concentrating trace levels of these estrogenic compounds in wastewater samples by combining a SPE step with an ES-based DLLME. They reported LODs ranging from 0.01 to 0.05 ng/L, although no LOQs were determined, making it difficult to assess whether the method meets EC requirements. The ES was prepared by mixing citric acid monohydrate and 1-octyl-3-methylimidazolium chloride in a 1:1 molar ratio. For sample preparation, a 300 mL wastewater sample was adjusted to pH 3 with HCl (37 %) and NaCl was added to achieve a 5 % w/v concentration. This solution was then passed through an SPE cartridge containing 200 mg of a polystyrene-divinylbenzene copolymeric sorbent. The retained analytes were eluted with 1 mL of acetone, to which 20 μL of the prepared ES were added. The mixture was subsequently injected into 5 mL of distilled water to form a cloudy solution. After centrifugation, the ES extraction phase floated to the surface and was collected by temporarily freezing and then scooping it out with a spatula. Prior to GC -MS analysis, the extract underwent a derivatization step. The method's precision, expressed as intra-day and inter-day RSD %, ranged from 1.5 % to 2.5 % and from 2.6 % to 3.8 %, respectively, for seven replicates at 0.50 ng/L for the target compounds and 0.30 ng/L for the internal standard. Relative recoveries ranged between 90 % and 108 % in wastewater samples spiked at various concentrations of the analytes.

3.1.3. Antidiabetics

The analysis of antidiabetic drugs as contaminants in various environments, particularly water bodies, is an emerging area of concern within environmental chemistry and toxicology [112]. Antidiabetic drugs, used to treat diabetes mellitus, can enter the environment through various pathways, including pharmaceutical manufacturing waste, improper disposal of unused medication, and excretion from treated individuals. When present in the environment, these drugsan potentially affect non-target organisms and disrupt aquatic ecosystems due to their biological activity [112,113].

Khodayari and Ebrahimzadeh developed a Quick, Easy, Cheap, Effective, Rugged, and Safe (QuEChERS) -based method incorporating an ES for the extraction and determination of five antidiabetic drugs (empagliflozin, metformin, sitagliptin, gliclazide, and repaglinide) in wastewater, serum, and plasma [74]. Among these compounds, metformin is of particular regulatory interest, as the EU has included it on a watch list of potential water pollutants, suggesting the use of an analytical method based on SPE-LC-MS/MS. The approach proposed by Khodayari and Ebrahimzadeh utilized a syringe filter-based micro-SPE device. The sorbent consisted of a hydrophobic ES formed by thymol and menthol at a 1:1 molar ratio, and curcumin, immobilized in polyvinyl alcohol electrospun nanofibers. This sorbent design was intended to enhance both hydrophobicity and functionality, thereby improving the absorption of target analytes. Prior to extraction, the sorbent was conditioned with a 3.0 mL mixture of water and MeOH (50:50, %v/v). A 5.0 mL sample aliquot was then passed through the sorbent three times to increase extraction efficiency, followed by a 2.0 mL water rinse. The analytes were subsequently eluted with 500 μL of a MeOH/acetonitrile (ACN) mixture (80:20, %v/v), and the entire process was completed in approximately 3 min. The sorbent holder was cleaned between runs to maintain reproducibility and reduce carry-over. After extraction, 20.0 μL of the enriched solution was analyzed via HPLC-UV at 230 nm (empagliflozin, metformin, gliclazide) and 210 nm (sitagliptin, repaglinide). Under optimized conditions, the method was validated for linearity (0.1–2000.0 μg/L), LOD (30–90 ng/L), and LOQ (100–250 ng/L), as well as precision (RSDs $\leq$ 2.03 %). Notably, for metformin the LOQ of 100 ng/L met the EU guidelines. The greenness of the analytical procedure was evaluated using the Green Analytical Procedure Index (GAPI) and Analytical GREEnness (AGREE), achieving an AGREE score of 0.61. Additionally, the sorbent maintained stable performance for up to 115 consecutive extraction cycles without significant loss of analyte signal.

3.1.4. Parabens & UV-filters

Among PCPI-associated compounds, UV filters and parabens have drawn particular attention due to their environmental persistence and potential health implications [98].

Butyl methoxydibenzoyl-methane, octocrylene, and benzophenone-3 were included on the EC's Watch List for emerging contaminants under the WFD [104]. UV filters, extensively incorporated into sunscreens and a wide range of cosmetics, are known for their ability to absorb or reflect harmful solar radiation. Their persistence and potential endocrine-disrupting effects classify them as contaminants of emerging concern [114,115].

In 2018, Ge *et al.* developed an approach employing air-assisted LLME using an ES for pre-concentrating benzophenone-type UV filters from aqueous samples [75]. The authors developed an air-assisted LLME method using a hydrophobic ES formulated from menthol and decanoic acid at a 1:1 molar ratio. The extraction method consists of a rapid injection of 100 μL of the hydrophobic ES in the water sample followed by five cycles of suction and injection. The resulting cloudy solution was centrifuged, and the upper ES layer was collected and analyzed using HPLC coupled to UV set at 254 nm for the detection of benzophenone-3 and 289 nm for the other analytes. Under optimal conditions, the method had LOD and LOQ of 50 and 200 ng/L, respectively, with RSD below 9.6 % and recovery rates ranging from 88.8 % to 105.9 %. The figure of merits met the performance required by the EC's watch list (ML of 670 ng/L).

In addition to UV filters, another group of chemicals commonly used as PCPI are parabens, which serve as stabilizers to prolong product shelf life. In contrast to UV filters, parabens have not received comparable attention in terms of formal environmental monitoring programs in the EU. While certain parabens are regulated under the EU Cosmetics Regulation [116], resulting in restrictions on their use or maximum concentration limits in consumer products, there is currently no EU-wide environmental watch list or harmonized environmental quality standards specifically targeting parabens in water. This regulatory gap persists despite increasing evidence of their ubiquitous presence in aquatic systems and their potential endocrine-disrupting effects [117]. In the US, parabens are generally considered safe when used within established limits in food and cosmetics, as determined by the FDA. However, similar to the EU, there is no federal-level environmental guideline or watch list focusing on parabens in natural waters.

In 2022, Zelinski *et al.* introduced a vortex-assisted LLME method to efficiently extract and concentrate four types of parabens—methyl-, ethyl-, propyl-, and butylparaben—from aqueous samples [76]. Their study tested three hydrophobic ESs, each formulated with menthol as the HBA and one of the following HBD: caprylic acid, lactic acid, or lauric acid. Under these conditions, the recovery yields of the parabens consistently followed the order butylparaben > propylparaben > ethylparaben > methylparaben, which notably differs from their solubility trend in water. Further investigation revealed that the extraction efficiency was closely linked to both the octanol-water partition coefficient (log K_{ow}) of the parabens and the carbon chain length of the HBD. Specifically, parabens with higher log K_{ow} values exhibited superior recoveries (72–98 %) when ES containing longer-chain HBD were employed. The experimental workflow involved performing the LLME, collecting the ES-rich upper phase from the test tube, and determining paraben concentrations via UV–Vis spectroscopy at 250 nm. To guide the selection of appropriate solvents, the authors employed the

COnductor-like Screening MOdel (COSMO), a predictive thermodynamic framework that enhances the understanding of equilibrium data, distribution coefficients, extraction selectivity, and solute–solvent interactions. Essentially, COSMO treats a solute molecule as if it were surrounded by a virtual conductive environment. Quantum chemical calculations determine the distribution of screening charges on the solute's molecular surface. These surface charge densities are then used to simulate how the solute would behave in different real solvents. By integrating statistical thermodynamics with these charge distributions, COSMO can predict key properties such as activity coefficients, partition coefficients, and phase equilibrium behavior.

Following the work by Zelinski *et al.*, a subsequent study by Padinhattath and colleagues combined experimental extraction methods with computational chemistry to refine the use of ES further [77]. Their approach focused on improving the extraction of methylparaben and 2-naphthol from aqueous samples using two carefully designed ES: menthol:decanoic acid (1:2 molar ratio) for methylparaben and thymol: decanoic acid (1:2 molar ratio) for 2-naphthol. Under optimized LLE conditions, recovery efficiencies reached up to 90 % for both target compounds. Quantification was performed via UV–Vis spectroscopy, with detection wavelengths set at 255 nm for methylparaben and 320 nm for 2-naphthol. Notably, the ES could be reused up to three times without substantial loss of extraction performance. To gain deeper insights into the underlying mechanisms, the authors employed the COSMO for Real Solvents (COSMO-RS) methodology. This computational tool enabled the analysis of σ-profiles and σ-potentials, which characterize the distribution of surface charge densities and chemical potentials within the solvent system. These parameters help elucidate the molecular interactions that favor pollutant extraction, ultimately guiding both the prediction and optimization of ES-based extraction strategies.

3.2. Plasticizers

Among the plasticizers, bisphenols and phthalates are two groups of chemicals that have gained significant attention as environmental pollutants due to their widespread use in various consumer products and potential adverse effects on human health and the environment [118]. Bisphenols, exemplified by bisphenol-A (BPA), are commonly found in plastics and epoxy resins used in food and beverage containers, while phthalates are plasticizers utilized to increase flexibility in numerous products, including vinyl flooring, personal care items, and medical devices [119,120].

Despite their utility in manufacturing, these compounds have raised concerns due to their propensity to leach from products into the environment, contaminating water, soil, and air. Research has linked bisphenols and phthalates to hormone disruption, reproductive abnormalities, developmental issues, and various other health risks in humans and wildlife [120,121]. Consequently, regulatory efforts have aimed to mitigate exposure and limit the environmental impact of these pollutants, emphasizing the importance of continued monitoring and research to safeguard public health and ecological integrity [122,123].

Efforts to find eco-friendly alternatives for the analysis of BPA and phthalates have also led to the exploration of ES as an extraction media.

3.2.1. Bisphenols

Bisphenol compounds, particularly BPA, have gathered international regulatory attention due to their endocrine-disrupting potential and prevalence in aquatic environments. In the EU, the revised Drinking Water Directive imposes a specific parametric limit for BPA of 2500 ng/L to safeguard public health [124]. Conversely, US policy is more decentralized: while no nationwide maximum contaminant level currently exists for BPA, the US EPA has listed it on the CCL and included it in periodic Unregulated Contaminant Monitoring Rules for data collection and risk assessment [125]. Despite these regulations, there is no mention of a limit of BPA in environmental waters nor a suggested analytical method.

Regarding the analysis of this contaminant in environmental waters, a handful of publications have been published reporting the use of hydrophobic ES as extraction media [78,126,127]. However, the only analytical method focusing on the analysis of trace levels of BPA is the environmental water sample, and therefore, potentially applicable in the context of environmental monitoring, was published by Cao and Li [78]. The authors used a pH-sensitive ES composed of thymol and dodecanoic acid in a 1:1 molar ratio [78]. The LLME process began by injecting 30 μL of the ES into the sample, followed by the addition of a KOH solution, which dissolved the ES components to form a homogeneous solution in water. The subsequent addition of HCl reverted the ES to its initial phase, enabling separation. Cooling the sample solidified the ES phase, which was then collected, left to melt at room temperature, and directly used for HPLC-UV analysis. The method demonstrated intra-day and inter-day precision rates of 2.2 % and 4.3 %, respectively, over seven replicates, with LOD and LOQ of 20 ng/L and 50 ng/L, respectively. BPA extraction recovery was 81.0 %.

3.2.2. Phthalates

Plastic-associated pollutants, particularly phthalic acid esters (PAE), are significant environmental and human health concerns due to their widespread use as plasticizers, especially in polyvinyl chloride (PVC) production [128]. PAEs, including bis(2-ethylhexyl) phthalate (DEHP) and dibutyl phthalate (DBP), are not chemically bound to polymers, leading to their gradual migration into the environment [129]. Industrial processes and wastewater treatment further facilitate their dispersion, contaminating soils, water, and crops through sludge and irrigation with polluted water [130,131]. These compounds act as endocrine disruptors and have been linked to immunotoxicity, genetic toxicity, and reproductive harm [132,133].

Regulatory efforts address these risks. In Europe, DEHP, DBP, benzyl butyl phthalate, and diisobutyl phthalate are listed in Annex XIV of Regulation (EC) No 1907/2006 for their reproductive toxicity [134]. The European Chemicals Agency and the US EPA have also included additional phthalates, such as diisopentyl phthalate (DIIP) and di-n-pentyl phthalate (DNPP), in their regulatory frameworks [135,136]. Furthermore, the World Health Organization (WHO) has established drinking water guidelines for DEHP, recognizing its carcinogenic potential and setting a limit of 8000 ng/L [137]. Despite these measures, phthalate concentrations in the environment vary from nanograms to milligrams per liter, posing ongoing risks to ecosystems and human health [133].

Regarding the extraction of phthalates from environmental water samples using ES, the majority of works employ hydrophobic ES, given the nature of the analytes of interest.

The first study in this direction was reported by Santana-Mayor *et al.* in 2021 [79]. The authors used a thymol:menthol ES (2:1 molar ratio) for LLME. Following pH adjustment of the sample solution, 100 μL of ES was rapidly injected into it. The solution was then vortexed, and the upper ES phase was collected after centrifugation. The ES was diluted with ACN before undergoing to UHPLC-QqQ-MS separation and detection. The system was equipped with an electrospray ionization source (ESI) operated in positive (+) mode. The method was optimized and validated for 14 phthalic acid esters and bis-(2-ethylhexyl) adipate. The authors reported recovery values ranging from 70 % to 127 %, with RSDs below 14 % in the studied matrices. LOQs ranged from 13 to 425 ng/L for all samples and analytes. The validated methodology was then applied to real samples, including wastewater, runoff water, and pond water, detecting phthalate esters in some of the samples within the range of 105.2 to 3414 ng/L.

A similar approach was developed in 2023 by Conde Dìaz *et al.*, using a menthol:carvacrol (1:1.78 molar ratio) hydrophobic ES, for the analysis of 15 phthalates, four metabolites and one adipate in groundwater, seawater, and wastewater samples [80]. The LLME procedure involved the addition of 1*g* of NaCl to 10 mL of sample, afterwards, the pH was

adjusted to 2 and subsequently, 100 μL of ES were rapidly injected to form a cloudy solution. After centrifugation, 10 μL of the upper ES-enriched phase was recovered and diluted with 200 μL of H_2O:ACN (50:50). This solution underwent chromatographic separation and detection on a UHPLC-ESI(+)-QqQ-MS system. Relative recovery values ranged from 61.3 % to 116.9 %, with LOQs from 910 to 8900 ng/L. The method's greenness was evaluated using AGREEPrep and Analytical Eco-Scale metrics, scoring 0.55 out of 1 and 65 out of 100, respectively.

In 2023, Niu *et al.* developed a method for the trace-level analysis of four phthalate esters (dimethyl phthalate, diethyl phthalate, dibutyl phthalate, and DNPP) by exploiting the in-situ formation of a hydrophobic ES composed of *p*-cresol and butyl lactate in a molar ratio of 4:1 [81]. They implemented DLLME by adding 0.2 g of *p*-cresol (HBD) to the water sample, followed by 20 μL of butyl lactate (HBA), resulting in a cloudy suspension indicating ES formation. The solution was vortexed and sonicated before withdrawing the enriched ES from the bottom of the vial. Finally, 1 μL of the extract was injected into a GC-flame ionization detector (FID). The validated method exhibited LODs ranging from 500 to 2000 ng/L and LOQs from 1000 to 4000 ng/L. Spiked recoveries ranged from 76.17 % to 118.09 %, with intra-day and inter-day RSDs below 8.19 % and 10.31 %, respectively. The method also received a 94 out of 100 scoresing the Analytical Eco-Scale metric [138].

The only work not reporting the use of a hydrophobic ES was presented by Jafari *et al.* [82]. The authors leveraged a different approach for the trace analysis of DBP, and DEHP from water samples. Their sample preparation approach extracted the PAE using a custom-made hollow fiber (HF). The fiber was modified by incorporating zeolitic imidazolate frameworks inside its pores, with detailed production methods provided in their work. The extraction of phthalate esters from water samples using the HF involved stirring the fiber in 10 mL of aqueous sample for 15 min. The fiber was then withdrawn, and the analytes were completely desorbed with an ES consisting of ChCl and ethylene glycol in a 1:4 molar ratio. After desorption, the ES-enriched solution was directly subjected to HPLC-UV analysis (λ=280 nm). The authors reported LODs in the range 26 – 58 ng/L and LOQs in the range 89 – 194 ng/L. Relative recoveries in real samples were ranging from 90 % to 103 % and RSDs below 4.7 %. This approach shows how pairing a hallow-fiber extraction approach and subsequent desorption with an ES is feasible and can lead to a sample preparation approach totally free of classic organic solvents.

3.3. Metals and metalloids

Heavy metals pose a significant threat to environmental health due to their persistence in soil and water resources. Anthropogenic activities, including industrial processes, mining operations, and improper waste disposal practices, are the primary drivers of heavy metal contamination [139]. The environmental concern is further amplified by the bioaccumulation potential of these metals. They are not readily eliminated from organisms and instead become concentrated within the food chain, posing a greater threat to higher-level predators [140]. This phenomenon disrupts ecosystem function at the foundational level and jeopardizes the health of wildlife populations. Furthermore, chronic exposure to heavy metals has been linked to several adverse health effects in humans, impacting neurological development, organ function, and overall well-being [141].

In the EU, water quality standards for heavy metals are primarily established under the WFD (and following amendments), which specify EQS for priority substances, including metals such as lead (set at 14 000 ng/L) and nickel (set at 34 000 ng/L) [142]. In the US the EPA provides guidance under the Clean Water Act for establishing water quality criteria to protect ecosystems from metal toxicity. These criteria, along with EPA-approved analytical methods (e.g., EPA Methods 200.7, 200.8, 200.9), support consistent and accurate monitoring of metal concentrations in environmental waters [143–146]. For instance, EPA's methods rely on the analysis of heavy metals via inductively coupled plasma-atomic emission spectrometry (ICP-EMS), ICP-MS, and electrothermal atomic absorption spectrometry (ETAAS).

Most studies in the literature focus on using ES to remove heavy metals from water and soil rather than employing ES solely for analytical purposes. Consequently, despite the promising applications, no method validation has been conducted, and no ranges for LODs or LOQs are available. Readers interested in these approaches are invited to check the following references [147,148].

To the best of our knowledge, the only publication dealing with the analysis of a metalloid in environmental water samples employing an ES was reported by Panhwar et al. [149]. The authors introduced a method using ultrasound-assisted LPME with 8-hydroxyquinoline as a chelating agent for quantifying Al^{3+} in environmental water samples. In this method, a solution containing the chelating agent and tetrahydrofuran (as the extraction solvent) was added to the water sample. Adding an ES made of ChCl and phenol in a 4:1 molar ratio resulted in a homogeneous mixture. Upon sonication, the ES separated from the system into tiny droplets. After centrifugation, the ES phase was collected and analyzed using ETAAS. Extraction conditions were optimized using a preliminary Plackett–Burman design, identifying ES type, pH, and chelating agent quantity as key variables. A subsequent three-variable central orthogonal composite design was employed, achieving recovery rates between 96.6 % and 98.8 % under optimal conditions. The method demonstrated a LOD of 0.032 ng/L and an RSD of 3.3 %. This method, able to detect ultra-trace levels of Al^{3+} in water samples, outperforms the LODs reported for the EPA methods 200.9 reporting the use of ETAAS for aluminum analysis scoring a LOD of 7800 ng/L [146].

3.4. Polycyclic aromatic hydrocarbons and phenols

PAH and phenols are among the most concerning environmental pollutants due to their widespread occurrence, persistence, and potential adverse effects on human health and ecosystems. Due to their harmful effects, certain phenolic compounds and PAH have been designated as priority pollutants by global organizations such as the EU, the US EPA, and the WHO [137,150,151].

PAH are a group of organic compounds composed of multiple aromatic rings, primarily formed during incomplete combustion of organic materials such as fossil fuels, wood, and tobacco [152]. Phenols, on the other hand, are organic compounds containing a hydroxyl group attached to an aromatic hydrocarbon group and can originate from industrial effluents, agricultural runoff, and domestic sewage [153]. Both PAH and phenols can enter the environment through various pathways, including atmospheric deposition, wastewater discharge, and accidental spills, leading to their presence in air, soil, water, and biota. Once released into the environment, these pollutants can undergo transformation processes such as photolysis, oxidation, and microbial degradation, which can alter their chemical structures and properties [152–154].

Various analytical techniques, ranging from chromatographic methods such as GC and HPLC to spectroscopic techniques like UV–Vis and fluorescence spectroscopy, have been employed to accurately detect and quantify these pollutants in environmental matrices [152,155]. The complexity of environmental samples, the low concentrations at which these pollutants may be present, and the presence of interfering substances necessitate the development of sensitive, selective, and robust analytical methods. Furthermore, the continuous monitoring and control of PAH and phenols in the environment are essential for implementing effective pollution control measures and safeguarding environmental quality. Several studies in recent years have demonstrated the effectiveness of ES in the extraction of PAH and phenols from environmental samples.

3.4.1. Polycyclic aromatic hydrocarbons

Both the EPA in the US and the EU have identified specific PAH as priority pollutants due to their prevalence and potential health risks.

The EPA has designated 16 PAH as priority pollutants [156]. Under the Clean Water Act, the EPA establishes water quality criteria and effluent limitations to control the discharge of harmful substances. However, specific numeric limits for PAH in discharge waters are typically determined on a case-by-case basis, considering factors such as the type of discharge, local water quality standards, and the designated uses of the water body [143].

In the EU the regulation of PAH in wastewater is primarily governed by the WFD, under which specific PAH are identified as priority substances. The directive sets EQS for these substances, defining the maximum allowable concentrations in surface waters. The relevant PAH and their EQS are detailed in the environmental quality standards directive [157]. A summary of the PAHs designated as pollutants in the US and EU (with relative EQS maximum levels) is reported in **Table S1**.

The analysis of PAH using ES has advanced in tandem with the development of hydrophobic ES. Using initially hydrophilic ES and then shifting towards their hydrophobic counterparts. In fact, between 2015 and 2016, shortly after the first hydrophobic ES were reported [47], the first analysis using ES for PAH extraction relied on ChCl-based solvents. The first of these works was published in 2015 by Khezeli *et al.* that implemented an emulsification LLME exploiting an ES for the extraction of fluorene, biphenyl, phenanthrene, anthracene, pyrene, chrysene, and benzo[a]pyrene in water samples [84]. Among the evaluated ES the authors chose the one composed of ChCl and phenol in 1:2 molar ratio. To the aqueous sample, 100 μL of ES were added, forming a homogenous solution. To separate the ES from the water phase 100 μL tetrahydrofuran, as an emulsification agent, was added, leading to the formation of a turbid solution. This was sonicated for 20 min and centrifuged, obtaining two clear phases. The ES upped phase was recovered and subjected to RP HPLC-UV analysis (λ=254 nm). At the optimal conditions, the authors reported recovery rates in the range 93.1–103.3 %. The reported LODs were in the 20–700 μg/L range, while the LOQs were in the 60–2300 μg/L range. The RSDs values were below 4.5 % for all analytes and spiking concentrations. However, when evaluated against EU WFD, the method met the LOQ requirement only for anthracene (60 ng/L vs. the EU's 100 ng/L) but not for benzo[a]pyrene (280 ng/L vs. the EU's 27 ng/L).

With the advent of hydrophobic ES, new applications started to be proposed, the first one was developed by Makoś *et al.* in 2018 for the analysis of 21 PAH in wastewaters coming from the production of bitumen [85]. An ultrasound-assisted DLLME procedure was implemented and optimized. ACN and an ES composed of thymol and camphor (1:1 molar ratio) were used as dispersion and extraction solvents, respectively. The optimized conditions involved the extraction of 10 mL of the sample with 200 μL of ES, 500 μL of ACN as disperser solvent, a 10 % w/v concentration of NaCl, and 14 min of sonication. After extraction and centrifugation, the ES extract was withdrawn and directly analyzed via GC-EI-Q-MS. The procedure was validated, obtaining LODs in the 3.9–9.8 μg/L range and LOQs in the 12–29 μg/L range. The method was also tested on wastewater samples to evaluate the matrix effect. Relative recoveries were obtained in the 90–99 % range, in line with the values obtained during validation, showing that the matrix has no significant effect on the method performance. In terms of EU compliance, the method met LOQ requirements for naphthalene (29 ng/L), anthracene (13 ng/L), fluoranthene (18 ng/L), and benzo[a]pyrene (24 ng/L) but did not comply for benzo[b]fluoranthene (22 ng/L), benzo[k]fluoranthene (27 ng/L), and benzo[ghi]perylene (63 ng/L), as their LOQs exceeded the EU's maximum allowable levels.

In the same year, Yousefi *et al.* proposed the extraction of six PAH (naphthalene, fluorene, phenanthrene, anthracene, fluoranthene, and pyrene) using a DLLME followed by solidification of the ES phase [86]. Their method utilized an ionic hydrophobic ES composed of tetra-n-butylammonium bromide as the HBA and decanoic acid as the HBD at a molar ratio 1:2. The sample preparation involved the rapid injection of 80 μL of ES in 20 mL of aqueous solution, followed by 1 min of ultrasonic bath at 35 °C and a final step of centrifugation for 2 min at 20 °C. The last step allowed the solidification and further recovery of the ES enriched fraction, which was diluted with water/ACN (30:70 v/v) to 100 μL and injected into an RP HPLC system equipped with a fluorimeter detector (FLD). The method achieved LODs between 0.7 and 6.6 ng/L and LOQs between 3.0 and 21.8 ng/L, with RSDs lower than 7 %.

An unconventional approach using a headspace single drop microextraction, based on ES, was developed by Mehravar *et al.* for the analysis of 16 PAHs [87]. The procedure involved the use of 15 μL of an ES composed of ChCl and oxalic acid (1:2 molar ratio). The ES was hung in the headspace of a vial containing 15 mL of working standard or sample solution by means of a custom-made syringe (Fig. 4). Once the extraction was completed, the ES droplet was drawn back to the syringe and subjected to back-extraction with water (100 μL) and hexane (100 μL) to have the analytes in an organic solvent suitable for GC -MS analysis. The MS detector was operated in single ion monitoring (SIM) mode. The extraction procedure was optimized via a Box-Behnken design considering extraction temperature, time, stirring rate and ionic strength, finding the following optimized parameters: 50 °C, 10 min, 2000 rpm, and a 10 % (w/v) aqueous solution. The optimized method underwent validation assessing LODs and LOQs in the concentration levels of 3–12 ng/L and 9–49 ng/L, respectively. Intra- and inter-day precision for all targeted compounds was <7.2 % and 11.3 %, respectively. The procedure achieved extraction recoveries for all 16 analytes in the 94.40–105.98 % range in 10 min of headspace extraction. Among the 16 PAH analyzed this method considered seven of the ones included in the EU framework, obtaining LOQs below the maximum allowable levels for naphthalene (LOQ: 24 ng/L), anthracene (LOQ: 9 ng/L), fluoranthene (LOQ: 21 ng/L, and benzo[a]pyrene (LOQ: 21 ng/L) while not for benzo[b]fluoranthene (LOQ: 24 ng/L), benzo[k]fluoranthene (LOQ: 22 ng/L), and benzo[ghi]perylene (49 ng/L).

3.4.2. Phenols

The EU and the US have established comprehensive regulatory frameworks to control phenolic compounds in water sources. However, their approaches and the range of regulated compounds vary significantly. A summary of the regulated phenols in each framework is provided in **Table S2**. In the EU, the introduction of the WFD established the principle of "priority substances" and set strict water quality targets. This approach has since evolved through legislative updates, with the recast Drinking Water Directive (2020/2184) now serving as the primary legislative instrument governing drinking water quality [142]. Although the EU has recently incorporated specific phenolic compounds, most notably BPA (discussed in Section 3.2), its current list of directly regulated phenols remains relatively narrow compared to the US. The EU also regulates nonylphenols and octylphenols in environmental waters, with stringent permissible levels of 2 μg/L and 0.1 μg/L respectively and sets a limit of 1 μg/L for pentachlorophenol [158–160]. Nonetheless, the sheer diversity of phenolic compounds, limited ecotoxicological data, and the complexity of establishing consistent regulatory infrastructure continueo pose substantial challenges to expanding EU regulations [161] . In contrast, the US EPA provides guidance for a broader suite of phenolic compounds, addressing eleven different species with maximum permitted concentrations in surface waters ranging from 0.03 μg/L (for pentachlorophenol) to 4000 μg/L (for phenol) [161]. Although federal guidelines under the Clean Water Act form a strong regulatory backbone, actual enforcement and the pace of updates often vary at the state level. This decentralized approach has allowed for the inclusion of more phenolic compounds, but it also leads to variations in standards and implementation across jurisdictions [161].

In recent years, several applications have been developed to remove phenolic compounds, including phenol, nitrophenols, and chlorophenols, from environmental waters using ES. Most of these studies have focused on type V ES, typically composed of thymol or menthol as the HBA and a fatty acid as the HBD [162–169]. These applications demonstrate the feasibility and potential of using such mixtures to achieve effective phenolic removal from wastewater. However,

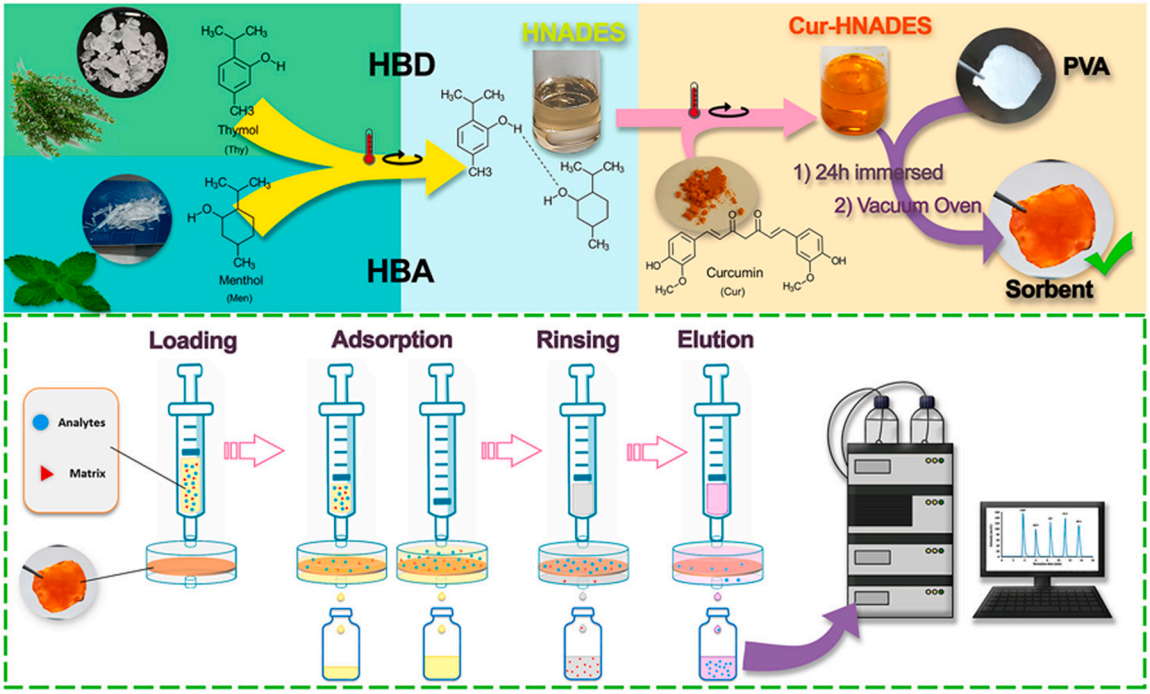

Fig. 4. Schematical workflow of the method proposed by Khodayari and Ebrahimzadeh exploiting a custom-made micro-SPE device. Reprinted with the permission of Khodayari and Ebrahimzadeh, 2023 [74].

although these approaches are innovative, this dissertation focuses on analytical methods for the quantification of phenols in real water samples, leveraging ES as extraction media. Readers interested in ES-based removal applications are referred to the aforementioned literature.

To the best of our knowledge, only a limited number of studies have applied ES. An, Ma, and Row employed a hydrophobic ES for the DLLME of chlorophenols from wastewater samples [88]. They pre-concentrated 4-chlorophenol, 2,4-dichlorophenol, and 2,4,6-trichlorophenol using eight different ES candidates, selecting methyltrioctylammonium chloride and octanoic acid in a 1:2 molar ratio. Their sample preparation involved adding 100 μL of ES to 1 mL of sample. The ES-rich upper layer was collected, and a 10 μL aliquot of this phase was injected into an RP HPLC-UV system ($\lambda = 225$ nm). The reported LODs ranged from 30 to 50 μg/L, and the LOQs from 100 to 170 μg/L, with RSD between 1.8 and 3.1 %. Recoveries were between 90.8 % and 93.0 % for all three analytes. However, LOQ for 2,4-dichlorophenol and 2,4,6-trichlorophenol were not compliant to meet the established limits.

Shortly after, Hu *et al.* presented the first ES-based approach meeting EPA requirements for the monitored chlorophenols [89]. They developed a DLLME method using an ES composed of α-terpineol and octanoic acid (1:2 molar ratio). In brief, 100 μL of ES and 100 μL of ACN were rapidly injected into a 3.2 mL aqueous sample, creating a cloudy dispersion. After 30 s of sonication and 5 min of centrifugation, the ES-rich phase was collected and analyzed by RP HPLC-UV ($\lambda = 270$ nm). Among the four phenolic compounds targeted (phenol, m-cresol, 2, 4-dichlorophenol, and 2,4,6-trichlorophenol), the latter two are EPA-regulated. This method achieved LODs and LOQs of 0.15 and 0.51 μg/L for 2,4-dichlorophenol, and 0.19 and 0.64 μg/L for 2,4,6-trichlorophenol, respectively, well below the EPA's maximum permitted concentrations. Recoveries ranged between 82 % and 99 %, with RSD values below 7.5 %, demonstrating that this ES-based approach not only met regulatory standards but also delivered satisfactory analytical performance.

3.5. Emerging contaminants

An emerging contaminant is defined as a substance that is not commonly monitored or regulated in the environment but has the potential to pose risks to ecosystems and human health [3].

These contaminants encompass a wide range of chemicals that are increasingly detected in environmental matrices such as water, soil, and air. Despite limited regulatory frameworks, emerging contaminants have gained significant attention from researchers, policymakers, and environmental agencies due to their persistence, mobility, and potential adverse effects [170].

3.5.1. Polyfluoroalkyl substances

In recent years, the body of literature on per- and polyfluoroalkyl substances (PFAS) has expanded substantially, reflecting their status as contaminants of emerging concern [171]. Although some PFAS were initially developed in the 1940s, their extensive use and potential health risks were not fully acknowledged until much later. These compounds are characterized by their resistance to degradation, tendency to bioaccumulate, and suspected links to a variety of health issues. As a result, PFAS have drawn considerable attention from environmental and public health authorities [172,173]. Although the use of ES in PFAS extraction is still in its early stages, some recent studies have begun exploring ES as alternative solvents for removing PFAS from environmental matrices.

New in silico approaches have broadened the prospects for identifying suitable ES as extraction media for PFAS. For instance, Gutiérrez *et al.* investigated an ES composed of cineole and linoleic acid (1:1 molar ratio) for the extraction of perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) from aqueous solutions [174]. Using density functional theory calculations and molecular dynamics simulations, the authors demonstrated a strong affinity of PFOA and PFOS for the ES. This interaction weakens the bonds between PFAS and water molecules, confirming the ES's capability to remove PFAS from aqueous environments.

Similarly, Fronchetti Guidugli and Reza employed COSMO-RS modeling to assess 456 potential ES combinations for the adsorption of perfluorobutanesulfonic acid (PFBS), perfluorobutanoic acid (PFBA), perfluorohexanesulfonic acid (PFHxS), and perfluorohexanoic acid (PFHxA) [175]. Their results showed that short-chain PFAS exhibit a higher affinity for ESs featuring five primary hydrogen bond

acceptors—trioctylphosphine oxide, trihexyltetradecylphosphonium chloride, tetraoctylammonium chloride, tetraoctylammonium bromide, and tetrabutylammonium bromide—and two hydrogen bond donors (camphor and l-arginine). The long-alkyl chain HBA provide extensive sigma density for nonpolar interactions and a large surface area conducive to hydrogen bonding, thereby enhancing short-chain PFAS affinity. Additionally, HBD with oxygen- and nitrogen-containing functional groups, such as ketones and amines, can form hydrogen bonds or engage in dipole–dipole interactions with PFAS, improving their extraction performance. After identifying the most promising solvent combinations, the authors conducted virtual modeling to evaluate human and environmental toxicity parameters (mutagenicity, carcinogenicity, bioaccumulation, and acute toxicity), concluding that these selected ES components exhibit minimal toxicity and pose negligible environmental risks. Although not yet tested experimentally, these in silico approaches lay the groundwork for future analytical methods that could enable more sustainable PFAS assessment in water samples.

To the best of our knowledge, only one practical ES-based application has been reported to date, focusing on the removal (rather than the analysis) of perfluoroheptanoic acid (PFHpA) [90]. Fortunato *et al.* developed LLE method using a hydrophobic ES composed of menthol and acetic acid (1:1 molar ratio). They extracted PFHpA from 5 mL spiked water samples by shaking with 5 mL of the ES for 5 s, then allowing the phases to separate. Optimal recoveries (80.2–90.1 %) were achieved after 120 min of phase contact at a neutral pH in the aqueous phase. The PFHpA concentration in the water phase was measured before and after extraction using UHPLC-Q-time-of-flight (ToF)-MS. Interestingly, the initial PFHpA concentration did not significantly affect extraction efficiency. Post-extraction, the aqueous solution's pH dropped to approximately 2.2 due to the partial leaching of acetic acid from the ES. Density functional theory calculations further confirmed strong non-covalent interactions between the hydrogen atom of the PFHpA carboxylic group and the oxygen atom in menthol, as well as between the hydrogen atom of the acetic acid carboxylic group and the oxygen atom in PFHpA. This work provides valuable insights into the molecular mechanisms underlying PFAS extraction by ESs and highlights the potential of ES-based strategies for PFAS remediation.

3.5.2. Flame retardants

The growing awareness of the potential risk associated with flame retardants has led these chemicals to be classified as emerging contaminants [176]. Flame retardants are chemicals added to materials to reduce their flammability and slow the spread of fires. Some flame retardants, such as organophosphate flame retardants (OPFR), have been found to possess toxic properties and are associated with various health concerns, including endocrine disruption, neurotoxicity, and reproductive effects [177]. Additionally, some flame retardants have been detected in remote regions far from their sources of use, indicating their widespread distribution and persistence in the environment [178,179]. In this field, some attempts have been made to exploit ES, as extraction media have been explored.

In 2020 Shahbodaghi *et al.* developed and optimized an extraction procedure for OPFR in river water, well water, and wastewaters [91]. The authors found the best candidate in the ES formed by benzyltriphenylphosphonium bromide (BTPPB) and 1-undecanol in 1:4 molar ratio. For sample preparation, 5 mL of water spiked with analytes at 1.5 μg/L was adjusted to pH 8.5. A 90 μL volume of the ES was injected into the sample, and the mixture was repeatedly drawn and ejected through a glass microsyringe to form a cloudy solution. This cloudy mixture was transferred to an SPE column containing 5 g of NaCl, and the dispersion passed through the salt layer in around 30 s at the flow rate of 2.5 mL/min. This step was implemented to promote phase separation, causing the ES phase to float to the top. The extracting layer containing the analytes was then collected into a widened bell-shaped extraction device. The ES phase was solidified by placing it in an ice water bath. After solidification of the ES phase, trapped in the bell-shaped extraction device, it was removed and placed in a vial. A schematic of the procedure is reported in Fig. 5. The ES rapidly melted at room temperature and was subjected to chromatographic analysis on a GC–MS/FID system. The method was validated by estimating LODs and LOQs between 2 and 23 ng/L and 9–56 ng/L, respectively, with relative recoveries in the range 95.6–104 %. Intra-day and inter-day repeatability values were estimated at ≤5.7 % and ≤8.2 %, respectively.

The same authors also developed a method for the same target analytes exploiting a magnetic ferrofluid incorporating the ES formed by BTPPB and 1-undecanol in 1:4 molar ratio [92]. The detailed ferrofluid synthesis procedure and its characterization are reported in the original work. Concerning the sample preparation, this involved the injection of 60 μL of ferrofluid in 5 mL of sample followed by 12 cycles of suction and injection to disperse the ferrofluid in the matrix thoroughly. The ferrofluid was then recovered with the aid of an external magnetic field. The analytes were desorbed from the ferrofluid using 30 μL of acetone under sonication for 4 min. The ferrofluid was once again removed using a magnet and the acetone phase was filtered prior GC-FID analysis. The method reported recoveries ranging from 98 to 103 %. LODs and LOQs were in the range of 2–23 ng/L and 10–50 ng/L respectively. Intra-day and inter-day repeatability values were estimated at ≤5.9 % and ≤8.1 %, respectively.

3.6. Multi-residue

In addition to ES-based extraction methods discussed earlier, some approaches have been developed to tackle a diverse range of contaminants in environmental samples. These multi-residue methods not only demonstrate the versatility of ES across various classes of pollutants, including explosives, emerging contaminants, and endocrine-disrupting compounds, but also reveal the evolving nature of ES applications in different matrices.

Zarei *et al.* introduced an approach for the analysis of explosive contaminants in environmental samples by combining a ferrofluid-based ES with directly suspended droplet microextraction (DSDME) [93]. In this approach, a drop of hydrophobic solvent, less dense than water, was directly introduced into the vortex of a stirring aqueous sample solution, allowing analytes to be extracted into the micro-droplet. A hydrophobic ES composed of menthol and decanoic acid (1:2) stabilized magnetic Fe_3O_4 nanoparticles immobilized on montmorillonite nanoclay. In this method, a 50 μL drop of the ferrofluid was added to a 10 mL sample containing 10 % w/v NaCl and stirred at 30 °C for 30 min. The analytes, including 2,4,6-trinitrotoluene, cyclotrimethylenetrinitramine, and various dinitrobenzene derivatives, were extracted into this droplet. After retrieval with a magnet, the ES phase was dissolved in ACN, desorbed, filtered, evaporated, and reconstituted prior to HPLC-PDA analysis. The method achieved LODs of 200–910 ng/L, enrichment factors of 23–93, and recoveries between 88 % and 104 %, with RSD values below 10 %.

In 2020, Morelli *et al.* developed a high-throughput technique that combined HF-microporous membrane LLE with an ES-based extraction phase [94]. The target analytes were 11 contaminants, including parabens, bisphenols, estrogens, and antibiotics in water samples. Thymol and camphor (1:1) were chosen as the ES due to their favorable viscosity and hydrophobicity, enabling effective impregnation of the polypropylene membrane pores. Utilizing a 96-well plate format, the authors extracted and then desorbed the analytes into ACN/water (50:50, %v/v) prior to HPLC-PDA analysis. Although the method achieved LODs of 300–6100 μg/L and LOQs of 1000–20,000 μg/L, it did not meet certain EU regulatory standards. For example, it reported a LOQ of 5000 ng/L for BPA, exceeding the EU Drinking Water Directive limit of 2500 ng/L. Similarly, for estrogens, the EU sets limits that are even more stringent, with EQS set at 0.4 ng/L and 0.035 ng/L for E2 and EE2, respectively, while the proposed method reported LOQ levels at 20 000 ng/L for E2 and 1000 ng/L for EE2.

More recently, Ortega-Zamora *et al.* developed a sample preparation

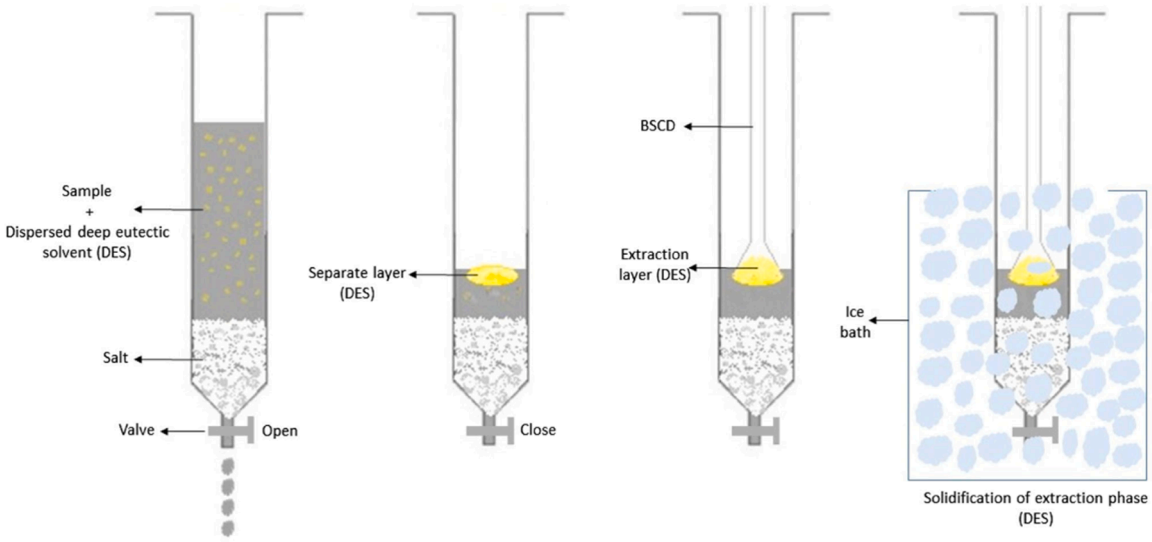

Fig. 5. Schematic workflow of the sample preparation procedure reported by Shahbodaghi *et al.*, 2020. From left to right: the dispersion is loaded onto an SPE cartridge consisting of a NaCl bed, the salting out effect promoted separation leading the ES to float on top, the ES is trapped in a widened bell-shaped extraction device (BSCD in the figure), finally the whole system is placed in an ice bath to solidify the ES phase and collect it. Reprinted with the permission of Shahbodaghi *et al.*, 2020 [91].

method using a hydrophobic ES made from fenchol and acetic acid (in 2:1 and 1:1 molar ratios) for DLLME followed by solidification of the ES [95]. This method was applied to extract 13 contaminants from different classes, including phthalates, bisphenols, estrogens, testosterone, and phenols, from seawater, wastewater, and urine. For extraction, 20 mL of sample was adjusted to pH 6.0, followed by the addition of either 100 μL (2:1 mixture) or 90 μL (1:1 mixture) of the ES. Vigorous stirring facilitated the transfer of analytes into the ES phase, after which centrifugation separated the ES from the aqueous phase. The ES was solidified by placing the sample in an ice bath, recovered with a spatula, and dissolved in ACN : MeOH (50:50, %v/v) for analysis. The authors optimized the method using HPLC-UV and validated it with UHPLC-ESI (±)-QqQ-MS. Chromatographic separation was performed in RP. The method achieved LOQs between 120 and 390 ng/L, with absolute recoveries ranging from 49 % to 100 % and RSDs below 19 %. Matrix effects were addressed through matrix-matched calibration due to ion suppression in all three sample types for most of the analytes. The method was applied to real samples and was aligned with green analytical principles, achieving an AGREEPrep score of 0.51 out of 1. Considering the analytes investigated, this method would be compliant for the analysis of 4-nonylphenol in the EU since it achieved an LOD in the range of 160–240 ng/L, depending on the matrix evaluated, against the 2000 ng/L imposed as maximum allowable concentration by the EU in wastewaters under the WFD. Other analytes such as EE2 and 4-octylphenols would not be compliant with EU standards since an LOD of at least 0.4 ng/L is required for the analysis of EE2 (this method achieved a LOD between 250 and 390 ng/L), while of 4-octylphenols the maximum allowable limit is set at 100 ng/L (this method achieved a LOD between 160 and 260 ng/L).

4. Future perspective and challenges

Although ES have demonstrated significant potential as greener alternatives to conventional organic solvents in the analysis of environmental contaminants, major challenges remain, and their broad implementation in regulatory frameworks is still in its infancy. From a methodological standpoint, a primary obstacle is the limited availability of fully characterized ES, including comprehensive solid–liquid phase diagrams and thermodynamic data. This restricts our ability to rationally design and select the most effective ES systems for specific analytes or matrices. This is further complicated by the vast theoretical number of possible ES combinations, making systematic screening and optimization a challenge. Additionally, while many ES are advertised as biodegradable and non-toxic, robust toxicity and biodegradability assessments are currently lacking, and the environmental fate of many ES, especially after repeated extraction cycles, remains insufficiently explored. Another pressing challenge is ensuring regulatory compliance: for emerging and established contaminants, existing ES-based methods frequently do not achieve the required sensitivity, selectivity, or reproducibility levels to meet strict international guidelines or maximum allowable concentration limits. To address these concerns, future research should adopt a more holistic approach, integrating in-depth toxicological evaluations, green analytical metrics, and machine learning or computational modeling tools (e.g., COSMO-RS) to guide solvent selection and method optimization.

In addition, integrating ES research with green analytical metrics and full life-cycle assessments will help quantify the overall environmental footprint of ES-based methods, ensuring that purported “green” benefits hold up under rigorous scrutiny. Tailoring ES formulations to novel extraction strategies, such as hybrid approaches with advanced sorbents or ferrofluids, can further improve efficiency and selectivity while minimizing solvent usage. Incorporating in situ solvent formation protocols may also reduce handling risks and drive down operational costs. Demonstrating that ES-based methods meet international guidelines for precision, accuracy, and reproducibility will be paramount for gaining broader regulatory acceptance. Finally, translating lab-scale findings into large-scale or commercial applications will require close engagement with industrial partners to refine production strategies, waste management, and cost analyses. By embracing these integrated, data-driven strategies and forging stronger collaborations across sectors, ES have the potential to become robust, sustainable alternatives in the monitoring of environmental contaminants, ultimately leading to greener and safer analytical practices.

CRediT authorship contribution statement

Andrea Schincaglia: Writing – original draft, Software, Investigation, Data curation, Conceptualization. **Alberto Cavazzini:** Visualization, Supervision, Resources. **Luisa Pasti:** Visualization, Supervision, Resources. **Giorgia Purcaro:** Writing – review & editing, Visualization,

Supervision, Project administration, Methodology, Conceptualization. **Marco Beccaria:** Writing – review & editing, Visualization, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

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

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.greeac.2025.100220.

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