High-throughput microscale extraction using ionic liquids and derivatives: A Review

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List of abbreviations: **γ-MAPS:** 3-(trimethoxysilyl) propylmethacrylate, **μ-SPE:** micro-solid phase extraction, **AAS:** atomic absorption spectroscopy, **ABS:** aqueous biphasic system, **APDC:** ammonium pyrrolidine dithiocarbamate, **[(AC$_3$)MIM$^+$]:** 1-aminopropyl-3-methylimidazolium, **[AlMIM$^+$]:** 1-allyl-3-methylimidazolium, **[Br$^-$]:** bromide, **[BEHPA$^-$]:** bis(2-ethylhexyl)phosphinate, **[BF$_4^-$]:** tetrafluoroborate, **[C$_4$MIM$^+$]:** 1-butyl-3-methylimidazolium, **[C$_6$MIM$^+$]:** 1-hexyl-3-methylimidazolium, **[C$_8$MIM$^+$]:** 1-octyl-3-methylimidazolium, **[C$_8$Py$^+$]:** 1-octyl-pyridinium, **[C$_n$MIM$^+$]:** 1-alkyl-3-methylimidazolium, **CD:** cyclodextrins, **[Cl$^-$]:** chloride, **CNTs:** carbon nanotubes, **CV:** cold vapor, **DAD:** diode array detection, **DDTC:** sodium diethyldithiocarbamate, **DI:** direct immersion, **DLLME:** dispersive liquid-liquid microextraction, **DVB:** divinylbenzene, **ETAAS:** electrothermal atomic absorption spectroscopy, **FAAS:** flame atomic absorption spectroscopy, **[FeCl$_4^-$]:** tetrachloroferrate, **[FeCl$_3$Br$^-$]:** bromotrichloroferrate(III), **FI:** flow injection, **FIA:** flow injection analysis, **FID:** flame ionization detection, **GFAAS:** graphite furnace atomic absorption spectroscopy, **HD:** headspace, **HF-LPME:** hollow fiber-liquid phase microextraction, **[I$^-$]:** iodate, **ICP:**

inductively coupled plasma, **IL:** ionic liquid, **LIS:** lab-on-syringe, **LOV:** lab-on-valve, **LPME:** liquid-phase microextraction, **MIBK:** methylisobutyl ketone, **MIL:** magnetic ionic liquid, **MNP:** magnetic nanoparticle, **[MnCl$_4$$^{2-}$]:** tetrachloromanganate(II), **[N$_{1,8,8,8}$$^+$]:** methyltrioctylammonium, **[N$_{Bn,8,8,8}$$^+$]:** benzyltrioctylammonium, **NP:** nanoparticle, **[NTf$_2$$^-$]:** bis[(trifluoromethyl)sulfonyl]imide, **OES:** optical emission spectrometry, **PADAP:** 2-(5-bromo-2-pyridylazo)-5-diethylaminophenol 5-diethylaminophenol, **PAH:** polycyclic aromatic hydrocarbons, **PAR:** 4-(2-pyridylazo)-resorcinol, **PEEK:** polyether ether ketone, **[P$_{6,6,6,14}$$^+$]:** tetrahexyl(tetradecyl)phosphonium, **PIL:** polymeric ionic liquid, **[PF$_6$$^-$]:** hexafluorophosphate, **SDME:** single-drop microextraction, **SIA:** sequential injection analysis, **SPME:** solid-phase microextraction, **TSIL:** task specific ionic liquid, **UHPLC:** ultra high-performance liquid chromatography, **[VC$_2$IM$^+$]:** 1-ethyl-3-vinylimidazolium, **[VC$_4$IM$^+$]:** 1-butyl-3-vinylimidazolium, **[VC$_6$IM$^+$]:** 1-hexyl-3-vinylimidazolium, **[VC$_8$IM$^+$]:** 1-octyl-3-vinylimidazolium, **[VC$_{12}$IM$^+$]:** 1-dodecyl-3-vinylimidazolium, **[VC$_{16}$IM$^+$]:** 1-hexadecyl-3-vinylimidazolium, **[(VIM)$_2$C$_6$$^{2+}$]:** 1,12-di(vinylimidazolium)hexane**,** **[(VIM)$_2$C$_{10}$$^{2+}$]:** 1,12-di(vinylimidazolium)decane, **[VIM$^+$C$_3$SO$_3$$^-$]:** vinyl-3-(propanesulfonate)imidazolium, **[VMIM$^+$]:** 1-methyl-3-vinylimidazolium, and **ZIL:** zwitterionic ionic liquid.

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49 **Abstract**

50 Ionic liquids ~~(ILs)~~ and derivatives – mainly polymeric ionic liquids ~~ILs (PILs)~~ and

51 magnetic ionic liquids ~~ILs (MILs)~~ – have been extensively used in microscale extraction

52 over the last few years. Current trends in analytical sample preparation gear toward

53 linking microextraction approaches with high-throughput sample processing to comply

54 with green analytical chemistry requirements. A variety of high sample throughput

55 strategies that are coupled to both ionic liquid~~IL~~-based solid phase microextraction and

56 ionic liquid~~IL~~-based liquid-phase microextraction are herein reported. The review is

57 focused on microscale extraction methods that use (i) custom-made and dedicated

58 extraction devices, (ii) parallel extraction, (iii) magnetic-based separation, and (iv)

59 miniaturized systems employing semi-automatic or fully automatic flow injection

60 methods, related micro/millifluidic devices, and robotic equipment.

61

1. Introduction

Laboratory analyses often require multiple steps of extraction, separation, purification or preconcentration to ensure reliable determination of the analytes in the sample. Sample preparation protocols enable: (i) adequate compatibility of the tested sample with the selected analytical technique, (ii) interference elimination when complex samples are analyzed, and/or (iii) adequate sensitivity for determination of analytes at low concentration levels, among others. However, sample preparation methods are often time-consuming and, in most cases, they are the limiting step of the overall analytical procedure [1–3].

Microscale extraction approaches are appropriate non-exhaustive sample preparation tools for the miniaturization of the analytical procedure while reducing the analysis time and ensuring acceptable preconcentration factors [1]. These methods use low amount of solvent or sorbent material as extraction phase for the isolation of the analytes in the sample [1]. Two main microextraction modes can be distinguished based on the nature of the extraction material, solid or liquid: solid phase-based microextraction [4,5] and liquid-phase microextraction (LPME) [6], respectively.

Ionic liquids (ILs) are a group of non-molecular solvents with melting points below 100 ºC and completely composed by ions, in general, organic cations containing heteroatoms and either inorganic or organic anions [7,8]. ILs are characterized by a low or negligible vapor pressure at room temperature, high thermal stability and conductivity, and variable and modulable viscosity and water solubility depending on the cation/anion combinations within the IL structure [7,8]. These physicochemical properties make ILs outstanding solvents for a wide variety of (bio)analytical applications [9]. Furthermore, the incorporation of functional groups of different polarity onto the IL structure might

86 promote different interactions with solutes, even permitting high solvation capabilities

87 for both polar and non-polar compounds.

88 Several IL derivatives have also been reported. Among all, polymeric ionic liquids (PILs)

89 and magnetic ionic liquids (MILs) are of especial interest. PILs are polymers generated

90 by the polymerization of an IL monomer [10]. Imidazolium-based PILs can also be

91 generated using the Radziszewski reaction, which involves the reaction between a

92 diamine, glyoxal and formaldehyde in acidic media [11]. The majority of PILs employed

93 in analytical applications are polycations based on IL monomers containing vinyl- or

94 allyl- groups within their cationic-counterpart [10]. MILs possess a paramagnetic

95 component in the IL structure [12,13]. The majority of MILs are composed by organic

96 cations and metal complexes as paramagnetic anions [12,13]. Both PILs and MILs present

97 some of the typical physicochemical properties of ILs, although other features are

98 enhanced or improved due to their polymeric or paramagnetic nature, respectively

99 [10,12].

100 ILs and PILs have been widely used as extraction and/or auxiliary solvents/sorbents in

101 several microscale extraction approaches [7,10,14], whereas the use of MILs in LPME

102 has attracted a great deal of attention more recently [7,12]. Despite the high number of

103 studies, most applications reported in the IL-field use *off line* or batchwise protocols that

104 require a large number of steps and the intensive intervention of the analyst, which might

105 have a detrimental effect on the method's intermediate precision.

106 In accordance with the current trends in analytical chemistry and green analytical

107 methodologies [15], novel strategies are gradually being incorporated in IL-based

108 microscale extraction approaches for additional increase the sample throughput while

109 ensuring the performance of the analytical process in an unsupervised mode. These

110 strategies utilize different tools, such as tailor-made extraction devices and parallel

extraction [16,17] or magnetic separation [18]. Other alternatives employ flow injection

(FI) approaches [19], robotic equipment [20] or microfluidics [21] for the development

of semi-automatic or even fully automatic/automated methodologies [22]. The specific

goals pursued with all the above approaches include (i) additional miniaturization of the

microscale extraction protocols, (ii) additional minimization of the sample and solvent

requirements, (iii) reduction of the analysis time, (iv) *on line* hyphenation of the IL-

microextraction protocol with the subsequent selected analytical technique, and (v)

additional minimization of the analyst intervention. However, it is important to note that

the implementation of FI and microfluidics in IL-based microextraction methods might

be challenging due to some IL characteristics: e.g., high viscosity or tendency to stick to

glass and plastic tubing [7,23]. To this end, research in this area should focus on designing

IL materials more compatible with automatic methods.

The objective of this review article is to critically overview recently developed analytical

methods in which ILs, PILs and MILs have been employed for high-throughput

microscale extraction. Attention will be paid to the system configuration that will factor

into the speed of the method and sample throughput, with especial focus on FI and related

approaches. This review also is aimed at encouraging analytical chemists to incorporate

high-throughput analytical tools to IL-based microextraction methods.

2. Ionic liquids and derivatives in high-throughput solid phase-based microextraction

2.1. Micro-solid-phase extraction

Solid-phase extraction (SPE) and its miniaturized version, micro-SPE (μ-SPE) are

attractive sample preparation approaches widely used nowadays as extraction,

preconcentration and clean-up steps in many analytical methods [3], with μ-SPE having "green" credentials compared to the classical SPE because it reduces the requirements of sample and sorbent materials.

ILs and PILs can be anchored to typical micrometer-sized SPE materials (e.g., silica beads, octadecyl-functionalized silica or primary-secondary amines) and μ-SPE (nano)materials (e.g., metal or magnetic nanoparticles, carbonaceous materials or molecularly imprinted polymers) [1,24]. The general procedure for IL-μ-SPE involves several consecutive steps in the static mode, including sorbent conditioning, sample loading, sorbent washing, and elution. On the contrary, when the method is performed in the dispersive mode, only sorbent dispersion in the sample, phase separation, and sometimes desorption are required. Several strategies have been recently proposed as alternatives for simplifying and automating the IL-μ-SPE procedure, making the analytical methods faster and simpler. Figure 1 summarizes the main configurational modifications proposed by several authors to increase sample throughput in IL-μ-SPE.

The simpler approaches imply packing the IL-based sorbent material in a pipette tip for dynamic μ-SPE [25–27]. Successive drawing/discharging cycles of the sample and elution solvent were easily performed using a mere electronic pipette for the extraction and the elution of the analytes, respectively. Dynamic μ-SPE, also termed pipette-tip μ-SPE, has been used with activated carbon cloth modified with the 1-butyl-3-methylimidazolium hexafluorophosphate ($[C_4MIM^+][PF_6^-]$) IL [25,26] or a composite based on Fe_3O_4 magnetic nanoparticles (MNPs)@graphene oxide and the 1-(3-aminopropyl)-3-methylimidazolium bromide ($[(AC_3)MIM^+][Br^-]$) IL [27]. In the latter, the MNP composite provided a 3D structure with ultra-high specific surface area, increasing the number of possible interactions between sorbent and analytes. At the same

159   time, the presence of graphene oxide and the IL in the material promoted π-π interactions

160   between the sorbent and the analytes (polycyclic aromatic hydrocarbons, PAHs), thereby

161   increasing the extraction efficiency [27]. The analytical applications developed using this

162   high-throughput mode also served for the determination of metals ions (i.e., Cd(II) [25],

163   Al(III) [25], and Cu(II) [26]). A chelating agent was added prior extraction, and the metal-

164   complex was subsequently extracted by the IL-laden sorbent.

165   In other applications, ILs and PILs have been combined with magnetic-based sorbent

166   materials such as α-Fe_3O_4 MNPs [28,29] or magnetic modified chitosan-graphene oxide

167   composite [30]. The objective of these studies was to perform magnetic separation of the

168   sorbent material after dispersive μ-SPE extraction/desorption. The analytical procedure

169   when using a magnetic separation is simpler and faster than traditional dispersive μ-SPE

170   because it does not require filtration and/or centrifugation, and neither does any highly

171   expensive instrumentation. Thus, it only utilizes a high-magnetic field neodymium

172   magnet that is placed at one side of the extraction container, thus ensuring the separation

173   of the sorbent from the remaining components of the sample/desorption solvent in few

174   seconds [31].

175   Significant increase in the sample throughput of IL-SPE is achieved when using *on line*

176   FI systems [32]. Representative applications using *on line* IL-μ-SPE protocols are

177   summarized in Table 1 [32–41]. For example, in an approach used for the extraction of a

178   group of dyes in a remediation protocol, a nanocomposite composed by β-cyclodextrin-

179   functionalized carbon nanotubes (CNTs) containing also TiO_2 nanoparticles (NPs), and

180   ultimately   modified   with   the   1-octyl-3-methylimidazolium   hexaflurophosphate

181   ([C_8MIM^+][PF_6^-]) IL, was employed. The nanocomposite was packed in a syringe to

182   perform the miniaturized method. The removal of dyes was achieved by flowing the

183   sample through the packed syringe with the help of a peristaltic pump. The remaining

184 amount of dye in the aqueous solution after the extraction was determined using

185 spectrophotometry, whereas the sorbent material could be regenerated by rinsing with

186 acetonitrile. The overall extraction time required less than 8 min per sample. The

187 combination of β-cyclodextrins and the IL in the extraction material increased the

188 capacity of the nanocomposite, and offered visible-light-induced photoactivity for further

189 degradation of the retained dyes [32].

190 Magnetic IL-SPE has also been accomplished using FI approaches [33,34]. In comparison

191 with the indirect SPE method previously reported in [32], *on line* elution and transfer of

192 the eluate to the subsequent detection technique was accomplished for analytical

193 quantification purposes [33,34]. For example, Hosseinzadegan *et al.* reported silica-

194 coated Co(II) MNPs covered with an outer layer of the trihexyltetradecylphosphonium

195 bis(2-ethylhexyl)hydrogenphosphate ($[P_{6,6,6,14}^+][BEHPA^-]$) task-specific IL for the

196 determination of Pb(II) in tap water [33]. Although the sorbent dispersion was carried out

197 *off line*, direct injection of the magnetic particles after extraction was performed using FI-

198 inductively coupled plasma optical emission spectrometry (FI-ICP-OES). An

199 electromagnet was located before the ICP-OES to trap the sorbent before its arrival to the

200 detection system. When the electromagnet was switched off, the trapped particles

201 containing the extracted Pb(II)-complex were released and brought to the detector, thus

202 obtaining an increase in the sensitivity with respect to the direct aspiration of the sorbent

203 suspension [33]. In a different study, Fe_3O_4@PIL core-shell microspheres were employed

204 in a totally automated magnetic SPE method [34]. The developed FI-system is

205 schematized in Figure 2(A) [34]. A vortex mixer with a microcolumn to which a

206 mechanically-actuated permanent magnet was attached served for the *on line* extraction

207 step, magnetic separation, elution, retrieval of the magnetic particles and even the *on line*

208 analysis of the eluate using spectrophotometry. All the procedure was carried out in less

209   than 10 min per sample and without the analyst intervention for the determination of food

210   colorants in liquid and solid food samples [34].

211

212   **2.2. Solid-phase microextraction**

213   Solid-phase microextraction (SPME) has been widely employed in a variety of research

214   fields due to its simplicity and high-preconcentration capability, being particularly

215   successful in analytical sample preparation [42]. In the most conventional configuration,

216   SPME employs coated fibers as sorbent material attached to a solid support.

217   Several IL- and PIL-based sorbent coatings have been specifically designed for SPME

218   using the fiber-type configuration [7,10]. In one study, four different PIL-based sorbent

219   coatings were employed in a totally automated SPME approach [43]. All steps performed

220   during extraction (in the direct immersion mode, DI-SPME) and thermal desorption were

221   carried out with the help of a CombiPAL autosampler (CTC Analytics) directly mounted

222   on the top of the separation and detection system (gas chromatography with flame

223   ionization detection, GC-FID). The CombiPAL autosampler used a XYZ robot arm that

224   was equipped with a holder to support the SPME fiber and a mixer for the incubation and

225   agitation of the sample during the extraction [44]. The sample throughput of the method

226   was significantly improved due to the high thermal stability of the developed PILs that

227   allowed thermal desorption of the analytes at 250 ºC in only 2 min without significant

228   *carry over*. This characteristic of the methodology allowed for a more efficient and

229   expedite methodology because extraction was performed using the software-controlled

230   automated system while the previous sample being analyzed in the GC-FID system [43].

231   ILs and PILs have also been adopted to the *in tube* SPME mode [7,10]. In particular, a

232   relatively large number of these applications performed the extraction/elution procedure

233   *on line* using a switchable 6 port injection valve directly connected to the analytical

234   detection technique [35–40], as summarized in Table 1 [35–41]. In these cases, the sample

235   loop of the valve was substituted for the *in tube* capillary containing the IL- or PIL-sorbent

236   material as shown in Figure 2(B) [38]. With this configuration, all the steps of the

237   extraction procedure, including liquid desorption with organic solvents and eluate

238   transport to the subsequent analytical detection technique, were undertaken automatically

239   with the aid of the FI-system. This type of configuration facilitated the combination of

240   the *in tube* SPME method with HPLC [35–39]. In several of these applications, the HPLC

241   mobile phase also served for the elution of the analytes from the capillary, and thus

242   resulting in a simpler system configuration [35,37–39]. Cold vapor atomic absorption

243   spectroscopy (CV-AAS) was also used with this configuration for the determination of

244   organic mercury [40]. Both open tubular [35] or fully packed capillaries [36–38,40] have

245   been employed in *in tube* FI-systems. Most of these papers reported the use of PILs

246   instead of ILs because of the higher viscosity of the former that prevented sorbent

247   deterioration when sample passed through the capillary, thus obtaining more robust

248   SPME devices with longer lifetime. For example, Souza *et al.* developed crosslinked PILs

249   generated by thermal polymerization using the 1-hexyl-3-vinylimidazolium chloride

250   ([VC$_6$IM$^+$][Cl$^-$]) or 1-hexadecyl-3-vinylimidazolium bromide ([VC$_{16}$IM$^+$][Br$^-$]) IL

251   monomers, and the 1,12-di(vinylimidazolum)decane bromide ([(VIM)$_2$C$_{10}$$^{2+}$]2[Br$^-$])

252   dicationic IL crosslinker [35]. Few *in tube* SPME methods used ILs [39,40]. Ferreira *et*

253   *al.* used a zwitterionic IL (1-vinyl-3-(propanesulfonate)imidazolium, [VIM$^+$C$_3$SO$_3$$^-$])

254   anchored to silica as a sorbent material instead of common ILs based on organic cations

255   and organic/inorganic anions [39].

256   Other important aspect to point out is the fact that several applications did not use neat

257   ILs or PILs but hybrid materials, where the IL-based component was combined with

258   polyethylene glycol (PEG) [36], copper wires [37] or basalt fibers [38], among others.

259   The liquid state of the ILs/PILs is lost when they are immobilized to a solid surface, but

260   the final hybrid material usually present important advantages, such as high surface area

261   and unique extraction capabilities. The IL/PIL can also avoid oxidation or aggregation of

262   the (nano)material because it acts as an important structural component of the sorbent.

263   A different *in tube* SPME configuration based on two interconnected switchable 6 port

264   valves was developed for the determination of UV filters [41]. One of the valves of this

265   system was connected to the *in tube* SPME silica capillary that contained a

266    $Fe_3O_4@SiO_2@\gamma$-MAPS@PIL monolith (being γ-MAPS the coupling agent 3-

267   (trimethoxysilyl) propylmethacrylate). During the extraction, an external magnetic field

268   was applied in the same direction as the sample was passing through the silica capillary.

269   This magnetic field induced the MNPs embedded in the monoliths to generate magnetic

270   field gradients. As a result, the diamagnetic UV filters tended to concentrate in the

271   monolith sections of minimum magnetic field, thereby increasing the extraction

272   efficiency [41].

273   The majority of the developed *on line in tube* SPME methods focused on the analytical

274   determination of organic pollutants, such as UV filters [41], bisphenol A~~BPA~~ and

275   estrogens [37] or phthalates [38] in environmental waters. Other studies determined

276   organic compounds in more complex samples, such as plasma [35] or milk [39].

277

278   **3. Ionic liquids and derivatives in high-throughput liquid-phase microextraction**

279   **3.1. Dispersive liquid-liquid microextraction**

280   Dispersive liquid-liquid microextraction (DLLME) is based on the use of a low volume

281   (in the microliter scale) of an extraction solvent that is dispersed into the sample during

282 the extraction [45]. Dispersion can be achieved by adding a dispersive solvent or by

283 heating/cooling, stirring, or applying any other external energy source to the system [45].

284 In the most classical DLLME mode, centrifugation is applied as the last step to separate

285 the extraction solvent from the sample matrix, and a microsyringe is used to manually

286 collect the final microdroplet containing the preconcentrated analytes for further analysis.

287 ILs have been successfully employed as both extraction and/or dispersive solvents in

288 several DLLME applications, most of them summarized in previously reported reviews

289 [46,47]. The recent innovations accomplished in IL-DLLME methods are schematized in

290 Figure 1. To increase sample throughput in IL-DLLME, centrifugation and microdroplet

291 sampling should be avoided. To this end, three distinct strategies can be distinguished:

292 IL-DLLME using special devices [48], IL-DLLME or MIL-DLLME with magnet-

293 assisted separation [49,50], and *on line* IL-DLLME [51–53]. With regard to the use of

294 special devices, some studies have performed *in syringe* IL-DLLME [48,54]. In these

295 cases, an extra time was set after dispersion to allow the IL to settle as the upper or lower

296 phase, depending on the IL density. To favor phase separation, cooling steps [48,54] or

297 salting out procedures [48] were sometimes performed. The two phases: the IL containing

298 the extracted analytes and the sample matrix, were then separated by simply depressing

299 the syringe plunger. Systems containing a filter in the syringe needle have also been

300 proposed to improve phase separation [48]. For example, Wang *et al.* obtained limits of

301 detection (LODs) from 0.97 to 2.0 $\mu g \cdot L^{-1}$ for the determination of benzoylurea

302 insecticides in water and tea using this type of extraction and HPLC-DAD [48]. In this

303 method, the hydrophobic IL (~~methylytetraoctylammonium~~ methylytrioctylammonium

304 hexaflurophosphate, $[N_{1,8,8,8}^{+}][PF_{6}^{-}]$) that acted as extraction solvent was *in situ* generated

305 during the *in syringe* extraction by mixing the analogous chloride-based IL ($[N_{1,8,8,8}^{+}][Cl^{-}$

306]) and KPF_{6} [48].

307   Other strategy to avoid centrifugation during IL-DLLME consists of adding a

308   paramagnetic material (in general, MNPs) together with the hydrophobic IL [49,55,56];

309   a procedure normally termed IL-DLLME with magnetic retrieval. In these applications,

310   the MNPs were added after the dispersion of the IL, and a high-magnetic field magnet

311   was used to separate the MNPs@IL containing the preconcentrated analytes. Back-

312   extraction/desorption of the analytes from the composite magnetic material is usually

313   performed using an appropriate solvent/solution compatible with the ensuing detection

314   system [49,55,56].

315   In an attempt to further reduce the extraction time and simplify the overall extraction

316   procedure, some authors have developed magnetic effervescence-assisted tablets for IL-

317   DLLME [57–59]. The effervescence tablets were prepared by mixing and compressing

318   the IL in a tablet-format. The tablet contained the IL, acting as the extraction solvent, two

319   effervescence precursors (an acid salt and an alkaline salt), and MNPs. The tablet-format

320   made the extraction simpler as it embraces all reagents required for performing DLLME

321   [57–59]. When the tablet was added to the aqueous sample, dispersion was promoted with

322   the aid of the *in situ* generated CO_2 bubbles. At the same time, as the tablet also contained

323   MNPs, magnetic separation was performed as in the case of DLLME with magnetic

324   retrieval.

325   Apart from the use of MNPs in IL-DLLME with magnetic retrieval (with or without the

326   effervescence-assisted table format), MILs have been also utilized. Indeed, an increasing

327   number of MIL-DLLME applications have been reported and reviewed in the last 5 years

328   [12,13]. The reason for this rapid increase is the inherent magnetism of MILs, that makes

329   them good candidates for performing magnetic separation. At the same time, MILs are

330   more stable and easier to prepare than the typical decorated α-Fe_3O_4 MNPs. It is well-

331   known that bare Fe_3O_4 MNPs are easily oxidized, tend to aggregate, and normally require

332 complex synthetic pathways for their functionalization. MIL-DLLME approaches are

333 based on the addition and dispersion of the MIL into the sample followed by its retrieval

334 using a high-magnetic field magnet. In the reported MIL-DLLME studies, high magnetic

335 susceptibility MILs such as those based on Fe(III) anions (e.g., methyltrioctylammonium

336 tetrachloroferrate or ~~$[N_{8,8,8,1}^+]$~~ $[N_{1,8,8,8}^+][FeCl_4^-]$ [60] and benzyltrioctylammonium

337 ~~tetrachloroferrate(III)~~ bromotrichloroferrate(III) or ~~$[N_{8,8,8,Bn}^+]$~~ $[N_{Bn,8,8,8}^+][FeCl_3Br^-]$ [61])

338 were easily separated by placing the magnet on one side of the extraction vessel. The MIL

339 was immediately attracted by the magnetic field and retained on the walls of the vessel,

340 following by pouring the matrix sample out. Other MILs with lower magnetic

341 susceptibility were collected by directly introducing a rod-shaped magnet into the sample

342 [62] or by adding extra magnetic reagents [63].

343 The desorption step when using MILs in DLLME has been accomplished using a back-

344 extraction procedure [61,63] or diluting the MIL with a low volume of organic solvent

345 [60], depending on the compatibility of the MIL with the subsequent analytical technique.

346 The majority of MILs used in sample preparation contained paramagnetic metals as

347 anions [12,13]. However, in recent reports, a new generation of MILs containing

348 paramagnetic cations have been developed and applied for *in situ* MIL-DLLME [50,64].

349 This new class of MILs resulted effective in the extraction of both polar and non-polar

350 pollutants, including UV filters, polycyclic aromatic hydrocarbons (PAHs), alkylphenols,

351 plasticizers and preservatives [50], as well as for the extraction of DNA [64].

352 All these innovative magnetic assisted IL-based LPME methods have provided simpler

353 and faster extraction pathways for IL-DLLME in comparison with the most classical

354 DLLME mode. However, a batchwise operational procedure was in all cases employed.

355 As a viable alternative for high-throughput analysis, automated or semi-automated IL-

356 DLLME procedures have been proposed by using FI and related systems. Table 2 lists

357 *on line* IL-DLLME applications recently reported in the literature [51–53,65–72]. Those

358 research studies in which a batchwise IL-DLLME step followed by FI-analysis analysis

359 were not covered in this review: e.g., FI-ICP [73] and FI-atomic absorption spectroscopy

360 [74]. Several authors have selected 1-alkyl-3-methylimidazolium hexafluorophosphate

361 ILs ([C_nMIM^+][PF_6^-], with n=4 [51,67], 6 [53,70,71], or 8 [68]) in FI-based systems.

362 Pyridinium- (1-octylpyridinium tetrafluoroborate or [C_8Py^+][BF_4^-] [66]), or

363 phosphonium-based ILs (trihexyl(tetradecyl)phosphonium chloride or [$P_{6,6,6,14}^+$][Cl^-]

364 [52,65,69], commercially available as CYPHOS® IL 101, have also been employed.

365 Imidazolium-based ILs are more appropriate for FI-based systems due to their lower

366 viscosity in comparison to analogous ILs composed of pyridinium or pyrrolidinium

367 cations, among others [23]. It is important to highlight that the viscosity of ILs is, in

368 general, 10-100 times higher than those of common organic solvents. For example,

369 viscosity values of 400, 800 and 810 cP at 25ºC were reported for [C_nMIM^+][PF_6^-], with

370 n = 4, 6, or 8, respectively [23]. In contrast, the viscosity of 1-octanol, commonly used in

371 DLLME applications, is 7.59 cP. As a solution, the majority of FI-IL-DLLME systems

372 handle a mixture of the IL in the sample [51–53,66–69], or in the dispersive solvent [70]

373 instead of the direct manipulation of the IL. The neat IL was used in the FI-system without

374 mixing in few *on line* IL-DLLME procedures [65,71]. Some FI studies have optimized

375 the type of IL employed as extraction solvent. However, the studies were focused on

376 homologous series of ILs (e.g, [C_nMIM^+][PF_6^-] [67]). There are few studies where ILs

377 based on cations/anions of different nature are compared, and, to the best of our

378 knowledge, the use of *on line* MIL-DLLME has not been reported in the literature.

379 Automated MIL-based microscale approaches are challenging due to the high viscosity

380 of the MILs and their tendency to stick onto polymeric materials, making their

381 manipulation in both FIA-/SIA-like and robotic systems troublesome.

382 With regard to the configuration of the *on line* IL-DLLME systems, the majority of the

383 flow methods incorporated at least one switchable valve connected via two ports to a SPE

384 microcolumn or a filter [51–53,66–69], as explained below. This configuration resembles

385 the one used for *in tube* SPME (Figure 2(B)). Using this FI arrangement, the test sample

386 is usually *off line* mixed with all reagents required for performing the extraction, including

387 IL, dispersive solvent, and chelating agent in the case of the determination of metals. The

388 mixture is then brought *on line* to the microcolumn where the IL containing analyte is

389 retained for further analyte back-extraction. After that, the valve is switched to the

390 "inject" position. The elution solvent is then passed through the microcolumn and, finally,

391 the eluted analytes are *on line* transferred to the selected analytical detection technique.

392 The simplest FI-system utilized two peristaltic pumps for propelling the sample and the

393 elution solvents at appropriate flow rates, and a silica gel microcolumn for trapping the

394 dispersed organic solvent after extraction [51]. Cd(II) was extracted in this application

395 using the $[C_4MIM^+][PF_6^-]$ IL and Triton X-100 as the extraction and the dispersive

396 solvents, respectively, with 2-(5-bromo-2-pyridylazo)-5-diethylaminophenol as the

397 chelating agent. This method allowed detection of Cd(II) at concentrations between 0.04

398 and 10.4 $\mu g \cdot g^{-1}$ in plastic food packing materials (after plastic digestion in acid media)

399 [51].

400 In a different flow arrangement for the determination of organic dyes, a T joint connection

401 attached to a sample loop was inserted prior to the switchable valve containing a PTFE

402 filter column [66]. The T joint connection merged the mixture of the sample and the

403 $[C_8Py^+][BF_4^-]$ IL (extraction solvent dissolved in the sample) with a $NaClO_4$ aqueous

404 solution. This increase in the ionic strength insolubilized the IL and created the cloudy

405 solution. The analyte containing IL was then separated using the PTFE filter [66]. The

406   extraction efficiency of the method increased by using the FI-system in comparison to

407   analogous counterparts using centrifugation or manual filtration [66].

408   Other *on line* IL-DLLME methods were implemented in a flow system configuration

409   composed of two switchable 6 port valves, each one connected to a peristaltic pump

410   [52,67–69], as shown in Figure 3(A). The main injection valve contained a microcolumn

411   filled with magnesium-silicate (Florisil) resin in the sample loop, in a configuration

412   similar to the previous mentioned systems [51–53,66–69]. The second switchable valve

413   possessed another loop and was only used for injection of the elution solvent. In the

414   method by Berton *et al.*, the cloudy suspension was accomplished by dispensing the

415   mixture of the $[C_4MIM^+][PF_6^-]$ IL and sample (sample previously heated at 45 ºC) into

416   an ice bath (see Figure 3(A)) [67]. This method was applied to the determination of V(V)

417   in saliva, tap and river water. Authors concluded that phase separation with the *on line*

418   system was accelerated in comparison to an analogous batchwise IL-DLLME method

419   [67].

420   In a different study, sequential injection analysis (SIA) approach was employed for the

421   determination of Tl(III) in water, urine and mussels tissue [53]. In this study, all the steps

422   of the IL-DLLME procedure, including the mixture of the sample with the IL and the

423   dispersive solvent, were performed *on line* using the SIA-like system. A syringe pump

424   connected through a holding coil to a multi-position selection valve was used, with water

425   as a carrier. The selection valve was also connected to a confluent point where two

426   additional syringe pumps (dispensing the sample and the dispersive solvent), and a

427   polyurethane foam microcolumn converged. The microcolumn was *on line* connected to

428   the detection system. The proposed fully enclosed method reduced contamination

429   problems and provided similar analytical performance using FAAS as a detection system

430   than that accomplished with batchwise IL-DLLME-ETAAS [53].

18

431 Other SIA-like configurations have been designed to perform *on line* stirring-assisted IL-

432 DLLME [70,71]. Suárez *et al.* utilized a *lab-in-syringe* system based on two syringe

433 pumps, each connected to a 3-way solenoid head valve, as depicted in Figure 3(B) [70].

434 Both syringes were attached through a T joint connection. A stir bar was placed inside

435 the main syringe pump, that was connected to a DC rotor to allow magnetic stirring. The

436 main syringe pump was also connected to an 8-port selection valve for automatic handling

437 of the sample, reagents and solvents. The key point in the design of the system was to

438 position both syringe pumps upside-down. The sample was aspirated, mixed with the IL

439 and dispersive solvents, and stirred. After that, the IL was settled at the bottom of the

440 syringe head, diluted with acetonitrile, and *on line* transferred for analysis by the second

441 syringe pump in a heart-cut injection mode [70]. This configuration served for the

442 determination of a group of UV filters in combination with HPLC-UV detection. The

443 entire *on line* IL-DLLME-HPLC-UV analysis was performed unattended in less than 12

444 min. In a more recent study, a similar system was developed for the determination of

445 As(V) using a non-chromatographic speciation analysis [71]. This system only required

446 one upside-down syringe and provided LODs lower than 5 ng·L^{-1} by hyphenating the *on*

447 *line* extraction system to graphite furnace atomic absorption spectroscopy (GFAAS).

448 Both As(III) and As(V) were determined by performing oxidation with KMnO$_4$ prior to

449 the extraction [71].

450 Some applications have utilized multiple syringe pumps for handling of the various

451 solvents required for extraction, including sample, IL, and dispersive solvent [65,72]. The

452 *in situ* IL-DLLME mode was applied to the automatic determination of benzoylurea

453 insecticides using a robotic station in a batch-flow configuration [72]. The *in situ*

454 generated IL (1-octyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl]imide,

455 [C$_8$MIM$^+$][NTf$_2^-$]) was separated from the sample matrix by using a SPE column filled

456 with nonwoven polypropylene, followed by analyte back-extraction. After that, the vial

457 containing the eluate was transferred to the HPLC with the help of a robotic arm [72].

458 Multi-syringe flow-injection analysis, which is a FIA/SIA hybrid approach, was used in

459 other application [65], with a configuration capitalized on multi-pumping using solenoid

460 rather than syringe pumps. In this case, a straightforward photometric determination of

461 formaldehyde, as shown in Figure 3(C) [65], was undertaken. The formaldehyde was

462 derivatized and extracted under temperature control in a mixing chamber, and detected in

463 this same chamber that was equipped with optical fibers. Pulsed flows were used for

464 improving the IL dispersion in the sample [65].

465 It is important to point out that the majority of *on line* IL-DLLME applications discussed

466 in this section were focused on the determination of metal species (Table 2 [51–53,67–

467 69,71]). On the contrary, MIL-DLLME has in general been employed for the

468 determination of triazine herbicides [63], PAHs [50,61,62], phenols [50,60] and other

469 aromatic compounds [50,62], ~~and~~ for the analysis of biomolecules such as DNA [64,75]

470 and for the isolation of bacteria [76]. Few applications have employed MIL-DLLME for

471 metal determination [77]. With regard to the type of sample analyzed, the majority of

472 high-throughput IL-DLLME applications were used in the analysis of environmental

473 water samples [50,57,69,70,72]. However, some applications have analyzed foods such

474 as milk [65], wine [68], oil seeds [60], and tea [48], or biological samples, like urine [53]

475 or saliva [67]. Solid samples have been also studied, including rice [71,72], garlic [69] or

476 plastic of food packing [51] in semi-automatic methods.

477

478 **3.2. Other liquid-phase microextraction procedures**

20

479   Single-drop microextraction (SDME) is a variant of LPME in which a droplet of

480   extraction solvent is directly exposed to the sample (in the direct immersion mode, DI-

481   SDME) or into the headspace (HS) created in the extraction vial containing the sample

482   (headspace mode, HS-SDME) [78]. In the HS-SDME mode, elevated temperatures are in

483   general employed during extraction, implying the possibility of partial evaporation of the

484   extraction solvent drop. The use of ILs is thus beneficial in this mode due to their low to

485   negligible vapor pressure. Several IL-SDME methods have been reported over the past

486   decade [79]. However, there are few studies focused on the increase of the sample

487   throughput in IL-SDME workflows, at least in comparison to IL-DLLME. This situation

488   has been gradually changing with the introduction of MILs in sample preparation. When

489   MILs are employed in SDME, the common microsyringe used for suspending the

490   microdroplet of extraction solvent can be replaced by a small rod magnet [80]. This

491   configuration increases the stability of the microdroplet and allows for suspending larger

492   volumes of extraction solvent during SDME [80]. Among the different MIL-SDME

493   applications, the work developed by Mafra *et al*. for the determination of a group of

494   contaminants of emerging concern including parabens, bisphenol A, benzophenone and

495   triclocarban [17] is worth mentioning. The high-throughput procedure, so-called parallel-

496   DI-SDME, was based on the use of a 96-well plate and a blade with a set of rod magnets

497   glued onto the blade pins, as shown in Figure 4 [17]. Each well of the plate served as

498   sample container while the rod magnets attached to the blade allowed for suspending

499   microdroplets of the trihexyl(tetradecyl)phosphonium tetrachloromanganate(II)

500   ($[P_{6,6,6,14}^{+}]_2[MnCl_4^{2-}]$) MIL, that acted as the extraction solvent. Under optimum

501   conditions, the MIL microdroplets were exposed during 90 min to the samples, followed

502   by dissolution/dilution of the MIL microdroplets in acetonitrile prior to HPLC-UV

503   analysis. As this configuration was able to perform simultaneously up to 96

504 extractions/dilutions, the sample throughput was highly increased: less than 1 min per

505 sample [17].

506 The combination of IL-SDME with GC is less usual than IL-SDME-HPLC because direct

507 injection of ILs in GC is not recommended due to the low volatility of the solvent. As

508 alternative, some authors have employed thermal desorption of the analytes extracted in

509 the IL or MIL using a thermal desorption unit [81] or an HS system [82,83] directly

510 coupled to the GC. Thermal desorption of the analytes from the IL/MIL clearly increased

511 the lifetime of the GC column. GC interfaces have also been reported for performing

512 direct analyte desorption from the IL toward the GC column [84,85]. These interfaces

513 were based on a stainless-steel tube filled with glass wool. The IL microdroplet after HS-

514 SDME was directly suspended in the interface with the same microsyringe used during

515 the extraction, and the analytes were desorbed by the action of high temperatures [84]

516 and/or retrieved by the carrier gas through the interface [84,85]. However, it should be

517 pointed out that these interfaces need frequent maintenance. In particular, high-

518 temperature desorption interfaces required a cleaning step after each 5 IL-desorption

519 steps, followed by 1 h of equilibration [84].

520 In a different study, a CombiPAL autosampler was employed for performing a fully

521 automated IL-HS-SDME-GC-MS/MS method for the determination of musk fragrances

522 in environmental water samples [86]. The $[C_8MIM^+][PF_6^-]$ IL was employed as extraction

523 solvent. With this accessory, all steps of the HS-SDME were mechanized, and the IL was

524 prevented of being injected into the GC column by using a GC liner with a piece of glass

525 wool, and a fused silica capillary column as a guard column prior the analytical column

526 [86].

527 IL-DI-SDME has been also coupled to capillary electrophoresis (CE) and demonstrated

528 for the determination of phenols [87]. In this approach, the IL was manipulated during

the extraction protocol by applying pressure in the capillary. The IL was first exposed to the sample for extraction on the tip of the capillary. After that, it was partially aspirated back into the capillary for CE analysis. Different $[C_nMIM^+][PF_6^-]$ ILs (n = 4, 6, 8) were explored as possible extraction solvents. The results indicated that ILs were promising solvents for SDME-CE as the IL droplet suspended at the capillary tip is more stable than common organic solvents [87].

Hollow fiber-liquid phase microextraction (HF-LPME) is another yet configuration based on supported liquid membranes. It uses a porous hollow fiber filled with only the extraction solvent (two-phase HF-LPME) or the extraction solvent embedded in the HF pores together with an acceptor aqueous solution in the lumen of the HF (three-phase HF-LPME) [80]. Two studies have developed an *on line* HF-LPME method using the ~~tetraoctylmethylammonium chloride (~~$[N_{1,8,8,8}^+][Cl^-]$~~)~~ IL, commercially termed as Aliquat 336©, as additive within the extraction solvent (kerosene) [88,89]. These methods also required an acceptor solution as in three-phase HF-LPME and were employed for the determination of Cr(VI) in water samples. In one of these studies, dynamic single-interface HF-LPME was performed [89], requiring two steps. In the first step, the sample was fed into the HF by the help of a peristaltic pump, with the HF already impregnated with the IL-containing extraction solvent, and the sample continuously recirculating for a certain period of time (15 min at optimum conditions). In the second step, the HF was perfused with the acceptor solution using a SIA system, followed by *off-line* UV-spectrophotometric analysis [89]. The results indicated that the recirculation of the sample significantly improved the extraction efficiency, as in the case with *in tube* SPME [89]. A different system, also based on SIA, was employed for automating the entire HF-LPME workflow [88]. With this purpose, a specially designed flow-through extraction chamber was assembled to accommodate the three-phase HF-LPME. The extraction chamber

554 enabled *on line* perfusion of the extraction solvent and acceptor phase through the HF

555 lumen, while passing the sample through the outer shell side [88]. One advantage of this

556 method was that the HF could automatically be regenerated with new extraction solution

557 containing IL in every individual assay, thus avoiding potential losses of the extraction

558 solvent. The results indicated that the HF tolerated around 100 extraction/regeneration

559 cycles without decrease of the extraction efficiency. Furthermore, an enrichment factor

560 of ~11 and a ~~limit of detection~~ LOD of 4.6 μg·L^{-1} was achieved in the determination of

561 Cr(V), by using a sample residence time of only 4.5 min [88].

562 Aqueous biphasic system (ABS) is another important sample extraction and purification

563 strategy, often employed in protein analysis. ABS is based on mixing in water two solutes

564 above their critical concentration to generate a two-phase system. In this procedure, all

565 the components in the initial aqueous sample can be enriched in one of the two phases

566 [90]. *Off line* miniaturized IL-ABS methods have been recently described [91]. Regarding

567 high throughput methods, a miniaturized IL-ABS was employed for the extraction and

568 purification of bovine serum albumin [92]. The ABS was based on the mixture of an

569 aqueous solution of the [C$_4$MIM$^+$][BF$_4^-$] IL and D-fructose. A microfluidic chip of only

570 45 × 15 mm was developed to perform the enrichment of the protein in the IL-phase,

571 followed by phase separation at the outlet of the microchannel. The IL-ABS presented

572 advantages *versus* conventional PEG/phosphate ABS such as lower viscosity, that was

573 deemed most appropriate for utilizing the microfluidic device [92].

574 Stir-bar dispersive liquid microextraction (SBDLME) is an innovative sample preparation

575 technique that uses a MIL as extraction solvent and combines the advantages of both stir

576 bar sorptive extraction and DLLME [93]. The method allows for MIL dispersion during

577 the extraction using high stirring rates along with a high magnetic field magnet. When

578 the stirring is stopped, the MIL is collected onto the magnet. The MIL can be easily

579 transferred to a thermal desorption unit [93] or a headspace system [94] for the direct
580 thermal desorption in the GC system.

581

582 **Conclusions and future perspectives**

583 The synergies between ILs and derivatives as smart and environmental-friendly materials,

584 the use of microextraction and miniaturized approaches, together with the advantages

585 derived from automation and high throughput, are undoubtedly successful keys to follow

586 green analytical chemistry requirements. In the last years, novel strategies capitalized on

587 flow setups, robotic stations, magnetic-assisted separation or dedicated miniaturized

588 platforms have been proposed for improving sample throughput of both IL-μ-SP(M)E

589 and IL-LPME. However, the number of applications using ILs together to FI, robotic

590 systems and microfluidic devices is limited, although an increment in the number of

591 reported applications is foreseen in the near future. Up to date, there is a larger number

592 of applications that use *on line* IL-DLLME rather than *on line* IL-SPE, which is quite

593 surprising because of the feasibility of FIA, SIA and their sequels, e.g., *lab-on-valve*

594 fluidic platforms, for *on line* handling of sorptive materials. We anticipate that the

595 coupling of MILs with fluidic systems furnished with electromagnets will path the way

596 for the development of novel fully automated/automatic LPME-based micro/millifluidic

597 platforms in the near future. To achieve this goal, attention should be paid to the design

598 of MILs with improved physicochemical properties, including lower viscosity and higher

599 magnetic susceptibility.

600

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610

611 **Conflict of interest**

612 The authors declare no conflict of interest.

613

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925 **Figure Captions**

926

927 **Fig. 1.** Scheme of recent improvements in IL-based microextraction approaches for high
928 sample throughput.

929 **Fig. 2** Representative *on line* systems used for IL-based sorbent phase (micro)extraction
930 methods. **(A)** FI-system used for *on line* magnetic IL-SPE. *Abbreviations:* **P1, P2,**
931 **P3**: peristaltic pumps. Adapted from [34] with permission from Springer Nature.
932 Note that the injection loop was incorrectly connected in the original publication
933 **(B)** FI-system employed for *in-tube* IL-SPE. Reproduced from [38] with
934 permission from Wiley.

935 **Fig. 3.** Representative *on line* IL-DLLME systems. **(A)** FI-system using a refrigerated
936 loop (**L$_1$**) for *in line* generation of the cloudy solution of the IL dispersed in the
937 sample, and a SPE column for separating the IL from the sample matrix.
938 *Abbreviations:* **ETAAS:** electrothermal atomic absorption spectroscopy; **P1, P2:**
939 peristaltic pumps; **V1, V2, V3:** injection valves; **HB:** hot bath; **CB:** cold bath; **L$_2$:**
940 elution solvent loop; **S:** sample; **B:** buffer; **E:** elution solvent; **A:** air; **W:** waste.
941 Reproduced from [67] with permission from Elsevier. **(B)** SIA-like system for *in*
942 *syringe* dispersion of the IL in the sample and direct injection of the diluted IL
943 into HPLC. *Abbreviations:* **MSP:** multisyringe pumps; **S1, S2:** syringes; **MPV:**
944 multiposition valve; **IV:** high injection valve, **M:** DC motor. Reproduced from
945 [70] with permission from Elsevier. **(C)** Multipumping-IL-DLLME system with
946 a pulsed-flow chamber for batch-flow analysis. *Abbreviations:* **P$_1$–P$_5$:** solenoid
947 micropumps; **S:** sample; **R:** derivatizing reagent; **E:** IL (extraction solvent); **W$_1$,**
948 **W$_2$:** auxiliary solvents; **F$_C$:** mixing/reaction chamber; **F$_1$, F$_2$:** optical fibers; **T$_S$:**

949   temperature sensor; **H$_t$:** heating bar; **V:** 3-way solenoid pinch valve; **P:** peristaltic

950   pump; **W:** waste. Reproduced from [65] with permission from Elsevier.

951   **Fig. 4** High-throughput extraction apparatus employed for parallel-MIL-SDME using a

952   96 blade configuration. Reproduced from [17] with permission from Elsevier.

Table 1.   Representative analytical applications using *on line* IL-μ-SPE and *in tube* IL-SPME.

Analytes / number	Sample / amount	Sorbent material[a] / amount or capillary dimensions	Microextraction approach	Analytical technique[b]	LOD[c] ($\mu g \cdot L^{-1}$)	Ref.
Dyes / 3	Aqueous samples / 50 mL	$[C_8MIM^+][PF_6^-]$ IL-CD-CNTs/TiO$_2$ nanocomposite / 30 mg	*On line* SPE using a peristaltic pump connected to the SPE column	Spectrophotometry	-	[32]
Pb(II) / 1	Tap water / 14 mL	Co(II) NPs@SiO$_2$@ $[P_{6,6,6,14}^+][BEHPA^-]$ TSIL / 1.5 mg	*Off line* dSPE with *on line* magnetic separation using an electromagnet in an FI-system	FI-ICP-OES	4	[33]
Food colorants / 5	Carbonated drink, cocktail, solid beverage, candy, jelly, ice cream / 8 mL	Fe$_3$O$_4$@PIL core-shell microspheres (IL monomers: $[VMIM^+][I^-]$, $[VC_2IM^+][Br^-]$, $[VC_4IM^+][Cl^-]$, $[VC_6IM^+][Br^-]$ or $[VC_8IM^+][Cl^-]$ and DVB as crosslinker) / 2 mL of adsorbent suspension	*On line* SPE by performing extraction in a sample loop, magnetic separation of the sorbent material, and elution	*On line* spectrophotometry	4.1–14	[34]
Endocanna-Binoids / 2	Plasma / 0.4 mL	PIL coated on the walls of a silica capillary (IL monomers: $[VC_6IM^+][Cl^-]$ or $[VC_{16}IM^+][Br^-]$ IL crosslinker: $[(VIM)_2C_{10}^{2+}]2[Br^-])$ / 11 cm L × 0.53 mm ID	*In tube* SPME using a rotary injection valve containing the *in tube* capillary	UHPLC-MS/MS	0.05–0.1[d]	[35]
Acidic food additives / 5	Soft drinks / 0.8 mL	PIL using PEG as porogel in a silica capillary (IL monomer: $[(AC_3)MIM^+][Cl^-]$ and acrylamide as crosslinker) / 0.25 mm ID	*In tube* SPME using a rotary injection valve containing the *in tube* capillary	HPLC-UV	1.2–13.5	[36]
Bisphenol A & estrogens / 5	Bottle water and sewage. / 35 mL	PIL supported onto 25 cm L copper wires of a copper capillary (IL monomer: $[VC_{12}IM^+][Br^-]$, IL crosslinker: $[(VIM)_2C_6^{2+}]2[Br^-])$ / 35 cm L × 0.5 cm ID	*In tube* SPME using a rotary injection valve containing the *in tube* capillary	HPLC-DAD	0.02–0.05	[37]

Analytes / Number	Sample / Volume	Sorbent / Dimensions	Methodology	Detection	LOD	Ref.
Phthalates / 4	Water in disposable plastic box / 50 mL	Basalt fiber@PIL on PEEK capillary (IL monomer: $[VC_{12}IM^+][Br^-]$) / 30 cm L × 0.75 mm ID	*In tube* SPME using a rotary injection valve containing the *in tube* capillary	HPLC-UV	0.01–0.05	[38]
Ceftiofur antibiotic / 1	Bovine milk / 0.5 mL	$[VIM^+C_4SO_3^-]$ ZIL@silica packed in a stainless-steel column / 0.40 cm L × 2 mm ID	*In tube* SPME using a rotary injection valve containing the *in tube* capillary	HPLC-MS/MS	0.1	[39]
Organic mercury / 1	Tap and river water / 40 mL	CYPHOS® 101 IL impregnated in Amberlite resin / 5 cm L × 2 mm ID	*In tube* SPME using a rotary injection valve containing the *in tube* capillary	FI-CV-AAS	2.4 ng·L^{-1}	[40]
UV filters / 5	Lake and river water, and wastewater / 1.5 mL	$Fe_3O_4@SiO_2@\gamma$-MAPS@PIL monolith on a silica capillary (IL monomer: $[AlMIM^+][NTf_2^-]$) / 15 cm L × 0.25 mm ID	*In tube* SPME in a FI-system with two switchable 6 port valves interconnected. One valve was employed for the extraction, and the second for the HPLC injection	HPLC-UV	0.04–0.3	[41]

[a] *IL cations:* **[(AC₃)MIM⁺]:** 1-aminopropyl-3-methylimidazolium, **[AlMIM⁺]:** 1-allyl-3-methylimidazolium, **[C₈MIM⁺]:** 1-octyl-3-methylimidazolium, **[P₆,₆,₆,₁₄⁺]:** tetrahexyl(tetradecyl)phosphonium, **[VC₂IM⁺]:** 1-ethyl-3-vinylimidazolium, **[VC₄IM⁺]:** 1-butyl-3-vinylimidazolium, **[VC₆IM⁺]:** 1-hexyl-3-vinylimidazolium, **[VC₈IM⁺]:** 1-octyl-3-vinylimidazolium, **[VC₁₂IM⁺]:** 1-dodecyl-3-vinylimidazolium, **[VC₁₆IM⁺]:** 1-hexadecyl-3-vinylimidazolium, **[(VIM)₂C₆²⁺]:** 1,12-di(vinylimidazolium)hexane, **[(VIM)₂C₁₀²⁺]:** 1,12-di(vinylimidazolium)decane, and **[VMIM⁺]:** 1-methyl-3-vinylimidazolium.

IL anions: **[Br⁻]:** bromide, **[BEHPA⁻]:** bis(2-ethylhexyl)phosphinate, **[Cl⁻]:** chloride, **[I⁻]:** iodate, **[NTf₂⁻]:** bis[(trifluoromethyl)sulfonyl]imide, and **[PF₆⁻]:** hexafluorophosphate.

Others: **γ-MAPS:** 3-(trimethoxysilyl) propylmethacrylate, **CD:** cyclodextrins, **CNTs:** carbon nanotubes, **DVB:** divinylbenzene, **NPs:** nanoparticles, **PEEK:** polyether ether ketone, **PEG:** polyethylene glycol, **TSIL:** task specific ionic liquid, and **ZIL:** zwitterionic ionic liquid.

[b] **AAS:** atomic absorption spectroscopy, **CV:** cold vapor, **DAD:** diode array detection, **FI:** flow injection, **HPLC:** high-performance liquid chromatography, **ICP:** inductively coupled plasma, **MS:** mass spectrometry, **OES:** optical emission spectroscopy, **UHPLC:** ultra high-performance liquid chromatography, and **UV:** ultraviolet detection.

[c] Limit of detection.

[d] Limit of analytical determination.

Table 2.   Representative analytical applications of *on line* IL-DLLME.

Analytes / number	Sample / amount	IL extraction solvent[a] / amount	FI-component used during DLLME[b]	Microcolumn sorbent	*On line* DLLME procedure[c]	Analytical technique[d]	LOD[e] ($\mu g \cdot L^{-1}$)	Ref.
Cd(II) / 1	Digested food packaging materials / 20 mL	$[C_4MIM^+][PF_6^-]$ / 0.7 g	A switchable 6 port valve equipped with a microcolumn	Silica gel	**1.** *Off line* mixing of sample, IL, Triton X-100 and PADAP (with stirring) **2.** Aspiration of the mixture to the microcolumn using the FI-system **3.** Phase separation, back-extraction, and transfer of the eluate to the detector	ETAAS	$6\ \mu g \cdot Kg^{-1}$	[51]
Dyes / 2	Soft drinks / 5 mL	$[C_8Py^+][BF_4^-]$ / 0.12 g	A switchable 6 port valve equipped with a filter	PTFE filter	**1.** *Off line* mixing of sample and IL **2.** On line addition of $NaClO_4$ to the mixture **3.** Phase separation, back-extraction, and transfer of the eluate to the detector	Spectro-photometry	10	[66]
Co(II) / 1	Tap and river water, and physiological solutions / 2 mL	CYPHOS® IL 101 / 35 mg	2 switchable 6 port valves (V_1, V_2). V_1 was connected to an extraction loop, and V_2 to a microcolumn	Florisil resin	**1.** *Off line* mixing of sample, IL, Triton X-114 and PAR (with vortex stirring) **2.** Aspiration of the mixture to the sample loop using the FI-system **3.** Phase separation of the IL in the microcolumn, back-extraction, and transfer of the eluate to the detector	ETAAS	0.008	[52]

Analyte	Sample	IL	Valve system	Resin	Procedure	Detector		Ref.
V(V) / 1	Saliva, tap and river water / 5 mL	$[C_4MIM^+][PF_6^-]$ / 40 μL	2 switchable 6 port valves (V_1, V_2). V_1 was connected to an extraction loop, and V_2 to a microcolumn	Florisil resin	**1.** *Off line* mixing of sample, IL, ethanol and PADAP (with stirring and heating) **2.** Aspiration of the mixture to the sample loop using the FI-system **3.** Cooling the mixture in the sample loop **4.** Phase separation of the IL in the microcolumn, back-extraction, and transfer of the eluate to the detector	ETAAS	15	[67]
As(III) and As(V) / 2	Wine / 4 mL	$[C_8MIM^+][PF_6^-]$ / 40 mg	2 switchable 6 port valves (V_1, V_2). V_1 was connected to an extraction loop, and V_2 to a microcolumn	Florisil resin	**1.** *Off line* mixing of sample, IL, Triton X-114, methanol, DDTC and $NaClO_4$ (with vortex stirring) **2.** Aspiration of the mixture to the sample loop using the FI-system **3.** Phase separation of the IL in the microcolumn, back-extraction, and transfer of the eluate to the detector	ETAAS	0.005	[68]
Se(IV) and Se(VI) / 2	Tap, river and lake water, and digested garlic / 4 mL	CYPHOS® IL 101 / 50 mg	2 switchable 6 port valves (V_1, V_2). V_1 was connected to an extraction loop, and V_2 to a microcolumn	Florisil resin	**1.** *Off line* mixing of sample, IL, Triton X-114, methanol, APCD and $NaClO_4$ (with vortex stirring) **2.** Aspiration of the mixture to the sample loop using the FI-system **3.** Phase separation of the IL in the microcolumn, back-extraction, and transfer of the eluate to the detector	ETAAS	15	[69]

Analyte / n	Sample / volume	IL / amount	System	Support	Procedure	Detector	LOD	Ref
Tl(I) and Tl(III) / 2	Tap, river and sea water, urine, and mussel tissue / 15 mL	[C$_6$MIM$^+$][PF$_6^-$] / 6 % (v/v dispersive solvent)	LOV system. The valve was connected to a confluence point in which other two syringe pumps and a microcolumn converged	Polyurethane foam in a glass column	**1.** *Off line* mixing of sample, IL, methanol (with stirring and heating) **2.** Aspiration of the mixture using the LOV-system **3.** Phase separation of the IL in the microcolumn, back-extraction with MIBK, and transfer of the eluate to the detector	FAAS	0.86	[53]
Ultraviolet filters / 6	Sea and pool water / 3.5 mL	[C$_6$MIM$^+$][PF$_6^-$] / 0.19 mg	LIS-like system: syringe pump upside-down connected to an 8-port selection valve. The selection valve was connected to a second syringe pump	-	**1.** Aspiration of the sample and IL (dissolved in acetonitrile) into the main syringe pump **2.** Magnetic-stirred extraction in the main syringe pump **3.** Phase separation by letting the IL settle at the bottom of the syringe **4.** IL dilution and transfer to the HPLC system	HPLC-UV	0.08–10.8	[70]
As(III) and As(V) / 2	Aqueous solution of extracted rice / 5 mL	[C$_6$MIM$^+$][PF$_6^-$] / 45 µL	LIS system: syringe pump upside-down connected to an 8-port selection valve	-	**1.** Aspiration of the sample and IL in dispersive solvent into the syringe pump **2.** Magnetic-stirred extraction in the syringe pump **3.** Phase separation by letting the IL settle at the bottom of the syringe **4.** IL dilution and transfer to the HPLC system	GFAAS	0.005	[71]

Insecticides / 4	River and reservoir water / 10 mL	[C$_8$MIM$^+$][NTf$_2^-$] *in situ* generated using [C$_8$MIM$^+$][Cl$^-$] (0.04 g) and LiNTf$_2$ / -	Commercial multi-syringe system and robotic arm	Nonwoven polypropylene	**1.** Mixing of the sample and IL (dissolved in water) on a vial using a multisyringe system **2.** *In situ* DLLME extraction **3.** Phase separation in a microcolumn, back-extraction and transfer of the eluate to HPLC using a robotic arm	HPLC-DAD	0.16–0.45	[72]
Formalde-hyde / 1	Milk / 0.672 mL	[P$_{6,6,6,14}^+$][Cl$^-$] / 150 μL	Multipumping system with a mixing chamber	-	**1.** Analyte derivatization in the mixing chamber of the multipumping system (with heating) **2.** IL aspiration **3.** IL dispersion using pulse flow **4.** *In situ* detection in the mixing chamber	Spectro-photometry	100	[65]

[a] *IL cations:* **[C$_4$MIM$^+$]:** 1-butyl-3-methylimidazolium, **[C$_6$MIM$^+$]:** 1-hexyl-3-methylimidazolium, **[C$_8$MIM$^+$]:** 1-octyl-3-methylimidazolium, **[C$_8$Py$^+$]:** 1-octyl-pyridinium, and **[P$_{6,6,6,14}^+$]:** tetrahexyl(tetradecyl)phosphonium.

IL anions: **[BF$_4^-$]:** tetrafluoroborate, **[Cl$^-$]:** chloride, **[NTf$_2^-$]:** bis[(trifluoromethyl)sulfonyl]imide, and **[PF$_6^-$]:** hexafluorophosphate.

[b] **LIS:** lab-on-syringe, and **LOV:** lab-on-valve.

[c] *Dispersive solvents:* Acetonitrile, ethanol, methanol, Triton X-100, and Triton X-114.

Chelating agent: **APDC:** ammonium pyrrolidine dithiocarbamate, **DDTC:** sodium diethyldithiocarbamate, **MIBK:** methylisobutyl ketone, **PADAP:** 2-(5-bromo-2-pyridylazo)-5-diethylaminophenol 5-diethylaminophenol, and **PAR:** 4-(2-pyridylazo)-resorcinol.

Salting out reagent: NaClO$_4$.

[d] **DAD:** diode array detection, **ETAAS:** electrothermal atomic absorption spectroscopy, **FAAS:** flame atomic absorption spectroscopy, **GFAAS:** graphite furnace atomic absorption spectroscopy, **HPLC:** high-performance liquid chromatography, and **UV:** ultraviolet detection.

[e] Limit of detection.