Task-specific ionic liquids: Applications in sample preparation and the chemistry behind their selectivity

Mauricio Llaver, Emiliano F. Fiorentini, Pamela Y. Quintas, María N. Oviedo, María B. Botella Arenas, Rodolfo G. Wuilloud*

Laboratorio de Química Analítica para Investigación y Desarrollo (QUIANID), Facultad de Ciencias Exactas y Naturales, Universidad Nacional de Cuyo / Instituto Interdisciplinario de Ciencias Básicas (ICB), CONICET UNCUYO, Padre J. Contreras 1300, (5500) Mendoza, Argentina

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ABSTRACT

Task-specific ionic liquids (TSILs) represent a sub-family of ionic liquids characterized by their high specificity towards a target analyte or group of analytes. This characteristic has made them valuable tools for sample preparation, where selectivity represents a key aspect, especially when other species represent a significant source of interference or when non-specific detectors are used. This review presents an overview of TSILs applications for sample preparation from the last ten years, with a special emphasis on their use as liquid-liquid microextraction solvents or as functionalizing agents for sorbents applied to solid-phase microextractions. TSILs applications for the treatment of environmental, food and biological samples are reviewed, including reports devoted to speciation analysis, a relevant trend in recent years regarding elemental studies. Additionally, focus is made on the 'task-specificity' of the presented TSILs, including a description of the chemical characteristics that made them selective towards the studied analytes. Finally, future trends and gaps to be covered in the field are also discussed.

Abbreviations

5-ASA	5-amino salicylic acid
8-HQ	8-hydroxyquinoline
ABS	Aqueous biphasic system
APDC	Ammonium pyrrolidine dithiocarbamate
CPE	Cloud point extraction
DI-SPE	Direct immersion solid phase extraction
DLLME	Dispersive liquid-liquid microextraction
ETAAS	Electrothermal atomic absorption spectrometry
FAAS	Flame atomic absorption spectrometry
GC-FID	Gas chromatography with flame ionization detection
HF-LPME	Hollow fiber-liquid phase microextraction
IL	Ionic liquid
LC-MS/MS	Liquid chromatography coupled to tandem mass spectrometry
LLE	Liquid-liquid extraction
MNP	Magnetic nanoparticle
MSPE	Magnetic solid phase extraction
MWCNT	Multi-walled carbon nanotube
PAH	Polycyclic aromatic hydrocarbon
POSS	Polyhedral oligomeric silsequioxane
PTFE	Polytetrafluoroethylene
SBME	Sorbent bar microextraction
SPE	Solid phase extraction
SPME	Solid phase microextraction
TH	2,2′-thiodiacetic acid
TOMATS	Trioctylmethylammonium thiosalicylate
TSIL	Task-specific ionic liquid
TSMPIL	Task-specific magnetic polymeric ionic liquid
TSPIL	Task-specific polymeric ionic liquid

1. Introduction

Sample preparation is considered an essential stage in the development of analytical methods, especially in the analysis of complex matrices, such as those presented by environmental, food and biological samples. The determination of the low concentrations in which the target analytes are found in this type of samples, added to the presence of numerous interferences, represent a highly challenging analytical task. From this point of view, sample preparation can be considered a process that allows the isolation of interfering species while separating and preconcentrating the analytes of interest. In this sense, the analysis of complex samples in a sensitive, selective and precise way has required the development of different strategies and materials for this purpose [1].

Thereby, extraction using selective solvents and adsorbents has been the focus of the developments that can be found in the literature from

recent years. Originally, classical sample preparation methods such as liquid-liquid extraction (LLE) or solid phase extraction (SPE) were characterized by the use of large volumes of toxic and volatile organic solvents. However, driven by the principles of Green Analytical Chemistry, modern analytical methods have sought to minimize the use of these solvents and to replace them with eco-friendly alternatives. This has resulted in the development of microextraction methods with excellent potentials for different types of applications [2].

Ionic liquids (ILs) have been the main alternative solvents used in microextraction methodologies in the last decade. They are defined as salts that are liquid below 100 °C and are composed by bulky organic cations and small anions of different nature. Their molecular structure allows them to interact with organic molecules or inorganic ions through different interactions, such as electrostatic, ion exchange, π-π stacking and hydrogen bonding, among others. They present unique physicochemical properties, such as high thermal and chemical stabilities, low vapor pressure, ease of synthesis and, more importantly, the possibility to tune their properties based on the stated objective; hence the use of the term 'designer solvents' to characterize them [3]. This has turned them into compounds of interest in many fields of chemistry, including of course analytical chemistry, in which ILs have progressively found applications in fields that range from sample preparation to electrochemical sensing [4].

Due to the significant number of ILs known to date and their various properties and structures, they have been classified into different groups. Among them, classical, magnetic, polymeric and task-specific ILs (TSILs) have been developed. TSILs present within their structure a functional group that allows them to interact specifically with a target analyte, and should not be confused with IL-based stimuli-responsive materials, which suffer changes in their properties (*e.g.* viscosity, volume, conductivity) as a consequence of the interaction with the species of interest [5]. It is also important to bear in mind in the context of this review that magnetic ILs (MILs) have been considered TSILs by some authors, which consider that the magnetic portion of their structure represents a task-specific functionality. Nevertheless, as the aim of this work is to describe TSILs developed with the aim of specifically interacting with an analyte of interest (added to the fact that several reviews on MILs have been recently published [6–8]) MIL-based sample treatment is not hereby covered.

Recent reviews have focused on sample preparation with classical, magnetic and polymeric ILs [1, 8], while only a general review about TSILs is available, which dates from over a decade ago [9]. On the other hand, recent literature includes reviews on the use of ILs in the preparation of environmental [10], food [11] and biological samples [12], albeit not specifically with TSILs. Taking this into account, this work aims to represent an updated and modern revision text on the application of TSILs for sample preparation. A general description of their nature is given in the following section, followed by a critical analysis of their application in the treatment of environmental, food and biological samples.

2. Task-specific ionic liquids

TSILs, also known as functionalized ILs, can be defined as any salt that has the typical properties of an IL in which a functional group with a target application is covalently bonded to the cation and/or anion [13]. In this sense, the characteristics of TSILs can be influenced not only by the cation-anion combination, but also by the nature of the introduced functional group and its position in the structure [14]. In recent years, due to the possibility of synthesizing ILs with specific physicochemical and biological properties, TSILs have attracted a great attention in a wide variety of fields. Fig. 1 shows the structure of some cations and anions usually found in the structure of TSILs in comparison to those of some conventional ILs, highlighting the functional groups responsible for their specificity.

For example, several reports exist on the modification of ILs with metal-chelating functional groups (*e.g.*, urea, thiourea, thioether, phosphoryl, ethylene glycol, maltolate or thioglycolate) to increase the efficiency and selectivity towards target metal cations [15]. For instance, two ammonium-based TSILs with bidentate and tridentate oxygen donating groups (thioglycolate) have been successfully applied for the separation and recovery of rare earth elements, taking advantage of the spatial distribution of the O atoms, which resulted optimal for the interaction with the analytes [16]. The field of sample preparation has profited immensely from this type of characteristics, as can be inferred from the following sections. Cases such as this are presented throughout this work, involving the extraction and/or preconcentration of several metallic cations, which turn out to be the most studied analytes when TSILs are employed for sample treatment, leaving organic and biological analytes far behind in terms of TSIL-based analysis. This is probably a consequence of coordinating interactions being very specific towards cationic species based on the positioning and identity of the chelating atoms in the TSIL, which is evidenced by the large amount of works reporting TSILs that act as complexant and extractants simultaneously. Meanwhile, organic and biological analytes can take part in less specific interactions, such as those derived from dispersion forces, electrostatic forces or from hydrogen bonding, making it harder to achieve molecule-specific TSILs for these species.

Asides from the applications reviewed in this work, numerous TSILs have been designed and synthesized to achieve specific tasks in diverse fields. For example, one of the most reported applications of TSILs is their use as solvents or as catalysts in organic reactions, where they offer a less environmentally harmful reaction media than conventional organic solvents and the possibility of recycling without losing their good catalytic performance [17]. Additionally, some TSILs have been used as solid catalyst surface modifiers with the aim of improving the activity and catalytic selectivity in different organic synthesis [18]. In this context, it is worthwhile to mention the extensive literature highlighting the use of TSILs in the chemistry of CO_2, a species of enormous interest currently, regarded as the most significant greenhouse gas. Due to their negligible volatility, TSILs have been used as green chemisorbents, catalysts or promoters for the absorption, capture and subsequent conversion of CO_2 [19]. Moreover, TSILs have been widely used in the synthesis of novel nanomaterials in the last years, with the aim of improving the conductivity, enhancing the thermal and electrochemical stability and decreasing the toxicity of the reaction medium, as well as for controlling the particle size and growth reactivity of various nanoparticles. These new nanomaterials have been used in modern areas such as electrosensors, catalysts, electronics, and photonics [20].

From the above, there is no doubt about the enormous progress in the use of TSILs in different areas. However, the attributed environment-friendly character of TSILs (and of ILs in general) is mainly derived from their low vapor pressure, non-inflammability and high stability, ignoring their potential toxicity and biodegradability [21]. Due to their low vapor pressure, TSILs cannot contaminate the air; however, most of them are highly miscible with water and therefore can potentially contaminate water and soil [22]. Therefore, the toxicity of various ILs, including TSILs, against certain micro and macro-organisms has been evaluated in the last decades [23]. For example, Kumar et al. studied the *in vitro* cytotoxicity of numerous TSILs using human breast cancer cells [24]. The data showed that the toxicity depended significantly on the nature of both the cations and anions of ILs and that the studied TSILs were less toxic than structurally similar conventional ILs. Also, a more recent study demonstrated that phosphonium- and ammonium-based TSILs used for Co(III), Ni(II) and Zn(II) extraction from aqueous solutions were toxic towards three freshwater green algae species, although their toxicity was lower than that of similar solvents [22]. Therefore, analyzing the ecotoxic potential of the proposed TSILs should be a prerequisite prior to their application, although the miniaturized fashion in which they are applied in modern sample treatment methods, as
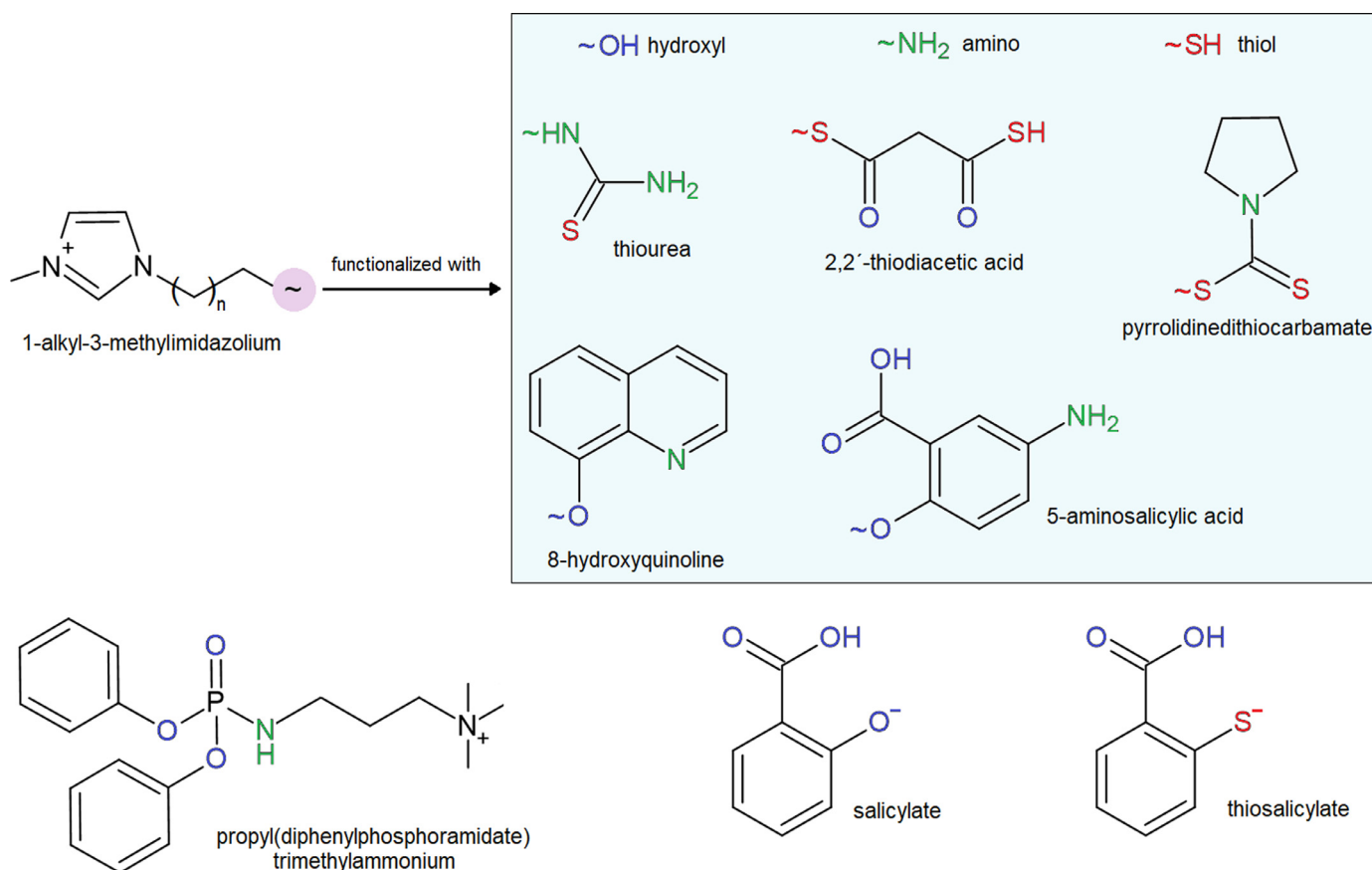
Fig. 1. Structures of some representative cations and anions of task-specific ionic liquids used for sample preparation.

will be discussed in the following section, certainly ameliorates their impact regarding these activities.

3. Task-specific ionic liquids in sample preparation

Regarding their application for sample preparation, typical characteristics of TSILs such as their non-volatility, wide liquid range, tunable viscosity and high thermal stability make them an attractive alternative over traditional organic solvents. Currently, TSILs are being applied mostly in sample preparation techniques as part of microextraction-based methods, such as LLE, SPE and solid-phase microextraction (SPME) [25]. A graphical representation of the distribution of TSILs applications for sample treatment is presented in Fig. 2, including all the revised works hereby presented.

Although the properties of TSILs can be tuned to achieve high separation efficiencies and selectivity, their use in LLE usually presents a major drawback regarding the greenness of their application. On one side, some TSILs show high viscosities, meaning they have to be dissolved in organic solvents to improve their dispersibility and, hence, their extraction efficiency. On the other side, the potential leachability of TSILs to aqueous phases in cases in which their water solubility is non-negligible, can challenge their use as an environmentally friendly alternative [26]. Consequently, applications of TSILs immobilized onto solid supports have also been developed for sample preparation methods based on SPE and SPME, avoiding the aforementioned drawbacks associated to LLE applications [27]. In these cases, the choice of both solid support and TSIL becomes key, since the resulting material can be made to have properties superior to those of the sum of its components [28]. This is especially true in the case of nanostructured supports, which provide high surface-to-mass ratios and usually present highly functionalized surfaces, ideal for the anchoring of TSILs; although other

materials, such as polytetrafluoroethylene (PTFE) and polymers, have also been used for the preparation of functional adsorbents [29,30]. The characteristics of TSILs are ideal for this approach, since the preparation of combined sorbents usually requires the formation of chemical bonds in harsh chemical conditions, making their high thermal and chemical stabilities fundamental.

The following sections present a thorough analysis of TSILs applications for sample treatment, both directly and as part of solid hybrid sorbents, in diverse samples. Special emphasis is made on the structural characteristics that make them task-specific, and relevant analytical characteristics of the reviewed methods are also presented. Also, a summary of the revised works including general aspects of the methods and analytical figures of merit is presented in Tables 1, 2 and 3.

3.1. Environmental samples

Table 1 presents a summary of the characteristics and analytical figures of merit of TSILs applications in environmental samples. To cite an example, a cloud point extraction (CPE) procedure with a TSIL for the selective extraction of UO_2^{2+} in sea, well and spring waters without any previous treatment has been developed with detection by total reflection X-ray fluorescence [31]. CPE involves the formation of a micellar extractant phase by heating the solution with the added TSIL and has the advantage of being fast and providing excellent extraction efficiencies, due to the high contact surface provided by the formed micelles [32]. In this case, the TSIL contained a phosphoramidate group and the interaction between this moiety and the analyte was studied by a series of techniques, including isothermal calorimetric titration and infrared spectroscopy. This revealed that, at high acidities, the extraction occurred via a solvation or ion-pair mechanism, whereas at low acidity it followed a cation exchange mechanism. The authors also highlighted
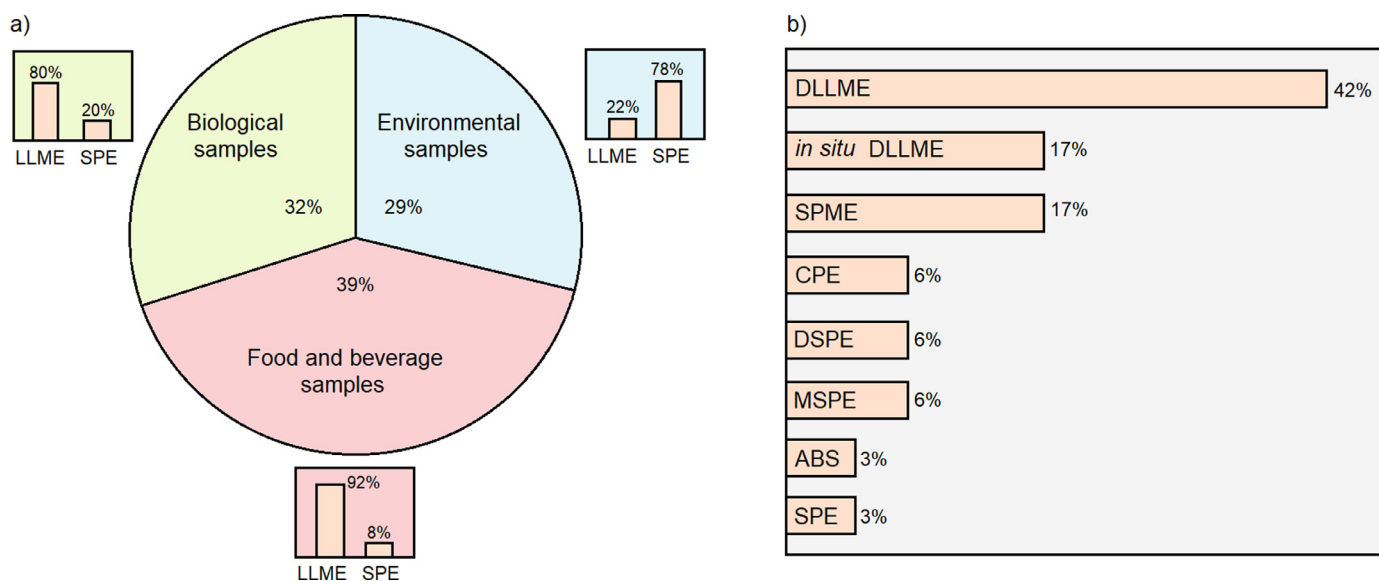
Fig. 2. Distribution of review reports involving TSILs for sample preparation as a function of: a) Type of sample and method family, b) Type of method.

Table 1

Summary of the reviewed TSIL-based environmental sample preparation methods.

TSIL	Analyte	Extraction technique	Detection technique	Sample/s	LOD[a] (μg L^{-1})	EF[b]	RSD[c] (%)	Reference
TOMATS coating a PTFE tube	Hg(II)	SPME	CVG-AAS	Soils	0.04	21	5	[29]
[VBIM][NTf$_2$]-POSS hybrid coating on stainless-steel fibres	PAHs	DI-SPME	GC–MS	River water and soil	4×10^{-6} - 5×10^{-4}	N.R.	< 6.7	[30]
[phamdNMe$_3$][NTf$_2$]	UO$_2^{2+}$	CPE	TXRF	Sea, well and spring waters	0.02	N.R.	$\leq$ 4	[31]
TOMATS	Pb(II)	CPE	ETAAS	Pine leaves and red lipstick	0.0010	48.7	4.9	[33]
Thiourea-containing TSIL coupled to MWCNTs	Pb(II)	SPE	ETAAS	Well water, pine leaves and red lipstick	0.13	N.R.	6.3	[34]
[Hemim][BF$_4$]-functionalized MWCNTs	Styrene	USA-DCC-μ-SPE	GC-FID	Petrochemical and paint factory wastewaters	0.26	N.R.	2.23	[35]
[Apmim][PF$_6$]-functionalized MWCNTs	Hg(II)organic Hg	UAS-DM-SPE	CVG-AAS	Waste, well and sea waters	0.00520.0058	19.919.7	< 1.9	[36]
(Ag$^+$(VIM)$_2$)[NTf$_2^-$])-based polymeric TSIL	Oleic acidLinoleic acidLinolenic acid	DI-SPME	GC-FID	Dairy farm rinse water	8.23.22.6	N.R	174.04.8	[37]
TSPIL-MNPs hybrid	Au(III) Pd(II) Pt(II)	MSPE	ETAAS	Tap, lake and sewage waters and mine soils	19.722.3107.0	197174168	2.11.41.5	[41]

[a] Limit of detection.

[b] Enhancement factor.

[c] Relative standard deviation, **N.R.:** Not reported, **TXRF:** Total reflection X-Ray fluorescence, **CVG-AAS:** Cold vapor generation-atomic absorption spectrometry, **USA-DCC-μ-SPE:** Ultra-assisted dispersive cyclic conjugation-micro-solid phase extraction, **GC-FID:** Gas chromatography with flame ionization detection, **UAS-DM-SPE:** Ultrasound assisted-dispersive-modification solid phase extraction, **HR-CS-FAAS:** High-resolution continuum source flame atomic absorption spectrometry.

the fact that the proposed methodology was eco-friendly, since it utilized micro- to millimolar concentrations of surfactants and TSIL, and no other hazardous reagents or solvents.

Regarding other TSILs used for environmental analysis, a very interesting case is that of trioctylmethylammonium thiosalicylate (TOMATS), which acts both as a hydrophobic solvent and as a metal complexant, avoiding the need of an external chelating agent for efficient and selective elemental microextractions. TOMATS is composed by the trioctylmethylammonium cation, which provides the water immiscibility necessary for its use as an extractant, and by the thiosalicylate anion, in which the *ortho*-positioned carboxylate group respect to the thiol functionality translates into its complexing properties. Hence, applications of TOMATS for the determination of Hg(II) in soils and Pb(II) in pine leaves and lipstick have been reported. In the former, the TSIL was used to coat a PTFE tube which was immersed in the acid-digested samples, prior to direct quantification of the analyte via cold vapor generation-

atomic absorption spectrometry [29]. In the latter, on the other hand, the TSIL was applied as extractant in a CPE method followed by electrothermal atomic absorption spectrometry (ETAAS) detection [33]. In this case, the samples were also subjected to an acid digestion prior to the application of the method and the authors highlighted the fact that the thermal stability of the TSIL was key to avoid its degradation during the heating step of the CPE protocol. In relation to this last work, the same authors have also reported the use of a thiourea-functionalized TSIL immobilized onto multi-walled carbon nanotubes (MWCNTs) for the SPE of ultra-trace amounts of Pb(II) [34]. The selectivity of the resulting sorbent was ascribed to the chelating properties of the thiourea moiety towards the analyte, and the coupling with MWCNTs allowed for its application in a SPE column for the fast and efficient analysis of well water, pine leaves and red lipstick, with ETAAS detection.

The coupling of TSILs with MWCNTs has also been exploited by other groups, taking advantage of the high surface-to-mass ratio of the

nanostructured material, which is key for the miniaturization of the resulting methods. In this respect, an ultra-assisted dispersive cyclic conjugation-micro-SPE method for the microextraction of styrene from petrochemical and paint factory wastewaters using 1-(2-hydroxyethyl)-3-methylimidazolium tetrafluoroborate ([Hemim][BF$_4$])-functionalized MWCNTs has been recently reported [35]. In this work, the authors reported that the π-π stacking and cation/anion-π interactions between the imidazolium ring of the TSIL and the aromatic ring of styrene were key for the efficient extraction of the analyte, which was posteriorly quantified by gas chromatography with flame ionization detection (GC-FID). In another interesting work, 1-(3-aminopropyl)-3-methylimidazolium hexafluorophosphate ([Apmim][PF$_6$]) was coupled to MWCNTs for the speciation analysis of Hg via ultrasound assisted-dispersive modification SPE [36]. Here, the extraction was performed into a polypropylene syringe filter with ultrasonic stirring to accelerate the mass transfer, and the separate quantification of Hg(II) and organic Hg was achieved by the treatment of two aliquots, one subjected to direct analysis and a second one subjected to a microwave pre-treatment. The pH was found to be the key aspect regulating the extraction efficiency in this case, since the charge state of the amino groups of the TSIL was responsible for the selectivity towards the positively charged analytes (Hg^{2+}, CH$_3$Hg$^+$ and C$_2$H$_5$Hg$^+$), without the need of a chelating agent.

An innovative approach has also been reported by Zhang et al., who fabricated a task-specific hybrid coating comprising the IL 1-butyl-3-vinylimidazolium bis[(trifluoromethyl)sulfonyl]imide ([VBIM][NTf$_2$]) and polyhedral oligomeric silsequioxane (POSS) [30]. The coating was copolymerized on a stainless-steel fiber and applied for the enrichment of polycyclic aromatic hydrocarbons (PAHs) by direct immersion SPME (DI-SPME) from river water and soil leachates. The DI-SPME method consisted on the submersion of the fiber directly into the sample for a well-defined period of time, followed by the thermal desorption of the analytes directly into the GC–MS instrument, allowing a fast, minimally invasive analysis. In this case, the incorporation of the C-F group from POSS and of the imidazolium ring of the IL onto the fiber coating was suggested to generate special "pseudo hydrogen bonds" and π-π stacking interactions with PAHs, which contributed to the extraction of the aromatic targets from the sample matrix. The authors highlighted that the resulting method was simple, environmentally friendly and cost-effective, since it avoided the use of a GC-compatible solvent to dissolve the TSIL after the extraction and, additionally, the photoinitiated synthesis of the fiber coating required only minimal chemicals and energy consumption. DI-SPME has also been applied for the preconcentration of unsaturated fatty acids (oleic, linoleic and linolenic) from rinse water of a dairy farm [37]. In this case, SPME fibres were coated with different Ag(I)-containing polymeric TSILs obtained after the polymerization of the silver di(vinylimidazolium) bis[(trifluoromethyl)sulfonyl]imide (Ag$^+$(VIM)$_2$][NTf$_2$$^-$]) monomer. These were particularly selective towards unsaturated compounds with terminal double bonds due to the formation of Ag(I)-double bond chelates, with sensitivities similar or better than those obtained with commercial polydimethylsiloxane fibres. The separation of the analytes and their quantification was carried out by GC-FID in this case, taking advantage of the high thermal stability of the developed TSILs, even in the presence of Ag(I).

In a similar fashion, hollow fiber-liquid phase microextraction (HF-LPME) involves the immobilization of the extractant solvent into the pores of a hollow permeable fiber, which is then submerged into a liquid or gaseous sample for the extraction of the analyte/s of interest [38]. TSILs have been applied in HF-LPME-based methods, particularly in the solvent bar microextraction (SBME) mode, in which the fiber is set up in the form of a solvent-filled bar that can be added to the sample and stirred to improve the mass transfer. Ag(I) and Cu(II) could be extracted via this approach from sea and hypersaline waters using the TSIL trihexyltetradecylphosphonium 3-hydroxy-2-naphthoate ([P$_{6,6,6,14}$][HNA]), which could withstand the high ionic strength of the

sample medium better than TSILs comprising the same anion but different cations [39]. The authors attributed this behavior to an anion exchange mechanism between the TSIL and diverse chlorocomplexes of the analytes, which favoured their extraction from highly saline media. A similar work has also been reported, albeit using TSILs with ammonium and phosphonium cations and the hexasulfonyl acetate anion. In this case the approach was similar to that of the previous work, and chlorocomplexes of Ag(I), Cu(II), Cd(II), Ni(II) and Zn(II) could be extracted from seawater, hyper-saline lagoon water and water from salt-work ponds [40]. Both of these works were presented as potential tools for trace metal analysis, if combined with a method for the quantification of the extracted species.

Finally, it is worthwhile to highlight the synthesis of a hybrid material composed of a task-specific polymeric IL (TSPIL) and magnetic nanoparticles (MNPs) [41]. Here, the MNPs were included in the polymeric structure of the TSPIL which, in turn, contained dual task-specific sites to preconcentrate Au(III), Pd(II) and Pt(II). These sites involved the bis[(trifluoromethyl)sulfonyl]imidate anion -which yields ILs with a high affinity towards noble metals- and thiol groups in the cation of the TSPIL, which have a great affinity towards noble metals located on the right side of the *D*-block. Additionally, the magnetic nature of the material allowed for a very simple separation of the sorbent using an external magnet after its dispersion, as part of a magnetic SPE (MSPE) method, avoiding time- and energy-consuming stages such as decantation or centrifugation. Tap, lake and sewage waters were analysed directly by the proposed method, along with mine soil samples that were digested with *aqua regia* and HF prior to analysis. In all cases, excellent results were achieved in the recovery experiments and, additionally, three certified reference materials were analysed to further confirm the accuracy of the method.

3.2. Food samples

The primary challenge in food analysis is to eliminate matrix interferences, such as fatty acids, lipids, proteins, sugars, and pigments, which represent the most important difficulties when aiming for the accurate identification and quantification of target analytes. In this context, TSILs have found numerous applications in food and beverage analysis in the last decade for the determination of organic and inorganic analytes. Table 2 presents a summary of the characteristics and analytical figures of merit of the reviewed TSIL-based methods for food and beverage sample treatment.

Several TSIL-based dispersive liquid-liquid microextraction (DLLME) methods have been reported in the literature for trace metals determination in tea samples. DLLME is based on the use of a dispersing agent with a water-immiscible extractant, which are added to an aqueous sample in order to produce a cloudy solution. The dispersant is usually an organic solvent miscible in both the extraction and aqueous phases that favors the dispersion of the former [10]. ILs (including TSILs) are used as alternatives to toxic organic solvents utilized in the classical DLLME technique. For example, TSIL ultrasound-assisted DLLME has been performed with the use of TOMATS as extraction solvent and complexing agent for Cd(II), Co(II) and Pb(II) preconcentration coupled to high performance liquid chromatography (HPLC) with UV–Vis detection [42]. Tea powder samples were analysed by this method after being subjected to microwave-assisted digestion. The properties of TOMATS as extraction solvent and chelating agent have been discussed in the previous section and, according to the authors, the use of this TSIL reduced the consumption of toxic volatile organic compounds, increased the extraction efficiency and allowed to develop an environmentally friendly green separation method. Additionally, TOMATS in an ultrasound-assisted DLLME method has been used for Co(II) preconcentration in tea samples and vitamin supplements prior to ETAAS analysis [43]. In this case, samples were pulverized before microwave-assisted digestion, and the clear digested solutions were diluted prior to analysis. An interesting aspect of this work was the thorough optimization of

Table 2
Summary of the reviewed TSIL-based food sample preparation methods.

TSIL	Analyte	Extraction technique	Detection technique	Sample/s	LOD[a] ($\mu g\ L^{-1}$)	EF[b]	RSD (%)	Reference
TSMPIL	K^+	DLLME	FAES	Oil	0.50	128	3.9	[15]
TOMATS	Cd(II) Co(III) Pb(II)	USA-DLLME	HPLC–UV	Tea powder	2 ng kg^{-1} 9 ng kg^{-1} 13 ng kg^{-1}	200	≤ 12	[42]
TOMATS	Co(II)	USA-DLLME	ETAAS	Tea leaves and vitamin supplements	0.011	24	7	[43]
[8-HQ-C$_2$im]Br	Fe(II), Fe(III)	In situ DLLME	FAAS	Apple, tomato juice and tea beverage	6.90	210	2.2	[44]
[C$_4$mim]HSO$_4$	Triazine herbicides	EA-DLLME	HPLC-UV	Tea beverages	0.08	N.R.	< 8.5	[45]
TOMATS	Cd(II)	DLLME	FAAS	Milk	1.16	45.4	1.8	[46]
[C$_4$mim-SH]Br	Bisphenols	DLLME	HPLC-FLD	Milk, orange and tangerine juices	0.13 – 0.82	N.R.	0.7 – 4.4	[47]
[CHCA]DEA and [C$_2$OHmim]BF$_4$	Cd(II) Ni(II)	TUSA-DMPμE	FAAS	Olive oils	1.300.60	19.319.6	4.45.1	[48]
[A336]TS-functionalized Fe$_3$O$_4$ MNPs	Cd(II)	MSPE	FAAS	Apple, banana and orange	0.50	50.0	< 3.1	[49]
[8-HQ-C$_2$Clmim]Cl	Cd(II)	In situ DLLME	FAAS	Lettuce, potato and rice	0.55	500	1.5	[50]
[TH–C$_1$C$_2$Im]Br and [5-ASA-C$_1$C$_2$Im]Br	Fe(II) Fe(III)	In situ DLLME	FAAS	Corn, lentils and red beans	7.6	207	2.0	[51]
[PDC–C$_1$C$_2$Im]Br	As(III), As(V)	In situ DLLME	ETAAS	Rice	8.10.01	210200	2.53.2	[52]

[a] Limit of detection.

[b] Enhancement factor, [c]Relative standard deviation, **N.R.:** Not reported, **TUSA-DMPμE:** Thermal ultrasound-assisted dispersive multiphasic microextraction, **EA-DLLME:** Effervescence-assisted dispersive liquid-liquid microextraction.

the ETAAS operation conditions, which allowed for the direct injection of the TSIL phase for the quantification of the analyte, avoiding a back-extraction step which is common practice in this type of methods and usually involves an organic solvent.

In situ DLLME is based on the use of a water-soluble extraction agent that is added to the aqueous sample and then subjected to a metathesis reaction with an ion exchange reagent, which reduces its solubility. In the case of the developments discussed in this review, hydrophilic TSILs which become hydrophobic were generated *in situ* and separated by centrifugation, eliminating the need for an organic dispersant. This approach was followed using 1-ethyl-3-methylimidazolium bromide functionalized with 8-hydroxyquinoline ([8-HQ-C$_2$*mim*][Br]) as a TSIL, for the speciation analysis of Fe using flame atomic absorption spectrometry (FAAS) detection and KPF$_6$ as ion exchanger [44]. Previous sample treatment consisted on the filtration and centrifugation of black tea samples and the subsequent additional filtration of the supernatant. In this case, only Fe(III) was extracted into the IL phase -thanks to the selectivity provided by the 8-hydroxiquinoline (8-HQ) molecule present in the structure- and the concentration of Fe(II) was determined by difference after the analysis of a second, pre-oxidized aliquot. The authors noted that the microextraction procedure was performed without the need of either an additional chelating agent or a back-extraction step, which significantly improved the analysis time and reduced the consumption of reagents.

TSILs have also been applied for preconcentration and extraction of organic analytes in tea beverage samples. The acidic TSIL 1-butyl-3-methylimidazolium hydrogen sulfate ([C$_4$mim][HSO$_4$]) was applied for the separation and microextraction of triazine herbicides by effervescence-assisted DLLME coupled to HPLC analysis [45]. The acidic TSIL was used both as extraction solvent and as activator for the effervescent method, with the cation acting as extractant and the anion as an acid to react with carbonate and produce the CO$_2$ bubbles that was responsible for the mixing of the phases. The authors highlighted that the microextraction with the proposed TSIL did not require an additional mechanical agitation source, making it a method with a minimal energy consumption.

Similarly, TSIL-DLLME methods have been applied for the preconcentration and extraction of organic and inorganic analytes in milk samples. For example, TOMATS has been used for the extraction and preconcentration of trace Cd(II) with FAAS determination [46]. The sample preparation strategy in this case consisted of a digestion with concentrated HNO$_3$, after which TOMATS was utilized as complexing agent and hydrophobic solvent simultaneously. This analytical methodology presented several advantages, such as high speed, high recovery, operational simplicity, low cost, minimum extracting solvent consumption, high enrichment factor, and no need for a chelating agent due to the use of the TSIL. Secondly, the IL 1-hexyl-3-methylimidazolium hexafluorophosphate ([C$_6$mim][PF$_6$]) as extraction phase along with the TSIL 1-(4-thiolbutyl)−3-methylimidazolium bromide ([C$_4$mim-SH][Br]) as dispersing agent were applied for the preconcentration of bisphenols [47]. The milk samples were treated with acetic acid and shaken using a vortex stirrer, followed by centrifugation and filtration with a PTFE membrane filter prior to the extraction. The authors commented that the used TSIL allowed to regulate the pH, keeping bisphenols in neutral form, facilitating their extraction via hydrogen bonds with the IL. In this way, the TSIL avoided an extra pH adjustment step and produced a clear stratification phenomenon, leading to a more efficient separation.

Additionally, reports of two TSIL-DLLME methods applied to oil samples for the determination of trace metals can be found in the recent literature. One of them was based on the application of a new task-specific magnetic polymeric ionic liquid (TSMPIL) as complexing and extracting solvent for the selective preconcentration and determination of K^+ by flame emission atomic spectrometry [15]. The used TSMPIL exhibited a negligible water solubility, chelating properties and a strong response to an external magnetic field. Therefore, it provided the possibility of a chelating agent- and centrifugation-free extraction, and offered an excellent preconcentration factor in a relatively short extraction time. In the other work, two hydrophilic TSILs, namely α-cyano-4-hydroxycinnamic acid diethylamine ([CHCA][DEA]) and 1-2-hydroxyethyl-3-methylimidazolium tetrafluoroborate ([C$_2$OHmim][BF$_4$]), were used as complexing agent and

extracting solvent for the separation and preconcentration of Cd(II) and Ni(II) by thermal ultrasound-assisted dispersive multiphasic microextraction [48]. In this study, ultrasound stirring and dispersive solvents were used to increase the TSILs extraction ability. The authors highlighted that extraction with [CHCA][DEA] was more efficient than with [C_2OHmim][BF_4] by the proposed method, but did not clarify how the chemical structure of the TSILs influenced this parameter.

Moreover, TSILs have been applied for the simultaneous separation and preconcentration of Cd(II) from fruit and vegetables samples. For example, Fe_3O_4 MNPs modified with the TSIL Aliquat®336 thiosalicylate ([A336][TS]) were applied for trace Cd(II) microextraction in apple, orange and banana, which were previously dried, grounded and digested with HNO_3 and H_2O_2 [49]. ETAAS was used for detection in this case. The authors commented that, as S-containing functional groups play an important role in binding to certain metal ions, [A336][TS] was used as potential Cd(II) extraction agent based on the carboxylic and thiol functional groups present in its structure. Furthermore, a magnetic separation step greatly reduced the analysis time which, added to the high affinity of the TSIL towards the target analyte, provided an efficient and simple MSPE method. On the other hand, the hydrophilic TSIL 1-chloroethyl-3-methylimidazolium chloride functionalized with 8-HQ ([8-HQ-C_2Clmim][Cl]) was used in a DLLME method for Cd(II) preconcentration in digested lettuce and potato samples, followed by FAAS detection [50]. The introduction of 8-HQ in the IL cation allowed an efficient chelation and extraction of Cd(II). It should be noted that the association of this TSIL with KPF_6 in an *in situ* metathesis reaction generated a hydrophobic TSIL, which favoured its separation as extractant phase. Therefore, the developed method was simple, easy to use, and did not require the use of organic solvents, heat, ultrasound or additional chemical reagents.

Finally, TSIL-DLLME methods have been developed for elemental speciation analysis in cereal and legume samples. For example, an *in situ* DLLME method based on two TSILs derived from N-methyl-N-ethylimidazolium bromide functionalized with 2,2′-thiodiacetic acid (TH) and with 5-amino salicylic acid (5-ASA) was employed for the sequential extraction of Fe(II) and Fe(III), prior to determination by FAAS [51]. Red beans, lentils and corn were analysed, after being crushed, cooked in deionized water, dried and weighed. In this case, TH was capable of forming a stable complex with Fe(III) in the pH range between 4 and 5, but it could not form a stable complex with Fe(II). On the other hand, 5-ASA chelated not only Fe(II), but also Fe(III) in these conditions. Therefore, these TSILs were utilized as extractant and as complexing agents to simultaneously chelate and extract Fe(III) and Fe(II). The authors highlighted that this allowed for the sequential extraction of these Fe species without the need to convert one into the other. Therefore, a single aliquot was used for the extraction and determination of the two species. In another procedure, an ammonium pyrrolidine dithiocarbamate (APDC)-functionalized TSIL was synthesized and used for the speciation analysis of inorganic As in rice samples by *in situ* DLLME, prior to determination by ETAAS [52]. The TSIL N-methyl-N-bromoethane imidazolium bromide functionalized with APDC [PDC–C_1C_2Im][Br] acted as complexing agent and extraction solvent of As(III), due to APDC having a higher selectivity towards As(III) than As(V) at pH values between 2 and 4. The APDC-functionalized TSIL was synthesized by the direct reaction between N-methyl-N-bromoethane imidazolium bromide and APDC in basic media and its transformation into a hydrophobic TSIL was achieved with KPF_6 as an anion-exchange reagent. In this case, a second aliquot in which As(V) was reduced to As(III) for total As determination was necessary. Interestingly, the authors referenced the difficulties derived from the sticking of the hydrophobic TSIL on the walls of the centrifuge tubes and the need of a surfactant to fully retrieve it prior to the instrumental quantification, an experimental fact that is scarcely studied in a systematic way in this type of works.

3.3. Biological samples

Bioanalysis has increasingly focused on the development of methodologies with high reliability, sensitivity, speed of analysis and sample throughput, for frequent monitoring of drugs, metabolites or biomarkers [53, 54]. A summary of TSILs applications for biological samples treatment can be found in Table 3.

Urine is one of the most widely used matrices for bioanalysis, since it is easily available. However, due to the high levels of dissolved inorganic salts, the dietary-dependent concentrations of its many compounds and the inter-individual variability of its biochemical parameters, its analysis becomes difficult and complex in terms of sensitivity and selectivity [55]. In whole blood, additionally, the concentration of analytes is usually very low; therefore, minimal contamination at any stage of sample collection, storage, handling or analysis may affect the accuracy of the method. In addition, matrix complexity, biochemical reactions, changes in pH, and the presence of anticoagulants can influence the integrity of the analytes, especially those with high lability [56].

In this sense, TSILs have been applied for the preconcentration and extraction of several inorganic compounds in biological samples, while applications for organic analytes are scarce [25]. For example, a method based on the use of 1-butyl-3-methylimidazolium salicylate ([C_4mim][Sal]) for the selective extraction of Cu(II) in a 24-h urine sample using an aqueous biphasic system (ABS), followed by its detection by differential pulse anodic stripping voltammetry, has been developed [57]. The authors highlighted that one of the most important advantages of ABS (where water-soluble solutes separate into two coexisting phases above a given concentration), was the possibility to perform the extraction in very alkaline solutions, thus achieving complete ligand deprotonation while avoiding metal hydroxide formation. In this work, the TSIL was designed to combine the capacity of its anion to act as a specific complexing agent for Cu(II), preventing its hydrolysis in strongly alkaline media, and the ability of its cation to extract the Cu(II)-salicylate complex in the presence of Zn(II), Cd(II), and Pb(II). It is important to highlight that no filtration step or any further treatment was applied before the extraction using the TSIL. In another work, TOMATS was applied for preconcentration and extraction of Cd(II) in serum and blood samples previously subjected to a microwave-assisted acid digestion using a mixture of concentrated HNO_3 and H_2O_2 (2:1 v/v) [58]. TOMATS was also applied for the complexation and extraction of Cd(II) in urine, blood and serum samples and its subsequent determination by ETAAS [59]. In this work, the chelating effect of the TSIL was compared to that of other conventional ILs such as [C_6mim][PF_6], [C_8mim][PF_6], [C_4mim][PF_4] and [C_8mim][PF_6] without complexing agents. According to the results, TOMATS was more efficient as a chelating reagent due to the interaction between its thiol group and the target analyte.

Moreover, a method based on the use of the TSIL trioctylmethyl ammonium salicylate for the separation and preconcentration of hemin from serum samples followed by differential pulse voltammetry has been reported [60]. The authors highlighted that this TSIL was applied both as extraction solvent, due to its low solubility in water, and as the electrode modifier due to its high conductivity and wide electrochemical window, both typical characteristics of ILs.

Furthermore, other interesting methodologies have been reported with the use of TSILs for the speciation analysis of inorganic analytes in biological samples. For instance, a method for Cr speciation analysis in human blood samples was developed using the TSIL 1-(3-aminopropyl)-3-methylimidazolium hexafluorophosphate [APmim][PF_6] by DLLME, with ETAAS determination [61]. The results showed that the TSIL acted as an extraction solvent as well as a complexing agent, since the propylamino group in its structure had a high affinity towards CrO_4^- and $Cr_2O_7^{2-}$. In this work, Cr(III) was oxidized to Cr(VI) using 100 μL of a H_2O_2 solution and its concentration was calculated by difference between total Cr and Cr(VI). In another work, TSILs obtained from the IL 1-bromoethyl-3-methylimidazolium bromide functional-

Table 3

Summary of the reviewed TSIL-based biological sample preparation methods.

TSIL	Analyte	Extraction technique	Detection technique	Sample/s	LOD[a] (μg L^{-1})	EF[b]	RSD (%)	Reference
[C$_4$mim][Salt]	Cu(II)	ABS	DPASV	Urine	0.008	54	7.8	[57]
TOMATS	Cd(II)	DLLME	ETAAS	Serum and blood	0.05	72	5	[58]
TOMATS	Cd(II)	DLLME	ETAAS	Urine, serum and blood	0.005	10.4	2.3	[59]
TOMAS	Hemin	DLLME	DPV	Serum	3.16×10^{-3} μmol L^{-1}	183.3	6.1	[60]
[APmim][PF$_6$]	Cr(III) Cr(VI)	DLLME	ETAAS	Blood	0.005	52	3.8	[61]
[8-HQ-C$_2$C$_1$Im][Br] and [PDC–C$_2$C$_1$Im][Br]	Cr(III) Cr(VI)	*In situ* TSIL-DLLME	FAAS	Urine	5.711.3	N.R.	1.12.0	[62]
TOMAS	As(III) As(V)	DLLME	HG-AAS	Blood	0.022	9.8	3.2	[63]
PIL fiber	DNA	SPME	RT-qPCR	Artificial sputum	N.R.	N.R.	3.1	[64]
PIL fiber	DNA	SPME	qPCR amplification	Crude bacterial cell lysate	N.R.	N.R.	2.7	[65]
11 TSILs	Benzodiazepines	DLLME	LC-MS/MS	Blood	0.003 – 5	N.R.	N.R.	[66]

[a] Limit of detection.

[b] Enhancement factor, [c]Relative standard deviation, N.R.: Not reported, ABS: Aqueous biphasic system, DPASV: differential pulse anodic stripping voltamme-try, TOMAS: trioctylmethyl ammonium salicylate, DPV: Differential pulse voltammetry, HG-AAS: Hydride generation atomic absorption spectrometry, RT-qPCR: Real time quantitative polymerase chain reaction, qPCR: Quantitative polymerase chain reaction.

ized with 8-hydroxyquinoline ([8-HQ-C$_2$C$_1$Im][Br]) and with APDC ([PDC–C$_2$C$_1$Im][Br]) were used for the sequential extraction of Cr(III) and Cr(VI) species in urine samples, followed by FAAS determination [62]. This method avoided the consumption of organic solvents or ox-idizing/reducing agents, because the TSILs acted both as complexing agents and as extraction solvents. The selectivity of the methodology was higher in comparison to that obtained by DLLME using 8-HQ or APDC as chelating reagents and 1-hexyl-3-methyl imidazolium bromide ([C$_6$mim][Br]) as the IL. According to the authors, this could be ex-plained due to the selective complexation of the target analytes by the TSIL in the presence of other transition metals. This is based on the fact that Cr(III) is able to form complexes with oxygen and/or nitrogen donor ligands, such as 8-HQ while Cr(VI) tends to form complexes with sulfur and/or nitrogen containing ligands, such as APDC.

In addition, the TSIL trioctylmethyl ammonium 2-mercaptobenzoate was used for the speciation analysis of inorganic As species by DLLME and hydride generation atomic absorption spectrometry in blood sam-ples [63]. In this work, the thiol group in the TSIL structure provided a high affinity and selectivity towards As(III) by specific chelation, while the As(V) species concentration was calculated by difference between total As and As(III) concentrations, after reducing As(V) to As(III) with KI (1 mol L^{-1}) and ascorbic acid.

Regarding biological analytes, two methods have been reported for DNA extraction by SPME. One of them was based on the use of an IL with imidazolium as cation, which specifically interacted with the anionic phosphate groups of DNA from mycobacteria in artificial spu-tum samples [64]. In the other work, the authors indicated that the incorporation of polar functional groups into the cationic structure of the IL, such as carboxylic acid groups, enhanced the DNA extrac-tion from a crude bacterial cell lysate [65]. In both cases, electro-static interactions and exchangeable anions played an important role in the extraction of DNA. In another work, eleven TSILs were evalu-ated as solvents for the extraction of benzodiazepines from whole blood by DLLME, followed by liquid chromatography – tandem mass spec-trometry (LC-MS/MS) [66]. According to the results, TSILs with imi-dazolium and pyridinium as aromatic planar cations were more effi-cient in comparison with ammonium or pyrrolidinium ones. Further-more, short alkyl chains sterically hindered π-π stacking interactions, negatively affecting the extraction, while TSILs with low viscosities fa-cilitated mass transference and electrospray ionization processes during LC-MS/MS.

4. Conclusions and future trends

TSILs have found diverse applications in chemistry in recent years, with a very interesting role in the field of sample treatment. As it has been discussed throughout this work, ILs designed for a specific analyte or group of analytes have been synthesized and applied for the treatment of diverse samples, that range from environmental waters to biological samples, including also several foods and beverages. The common factor throughout these reports has been the selectivity provided by the TSILs, which demonstrates their great usefulness for the microextraction of analytes in the context of high complexity matrices. In this sense, ap-plications in liquid- and solid-phase-based methods have been reported, involving their direct application of TSILs or their use as part of func-tional materials. Regarding the former, DLLME methods have been by far the most reported, representing over 40% of the total published uses of as-obtained TSILs for sample preparation. As for materials combining TSILs with solids, SPME has been preferred over SPE, MSPE and DSPE, whereas nanomaterials have been the most common supports, given the advantages they represent in terms of miniaturization and added func-tionalities, such as those provided by magnetic nanomaterials.

The possibility of miniaturization is, in fact, one of the key bene-ficial aspects of the use of TSILs for sample preparation, asides from their selectivity. This becomes doubly important when taking into ac-count the fact that TSILs (and ILs in general) stand further and further from their green solvent status as studies on their toxicity become more common and extended. In this regard, room for improvement can be found in terms of their stability and water solubility (both aspects di-rectly related to the possibility of recycling them) and on their origin. In terms of the latter, important advances have been reported in the last years in the field of ILs with ions from natural sources (natural ILs) and in other alternatives such as natural deep eutectic solvents or biomass-based sorbents, which should be considered as standing points for the development of greener, more sustainable task-specific alternatives.

In addition to this, and despite the evident advantages related to their use, it is important to recognize that total specificity towards sin-gle analytes, as has been achieved with extractants such as molecularly or atomic imprinted polymers, has still not been widely attained with TSILs. This is evidenced in the reviewed reports by the still necessary use of selective detectors such as atomic spectrometries or of secondary separation stages, such as GC, to achieve specific quantifications. This represents not a drawback, but a challenge for future developments,

making TSILs with an enhanced selectivity a very interesting goal to work towards.

Acknowledgments

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