



Magnetic deep eutectic solvents in microextraction techniques

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ABSTRACT

Magnetic deep eutectic solvents (MDESs) have recently produced a torrent of pioneering applications in endless areas of sample preparation. By including a magnetic nanomaterial (e.g., magnetic nanoparticles) or a paramagnetic anion (e.g., $[\text{FeCl}_4]^-$) in their structure, MDESs exhibit a strong response under the application of an external magnetic field. Furthermore, the use of MDESs, as a sorbent or solvent in extraction techniques, have been scarcely employed to develop green analytical methods, characterized by the avoid of time-consuming steps and the use of toxic organic solvents, as well as the application of small amounts of MDESs, for the determination of organic and inorganic contaminants, drugs, proteins, among others in environmental, food and biological matrices. This review highlights the application of MDESs in sample preparation in analytical chemistry. Challenges and future outlooks of new MDESs are also presented.

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1. Introduction

A cutting-edge solvent, deep eutectic solvent (DES) has been gradually emerging since 2003 as a greener alternative to ionic liquids. DES is commonly defined as a certain class of liquid at ambient conditions composed of two or more compounds, in which the melting point of the mixture is much lower than either of the pure compounds. For the preparation of DES it is necessary the formation of a hydrogen bonding complex between a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) at a well-defined stoichiometric proportion. One of the most employed DES is the one formed by complexing a quaternary ammonium (i.e., HBA) with urea, carboxylic acids or ammine (i.e., HBD) [1].

Recently, a new subclass of DES known as magnetic DES (MDES) has been the subject of intensified interest in the bibliography. Although early research in MDES was oriented toward synthesis and fundamental studies, the paramagnetic properties MDES have been an inspiration for new magnet-based technologies in analytical chemistry. This review will provide an overview of the applications of MDESs in (micro)extraction techniques.

2. DES-based magnetic solid phase extraction

In the conventional solid phase extraction (SPE), a cartridge containing the solid sorbent is employed for the purification and preconcentration of samples, since it removes the interfering compounds coexisting with the target analytes as far as possible, improving the sensitivity of the method. However, the conventional SPE presents the drawback of reduced selectivity and requiring too much labor and time-consuming.

Currently, magnetic solid-phase extraction (MSPE), as a type of SPE, is a new procedure for the preconcentration of target analytes from large volumes based on the use of magnetic sorbents. The sorbent particles can be simply separated and collected with an external magnet, which causes the sample pre-treatment procedure more convenient and time-saving, since the centrifugation step is avoided [2]. In addition, the sorbent can be reused, which enhances economy of use and decreases waste generation [3]. A high number of miniaturized versions of MSPE have been developed in the last years where one of the most important miniaturized modalities of MSPE is the magnetic dispersive micro-solid phase extraction (MD- μ -SPE) [4]. In this modality, a low magnetic sorbent amount (in the low milligram range) is directly dispersed into the sample matrix. In order to achieve adequate dispersion during the extraction, an external energy source to ensure strong forces, typically vortex or ultrasounds, is applied [5].

MSPE has greatly benefited from recent advances in magnetic nanomaterials (MNMs) as sorbents. This is the case of magnetic

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Abbreviation			
[ATEAm]Cl	Allyltriethylammonium chloride	MA	Mefenamic acid
3-MPA	3-Mercaptopropionic acid	MAA	Methacrylic acid
AA	Acrylamide	MCNT	Magnetic carbon nanotube
AcA	Acrylic Acid	MDES	Magnetic deep eutectic solvent
AFS	Atomic Fluorescence Spectrometry	MET	Magnetic effervescent tablet
AIBN	2,2-Azobisisobutyronitrile	MG	Malachite green
APTAC	(3-Acrylamidopropyl)trimethylammonium chloride	MGO	Magnetic graphene oxide
ATEA	Allyltriethylammonium	MIP	Molecular imprinting polymers
BHb	Bovine hemoglobin	MLPME	Magnetic liquid-phase microextraction
BSA	Bovine serum albumin	MMIP	Magnetic molecular imprinting polymers
ChCl	Choline chloride	MMOF	Magnetic metal-organic framework
CIP	Carbonyl iron powder	MMWCNT	Magnetic multi-walled carbon nanotube
CNT	Carbon nanotube	MNM	Magnetic nanomaterial
CV	Crystal violet	MNP	Magnetic nanoparticle
Cyt C	Cytochrome C	MOF	Metal-organic framework
DES	Deep eutectic solvent	MOIC	1-Methyl-3-octylimidazolium chloride
DNA	Deoxyribonucleic acid	MSPE	Magnetic solid-phase extraction
DODAC	dioctadecyl dimethyl ammonium chloride	MWCNT	Multi-walled carbon nanotube
DSDME	Directly suspended droplet microextraction	OA	Oxalic acid
EG	Ethylene glycol	OC	Ofloxacin
EGDMA	Ethylene glycol dimethyl acrylate	OVA	Ovalbumin
ETAAS	Electrothermal atomic absorption spectrometry	pCP	4-Chlorophenol
FAAS	Flame atomic absorption spectrometry	PEG	Polyethylene glycol
FF	Ferrofluids	Pg	Propylene glycol
GC-FID	Gas chromatograph with flame ionization detector	Pro	Proline
GC- μ ECD	Gas chromatograph with a micro electron capture detector	RNA	Ribonucleic acid
Gly	Glycerol	SBSDME	Stir bar sorptive dispersive microextraction
HBA	Hydrogen bond acceptor	SDS-PAGE-UV	Sodium dodecyl sulfate polyacrylamide gel electrophoresis and ultraviolet detection
HBD	Hydrogen bond donor	Sor	D-Sorbitol
HEMA	Hydroxyethylmethacrylate	SPE	Solid phase extraction
HPLC-DAD	High performance liquid chromatography with a diode array detector	TB	1-(<i>o</i> -tolyl)biguanide
HPLC-FLD	High performance liquid chromatography with a fluorescence detector	TBAC	Tetrabutylammonium chloride
HPLC-UV/Vis	High performance liquid chromatography with an ultraviolet visible detector	TCP	2,4,6-Trichlorophenol
HS-SDME	Headspace single drop microextraction	TEAC	Tetraethylammonium chloride
HTMAB	Hexyltrimethylammonium bromide	TNO	5,6,7,8-Tetrahydro-5,5,8,8-tetramethylnaphthalen-2-ol
IL	Ionic liquid	TNT	Trinitrotoluene
Ita	Itaconic acid	UA-LLME	Ultrasound assisted liquid-liquid microextraction
Lac	Lactic acid	UPLC-PDA	Ultra-high-performance liquid chromatography-photodiode array detector
LOD	Limit of detection	UPLC-QTOF-MS	Ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometer
Lys	Lysozyme	UV	Ultraviolet
		VP	Vinylpyrrolidone
		VTEO	Vinyltriethoxysilane
		Xyl	Xylitol

nanoparticles (MNPs), which are easily synthesized from a wide range of materials with ferromagnetic or superparamagnetic properties [6]. Among them, iron oxides like magnetite (Fe_2O_3) and maghemite ($\gamma\text{-Fe}_3\text{O}_4$) have been mostly used owing to their high magnetic moments, small size, high surface area, biocompatibility and ease of preparation [7,8].

Either bare or modified MNPs add unequal sorbent properties and custom selectivity to MSPE, which is intrinsically fast, simple, easy to operate and able to provide high preconcentration. It is also possible to functionalize these MNPs to achieve a selective extraction towards a particular species in the presence of others,

which avoids the use of instrumental separation techniques or other sophisticated equipment prior to detection. Speciation can greatly benefit from these features and hence the increasing number of papers using this strategy in the last years. Up to present, reviews have mainly focused on different topics related to new nanomaterials and SPE [9–13] and, in some of them, the use of MNMs in sample preparation for the determination of trace elements and organic compounds has been addressed.

Among all functionalized agents employed in the bibliography, DESs own the advantages of biodegradability, inexpensive and low toxicity, which make the entire regulatory process more in line

with the concept of green sustainable chemistry [14]. Thus, DESs have been extensively employed to extract both metals and organic compounds and many researchers have devoted to modify MNMs with DESs to improve performance, such as MNMs based on: (i) MNP, (ii) graphene, (iii) metal-organic framework (MOF), (iv) molecular imprinting polymer (MIP).

2.1. Magnetite nanoparticles

The most popular MNMs in MSPE are the MNPs based on Fe_3O_4 (i.e., magnetite). They show excellent features such as small size, high surface area, high magnetic moment, simple synthesis and low cost of production [15]. Nevertheless, bare MNPs based on magnetite possess few drawbacks such as (i) they tend to form assemblies, either aggregates, if the union is permanent, or agglomerates, if it is reversible [16], and (ii) poor selectivity towards the analyte [17]. In order to prevent aggregation and increase selectivity, the magnetic cores are usually modified with polymers, proteins, small organic compounds, carbon, metals and metal oxides or sulfides [18]. In recent years, DESs have been gradually applied to functionalize magnetite nanoparticles due to their unique physicochemical properties. For instance, they are simple to design, obtain, and they are biodegradable and nontoxic compared with conventional ILs and organic reagents [19]. However, their biodegradability and toxicity is in controversy [20]. As a result of these features, MNPs functionalization with different DESs have been employed as adsorbents for both organic compounds and elemental analysis.

Regarding elemental analysis, in 2016 Karimi et al. [21] reported for the first time a DES-based MNPs as a sorbent for ligand-less metal separation and preconcentration of lead and cadmium. The metal ions interact with the DES (a mixture of 1:2.5 M ratio of ChCl -urea) adhering to the MNPs and the trapped analytes can be easily desorbed with nitric acid and determined by FAAS. The method was successfully applied to the determination of lead and cadmium in soil, hair and several water samples (i.e., river, tap, well and sea water). In comparison with other reported methods in the bibliography, the MNM provides a higher enrichment factor (i.e., 100 for both metals) and a lower LOD (i.e., $0.4 \mu\text{g L}^{-1}$ for Pb and $0.1 \mu\text{g L}^{-1}$ for Cd) in comparison with those obtained by direct FAAS. Recently, Liu et al. [22] studied the use of magnetite nanoparticles functionalized with DES (i.e., mixture 1:2 of ChCl :urea) as a sorbent in MSPE for preconcentration of Cu and Pb in certified reference materials (i.e., soil and stream sediments) and real-world samples (i.e., lake and tap water and soil). In addition to the optimization of the conditions affecting the extraction efficiency, the effect of common coexisting ions on the adsorption of Cu and Pb on the MNM was also investigated. The authors confirmed that the presence of major cations and anions has no significant influence on the preconcentration of Cu and Pb, obtaining recovery values in the range of 94–102%. These results demonstrated the feasibility of this method in environmental samples.

Regarding organic analysis, Wang et al. [23] developed an analytical method combining MSPE with UPLC-PDA for the determination of four sulfonylurea herbicides (i.e., sulfosulfuron, bensulfuron-methyl, pyrazosulfuron-ethyl and halosulfuron-methyl) in real-world samples (i.e., lake, rice field and drinking water). They synthesized magnetite nanoparticles covered by polydopamine and DES and they employed as a sorbent in MSPE procedure. The author concluded that the proposed method has potential to be applied in the analysis of pesticide residue and provide a promising alternative for sample pretreatment in complex matrix. More recently, Jamshidi et al. [24] synthesized a DES-based hydrogel using AcA-menthol DES (as a functional

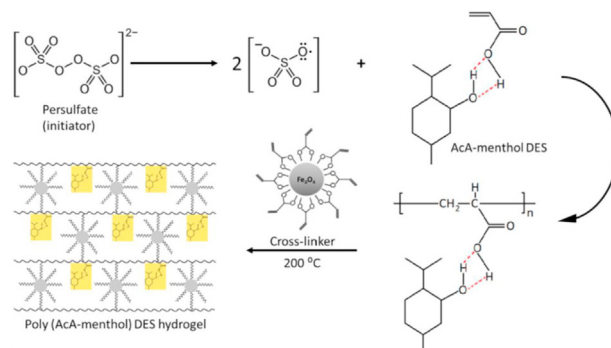


Fig. 1. The frontal thermal polymerization reaction of AcA-menthol DES via radical polymerization by ammonium persulfate (as initiator) and AcA- Fe_3O_4 (as cross-linker) to form the poly (AcA-menthol) DES- Fe_3O_4 hydrogel. Reprinted from Ref. [24]. Copyright (2020), with permission from Elsevier.

monomer), ammonium persulfate (as initiator), and AcA- Fe_3O_4 nanoparticles (as cross-linker) (Fig. 1).

In this synthesis, the polymerization of AcA proceeded with a radical polymerization mechanism. The side chain polymerization also occurs via radical transfer from ammonium persulfate radicals to carbon atoms of the AcA growing chain. After heating up to 200°C , the magnetic hydrogel was utilized in MSPE as sorptive phase. The authors compared the extraction efficiencies obtained with the magnetic hydrogel functionalized with and without DES and they confirmed a significant increase (i.e., nearly two times over) in the extraction efficiencies of the pesticides when the magnetic DES-based hydrogel was used. The LOD values obtained by the authors using GC- μECD (i.e., 0.002 – $0.120 \mu\text{g L}^{-1}$) were slightly lower than other methods, even those coupled with the sensitive MS detection systems [25] (i.e., 0.002 – $0.597 \mu\text{g L}^{-1}$), indicating the higher sensitivity of the developed method.

The use of DES as a functionalization agent of Fe_3O_4 MNPs coated with SiO_2 [26] or TiO_2 [27] is also possible. Xu et al. [26] applied for the first time the magnetic composite for determination of trypsin in crude bovine pancreas extract. The DES was obtained by mixing ChCl and itaconic acid (molar ratio 1:1), and then, was coated on the surface of the magnetic composite. The authors compared the extraction capacity of the proposed magnetic material with those from the bibliography [28–31] and they conclude that the magnetic microspheres functionalized with DES displayed a higher extraction capacity (287.5 mg/g) on trypsin. In addition, a slight loss in extraction capacity was detected after six consecutive extraction-desorption cycles, which demonstrated the good stability and reusability of the prepared magnetic microspheres. More recently, Li et al. [27] synthesized a magnetic titanium dioxide nanoparticles (i.e., Fe_3O_4 MNPs coated with TiO_2) functionalized with DES composed of ChCl and Xyl for the determination of a cancer biomarker (i.e., chymotrypsin) in porcine pancreas crude extract.

2.2. Carbon-based magnetic nanomaterials

In the past decade, it has been seen intense interest grow in carbon-based nanomaterials as a sorbent in analytical chemistry [32]. Specially, graphene has been widely used as adsorbent [33], since its high specific surface area, inherent hydrophobicity, tunable chemical structure, cost-effective and scalable synthesis [34]. Among all carbon-based MNMs, magnetic graphene oxide (MGO), magnetic carbon nanotube (MCNT) and magnetic multi-walled carbon nanotube (MMWCNT) have been functionalized with DESs in order to increase the water dispersion and improve

the extraction efficiency of analytes in water samples. For the first time, Huang et al. [35] reported the functionalization of MGO (i.e., graphene oxide decorated with magnetite nanoparticles) with DES (i.e., mixture 1:1 of ChCl:D-Glucose) for the extraction of four proteins (BSA, OVA, Lys, BHB) in model samples. Unfortunately, the authors did not assess the MNM extraction capability in real-world applications. When the authors compared the extraction efficiency using the MGO coated with and without DES, they observed that three forces (i.e., hydrogen bonding, hydrophobic interaction and electrostatic interaction) affected in different extent for both MNMs. For MGO-DES, the functionalization makes the hydrogen bonding stronger, because there are many hydroxyl groups in DES. In contrast, hydrophobic interaction may be little, since there are no long alkyl chains. In addition, the surface charge is positive, and therefore, the electrostatic interaction improves the extraction capacity only for negatively charged proteins (i.e., isoelectric point below the sample pH) but not neutral and positively charged proteins. In their experiments in ultrapure water (i.e., pH = 6.32), the MGO-DES (i.e., positively charged surface) improved the extraction efficiency only for BSA (pI = 4.8) and OVA (pI = 4.7). In contrast, MGO (i.e., negatively charged surface) enhanced the extraction efficiency of BHB (pI = 6.9) and Lys (pI = 11.0). Therefore, the existence of DES can help to improve the extraction capacity only for acidic proteins. Finally, the authors exposed that the MNMs can be easily recycled, but the extraction capacity shows significant loss when reusing, making them a single use sorbent. One year later, the same research group [36] reported the use of MGO functionalized with a different DES (i.e., mixture 1:1 of ChCl:Glycerol) for the extraction of the same proteins. In this work, the researchers evaluated the analytical method with real-world samples (i.e., bovine whole blood) with satisfactory result. Finally, in 2020 [37], the researchers successfully extracted BSA from calf serum using MCNT decorated with MNPs and coated with DES (i.e., mixture 1:1 of APTAC:Xyl). In addition, the MNM was applied to sequential extraction-elution procedure, in order to demonstrate its reusability. For this propose, the sorbent was magnetically separated, eluted, dried and recycled, repeating the procedure several times. After seven cycles of regeneration, the extraction capacity of the MNM remained relatively stable. To conclude, the authors compared with previous sorbents and the proposed MNM shows a series of advantages, including faster magnetic separation, less dosage, shorter extraction time and higher extraction capacity. Another research group developed an analytical method for pre-concentration of methadone in urine and plasma samples followed by GC-FID and GC-MS [38]. In this research, the GO are decorated with Fe₃O₄ MNPs and functionalized with the DES composed of ChCl and TNO (molar ratio 1:2). The authors confirmed the strong interaction between them by comparison of infrared spectra of pure DES with and without the MNPs. The authors concluded that the simplicity of this method, with a high enrichment factor (i.e., 250), were the main advantages of this method.

In the field of elemental analysis, Chen et al. [39] employed for the first time MGO functionalize with DES (i.e., mixture 2:1:1 of ChCl:Ita:3-MPA) for removing mercury in contaminated water from ore deposits. The authors demonstrated that the pH was a critical factor to the removal efficiency, and they investigated the sample pH from 3.0 to 10.0. The removal efficiency was raised with the increased of the sample pH, reaching a maximum (i.e., 99.91%) at pH 6. The authors observed that removal efficiency decreased when the pH value increased. The researchers explained that at pH 6 the dominant species were Hg²⁺ and Hg(OH)⁺ ions and the opposite-charged of both ions and surface charge of the MNM (pI = 2.5) promoted the removal process. On the contrary, at pH 7 the dominant species were Hg(OH)₂ and Hg(OH)₃⁻. Furthermore, the MNM can be recycled, since after seven consecutive adsorption-

desorption cycles, the removal efficiency had a slight loss (from 99.91 to 90.23% of removal efficiency). Therefore, these results demonstrated that the successfully regeneration of the synthesized MNM. In addition, the authors also studied the effect of different kinds of ions to evaluate the interferences of the proposed method. The results indicated that the MNM had high tolerable limit (i.e., in case of Na, 40 M ratio of interfering ions to Hg²⁺), being the recovery error caused by interfering ions less than ± 5%.

If graphene sheets are rolled into a cylindrical shape, CNTs are obtained, and what is more, if several CNT are nested inside one another, MWCNTs are formed. In recent years, MMWCNTs, especially after suitable functionalization, are being proposed as emerging sorbents for numerous MSPE procedures [40]. Nevertheless, the functionalization of MMWCNT using DES has not been wide explored so far and only one application can be found in the bibliography where Xu et al. [41] developed an analytical method for DNA extraction. In this work, the authors reported the use of MMWCNT (i.e., MWCNT decorated with Fe₃O₄ nanoparticles) coated with DES (i.e., mixture 1:1 of TEAC:PEG).

Another carbon-based MNM employed in the bibliography was activated carbon. Zhao et al. [42] employed a MNM based on porous activated carbon decorated with Fe₃O₄ MNPs to perform a quite promising extraction procedure using a magnetic effervescent tablet (MET). The authors applied this analytical method for the analysis of phenolic endocrine disrupting chemicals (i.e., bisphenol A, *p*-*tert*-octylphenol, and nonylphenol) in three types of environmental waters (i.e., well water, river water, sea water). In this procedure (Fig. 2), the sample was rapidly injected into a centrifuge tube containing the DES (a mixture 1:3 of HTMAB and 1-dodecanol). Then, the magnetic effervescent tablet containing CO₂ source (sodium bicarbonate and citric acid) and the carbon-based MNM was used to combine extractant dispersion and magnetic phase separation into a single step. In the process of magnetic effervescence, the MNM was homogeneously distributed into the aqueous sample, facilitating the collection of extraction solvent. Then, the MNM containing the extraction solvent was isolated from the aqueous phase by an external magnet. After sample removal, acetonitrile was added as the eluent and was analyzed by HPLC-FLD.

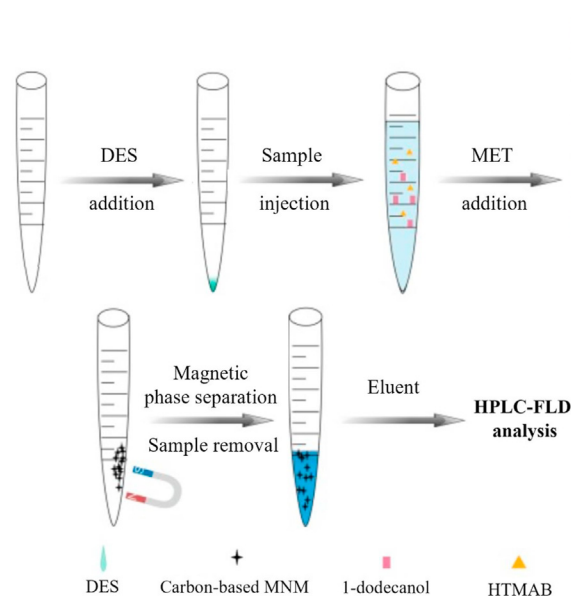


Fig. 2. Schematic diagram of the extraction procedure using the magnetic effervescent tablet. Reprinted from Ref. [42]. Copyright (2020), with permission from Elsevier.

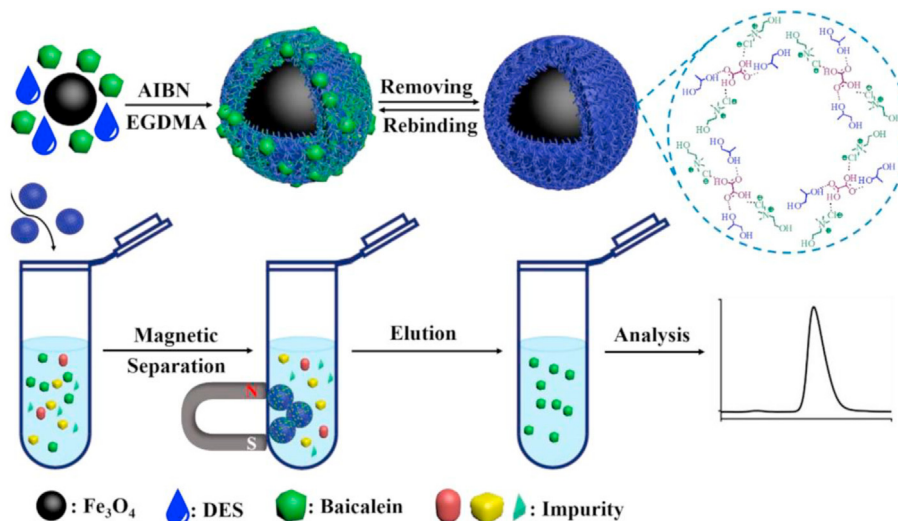


Fig. 3. Schematic diagram of separation and enrichment of baicalin by DES-MMIPs from the extract of *S. baicalensis*. Reprinted from Ref. [54]. Copyright (2020), with permission from Elsevier.

2.3. MOF-based magnetic nanomaterials

Metal-organic frameworks (MOFs) are highly porous-crystalline hybrid materials assembled by metal ions or metal clusters and organic ligands through coordination interaction [43]. The superior adsorption capacities provide effective extraction of several target analytes as ionic forms. The incorporation of MNMs into MOFs results in the formation of a promising composite materials with property synergies unmatched by the individual constituting components [44]. Subsequently, magnetic metal-organic framework (i.e., MMOF) composites, have received considerable attention from researchers in recent times due to their properties such as magnetism and surface area. Furthermore, the combination of MMOF and MSPE is fortified because of excellent properties of each one individually, leading to fast, convenient, and high-yield extraction in complex matrices [45]. In addition, DESs have been found a special position in the functionalization of MMOF since their unique physicochemical properties like rich biodegradability, biocompatibility, proper stability, simple synthesis route, and low price. The MMOF (i.e., MOF decorated with iron-based MNPs) coated with DES for the selective separation of cationic dyes (i.e., MG and CV) from real fish samples was performed by Wei et al. [46]. The DES is composed of APTAC and Sor (molar ratio 2:1), which readily prepared only by stirring the two components at 95°C until forming a homogeneous transparent liquid. The authors explained the extraction phenomenon through Lewis acid-base reaction. In this study, the magnetic composite possessed numerous nitrogen atom owning lone pair electrons, which can be acted as an electron-donating Lewis base, whereas cationic dyes can be seen as Lewis acid. The analytical technique used was a UV-vis spectrophotometer and the proposed analytical method exhibited a limit of detection of 98.19 ng mL⁻¹ for MG and 23.97 ng mL⁻¹ for CV. Finally, the authors claimed that even though the extraction amount of MG and CV decreased every cyclic extraction, the magnetic sorbent maintained a considerable extraction amount after five consecutive extraction-desorption cycles. The same research group investigated the use of DES-MMOF for selective adsorption of pharmaceutical and personal care products (i.e., MA and OC) [47] and for extraction of RNA from medicinal yeast [48].

Recently, a new class of MOF called zeolitic imidazolate framework (ZIF) has received significant attention in catalysis, gas separation and sensing due to its unique performance of high surface area, excellent chemical stability and abundant structural diversity [49]. ZIFs are composed of tetrahedrally-coordinated transition metal ions connected by imidazolate linkers. Since the metal-imidazole-metal angle is similar to the angle in zeolites, ZIF has zeolite-like topologies. Liu et al. [50] fabricates for the first time a composite using DES (i.e., mixture 1:2 of MOIC:1-undecanol) and magnetic ZIF (i.e., ZIF functionalized with Fe₃O₄ MNPs). The magnetic composite was applied as an adsorbent for MSPE of pyrethroid pesticides from environmental water samples. After the optimization of adsorption and desorption parameters and the validation of the proposed method in terms of linearity, LOD, and precision, the authors successfully analyzed four pyrethroid pesticides (i.e., cyhalothrin, cyfluthrin, cypermethrin, flucythrinate) in well, river and ground water samples.

2.4. MIP-based magnetic nanomaterials

Molecular imprinting polymers (MIPs) are a type of molecular specific recognition sorbent that has developed rapidly in recent years [51]. In this way, molecular imprinting is a powerful and versatile technique, where the imprint molecule (i.e., template) is added along with functional monomers, and high proportions of cross-linker, which are polymerized under appropriate conditions. During the reaction, polymeric chains self-organize around the imprint molecules through functional group interactions. Finally, the imprint molecules can be removed from the polymeric matrix, as a result, the MIP contains tailor-made binding sites in terms of their shape, size, and functional groups for the precise recognition of specific biological and chemical compounds. Lately, magnetic molecularly imprinted polymers (MMIPs), in which polymers are prepared producing the MIP on the surface of a magnetic substrate, have attracted significant attention attributing to the fact that they not only exhibit specific selective binding for the template molecule but also have magnetic properties [52]. Therefore, the MMIPs, compared with conventional MIPs, show many superior characteristics involving fast and effective binding to target analytes, magnetically susceptible characteristic, and shorter pretreatment

time [52]. It is well-known that the powerful analyte recognition ability of MMIPs is attributed to the interaction between the template molecules and the functional monomer, as a consequence, functional monomer plays an important role in the preparation of MMIPs, which is a key factor to enhance the extraction efficiency and selectivity [53]. However, most functional monomers commonly used in the synthesis of MMIPs are toxic and several researchers have proposed the use of DES as a green functional monomer. Furthermore, DESs have more functional groups ($-\text{COOH}$, $-\text{NH}_2$ and $-\text{OH}$) than traditional functional monomers, and therefore, there are more binding sites and stronger interaction between functional monomers with template molecules in DES-MMIPs than traditional MMIPs. Moreover, DESs have good solubility to polyphenols, which can make the templates completely dissolved in the system [54]. For all these reasons DES-MMIPs have been widely used in recognition of small molecules in recent years. For instance, in the determination of catechins from green tea [55] and black tea [56], flavonoids from the *Scutellaria baicalensis* [54], chlorophenols from environmental water [57], aristolochic acid in biological samples [58], tanshinones from *Salvia miltiorrhiza bunge*, *Glycine max* and green tea [59], alkaloids from green tea [60], monosaccharide and polysaccharides from seaweed [61,62].

An example of synthesis and application of the DES-MMIP in separation and enrichment of baicalein from an extract of *S. baicalensis* is shown in Fig. 3. First, the DES, baicalein (i.e., template), and the Fe_3O_4 MNPs were mixed and dispersed by ultrasound. Later, it was added the EGDMA (i.e., cross-linker) and the AIBN (i.e., initiator) and the polymerization was performed. Then, the prepared DES-MMIP particles were collected by a magnet and washed for removing the template. Afterwards, the DES-MMIPs were added into an extract solution to enrich baicalein from the *S. baicalensis*. The mixture was shaken and the DES-MMIPs were collected and separated from the extract solution by a magnet. Subsequently, DES-MMIPs were washed, and the eluent was analyzed by HPLC-DAD.

While the imprinting of small molecules is straightforward, the preparation of MMIP against biomacromolecules, such as proteins, remains a challenge due to its complex conformation, flexible structure and large size [63]. Due to the fact that DESs have abundant functional groups, some efforts have been made to introduce DESs in the synthesis procedure of MMIPs to improve the affinity and selectivity of proteins. Liu et al. [64] synthesized a MMIP for the selective recognition and separation of BHB from the mixture of proteins in real samples. The DES-MMIP showed a high recognition and selectivity (i.e., high imprinting factor) when proteins like Lyz, BSA and OVA are presented with BHB. The imprinting factor is defined as the ratio of adsorption capacity of the protein on the DES-MMIP and the non-imprinted polymer. In this study, the imprinting factor values of DES-MMIPs for BHB, Lyz, BSA and OVA were 4.40, 2.22, 2.41 and 0.36, respectively. The authors also evaluated the reusability and stability of the DES-MMIP by repeating the adsorption-elution cycle using the same sorbent. After three adsorption-elution cycles, the adsorption capacity decreased 7.93%, and the authors claimed that the reduction in adsorption capacity may be as a consequence of the damage of some imprinted cavities for BHB in the repeated adsorption-elution cycles. For verifying the effective applicability of the DES-MMIP in real-world sample, the calf blood was analyzed by gel electrophoresis with UV detector. The analysis showed a high selectivity toward BHB in real-world sample, showing a great potential to separate BHB from the calf blood.

In later years, the same research group study the use of different DES-MMIPs for specific adsorption of different proteins: (i) a mixture 1:1 of ATEA:Gly was chosen as functional monomer supported on silica-coated MNPs ($\text{Fe}_3\text{O}_4@/\text{SiO}_2$) for specific recognition

of Lyz in chicken egg white [65], (ii) a mixture 1:2 of APTAC:urea was prepared as functional monomer supported on MNPs (i.e., Fe_3O_4) functionalized with VTEO for specific extraction of BHB in calf blood [66], and (iii) a mixture 2:1 of HEMA:TEAC was employed as functional monomer and the mixture 1:1 of AA:APTAC was used as cross-linker for the specific recognition of BHB in bovine blood [67].

Although the research on the DES-MMIPs is still in its infancy, it provides a new perspective for the combination of DESs and MMIPs in recognition and separation of proteins, promoting a new research field with a promising prospect.

3. DES-based ferrofluid microextraction

Ferrofluids (FFs) are stable and uniform solid-liquid composite materials consisting of MNMs suspended in base fluids. They were used for the first time in 2010 by Shi et al. in microextraction technique [68]. In recent years, significant efforts have been devoted to change the common base fluids for DESs to make new FFs with suitable features.

3.1. Metal oxide-based ferrofluids

The first work using a DES-based FF was reported by Zarei et al. [69]. In this work the authors employed a DES-based FF to analyze explosives in water and soil samples. The FF was composed of montmorillonite clay and Fe_3O_4 -based MNPs, as an MNM, and a mixture 1:2 of menthol and decanoic acid, as a base fluid. The proposed DES-based FF has high adsorption capacity, and stability against sedimentation that makes it as a suitable extraction solvent in DSDME. In this extraction procedure, a micro-droplet of FF was suspended into the vortex of a stirring aqueous solution and after completing the extraction process, it was separated from the solution by a magnetic rod.

Fan et al. [70] described a method using a FF based on DES for the extraction of polycyclic aromatic hydrocarbons in coffee samples. In this work, the authors selected the optimal DES employing a predictive model, providing a fast and effective route for the DES selection with remarkable economic and environmental advantages. Besides, the microextraction mechanism of the FF was elucidated in depth via quantum chemical calculations. The FF consisted of MNPs (i.e., Fe_3O_4) and a mixture of menthol, borneol and camphor in a molar ratio of 5:1:4. The analytical technique used was a HPLC-DAD and the proposed analytical method offered noticeable improvements toward ecofriendly analysis of polycyclic aromatic hydrocarbons with high selectivity, high sensitivity (LOD 0.31–5.9 ng L^{-1}) and high recovery values (91.3–121%). Finally, this method was successfully applied to determinate the ultratrace polycyclic aromatic hydrocarbons in coffee samples with total concentration ranged from 0.05 to 0.58 $\mu\text{g kg}^{-1}$. Other research group investigated the determination of polycyclic aromatic hydrocarbons in grilled meats [71] and in urine and saliva samples of tobacco smokers [72]. Interesting results were obtained in both works. From the first one, fluoranthene and pyrene were found in all Kebab Koobideh samples and three of four grilled hamburger samples in the ranges of 319–742 and 386–725 ng kg^{-1} , respectively. In case of fluorene was found in two grilled hamburger samples at the concentrations of 319 ± 23 and 436 ± 29 ng kg^{-1} . Fortunately, the concentration levels are lower than the Commission Regulation (EU) No 835/2011 [71]. From the second research work [72], six samples of urine and saliva were obtained from six male smokers at 0, 1, and 3 h after smoking. The obtained results show that anthracene, chrysene, fluoranthene, fluorene, naphthalene, and phenanthrene were found in all samples in different sampling times and the analytes concentrations in urine and saliva

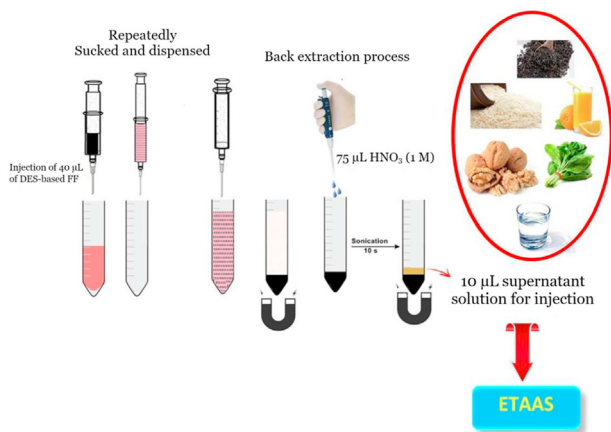


Fig. 4. Scheme of the proposed analytical method for the metal extraction using DES-based FF. Adapted from Ref. [81]. Copyright (2019), with permission from Elsevier.

samples were in the range of 42–489, and 89–641 ng L⁻¹, respectively.

Another research group investigated the use of Fe₃O₄ MNPs coated with SiO₂ in the DES-based FF for the determination of organic compounds in food [73] and biological [74] samples. Majidi et al. [73] developed an analytical method for the preconcentration and determination of morin in dried onion and green tea infusion samples, and apple and grape juices. The authors synthesized a stable DES-based FF since the formation of hydrogen bonds between the hydroxyl groups on the surfaces of the magnetic sorbent and the hydroxyl groups of the DES. In this work the DES was obtained mixing TEAC:EG in a molar ratio of 1:3. In order to evaluate the role of the DES in the FF, the authors compared the extraction efficiency of the proposed method with the FF and only the magnetic composite (i.e., Fe₃O₄ MNPs coated with SiO₂). The authors claimed that the synergistic effect of DES and the magnetic composite in the FF improves the adsorbing properties and extraction performance. To confirm this claim, they performed the same analysis using only the magnetic composite in optimum condition and the obtained recovery was 56% ± 2. One year later, the same research group [74] developed a DES-based FF containing silica-coated Fe₃O₄ MNPs and a mixture of ChCl and EG (molar ratio 1:2) for the determination of meloxicam in human blood plasma and urine samples. The authors concluded that the proposed method exhibited remarkable features such as low-cost, a fast extraction process (lower than 1 min), a simple extraction process, and high recovery (above 90%), which make it suitable for clinical and routine use analyses. More recently, Fan et al. [75] described the preparation of a FF based on the mixture of ChCl and TB (molar ratio 1:1) with Fe₃O₄ MNPs. The DES-based FF was employed for direct extraction of perfluoroalkyl carboxylic acids from edible oils by UPLC-QTOF-MS. The authors conducted a comprehensive comparison with reported studies using other mass spectrometric techniques for the determination of perfluoroalkyl substances in oils and they concluded that the proposed analytical method resulted in a rapid (15 min for pretreatment), simple, sensitive (detection limit: 0.3–1.6 pg g⁻¹), and efficient analytical method for the enrichment and determination of trace perfluoroalkyl substances. In addition, the authors highlighted that the synthesis of the DES-based FF is extremely easy without complicated steps and hazardous organic solvents.

To our knowledge, only one publication has reported up to now about the use of metal oxide-based ferrofluid for the preconcentration of heavy metals. Kasa et al. [76] developed a method for the determination of cadmium at trace levels in eucalyptus and

rosemary tea samples using Fe₃O₄ MNPs suspended in DES (i.e., mixture of 1:3 M ratio of ChCl:Phenol). The authors compared the proposed method with and without the use of the FF-based microextraction, and an enhancement factor of 80 was achieved.

3.2. MMWCNT-based ferrofluids

Among the mentioned MNMs from the above section, MMWCNTs have been widely used as MNM in FFs. In recent years, attention has been paid to elaborate new MMWCNT suspension in DES matrix to make new FFs with favorable properties. Particularly, the research group of Ghorbanian et al. have been working in the development of MMWCNT-based ferrofluid since 2017. In the first study [77], they investigated the use of a FF obtained from the combination of ChCl:urea at molar ratio 1:2 as a DES with MMWCNT for ultra-trace analysis of 18 organochlorine pesticides in four environmental water samples (i.e., farm water, rural water, lake water and river water). In this work, the authors highlight the advantages of functionalization with hydrophilic DES, since it acts as a bridge between MMWCNTs and water samples. Consequently, it improves the dispersion of MMWCNTs and makes a stable dispersion in water against sedimentation. In addition, the FF was stable for weeks without visually observable sedimentation. The researchers claimed that the extraction time is dramatically decreased due to the highly stable dispersion of magnetic sorbent in the bulk solution and extraction can be achieved in few seconds. In a second article [78], they employed the same DES-based FF for ultra-trace determination of nitroaromatic explosives in wastewater from TNT purification process by GC-μECD, obtaining extremely low LOD (i.e., 0.8–12.4 ng L⁻¹). In a third work [79], they decreased the LOD in the analysis of nitroaromatic explosives using the same analytical technique (i.e., GC-μECD). For this propose, the stir bar sorptive dispersive microextraction (SBSDE) was employed to enhance the extraction efficiency. In this extraction technique, the DES-based FF was attached to the coating of neodymium core magnetic stir bar by means of magnetism. Besides, they prepared another FF based on the mixture of ChCl and resorcinol with a molar ratio of 1:2. With the combination of the SBSDE and the new FF, a lower LOD was achieved (i.e., 0.22–4.92 ng L⁻¹). Finally, in a fourth research [80], an analytical method was proposed for the determination of benzene, toluene, ethylbenzene, and xylene isomers as harmful volatile organic compounds in water and urine samples by GC-FID. In this study, the FF based on the mixture of ChCl and chlorophenol (i.e., 1:2 M ratio) was coupled for the first time to headspace single drop microextraction (HS-SDME) technique. The appropriate characteristics of the FF (i.e., high magnetic susceptibility and high viscosity) resulted in a highly stable droplet, eliminating the possibility of drop dislodgement. In addition, the DES-based FF droplet made it possible to complete the extraction process with high temperatures and elevated agitation rates, achieving an enrichment factor of 520–587 and LOD values of 0.05–0.90 μg L⁻¹.

Other research groups also investigated with MMWCNT-based FF to separate and preconcentrate trace/ultra-trace level of inorganic [81] and organic [82] analytes. Shirani et al. [81] proposed an analytical method for the determination of cadmium, lead, copper, and arsenic from walnut, rice, tomato paste, spinach, orange juice, black tea, and water samples by ETAAS. The authors prepared the FF dispersing the MMWCNT in urea:ChCl DES (molar ratio 2:1). In this work, the FF was added to the sample solution containing the inorganic analytes. Then, the mixture was repeatedly and rapidly sucked from the tube and dispensed into it with a syringe for six times. A turbid solution consisting of fine droplets of DES-based FF dispersed in the sample solution was formed. Subsequently, the FF was separated from the solution using an external magnet and the

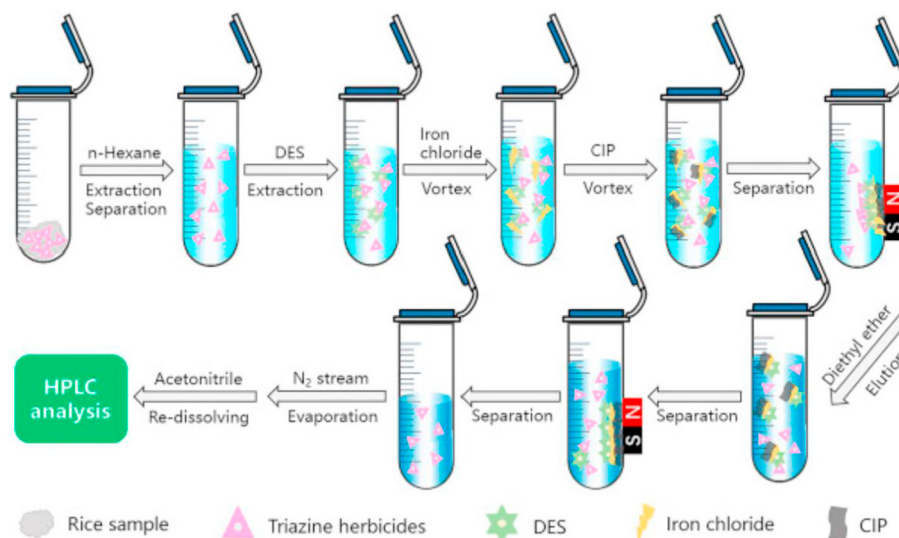


Fig. 5. Analytical methodology based on the in-situ generation of MDES. Reprinted from Ref. [85]. Copyright (2021), with permission from Elsevier.

supernatant was taken away. Since the DES-based FF is not a suitable solvent for ETAAS measurements, the authors performed a back-extraction step with nitric acid. After nitric acid solution addition, analytes from FF were transferred by sonication into the acid solution and finally detected by ETAAS. The analytical procedure is shown in Fig. 4.

In case of organic analysis, Zhao et al. [82] established a DES-based FF extraction method for the simultaneous determination of four sex hormones (i.e., ethinylestradiol, norgestrel, megestrol acetate and medroxyprogesterone acetate) in cosmetic skin care toners (i.e., moisturizing, whitening and anti-wrinkle) followed by HPLC-DAD.

4. Intrinsic MDES-based microextraction

Intrinsic MDES strongly respond to external magnetic field in addition to having unique and tunable physicochemical properties of DES, allowing their application as extraction solvents in both aqueous and non-aqueous samples. Contrasting with FFs, intrinsic MDESs are MNM-free magnetic liquids, this mean that they are intrinsically paramagnetic due to the magnetic component is part of the DES structure, being the anion $[\text{FeCl}_4]^-$ the most employed in intrinsic MDESs. The recent advances in analytical chemistry indicate that they have been employed in magnetic liquid-phase extraction (MLPE). As in MSPE, the extraction procedure can be accelerated by magnetic phase separation. Therefore, the time-consuming step of centrifugation is eliminated. The development of MLPE procedures using intrinsic MDESs is relatively new and the first research was published in 2016 by Khezeli and Daneshfar [83]. They demonstrated for the first time the application of two new intrinsic MDESs as extractant solvents for UA-LLME of thiophene. Two ternary MDESs were evaluated including $[\text{ChCl}/\text{phenol}][\text{FeCl}_4]$ (molar ratio 1:2:1) and $[\text{ChCl}/\text{EG}][\text{FeCl}_4]$ (molar ratio 1:4:1). The results obtained in this work showed that 20 μL of the first MDES was enough to achieve a high extraction efficiency (close to 100%) of thiophene in a model solution of n-heptane. The second research involving the use of intrinsic MDES was carried out by the same research group [84] for determination of hexanal and heptanal in commercial edible oils (i.e., olive, sunflower, and soybean oils). They synthesized a new MDES composed by $[\text{ChCl}/p\text{-cresol}][\text{FeCl}_4]$ in a molar ratio of 1:3:1. In this work, the MDES used was not compatible with the analytical instrument (i.e., GC-FID) and a back-

extraction procedure using a mixture 1:1 of ethyl acetate and cyclohexane was performed. Back-extraction solvent and MDES were sonicated and the back-extraction solvent was injected into the GC-FID system.

Recently, Piao et al. [85] developed for the first time the in-situ generation of a MDES for the determination of triazine herbicides in rice. The ternary MDES $[\text{TBAC}/\text{EG}][\text{FeCl}_4]$ has high affinity for triazine herbicides and greatly simplifies the extraction procedure through the in-situ generation by simple agitation. The DLLME procedure based on *in-situ* generation of MDES is shown graphically in Fig. 5. First, the sample was weighed and sonicated in n-hexane and, after centrifugation, the supernatant was then separated for further analysis. Afterwards, the DES (molar ratio was 1:2 of TBAC:EG) was added to the sample solution and vortexed to enrich the analytes to the DES phase. After extraction, the iron chloride was added into the solution to in-situ formation of the MDES. After homogenization, a carbonyl iron powder (i.e., CIP) was added to enhance the magnetic properties and shorten the magnetic separation time. Following the dissolution of target analytes in diethyl ether, the diethyl ether phase was separated and dried under a nitrogen gas stream. Finally, an aliquot of chromatographical acetonitrile was added to re-dissolve the target analytes and was injected into the HPLC-UV/Vis technique for analysis.

To sum up, Table 1 summarizes all the manuscripts reviewed in this work. As it can be observed, all these studies are difficult to compare quantitatively due to the variability of the analytes analyzed and the analytical technique used, among other factors.

5. Conclusion

Undoubtedly, the application of MDESs in Analytical Chemistry is rapidly expanding since the chemistry society is aware about the ecological impact of its activity, in particular when considering the use of toxic reagents/solvents and the production of wastes and residues. In that regard, researchers must provide a balance between environmental safety and accuracy improvement when they developed a new analytical method. Therefore, an environmentally friendly perspective is arisen dealing with the new green analytical challenges and opening new horizons in both academic and industrial fields.

Nowadays, MDESs could be considered as the next generation of solvents or sorbent due to the extraordinary physicochemical and

Table 1
Resume of applications of MDES-based microextraction techniques.

Analyte	Sample	Instrument	DES (molar ratio)	EF	LOD	References
1. DES on magnetite nanoparticles						
<i>1.1. Inorganic analytes</i>						
Pb and Cd	Soil, hair and several water samples	FAAS	ChCl:urea (1:2.5)	Pb (100) Cd (100)	Pb (0.4 µg L ⁻¹) Cd (0.1 µg L ⁻¹)	[21]
Cu and Pb	In certified reference materials (i.e., soil and stream sediments) and real-world samples (i.e., lake and tap water and soil).	ICP-OES	ChCl:urea (1:2)	Cu (192) Pb (198)	Cu (0.29 µg L ⁻¹) Pb (0.50 µg L ⁻¹)	[22]
<i>1.2. Organic analytes</i>						
Sulfonylurea herbicides	Lake, rice field and drinking water)	UPLC-PDA	DODAC:pCP (1:5)	495–630	0.0098–0.0110 µg L ⁻¹	[23]
Pesticides	Sea, river, spring, agricultural, and underground water	GC-µECD	AA:menthol (1:2)	152–550	0.002–0.120 µg L ⁻¹	[24]
Trypsin	Crude bovine pancreas extract	SDS-PAGE-UV	ChCl:Ita (1:1)	NI	7.7 µg mL ⁻¹	[26]
Chymotrypsin	Porcine pancreas crude extract	SDS-PAGE-UV	ChCl:Xyl (1:1)	NI	3.76 µg mL ⁻¹	[27]
2. DES on carbon-based magnetic nanomaterials						
<i>2.1. Inorganic analytes</i>						
Hg	Agricultural water	AFS	ChCl:Ita:3-MPA (2:1:1)	NI	NI	[39]
<i>2.2. Organic analytes</i>						
BSA, OVA, Lys, BHb	Model samples	UV-vis spectrophotometer	ChCl:D-Glucose (1:1)	NI	NI	[35]
BSA	Bovine whole blood	SDS-PAGE-UV	ChCl:Glycerol (1:1)	NI	13.74 µg mL ⁻¹	[36]
BSA	Calf serum	SDS-PAGE-UV	APTAC:Xyl (1:1)	NI	2.67 µg mL ⁻¹	[37]
Methadone	Urine, and plasma samples	GC-FID and GC-MS	ChCl:TNO (1:2)	250	0.8 µg L ⁻¹ (GC-FID) 0.03 µg L ⁻¹ (GC-MS)	[38]
DNA	Bovine whole blood	UV-visible spectroscopy	TEAC:PEG (1:1)	NI	NI	[41]
Phenolic endocrine disrupting chemicals	Well, river and sea water samples	HPLC-FLD.	HTMAB:1-dodecanol (1:3)	21.2–23.6	0.82–1.7 µg L ⁻¹	[42]
3. DES on MOF-based magnetic nanomaterials						
<i>3.1. Organic analytes</i>						
MG and CV	Fish samples	UV-vis spectrophotometer	APTAC: Sor (2:1)	NI	98.19 ng mL ⁻¹ (MG) 23.97 ng mL ⁻¹ (CV)	[46]
RNA	Medicinal yeast	UV-vis spectrophotometer	TBAC:Lac (NI)	NI	NI	[48]
Pyrethroid pesticides	Well, river and ground water samples	GC-MS/MS	MOIC:1-undecanol (1:2)	NI	0.05–0.21 µg L ⁻¹	[50]
4. DES on MIP-based magnetic nanomaterials						
<i>4.1. Organic analytes</i>						
Baicalein	Scutellaria baicalensis	HPLC-DAD	ChCl:OA:Pg (1:1:2)	NI	0.0387 µg mL ⁻¹	[54]
Catechins	Green tea samples	HPLC- UV/Vis	VP:MA (1:1)	NI	0.10–0.40 mg L ⁻¹	[55]
Catechins	Black tea samples	HPLC- UV/Vis	ChCl:MAA (1:2)	NI	0.15–0.50 µg mL ⁻¹	[56]
Chlorophenol compounds	Environmental water samples	HPLC- UV/Vis	ChCl:TCP (1:1)	NI	0.18–0.23 µg mL ⁻¹	[57]
Aristolochic acid I and II	Rat urine	HPLC- UV/Vis	ChCl:EG (1:2)	NI	0.03–0.17 µg mL ⁻¹	[58]
Tanshinones, isoflavones and Catechins	<i>Salvia miltiorrhiza bunge</i> , <i>Glycine max (Linn.) Merr</i> and green tea samples	HPLC- UV/Vis	ChCl:Gly (1:2)	NI	0.05 for all analytes (µg mL ⁻¹)	[59]
Theobromine and theophylline	Green tea samples	HPLC- UV/Vis	ChCl:urea (1:2)	NI	NI	[60]
Monosaccharide	Seaweed	HPLC- UV/Vis	ChCl:urea (1:2)	NI	NI	[61]
Polysaccharides	Seaweed	HPLC- UV/Vis	ChCl:urea (1:3)	NI	NI	[62]
BSA	Calf blood	SDS-PAGE-UV	ChCl:MAA (1:2)	NI	NI	[64]
Lys	Chicken egg white	SDS-PAGE-UV	ATEA:Gly (1:1)	NI	12.8 µg mL ⁻¹	[65]
BHb and BSA	Calf blood	SDS-PAGE-UV	APTAC:urea (1:2)	NI	NI	[66]
BHb	Bovine blood	SDS-PAGE-UV	HEMA:TEAC (2:1)	NI	NI	[67]
5. MDES-based ferrofluids						
<i>5.1. Inorganic analytes</i>						
Cd	Rosemary and eucalyptus samples	FAAS	ChCl:Phenol (1:3)	80	0.25 ng mL ⁻¹	[76]
As, Cd, Cu, and Pb	Walnut, rice, tomato paste, spinach, orange juice, black tea, and water samples	ETAAS	ChCl:urea (1:2)	635–644.5	3–4.2 ng L ⁻¹	[81]
<i>5.2. Organic analytes</i>						
Explosives	Soil sample, and well and surface water samples	HPLC-UV	Menthol:decanoic acid (1:2)	23–93	0.22–0.91 µg L ⁻¹	[69]
Polycyclic aromatic hydrocarbons	Coffee samples	HPLC-DAD	Menthol:borneol:camphor (5:1:4)	181–215	0.31–5.9 ng L ⁻¹	[70]
Polycyclic aromatic hydrocarbons	Grilled meat samples	GC-MS	PChCl:menthol:decanoic acid (1:1:1)	730–920	29–82 ng kg ⁻¹	[71]

(continued on next page)

Table 1 (continued)

Analyte	Sample	Instrument	DES (molar ratio)	EF	LOD	References
Polycyclic aromatic hydrocarbons	Urine and saliva samples from smokers	GC-MS	ChCl:stearic acid (1:2)	305 –420	18–63 ng L ⁻¹	[72]
Morin	Dried onion and green tea infusion samples, and apple and grape juices.	HPLC-UV	TEAC:EG (1:3)	39.1	0.91 an µg L ⁻¹	[73]
Meloxicam	Human blood plasma and urine samples	HPLC-UV	ChCl and EG (1:2)	44.6 –49.2	3.0 µg L ⁻¹ (Plasma) 2.5 µg L ⁻¹ (Urine)	[74]
Perfluoroalkyl carboxylic acids	Edible oils	UPLC-QTOF-MS	ChCl:TB (1:1)	NI	0.3–1.6 pg g ⁻¹	[75]
Organochlorine pesticides	Farm, rural, lake, and river water samples	GC-µECD	ChCl:urea (1:2)	270 –340	0.03–0.27 ng L ⁻¹	[77]
Explosives	Wastewater sample	GC-µECD	ChCl:urea (1:2)	267 –415	0.8–12.4 ng L ⁻¹	[78]
Explosives	Wastewater sample	GC-µECD	ChCl:resorcinol (1:2)	852 –1480	0.22–4.92 ng L ⁻¹	[79]
Volatile aromatic hydrocarbons	Water and urine samples	GC-FID	ChCl:chlorophenol (1:2)	520 –587	0.05–0.90 µg L ⁻¹	[80]
Sex hormones	Cosmetic skin care toners	HPLC-DAD	ChCl:urea (1:2)	NI	0.06–0.33 µg mL ⁻¹	[82]
6. Intrinsic MDES						
6.1. Organic analysis						
Thiophene	Model solution of n-heptane	GC-FID	ChCl:phenol:FeCl ₄ (1:2:1)	NI	NI	[83]
Hexanal and heptanal	Edible oils	GC-FID	ChCl:p-cresol:FeCl ₄ (1:3:1)	NI	19–25 µg L ⁻¹	[84]
Triazine herbicides	Rice samples	HPLC-UV/Vis	TBAC:EG:FeCl ₄ (1:2:NI)	NI	1.49–3.10 ng g ⁻¹	[85]

NI: not included.

magnetic properties. By synergetic combination of magnetic properties and structural tunability within the DES structure, new magnet-based analytical methods can be readily customized to meet the requirements of any specific application. Furthermore, other properties mentioned in this review such as the limited toxicity, easy synthesis, specific polarity, thermal stability, and high biodegradability also contribute to their popularity.

Apart from the exciting applications shown in the bibliography, MDESs in sample preparation are still in their infancy and, in our opinion, some other issues must be addressed.

The major drawback of DESs are their relatively high viscosity and density. These properties hinder the direct introduction of the DES in the majority of analytical instrument. At present, the most popular solutions are to perform a back-extraction procedure or to use additional solvents to reduce the viscosity, but those solutions are still controversial. This is because the use of an additional solvent can limit, to some extent, the greenness of the whole analytical method and it increases the time of the analysis. However, some of the probable challenges regarding the direct introduction of the MDES into the instrumentation may be addressed through careful design of the MDES structure.

The hydrophilic/hydrophobic property of DESs is another significant feature of these solvents. Until recently, most of the studied DESs were hydrophilic, which disallowed their use in the extraction in aqueous samples. Nevertheless, the use of hydrophobic DES experimented a sharp increment, providing a promising alternative to the traditional organic solvents employed in sample preparation [86–89].

The greenness and low toxicity of DES and/or magnetic (nano) materials have been demonstrated and accepted. However, the preparation of these solid materials is not always as green as desirable. Therefore, special efforts should be done on the preparation of greener solid magnetic (nano)materials [90].

Regarding intrinsic MDESs, only the [FeCl₄]⁻ anion was used for MDES synthesis. However, it can be used other transition metal coordination complexes such as Co and Mn [91]. In addition, lanthanide complexes (e.g., Gd, Nd or Dy) can also be explored due to their strong response to an external magnetic field and, in some cases, luminescence properties. It is well-known that the incorporation of lanthanide ions into the DES structure offers the

advantage of a metal ion that has a considerably higher effective magnetic moment than any known transition metal.

New applications of MDES-based microextraction in well-known configurations and new miniaturized and automated in-line applications using MDESs to reduce the sample preparation impact should be investigated.

Finally, additional studies about the physicochemical and thermodynamic properties of these materials by both experimental and theoretical approaches are still required to establish clear and rational criteria for the proper selection of a certain MDESs for a targeted analytical application. This could cut-down cost, save time and labor.

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.

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