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## **Combined extraction and microextraction techniques: recent trends and future perspectives**

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### **Abstract**

The latest advancements in the analytical sample preparation indicate a trend of combining different extraction techniques with targeting an improvement in separation, cleanup, detection limits, enrichment factors, and dealing with complex matrices. This manuscript identifies mainly two groups of combined sample preparation techniques. The first group integrates conventional or enhanced extraction techniques with microextraction. The second group combines microextraction with each other. The objectives and merits of each combination are critically appraised with respect to nature of the samples, analytical figure of merits, and certain application scenarios. Green aspects of combined extraction methods are described with some examples. At the end, a brief account is provided on accomplishments, limitations, and future directions.

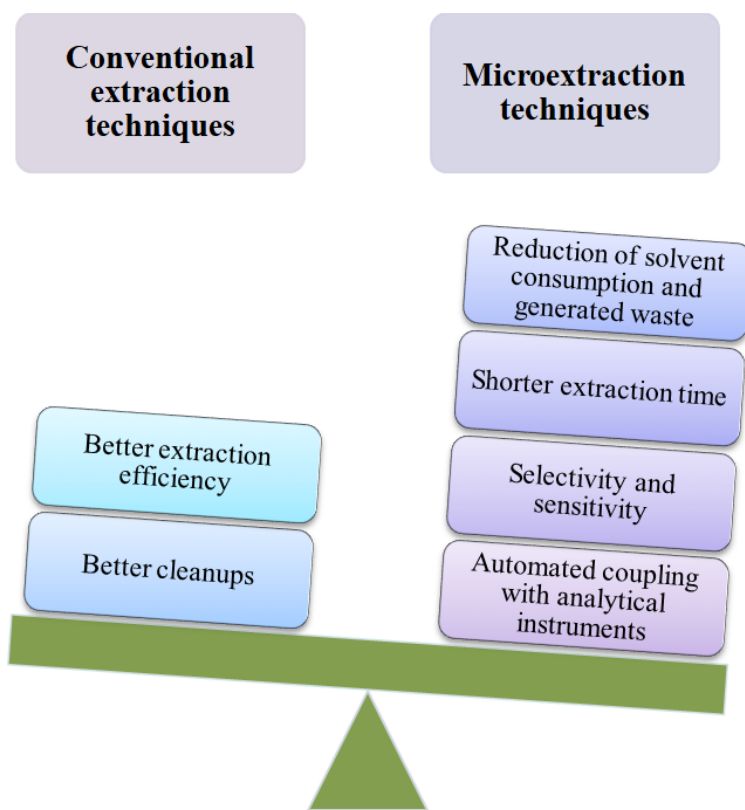
### **Keywords**

Combined extraction techniques; Sample preparation; Microextraction; Preconcentration; Chromatographic analysis; Enrichment factors; Green Analytical Chemistry

### **1. Introduction**

Despite all the major advancements in analytical instrumentation, sample preparation is still of critically importance in the determination of target analytes in various matrices. The requirement of sample preparation arises from several facts including the demand of trace level analysis, the new regulatory obligations, and the complex nature of the sample matrices that are not compatible with analytical instrumentation for direct analysis. In this

37 way, sample preparation is performed to get better separation, clean up, and enrichment of  
38 analytes. It is also performed to bring the analytes into a medium that is compatible with  
39 analytical instruments [1]. Both conventional extraction and microextraction techniques  
40 have been widely adopted as sample preparation methods and they have their own merits  
41 and demerits. Generally, conventional extractions provide better extraction efficiency and  
42 cleanups as they are exhaustive in nature. In contrast, equilibrium based microextraction  
43 techniques are directed toward the reduced use of solvents and extracting phases,  
44 miniaturizing the dimensions of extracting devices, and automated coupling with analytical  
45 instruments. Such objectives are also in accordance with the principles of green analytical  
46 chemistry [2]. At the same time, microextraction are efficient in terms of extraction time,  
47 sensitivity, selectivity, enrichment factors and extraction performance (Figure 1).



48

49 Figure 1. Advantages of conventional extraction and microextraction techniques.

50 Recently, a trend has been seen combining conventional and micro- extraction techniques  
51 together as well as microextraction techniques with each other. A combination of sample  
52 preparation methods is a viable way to introduce a new extraction approach that may  
53 synergistically originate advantages from current individual methods, yet with its own  
54 innovative merits [3]. Such combinations may overcome the disadvantages of individual  
55 techniques and provide benefits specifically related to certain scenario or applications.  
56 Recently, combined sample preparation techniques are shown to be excellent approaches  
57 for improving the extraction performance through analyte separation, enrichment, and  
58 coping with complex matrices and, thus enhancing the quality of the entire analysis [4].

59 This review aims to critically examine and discuss the combined methods and appraise  
60 their role in improving overall efficiency of the analytical process from extraction to  
61 determination. In addition, it can provide a guidance on the selection of combined methods  
62 when dealing with a particular type of extraction challenges or complex matrices.

63 Combined sample preparation techniques can be broadly classified into two categories

- 64 (i) Conventional or enhanced extractions combined with microextraction
- 65 (ii) Binary Miniaturized or microextraction techniques.

66 In this article, only certain trends are highlighted instead of comprehensively covering all  
67 the published literature. The articles published in 2015 or later were mainly considered.

68

## 69 **2. Conventional or enhanced extraction techniques combined with** 70 **microextraction techniques**

71 Liquid phase extraction is associated with a high organic solvents consumption as well as  
72 generation of high volume of wastes. Moreover, long time extraction is needed, which  
73 involves high energy consumption what impact on an incremental cost. Thus, in order to  
74 accelerate the extraction process as well as to improve the analyte separation, the  
75 implementation of other extraction technologies, applying different mechanisms such as  
76 ultrasound and microwave energy has been promoted. Lowering the final costs through  
77 reduction of extraction time and energy consumption are the main objectives of these  
78 methods. In addition, enhanced conventional extraction techniques are sustainable, due to  
79 the fact that they protect the environment as well as consumers' health. In addition, they  
80 are enhancing the economically and innovatively competitiveness of industries. Moreover,  
81 application of these techniques in combination with novel microextraction techniques  
82 brings additional advantages such as improving the target isolation, and, therefore,  
83 enhancing the quality of the whole analysis. The information on microwave- and  
84 ultrasound assisted extraction as well as conventional extraction techniques such as Soxhlet  
85 and extraction with mechanical agitation are presented in Table 1.

86 Conventional or enhanced extraction techniques combined with microextraction can be  
87 categorized into two types based on the nature of the samples i.e. solid and liquid samples

### 88 **2.1. Combined techniques for the solid samples**

89 In this combination, conventional or enhanced extraction technique is used for the  
90 dissolution or releasing of analytes from the solid samples into a liquid medium. The liquid  
91 medium containing analytes is further subjected to microextraction to achieve the goals  
92 related to sample cleanup and preconcentration of the analytes. The examples of this  
93 category include microwave or ultrasound assisted extraction combined with  
94 microextraction techniques.

#### 95 **2.1.1. Microwave assisted extraction combined with microextraction**

96 Microwave radiation has ability to penetrate and produce heat inside the biological/solid  
97 samples in presence of the polar solvents. Compared to traditional solvent extraction,  
98 microwave assisted extraction (MAE) derives benefits from microwave irradiation. The  
99 extraction efficiency of MAE is dependent on many factors, including extraction solvent,



100 extraction temperature and time, as well as liquid-to-solid ratio. MAE is relatively greener  
101 method compared to liquid-liquid extraction (LLE) because it utilizes very low volume of  
102 solvents and generates less waste. Moreover, it is efficient in terms of extraction, time, and  
103 energy.

104 MAE is a preferable choice particularly when the analytes are to be extracted from solid  
105 samples such as plants, sediments, soil, meat, rice etc. It can be performed simultaneously  
106 or prior to microextraction. MAE digests/dissolves the solid samples into a suitable solvent  
107 with the aid of microwave energy and resulting extract can be further concentrated with  
108 microextraction. This combination provides high enrichment factors and better sensitivity.

#### 109 *2.1.1.1. Microwave assisted extraction followed by dispersive liquid liquid* 110 *microextraction*

111 Dispersive liquid-liquid microextraction (DLLME) is a technique that offers the  
112 unbeatably quick extraction rates, however this is accompanied by extensive human  
113 manipulation which lead to extra steps that could be a gateway for sample loss, inadvertent  
114 contamination, and poor automation. However, when applied with enhanced conventional  
115 extraction techniques including microwave assisted extraction, these disadvantages are  
116 limited.

117 The first application combining MAE and DLLME was reported in 2011 for extraction of  
118 N-nitrosamines in meat samples. MAE was performed using 10 mL of 0.05 M NaOH and  
119 this extract was subjected to DLLME. DLLME utilized only 20  $\mu$ L of carbon tetrachloride  
120 as an extraction solvent. Due to use of NaOH in MAE and extremely small volume of  
121 organic solvent in DLLME, this method can be considered relatively environment friendly.  
122 MAE provided good extraction efficiency from complex food samples which was not only  
123 confirmed by good recoveries but also by the quantification which was possible using  
124 aqueous calibration. The enrichment factors were in between 220 and 342. Low LODs  
125 were obtained due to the enrichment of analytes provided by DLLME [5].

126 MAE-DLLME-derivatization was used for extraction of haloanisoles and halophenols in  
127 cork stoppers and oak barrel sawdust and then final determination by GC-ECD. The  
128 method is fascinating from several features such as MAE was performed using methanol  
129 and the same extract was employed as disperser solvent in forthcoming DLLME. In  
130 DLLME, extraction solvent, derivatizing reagent, and methanolic extract were combined  
131 and rapidly injected into an aqueous solution containing potassium carbonate leading to  
132 cloudy solution. Moreover, DLLME and derivatization was performed in a single step [6].  
133 MAE-DLLME for extraction of polyamine in turkey breast meat [7], pharmaceutical  
134 antimicrobials in fish [8], nitrosamines in food samples[9], PAHs in smoked rice [10], and  
135 pesticides from pulp and pericarp of Litchi fruit [11].

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140 *2.1.1.2. Dynamic microwave assisted extraction followed by single drop*  
141 *microextraction*

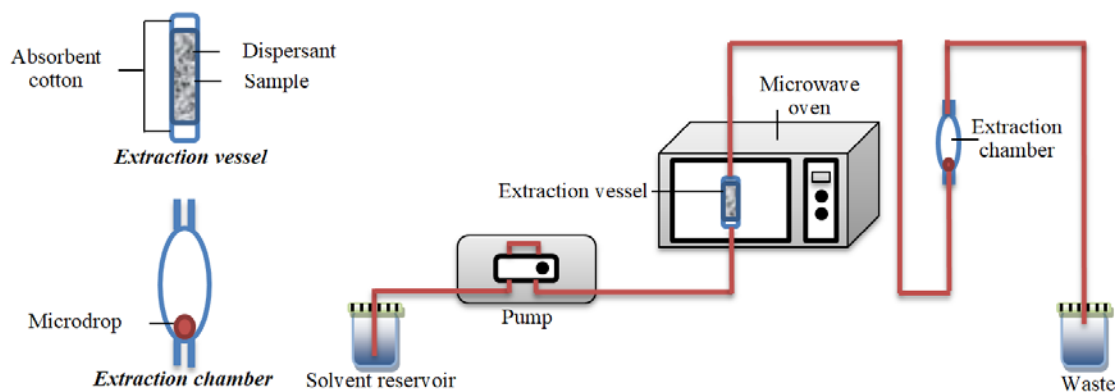
142 Single-drop microextraction (SDME) has become a popular liquid-phase microextraction  
143 technique due to the fact that it is inexpensive, nearly solvent-free and easy to  
144 operate. From the other site, stirring is mainly performed to accelerate the extraction  
145 kinetics by minimizing the interfacial film thickness, which affects the extension of the  
146 extraction time as well as lowering extraction efficiency. To overcome these limitations,  
147 SDME can be combined with MAE.

148 Traditional MAE is performed at high pressure and temperature that may cause partial  
149 decomposition of some target compounds. Moreover, after every extraction cycle, vessels  
150 need to be cooled and extract need to be filtered or centrifuged that leads to longer time  
151 consumption. However, dynamic MAE (DMAE) can resolve these issues by continuous  
152 provision of fresh solvents and transfer of analytes out of the vessel right after completion  
153 of extraction process. Furthermore, the extract is amenable to online filtration and DMAE  
154 can be coupled with other extraction techniques.

155 The key objective of this combination is the extraction of analytes in complex solid  
156 matrices. DMAE was combined online with single drop microextraction (SDME) for  
157 extraction of organophosphorus pesticides (OPPs) in tea samples. The microdrop was held  
158 in a specially designed chamber that allows the introduction of the microdrop at the bottom  
159 of the filled chamber through a micro syringe. A continuous flow of aqueous solution can  
160 be passed through the microdrop by means of a microinfusion pump. The droplet formed  
161 was quite stable. The generation of the bubbles would push the microdrop to float up  
162 slightly, and then the microdrop returns back once the bubbles pass through. This dynamic  
163 system provides quick equilibrium achievement. The setup is shown in Figure 2. This  
164 combination provides clean up, extraction, separation, and enrichment in a single step  
165 process. This method provided LODs of 0.4 to 1.7  $\mu\text{g}/\text{kg}$  [12].

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169 Figure 2. Schematic diagram of DMAE-SDME system [12].

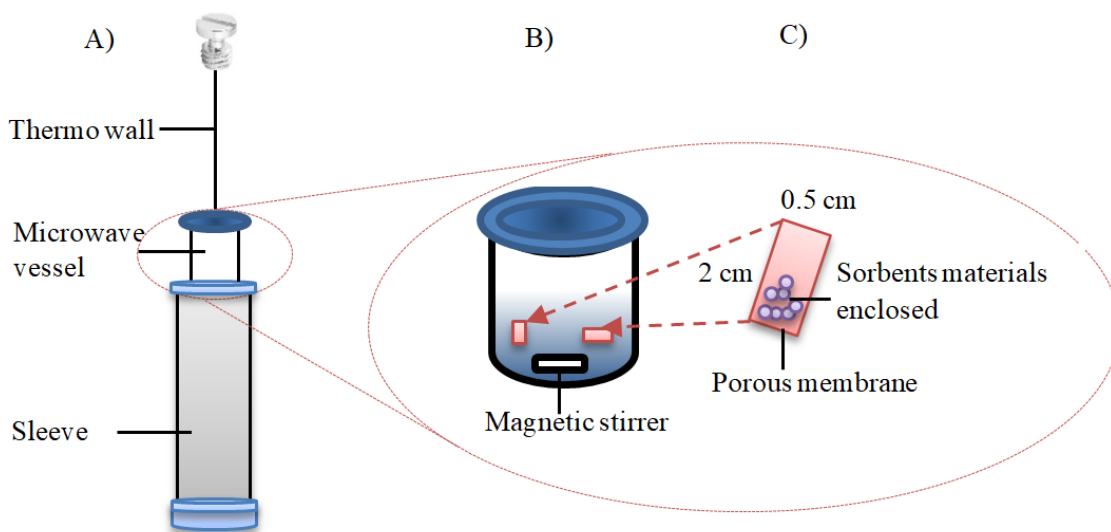
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171 In another work, DMAE was coupled with continuous flow microextraction (CFME) for  
172 extraction of OPPs in the vegetables. In the extraction chamber, single drop was suspended  
173 at the tip of microsyringe. There was a cooling bath containing ice between CFME and  
174 DMAE unit [13].

### 175 *2.1.1.3. Simultaneous microwave assisted extraction and micro-solid phase* 176 *extraction*

177 In this approach solid sample, extraction solvent, and a membrane bag consisting of sorbent  
178 ( $\mu$ -SPE device) are taken together in a microwave vessel and subjected to MAE. With this  
179 strategy, digestion and extraction takes place simultaneously. Solid sample is digested with  
180 the help of the microwave irradiation in a suitable solvent and target analytes are released  
181 to the same solvent. These analytes simultaneously adsorb on the sorbent inside the porous  
182 membrane bag. The protection of the sorbent inside the porous bag is highly suitable for  
183 complex matrices as the membrane allows the analytes pass through while interfering  
184 complex matrices cannot. After the extraction,  $\mu$ -SPE device is taken out of the microwave  
185 vessel and analytes are back-extracted into a suitable solvent, a part of which is injected to  
186 analytical instrument for the quantitation. This approach was used for extraction of  
187 parabens in human ovarian cancer tissues and finally their analysis by HPLC-UV [3]. The  
188 schematic diagram of this combination is shown in the Figure 3.

189



190

191 Figure 3. Schematic representation of A) MASE –  $\mu$ -SPE setup, B)  $\mu$ -SPE system and  
192 C) enlarge image of extraction device (not drawn to scale) [3].

### 193 *2.1.1.4. Simultaneous microwave assisted extraction and liquid phase* 194 *microextraction*

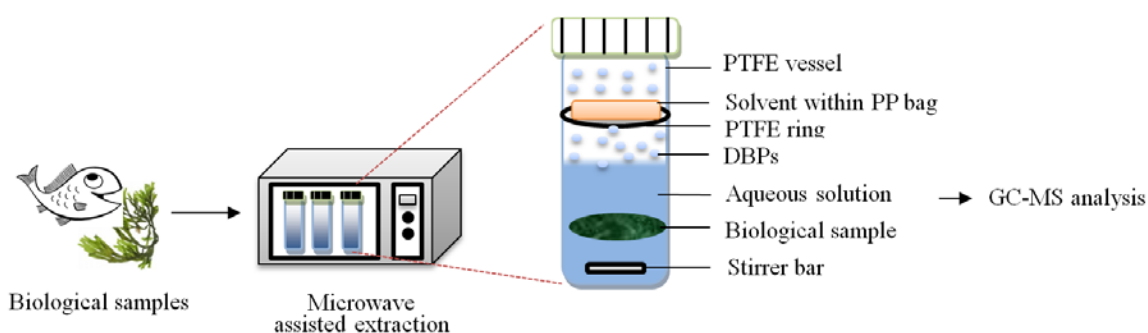
195 The headspace liquid phase microextraction (HS-LPME) is a very popular technique and  
196 thus, have been described in many papers. This is because this method is very useful for  
197 the extraction of wide range of compounds including volatile and semi-volatile organic



198 compounds in various types of analyses. However, to reduce the time of extraction,  
199 HS-LPME could be coupled with MAE.

200 A single-step microwave assisted headspace liquid-phase microextraction (MA-HS-  
201 LPME) method was developed for extraction of trihalomethanes (THMs) and haloketones  
202 (HKs) in biological samples. In this method, an optimum amount of biological sample  
203 along with optimum volume of acid was taken inside the microwave vessel. Within the  
204 vessel, a porous membrane bag filled with extraction solvent was supported on a PTFE  
205 ring over a certain height above the sample. This set up was then subjected to microwave  
206 irradiation to get simultaneous digestion of biological samples and extraction of target  
207 analytes in headspace into the solvent containing porous membrane bag (LPME device).  
208 The schematic is shown Figure 4.

209



210

211 Figure 4. Schematic of extraction methods using MA-HS-LPME system [4].

212

### 213 2.1.2. Ultrasound assisted extraction and microextraction

214 Ultrasound assisted extraction (UAE) has some advantages for extraction of solid samples  
215 (natural products, sediments, etc.) due to flexible and adjustable nature of ultrasonic  
216 energy. UAE is rapid and significantly increases extraction yield. This is because it has the  
217 plenty of power to break up the inner structures of the solid samples (plant cells, tissues,  
218 sediments, etc.) and provides high contact surface between sample and extracting phase.  
219 UAE extract can be further combined with microextraction to derive benefits of better  
220 cleanup, sensitivity and enrichment factor. The most popular microextraction technique  
221 that is coupled with UAE is DLLME.

222 The first study combining UAE and DLLME was reported in 2011 for extraction and  
223 preconcentration of OPP residues in tomato samples. UAE was performed at small scale  
224 (5 mL solvent). Briefly, the sample was homogenized and subjected to UAE in acetone.  
225 No clean-up or evaporation were required after extraction. UAE extract was further  
226 concentrated by DLLME and injected to gas chromatography–flame photometric detection  
227 (GC–FPD) for final determination [14]. UAE was used for elution of PCBs from marine  
228 sediments into the extraction solvent under optimum conditions. The extract was then dried  
229 under nitrogen stream and reconstituted using 1 mL of the extraction solvent. This extract  
230 was then used for DLLME. This method provided LODs in the range of 0.021 to  
231 0.057 ng/g, GC-MS being the final determination instrument. The authors did not discuss

232 the enrichment factors achieved, however, one obvious advantage of UAE is to convert the  
233 sample into a form which can be combined with microextraction [15].

234 UAE-DLLME was also used for extraction and enrichment of acrylamide from various  
235 bread samples. Before DLLME, analyte was derivatized using xanthyrol, GC-MS being  
236 the final instrument for analysis [16]. Another example is extraction of Ochratoxin A and  
237 citrinin in fruit samples were extracted. The fruit samples were first extracted with 1%  
238 acetic acid in acetonitrile by UAE. After centrifugation, the upper phase (acetonitrile) was  
239 further employed as disperser solvent in the subsequent DLLME. This is a green aspect  
240 that allows the use of extraction solvent of first technique to be disperser solvent of the  
241 other technique leading to reduction of overall solvent consumption [17]. The other  
242 examples are listed in Table 2.

### 243 ***2.1.3. Ultrasound-microwave synergistic extraction combined with microextraction***

244 Combining UAE and MAE with microextraction provides synergistically enhanced  
245 extraction performance. Ultrasound-microwave synergistic extraction (UMSE) was  
246 combined with headspace solid phase microextraction (HS-SPME) for extraction of  
247 volatile components in tobacco. UMSE-HS-SPME combines separation, extraction, and  
248 enrichment in a single step. UMSE-HS-SPME provided more type of volatile components  
249 compared to MAE-HS-SPME and HS-SPME, favoring synergistic effects. These effects  
250 were explained with the help of SEM images of ultrasound and microwave irradiated  
251 tobacco during extraction [18]

252 The key characteristics of conventional extractions combined with microextractions are  
253 provided in Table 2.

## 254 **2.2. Combined techniques for liquid samples**

255 In this combination, conventional technique is used for the cleanup and isolation of target  
256 analytes from relatively large volume of liquid samples. The analytes in the extract of the  
257 conventional technique are further concentrated using microextraction approach. The  
258 example of this category is hyphenation of solid phase extraction with other  
259 microextraction approaches.

### 260 **2.2.1. Solid phase extraction combined with microextraction techniques**

261 Solid phase extraction (SPE) is combined with microextraction to achieve certain goals  
262 related to matrix complexity. SPE provides both concentration and cleanup of the target  
263 analytes. SPE is usually selected to deal with dirty or complex matrices. However, it  
264 requires large volume of elution solvent and thus decreases enrichment factors (EFs).  
265 Microextraction alone can provide reasonably high EFs but still they have some challenges  
266 to deal with complex matrices. Large volume SPE extracts can be further enriched by  
267 microextraction and this combination will provide both cleanup and high EFs [19].

268 SPE and solidified organic drop microextraction (SODME) was coupled for extraction of  
269 total, suspended, dissolved, organic, and inorganic arsenic species (speciation) in tea leaves  
270 and tea infusions after combining with electrothermal vaporization ICP-MS. SPE was  
271 performed using a micro PTFE column with titanium dioxide as an adsorbent. NaOH  
272 solution was used for desorption of retained analytes. For SODME, chelating reagent along



273 with few microliters of organic solvent (extracting phase) was added to extract of SPE and  
274 stirred. After the extraction, organic drop was solidified by placing the vial in an ice bath.  
275 Organic phase was separated and melted and made up to 100  $\mu\text{L}$ . Only 10  $\mu\text{L}$  extract was  
276 injected in ETV-ICP-MS. This method provided very low LODs (ppt levels) as well as  
277 enrichment factors of 500 folds for As (III) and As (V). The method also showed good  
278 tolerance against very high concentration of common interfering ions mainly due to  
279 selective chelating reagent [19].

280 DLLME alone cannot provide proper cleanup when dealing with complex matrix. A kind  
281 of sample preparation is needed. The combination of SPE and DLLME can provide better  
282 cleanups as well as enhanced EFs. This combination is widely used for extraction in  
283 complex matrices. This is a good choice for cleanup and preconcentration of large volume  
284 samples as well as their preconcentration. EFs using DLLME mostly in the range of  
285 50–1000, which still cannot fulfill the requirement of the ultra-trace residue analysis.  
286 However, SPE combined with DLLME can provide very high EFs (up to 50,000), and it  
287 can be also used in complex matrices [20].

288 SPE-DLLME combination was used for the extraction of chlorophenols in aqueous  
289 samples [21]. SPE-DLLME was also used for extraction of OPPs in water samples before  
290 their determination by GC-MS. The elution solvent of SPE was used as disperser solvent  
291 in DLLME. This method resulted in very high enrichment factors and excellent LODs in  
292 the range of  $\text{pg/L}$ , which were not attainable using either of the methods alone [22]. SPE-  
293 DLLME-SFO was used for extraction of parabens in different matrices and EFs up to 1886  
294 were reported [23]. Similarly, some other studies reported even higher EFs, for example  
295 up to 2615 for extraction of OPPs in water [24], up to 7873 for amide herbicides in water  
296 [25], up to 9405 for extraction of PBDEs in water [20], up to 18,000 for extraction of  
297 chlorophenols in water [21], up to 21,000 for extraction of OPPs in water [26].

298 The values for enrichment factors depend on the selection of different parameters related  
299 to both SPE and DLLME. The selection of sample volume, suitable sorbent and elution  
300 solvent in SPE, and extraction solvent in DLLME are more critical. The analytical  
301 instrument can also have substantial effect on the sensitivity.

302 SPE-DLLME was developed for the extraction of eight pyrethroids in cereal samples  
303 which were further determined by GC-MS. LOQs with combined method were almost 10  
304 times better than SPE alone except for few analytes [27]. Similarly, SPE in combination  
305 with ion pair based surfactant assisted DLLME-SFO followed by graphite furnace atomic  
306 absorption spectroscopy was used for determination and speciation of mercury. The LOD  
307 was 0.009  $\mu\text{g/L}$  [28]. SPE-DLLME was also employed for extraction of different analytes  
308 in water [24], honey [29], human urine and plasma [30]. The analytical features of SPE-  
309 DLLME are provided in Table 3.

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### 314 **3. Miniaturized or microextraction techniques combined with each other**

315 Combined or binary microextraction techniques are also used to accomplish certain goals  
316 related complex matrices, analyte isolation, and preconcentration. These techniques are  
317 mostly used for liquid samples. However, QuEChERS followed by other microextraction  
318 technique, is a combination which is also used for the solid samples.

319

#### 320 ***3.1. Dual or tandem dispersive liquid-liquid microextraction***

321 DLLME has been widely accepted as an extraction technique both in its original and  
322 modified formats due to low consumption of toxic solvents. Dual or tandem DLLME  
323 involves coupling of two DLLME procedures. The major aim of this combination is to  
324 reduce the interferences that are co-eluted in the first DLLME by back extracting the  
325 analytes into the extraction solvent of second DLLME. In case, derivatization is combined  
326 with DLLME, second DLLME can remove excess catalysts and derivatizing reagents that  
327 otherwise may cause serious interference in separation and detection of target analytes.

328 To introduce further greenness in the procedure and deal with complex matrices, various  
329 variations in the original DLLME have been proposed. For example, the use of the toxic  
330 organic dispersants can be avoided by using surfactants. However, these surfactants can  
331 damage the stationary phase inside the capillary columns. To resolve this, reverse-phase  
332 DLLME and standard DLLME can be coupled. Such coupling was used for extraction of  
333 phenylpropenes in the oil samples. In the first DLLME oil sample was diluted using n-  
334 hexane and analytes are extracted using 160- $\mu$ L of 0.2 mM Triton X-100 in acetonitrile  
335 following all conventional procedure of DLLME. Then to the extract of first DLLME  
336 (110  $\mu$ L), water and ethyl acetate was added and analytes were extracted back into ethyl  
337 acetate. The solvent of the first extract served as a dispersant in the second DLLME. The  
338 purpose of the second DLLME was to reduce the concentration of the surfactant [31].

339 In another work, tandem-DLLME (TDLLME) was consisted of two hyphenated DLLME  
340 methods; the first was accompanied by air agitation in the presence of ultrasound  
341 irradiation and the last with only several air agitation cycles. The need of this combination  
342 arises from the situation when in first DLLME interference are co-eluted with analytes  
343 resulting in low sample cleanup. In the second DLLME analytes are extracted into  
344 relatively small volume of the extracting phase leading to further cleanup and  
345 preconcentration. The selection of extraction parameters such as extraction solvents, pHs  
346 are dependent on the nature of the target analytes and target instrumentation. The example  
347 of this kind is TDLLME of beta blockers in human plasma and pharmaceutical wastewater  
348 samples [32].

349 TDLLME was also used for the extraction of doxepin, citalopram, and fluvoxamine in  
350 aqueous samples. This method provided a high sample clean-up, and suitable for complex  
351 matrices. In the first DLLME, the analytes in an aqueous sample were extracted (by  
352 adjusting pH) into an organic solvent. This step provides a low sample cleanup as some  
353 interferences may coextract. In second DLLME, these analytes were simply back-extracted  
354 into an aqueous acceptor phase and sample cleanup was significantly enhanced. This step  
355 can also solve the problem of the final extract that should be aqueous with some  
356 instruments. The overall extraction time was 7 min, and very simple equipment was



357 required for this whole process [33]. TDLLME combining USAEME and AADLLME was  
358 used for extraction of tricyclic antidepressant drugs (TCA) wastewater and human plasma  
359 samples. Enrichment factors were in between 50 – 101 [34].

360 Dual DLLME can also be combined with derivatization. As an example of this, facile  
361 microwave assisted derivatization (MAD) was performed between forward-UADLLME  
362 and back-UADLLME. Because of complex matrix and low concentrations of target  
363 analytes (PPD and PPT) in rat plasma, the objective of forward-UADLLME was cleanup  
364 and enrichment. MAD was used for enhancing the detection sensitivity of target analytes.  
365 However, the excess use derivatization reagents and catalysts cause severe interferences in  
366 detection. The purpose of the back-UADLLME was removal of these excess reagents and  
367 simultaneously enriching derivatized analytes before LC–MS analysis [35]. Key features  
368 of TDLLME methods are listed in Table 4.

### 369 ***3.2. Electromembrane extraction combined with liquid phase microextraction***

370 Hollow fiber liquid-phase microextraction (HF-LPME) in three phase mode is performed  
371 by using a supported liquid membrane (SLM) which is an organic solvent impregnated in  
372 the pores of a hollow fiber membrane. The acceptor phase is aqueous and it is filled inside  
373 the lumen of the hollow fiber. The extraction is based on passive diffusion of neutral  
374 species from the sample through the SLM and into the acceptor solution. Although HF-  
375 LPME offers tremendous cleanup due to the high selectivity of the SLM and good  
376 enrichment factors due to the adjustable ratio between the sample volume and the acceptor  
377 volume. However, LPME is not suitable for simultaneous extraction of acidic and basic  
378 drugs.

379 Electromembrane extraction (EME) is a miniaturized sample preparation technique, which  
380 offers many benefits such as low cost, simple operation, and fast extraction as well as green  
381 in nature. EME is also used to selectively extract charged analytes using SLM using electric  
382 field and finally into acceptor phase. It provides isolation and cleanup. EME has mostly  
383 been used for extraction of basic drugs and acidic drugs individually. Recently, EME has  
384 also been used for simultaneous group separation of basic and acidic drugs at a certain  
385 sample pH, where the acidic drugs were negatively charged and the basic drugs were  
386 positively charged. However, recoveries were very low in such instances.

387 The coupling of EME and LPME has been proposed for single step and simultaneous  
388 extraction and clear group separation of acidic and basic drugs with some reasonably high  
389 recoveries. The concept took advantage of the fact that low sample pH is optimum pH for  
390 the extraction of basic analytes by EME and basic analytes by LPME. Compared to dual  
391 EME, this combination provided uniform electric field distribution as well as purity of the  
392 separated drugs. Basic drugs were extracted exhaustively by EME while slightly lower  
393 recoveries for acidic drugs were obtained because a small fraction of acidic drugs were  
394 trapped in SLMs of both EME and LPME. This combination has good potential for  
395 extraction in biological samples. Moreover, the low cost device can be used for single  
396 extraction to avoid any carry over effects [36].

397

398

### 399 **3.3. Hollow fiber supported liquid membrane and DLLME**

400 This combination was used for extraction of HF-DLLME for direct extraction of pesticides  
401 in grape juice samples. This combination resulted in reduction of some steps involved in  
402 conventional DLLME. It is important here to describe some procedural details to  
403 understand the underlying objectives of this combination.

404 Previously washed and dried HF membrane was cut into pieces of 2.0 cm length. A  
405 stainless-steel wire with diameter equal to the inner diameter of HF membrane was passed  
406 through the silicone septum with polypropylene screw cap. HF membrane piece was  
407 slipped over the stainless-steel wire in a way that its outer surface and the pores were  
408 available for the extraction of the analytes. This porous membrane fixed on the stainless-  
409 steel wire was then impregnated with dodecanol by direct immersion. Then it was fixed on  
410 the glass vial containing grape juice, buffer solution (to adjust pH), solution containing a  
411 mixture of the analytes and a solution containing a mixture of extraction and disperser  
412 solvent. The mixture was stirred to transfer the target analytes to SLM. After the extraction,  
413 HF membrane was removed from the sample and from the stainless-steel wire and to  
414 transfer it to an Eppendorf flask containing desorption solvent. This method does not  
415 involve centrifugation like standard DLLME methods and is less laborious [37].

416 The same combination of HF-DLLME with derivatization was used for extraction of  
417 aflatoxins in soybean juice followed by HPLC-FD determination. The main benefit of this  
418 method is the use of non-chlorinated solvent and insignificant amounts of organic solvents  
419 [38].

### 420 **3.4. Stir-bar sorptive extraction followed by DLLME**

421 Stir bar sorptive extraction (SBSE) is performed by coating the sorbent on a stir-bar which  
422 is stirred in the sample solution for an optimum time. The analytes are then desorbed  
423 thermally for GC and with solvent for HPLC. SBSE has similar advantages like SPME but  
424 EFs are much higher in case of SBSE. SBSE has been combined with DLLME-SFO for  
425 extraction of PAHs in water samples. The extracted PAHs were quantified using HPLC-  
426 UV. This combination provided very low LODs (0.0067 – 0.010 ppb) and very high EFs  
427 (1630 – 2637) [39].

### 428 **3.5. Dispersive/magnetic solid phase extraction combined with DLLME**

429 Here we describe some examples of single and two-step DSPE-DLLME and their  
430 advantages in sample preparation, which mainly rely on purifying target analytes as well  
431 as minimizing matrix effect.

432 Single step combination utilizes the benefits of both adsorption and solvent extraction in  
433 addition to the in-situ derivatization of the analytes. High enrichment factors can be  
434 obtained using this combination. This method was used for the extraction of aliphatic  
435 amines on the atmospheric fine particles. The disperser solvent (0.3 mL) was distributed  
436 into two parts, extraction solvent and derivatizing reagent was added to first part and 3 mg  
437 of the reduced graphene oxide was added to the second part and ultrasonicated for 1 min.  
438 First part was rapidly mixed to the sample solution and then the second part was added.  
439 Mixture was vortex agitated for 7 min and then centrifuged. The upper aqueous layer was  
440 carefully withdrawn by a syringe. The acetone (100  $\mu$ L) was added to the remaining

441 mixture to desorb the analytes with aid of sonication. After that it was centrifuged, and  
442 supernatant was transferred to a glass micro-insert and it was dried and reconstituted in  
443 20  $\mu$ L of acetone. High enrichment factors in the range of 307 – 382 were obtained [40].

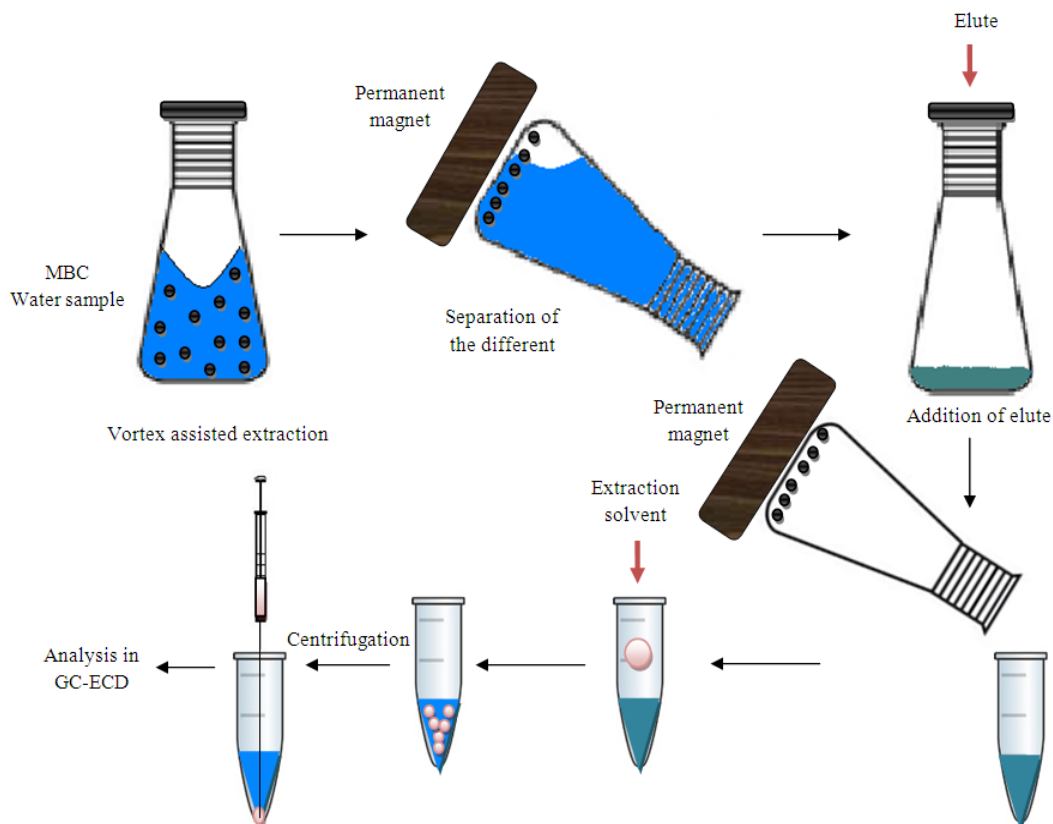
444 In the two-step combination, DSPE is performed first with the objectives of better sample  
445 clean up using selective adsorbent. The method was designed for extraction of benzoylurea  
446 insecticides in soil and sewage sludge. The analytes were first leached from the certain  
447 amount of the sample into acetone with aid of sonication. After filtration, activated carbon  
448 was used for DSPE to selective cleanup co-eluting colored species. Again, the filtered  
449 acetone was used for VA-DLLME-SFO. Acetone not only worked as leaching solvent but  
450 the dispersive solvent for DLLME. 1-undecanol was used as extraction solvent [41].

451 Nano polypyrrole based MSPE was followed by DLLME for extraction of megestrol  
452 acetate and levonorgestrel in biological samples prior to their determination by HPLC-UV.  
453 In DLLME, sedimented phase was separated using filtration based phase separation.  
454 Reasonably high EFs (3680 – 3750) were obtained with corresponding LODs of  
455 0.03 ng/mL [42]. Octadecyl modified magnetic silica nanoparticles based MSPE was also  
456 combined with DLLME for extraction of phthalates in water. The eluent of MSPE was  
457 used as disperser for following DLLME. This combination eliminates the step of  
458 evaporative concentration. The average EFs of 20000 were obtained with LODs lying in  
459 part per trillion range. This method can be beneficial for ultra-trace analysis in complex  
460 matrices [43].

461 Magnetic matrix solid phase dispersion (MMSPD) was also combined with DLLME. The  
462 extract of MMSPD was further subjected to DLLME. This combination provided LODs  
463 lower than MMSPD or DLLME alone [44]. The schematic is shown in the Figure 5.

464

465



466

467 Figure 5. Schematic procedure of the MMSPD assisted DLLME method [44].

468

### 469 **3.6. Quick, Easy, Cheap, Effective, Rugged, and Safe Method Followed by DLLME**

470 Quick, Easy, Cheap, Effective, Rugged, and Safe Method (QuEChERS) is initially  
 471 developed for sample cleanup. The complex biological and environmental samples are first  
 472 treated with QuEChERS using acetonitrile as a solvent. Despite the fact QuEChERS can  
 473 provide an efficient cleanup but the EFs are not very high. The cleaned extracts then can  
 474 be employed for microextraction to achieve low LODs through attainment of high EFs.  
 475 The other advantage is better chromatographic separations. DLLME is a rapid, easy to  
 476 operate, efficient microextraction technique which provides very high EFs.

477 The initial work combining QuEChERS with DLLME was reported in 2011 for extraction  
 478 of multi pesticide residues in maize samples prior to their determination by GC-MS. Apart  
 479 from the high EFs, DLLME provided better cleanup of some polar matrix components  
 480 maximizing the sensitivity of single quadruple MS. The enrichment was about ten times  
 481 than QuEChERS alone. The LODs were in between 8 to 55  $\mu\text{g}/\text{kg}$  [45].

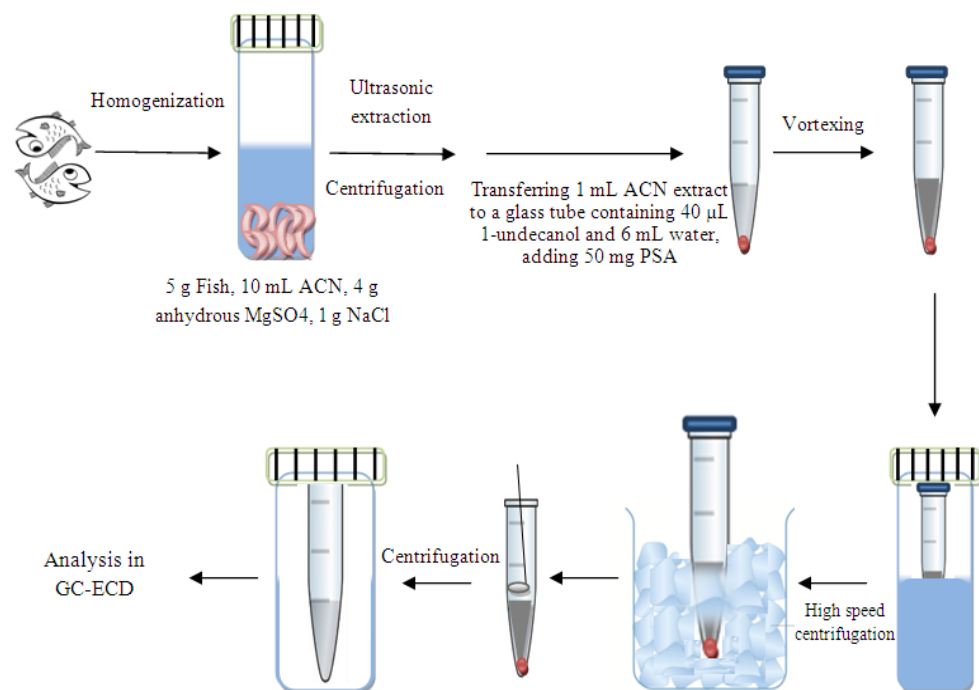
482 QuEChERS-IL-DLLME was also used to extract bis-phenol A (BPA) in canned food  
 483 samples. The acetonitrile extract (1 mL) obtained from QuEChERS was subjected to  
 484 IL-DLLME. IL was used as extraction phase while acetonitrile from first part worked as  
 485 disperser solvent. The used IL, 1-hexyl-3-methylimidazolium  
 486 bis(trifluoromethylsulfonyl)imide  $[\text{C}_6\text{mim}][\text{Tf}_2\text{N}]$  has lower viscosity, surface tension, and





487 water solubility, and higher density than water; it is greener alternative to conventional  
488 DLLME solvents (haloalkanes). In this way, this combination provided various  
489 advantages. EF of 98 was obtained for BPA [46].

490 For the complex matrices like fish DLLME cannot be used alone, a cleanup is usually  
491 required. QuEChERS was combined with DLLME based on solidification of floating  
492 organic droplet (SFOD) for determination of organochlorine pesticides (OCPs) in fish.  
493 SFOD relies on the use of the extraction solvent with density lower than water and melting  
494 point near the room temperature. ACN worked as dispersive solvent while 1-Undecanol  
495 was the extraction solvent [47]. The procedural steps of this combination are indicated in  
496 the Figure 6.



497

498 Figure 6. The combination of QuEChERS-DLLME (SFOD) [47].

499 There are several other examples where this combination was successfully applied for the  
500 extraction of analytes from complex matrices. In most of the cases, acetonitrile of  
501 QuEChERS was employed as dispersive solvent for DLLME which is a green aspect of  
502 this combination. QuEChERS-DLLME was used for preconcentration of pesticide residues  
503 in fatty food [48], OPPs in milk samples [49], and diflubenzuron and chlorbenzuron in  
504 fruits [50].

505 The key characteristics of binary microextraction are provided in Table 5.

#### 506 4. Comparison and scope of combined extraction methods

507 Microwave or ultrasound assisted extraction combined with microextraction is usually  
508 used for solid samples. Here, microwave or ultrasound assisted extraction releases analytes  
509 from the solid samples into the suitable solvent. The analytes in the extract of MAE or  
510 UAE are further concentrated using microextraction. The combination serves the purpose

511 of analyte release, cleanup, and further enrichment. With this combination, EFs up to 300  
512 have been reported. Although, LODs are highly dependent on the sensitivity of the final  
513 determination instrument, LODs down to low ppb levels have been achieved.

514 SPE-DLLME has been widely used for large volume liquid samples. SPE performs both  
515 separation and cleanup of the analytes while DLLME can further concentrate the analytes  
516 into microliter range of extraction solvent. This combination has provided ultrahigh EFs  
517 (up to 50000 times) and LODs in some cases in the ppq range.

518 Binary microextractions are also designed to address certain challenges of sample  
519 preparation. For example, in dual or tandem DLLME, the interferences that are co-eluted  
520 in the first DLLME are removed by back extracting the analytes in second DLLME. In  
521 case, derivatization is combined with DLLME, second DLLME can remove excess  
522 catalysts and derivatizing reagents that otherwise may cause serious interference in  
523 separation and detection of target analytes. EFs up to 200 have been reported using tandem  
524 or dual DLLME. QuEChERS can provide better cleanup for complex samples, but EFs are  
525 not very high. Its combination with DLLME can significantly improve EFs.  
526 Dispersive/Magnetic SPE-DLLME takes advantage of both adsorption and solvent  
527 extraction. EFs as high as 21000 and LODs as low as ppt range were achieved.

528

## 529 **5. Green Analytical Chemistry and combined extraction methods**

530 The role and impact of Green Analytical Chemistry (GAC) has significantly increased on  
531 all analytical procedures. Some of the GAC principles emphasize on the reduction of  
532 energy, miniaturization and automation of methods, reduction in the use of toxic reagents  
533 and solvents, integration of analytical processes, minimizing sample size or number of  
534 samples, and avoiding derivatization [51].

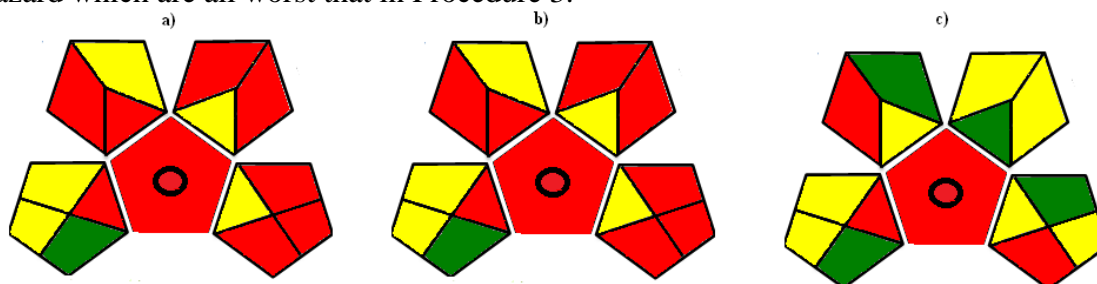
535 Above presented literature depicts some combined extraction methods which present  
536 several opportunities to move toward GAC practices. For example, the use of relatively  
537 greener energy sources such as microwave and ultrasound for extraction applications is  
538 described [5,9]. This will reduce the impact on the environment and the analyst compared  
539 to conventional heating sources.

540 In order to present the differences in the green nature of selected procedures [52, 53, 54]  
541 based on LLE (Procedure 1 [52]), UAE (Procedure 2 [53]) and UAE-DLLME (Procedure  
542 3 [54]) for target compound determination in oil samples, a Green Analytical Procedure  
543 Index (GAPI) and Analytical Eco-Scale were applied. GAPI is a “green” assessment tool  
544 of analytical methodologies which rates analytical methods against amount and type of  
545 waste, environmental hazard and chemical health, and energy requirements [55]. This tool  
546 presents information on the entire analytical protocol, from sampling, through sample  
547 preparation to final determination. The second tool named Analytical Eco-Scale, is a tool  
548 based on penalty points (PPs) which are subtracted from a base of 100. Penalty points are  
549 assigned for each reagent/ chemical compound relating to the amount, chemicals  
550 utilization, occupational hazards, high energy consumption, and generation of waste [56].  
551 In the case of analytical procedures comparison, this one is assigned as greener and more  
552 economical, which is characterized by the highest score.



553 The evaluation of examined procedures using GAPI and Analytical Eco-Scale tool is  
554 presented in Figure 7 and Table 6, respectively.

555 Taking into consideration examined, it is visible at first glance that Procedure 3: UAE-  
556 DLLME can be considered greener than the other two methodologies. This is mainly  
557 because a microextraction instead of extraction at macro scale is performed, thus less  
558 reagents/solvents are applied affecting the reduction of generated waste. The main critical  
559 point of Procedure 1 and 2 are extraction procedure performed at macro scale, the character  
560 and aliquot of solvents and reagents used, aliquot of generated waste and occupational  
561 hazard which are all worst than in Procedure 3.



562

563 Figure 7. Assessment of the green profile of evaluated procedures (Procedure 1 [52],  
564 Procedure 2 [53] and Procedure 3 [54]) using GAPI tool.

565 In solvent based extraction, it is not possible to eliminate the extraction solvents completely  
566 but their quantities can be significantly decreased. Solvent based microextraction are best  
567 examples of this. However, when integration of two analytical extraction techniques is only  
568 a viable way to cope with complex matrices or certain application scenario in sample  
569 preparation, there should be some ways to reduce the use of reagents and solvents. This  
570 has been demonstrated in many combined methods that extraction solvent of first technique  
571 can be used as disperser solvent of the upcoming DLLME [41,47]. Another development  
572 with regards to GAC in combined methods is the use of greener solvents such as ionic  
573 liquids, surfactants [31].

574 In order to deal with certain type of solid samples (tissues, plant, meat etc.), a kind of  
575 pretreatment or digestion is required. This increases overall steps related to pretreatment  
576 and then extraction. The one solution is to perform pretreatment/digestion and extraction  
577 in a single step. Combined extraction methods based on simultaneous digestion and  
578 extraction have been discussed above [3,4]. In some cases, these combined methods,  
579 reduce the number of steps as well as the requirement of special equipment [37].

580 The 6<sup>th</sup> principle of the GAC says avoid derivatization. However, this is not possible to  
581 eliminate such derivatizations due to certain limitations related to nature of the analytes  
582 and available instrumentation. Different ways to make derivatization process greener  
583 include use of less-toxic reagents and solvents, and in situ derivatization using  
584 microextraction [57]. This has been practiced in combined extractions [6,35].

585

586

587

## 588 6. Conclusion and future recommendations

589 The idea of combining different extraction techniques together mostly arises from the  
590 special extraction and analysis requirements or underlying limitations of individual  
591 approaches. In most of the cases, the combined methods provide a better way of dealing  
592 with complex matrices, enhanced cleanups, ultra-high enrichment factors, and trace level  
593 detection. In some cases, they also reduce the overall number of steps associated with an  
594 individual extraction procedure, or eliminate some procedural steps or reduce the  
595 requirement of the electric or special equipment.

596 Based on the literature presented above, it can be suggested that microwave/ultrasound  
597 assisted extractions combined with microextraction can be a preferable choice for solid  
598 samples. This combination can provide extraction as well as high enrichment factors.  
599 Simultaneous MAE and  $\mu$ -SPE or LPME can provide single step digestion and extraction  
600 [3]. SPE-DLLME is a good choice for high volume liquid samples; SPE can provide  
601 extraction as well as better clean up, while DLLME can further concentrate the target  
602 analytes leading to improved sensitivity of detection. In some cases, EFs of more than  
603 50,000 have been attained. Tandem DLLME can provide efficient sample clean up while  
604 dealing with complex matrices. Dispersive/magnetic SPE combined with DLLME takes  
605 benefit of both adsorption and solvent extraction. QuEChERS can provide an efficient  
606 cleanup but the EFs are not very high, however, its combination with DLLME can serve  
607 the purpose.

608 Some difficulties may also arise while combining these methods. When each method is  
609 performed separately in the combination, it increases overall number of steps as well as  
610 extraction time compared to any individual method. Combined methods may have  
611 limitations in certain aspects such as requirement of certain volume of the sample and  
612 extraction time, to get an efficient performance. For example, in SPE-DLLME, SPE part  
613 usually requires a large volume sample. On the other hand, this combination provides not  
614 only better cleanups also very high enrichment factors and detection limits. In such cases,  
615 the analyst should decide what preferred analytical figure of merits in his analysis are. It  
616 has also been noticed that most of the combined methods involve one extraction followed  
617 by other, this can be time-consuming and laborious compared to individual techniques.

618 The online coupling of these methods is challenging and it should be considered for future  
619 research in this area. Another aspect that needs additional research efforts is the automation  
620 of such combinations with analytical instruments as it can greatly reduce the human effort  
621 and chances of error. In addition to that these methods should not be developed for the sake  
622 of the new combination but with clear objectives and as a solution to existing problems.  
623 Different variables involved in combined methods such as time of extraction, number of  
624 steps, use of solvents and reagents, and requirement of energy sources should be considered  
625 in accordance with recent trends of GAC.

626

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629



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635

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*Table 1. Main characteristics, advantages and limitations of enhanced and conventional extraction technologies*

Issue	Conventional methods		Enhanced extraction techniques	
	<i>Soxhlet</i>	<i>Extraction with mechanical agitation</i>	<i>Microwave-assisted</i>	<i>Ultrasound-assisted</i>
<b>Force of driving</b>	Heat	Solvent contact	Microwave power	Acoustic cavitation
<b>Sample size</b>	1-30 g	1-30 g	1-10 g	1-30 g
<b>Extraction time</b>	6-24 h	Several hours	3-30 min	10-60 min
<b>Solvent amount</b>	150-500 mL	50-500 mL	10-40 mL	50-200 mL
<b>Power amount</b>	High	High	High	Moderate
<b>Advantages</b>	Not use of sophisticated equipment	Not use of sophisticated equipment	Fast. Easy to handle. Moderate use of solvent.	Safe (atmospheric pressure and ambient temperature). Easy to handle. Moderate use of solvent. Reproducible.
<b>Limitations</b>	Exposure risk to organic vapors. Thermo-labile compounds degradation.	Spills risk. Exposure to organic vapors. Thermo-labile compounds degradation. Filtration step is required.	Explosion risk (solvent must absorb microwave power). Filtration step is required. Expensive.	Filtration step is required.

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**Table 2.** Key characteristics of conventional extractions combined with microextractions

Combination	Analytes	Matrix	Instrument	EFs	LODs (ppb)	Ref.
MAE-UADLLME	Pyrethroids residues	Litchi fruit	HPLC-UV	56.4 – 68.3	1.15–2.46	[11]
MAE-DLLME	Polyamines	Meat	HPLC-UV	190 – 305	0.24 – 0.42	[7]
MAE-SPP-DLLME	Antimicrobial pharmaceuticals	Fish	LC-MS/MS		(4.54 – 101.3) ×10 <sup>-6</sup>	[8]
MAE-DLLME	PAHs	Smoked rice	HPLC-UV	258 - 307	0.05 – 0.12	[10]
MAE-DLLME	Nitrosamines	Food	GC-MS		0.1 – 0.5	[9]
DMAE-SDME	OPPs	Tea	GC-MS		0.4 – 1.7	[12]
DMAE-CFME	OPPs	Vegetables	GC-MS		0.59 – 1.57	[13]
MASE-μ-SPE	Parabens	Human ovarian cancer tissues	HPLC-UV	27 – 314	0.005 – 0.024	[3]
MAE-DLLME	Aromatic amines	Hamburger patties	HPLC-UV	112 – 174	0.06 – 0.21	[58]
MA-HS-LPME	Trihalomethanes and haloketones	Fish tissue and alga	GC-MS		0.051 – 0.110	[4]
UAE-DLLME	PCBs	Marine sediments	GC-MS	-	0.021 – 0.057	[15]
UAE-DLLME	Acrylamide	Bread	GC-MS	230	0.54	[16]
UAE-DLLME	Acrylamide	Potato chips	GC-MS	192	0.6	[59]
UAE-DLLME	Ochratoxin A and citrinin	Fruit	HPLC-FLD		0.06 – 0.16	[17]
USL-SPE-DSLLME	OPPs	Soil samples	GC-MS	6890–8830	0.012 – 0.2	[60]

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941 **Table 3.** List of methods combining SPE and microextraction

Combination	Analytes	Matrix	Instrument	EFs	LODs (ppb)	Ref.
SPE-SODME	Arsenic species	Tea leaves and tea infusions	ETV-ICP-MS	500	0.000046 – 0.000072	[19]
SPE-DLLME	PBDEs	Water	GC-MS	6838 – 9405	0.04 – 0.16	[20]
SPE-DLLME	Chlorophenols	Water	GC-ECD	4390 – 17870	0.0005 – 0.1	[21]
SPE-DLLME	OPPs	Water	GC-MS		0.000038 – 0.000230	[22]
SPE-DLLME-SFO	Parabens	Water, shampoo, mouth rinse solution.	HPLC-UV	245 – 1886	0.3 – 1.7	[23]
SPE-DLLME	OPPs	Water	HPLC-UV	2219 – 2615	0.021 – 0.15	[24]
SPE-DLLME	Amide herbicides	Water	GC-MS	6593 - 7873	0.002 – 0.006	[25]
SPE-DLLME	OPPs	Water	GC-FPD	15160 – 21000	0.0002 – 0.0015	[26]
SPE-DLLME	Pyrethroids	Cereals	GC-MS	18.1 – 25.7	0.2 – 4.0	[27]
SPE-SA-DLLME-SFO	Hg <sup>2+</sup>	Fish, sand, cigarette, pine leaf, well water, river water	GFAAS	1540	0.009	[28]
SPE-DLLME	Pyrethroids	Honey	GC-MS		0.02 – 0.04	[29]
SPE-DLLME	Benzodiazepines	Human urine and plasma	HPLC-UV		0.07 – 0.7	[30]

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*Table 4. Key features of tandem-DLLME methods*

Combination	Analytes	Matrix	Instrument	EFs	LODs (ppb)	Ref.
TDLLME	Beta blockers	Human plasma and pharmaceutical wastewater	HPLC-UV	75 – 100	0.8 – 1.0	[32]
TDLLME	Pharmaceutical drugs	Aqueous matrices	HPLC-UV	63 – 94	3 – 10	[33]
TDLLME	TCAs	Wastewater and plasma	HPLC-UV	50 – 101	0.7 – 1.0	[34]
DUADLLME-MAD	PPD and PPT	Rat plasma	UHPLC-MS/MS	164 – 182	0.010 – 0.015	[35]

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**Table 5.** List and analytical features of the methods based on binary microextraction

Combination	Analytes	Matrix	Instrument	EFs	LODs (ppb)	Ref.
SBSE-DLLME-SFO	PAHs	Water	HPLC-UV	1630 – 2637	0.0067 – 0.010	[39]
DSPE-DLLME	Aliphatic amines	Atmospheric fine particles	GC-MS	307 – 382	0.03 – 0.09	[40]
DSPE-VA-DLLME	Benzoylurea insecticides (BUs)	Soil and sludge	HPLC-UV	104 – 118	0.08 – 0.56	[41]
MMSPD-DLLME	PCBs	Water	GC-ECD		0.00005 – 0.0001	[44]
MSPE-DLLME	Megestrol acetate and levonorgestrel	Biological samples	HPLC-UV	3680 – 3750	0.03	[42]
MSPE-DLLME	Phthalates	Water	GC-FID	17749 – 21278	0.002 – 0.003	[43]
QuEChERS-IL-DLLME	BPA	Canned food	HPLC-UV	98	0.1	[46]
QuEChERS-DLLME (SFOD)	OCPs	Fish	GC-ECD		0.65 – 1.58	[47]
QuEChERS-DLLME	Pesticide residues	Oil seeds	GC-MS	6 – 17	0.01 – 12.17	[48]
Modified QuEChERS-DLLME-SFO	OPPs	Milk	GC-FPD	159 - 213	0.1 – 0.3	[49]
Acetonitrile-based extraction with DLLME	Diflubenzuron and chlorbenzuron	Fruits	HPLC-UV		5.0	[50]

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979 Table 6. Calculated PPs for evaluated analytical procedures for PAHs determination in oil samples (Procedures 1-3)

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PROCEDURE 1: LLE-SPE [52]		PROCEDURE 2: UAE-SPE [53]		PROCEDURE 3: UAE-DLLME [54]	
Reagents	PPs	Reagents	PPs	Reagents	PPs
n-hexane: 16 mL	16	Acetonitrile: 27 mL	16	Water: 3 mL	0
N,N-dimethyl formamide: 8 mL	8 4	Internal standard	4	Acetone: 1 mL	4
Internal standard	0	Dichlorometane: 70 mL	6	Toluene: 100 µL	3
Saline solution: 50 mL	0	n-hexane: 20 mL	16		
Dichloromethane: 20 ML	6				
Acetonitrile: 1 mL	8				
	Σ 42		Σ 42		Σ 7
Instruments	PPs	Instruments	PPs	Instruments	PPs
Transport	1	Transport	1	Transport	1
GC-MS	2	LC-FD	2	GC-MS	2
Occupational hazard	2	Occupational hazard	2	Occupational hazard	1
Centrifugation	1	Waste	5	Waste	3
Sonification	1	Centrifugation	1		
Waste	5				
	Σ 12		Σ 11		Σ 7
<b>Total PPs: 54</b>		<b>Total PPs: 53</b>		<b>Total PPs: 14</b>	
<b>Score: 46</b>		<b>Score: 47</b>		<b>Score: 86</b>	