

Hydrophobic deep eutectic solvents in microextraction techniques—A review

Patrycja Makos^{*}, Edyta Słupek, Jacek Gębicki

Faculty of Chemistry, Department of Process Engineering and Chemical Technology, Gdansk University of Technology, 80 – 233 Gdansk, G. Narutowicza St. 11/12, Poland



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ABSTRACT

Over the past decade, deep eutectic solvents (DES) have been widely studied and applied in sample preparation techniques. Until recently, most of the synthesized DES were hydrophilic, which prevented their use in the extraction of aqueous samples. However, after 2015 studies on the synthesis and application of hydrophobic deep eutectic solvents (HDES) has rapidly expanded. Due to unique properties of HDES i.e. density, viscosity, acidity or basicity, polarity and volatility, good extractabilities for various target analytes, which could be altered by careful selection of the hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) components, HDES are promising alternatives to the traditional organic solvents employed in sample preparation. Moreover, the possibility HDES synthesis of non-toxic ingredients, makes HDES meet all the standards of green analytical chemistry. Practical applications of HDES in sample preparation include conventional liquid-liquid extraction, and several types of liquid-phase microextraction, as well as solid phase extraction. The present review covers a comprehensive summarizing of available literature data on the most important physicochemical properties of HDES playing a key role in aqueous sample preparation methods, their limitations as well as challenges in this area, and a perspective of their future are described.

1. Introduction

Sample preparation is considered to be the most important step of the analytical procedure, due to the fact that the precision and accuracy of the analytical method is largely based upon this step. The main aims of the sample preparation step are to purify the sample, extraction and enrichment of the analytes, and possibly modify the sample to adapt it

to the requirements of the analytical apparatus. In many cases, a step of isolation and enrichment of sample is necessary because only a limited number of analytical techniques are sensitive enough for direct determination of trace pollutants in aqueous samples [1,2]. In recent years, more and more attention has been devoted to replacing conventional extraction techniques, so-called “green” extraction techniques [3,4]. The main trend of green analytical sample preparation methods

Abbreviations: AceA, Acetic acid; AcrA, Acrylic acid; AA-DLLME, Air-assisted dispersive liquid-liquid microextraction; C6H6[N1112]Cl, Benzyl tri-methyl ammonium chloride; BTPPB, Benzyltriphenylphosphonium bromide; BuOH), Butanol; BuA, Butyric acid; ChCl, Choline chloride; DecA, Decanoic acid; DES, Density ρ , Deep Eutectic solvents; DI-SDME, Direct immersion single-drop microextraction; DLLME, Dispersive liquid-liquid microextraction; DSPE, Dispersive solid phase extraction; DoDecNa, Dodecanoate sodium salt; DoDecA, Dodecanoic acid; DoDecOH, Dodecanol; DHS, Dynamic headspace; FAAS, Flame atomic absorption spectrometry; ForA, Formic acid; VADLLME – FDES, Freezing of deep eutectic solvent; ΔT_f , Freezing point; EG, Glycol; HS-SPME, Headspace solid phase microextraction; HS-SDME, Headspace single-drop microextraction; HexDecA, Hexadecanoic acid; HFIP, Hexafluoroisopropanol; HexA, Hexanoic acid; HF-LPME, Hollow fiber-based liquid phase microextraction; HBA, Hydrogen bond acceptor; HBD, Hydrogen bond donor; HDES, Hydrophobic deep eutectic solvents; IBP, Ibuprofen; ILS, Ionic liquids; LacA, Lactic acid; LPME, Liquid – phase microextraction; LLE, Liquid-liquid extraction; LLME, Liquid-liquid microextraction; DES-MBG, Magnetic multiwall carbon nanotube nanocomposite; MSPE, Magnetic solid-phase extraction; M-GO, Magnetic graphene oxide; mp, Melting point; [N8881]Cl, Methyl trioctyl ammonium chloride; [N8881]Cl, Methyltrioctylammonium chloride; MePh)3PI, Methyltriphenylphosphonium iodide; OctDecA, Octadecanoic acids; OcDecOH, Octadecanol; OctA, Octanoic acid; OctOH, Octanol; OleA, Oleic acid; OLA, Oleyl alcohol; OxaA, Oxalic acid; Ph-EtOH, Phenethyl alcohol; Salol, Phenyl salicylate; PT-SPE, Pipette-tip solid phase extraction; PDMS, Polydimethylsiloxane); ProA, Propionic acid; PTSA, p-toluenesulfonic acid; PyrA, Pyruvic acid; Se, Selenium; SDME, Single drop microextraction; SPE, Solid phase extraction; SPME, Solid phase microextraction; SFD-DLLME, Solidification of floating drop dispersive liquid-liquid microextraction; SPD, Solidification of floating organic drops; SME, Solvent microextraction; SHS, Static headspace; THS-DES, Ternary hydrosulphonyl-based deep eutectic solvent; N4444, Tetrabutylammonium; tDecA, Tetradecanoic; tDecA, Tetradecanoic Acid; N7777, Tetraheptylammonium; THF, Tetrahydrofuran; [N4444]Br, Tetra-n-butylammonium bromide; N8888, Tetraoctylammonium; TNO, 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-ol; UA-DSPE, Ultrasonic energy dispersive solid phase extraction; USA-DLLME, Ultrasound-assisted dispersive liquid-liquid microextraction; ValA, Valeric Acid; η , Viscosity; 1,2-DecOH, 1,2-decanediol; 10-UnDecA, 10-Undecylenic Acid; [C10MIM][Cl], 1-decyl-3-methylimidazolium chloride; 1-tDecOH, 1-tetradecanol; 1-UnDecOH, 1-undecanol; 4-CPh., 4-chlorophenol

^{*} Corresponding author.

E-mail address: patrycja.makos@pg.edu.pl (P. Makos).

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focuses on the elimination of toxic and volatile organic solvents [5]. Some of the available extraction techniques, i.e. static headspace (SHS), dynamic headspace (DHS), solid phase microextraction (SPME) etc. do not require the use of solvents. However, their use in many cases is very limited due to insufficient sensitivity for compounds with higher boiling points when gas chromatography is used, time-consuming and the need to use expensive equipment [6]. Therefore, in the research, the methods based on liquid-liquid extraction (LLE) are commonly used, which are characterized by a more universal character, and the search of new, alternative and non-toxic solvents is now a major object of interest [7,8].

Recently, the research has been focused on ionic liquids (ILs) as an extraction solvents due to their unique properties, such as viscosity, density, hydrophobicity or hydrophilicity, which could be adjusted by the selection of the appropriate cation and anion [9–14]. However, the problems with their biodegradability, toxicity, stability and an often-expensive synthesis make them less than perfect solvents [15]. An alternative to extraction solvents based on ILs are deep eutectic solvents (DES). According to the definition, DES are liquids which are formed upon mixing mostly two solids which are involved in hydrogen bond interactions with each other to obtain a eutectic mixture with a melting point much lower than that of each component species [16–19]. The DES have similar favorable properties to ILs, but their synthesis is much cheaper, simpler and they are more biodegradable and often less toxic than ILs. Due to the possibility of improvement of many processes by using deep eutectic solvents, the concept of synthesis of DES is currently the object of growing interest, which is illustrated by the number of relevant papers published between 2005 and 2019 (Fig. 1). However, the majority of DES are hydrophilic which precludes their use for separation processes of aqueous samples. Until now, hydrophobic deep eutectic solvents (HDES) has been successfully applied in the purification of water [20], preparation of new materials i.e. magnetic gels, nanoparticles based on carbon nanotubes and graphene for the removal of organic micropollutants as well as metal ions from water [21–23], capture of CO₂ [24], electrolyte medium for solar cells [25] and extraction of bioactive compounds [26,27].

The paper presents an overview of the available HDES, their properties, synthesis methods, as well as the use in various types of miniaturized liquid-liquid extraction and solid-phase extraction techniques. The advantages and challenges of application of HDES as extraction materials for aqueous sample preparation were discussed.

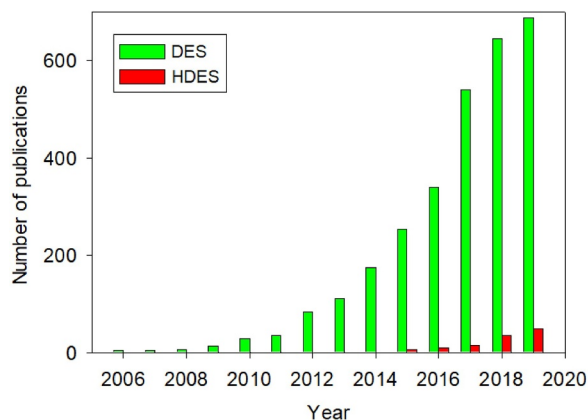


Fig. 1. Number of papers published during 2006–2019 on the hydrophobic deep eutectic solvents – based on Scopus database (searched keywords: deep eutectic solvents and hydrophobic deep eutectic solvents; accessed on 16.09.2019).

2. Hydrophobic deep eutectic solvents – formation and structures

2.1. Synthesis of HDES

The most common approach for the synthesis of HDES involves mixing and heating two or three components until a homogenous liquid is formed. This method was proposed by Abbott in 2003 [19]. According to these studies, DES can be divided into four main types: type (I) - a combination of a quaternary salt with a metal chloride, type (II) - a combination of a quaternary salt with a hydrated metal chloride, type (III) - a combination of a quaternary salt (HBA) with a donor hydrogen compound (HBD), type (IV) - a combination of metal chloride with HBD (Table 1).

Via using DES synthesis based on I and II, hydrophilic DES is obtained, which has some disadvantages. One of them is the interaction and significant solubility of DES in water. This plays a very important role because water modifies the structural properties of DES. The interactions between the DES components systematically weakened as the water solubility in HDES increases [28,29]. That is why scientists are increasingly focusing their attention on the synthesis of hydrophobic DES (types III and IV), which are stable in the aquatic environment [30].

2.2. Structures of hydrophobic deep eutectic solvents

HDES synthesis is carried out using poorly water-soluble components. HBA can be divided into two categories based on ionic compounds (e.g. tetraalkyl quaternary ammonium/phosphorous salts) and based on non-ionic compounds (e.g. monoterpenes). The most popular HBD include phenols, carboxylic acids, alcohols and glycols. However, some of them can be both a donor and a hydrogen bond acceptor. The most common structures of HBD and HBA are presented in Fig. 2.

2.2.1. Ionic hydrophobic deep eutectic solvents

In 2015, van Osch et al. described for the first time the ionic HDES synthesis. In the studies, HDES were created by combining long-chain quaternary ammonium salts i.e. tetrabutylammonium (N4444), tetraheptylammonium (N7777), and tetraoctylammonium (N8888) (HBA) and decanoic acid (DecA) as HBD [31]. For HDES synthesis, HBA based on long-chain ammonium salts are preferred because imparting greater hydrophobicity compared to that of short-chain ammonium salts such as choline chloride (ChCl). Quaternary ammonium salts are typically combined with long-chain alcohols [30], amino acids [13], sugars [27], as well as fatty alcohols (i.e. butanol (BuOH), octanol (OctOH), dodecanol (DoDecOH), octadecanol (OcDecOH), oleyl alcohol (OLA)) [32], saturated acids (i.e. hexanoic (HexA), octanoic (OctA) and DecA) [32,33] and unsaturated acids (e.g. oleic acid (OleA)) [10]. However, sometimes the combination of two compounds makes it impossible to obtain HDES, which was observed, among others for saturated and unsaturated short chain acids (acetic (AceA), propionic (ProA), butyric (BuA) or acrylic (AcrA) acid in combination with tetra-n-butylammonium bromide ([N4444]Br). However, to overcome this problem, three compounds can be used for synthesis (e.g. methyltrioctylammonium chloride ([N8881]Cl) and two HBD OctOH and OctA) in a 1:2:3 molar ratio [34].

2.2.2. Non-ionic hydrophobic deep eutectic solvents

The number of non-ionic HDES is quite limited due to the relative small number of cheap and readily available organic compounds from which HDES can be synthesized. In non-ionic HDES, it is difficult to differentiate between HBA and HBD. However, for simplicity, in several report, it was assumed that DL-menthol (a natural monoterpene - having very low solubility in water) has HBA properties while long chain organic acids (OctA, DecA, dodecanoic acid (DoDecA), tetradecanoic (tDecA), HexDecA and octadecanoic acids (OctDecA) [35] [15–17] and short chain organic acids ((AceA), pyruvic (PyrA) and

Table 1
Types of DES [18].

Types	General Formula	Terms	Example
I	$Cat^+ X^- + zMCl_x$	M (Zn, In, Sn, Al, Fe)	$C_2mimCl + AlCl_3$
II	$Cat^+ X^- + zMCl_x + yH_2O$	M (Cr, Ni, Cu, Fe, Co)	$ChCl + MgCl_2 + 6H_2O$
III	$Cat^+ X^- + zRZ$	Z (OH, COOH, CONH ₂)	ChCl + Urea (U)
IV	$MCl_x + zRZ$	M (Zn, Al)	
Z (OH, CONH ₂)	$ZnCl_2 + U$		

lactic acid (LacA) [35], phenolic compounds such as salol (phenyl salicylate (Salol)) [39] were defined as HBD. In addition to DL-menthol, and other terpenoid-based compounds such as L-menthol, thymol which were combined with carboxylic acids, can be used for synthesis of HDES [40]. However, the molar ratios between thymol:HBA or menthol:HBA were usually different. In subsequent studies in which HDES was synthesized, compounds from the same family (long chain organic acids - e.g. DecA and acetic acid (AceA)) were used as HBA and HBD [41]. Other HDES were synthesized using painkillers (e.g. Lidocaine) in combination with organic acids (e.g. DecA) [42], or painkillers were used in combination with terpenes (e.g. menthol and testosterone [43], ibuprofen (IBP) [44], lidocaine [45], ubiquinone [46]).

2.3. Physico-chemical properties of hydrophobic deep eutectic solvents affecting on extraction processes

Commonly approach used for the aqueous sample preparation methods are based on liquid-liquid or solid-liquid extraction with organic solvents. However, many compounds are unstable in organic solvents. Instability makes it difficult not only to extract analyte but also to analyze and store. In addition, pure organic compounds (e.g., toluene, dichloromethane) are volatile solvents with high toxicity [47]. Therefore, it is necessary to develop new "green solvents" with similar physicochemical properties and extraction efficiency to conventional solvents.

The physicochemical properties of HDES are usually attributed to various combinations of HBA and HBD that result in unique interactions (such as hydrogen bonding, π - π bonding or anion exchange) during the extraction process [48]. Physicochemical properties such as density and

viscosity, melting/freezing point, conductivity depend on the HDES structure. In addition, some properties, such as thermal stability, toxicity, and biodegradability, affect HDES application options. Therefore, in the following subsections, the basic physicochemical properties of both ionic and non-ionic HDES will be discussed and compared.

2.3.1. Hydrophobicity

Due to hydrogen bonding formation ability between HBD and HBA, most of DES are generally hydrophilic and thus dissolve rather easily in water. Hydrophobicity of DES is strongly affected by structure of individual components HBD and HBA. In general, the longer alkyl chain in both HBA and HBD provide to the lower solubility of individual components as well as DES in aqueous phase. For example, the water solubility in HDES decreases according to [N4444]Cl:DecA (1:2) < [N7777]Cl:DecA (1:2) < [N8888]Cl:DecA (1:2) [31] as well as [N4111]Cl:ButA (1:2) < [N4111]Cl:Valeric Acid (ValA) (1:2) < [N4111]Cl:HexA (1:2) < [N4111]Cl:OctA (1:2) [49].

The type of ion in HBA (Cl^- or Br^-) have only minor effect on hydrophobicity of DES. The difference between solubility water in [N8888]Cl:DecA (1:2) and [N8888]Br:DecA (1:2) is only 2.2 g/L [31]. In addition, DES composed of hydrophobic components show greater stability in water than HDES composed of both hydrophobic and hydrophilic compounds. The hydrophilic compounds in HDES can dissolve in the aqueous phase according to their solubility, which reduces HDES stability. It has been confirmed that terpenes and long chain ammonium and phosphonium salts in combination with long chain organic acids indicate the high stability in aqueous samples. Among the available HDES, ionic solvents i.e. [N4444]Cl:DecA (1:2 molar ratio) and [N8881]Cl:DecA (1:2 molar ratio) had the highest water solubility,

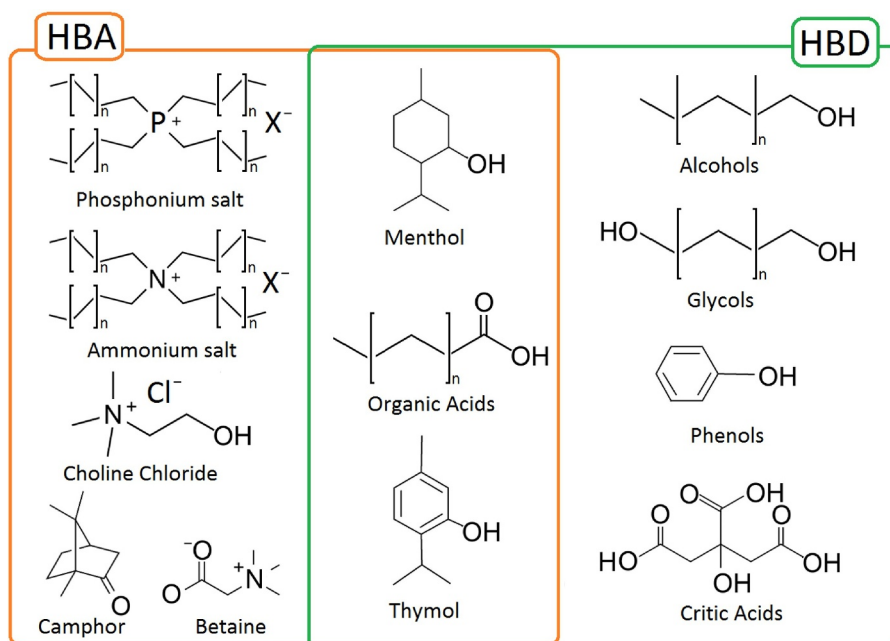


Fig. 2. Structures of typical HBAs and HBDs.

Table 2
Physicochemical properties of some selected ionic and non-ionic HDES.

HDA	HBD	Molar ratio	Mw [g/mol]	MP [°C]	Density ρ [kg/m ³]	Viscosity η [mPas]	Water solubility [%g/L] / Water activity [-]	Ref.		
Ionic HDES										
[N4111]Cl	BuA	1:2	312.7	-17.96	n.d.	1757	0.09	[49]		
		1:3	400.8	-20.21	n.d.	54.1	0.08			
		1:4	488.9	-13.15	n.d.	13.3	0.08			
	ValA	1:2	340.8	-35.31	n.d.	1497	0.125			
		1:3	442.9	-34.96	n.d.	44.5	0.150			
		1:4	545.1	-34.89	n.d.	36.8	0.135			
	HexA	1:2	368.8	-5.45	n.d.	1778.7	0.155			
		1:3	484.9	-5.36	n.d.	1563	0.145			
		1:4	601.1	-5.71	n.d.	1808.5	0.175			
	OctA	1:2	424.9	14.39	n.d.	1594.7	0.250			
		1:3	569.1	16.96	n.d.	1561.3	0.240			
		1:4	713.3	17.91	n.d.	1723.7	0.235			
	[N4444]Br	DecA	1:2	665.5	16.17	957	n.d.		6.21%	[70]
		OleA	1:2	885.9	1.86	959	n.d.		4.25%	
OctA		1:2	516.4	0.58	974	n.d.	6.92%			
[N4444]Cl	DecA	1:2	622.0	-11.95	916.8	265.3	69.4 g/L	[31]		
[N7777]Cl	DecA	1:2	790.0	-16.65	890.7	172.9	23.4 g/L	[31]		
	OleA	1:2	1010.4	-	867.0	244.7	3.09%	[71]		
[N8888]Cl	IBP	7:3	894.8	-	1029.0	892.0	9.99%			
	DecA	1:2	832.0	1.95	888.9	472.6	17.8 g/L	[31]		
[N8881]Br	DecA	1:2	792.4	8.95	942.2	576.5	42.4 g/L	[31]		
[N8888]Br	DecA	1:2	890.4	8.95	929.8	636.4	20.0 g/L	[31]		
[P888]O	Ph	1:2	364.2	-33	935	12.38	n.d.	[72]		
		1:1	252.1	-11	910 ^a	54.0 ^a	1.34 g/L			
Betaine	HFIP	1:2	435.5	-39.4	1476	76	n.d.	[52]		
	HFIP	1:2.5	537.5	-33.3	1490	55	n.d.			
	HFIP	1:3	624.5	-34.7	1525	46	n.d.			
Dodecanoate sodium salt (DoDecNa)	DecA	1:4	739.2	-3.0	925.5	201.0	n.d.	[73]		
Lidocaine	DecA	1:2	344.5	-	962.4	325.5	n.d.	[42,66]		
		1:4	689.1	-	946.1	197.5	n.d.			
	Menthol	1:2	546.3	-	942.2	59.0	2.41%	[37]		
	Thymol	1:1	384.6	-	994.4	149.8	1.77%			
	DoDecA	1:2	634.9	-	949.5	370.6	1.52%			
Non-ionic HDES										
DL-Menthol	AceA	1:1	216.1	-	935.0	11.3	n.d.	[36,39,40,71,74,75]		
	LacA	1:2	336.2	-	1038.0	370.9	n.d.			
	PyrA	1:2	332.1	-	999.0	44.6	n.d.			
	OctA	1:1	300.2	-3.42	920.0	-	n.d.			
	DoDecA	2:1	512.3	21.23	897.0	33.1	n.d.			
	Salol	1:1	370.2	22.28	1070	-	n.d.			
	OleA	1:1	300.2	-0.51	910.0	-	n.d.			
	L-Menthol	OctA	1.5:1	378.2	-1.82	888.7 ^b	7.80 ^b		n.d.	[38,41,66,76]
DoDecA		3:1	668.3	-	882.3 ^b	12.40 ^b	n.d.			
DecA		1.5:1	406.3	8.86	885.5 ^b	9.43 ^b	n.d.			
OctA		3:2	756.4	-1.82	888.7 ^b	4.54 ^d	0.177			
DecA		3:2	812.6	8.86	885.5 ^b	5.39 ^d	0.157			
LauA		2:1	512.3	-	894.0	27.31	1.23%			
		3:1	668.3	21.23	882.3 ^b	6.50 ^d	0.148			
Tetradecanoic Acid (tDecA)		4:1	853.5	26.62	881.2 ^b	7.17 ^d	0.136			
HexDecA		5.6:1	1131.5	33.18	881.4 ^b	7.46 ^d	n.d.			
OctDecA		9:1	1690.9	37.88	881.0 ^b	7.77 ^d	n.d.			
1-tetradecanol (1-tDecOH)	2:1	526.3	-	874.22	36.6	1.73%	[37]			
Thymol	OctA	1:1.4	351.9	6.68	914.4 ^c	3.20 ^d	0.240	[38,40]		
	DecA	1:1	322.3	18.86	914.7 ^c	4.24 ^d	0.224			
	LauA	1.2:1	380.3	24.83	910.7 ^c	5.10 ^d	0.222			
	(tDecA)	3:1	678.3	38.16	924.0 ^c	5.07 ^d	0.204			
	HexDecA	4:1	856.5	41.22	925.5 ^c	5.31 ^d	n.d.			
	OctDecA	9:1	1634.5	46.22	935.7 ^c	4.77 ^d	n.d.			
	10-Undecylenic Acid	1:1	339.3	11.0	987.3	25.8	n.d.			
	DecA	1:1	322.3	17.0	943.7 ^b	11.2 ^b	n.d.			
	DoDecA	11:9	1850.3	-	910.7 ^b	7.01 ^b	n.d.			
	(tDecA)	3:1	906.7	-	924.0 ^b	7.16 ^b	n.d.			
	OctDecA	9:1	1634.5	-	935.7 ^b	6.88 ^b	n.d.			
	1,2-decanediol (1,2-DecOH)	2:1	640.1	-	956.3	42.6	5.14%		[37]	
DL-Camphor	Thymol	1:1	302.2	-44.0	987.3	25.8	n.d.	[76]		
Atropine	DecA	1:2	634.0	-	1026.5	5985.0	33.86%	[37]		
Cumarin	Thymol	1:1	290.1	-	1091.8	29.2	2.54%			
		1:2	446.1	-	1050.5	31.4	2.48			

(continued on next page)

Table 2 (continued)

HDA	HBD	Molar ratio	Mw [g/mol]	MP [°C]	Density ρ [kg/m ³]	Viscosity η [mPas]	Water solubility [%g/L] / Water activity [-]	Ref.
DoDecA	OctA	1:3	632.9	9.0	904.0	8.223	n.d.	[41]
	Nonanoic Acid (NonA)	1:3	674.9	9.0	901.0	10.115	n.d.	
	DecA	1:2	544.6	18.0	898.0	12.886	n.d.	

which was 7 and 6.22 (% w/w) respectively. The high solubility was explained by the greater availability of a nitrogen atom that results from at least one short alkyl chain. This theory was also confirmed by HDES composed of NaCl₂:DecA (1:4), which occurred in the form of a hydrogel [50]. The affinity of HDES to water was explained by the presence of a charged sodium atom [51].

The comprehensive studies on the chemical and aqueous stability of ionic and non-ionic DES can be performed using NMR analysis, where the affinity of the aqueous phase for HDES is analyzed [36]. In addition, Karl Fisher titration can be used to determine trace amounts of water in a HDES.

Water solubility in ionic and non-ionic HDES is summarized in Table 2-3 and Fig. S1-S2.

2.3.2. Melting point / freezing point

According to the definition, melting point (m_p) or freezing point (ΔT_f) of deep eutectic solvents is much lower than those of their individual components. The decrease in melting/freezing point is related to the magnitude of the specific interactions i.e. hydrogen bonds, or Van der Waals between HBA and HBD. The increase in interactions between the HDES components results in a lower melting / freezing point. Fig. 3 shows the theoretical phase diagram for binary mixtures of HBD and HBA [18,31].

The HDES with melting point below 20 °C favorably affect the use of HDES in the sample preparation process, due to the fact that no additional heat source is needed, which increases the cost of the process, and in addition some of the analytes are volatile enough to evaporate during HDES heating. The melting/freezing point of ionic HDES increases with increasing tetraalkyl ammonium/phosphonium quaternary chain as well as increasing alkyl chain in HBD. The lowest melting points (−39.4 and −35.3 °C) were observed for [52] Betane:Hexafluoroisopropanol (HFID) (1:2) and [N4111]Cl:ValA (1:2) [49] respectively. For comparison, the melting point of HDES composed of the same HBA and OctA in 1:2 molar ratio, was 14.4 °C [49]. For non-ionic HDES, the lowest melting point (−44 °C) was obtained for DL-Camphor:Thymol (1:1). In addition, HDES only composed of organic acids shows the same tendency to increase the melting point as HDES consisting of quaternary ammonium tetraalkyl salts and monoterpenes. In addition, the replacement of DoDecA with its sodium salt leads to an increase in the melting point of HDES, this relationship can be attributed to the presence of coulombic interactions [40,41].

The values of melting point of ionic and non-ionic HDES are listed in the Table 2. For graphical interpretation, the melting points of ionic HDES and non-ionic HDES were shown in Fig. S3 and Fig. S4, respectively.

2.3.3. Density

Density (ρ) is important parameter in extraction processes. HDES should have higher or lower density than water. The disadvantage of HDES, which have a similar density to water is the extended separation time into two phases during extraction. Depending on the type of sample preparation method, HDES densities smaller or higher than water are preferred [37].

The density strongly depends on structures of HBD and HBA. The density values of ionic HDES varies in the range of 850 to 980 kg/m³ (Fig. S5), while non-ionic HDES in the range of 870 to 1091.8 kg/m³ at 25 °C (Fig. S6). For all ionic HDES, it has been observed that as the

tetraalkyl quaternary ammonium (HBA) and organic acids (HBD) chain increases, the density decreases. The changes in chain length in carboxylic acids (HBD) combined with Thymol as HBA slightly affected the changes in density. The highest density values (1091.8 kg/m³) were observed for non-ionic HDES composed of Cumarin and Thymol in 1:2 molar ratio. In addition, density changes slightly due to the solubility of HDES in the aqueous phase and its depends on the ingredients from which HDES was synthesized. It is well known that density strongly depends on temperature, therefore the density of HDES are listed in Table 2 and Fig. S5-S6 at 25 °C.

2.3.4. Viscosity

Viscosity (η) is another very important parameter strongly affected on extraction processes. Most of the HDES exhibit relatively high viscosities (>100 mPas) at room temperature. However, owing their application as extractants, the uses of HDES with low viscosity is preferred. The relatively high viscosity values of HDES is attributed to the presence of an extensive hydrogen bond network between HBA and HBD, which provide to lower mobility of free species within the HDES [16]. Other specific interactions (i.e. electrostatic or van der Waals) have less effect on increasing viscosity of HDES. Viscosity is correlated with the solubility of there in the aqueous phase. The addition of small amount of water to HDES usually leads to decrease in viscosity. This is explained by the fact that the higher solubility of HDES in the aqueous phase, the lower HDES viscosity due to the lower water viscosity. This observation applies to most HDES, the exception is HDES – l-Menthol:DecA (1:1), where an increase in viscosity was observed [37]. However, an increase in water content in the range of 1.64–5.14% m/m does not provide significant changes in viscosity. In addition, the highly hydrophobic nature of some of the HDES prevents the addition of large amounts of water. Theoretically, HDES could be dissolved in organic solvents, i.e. methanol, acetone, dichloromethane to reduce viscosity. Nevertheless, depending on the type of solvent, this can lead to an increase in HDES toxicity.

In addition, viscosity strongly depend on the chemical structure of the components (HBD and HBA). Viscosity increases as the tetraalkyl quaternary ammonium chain increases. However, a decrease in viscosity is visible when long branched chains are used. In HBA, which has an extensive structure, the effect of shielding the charge on the nitrogen atom appears (Fig. S7). The shielding effect results from the large volume of side chains that reduce viscosity. In ionic and non-ionic HDES, the viscosity increases as the HBD chain (organic acids) increases, in contrast to the density value. The lowest viscosity values are observed in non-ionic HDES, which were created using DL-menthol:PyrA (1:2) (Fig. S8). The high values of viscosities are obtained when organic acid salts are used as HBA (Fig. S8). However, higher values viscosity is obtained for DES created from natural compounds e.g. Lidocaine:DecA (1:2) and [N7777]Cl:IBP (7:3) which are in the range 325–895 mPas.

Viscosity of HDES changes significantly as a function of the temperature. As the temperature increases, the viscosity decreases, which could be demonstrated as Arrhenius-like behaviour. Due to this, in several studies the extraction process were carried out at higher temperatures.

2.3.5. Acidity

Acidity is an important parameter characterizing new solvents. The Brønsted acidity of DES could be determined by measuring the pH or

Table 3
Compilation of application of HDES as extraction solvents in various types of LLE procedures.

Extraction technique	HDES (molar ratio HBA: HBD)	Analytes	Sample matrix	Instrument	LOD	LOQ	RSD [%]	R [%]	Ref.
LLE	[N888]Cl:Deca (1:2) [N888]Cl:Deca (1:2) [N777]Cl:Deca (1:2) [N888]Cl:Deca (1:2) [N888]Cl:Deca (1:2) [N888]Br:Deca (1:2) OctA:NonA:DoDeca (3:2:1)	OctA, ProA, ButA	water	HPLC-UV	–	–	–	25–92	[31]
<i>In-situ</i> LPME	DL-Menthol:Deca (1:1) DL-menthol:analytes [N4444]Br 1-heptanol (1:2) Fe ₃ O ₄ -OA-DES (DL-menthol:AcceA 1:1)	bisphenol-A, bisphenol-AF, tetrabromobisphenol-A, 4-tert-octylphenol parabens Ketoprofen, diclofenac 17 β -estradiol mefenamic acid	tap water, lake water and river water environmental water human urine transdermal gel urine	HPLC-UV	0.22–0.53 μ g/L	0.73–1.77 μ g/L	2.6–6.7	87–107	[81]
DLLME	ChCl:4-CPh (1:2) L-carnitine:HFTP (1:2) [N4444]Cl:Deca (1:3) [N888]Cl:Octa (1:2) [HMIM]Br:salicylic acid (1:1) ChCl:Ph (1:4) [N4444]Br:ForA (1:2) (<i>disperser solvent</i>)	pesticides pyrethroids β -agonists chlorophenols Th(IV) caffeine chromium (VI)	fruit and vegetables juices tea beverages and fruit juices environmental water wastewater river and seawater beverages beverages	GC-FID HPLC-DAD HPLC-DAD LC-MS HPLC-UV UV-VIS HPLC-UV UV-VIS	0.46–3.1 ng/mL 0.06–0.17 ng/mL 0.4–0.8 ng/L 0.03–0.05 mg/mL 2.1 ng/mL 0.03 mg/L 0.2 μ g/L	1.5–11.0 ng/mL 0.2–0.57 ng/mL 0.8–1.2 ng/L 0.1–0.16 mg/mL – – 0.5 μ g/L	4–8 <7.5 2–12 1.8–3.1 1.7 5 6	62–96 85–109 56–91 91–93 100–109 94 91	[97] [52] [98] [99] [100] [104] [105]
Automated-DLLME Automated-in syringe-DLLME	[DMIM]Cl:1-DoDecOH (1:2) [N4444]Br:Deca (1:2) DL-menthol:Deca (1:1) ChCl:Ph-ETOH (1:4) ChCl:TNO (1:2) ChCl:Ph (1:4)	Benzoylureas (pesticide residue) PAHs UV filters amphetamine and methylamphetamine methadone anti-depressant drugs	water environmental water aqueous samples human plasma and wastewater water and biological samples pharmaceutical wastewater and human plasma	HPLC-UV-DAD HPLC-FID HPLC-DAD HPLC-UV GC-FID HPLC-UV	0.09–0.16 μ g/L 0.7–6.6 μ g/L 0.05–0.2 ng/mL 2–5 ng/mL 0.7 μ g/L 3.0–4.5 ng/mL	0.3–0.53 μ g/L 3.0–21.8 μ g/L 0.2–0.5 ng/mL 8–15 ng/mL 2.3 μ g/L 9–15 ng/mL	1.7–5.7 4.0–7.1 0.6–5.6 5.7–7.8 5.4 3.6–5.7	87–98 83–117 90–97 63–66 97.4 42–68	[113] [70] [106] [107] [109] [110]
USA-DLLME	ChCl:Ph (1:4) THTDP-Cl:DoDeca (1:2) [N888]Cl:2-OctOH (1:2) [N888]Cl:Deca (1:3) [N4444]Cl:2,3-butanediol (1:3) ChCl:Ph (1:4) \pm Camphor:Thymol (1:1) ChCl:Ph (1:3) ChCl:Ph (1:2) ChCl:p-cresol (1:2) [N888]Cl:1-OctOH (1:4)	Pb ²⁺ pyrethroid insecticides sulfonamides UV filters patulin Patent Blue V PAHs Hg ²⁺ , CH ₃ Hg ⁺ Cr ³⁺ , Cr ⁶⁺ Carboxylic acids Antibiotics (Levofloxacin, Ciprofloxacin)	food and water samples environmental water fruit juices swimming pool and river water fruit juices water industrial wastewater water and freshwater fish environmental water industrial wastewater environmental waters	GFAAS HPLC-UV HPLC-UV HPLC-UV UV-VIS UV-VIS GC-MS ETAAS FAAS GC-MS HPLC-UV	0.6 ng/L 0.3–0.6 μ g/L 0.02–0.05 μ g/mL 0.15–0.13 ng/mL 9.2–139.7 μ g/L 0.37 μ g/L 3.9–9.8 ng/L 0.073–0.091 μ g/L 5.5 μ g/L 1.7–8.3 μ g/L 0.016–0.024 μ g/mL	1.98 ng/L 1–2 μ g/L 0.1 μ g/mL 0.5–1.0 ng/mL – 1.22 μ g/L 12–29 ng/L 0.24–0.31 μ g/L 18.2 μ g/L 5.1–25 μ g/L 0.05–0.08 μ g/mL	2.9 1.4–4.9 0.9–3.0 <5.9 <4.2 <6 <6.1 3.6–4.1 6 4–6.7 1.8–3.7	99 81–110 88–98 90–104 90–107 92–109 74–126 84–114 93–94 82–106 88–94	[111] [137] [138] [139] [140] [141] [76] [142] [143] [144] [32]
VA-DLLME	[N888]Cl:1-OctOH (1:4) MTtOA-Br:Deca (1:2)	malondialdehyde, formaldehyde	human urine, apple juice and rain water	HPLC-UV	15.5–32.7 ng/mL	51.8–108.9 ng/mL	<6.54	91–112	[145]
AA-DLLME-SFD DI-SDME	[N888]Cl:IsoAOH (1:4) [N888]Cl:OleA (1:2) BTTPP:1-UnDecOH (1:4) MMT@Fe ₃ O ₄ -DES (DL-menthol:Deca 1:2)	indole-3-acetic acid, 1-naphthaleneacetic acid nitrite Se explosives	water and fruit juice water, biological samples aqueous samples water	HPLC-UV HPLC-PDA UV-Vis HPLC-UV	0.2–0.3 μ g/L 0.2 μ g/L 0.72 μ g/L 0.22–0.91 μ g/L	0.6–3.0 μ g/L 1 μ g/L 1.96 μ g/L 0.73–3 μ g/L	<8% 4–6 2.8–8.3 3.9–8.0	94–100 90–115 96–98 88–104	[146] [61] [114] [116]
HS-SDME HF-LPME	DES-MBG (ChCl:2-CPh 1:2) Me(Ph)3PEG (1:4) ChCl:Ph-ETOH (1:4)	BTEX hydrocortisone, cyproterone acetate propranolol, carvedilol, verapamil, amlodipine	water, urine urine and plasma samples human plasma and urine, pharmaceutical waste water	GC-FID HPLC-UV HPLC-UV	0.05–0.90 ng/mL 0.5–2 μ g/L 0.3–0.8 ng/mL	0.17–3.0 ng/mL – 0.8–2.5 ng/mL	<10 <6.3 5.2–6.5	87–106 95–117 95–104	[117] [120] [121]

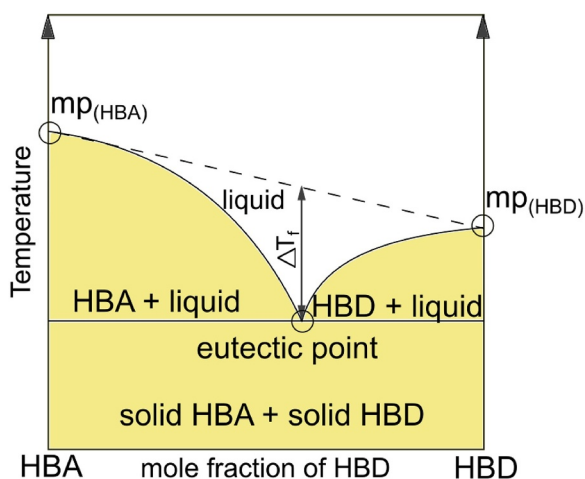


Fig. 3. Eutectic point formation in a two components (HBA and HBD) phase diagram.

the Hammett acidity function while the Lewis acidity can be examined by FT-IR analysis [53–55]. The acidity of HDES can be modified by selecting the appropriate HBD. This was confirmed in the studies on the HDES composed of benzyl tri-methyl ammonium chloride ($C_6H_6[N1112]Cl$) and various carboxylic acids. The pK_a of the studied carboxylic acids was -2.8 , 1.25 and 4.14 for *p*-toluenesulfonic acid (PTSA), oxalic acid (OxaA) and citric acid (CitA) respectively, which was in accordance with the acidity order of the new HDES ($C_6H_6[N1112]Cl: CitA > C_6H_6[N1112]Cl: OxaA > C_6H_6[N1112]Cl: PTSA$). In addition, studies showed that temperature has only a slight effect on pH values of HDES. The pH of most of HDES was stable at various temperatures, except for $C_6H_6[N1112]Cl: PTSA$ for which the pH values have decreased with increasing temperatures tending to the higher dissociation of the acid at high temperature [56].

The reports on the acidity properties of HDES are quite limited to date, due to the fact that the pH of aqueous sample is more important, than pH of extraction solvent in sample preparation methods. The appropriate pH value of the aqueous sample is selected for the studies group of analytes to obtain a partially or completely non-ionic form of the chemical compounds. However under acidic or basic conditions, HBD dissociation or HBA leaching may occur, which consequently changes the HDES molar ratio and adversely affects the efficiency of the extraction process. Therefore, when choosing the appropriate extraction solvent, it is also important to study the solubility of HDES in aqueous samples [24,57].

2.3.6. Volatility

Most of HDES are ionic, which makes them non-volatile. This is particularly unfavorable for final determinations using gas chromatography because non-volatile ionic components can cause sorption inside the liner and capillary column. However, the use of split/splitless liner packed with deactivated silanized glass wool minimizes the risk of the contamination of chromatographic column [58]. That is why in separation techniques more and more attention is paid to the use of non-ionic HDES, which are characterized by higher volatility [59]. On the other hand, according to the principles of green chemistry, solvents used should have vapor pressure as low as possible [60,61]. The vapor pressure of HDES strongly depends on the temperature. As the temperature increases, the HDES vapor pressure increases. The volatility of HDES can be determined by means of thermogravimetric analysis [62,63], Knudsen method [64] or using headspace gas chromatography–mass spectrometry [65,66]. However, the vapor pressure of HDES is not widely reported in the literature.

2.3.7. Surface tensions

Surface tension determines the suitability of DES in interfacial processes in which mass transfer occurs. HDES surface tension values are higher than most popular organic solvents but are comparable to the ILs. The interaction between HBA and HBD has a great effect on the surface tension value. The strong interactions provide the higher surface tension. Which is very beneficial because higher surface tension values ensure higher extraction efficiency. However, only a few papers describe the effect of surface tension on extraction processes. Francisco et al. examined surface tension of HDES composed of $ChCl$ and lactic acid (LacA). In the studies, the reduction in surface tension was achieved by increasing the temperature. The linear decrease in surface tension is most likely caused by the disruption and break of hydrogen bonds in HDES. However, higher temperatures during the extraction process may increase the solubility of the target compounds in HDES [67,68]. In other studies, the influence of HBA chain length on the value of surface tension was examined. Four HDES were prepared, which differed in the length of the HBA chain and HBD ($[N8881]Cl: DecA$ 1:2, $[N8881]Cl: OctA$ 1:2, $[N4444]Cl: DecA$ 1:2, $[N4444]Cl: OctA$ 1:2). The studies showed the highest extraction efficiency using HDES consisting of the shortest alkyl chain of both HBA and HBD ($[N4444]Cl: OctA$). HDES consisting of $[N4444]Cl: OctA$ also obtained the lowest viscosity and surface tension. Extraction efficiency was found to increase with reduced alkyl chain length - miscibility similarity [69].

3. Application of hydrophobic deep eutectic solvents in sample preparation

The application of HDES in green sample preparation methods is rapidly expanding. HDES are currently widely used both as liquid extractants in many types of miniaturized version of LLE techniques and as new sorbents in various kind of solid phase extraction technique.

3.1. Conventional liquid-liquid extraction

Conventional liquid-liquid extraction is a popular sample preparation technique that relies on the partitioning of analytes between two immiscible phases, an organic solvent and aqueous sample. Upon mixing, analyte-rich phase is subsequently isolated. Commonly used organic solvents in LLE may be limited in their selectivity for certain analytes. HDES demonstrated great potential as extraction solvents because of the possibility to structurally tune for facilitate the extraction of wide range of metals and ions i.e. ^{111}In (III) [71], $^{99m}TcO_4^-$ [77], Cr (VI) [78], Cu (II) [40] and UO_2^{2+} [72] as well as organic compounds i.e. organic acids [79], flavonoids [80], pesticides [81], alcohols [75] from aqueous samples. Despite the universal application of LLE technique, it has a several disadvantages such as time-consuming, labor-intensive, insufficient sensitivity for trace analysis, using large amounts of real samples, and consuming of large amounts of solvents. Miniaturization in extraction techniques is a key to overcome this disadvantages.

3.2. Liquid-liquid microextraction techniques

Liquid – phase microextraction (LPME), which is also called solvent microextraction (SME) or liquid-liquid microextraction (LLME) is a miniaturized form of conventional LLE in which the volume of extraction solvent is limited to a few microliters. The LPME offering numerous advantages such as a high enrichment factor, and low consumption of organic solvents and aqueous samples [82]. HDES have been successfully applied to the various LPME mode as a less toxic alternative to conventional organic solvents.

3.2.1. In-situ liquid-phase microextraction

In-situ LPME mode, consists of adding HDES ingredients into the

aqueous sample, then heating the solution and stirring until obtaining complete formation of the HDES and dispersion of the HDES into the aqueous phase. *In-situ* LPME was used to extract parabens from environmental water samples. Application of HDES synthesized from DL-menthol and DecA (1:1 molar ratio) ensured short extraction time, high extraction efficiency and absence of emulsifier [83].

Shishov et al. proposed a method in which HDES is formed directly in an aqueous sample between hydrogen bond donor (DL-menthol) and analytes (ketoprofen and diclofenac). In this method, solid DL-menthol was added into the aqueous sample (urine) and the mixture was heat and mixed and as a results the HDES formation was observed. Then the mixture was cooled and the liquid phase was removed while the solid menthol phase was dissolved in methanol [84].

A novel approach for effective *In-situ* LPME based on HDES decomposition was studied for the determination of 17- β -estradiol in transdermal gel samples. In this propose, HDES composed of [N4444]Br and 1-heptanol in 1:2 molar ratio was decomposed in aqueous phase resulting in-situ dispersed organic phase formation. In the process 1-heptanol acted as an extraction solvent and while [N4444]Br acted as a dispersive agent and promoted mass transfer between aqueous and organic phases as a salting out agent [85].

3.2.2. Ferrofluid-based liquid-phase microextraction

Another interesting modification of LPME technique is the use of ferrofluid as an extraction solvent. In one of the studies, ferrofluid from magnetic nanoparticles, OleA in combination with a hydrophobic deep eutectic solvent composed of AceA and DL-menthol (1:1 molar ratio) Fe₃O₄-OA-DES (DL-menthol:AceA 1:1) was used for extraction of mefenamic acid from urine samples. In this procedure, the magnet was used to separate the organic phase from the aqueous phase, which reduced time of extraction due to the lack of the sample centrifugation [86].

3.3. Dispersive liquid-liquid microextraction

Dispersive liquid-liquid microextraction (DLLME) is an attractive alternative to conventional LLE tool for the miniaturized sample pretreatment of wide range matrix samples including aqueous samples. In conventional DLLME, an aqueous sample is placed in a conical centrifuge tube and a mixture of disperser and extraction solvent is added. The disperser solvent disperse the extractant into small organic droplets and the volume of the extractant droplet decreases, the extraction process reaches equilibrium quickly, and the surface area of the extractant increases, which can be completely extracted in a relatively short time. Then the mixture is agitated, centrifuged and the organic phase is collected. The most important parameters of DLLME is the choice of appropriate extractant as well as a dispersive solvent for the extraction of analytes [87,88]. Extraction solvents should meet several requirements, including a high affinity for analytes, density significantly different from that of the sample, low solubility, high stability in the sample, good solubility in disperser solvents and ease of dispersion in a sample and it should be a liquid under standard conditions and should have a low vapor pressure. The most popular extraction solvents are hazardous chlorinated organic solvents (e.g. dichloroethane, chlorobenzene, trichloromethane, tetrachloroethylene) with a density higher than water [89–94]. Extractant having a density lower than water (e.g. toluene, n-hexane, DoDecOH, ILs) can also be used but a collection of the extract is more difficult as it requires an additional step of solidification of an organic drop or the use of special vials which are not yet available commercially [95,96].

For the first time, ionic HDES were used as an extraction medium in the DLLME technique in 2016, for the extraction and preconcentration of selected pesticides from fruit juices and vegetables prior to gas chromatography-flame ionization detection [97]. For this propose HDES based on ChCl and 4-chlorophenol (4-CPh) in 1:2 molar ratio was synthesis. The obtained results showed low LOD and LOQ values

(0.46–3.1 ng/mL and 1.5–11 ng/mL) as well as satisfying RSD values (> 8%). However, due to the ionic nature, and thus the non-volatile character, these type of HDES are not preferred for gas chromatography applications. Ionic HDES can be successfully used in combination with liquid chromatography technique. For the extraction of residues of pyrethroids in tea beverages and fruit juices, HDES based on L-carnitine:HFTP, and betaine:HFTP in 1:2, 1:2.5, and 1:3 molar ratio were tested. DLLME with L-carnitine:HFTP (1:2) as extractant provided the highest extraction efficiency than betaine-based HDES. This phenomenon may result from the more -OH group of L-carnitine than betaine, which could provide stronger hydrogen-bonding force between HDES and analytes. Furthermore, the higher viscosity of L-carnitine:HFTP may need longer emulsification time, which increases the time of interaction between HDES aggregates and analytes before phase separation [52]. DLLME technique was also used for extraction of five β -agonists, including terbutaline, clorprenaline, tulobuterol, clenbuterol and salbutamol from aqueous samples. In this research, HDES mixtures composed of [N8881]Cl, [N4444]Cl and dodecyl trimethyl ammonium chloride ([N111(12)]Cl) as a HBA and OctA, DecA and DoDecA were tested. Low viscosity of HDES based on [N4444]Cl:DecA (1:3 molar ratio) which contributed to high diffusivity, resulted in high extraction efficiency of β -agonists from aqueous samples [98]. Hydrophobic DES based on quaternary ammonium salts as well as imidazolium ionic liquids in combination with conventional DLLME have also been used to extract chlorophenols from wastewater [99], and thorium (Th⁴⁺) from water samples [100], respectively.

3.3.1. Automated - dispersive liquid-liquid microextraction

DLLME technique is difficult to automate which constitutes its main drawback. However, literature search revealed several attempts at fully-automation of DLLME [101–103]. Automated-DLLME procedure with DES as extractant was proposed for the extraction of caffeine from beverages. In research, procedure assumes mixing aqueous sample and HDES composed of ChCl and pH (1:4 molar ratio) into a mixing chamber of a flow system resulting formation of homogeneous solution, injection of tetrahydrofuran as aprotic solvent followed by the fine HDES droplets formation and analyte extraction into HDES phase separated. The presented procedure has advantages such as quickness, low cost, simplicity, as well as low LOD value (0.03 mg/L) and good recovery (94%) [104]. Shishov et al. proposed fully automated in-syringe DLLME for the extraction of chromium (VI) from beverages. In this approach, DES composed of [N4444]Br: formic acid (ForA) in molar ratio of 1:2 was used as a disperser solvent. The results demonstrated, that [N4444]Br:ForA (1:2) promoted extraction solvent dispersion resulting fast extraction kinetics, and high extraction yield [105].

3.3.2. Air-assisted dispersive liquid-liquid microextraction

The degree of HDES dispersion is one of the most significant parameters for the extraction of analytes using DLLME technique. Conventional DLLME based on HDES requires the use of a dispersing solvent, e.g. methanol, ethanol, acetone, acetonitrile or tetrahydrofuran (THF). Utilization of the disperser could leads to decreasing the partition coefficients for extraction of the analytes into the extracting solvent and increasing the cost and environmental pollution. For making DLLME greener, the dispersion procedure could be performed by using air assisted procedure (AA-DLLME). In this mode, fine droplets of HDES is formed by pulling in and pushing out the HDES and sample mixture repeatedly using syringe. AA-LPME technique was successfully applied for extraction of six benzophenone-type UV filters from aqueous samples, using HDES based on DL-menthol:DecA (1:1 molar ratio) [106]. AA-LPME extraction procedure was also used for trace analyses of amphetamine based drugs of abuse in human plasma and wastewater via a homemade extraction cell with a narrow neck was used to transfer the organic phase to the narrow portion. In the research, HDES based on ChCl and phenethyl alcohol (Ph-EtOH) (compound usually applied in perfumery, cosmetics, food, and pharmaceutical industries) in 1:4

molar ratio was used. The procedure enjoys a relatively low LOD (2–5 ng/mL) value and good repeatability. The method is characterized by a relatively low extraction recovery of analytes (63 – 66%) [107] in comparison to method based on toxic butylchloroformate as extraction solvent [108].

However, in order to increase the dispersion efficiency, several works describe the of combination of air-assisted with a dispersing solvent. For this propose, the new HDES composed of ChCl and 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-ol (TNO) in 1:2 molar ratio was used for extraction of methadone from water and biological samples. In this method, the aggregated ChCl:TNO (1:2) droplets were dispersed into sample solution by the repeated pulling in and pushing out of the mixture of HDES and sample in a conical test tube by a syringe. The HDES was separated from aqueous sample by adding THF as an aprotic solvent. The AA-DLLME method, in comparison with method based on USA-DLLME, ensures greater enrichment of the sample in a much shorter time (< 4 min) [109]. The similar studies in which THF was used as an emulsifier agent was also provided by Moghadam et al. In this work, low density HDES composed of ChCl and Ph (1:4) was used as extraction solvents in AA-DLLME [110]. AA-DLLME was also successfully used for the determination of Pb (II) in food and water samples [111]. For this propose, DES as hydrophilic extraction solvent was added into aqueous samples. After that THF was added into homogeneous solution and a turbid solution was achieved. THF was used as demulsifying solvent to facilitate the extraction, because it interacts with water and cause ease in separation.

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molar ratio was used. The procedure enjoys a relatively low LOD (2–5 ng/mL) value and good repeatability. The method is characterized by a relatively low extraction recovery of analytes (63 – 66%) [107] in comparison to method based on toxic butylchloroformate as extraction solvent [108].

However, in order to increase the dispersion efficiency, several works describe the of combination of air-assisted with a dispersing solvent. For this propose, the new HDES composed of ChCl and 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalen-2-ol (TNO) in 1:2 molar ratio was used for extraction of methadone from water and biological samples. In this method, the aggregated ChCl:TNO (1:2) droplets were dispersed into sample solution by the repeated pulling in and pushing out of the mixture of HDES and sample in a conical test tube by a syringe. The HDES was separated from aqueous sample by adding THF as an aprotic solvent. The AA-DLLME method, in comparison with method based on USA-DLLME, ensures greater enrichment of the sample in a much shorter time (< 4 min) [109]. The similar studies in which THF was used as an emulsifier agent was also provided by Moghadam et al. In this work, low density HDES composed of ChCl and Ph (1:4) was used as extraction solvents in AA-DLLME [110]. AA-DLLME was also successfully used for the determination of Pb (II) in food and water samples [111]. For this propose, DES as hydrophilic extraction solvent was added into aqueous samples. After that THF was added into homogeneous solution and a turbid solution was achieved. THF was used as demulsifying solvent to facilitate the extraction, because it interacts with water and cause ease in separation.

3.3.5. Solidification of floating drop dispersive liquid-liquid microextraction

Several lighter than water HDES were also successfully applied in DLLME for extraction of organic and inorganic compounds from aqueous samples. Nevertheless, if less dense extractants are used the recovery step is relatively tedious and an additional step is generally necessary, i.e. solidification of the floating organic drops (SFD), adsorption by nanoparticles or centrifugation and collection of organic phase in special apparatuses [112]. For these propose HDES consisting of 1-decyl-3-methylimidazolium chloride [C10MIM][Cl] and 1-DodecOH (1:2 molar ratio) was used as an extraction solvent in DLLME method based on the solidification (SFD-DLLME) coupled with high-performance liquid chromatography for the determination of five benzoylureas in real water samples. Low limit of detection (LOD) values ranging from 0.09–0.16 µg/L, satisfactory recovery, and precision were obtained for all the pesticide residue analytes using these method [113]. Similar procedure was used for the extraction of selected PAHs from environmental waters using HDES composed of [N4444]Br and DecA (1:2 molar ratio) [70].

For the determination of selenium (Se) in aqueous samples procedure centrifuge less air-assisted LLME based on solidification of dispersed fine droplets of a hydrophobic DES combined with UV-Vis spectrophotometry was proposed. As extraction solvent HDES composed of benzyltriphenylphosphonium bromide (BTPPB) and 1-undecanol (1-UnDecOH) (1:4 molar ratio was used). In this procedure, the centrifugation step was omitted by using salting-out effect and to facilitate the extracting phase collection after the phase separation, the floating extraction solvent was solidified and a bell-shaped collection device was used [114].

However, DLLME is based upon a ternary component solvent system, in which utilization of the disperser could leads to decreasing the partition coefficients for extraction of the analytes into the extracting solvent and increasing the cost and environmental pollution. An alternative to this method, which does not require the use of a dispersing solvent is vortex assisted dispersive liquid–liquid microextraction based on the freezing of deep eutectic solvent (VADLLME – FDES).

3.4. Single-drop microextraction

3.4.1. Direct immersion single-drop microextraction

Among different liquid – phase microextraction methods, single drop microextraction (SDME) is one of the simplest and most powerful preconcentration technique. Single-drop microextraction is based on the analyte transferring from the aqueous sample to the micro drop (usually less than 3 μL) of extraction solvent which is suspended at the tip of a micro-syringe needle. The droplet is directly immersed in the sample. The main disadvantage of DI-SDME is the problem with stability of droplet which strongly depend on used organic solvent. Organic solvents characterized by low viscosity and high vapor pressure reduce the efficiency of the extraction process [115]. Therefore, theoretically HDES can be an excellent alternative to traditional solvents used in DI-SDME. However, until now there are no reports on the use of conventional HDES in the DI-SDME technique. The only studies in which HDES was used in DI-SDME technique, concerned the use of ferrofluid of montmorillonite nanocomposite and DES composed of DL-menthol:DecA in 1:2 molar ratio (MMT@Fe₃O₄-DES) without any additional stabilizer was used for the extraction and preconcentration of explosives in water. After extraction process ferrofluid was easily isolated from aqueous sample by rod magnet [116]. The use of ferrofluid based on HDES eliminated an additional problem regarding exact collection of the micro-drop by microsyringe.

3.4.2. Headspace single-drop microextraction

In HS-SDME technique the analytes are extracted from the headspace on top of the aqueous sample. HS-SDME has some benefits over DI-SDME like fastest and cleaner extraction of volatile and semi-volatile compounds from dirty and complex matrixes and higher efficiencies for extraction of organic compounds. However, the problem of instability of the micro-drop, limited drop volume, volatility, and low viscosity of extraction solvent and poor repeatability of extraction are also existence in HS-SDME mode. The application of HDES composed of ChCl and 2-CPh in 1:2 molar ratio as a base fluid and magnetic multiwall carbon nanotube nanocomposite (DES-MBG) overcame these problems. The nanofluid was characterized by high viscosity, high sorbing ability, tunable extractability, magnetic susceptibility which provided to high stability of the micro-droplet that permitted extraction in high temperatures and fast agitation rates. The new solvent was successfully applied for the determination of BTEX (benzene, toluene, ethylbenzene, o-xylene) in water and urine samples [117].

3.5. Hollow fiber-protected liquid phase microextraction

To overcome the problem with instability of the micro-drop in SDME technique, in 1999 the new hollow fiber-based liquid phase microextraction (HF-LPME) technique was introduced [118]. In HF-LPME, the analytes are extracted from the sample (donor phase) into supported liquid membrane (extraction phase) located inside the pores of a porous hollow fiber and back extracted into acceptor phase located in the lumen of hollow fiber. This makes the extraction solvent is not in direct contact with the aqueous sample. The HF-LPME could be used in two-phase and three phase. In two-phase HF-LPME, the lumen of the fiber is filled by the extraction solvent (acceptor phase). In three-phases HF-LPME, an acceptor phase (usually an aqueous solvent) fills the lumen of the hollow fiber [119]. However, there are no reports on the use of HDES in a two-phase system. While HDES were successfully applied in three-phase HF-LPME as an acceptor phase. The acceptor phase should be immiscible with each other solvents, have low volatility, and convenient immobilization in the hollow fiber. These features have HDES composed of methyltriphenylphosphonium iodide (Me(Ph)3PI) as the HBA and ethylene glycol (EG) as HBD in 1:4 molar ratio, and was used for extraction of hydrogesterone and cyproterone acetate from urine and plasma samples. Despite, high affinity of Me(Ph)3PI:EG (1:4) to analytes, the high viscosity of HDES hinders mass transfer of analytes

into them. Thus MeOH was used to dilute of HDES [120]. This problem wasn't observed in other report in which ChCl:Ph-ETOH (1:4) was applied as extraction solvent in carrier-less three phase HF-LPME procedure [121].

Table 3 lists the key features of HDES-based LLE techniques.

3.6. Solid phase extraction

Solid phase extraction (SPE) is popular technique to prepare aqueous samples and extract semivolatile or nonvolatile analytes, due to the simplicity, low cost and possibility of automation. The SPE uses sorbents to isolate the target compounds from a sample. Currently, a large variety of sorbents are available to cover almost all the potential interaction with the analytes. However, analytes and interferences could coelute from the SPE sorbent due to the limited selectivity of conventional solid sorbents. In addition, due to the consumption of large amounts of sample, sorbents, and organic solvents, the SPE technique is still improved [122].

Very recently, Liu et al. investigated the cross-linking porous and planar-structure DES-graphene for the extraction of sulfamerazine in a river water samples using pipette-tip solid phase extraction (PT-SPE). In this study, the PT-SPE method was specially designed for handling small volume of solution consumption. The results demonstrated that the DES-graphene had the higher adsorption ability (18.62 mg/g) than graphene (17.36 mg/g), due to the DES-graphene had a larger winkle than graphene [123].

Another modification of conventional SPE, is the technique in which it is used magnetic or magnetizable adsorbents called magnetic solid-phase extraction (MSPE). In this method, magnetic adsorbent is added to the sample. In this step analytes and interferences are bound to the extraction sorbent, then for removal of interferences adsorbent is washed and target analytes are eluted from the material in organic solvents. The analytes are desorbed from the suspension using an appropriate magnetic separator, which often speeds up recovery of the analyte enriched extraction phase. The most popular magnetic sorbents include inorganic composites i.e. Fe₃O₄@SiO₂ and Fe₃O₄@graphene, which characterized by poor selectivity for different analyte groups. Therefore, research is still being carried out on the use of new sorbent modifiers that will allow the selective extraction of a wide group of compounds from aqueous samples.

Wang et al. investigated the new magnetic nanomaterial, based on Fe₃O₄ coated with polydopamine and DES (Fe₃O₄@PDA-DES) for the extraction of sulfonyleurea herbicides (sulfosulfuron, bensulfuron-methyl, pyrazosulfuron-ethyl and halosulfuron-methyl) in aqueous samples. In this studies, HDES was composed of dioctadecyl dimethyl ammonium chloride ([N11(18)18]Cl) and 4-CPh in 1:5 molar ratio. For the desorption of analytes acetonitrile was used. The presented method, characterized by low LOD, good repeatability, high preconcentration factors and extraction recoveries [124].

MSPE was also successfully applied for the extraction of mercury from water by means of new ternary hydrosulphonyl-based deep eutectic solvent (THS-DES) comprised of ChCl, itaconic acid and 3-mercaptopropionic acid (molar ratio 2:1:1). In the studies, THS-DES was used for the modification of magnetic graphene oxide (M-GO). The new THS-DES@M-GO sorbent demonstrated higher removal efficiency than adsorbent without DES, as well as Fe₂O₃, because of strong interaction of Hg²⁺ with the -SH groups [125].

Karimi et al. described application of DES (ChCl-U 1:2.5) - mediated magnetic nanoparticles (DES-MNPs) for the ligandless separation and preconcentration of lead and cadmium from aqueous samples. In this studies, DES and Fe₃O₄ nanoparticles were simply added to the aqueous sample then DES containing analytes was trapped on the sorbent and separated by the using a strong magnet. The desorption processes was provide by means of nitric acid, and the extracted metal ions were then introduced to flame atomic absorption spectrometry (FAAS) [126].

Most of the described DES that have been used to extract various

compounds from aqueous samples are liquid and hydrophilic. However, they lose their liquid state and sorbed on the surface of nanoparticles through strong hydrogen bonds and electrostatic interaction with the functional groups on the surface of particles, and separates from the aqueous sample [126].

3.7. Solid phase microextraction

Solid phase microextraction (SPME) is a miniaturized version of SPE, which was developed by Pawliszyn in 1990 [127]. In this technique, analytes are extracted from a aqueous sample by exposing sorbent to either the sample headspace (HS-SPME) or by direct immersion (DI-SPME) in the aqueous sample. In the next step, analytes are desorbed by means of high temperature or organic solvent. The selectivity of SPME method strongly depends on the chemical composition of the coating on the solid support.

Very recently, Li et al. investigated the HDES mediated sol-gel sorbent as an adsorptive coating of poly(dimethylsiloxane) (PDMS) fiber for extraction of BTEX from water. In this studies, HDES was prepared by mixing methyl trioctyl ammonium chloride ([N8881]Cl) and 4-hydroxybenzoate in 1:2 molar ratio. The results indicate that the addition of HDES could generate a lot of neat pores in the PDMS fiber surface, thus significantly improving the performance of PDMS fiber coating. The limit of detection for presented method based on PDMS-DES sorbent was much lower than the commercial 100 μm -PDMS fiber coating [128].

3.8. Dispersive solid phase extraction

Dispersive solid phase extraction (DSPE) is an another alternative approach to conventional SPE. DSPE is based on the addition of a sorbent directly into the aqueous sample, then followed by dispersion which favoring the contact between the sorbent particles and the analytes. After dispersion, the sorbent containing analytes on its surface, is separated by means of centrifugation [129]. Currently, deep eutectic solvents in the DSPE technique have been used as sorbent modifiers or eluents for improve of extraction recovery of DSPE.

Lamei et al. studied application of DES composed of ChCl and TNO in 1:2 molar ratio as novel functionalizing agent on the surface of $\text{Fe}_3\text{O}_4@\text{GO}$ nanoparticles. The new sorbent was successfully applied for efficient preconcentration of methadone from urine and plasma samples. In this studies, analyte was preconcentrated in the new sorbent $\text{Fe}_3\text{O}_4@\text{GO}$ -DES, then methadone was dispersed in the aqueous solution by use of ultrasonic energy (UA-DSPE). The ultrasound accelerated the dispersion of the sorbent in the biological samples and enhanced the speed of migration of the methadone into the $\text{Fe}_3\text{O}_4@\text{GO}$ -DES sorbent, which ensured high analyte recovery [130].

Zarei et al. synthesized colloidal gel of magnetic carbon nanotube and deep eutectic solvent (ChCl:U 1:2) for enrichment of ultra-trace amounts of nitroaromatic explosives in water samples. In the prepared gel, DES acts simultaneously as both carrier and stabilizer for magnetic nanotubes. Prepared gel was characterized by high stability stable for weeks without visually observable sedimentation. In the procedure the magnetic colloidal gel (MCG) was dispersed thoroughly in aqueous sample and cloudy suspension was created. The proposed method provided increase in mass transfer coefficient and shorted the extraction time without need to agitation by vortex or ultrasounds the sample. The magnetic properties provide to no centrifugation step was required for phase separation [131]. The similar studies was also provided for the determination of organochlorine pesticides in environmental waters [132].

A different approach to the use of DES in DSPE was proposed by Khezeli and Daneshfar. They investigated the new adsorbent $\text{Fe}_3\text{O}_4@\text{MIL-100}$ (Fe) core-shell nanoparticles grafted with pyrocatechol for the selective extraction of dopamine, epinephrine and norepinephrine from biological samples. The hazardous solvents that many used in

desorption step were substituted with environmental friendliness and safety DES composed of ChCl and U, EG and glycerol in 1:2 molar ratio. The results showed that the new method a simple, is fast, sensitive and selective way for the determination of target analytes. However, the DES used were solvents with hydrophilic properties [133]. In another work, water-immiscible DES composed of ChCl:4-CPh 1:2 was also successfully used to desorb the analytes (tricyclic antidepressant drugs) from the sorbent (C18) [134].

3.9. Stir bar sorptive dispersive microextraction

Stir bar sorptive dispersive microextraction (SBSDE) was initially introduced in 2014 by Benede and co-workers [135]. SBSDE is based on the combination of DSPE and stir bar sorptive extraction. SBSDE consists of a magnetic stir bar coated with magnetic nanoparticles (MNPs) by magnetic interaction which is placed into the sample. During extraction process at high stirring rate, MNPs is detached from the rotating bar and dispersed in the sample solution as in DSPE method. When the stirring stops, MNPs come back to the stir bar surface. Then, the liquid is discarded and the back-extraction is carried out with the solvent. Zarei et al. prepared stable nanofluid composed of ChCl and Resorcinol (1:2) and magnetic MWCNTs for the extraction of nitroaromatic compounds from water samples. In the fluids, HDES acted simultaneously as both carrier and stabilizer for magnetic nanotubes. The prepared nanofluid was characterized by strong magnetic and sorbing properties with provide to high extraction efficiency and low LOD and LOQ values [136].

Reports on HDES-based various type of solid phase extraction are summarized in Table 4.

Advantages and limitations of HDES application in selected microextraction techniques in comparison to traditional solvents are present in Table S1.

4. Conclusions and future trends

The application of HDES in analytical aqueous sample preparation techniques is rapidly expanding. However, the most commonly DES includes solvents with hydrophilic properties. Despite the increased interest in the synthesis of hydrophobic DES, their number is still limited and further efforts are needed to synthesize and study new HDES as extraction solvents. In addition, HDES are still not commercially available, which significantly limits their use for routine analysis of water samples performed in certified or industrial laboratories. Nevertheless, in the coming years, there will probably be many more HDES combinations, and some of them will be available for purchase.

Part of HDES are compounds composed of substances that have dubious toxicity. On the one hand, the combination of a toxic compound with a non-toxic compound can create HDES with less toxicity compared to a single component. However, it can also lead to the formation of HDES with higher toxicity. For HDES to be more widely adopted in the extraction techniques, their toxicity and environmental effects need to be further investigated.

The relatively low volatility most of HDES, prevents evaporation in most popular GC injectors. This can result in contamination of the liner and chromatography column, unstable of baselines as well as possibly unstable carrier gas-flow rates. However, in the literature there are several solutions to this problem, including introduction of a removable GC interface [147] or application of liner packed with deactivated silyanized glass wool packet liner [58]. These solutions are expected to contribute to expand the application field of HDES coupled to gas chromatography in the years ahead.

The high viscosity of most HDESs, provide in some challenges for the extraction processes as well as analysis of HDES extracts due to the problem with collecting and injecting the exact volume of HDES with analytes into HPLC or GC injector using a microliter syringe, which consequently limits the possibility of using an autosampler. Currently,

Table 4
Compilation of application of HDES in various types of solid-phase extraction procedures.

Extraction technique	Analytes	Sorbent (HDES)	Sample matrix	Instrument	Extraction temp. / time	Thermal desorption temperature / time	Eluent / time	LOD	LOQ	RSD [%]	R [%]	Ref.
PT-SPPE	Sulfamerazine	DES-graphene (ChCl:EG 1:2)	River water	HPLC-UV-VIS	RT / -	-	Petroleum ether (washing solvent), eluent: ammonia/methanol/ acetonitrile (5:4:50, v/v/v) 3 × 0.5 mL acetonitrile, and vortexed for 1 min each time	0.01 ug/mL	0.03	0.7 – 3.8	95.38	[123]
MSPE	sulfonyleurea herbicides	Fe ₃ O ₄ @ PDA-DES (DODDMA-Cl: 4-CPh 1:5)	Environmental water	UPLC-PDA	RT / 5 min	-		9.8–11 ng/L	-	1.2 - 3.6	61–109	[124]
	Hg ²⁺	THS-DES@M-GO	Water	atomic fluorescence spectrometer (AFS)	RT / 30 min	-	Ethylenediaminetetraacetic acid solution EDTA 0.05 M	-	-	1.55	99	[125]
	Pb ²⁺ , Cd ²⁺	Fe ₃ O ₄ @ DES (ChCl: U 1:2.5)	Environmental waters	FAAS	RT / 10 min	-	Nitric acid (1.0 mol/L)	0.5 - 2	-	1.8–2.1	95 - 103	[126]
HS-SPME	toluene, ethylbenzene and o-xylene	PDMS-DES [N8881]Cl: 4-hydroxybenzoate 1:2)	Environmental water	GC-FID	40 °C / 15 min	200 °C / 1 min	-	5–25 ng/L	-	4.2 – 6.7	89–113	[128]
UA- DSPE	methadone	Fe ₃ O ₄ @GO-DES (ChCl: TNO 1:2)	Plasma, urine, water	GC-FID (MS)	RT / 2 min	-	Ethanol	0.8 ug/L (0.03 ug/L)	2.5 (0.099)	5.8 – 8.4	95–102	[130]
DSPE	nitroaromatic explosives	DES-MCG (ChCl:U 1:2)	Well water, treated red and yellow waters	GC-µECD	RT / 5 min	-	Acetone	0.8–12.4 ng L - 1	2.7 – 41.3	4.6 – 8.5	90–110	[131]
	organochlorine pesticides	DES-MCG (ChCl:U 1:2)	Environmental waters	GC-µECD	RT / few seconds	-	acetonitrile	0.04–0.27 ng/L	0.13–0.89	1.3–5.3	86–115	[132]
	dopamine, epinephrine, norepinephrine	Fe ₃ O ₄ @MIL-100 (Fe) core-shell nanoparticles grafted with pyrocatechol C18	serum and urine	HPLC-UV	RT / 5 min	-	phosphate buffer:DES (7:3 v/v) DES (ChCl:U 1:2)	0.22–0.36 ug/L	0.78–1.2 ug/L	<5.4	91–103	[133]
DSPE-AA-LPME	tricyclic antidepressant drugs		Urine, plasma	GC-MS	RT / 3 min	-	ChCl:4CPh (1:2)	8 – 60 ng/L	-	2–5	62–74	[134]
SBSDME	Nitroaromatic explosives	DES-MNF (ChCl: resorcinol 1:2)	Well water, treated red and yellow waters	GC-µECD	RT / 5 min	-	Acetone	0.22–4.92 ng/L	-	5.6–10.2	80 - 114	[136]

HDES are mixed with organic solvents to reduce their viscosity. However, this is not in line with the trends of green chemistry, according to which the use of organic solvents should be reduced. There are several ways to overcome this limitation, i.e. working at higher temperatures, or using mechanical force in extraction processes and using heated autosamplers. However, further development of novel technologies for reduce viscosity of HDES probably will be observed.

Among the most important physicochemical parameters of extraction solvents, polarity is important to explain the extraction capacity and miscibility of HDES in water. However, the polarity of HDES has been little investigated, and further studies should be provided.

The high surface tension of HDES is necessary for avoiding the presence of emulsions. However, this parameter has not been systematically studied and further studies is needed.

Due to the fact, that interests within the field of sample preparation are expanding toward the analysis of samples with very complicated matrices, i.e. environmental, wastewater or biological samples, concerns over reduction in sensitivity can arise in LLE as well as solid-phase extraction techniques. Therefore, novel HDES that can both exhibit high analyte selectivity and resist the potentially damaging components of the sample matrix will be likely studied.

In addition, tunable selectivity, negligible vapor pressure, as well as thermal stability of HDES may contribute to the development of new fibers used in SPME. However, currently the application of HDES in SPME technique are still limited.

Given the flexibility offered by HDES in sample preparation, their use will continue to grow, and they will probably soon replace organic solvents in some analytical applications.

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Supplementary materials

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