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Review

Ionic liquids in dispersive liquid-liquid microextraction

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ABSTRACT

In this review, we summarize the most recent analytical developments aimed at employing Ionic liquids (ILs) in dispersive liquid-liquid microextraction (DLLME). Four main operation modes can be distinguished: (1) conventional IL-DLLME; (2) temperature-controlled IL-DLLME; (3a) ultrasound-assisted, (3b) microwave-assisted or (3c) vortex-assisted IL-DLLME; and, (4) *in-situ* IL-DLLME. In these modes, the dispersive solvent can be an organic solvent, a surfactant, or a hydrophilic IL. In some cases, a dispersive solvent is not even necessary. We discuss practical applications of IL-DLLME to determine metals and organic compounds in a variety of samples.

Contents

Abbreviations: 1N2N, 1-nitroso-2-naphtol; 4-AAP, 4-aminoantipyrine; 5-Br-PADAP, (5-bromo-2-pyridylazo)-5-diethylaminophenol; 8-QOH, 8-hydroxyquinoline; ACN, Acetonitrile; APDC, Ammonium pyrrolidinedithiocarbamate; BF_4^-, Tetrafluoroborate anion; C_2, Ethyl; C_3, Propyl; C_4, Butyl; C_6, Hexyl; C_8, Octyl; C_{16}, Hexadecyl; C_{drop}, Concentration of the analyte in the final microdroplet; CE, Capillary electrophoresis; CIAME, Cold-induced aggregation microextraction; $C_{initial}$, Initial concentration of the analyte in the water sample; CRM, Certified reference material; DAD, Diode array; DDTC, Diethyldithiocarbame; DDTP, o,o-diethylthiophosphate; DLLME, Dispersive liquid-liquid microextraction; DNPH, 2,4-dinitrophenylhydrazine; E_F, Enrichment factor; EF_{max}, Maximum preconcentration factor; E_R, Extraction efficiency; ESI, Electrospray ionization; ETAAS, Electrothermal atomic absorption spectrometry; EtOH, Ethanol; FAAS, Flame atomic absorption spectrometry; FAP, Tris(pentafluoroethyl)trifluorophosphate anion; FD, Fluorescence detection; FI-HG, Flow injection-hydride generation; FO-LADS, Fiber optic-linear array detection spectrophotometry; GC, Gas chromatography; GFAAS, Atomic absorption spectrometry with graphite furnace; HPLC, High-performance liquid chromatography; HYD, 1-hydroxy-2,5-pyrrolidinedione; ICP, Inductively coupled plasma; IL, Ionic liquid; Im, Imidazolium; ISFME, *In-situ* solvent-formation microextraction; LLE, Liquid-liquid extraction; LOD, Limit of detection; LPME, Liquid-phase microextraction; M, Methyl; MeOH, Methanol; MS, Mass spectrometry; MW, Microwaves; NTf_2, Bis[(trifluoromethane)sulfonyl]imide anion; OES, Optical emission spectrometry; PAH, Polycyclic aromatic hydrocarbon; PAR, 4-(2-pyridylazo)-resorcinol; Py, Pyridinium; Pyrr, Pyrrolidinium; RR, Relative recovery; RSD, Relative standard deviation; SDME, Single-drop microextraction; SDS, Sodium dodecyl sulfate; SPE, Solid-phase extraction; SPME, Solid-phase microextraction; TMK, 4,4′-bis(dimethylamino)thiobenzophenone or Michler thioketone; US, Ultrasound; V_{drop}, Microdroplet volume including its further dilution; $V_{initial}$, Initial aqueous solution volume; Vis-UV, Visible-ultraviolet; VWD, Variable wavelength detection.

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1. Introduction

Dispersive liquid-liquid microextraction (DLLME) is a successful extraction procedure developed by Rezaee et al. in 2006 [1]. Since then, an impressive number of applications of the technique have appeared in the literature [2–5]. The fundamentals of the microextraction technique are quite simple: the mixing of an aqueous sample containing analytes with a low amount (normally in the order of microliters) of an extractant solvent, which is non-miscible with water, with the aid of a dispersive solvent (normally 0.5–1 mL), which is miscible in both water and the extractant solvent. Thus, solely the mixing of the three components forms multiple microdroplets in solution in which partition of the analytes takes place. Analytes experience enrichment in the low volume of extraction solvent, which was dispersed into the bulk aqueous solution, and are then commonly separated by centrifugation.

DLLME is a successful extraction technique due to the high contact surface of fine droplets of extractant solvent and analytes, which speeds up the mass-transfer processes of analytes. DLLME in its more classical variant has characteristics of cloud-point extraction, whereas some DLLME modes also resemble homogeneous liquid-liquid extraction.

The method is useful because of its high preconcentration factor, high extraction efficiency, and minimum requirements for sample and organic solvents. The requirement of dispersive solvent is in the mL range (and so accompanied by sample dilution) and the necessity of a centrifugation step in order to facilitate the separation of the phases can be cited among the shortcomings.

To date, the method has undergone a number of modifications, which include the application of vortex or ultrasound if a solvent less dense than water is used as extraction solvent [6–8], the use of DLLME with simultaneous derivatization of analytes [5,9], and the connection of DLLME to other sample-preparation techniques [9]. Andruch et al. recently summarized the applications involving DLLME in the past five years [10], whereas Ma et al. recently reviewed analytical advances regarding DLLME [11].

Ionic liquids (ILs) are ionic, non-molecular solvents with melting points below 100°C. The most notable properties include their negligible vapor pressure at room temperature, high thermal stability, and variable viscosity. Their miscibility in water and organic solvents can be controlled by selecting the cation/anion combination or by incorporating certain functional groups in the IL molecule. In addition, they possess a multitude of tunable physicochemical properties. There has been enormous interest in the development of analytical methods that exploit the unique physicochemical properties of ILs, as they can be tuned and manipulated for specific applications. Thus, many review articles have covered the intense use of ILs in different fields within analytical chemistry [12–16].

The utilization of ILs in DLLME was first proposed by Zhou et al. [17] and Baghdadi and Shemirani [18].

Zhou et al. proposed the use of one IL as extractant solvent in DLLME to determine a group of organophosphorus pesticides in environmental samples in a temperature-controlled mode. They heated the aqueous solution containing analytes and the hydrophobic IL, followed by cooling with iced water to settle the IL microdroplet with preconcentrated analytes and centrifugation [17]. Heating the solution avoided the need to use a dispersive solvent.

Baghdadi and Shemirani proposed the determination of mercury in water using a DLLME method with ILs, which was named cold-induced aggregation microextraction (CIAME). CIAME can be classified as a temperature-controlled mode of IL-DLLME, which uses lower heating temperatures. Thus, they used a mixture of two hydrophobic ILs as extractant solvents to facilitate the extraction in salty aqueous matrices. The method required the use of a chelating agent to trap the metal, and a surfactant as an anti-sticking agent. The aqueous mixture needed to be heated, followed by cooling. Afterwards, the microdroplet of the mixture of hydrophobic ILs containing mercury (trapped by the chelating agent) was also separated by centrifugation. In this case, small amounts of dispersive solvents (mainly acetone and ethanol) were needed in the method [18].

Since the publication of these original ideas in 2008, an enormous number of works have proposed the IL-DLLME method as a successful alternative to conventional DLLME. However, in spite of the wide utilization of ILs in DLLME, no review article has exclusively focused on the utilization of ILs in DLLME.

A recent review article of Han et al. focused on the use of ILs in liquid-phase microextraction (LPME), as a general microextraction technique [19]. The article focused on analytical applications, and it included a section devoted to ILs in DLLME. However, it did not include any classification of the operational modes in which the method can be accomplished.

In December 2011, Vičkačkaitė and Padarauskas also nicely reviewed the applications of ILs in different microextraction techniques, such as solid-phase microextraction (SPME) and LPME, so they included an IL-DLLME section [20].

In 2010, Aguilera-Herrador et al. also covered the use of ILs in sorptive microextraction techniques [14] including an IL-DLLME section, but, since then, a large number of applications and developments of the technique have taken place. Other recent review articles related more to ILs in SPME [21,22].

The literature shows that the majority of the works in IL-DLLME are characterized with relatively complex titles. The length and the depth of the titles add more confusion to the readers about the complexity of the IL-DLLME method. We believe it is necessary to distinguish, in a simple manner, the different modes with which IL-DLLME can be carried out.

This review summarizes the current modes of IL-DLLME, making clear, simple distinctions between them. This review also gives an overview of the utilization of ILs in DLLME for the determination of organic compounds and metals in a variety of samples.

2. Modes of IL-DLLME

It is possible to distinguish four main modes to perform an IL-DLLME method:

(1) conventional IL-DLLME without the need for energy requirements other than the simple ternary mixture of components (aqueous sample containing analytes, IL extractant, and dispersive solvent);
(2) temperature-controlled IL-DLLME;
(3) ultrasound-assisted, microwave-assisted, or vortex-assisted IL-DLLME; and,
(4) *in-situ* IL-DLLME.

Fig. 1 summarizes each operation mode. The fundamentals of each strategy and their applications are described in the following sections.

The abbreviations used for the ILs in this review follow common usage. Thus, alkyl substituents of the IL cation are first written showing their length (i.e.: C_8 for octyl, C_2 for ethyl, or M for methyl); followed by the terms Im for imidazolium, Pyrr for pyrrolidinium, and Py for pyridinium; and finally, by the anion {e.g., $-PF_6$ for hexafluorophosphate, –Br for bromide, and $-NTf_2$ for bis[(trifluoromethane)sulfonyl]imide}. In the case of Im-based ILs, the substituent located in position 1 is written first, followed by the substituent in position 3.

2.1. Conventional IL-DLLME

The conventional IL-DLLME method is based on the simple mixture of the aqueous sample containing analytes with the IL used as

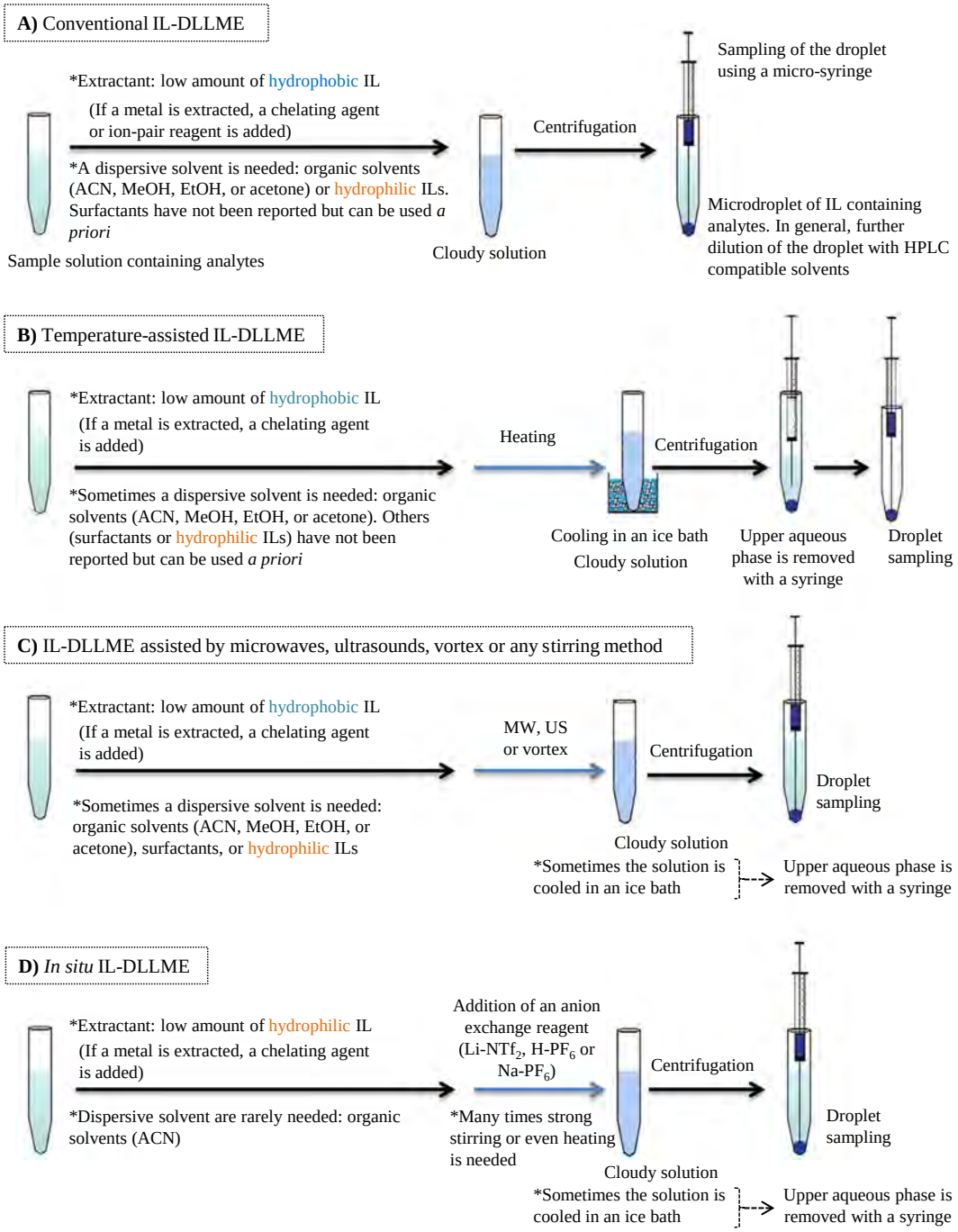

Fig. 1. Modes of performance for the IL-DLLME method when determining organics and metals in aqueous samples: A) conventional IL-DLLME; B) temperature-assisted IL-DLLME; C) microwave-, vortex-, ultrasound-assisted (or any strong stirring mode) IL-DLLME; and D) *in situ* IL-DLLME.

extractant solvent and the dispersive solvent. The mixture can be manually stirred, and the preconcentrated analytes in the IL microdroplet are then separated by centrifugation. This is the simplest mode for the IL-DLLME method, because it does not need any extra step. Organic solvents (mainly methanol) have been commonly used as dispersive solvents. This operational mode of IL-DLLME most resembles the conventional DLLME procedure, simply utilizing an IL as extractant solvent instead of a conventional organic solvent. The procedure is depicted in Fig. 1(A).

The first description of the method was by Liu et al. [23] for the determination of four heterocyclic insecticides in water. They used methanol as dispersive solvent, and IL $C_6MIm\text{-}PF_6$ as the extractant solvent. The simplicity of the method was also accompanied by low limits of detection (LODs), down to 0.53 μg L^{-1}.

Table 1 includes a summary of the most significant works regarding conventional IL-DLLME for the determination of organic analytes [23–42]. It is clear that the majority of the works used Im-based ILs containing hexafluorophosphate as extractant solvents. It is noticeable that in most cases it is also necessary to dilute the final IL microdroplet with a small amount of an organic solvent to decrease IL viscosity (and facilitate its handling) and to ensure further compatibility with the analytical instrument. The analytical determinations are commonly carried out in combination with high-performance liquid chromatography (HPLC) and a number

Table 1
Determination of organic compounds using conventional IL-DLLME.

Analytes (number)	Sample (mL)/sample requirements	IL extractant (amount)	Dispersive solvent (μL)	Centrifuge conditions	V_{drop} in μL/further diluent (μL)	Comments	Analytical technique	E_F/E_R (%)/RSD in % (spiked level in μg L^{-1})	LOD (μg L^{-1})	Ref.
heterocyclic insecticides (4)	water (5)/-	C_6MIm-PF_6 (52 mg)	MeOH[a] (500)	10 min 4000 rpm	19/MeOH (50)	–	HPLC-DAD	E_F = 209 – 276/ E_R = 82–106/ RSD < 10.7 (5.0)	0.53–1.28	[23]
pesticides(4)	water (5)/-	C_8MIm-PF_6[a] (436 mg)	MeOH (1000)	5 min 4000 rpm	-/-	–	HPLC-UV	E_F = 200–250/ E_R = 71.0–81.3/RSD < 4.7 (1000)	0.1–5.0	[24]
drugs (4)	urine (10)/pH 3.0	C_4MIm-PF_6 (280 μL)	MeOH[a] (720)	-	-/dilution 1:1 (v/v) with HPLC mobile phase	-one–step in a syringe setup	HPLC-UV	E_F = 73.7–84.6/ E_R = 36.8–42.3/RSD < 8.6 (200)	8.3–32	[25]
pesticides (8)	aqueous extract of bananas (10)/pH 2.7 and NaCl (28.9 %, w/v)	C_6MIm-PF_6[a] (88 mg)	MeOH[a](714)	20 min 4000 rpm	20/ACN (~105)	-fruits were extracted with ACN, evaporated, and reconstituted with water -optimization with an experimental design	HPLC-DAD	-/E_R = 53–97/ RSD[b] < 4.8 (1000)	0.320–4.66 μg kg^{-1}	[26]
multi-class pesticides (8)	aqueous extract of grapes or plums (10)/pH 2.7 and NaCl (28.9 %, w/v)	C_6MIm-PF_6 (88 mg)	MeOH (714)	20 min 4000 rpm	20/ACN (~105)	-fruits were extracted with ACN, evaporated, and reconstituted with water	HPLC-DAD	-/E_R = 58–105 /-(-)	0.651–5.44 μg kg^{-1}	[27]
tetrabromobisphenol A	water (5)/pH 7	C_6MIm-PF_6[a] (70 μL)	ACN[a] (500)	6 min 3000 rpm	-/MeOH (50)	–	HPLC-ESI-MS/MS	-/-/RSD = 6.95 (5.0)	0.06	[28]
persistent organic pollutants (3)	water (5)/pH 7	C_6MIm-PF_6[a] (70 μL)	acetone[a] (600)	10 min 3000 rpm	-/MeOH (50)	–	HPLC-UV	-/-/RSD < 6.73 (5.0)	0.33–0.63	[29]
parabens (4)	aqueous extract of pancakes (10)/NaCl (3.0 g) and pH 6	C_8MIm-PF_6[a] (100 μL)	ACN (100)	5 min 2500 rpm	~60/MeOH (~20)	-pancakes were extracted with MeOH, evaporated, and reconstituted with water	HPLC-UV	E_F = 68.2–90.4/ E_R = 60.1–79.5/RSD < 7.0 (100 ng g^{-1})	1.0–1.5 ng g^{-1}	[30]
rhodamine B	water or aqueous solution of soap, matches tips, pencil colored or textile dyes mixture (10)/acetate-acetic acid buffer (pH 5, 0.2 mol L^{-1}) and $NaPF_6$ (0.8 mL, 200 mg L^{-1})	C_6MIm-PF_6 (75 mg)	EtOH (500)	5 min 5000 rpm	-/acetone (80)	-study of coexisting species	FO-LADS[c]	E_F = 65.5/-/ RSD = 1.3 (50)	1.05	[31]
drugs (2)	aqueous extract of human urine (5)/pH 3–4	C_8MIm-PF_6[a] (50 mg)	acetone (300)	10 min 3500 rpm	-/MeOH (50)	-human urine was mixed with MeOH 1:2 (v/v), incubated (-20°C, 10 h), centrifuged, followed by filtration of supernatants	HPLC-DAD	-/E_R = 83.5–89.6/RSD < 1 (-)	1.5–3.3	[32]
phenols (4)	aqueous cosmetics (10)/NaCl (10%, w/v)	C_8MIm-PF_6[a] (960 mg)	acetone[a] (900)	5 min 4000 rpm	-/back-extraction with NaOH (150 μL, 0.1 mol L^{-1}) and centrifugation	-cosmetics were extracted with ACN and 200 μL of ACN-extract were diluted up to 10 mL	CE-UV	E_F = 18.0–60.1/-/ RSD < 12.8 (200)	5–100	[33]

formaldehyde	detergent and water (10)/methyl acetoacetate (0.05 mol L^{-1}) and NaCl (20%, w/v) at pH 6.4	$C_6MIm\text{-}PF_6$[a] (75 μL)	EtOH[a] (1000)	5 min 3000 rpm	-/EtOH (100)	-derivatization using methyl acetoacetate -study of foreign ions	spectrophotometry	E_F = 158.5/-/ RSD = 2.5 (0.8)	0.02	[34]
coumarins (8)	aqueous extract of roots (0.5 mL MeOH-extract diluted up to 5 mL)	$C_6MIm\text{-}PF_6$[a] (50 μL)	EtOH[a](200)	4 min 3000 rpm	20/MeOH (60)	-comparison with conventional DLLME	HPLC-UV	E_F = 130–230/ E_R[d] = 52–92/ RSD[b] < 8.2 (-)	0.013 – 0.66	[35]
emodin and metabolites (7)	rats urine (0.5 mL of urine diluted up to 5 mL, 10 mmol L^{-1} of HCl)/pH 2.4	$C_6MIm\text{-}PF_6$[a] (70 mg)	acetone[a] (300)	10 min 3500 rpm	25/MeOH (50)	-comparison with conventional DLLME	HPLC-UV	E_F = 63– 192/ E_R[d] = 32– 96/ RSD[b] < 6.4 (40 – 100)	0.5–1	[36]
ursolic acid	organic extract of force loquat capsule (1.5)/ 2.5 mL acid solution (pH 2)	$C_8MIm\text{-}PF_6$[a] (100 μL)	-(EtOH was used as solvent of the samples, 1.5 mL were added)	5 min 3000 rpm	~20/-	-ultrasound-assisted extraction of the force loquat capsule with EtOH	HPLC-UV	-/-/RSD < 2.4 (13000)	–	[37]
emerging contaminants (17)	water (10)/NaCl (25%, w/v)	$(NH_2C_6)MPyrr\text{-}FAP$[a,e] (30 μL)	MeOH (500)	5 min 3400 rpm	~13/-	-comparison with *in situ*-ILs DLLME	HPLC-UV	E_F = 0.81–379/ E_R[d] = 0.10 49.3/RSD < 5.8 (-)	0.1–55.1	[38]
polycyclic aromatic hydrocarbons (18)	water (10)/2-propanol (10%, v/v)	$C_8MIm\text{-}PF_6$[a] (50 μL)	acetone[a] (1000)	5 min 4000 rpm	27/MeOH (500)	-droplet is cooled in an ice-bath (2 min) -comparison with LLE[f]	HPLC-FD	E_F = 315.6 – 346/ E_R[d] = 81.3– 93.4/RSD < 5.7 (0.002–0.02)	0.03–2.0 ng L^{-1}	[39]
antimicrobials (2)	water (5)/-	$C_8MIm\text{-}PF_6$[a] (50 μL)	$C_4MIm\text{-}BF_4$[a] (300)	6 min 5000 rpm	-/MeOH (50)	–	HPLC-ESI-MS/MS	-/- /RSD[b] < 4.8 (1000)	0.23–0.35	[40]
pyrethroid pesticides (2)	water (5)/pH 6	$C_8MIm\text{-}PF_6$[a] (50 μL)	$C_4MIm\text{-}BF_4$[a] (300)	6 min 5000 rpm	-/MeOH (90)	–	HPLC-UV	-/- /RSD < 7.78 (10)	0.28–0.83	[41]
hexabromocyclododecane diastereomers (2)	water (5)/pH 7	$C_8MIm\text{-}PF_6$[a] (40 μL)	$C_2MIm\text{-}BF_4$[a] (400)	6 min 5000 rpm	-/MeOH (50)	–	LC-ESI-MS/ MS	-/-/RSD < 6.7 (0.73–7.69)	0.12–0.22	[42]

[a] IL or dispersive solvent selected (others were also tried in the study).
[b] inter-day precision.
[c] fiber optic-linear array detection spectrophotometry.
[d] extraction efficiency was calculated as $E_R = 100 \cdot E_F/E_{Fmax}$; being $E_{Fmax} = V_{sample}/V_{drop.}$
[e] 1-(6-aminohexyl)-1-methylpyrrolidinium tris(pentafluoroethyl)trifluorophosphate.
[f] liquid-liquid extraction.

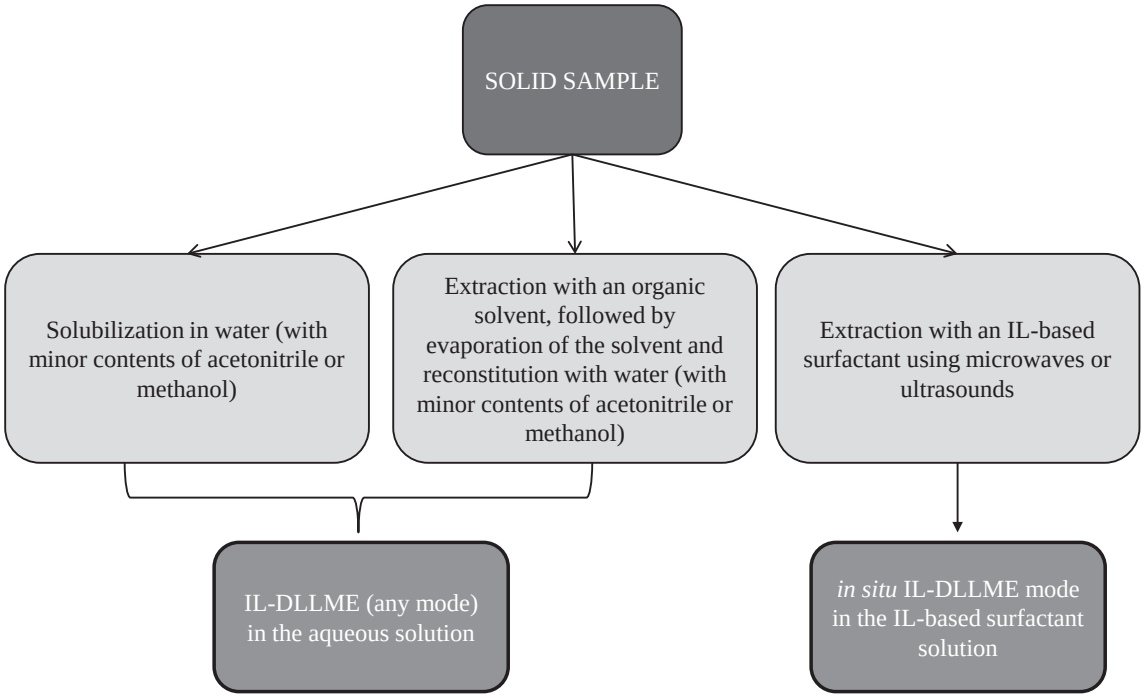

Fig. 2. General procedure when extracting solid samples using an IL-DLLME method.

of different detection systems, including visible-ultraviolet (Vis-UV), diode-array detection (DAD), fluorescence detection (FD), and mass spectrometry (MS). Spectrophotometry and capillary electrophoresis (CE) have been also utilized in these applications.

Cruz-Vera et al. simplified the conventional IL-DLLME method to avoid the centrifugation step by using a one-step in-syringe set-up [25].

Recent modifications of conventional IL-DLLME include those works in which the dispersive solvent is not an organic solvent, but a hydrophilic IL. The first application was developed by Zhao et al. [40] and further applied by the same group in a number of works [41,42]. The most common hydrophilic IL used as dispersive solvent is C_4MIm-BF_4. In these applications, the utilization of organic solvents is solely limited to the further dilution of the microdroplet obtained before HPLC injection, generally being methanol (50–90 μL).

The analytical applications of conventional IL-DLLME have been carried out with not only aqueous samples but also solid samples. When solid samples are utilized in combination with IL-DLLME, it is necessary to have a previous step of sample dissolution, or sample extraction followed by reconstitution of the sample extract with water, as shown in Fig. 2. Thus, conventional IL-DLLME has been used for the determination of organic compounds in aqueous extracts or in aqueous solutions of bananas [26], grapes and plums [27], pancakes [30], soaps and match tips [31], cosmetics [33], and roots [35].

Conventional IL-DLLME has also been used simultaneously with derivatization by Arvand et al. in the determination of formaldehyde in wastewaters and detergents [34]. They used the Hantzsch reaction, which involves cycling between methyl acetoacetate and formaldehyde in the presence of ammonium acetate, followed by the conventional IL-DLLME method within the same extraction tube.

Conventional IL-DLLME has also been utilized for the determination of metals [43–51], mostly for liquid samples, as can be observed in Table 2. We need to consider that these determinations require employment of a chelating agent to trap the metal in the aqueous solution into an organic assembly. Chelating agents used in these applications are the common ones used in the analytical determination of metals, which simplifies the resulting methodology. In any case, only up-to-date organic solvents (and not hydrophilic ILs or surfactants) have been used as dispersive solvents in conventional IL-DLLME for the determination of metals, methanol being the most common dispersive solvent. Most common analytical determinations of conventional IL-DLLME for metals have been carried out in combination with electrothermal absorption spectrometry (ETAAS), flame atomic absorption spectrometry (FAAS), atomic absorption spectrometry with graphite furnace (GFAAS), and inductively-coupled plasma (ICP).

2.2. Temperature-assisted IL-DLLME

The temperature-assisted IL-DLLME mode requires heating of the aqueous solution containing analytes and the hydrophobic IL used as extractant solvent to ensure adequate formation of microdroplets. The solubility of ILs evidently increases with temperature, so the heating favors dispersion of the IL into the aqueous solution. The method further requires cooling of the solution to facilitate settling of the IL microdroplet containing extracted analytes. In some cases, the method can require the utilization of dispersive organic solvents, such as methanol, ethanol, acetonitrile or acetone. Its operating procedure is shown in Fig. 1(B). In this mode, the turbidity of the solution appears in the cooling step as long as a dispersive solvent has not been used in the method. When dispersive solvents are used, turbidity appears from the beginning.

It is not easy to sample the frozen droplet to measure its volume after the cooling step, so droplet volumes are rarely reported in temperature-controlled IL-DLLME applications, unless a dispersive solvent has been used to assist the method.

The first report of the technique was by Zhou et al. [17] regarding determination of organic compounds, and Baghdadi and Shemirani [18] regarding determination of metals. The main difference between their procedures described, apart from the obvious need to use chelating agents when extracting metals, was that Baghdadi

Table 2
Determination of metals using conventional IL-DLLME.

Metal	Sample (mL)/sample requirements	IL extractant (amount)	Dispersive solvent (μL)	Chelating agent (amount)	Centrifuge conditions	V_{drop} in μL/ further diluent (μL)	Comments	Analytical technique	E_F/E_R (%)/RDS in % (spiked level in $\mu g \cdot L^{-1}$)	LOD ($\mu g\ L^{-1}$)	Ref.
Ta (I), Ta (III) species	water (5)/HCl (0.5 mol· L^{-1})	C_6MIm-PF_6 (60 mg)	EtOH (500)	CYPHOS® IL 101[a] as ion-pairing reagent (40 μL, $3.8 \cdot 10^{-3}$ mol L^{-1} in toluene)	15 min 1200 rpm	-/MeOH (50)	-study of interfering species -validation with CRM[b]	ETAAS	E_F = 50–125 / E_R = 77 /RSD < 5.3 (0.4)	3.3 ng L^{-1}	[43]
Hg^{2+}, $MeHg^+$, $EtHg^+$	aqueous solution of liquid cosmetic 1:10 (5)/-	C_6MIm-PF_6[c] (52 mg)	MeOH (500)	APDC[d] (30 μL, 2 $g \cdot L^{-1}$)	10 min 4000 rpm	~8/MeOH (60)	-study of coexisting ions	HPLC-ICP-MS	E_F = 115–760/-/ RSD < 7.4 (0.5)	1.3–7.2 ng L^{-1}	[44]
As (III) species	wines (4)/acetate-acetic acid buffer (50 μL, 2 mol L^{-1}) and $NaClO_4$ (250 μL, 24% w/v, pH 4)	C_8MIm-PF_6 (40 mg)	MeOH (100)	DDTC[e] (300 μL, $1 \cdot 10^{-2}$ mol L^{-1})	–	-/MeOH (100) with 10% HNO_3 (v/v)	-Triton X-114 (40 μL, 5% w/v) as anti-sticking agent -study of coexisting ions -flow injection system to retain the droplet	ETAAS	E_F = 46/E_R = 100/ RSD < 5.7 (0.2)	5 ng L^{-1}	[45]
Cr (VI), Co (II), Cu (II), Ni (II)	water (10)/formic acid buffer (500 μL, 1 mol L^{-1})	C_6MIm-FAP[f,c] (80 μL)	MeOH (500)	APDC[d] (500 μL, 4% w/v)	3 min 5000 rpm	-/ACN (100)	-study of coexisting ions -validation with two CRMs[b]	UPLC-UV	E_F = 68–75/ E_R = 80–95/ RSD < 3.3 (-)	0.3–2	[46]
Zn (II) species	water and aqueous solution of deproteinized milk (30)/ borate buffer (0.03 mol L^{-1}, pH 9.5)	C_6Py-PF_6 (300 mg)	ACN (-)	oxine ($5.5 \cdot 10^{-5}$–7.8 10^{-5} mol L^{-1})	6 min 4000 rpm	-/ACN (500)	-validation with CRM[b] - study of coexisting ions -cooling of the droplet in an ice bath	FAAS	E_F = 71/E_R > 97.0/ RSD = 1.92 (13)	0.22	[47]
Dy (III), Sm (III), Eu (III), Gd (III)	aqueous extract of uranium dioxide powder (80)/ ammonium buffer (1% w/w, pH 9.5)	C_6MIm-PF_6 (600 μL)	MeOH (8 mL)	HYD[g] (1 mL, 10^{-3} mol·L^{-1})	6 min 3500 rpm	500/HNO_3 1 mol L^{-1} (500)	-SDS[h] (0.02%, w/v) as anti-sticking agent -heat to 160 °C to eliminate HYD[g] excess	ICP-OES[i]	E_F = 19.34–86.04/ E_R[j] = 12.1–53.8/ RSD < 1.5 (20–200)	0.34–1.29	[48]
Cu (II)	water (10)/acetate-acetic acid buffer	C_6MIm-NTf_2 (65 mg)	acetone (550)	TMK[k] ($2 \cdot 10^{-4}$ mol L^{-1})	5 min 5000 rpm	20/EtOH (40)	-study of coexisting ions	FAAS	E_F = 136.6/ E_R[j] = 82/RSD = 3.3 (10)	0.45	[49]
Co (II)	water, urine and saliva (6)/pH 2, HCl (1 mol L^{-1}), $NaNO_3$ 1.5%, w/v	C_6MIm-PF_6 (60 mg)	MeOH (500)	1N2N[l] (200 μL, $4 \cdot 10^{-3}$ mol L^{-1})	15 min 1500 rpm	-/MeOH (50)	-complexation needs heating (50 °C, 15 min), pH 4, and further cooling (10 min) -Triton X-114 ($3.9 \cdot 10^{-5}$ mol L^{-1}) as anti-sticking agent -urine samples were digested by UV-photolysis -study of coexisting ions -validation with CRM[b]	ETAAS	E_F = 120/ E_R = 99.9/ RSD = 3.4 (1)	3.8 ng L^{-1}	[50]
Se (IV)	water and aqueous garlic extract (4)/HCl (0.5 mol L^{-1}) and $NaClO_4$ (1.5 %, w/v)	CYPHOS® IL 101[a] (50 mg)	MeOH (100)	APDC[d] ($7.9 \cdot 10^{-5}$ mol·L^{-1})	–	-/MeOH with 10 %, v/v HNO_3 (200)	-ultrasound-assisted extraction of garlic with H_2SO_4, filtration, washing with water, HCl addition and heating -on-line ILs DLLME in a column -Triton X-114 (0.05 %, w/v) as anti-sticking agent -study of coexisting ions	ETAAS	E_F = 20/-/ RSD = 5.1 (0.5)	15 ng·L^{-1}	[51]

[a] tetradecyl(trihexyl)phosphonium chloride.
[b] certificate reference material.
[c] IL selected (others were also tried in the study).
[d] ammonium pyrrolidinedithiocarbamate.
[e] sodium diethyldithiocarbamate.
[f] 1-hexyl-3-methylimidazolium tris (pentafluoroethyl) trifluorophosphate.
[g] 1-hydroxy-2, 5-pyrrolidinedione.
[h] sodium dodecyl sulfate.
[i] optical spectrometry.
[j] extraction efficiency calculated as $E_R = 100 \cdot E_F/E_{Fmax}$; being $E_{Fmax} = V_{sample}/V_{drop}$.
[k] 4,4′-bis(dimethylamino)thiobenzophenone.
[l] 1-nitroso-2-naphtol.

and Shemirani could work at lower heating temperatures. These authors also employed a mixture of two hydrophobic ILs containing the same cation but different anions (C_6MIm-PF_6 and C_6MIm-NTf_2) to avoid solubilization of the main extracting IL, C_6MIm-PF_6, in aqueous salty matrices.

Table 3 includes significant applications of the temperature-controlled IL-DLLME method for determining organics [17,52–64], and Table 4 summarizes the applications for determining metals [18,65–68].

Extraction temperatures normally required in temperature-assisted IL-DLLME were in the range 50–90°C. Evidently, temperatures higher than 90°C cannot be used due to water evaporation. The limiting step in this extraction mode is the cooling step, so the extraction time is normally assumed as the cooling time. However, use of the temperature-assisted IL-DLLME method for determination of metals normally requires a heating time to ensure the formation of an adequate complex between the metal and the chelating agent. In this case, the extraction time includes not only cooling time but also heating time. It must be noted that extraction times are much shorter when water-miscible organic solvents are used as dispersive solvents in the temperature-assisted IL-DLLME method. In any case, extraction times greater than 30 min are rarely reported.

No works have been reported on the development of derivatization reactions in combination with the temperature-assisted IL-DLLME method.

The temperature-assisted microextraction mode has mainly been carried out with Im-based ILs containing the hexafluorophosphate anion, as can be clearly observed in Tables 3 and 4.

The temperature-assisted IL-DLLME mode has also been applied for the determination of analytes in solid samples, using previous sample-extraction or solubilization steps (Fig. 2). Thus, solid samples analyzed include roots [52], powdered pharmacy tablets [56], flours, potatoes and apples [67], and hair [68].

2.3. Ultrasound-assisted, microwave-assisted, or vortex-assisted IL-DLLME

This IL-DLLME mode requires application of ultrasound, microwaves, vortex, or any additional strong mixing requirement to facilitate dispersion of the hydrophobic IL into the aqueous solution and so to ensure the adequate formation of microdroplets. The application of vortex, microwaves or ultrasounds is evidently accompanied by an increase of the temperature in the extraction tube. In some cases, a dispersive solvent is needed to improve the kinetics, and it can be an organic solvent, a surfactant, or a hydrophilic IL. In any case, extraction times are less than 7 min, or a bit longer if a cooling step is included. Thus, short extraction times are still kept in this mode. Fig. 1(C) summarizes this IL-DLLME mode, while the main applications are included in Table 5 [69–94].

Of the different modes, ultrasound-assisted IL-DLLME has been the most utilized for determination of both organic compounds [69–81] and metals [91,92]. Historically, it was also the first proposed alternative to conventional IL-DLLME and to temperature-assisted IL-DLLME. The utilization of ultrasound in combination with IL-DLLME was first described, almost simultaneously, by Zhou et al. [69] for the determination of aromatic amines in water, and by Li et al. [91] for the determination of cadmium in water.

The utilization of vortex-assisted IL-DLLME has also been quite prolific [85–89,93,94]. The appearance of this IL-DLLME mode in the literature is more recent, being described, almost simultaneously, by Asensio-Ramos et al. [85] for the determination of pesticides in soils, and Ye et al. [86] for the determination of UV filters in waters.

With regards to microwaves, Xu et al. were the first to report employment of this extraction technique in combination with IL-DLLME [83]. They were able simultaneously to derivatize and to extract formaldehyde from beverages using microwave-assisted IL-DLLME. This extraction mode involving microwaves has been used in a smaller number of works [82–84] than ultrasound or vortex.

Ku et al. have reported the use of an up-and down-shaker as a stirring device in the determination of UV filters from waters using IL-DLLME [90], as a simpler alternative to microwaves, ultrasound, or even vortex.

Fan et al. [95] proposed to carry out the conventional IL-DLLME method using a syringe in which the aqueous solution containing analytes was mixed three times with the hydrophobic IL acting as extractant solvent.

Quite recently, surfactants were proposed as adequate dispersive solvents in IL-DLLME, first in a microwave-assisted mode [84], and soon after in a vortex-assisted mode [89]. Although surfactants have not been used as dispersive solvents in other IL-DLLME modes, we expect that they can perform well and that more works will probably appear soon in the literature.

With regards to the use of hydrophilic ILs as dispersive solvents, Gao et al. have reported an application with C_4MIm-BF_4 in an ultrasound-assisted IL-DLLME mode for the determination of sulfonamides in infant-formula milk powder [81]. They named their method as ultrasound-assisted IL/IL-DLLME, given that two ILs were needed in the method: one hydrophobic acting as the extractant; and, one hydrophilic acting as the dispersive solvent. As mentioned above for surfactants, we expect these hydrophilic ILs to be used as dispersive solvents in other IL-DLLME modes, such as temperature-assisted IL-DLLME. So far, no works have been carried out comparing the utility of these agents as dispersive solvents in the current modes of IL-DLLME.

One of the main advantages of using microwaves or ultrasound in combination with IL-DLLME is the intrinsic possibility of carrying out reactions within the extraction tube. This is mainly due to the ease of developing organic reactions with the help of microwaves or ultrasound. Thus, several simultaneous derivatization reactions have been described. Xu et al. used microwaves simultaneously to derivatize and to extract formaldehyde by IL-DLLME [83], with HPLC-UV determination. In a further work, the same group used microwaves to derivatize sulfonamides with fluorescamine, followed by IL-DLLME in the same extraction tube [82] and HPLC-FD determination. More recently, these authors proposed the derivatization of aminoglycosides present in milk samples using microwave-assisted IL-DLLME [84], in this case using a surfactant (Triton X-100) as dispersive solvent and HPLC-FD determination.

The magnetic retrieval of the IL microdroplet obtained after IL-DLLME was proposed by Zhang et al. [78] for the determination of insecticides in water. They added Fe_3O_4 magnetic nanoparticles after IL-DLLME to facilitate the removal of the IL microdroplet from the aqueous sample using a magnet. After this magnetic isolation of the droplet, insecticides were removed by adding acetonitrile and further injected for HPLC with UV detection.

Ge and Lee quite recently proposed combination of ultrasound-assisted IL-DLLME with a micro solid-phase extraction (μ-SPE) device, containing a novel material zeolite imidazolate framework, to determine antidepressants in water using HPLC-UV [80]. The transfer of analytes from the emulsion to the μ-SPE device is assisted by vortex. The extraction time for ultrasound is only 1 min, and the vortex time to transfer the analytes to the μ-SPE device is also 1 min. Finally, desorption of analytes from the device is assisted by ultrasound and it takes only 5 min. Thus, analytes are not only extracted and preconcentrated but also subjected to a clean-up procedure, while keeping the extraction time short and minimizing solvent requirements.

Table 3
Determination of organic compounds by temperature-assisted IL-DLLME.

Analytes (number)	Sample (mL)/sample requirements	IL extractant (amount)	Dispersive solvent (μL)	Heating temp. in °C/ cooling step in min	Centrifuge conditions	V_{drop} in μL/ further diluent (μL)	Comments	Analytical technique	E_F/E_R (%)/RSD in % (spiked level in $\mu g \cdot L^{-1}$)	LOD ($\mu g \cdot L^{-1}$)	Ref.
organo-phosphorus pesticides (2)	water (10)/-	C_6MIm-PF_6 (50 μL)	–	80/30	20 min 4000 rpm	-/MeOH (200)	-comparison with conventional DLLME	HPLC-UV	E_F = 50 /-/RSD < 2.7 (5)	0.17–0.29	[17]
anthraquinones (5)	aqueous solution of MeoH extract of root (5 mL)/H_3PO_4, pH 2.0	C_6MIm-PF_6[a] (55 μL)	MeOH[b] (400)	60/5	10 min 3000 rpm	20/-	-powered root extracted with MeOH, evaporated to dryness, hydrolyzed with HCl 8 mol · L^{-1}, evaporated to near-dryness, and reconstituted with MeOH -comparison with conventional extraction method	HPLC-DAD	E_F = 174–213/ E_R[c] = 63.2– 78.9/ RSD[d] < 7.7 (-)	0.50–2.02	[52]
fungicides (5)	water (10)/-	C_8MIm-PF_6 (55 μL)	MeOH[e]	90/30	10 min 4000 rpm	-/MeOH 75%, v/v (200)	-	HPLC-UV	-/-/RSD[d] < 11 (-)	0.32–0.79	[53]
phthalate esters and pyrethroid insecticides (4)	water (10)/pH 6	C_8MIm-PF_6 (40 μL)	-	90/-	10 min -	-/MeOH 80%, v/v (200)	-	HPLC-UV	-/-/RSD < 5.6 (10)	0.23–0.47	[54]
pyrethroid insecticides (3)	water (10)/pH 5	C_8MIm-PF_6[a] (40 μL)	ACN[e]	80/30	15 min -	-/ACN 70%, v/ v (200)	-	HPLC	E_F = 50/-/RSD < 3.4 (20)	0.34–0.48	[55]
ofloxacin antibiotic (1)	aqueous extract of powered tablet, aqueous solution of deproteinized human plasma and human urine (10)/pH 4.5, $NaPF_6$ (175 mg)	C_6MIm-PF_6 (45 mg)	EtOH[b,f](500)	40/4	7 min 4000 rpm	-/EtOH (200)	-influence of coexisting substances -comparison with a reference method	spectro-fluorimetry	E_F = 50/-/RSD = 2.7 (50)	0.029	[56]
phenols (4)	water (10)/HCl (60 μL, 1 mol L^{-1}), NaCl 15%, w/v	C_8MIm-PF_6 (50 μL)	EtOH[b] (700)	60/20	20 min 4000 rpm	-/MeOH (200)	-	HPLC-DAD	E_F = 334 –371/-/ RSD[d] < 7.2 (-)	0.27–0.68	[57]
dichloro-diphenyl-trichloroethane (DDT) and its main metabolites (4)	water (10)/pH 6	C_6MIm-PF_6 (50 μL)	-	75/35	15 min 4000 rpm	-/MeOH (200)	-	HPLC-UV	E_F = 50/-/RSD < 6.7 (5)	0.24–0.45	[58]
pesticides (3)	water (10)/pH 7, NaCl 15%, w/v	C_6MIm-PF_6 (65 μL)	ACN 5%[g] (v/ v)	80/30	20 min -	-/ACN 45%, v/ v (200)	-	HPLC-UV	-/-/RSD < 4.7 (-)	0.04–0.43	[59]
phenolic compounds (2)	water (5)/-	C_8MIm-PF_6 (35 μL)	acetone[b] (1000)	60/3	10 min 4000 rpm	~20/MeOH (200)	-comparison with conventional IL-DLLME	HPLC-VWD	E_F = 112–168/ E_R[c] = 44.8–67.2/ RSD < 4.1 (20)	0.58–0.86	[60]
phthalate esters (3)	water (5)/-	C_8MIm-PF_6[a] (32 μL)	ACN[b] (750)	50/3	10 min 4000 rpm	-/MeOH (200)	-comparison with conventional IL-DLLME	HPLC-VWD	E_F = 174–212/ E_R[c] = 69.6–84.8/ RSD < 3.7 (20)	0.68–1.36	[61]
carbamate pesticides (3)	water (10)/pH 6, NaCl 15%, w/v	C_8MIm-PF_6 (40 μL)	-	70/20	15 min 3000 rpm	-/MeOH (200)	-	HPLC-VWD	-/-/RSD < 1.8 (-)	0.45–1.40	[62]
endocrine disruptors (3)	water (10)/pH 7	C_8MIm-PF_6 (65 μL)	-	80/20	10 min 4000 rpm	-/MeOH (200)	-comparison with SPE[h]	HPLC-FD	-/-/RSD[d] < 13.13 (-)	0.23–0.48	[63]
hexabromo-cyclododecane diastereomers (3)	water (10)/pH 6	C_8MIm-PF_6 (70 μL)	-	75/30	15 min 3000 rpm	-/MeOH (200)	-	HPLC-ESI-MS/MS	-/-/RSD < 8.43 (-)	0.1	[64]

[a] IL selected (others were also tried in the study).
[b] Dispersive solvent selected (others were also tried in the study).
[c] Extraction efficiency calculated as $E_R = 100 \cdot E_F/E_{Fmax}$; being $E_{Fmax} = V_{sample}/V_{drop}$.
[d] Inter-day precision.
[e] Organic solvent used to dissolve the analytes.
[f] Organic solvent used to dissolve the IL.
[g] Initially used to avoid sorption of analytes on the vial walls.
[h] Solid-phase extraction.

Table 4
Determination of metals using temperature-assisted IL-DLLME.

Metal	Sample (mL)/sample requirements	IL extractant (amount)	Dispersive solvent (μL)	Chelating agent (amount)	Heating temp in °C (time in min)/cooling step in min	Centrifuge conditions	V_{drop} in μL/ further diluent (μL)	Comments	Analytical Technique	E_F/E_R (%)/ RDS in % (spiked level in $\mu g \cdot L^{-1}$)	LOD ($\mu g \cdot L^{-1}$)	Ref.
Hg (II)	water (10)/acetate-acetic acid buffer, pH 4, $NaNO_3$ 0.2%, w/v	$C_6MIm\text{-}PF_6$[a] (64 mg) + $C_6MIm\text{-}NTf_2$[a] (5 mg), both dissolved in acetone	acetone (350 μL)	TMK[b] ($2.4 \cdot 10^{-6}$ mol $\cdot L^{-1}$ in 1-propanol)	35 (4)/10	5 min 5000 rpm	~8/EtOH 85%, v/v (350)	-Triton X-114 (0.033%, w/v) as anti-sticking agent -study of coexisting ions	spectro-photometry	E_F = 30.8/-/ RSD = 1.32 (30)	0.3	[18]
Pb (II)	water (10)/pH 8	$C_6MIm\text{-}PF_6$ (50 μL)	-	dithizone (50 μL, 200 $\mu g\ L^{-1}$ in EtOH)	80 (-)/15	15 min 4000 rpm	-/MeOH (150) and HNO_3 1.5 mol L^{-1} (up to 800)	-study of coexisting ions -validation with CRM[c]	FAAS	-/-/ RSD = 4.4 (50)	9.5	[65]
V (IV) and V (V) species	water (2)/pH 4.75, acetic-acetate buffer	$C_4MIm\text{-}PF_6$ (45 μL)	EtOH (100)	5-Br-PADAP[d] (200 μL, 10^{-3} mol $\cdot L^{-1}$ in EtOH)	60 (4)/10	15 min 1500 rpm	-/MeOH (50)	-vortex to improve IL dispersion -study of coexisting ions	ETAAS	E_F = 40/ E_R = 75/ RSD = 4.3 (0.5)	4.9 ng L^{-1}	[66]
Zn (II)	water and aqueous solid food extract (30)/pH 9, ammonium-ammonia buffer, 225 mg $NaPF_6$	$C_6MIm\text{-}PF_6$[a] (95 mg)	EtOH[e] (650)	8-QOH[f] ($8.5 \cdot 10^{-5}$ mol $\cdot L^{-1}$)	50 (5)/4	7 min 4000 rpm	-/EtOH (500)	-study of coexisting ions -dried food (flours, potatoes and apples) oxidized with HNO_3 and H_2O_2, dried again, treated with HCl and $HClO_4$, and diluted with water -validation with CRM[c]	FAAS	E_F = 60/-/ RSD = 3 (10)	0.18	[67]
Ag nano-particles	water and aqueous extract of hair (6)/pH 5.0	$C_6MIm\text{-}PF_6$[a] (50)	-	disulfiram (50 μL, $3 \cdot 10^{-5}$ mol L^{-1} in EtOH)	77 (10)/20	20 min -	~43/-	-Triton X-114 (10%, w/v) as anti-sticking agent -study of coexisting ions -dried hair is treated with HNO_3 and H_2O_2, dried again, and diluted with water	GFAAS	E_F = 120/-/ RSD = 4.5 (0.02)	5.2 ng $\cdot L^{-1}$	[68]

[a] IL selected (others were also tried in the study).
[b] 4,4′-bis(dimethylamino)thiobenzophenone.
[c] Certified reference material.
[d] (5-bromo-2-pyridylazo)-5-diethylaminophenol.
[e] Organic solvent used to dissolve the IL added.
[f] 8-Hydroxyquinoline.

Table 5
Determination of organics and metals by ultrasound-assisted, microwave-assisted, vortex-assisted (or any stirring method) IL-DLLME.

Analytes (number)	Sample (mL)/sample requirements	IL extractant (amount)	Dispersive solvent (μL)	US-MW-vortex-stirring (conditions)/ further cooling (time)	Centrifuge conditions	V_{drop} in μL/ further diluent (μL)	Comments	Analytical Technique	E_F/E_R (%)/RSD in % (spiked level in μg L^{-1})	LOD (μg L^{-1})	Ref.
aromatic amines (4)	water (10)/pH 13	C_6MIm-PF_6 (60 μL)	ACN[a](7 %, v/v)	US (5 min)/ice bath (30 min)	15 min 4000 rpm	−/HPLC mobile phase (200)	-	HPLC-UV	-/-/RSD < 6.1 (10)	0.17–0.49	[69]
drugs (2)	water (50)/NaCl (5 %, w/v), pH 6	C_6MIm-PF_6(500 μL)	-	US (250 W, 6.7 min 40°C)/ice bath (20 min)	10 min 4000 rpm 4°C	-/MeOH (up to 500)	-	HPLC-UV	-/-/RSD <4.52 (5)	0.17–0.29	[70]
celastrol	aqueous solution of human urine (5)/HCl, pH 2	C_6MIm-PF_6[a] (45 μL)	MeOH[a] (100)	US (200 W, 1 min)/ice bath (10 min)	10 min 3000 rpm	-/MeOH (50)	-human urine diluted with aqueous solution of HCl (pH 2)	HPLC-DAD	E_F = 110/-/RSD = 2.78 (-)	1.6	[71]
pyrethroid pesticides (4)	aqueous solution of honey (10)/NaCl (0.2 g)	C_8MIm-PF_6[a](60 μL)	MeOH[a](200)	US (2 min)/-	10 min 3500 rpm	~20/ACN (20)	-honey was mixed with water (10 g in 100 mL) and filtered -comparison with conventional IL-DLLME and temperature-controlled IL -DLLME	HPLC-DAD	E_F = 506–515/ E_R[b] = 101–103/ RSD < 5.7 (-)	0.21–0.38	[72]
fungicides (7)	red wine (5)/pH 4	C_6MIm-PF_6[a] (50 μL)	-	US (5 min)/ice bath (5 min)	15 min 4000 rpm	~20/MeOH (200)	-	HPLC-DAD	-/E_R = 34.0–90.4/ RSD < 9.9 (50)	2.8–16.8	[73]
aromatic amines(3)	water (10)/NaOH, pH 12	C_4MIm-PF_6[a](100 μl)	MeOH[a](750)	US (200 W, 25 min) /-	15 min 3000 rpm	~50/-	-comparison with conventional DLLME	HPLC-UV	E_F = 54.7–128/ E_R = 40.3–61.3/ RSD < 4.73 (5)	15–26 ng L^{-1}	[74]
total content of alkylbenzene sulfonates	water (10)/NaCl (17.2 %, w/v) and phosphate buffer, pH 8.3	C_6MIm-PF_6[a](72 μL)	-	US (0.5 min, 25°C)/-	5 min 3500 rpm	20/washing with 200 μL of H_2SO_4 (0.12 mol L^{-1}) and NaH_2PO_4 (0.36 mol L^{-1}) and centrifugation. Then, EtOH (200)	-methylene blue (49.2 mg L^{-1}) as an ion pair reagent -optimization using an experimental design -study of coexisting ions	spectrophotometry	E_F = 79.1/ E_R[b] = 15.8/RSD = 2 (40)	0.37	[75]
UV filters (4)	water (10)/pH 4	C_6MIm-FAP[a,c] (20 μL)	MeOH[a](100)	US (320 W, 3 min)/-	5 min 4000 rpm	~17/-	-	HPLC-UV	E_F = 354–464/ E_R[b] = 60.2–78.9/ RSD < 6.3 (50)	0.2–5.0	[76]
phenylurea herbicides (4)	water (5)/pH 7	C_6MIm-PF_6[a] (60 μL)	-	US (5 min)/ice bath (5 min)	5 min 4000 rpm	25/MeOH (200)	-	HPLC-UV	-/E_R = 68–100/ RSD < 9.5 (5–50)	0.10–0.24	[77]
insecticides (5)	water (10)/F_3O_4 (20 mg, 20 nm)	C_6MIm-PF_6[a] (70 μL)	ACN[a](300)	US (1 min)/-	-	-/ ACN (50)	-magnetic retrieval of the drops with Fe_3O_4 MNPs	HPLC-UV	E_F = 261–302 E_R = 80.4–90.5 RSD < 4.84 (-)	0.05–0.15	[78]
phenol	water (10)/NH_3, pH 10	C_6MIm-PF_6 (74 mg)	-	US (1 min, 23°C)/ ice bath (2 min)	2 min 4000 rpm	-/acetone (40)	-4-AAP[d] (70 μL, 2 % w/v) as colorimetric reagent -potassium hexacyanoferrate (70 μL, 8% w/v) as oxidant -study of coexisting ions	FO-LADS[e]	E_F = 75/-/ RSD < 2.65 (50)	0.86	[79]
tricyclic antidepressants (5)	water (5)/NaOH (0.1 mol L^{-1}) and NaCl (50 mg mL^{-1})	C_6MIm-FAP[c] (20 μL)	MeOH[a](200)	US (1 min) and subjected to μ-SPE device/-	-	- / clean-up step in a μ-SPE device, vortex (1 min) and US (5 min) with MeOH (70 μL)	-comparison with conventional μ-SPE (without DLLME step)	HPLC-UV	E_F = 17–43/– / RSD < 7.8 (4)	0.3–1.0	[80]
sulfonamides (6)	infant formula milk (4) / H_3PO_4 (20 μL, pH 2) and shaking (5 min)	C_6MIm-PF_6[a] (70 μL)	C_4MIm-BF_4[a] (100)	US (10 min, 30°C) before NH_4PF_6 addition, followed by US (2 min)/-	10 min 15000 rpm 5°C	-/ACN with 0.1 % formic acid (200) and filtration	-infant formula milk powder was mixed with hot water at 50°C (solid:liquid 1:8) -NH_4PF_6 (0.08 g) as ion-pair	HPLC-UV	- /- /RSD[f] < 5.6 (100 mg kg^{-1})	2.94–16.7 μg kg^{-1}	[81]

(*continued on next page*)

Table 5 (*continued*)

Analytes (number)	Sample (mL)/sample requirements	IL extractant (amount)	Dispersive solvent (μL)	US-MW-vortex-stirring (conditions)/ further cooling (time)	Centrifuge conditions	V_{drop} in μL/ further diluent (μL)	Comments	Analytical Technique	E_F/E_R (%)/RSD in % (spiked level in μg L^{-1})	LOD (μg L^{-1})	Ref.
sulfonamides(6)	water, aqueous solution of honey, and aqueous extract of milk or pig plasma (10)/acetate buffer pH 3.5, NaCl (0.3 g) and fluorescamine solution (200 μL, 0.2% w/ v in acetone)	$C_6MIm\text{-}PF_6$[a] (100 μL)	MeOH[a] (750)	MW (240 W, 1.5 min) /-	10 min 15000 rpm 0°C	-/ACN (100)	reagent -milk was treated with trichloroacetic acid, centrifuged and the supernatant was collected -pig plasma was extracted with MeOH (1:2), centrifuged, the supernatant was evaporated to dryness, and the residue was diluted with water -simultaneous derivatization	HPLC-FD	E_F = 24–44/-/ RSD < 7.3 (-)	11–33 ng L^{-1}	[82]
formaldehyde	aqueous solution of beverages (5)/formic acid pH 3	$C_6MIm\text{-}PF_6$[a] (70 μL)	ACN[a] (400)	MW (120 W, 1.5 min) /-	10 min 4000 rpm	-/ACN (100)	-beverages (draft beer, cola, apple, orange and peach juices): water 1:1 -derivatization using DNPH[g] (40 μL, 200 μg mL^{-1} in ACN)	HPLC-UV	-/-/RSD[f] < 8.1 (2 – 20)	0.12	[83]
aminoglycosides (3)	aqueous extract of milk (5)/H_3BO_3–$Na_2B_4O_7$ buffer (500 μL, pH 8)	$C_6MIm\text{-}PF_6$[a] (60 μL)	Triton X-100[a] (100 μL, 10 mmol L^{-1})	MW (180 W, 1 min)/-	10 min 4000 rpm	-/ACN (100)	-milk was centrifuged (10 min, 15000 rpm) and the supernatant was diluted with NaOH (5 mL, pH 8) -derivatization using FMOC-Cl[h] (50 μL, 2.5 mmol L^{-1})	HPLC-FD	E_F = 22–34/-/RSD[f] < 7.8 (0.4–20)	0.11–0.50	[84]
pesticides (5) and metabolites (4)	aqueous extract of soils (10)/pH 5.2 and NaCl (30%, w/v)	$C_6MIm\text{-}PF_6$ (117.5 mg)	MeOH (418)	vortex (1 min) and waiting 8 min for the extraction to take place/-	10 min 4400 rpm	80/59:41 (v/v) ACN: 10 mmol L^{-1} phosphate buffer at pH 8.70 (1120)	-soil was extracted with 20 mL MeOH and 2.5 %, w/v NaCl, US (100 W, 10 min) followed by centrifugation (5 min, 4400 rpm) and filtration. Solvent was evaporated to dryness and the residue was dissolved in water and filtered -optimization with an experimental design	HPLC-FD	-/-/RSD[i] < 20 (0.18–880 mg g^{-1})	0.02–90.2 ng g^{-1}	[85]
UV filters (4)	water (1.5)/NaCl (60 mg mL^{-1}), pH 2.63	$C_4MIm\text{-}PF_6$[a] (30 μL)	MeOH (15)	vortex (4 min)/-	10 min 8000 rpm	-/MeOH (8)	-optimization with an experimental design	HPLC-UV	E_F = 18.9–26.8/-/ RSD < 8.0 (-)	1.9–6.4	[86]
organophosphorus pesticides (6)	aqueous solution of fruit juices (5 g of juice in 5 mL of water) / pH 6 – 7	$C_8MIm\text{-}PF_6$[a] (62.3 mg)	MeOH[a] (1000)	vortex (1 min, 2000 rpm)/-	5 min 4000 rpm	~32.5/-	-apple and pear were cut, homogenized and centrifuged to obtain juices	HPLC-UV	-/-/RSD < 5.7 (-)	0.061–0.73 μg kg^{-1}	[87]
fluoroquinolones (8)	ground waters (10)/NH_3 solution (1.0 %, pH 9)	$C_8MIm\text{-}PF_6$[a] (65 mg)	MeOH[a] (400)	vortex (1 min) and US (5 min)/ice bath (3 min)	10 min 4000 rpm	~41/20:80, (v/v) MeOH: H_3PO_4 50 mmol L^{-1} (459)	-	HPLC-FD	E_F = 122–205/ E_R[b] = 50.0–84.1/ RSD < 9.3 (0.009–0.045)	0.8–13 ng L^{-1}	[88]
glucocorticoids (3)	water (5)/Na_2HPO_4 (1%, w/v)	$C_4MIm\text{-}PF_6$ (200 μL)	Triton X-100 (500 μL, 0.05%, v/v)	vortex (3 min)/ice bath (5 min)	-	-/ACN (500)	-	HPLC-UV	E_F = 99.80–99.85/-/RSD < 1.81 (1)	4.11–9.19	[89]
UV filters(3)	water (5)/pH 7	$C_8MIm\text{-}PF_6$[a] (40 μL)	MeOH[a] (200)	shaking (3 min, 360 rpm) with an up-and-down shaker/-	3 min 5000 rpm	-/MeOH (20)	-	UHPLC-DAD[l]	E_F = 146–260/- / RSD[f] < 2.9 (50)	0.23–1.30	[90]
Cd (II)	water (10) / ammonia-acetic acid (both at 0.10 mol·L^{-1}), pH 5.6, NaCl (6 %, w/v)	$C_6MIm\text{-}PF_6$[a] (73 μL)	-	US (1 min)/ice bath (2 min)	5 min 6000 rpm	15/HNO_3 50%, v/ v (30) and EtOH 95% (105)	-DDTC[j] as a complexing agent (0.05%, w/v) -study of coexisting ions -validation with CRM[k]	ETAAS	E_F = 63/E_R[d] = 94.0/ RSD = 3.3 (0.050)	7.4 ng L^{-1}	[91]

Rh (III)	water and aqueous extract of leaves of roses (10) / pH 3.7, $NaNO_3$ (0.6 %, w/v)	C_8MIm-NTf_2 (30 mg)	-	US (2 min) /-	4 min 2500 rpm	-/EtOH 96% (300)	-leaves of roses were burned and kept in a furnace (3 h, 600 °C). The residue was cooled, treated with HCl and evaporated, to be finally diluted in water -complexation using 5Br-PADAP[k] ($1.7{\cdot}10^{-5}$ mol L^{-1}), and heating (95°C, 40 min) -Triton X-100 (0.03%, w/v) as anti-sticking agent -study of coexisting ions	FAAS	E_F = 29.3/- RSD = 1.63 (200)	0.37	[92]
As (III) and As (IV)	urine and blood (15) / pH 4	C_6MIm-PF_6 (200 mg)	-	vortex (2 min) /-	3 min 3500 rpm	- / HCl (500 μL, 2 mol L^{-1}), shaking (1 min) and water (1 mL)	-APCD[m] ($1.2{\cdot}10^{-7}$ mol L^{-1}) as chelating agent -study of coexisting ions -validation with CRM[k]	FI-HG-AAS[n]	E_F = 10/- / RSD < 5 (-)	urine: 0.02–10 blood: 5 ng L^{-1}	[93]
Co (II)	water and pharmaceutical formulations (2) / acetate-acetic acid buffer (pH 4.8), $NaClO_4$ (2.4 %, w/v)	CYPHOS® IL 101[o] (35 mg)	acetone (100)	vortex before loading the column /-	-	- / droplet is removed from de μ-column using HNO_3 (10 %, v/v) and acetone	-on line system for the DLLME -frequency of on-line analysis: 10 samples per hour -PAR[a,p] (17 μL, 10^{-2} mol L^{-1}) as chelating agent -Triton X-114 (0.1%, w/v) as anti-sticking agent -study of coexisting ions -validation with CRM[k]	ETAAS	$E_F = 20/E_R = 95$/ RSD = 5.1 (1)	8 ng L^{-1}	[94]

[a] IL, or dispersive solvent, or chelating agent selected (others were also tried in the study).
[b] Extraction efficiency calculated as $E_R = 100{\cdot}E_F/E_{Fmax}$; being $E_{Fmax} = V_{sample}/V_{drop}$.
[c] tris(pentafluoroethyl)trifluorophosphate anion.
[d] 4-aminoantipyrine.
[e] fiber optic-linear array detection spectrophotometry.
[f] inter-day precision.
[g] 2,4-dinitrophenylhydrazine.
[h] 9-fluorenylmethyl chloroformate.
[i] for the overall extraction method, including the solid sample treatment.
[j] diethyldithiocarbamate.
[k] certificate reference material.
[l] 2-(5-bromo-2-pyridylazo)-5-diethylamino phenol.
[m] ammonium pyrrolidine dithiocarbamate.
[n] flow injection coupled with hydride generation atomic absorption spectrometry.
[o] tetradecyl(trihexyl)phosphonium chloride.
[p] 4-(2-pyridylazo)-resorcinol.

Table 6
Determination of organics and metals by *in situ* IL-DLLME.

Analytes (number)	Sample (mL)/sample requirements	Hydrophilic IL (amount)	Anion exchange reagent (amount)	Chelating agent (amount)	V_{drop} in μL/ further diluent (μL)	Centrifuge conditions	Comments	Analytical Technique	E_F/E_R (%)/RSD in % (spiked level in μg L^{-1})	LOD (μg L^{-1})	Ref
aromatic compounds (13)	water (10)/-	C_4MIm-Cl (38 μL)	Li-NTf_2 (471 μL, 0.2 g·mL^{-1})	-	~12/-	5 min 3400 rpm	-shaking (0.5 min) before centrifugation -comparison with conventional-DLLME and IL-SDME[a]	HPLC-UV	E_F = 184–935/ E_R[b] = 22–112/ RSD < 6.9 (-)	0.02–34.5	[98]
triazine herbicides (4)	water (5)/-	C_4MIm-BF_4[c] (40 μL)	Li-NTf_2[c] (500 μL, 0.2 g mL^{-1})	-	-/-	6 min 5000 rpm	-shaking (1 min) and microwaves (30 W, 50°C, 1.5 min) before centrifugation	HPLC-UV	E_F = 103–132/ E_R = 88–114/ RSD < 6.2 (40)	0.52–1.3	[99]
endocrine disrupting phenols (6)	seawater and industrial effluents (10)/-	C_4MIm-Cl (38 μL)	Li-NTf_2 (340 μL, 0.2 gm L^{-1})	-	~10/ ACN (1:10)	5 min 3400 rpm	-vortex (4 min) before centrifugation	HPLC-DAD	E_F = 130–1037/ E_R = 12–96/ RSD < 11 (10)	0.8–4.8	[100]
medicinal products (3)	aqueous extract of herb in the hydrophilic IL (1)/NaCl (15.0%, w/v)	C_8MIm-Cl[c] (0.50 mol L^{-1})	H-PF_6[c] (20 μL)	-	-/-	5 min 10000 rpm	-herbs were extracted with the IL (solid: liquid ratio 1:40) using ultrasounds (105 W, 80 min) -ultrasounds were also needed for *in situ* IL-DLLME (135 W, 6 min)	HPLC-UV	E_F = 25–29/ E_R = 84–96/ RSD < 4.6 (-)	80.0–97.0	[101]
insecticides (4)	water (8)/-	C_6MIm-Cl (27 mg)	Li-NTf_2 (1280 μL, 0.03 gm L^{-1})	-	~25/-	10 min 3500 rpm	-cooling in an ice bath (1 min) before centrifugation	HPLC-VWD	E_F = 260–326/ E_R = 82–102/ RSD < 4.6 (20)	0.98–2.54	[102]
emerging contaminants (17)	water (10)/pH 3	C_4MIm-BF_4[c] (40 μL)	Li-NTf_2 (ratio 1:1)	-	~13/-	5 min 3400 rpm	-shaking (0.5 min) before Li-NTf_2 addition -comparison with conventional IL-DLLME	HPLC-UV	E_F = 0.91–452/ E_R[b] = 0.12–58.8/ RSD < 6.1 (-)	0.1–55.8	[38]
DNA	aqueous DNA solution (2) / -	$C_{16}(C_3(OH)_2)$Im-Br[c,d] (0.5 mg)	Li-NTf_2 (1.0 gm L^{-1}, ratio 1:1)	-	-/-	10 min 3400 rpm	-shaking (5 min) before centrifugation -the amount of DNA extracted was determined indirectly by analyzing the remaining amount of DNA in the aqueous phase	HPLC-UV	E_F = 95.2/-/ RSD = 3.7 (-)	-	[103]
PAHs[e] (3), alkylphenols (5) and parabens (1)	aqueous extract of sediments (4) / ACN (800 μL)	C_{16}MIm-Br[c] (0.16 mmol)	Li-NTf_2 (92 μL, 0.5 gm L^{-1}, ratio 1:1)	-	~90/ ACN (~110) and vortex (1 min)	4 min 3400 rpm	-sediments were extracted with C_{16}MIm-Br (5 mL, 40 mmol L^{-1}) and microwaves (140 W, 90°C, 6 min), followed by centrifugation (5 min, 3600 rpm) and filtration -heating (65°C, 5 min) and vortex (3 min) for the *in situ* IL-DLLME -validation with CRM[f]	HPLC-DAD	E_F = 5.4–24/ E_R = 27.1–106/RSD < 3.4 (0.8–2.3 mg L^{-1})	LOQs: 0.04–1 mg kg^{-1}	[96]
PAHs[e] (16)	aqueous extract of toasted cereals (1.5)/-	$C_{16}C_4$Im-Br (0.06 mmol)	Li-NTf_2 (34 μL, 0.5 g mL^{-1}, ratio 1:1)	-	~65/ ACN (~30) and vortex (1 min)	4 min 3400 rpm	-toasted cereals were extracted with $C_{16}C_4$Im-Br (4.5 mL, 40 mmol L^{-1}) and microwaves (50 W, 80°C, ~14 min), followed by centrifugation (5 min, 4000 rpm) and filtration -vortex (2.5 min) and cooling in the freezer (1 hour) for the *in situ* IL-DLLME	HPLC-UV-FD	E_F = 5.6–14/ E_R = 68.4–119/RSD < 22 (9–4500 μg kg^{-1})	0.03–83 μg kg^{-1}	[104]

Hg (II)	water (5)/acetate-acetic acid buffer (0.2 mol L^{-1}, pH 4)	C_6MIm-BF_4 (30 mg)	Na-PF_6 (600 μL, 120 mg mL^{-1})	TMK[g] ($2{\cdot}10^{-6}$ mol$\cdot L^{-1}$in 1-propanol)	~7/ EtOH 85% (150)	6 min 5000 rpm	-study of coexisting ions -validation with CRM[f]	spectrophotometry	E_F = 37/E_R[b] = 5/RSD = 1.94 (40)	0.7	[97]
Cd (II)	saline water (5)/pH 2	C_6MIm-BF_4 (30 mg)	Na-PF_6 (1 mL, 120 mg mL^{-1})	DDTP[h] (0.03 mol$\cdot L^{-1}$ in ethanol)	~8 / EtOH (50)	5 min 5000 rpm	-saline solutions (up to 40%, w/v) -study of coexisting ions	FAAS	E_F = 78/ E_R[b] = 13/ RSD = 2.42 (20)	0.07	[105]
Pd (II)	seawater, food additive, and aqueous solutions of tea and blood (10)/acetate-acetic acid buffer (0.2 mol L^{-1}, pH 4)	C_6MIm-BF_4 (3.6 g)	Na-PF_6 (1.2 mL, 120 mg mL^{-1})	TMK[g] ($5.2{\cdot}10^{-6}$ mol L^{-1})	-/EtOH 85% (100)	5 min 5000 rpm	-different sample treatments (oxidation with HNO_3 and H_2O_2 for blood and dry tea), followed by dilution up to 10 mL with water -heating (50°C, 4 min) before Na-PF_6 addition -cooling in an ice bath (10 min) before centrifugation -study of coexisting ions	spectrophotometry	E_F = 97/-/ RSD = 1.7 (40)	0.2	[106]
Ag (I)	photographic and X-ray waste (10)/acetate-acetic acid buffer (0.2 mol L^{-1}, pH 3.5)	C_6MIm-BF_4 (36 mg)	Na-PF_6 (800 μL, 120 mg mL^{-1})	TMK[g] ($7.5{\cdot}10^{-6}$ mol L^{-1})	- / EtOH 85% (100)	5 min 5000 rpm	-heating (50°C, 4 min) before Na-PF_6 addition -cooling in an ice bath (10 min) before centrifugation -study of coexisting ions	spectrophotometry	E_F = 95.5/-/ RSD = 1.8 (50)	0.4	[107]

[a] Single-drop microextraction.
[b] Extraction efficiency was calculated as $E_R = 100{\cdot}E_F/E_{Fmax}$; being $E_{Fmax} = V_{sample}/V_{drop}$.
[c] IL or anion exchange reagent selected (others were also tried in the study).
[d] 1-(1,2-dihydroxyprophyl)-3-hexadecylimidazolium bromide.
[e] Polycyclic aromatic hydrocarbons.
[f] Certificate reference material.
[g] Michler thioketone.
[h] o,o-diethylthiophosphate.

It is worth mentioning that Berton and Wuilloud [94] have proposed an on-line IL-DLLME set-up for the determination of cobalt in environmental samples and pharmaceutical formulations. They employed a microcolumn filled with Florisil, in which an IL-droplet containing analytes was retained, using a flow-injection system. The IL-DLLME method was assisted by vortex before loading the microcolumn. The system was optimized in terms of chelating agent, surfactant as anti-sticking agent, and elution conditions.

2.4. In situ IL-DLLME

The *in situ* solvent formation for microextraction based on ILs, which can be simplified as *in-situ* IL-DLLME method, is based on utilizing a hydrophilic IL as extractant solvent of the analytes contained in the aqueous solution. An anion-exchange reagent is then added to promote a metathesis reaction, and the hydrophilic IL is transformed into a hydrophobic IL, which settles to contain the preconcentrated analytes. The method generally requires the utilization of vortex, microwaves, ultrasound, or shaking to improve the kinetics of the metathesis reaction. Fig. 1(D) shows this IL-DLLME mode. The anion-exchange reagent is normally added keeping a 1:1 molar ratio with the hydrophilic IL. The utilization of a dispersive solvent to favor the reaction has rarely been reported [96].

The first description of the method was by Baghdadi and Shemirani [97] in the determination of Hg(II) in saline solutions. They named their microextraction technique "*in situ* solvent-formation microextraction" (ISFME) based on ILs, which is an accurate definition of this IL-DLLME mode. They used sodium hexafluorophosphate ($Na\text{-}PF_6$) as the anion-exchange reagent and $C_6MIm\text{-}BF_4$ as the initial hydrophilic IL. The method performed particularly well when dealing with salty aqueous samples. Hg(II) was complexed with 4,4′-bis(dimethylamino)thiobenzophenone (TMK) as chelating agent.

With regards to the determination of organic compounds, Yao and Anderson were the first to perform this IL-DLLME mode [98]. In this case, the preferred anion-exchange reagent was lithium bis[(trifluoromethane)sulfonyl]imide ($Li\text{-}NTf_2$), and the hydrophilic IL used was $C_4MIm\text{-}Cl$.

Table 6 includes most significant applications of determining metals and organic compounds using the *in situ* IL-DLLME method [38,96–107].

The *in situ* IL-DLLME mode has been applied to the analysis of the analysis of aqueous samples but also solid samples. In the most classical applications, the aqueous solution of the solid samples was subjected to the *in situ* IL-DLLME mode [101,106]. More recently, novel applications involving IL-based surfactants were described in the literature for the analysis of solid samples [96,104]. IL-based surfactants are surface-active molecules, which normally contain long alkyl chains attached to an IL skeleton [108]. Because of the variety of structurally diverse IL-based surfactants that can be synthesized, compared to more classical surfactants, they have great potential to impact the field of surfactants impact the field of surfactants. IL-based surfactants have been used in the determination of a number of organic compounds present in solid samples, as adequate substituents of organic solvents or even conventional surfactants.

The utilization of the *in-situ* IL-DLLME mode with IL-based surfactants was first reported by Germán-Hernández et al. [104], who extracted polycyclic aromatic hydrocarbons (PAHs) from toasted cereal samples using the IL-based surfactant $C_{16}C_4Im\text{-}Br$. Once analytes were dissolved in the IL-based surfactant aqueous solution, *in situ* IL-DLLME was performed in the same extraction tube, and the hydrophobic IL $C_{16}C_4Im\text{-}NTf_2$ was formed and settled in the tube containing the preconcentrated PAHs. Thus, the IL-based surfactant was used as both extractant solvent and preconcentration agent. Furthermore, no organic solvents are needed in the extraction step despite the complexity of the solid sample; no further solvent-exchange steps are required. This alternative to the extraction of solid samples has also been included in Fig. 2.

A recent work of Delgado et al. from the same research group also reported the use of IL-based surfactants in an *in situ* IL-DLLME method, in this case for the determination of a group of parabens, alkylphenols and PAHs from sediment samples [96]. The group of Anderson described the extraction of DNA using an *in situ* IL-DLLME method, using an hydrophilic IL that it is probably an IL-based surfactant [103]. However, they were more interested in selecting an IL that would promote dispersive interactions with the nucleic acid, while also having hydrogen-bonding capabilities with the phosphate (phosphodiester) backbone, than in the potential aggregation of the IL used as the extraction solvent. In any case, an *in situ* IL-DLLME method was performed with this potential IL-based surfactant.

To date, no derivatization reaction has been carried out in combination with the *in situ* IL-DLLME mode.

With regards to the determination of metals using the *in situ* IL-DLLME mode, the hydrophilic IL of choice has been $C_6MIm\text{-}BF_4$ in all cases, followed by $Na\text{-}PF_6$ as anion-exchange reagent [97,105–107]. By contrast, $Li\text{-}NTf_2$ has been the anion-exchange reagent of choice when determining organic compounds [38,96,98–100,102–104].

3. Analytical applications of IL-DLLME

An important aspect that needs to be considered when developing an IL-DLLME method is the compatibility of the IL microdroplet containing analytes with the following analytical instrument. For example, if HPLC is going to be used, it is important to ensure that the IL is soluble in the mobile-phase mixture used for the separation. A typical step of solvent evaporation followed by solvent exchange is impossible when dealing with ILs as solvents. Regarding GC, direct injection of ILs is impossible (an interface would be needed to remove the IL). This explains why HPLC is normally the analytical technique of choice when using IL-DLLME for determining organic compounds, whereas both GC and HPLC can be used in classical DLLME. Moreover, considerations related to possible interferences coming from the IL itself in the chromatographic detector or even incompatibilities with the detection system need to be addressed. However, the IL can positively enhance the fluorescence signals when using FD. ILs can also be quite successful when using ECD, due to their wide electrochemical window. Thus, the IL selected can exert a tremendous influence on the analytical sensitivity.

The different modes of IL-DLLME have been utilized in a number of analytical applications, including the determination of metals and organic compounds in a variety of samples of quite different nature. Tables 1–6 include such determinations. Several quality analytical parameters have been included in Tables 1–6 to compare the different analytical performances. They include LOD, enrichment factor (E_F), extraction efficiency (E_R), and precision as relative standard deviation (RSD) in %. The enrichment factor is given by:

$$E_F = C_{drop}/C_{initial} \quad (1)$$

where $C_{initial}$ corresponds to the concentration of the analyte in the water sample (before IL-DLLME), and C_{drop} is the concentration of the analyte in the final microdroplet obtained by the IL-DLLME method, which, to be realistic, should take into account its further dilution before analysis. Otherwise, reported E_F values are much higher than those that can really be attained with the method. Other authors also correctly calculate E_F from the ratio of the calibration slopes obtained before and after the IL-DLLME method.

The real extraction recovery is calculated from:

$$E_R(\%) = 100 \times E_F/E_{Fmax} \quad (2)$$

where E_{Fmax} is the maximum preconcentration achieved if all analytes are effectively concentrated in the final microdroplet of the IL-DLLME method. E_{Fmax} can be calculated from the ratio $V_{initial}/V_{drop}$, $V_{initial}$ being the initial aqueous solution volume, and V_{drop} the microdroplet volume, including its further dilution. E_R is an adequate measure of the real extraction efficiency of the method. We need to highlight that it is difficult to achieve E_R values close to 100% in any microextraction procedure, so E_R values are valid as long as the LODs, E_F values, and the reproducibility of the method are sufficient for a given application. Several E_R values in Tables 1–6 were not reported, but they could be estimated using the reported values of $V_{initial}$, V_{drop} (and further dilution) and E_F.

We need to note that V_{drop} values included in Tables 1–6 correspond to the overall droplet volume obtained after the IL-DLLME method, and not to the droplet aliquot that authors normally use for further analysis. Several works report only the size of the aliquot, and thus the overall droplet volume is unknown to readers. In temperature-controlled IL-DLLME applications, or in those works in which a cooling step is needed, measuring the volumes of the frozen droplets is quite complicated, so their values are rarely reported.

Several works report the relative recoveries (RR in %) or accuracy values, as if they were extraction efficiencies. Given that accuracy values should be around 100% in order to have a method adequately validated, and that they do not reflect the real extraction ability of the IL-DLLME method, RR values have not been reported in Tables 1–6.

Values of precision as RSD have also been included in Tables 1–6. We observe that, in all cases, they are completely acceptable from an analytical point of view.

3.1. Determination of organic compounds

The analytical determinations regarding organic compounds utilizing different IL-DLLME modes have been included in Tables 1, 3, 5 and 6. Conventional IL-DLLME and microwave-assisted, vortex-assisted and ultrasound-assisted IL-DLLME have been the modes used most for the determination of organics.

A wide variety of organic compounds have been determined using IL-DLLME, including amines, pharmaceuticals and drugs, pesticides, hydrocarbons, aldehydes, UV filters, phenols, parabens, antibiotics and even DNA. With regards to the variety of samples, not only liquid samples, such as all kind of waters, urine, blood or fruit juice, but also solid samples, such as bananas, grapes, pancakes, roots, herbs, sediments, cereals or tea, have been analyzed using IL-DLLME.

The hydrophobic IL most frequently used in these applications is $C_6MIm\text{-}PF_6$, followed by $C_8MIm\text{-}PF_6$. With regard to the dispersive solvent, methanol is undoubtedly the solvent of choice. To a lesser extent, the choice in the selection of dispersive solvent is acetonitrile, acetone, and ethanol (in this order).

The preconcentration factors reported are in the range 18–1037, showing the excellent preconcentration achieved with the technique. For few analytes, E^F values are low, in the range 0.81–5.6 [38,96,104]. In the same way, LODs down to 0.03 ng L^{-1} have been achieved for liquid samples, and down to 0.02 ng g^{-1} for solid samples. Common LODs for organics in liquid samples are at the low μg L^{-1} level.

With regards to extraction efficiencies (E_R values), they were in the range 12–119%. As mentioned above, it is not that important to achieve efficiencies up to 100%, as long as the reproducibility and the E_F of the method are sufficient for the application. By comparison, real extraction efficiencies in solid-phase microextraction (SPME) are hardly 100% and this does not detract from the extraction ability and enormous preconcentration achieved with the technique.

It must be noted that few works report comparisons with conventional extraction techniques [39,52,56,63], or among different DLLME modes [17,35,36,38,60,61,72,74].

The use of derivatization reactions in combination with IL-DLLME to determine organics has been described in a number of works [34,82–84], which extends the advantages of the IL-DLLME technique to a higher variety of analytes.

3.2. Determination of metals

Tables 2 and 4–6 cover the main analytical applications aimed to determine metals using ILs in DLLME with different variants. Martinis et al. reviewed the determination of metals using IL-based techniques in 2010 [109]. Among the techniques described, DLLME was also considered.

It is worth mentioning the efforts made by two independent teams regarding the development of IL-DLLME methods devoted to the determination of metals in a wide variety of samples: Willoud et al. [43,45,50,51,66,94] and Shemirani et al. [18,48,49,97,105–107].

Conventional IL-DLLME has been the most frequently used IL-DLLME mode for the determination of metals. As for the determination of organic compounds, IL $C_6MIm\text{-}PF_6$ has been employed the most successfully. With regards to the dispersive solvent, methanol has also been the primary choice.

Chelating agents employed in these applications are common reagents, such as ammonium pyrrolidinedithiocarbamate (APDC), sodium diethyldithiocarbamate (DDTC), 4,4'-bis(dimethylamino)thiobenzophenone or thioketone Michler (TMK), 8-hydroxyquinoline (oxine). Oxine is one of the most sensitive organic ligands used for the determination of Al(III) by fluorimetric detection. TMK is a sensitive spectrophotometric reagent for Au, Ag, Hg and Pd. APDC is widely used for the microextraction of lead, since it can form an extractable complex with lead in an acid medium. We need to highlight that all these chelating agents are quite common, so there is no need to utilize specific and/or complex chelating agents when determining metals by IL-DLLME.

Applications of IL-DLLME for metals include the determination of Ta, Hg, As, Cr, Ni, Co, Zn, Se, Pb, V, Cd, Rh, Pd, Ag, or even lanthanoids in a wide variety of (mainly) aqueous samples, such as waters of different nature, liquid cosmetics, wines, milk, urine, saliva, and blood, but also solid samples, such as garlic, uranium dioxide powder, dried foods (flour, potatoes and apples), hair, and leaves.

Preconcentration factors achieved in the determination of metals by IL-DLLME were in the range 10–760, and LODs were down to 1.3 ng L^{-1}. Extraction efficiencies (E^R values) were 5–100%. At this point, similar comments to those given above on the determination of organic compounds can be applied.

It is a remarkable that a significant number of works regarding metals utilize certified reference materials to validate their IL-DLLME methods [43,46,47,50,65,67,91,93,94,97].

4. Conclusions and trends

There are a significant number of successful analytical applications that use IL in combination with DLLME. The resulting methods combine the inherent advantages of ILs, such as low vapor pressure at room temperature, lower toxicity when compared to conventional organic solvents, and tunable properties, among others, with the interesting advantages of DLLME, such as low consumption of reagents, high preconcentration factors and rapidity.

There is no single way for ILs to be used in conjunction with DLLME. However, the enormous variety of works on IL-DLLME in the current literature can be divided into four modes: conventional, temperature-assisted, microwave-/ultrasound-/vortex-assisted, and *in situ*. This simple division helps the reader to understand the performance of the IL-DLLME method described in a work, for example, independently of the nature of the dispersive solvent, the absence of a dispersive solvent, the use or not of hydrophilic ILs, the use of surfactants, the way the droplet is removed, and the necessity or not of a cooling step, and the stirring mode.

The combination of ILs and DLLME has been quite successful, independently of the nature of the analytes under determination or the complexity of the sample. Thus, we expect more work in this field in the near future, addressing the ease of the combination. In addition to this, we can predict the appearance of more works that use hydrophilic ILs or surfactants as dispersive solvents, in order to avoid the use of conventional organic solvents in the extraction step.

Furthermore, we expect more works regarding the analysis of solid samples in combination with IL-DLLME, mainly those exploring novel variants that use IL-based surfactants. This would permit the elimination of organic solvents in the extraction method when dealing with complex solid samples as well as avoiding solvent-exchange steps. New trends are the employment of hemimicelles of IL-based surfactants with nanoparticles in a hybrid solid/liquid mode of dispersive extraction.

It is also desirable to employ tailored ILs with greener properties in future applications of the IL-DLLME method in its different variants.

With regards to the determination of metals, it could be interesting to employ ILs with the double purpose of acting as extractive and chelating agents, so performing IL-DLLME. This possibility has not been explored to date.

In any case, we need more works in which detailed comparison of all IL-DLLME modes is carried out for a specific determination, to point out clearly the advantages and/or the disadvantages of each variant. Comparison with conventional DLLME without ILs would also be desirable to highlight the real advantages of combining ILs in DLLME.

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