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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 microextration 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

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

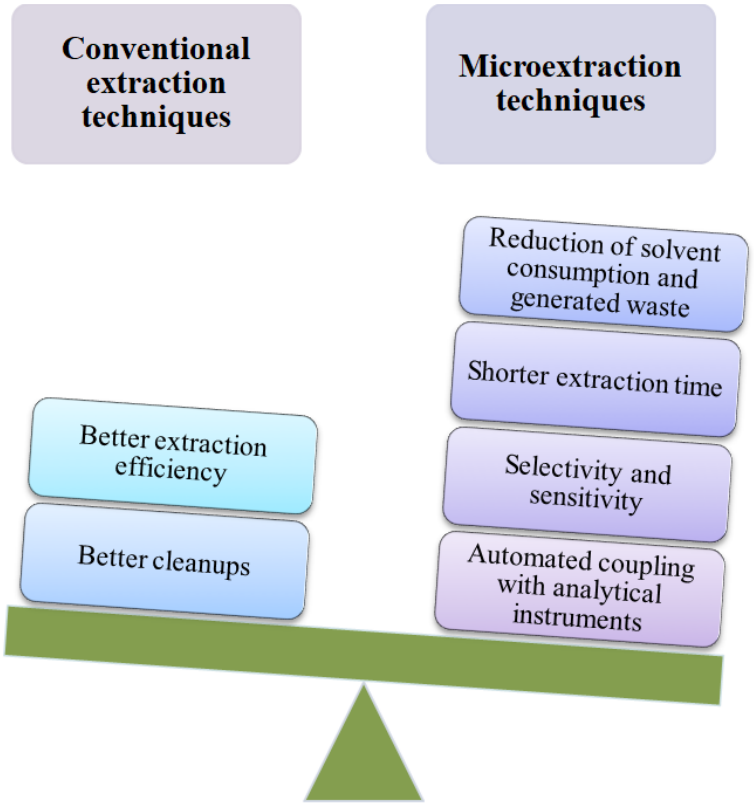

Figure 1. Advantages of conventional extraction and microextraction techniques.

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

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

Combined sample preparation techniques can be broadly classified into two categories

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

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

2. Conventional or enhanced extraction techniques combined with microextraction techniques

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

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

2.1.Combined techniques for the solid samples

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

2.1.1. Microwave assisted extraction combined with microextraction

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

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

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

2.1.1.1. Microwave assisted extraction followed by dispersive liquid liquid microextraction

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

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

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

2.1.1.2. Dynamic microwave assisted extraction followed by single drop microextraction

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

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

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

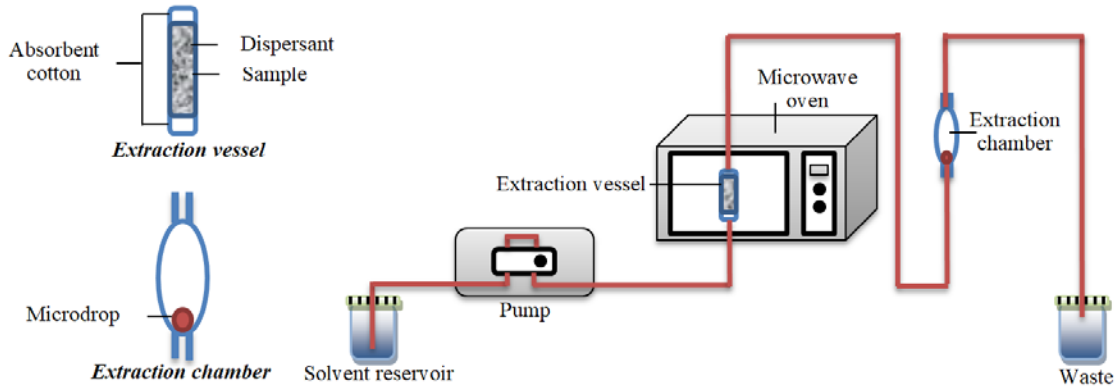

Figure 2. Schematic diagram of DMAE-SDME system [12].

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

2.1.1.3. Simultaneous microwave assisted extraction and micro-solid phase extraction

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

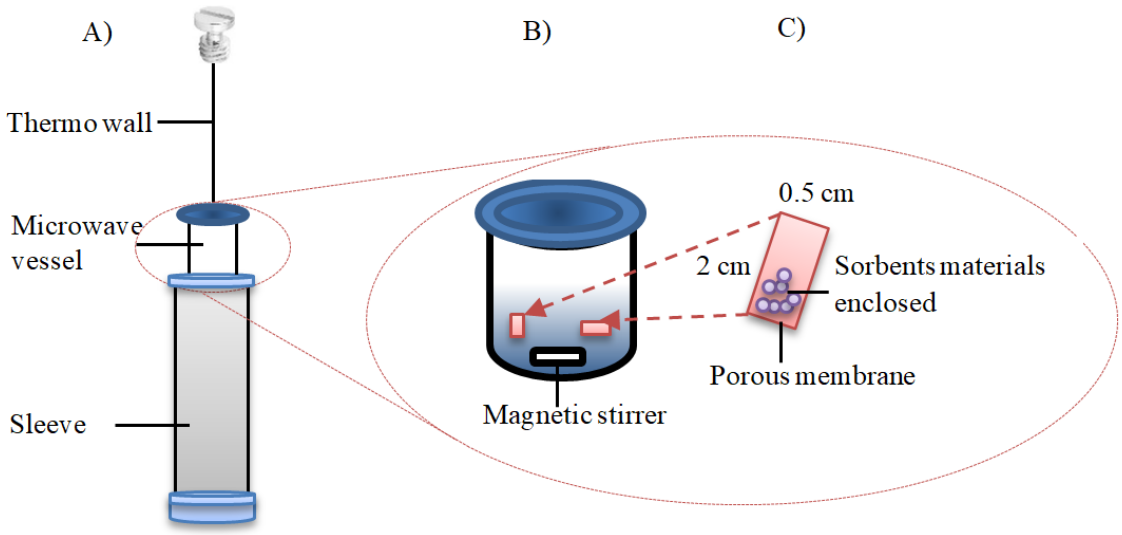

Figure 3. Schematic representation of A) MASE – μ-SPE setup, B) μ-SPE system and C) enlarge image of extraction device (not drawn to scale) [3].

2.1.1.4. Simultaneous microwave assisted extraction and liquid phase microextraction

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

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

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

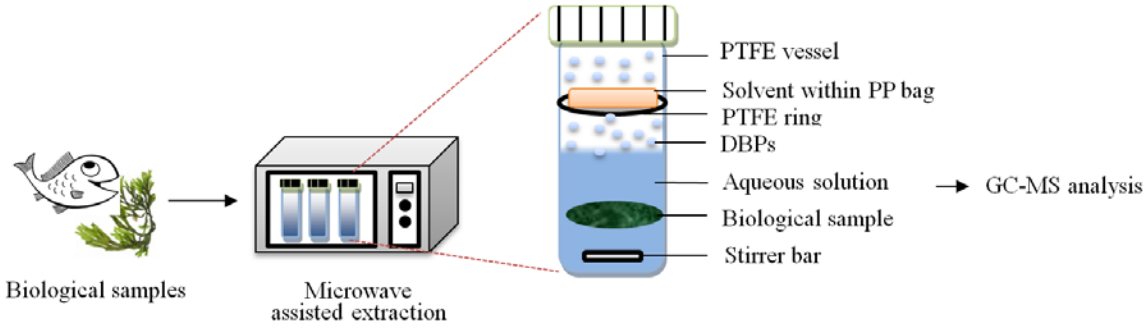

Figure 4. Schematic of extraction methods using MA-HS-LPME system [4].

2.1.2. Ultrasound assisted extraction and microextraction

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

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

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

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

2.1.3. Ultrasound-microwave synergistic extraction combined with microextraction

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

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

2.2. Combined techniques for liquid samples

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

2.2.1. Solid phase extraction combined with microextraction techniques

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

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

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

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

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

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

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

3. Miniaturized or microextraction techniques combined with each other

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

3.1.Dual or tandem dispersive liquid-liquid microextraction

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

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

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

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

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

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

3.2. Electromembrane extraction combined with liquid phase microextraction

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

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

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

3.3.Hollow fiber supported liquid membrane and DLLME

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

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

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

3.4.Stir-bar sorptive extraction followed by DLLME

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

3.5. Dispersive/magnetic solid phase extraction combined with DLLME

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

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

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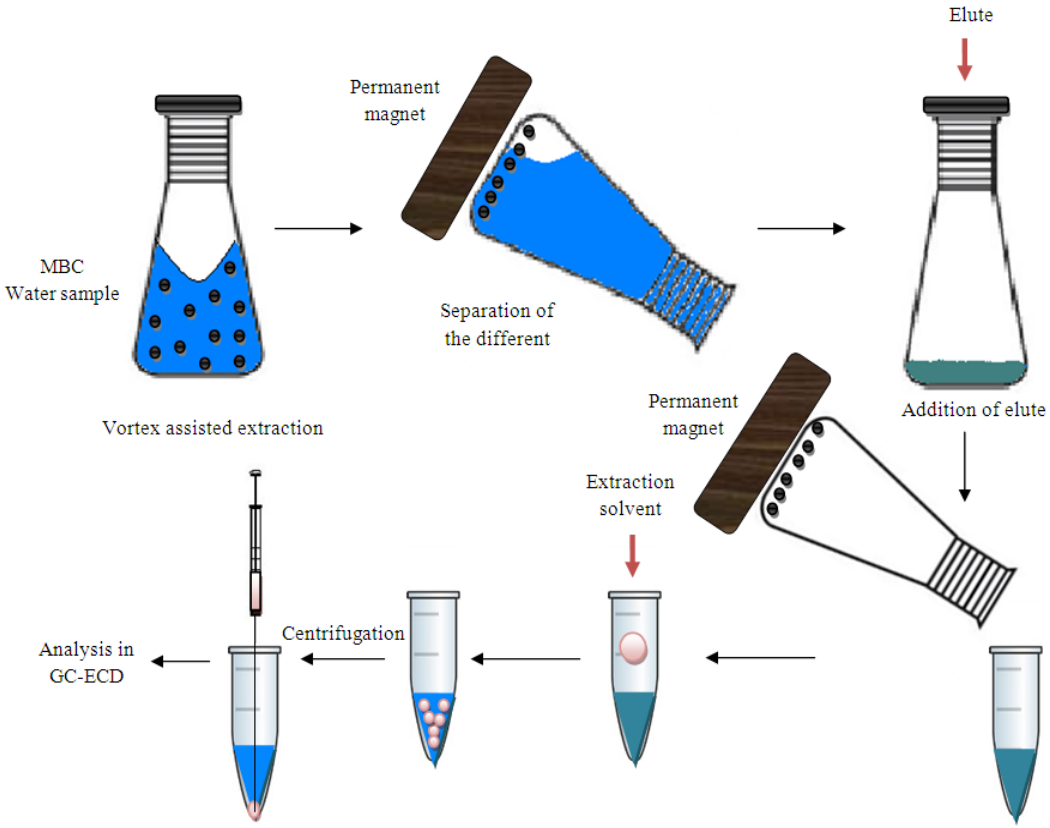


Figure 5. Schematic procedure of the MMSPD assisted DLLME method [44].

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

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

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

QuEChERS-IL-DLLLME was also used to extract bis-phenol A (BPA) in canned food samples. The acetonitrile extract (1 mL) obtained from QuEChERS was subjected to IL-DLLME. IL was used as extraction phase while acetonitrile from first part worked as disperser solvent. The used IL, 1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide [C_6mim][Tf_2N] has lower viscosity, surface tension, and

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

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

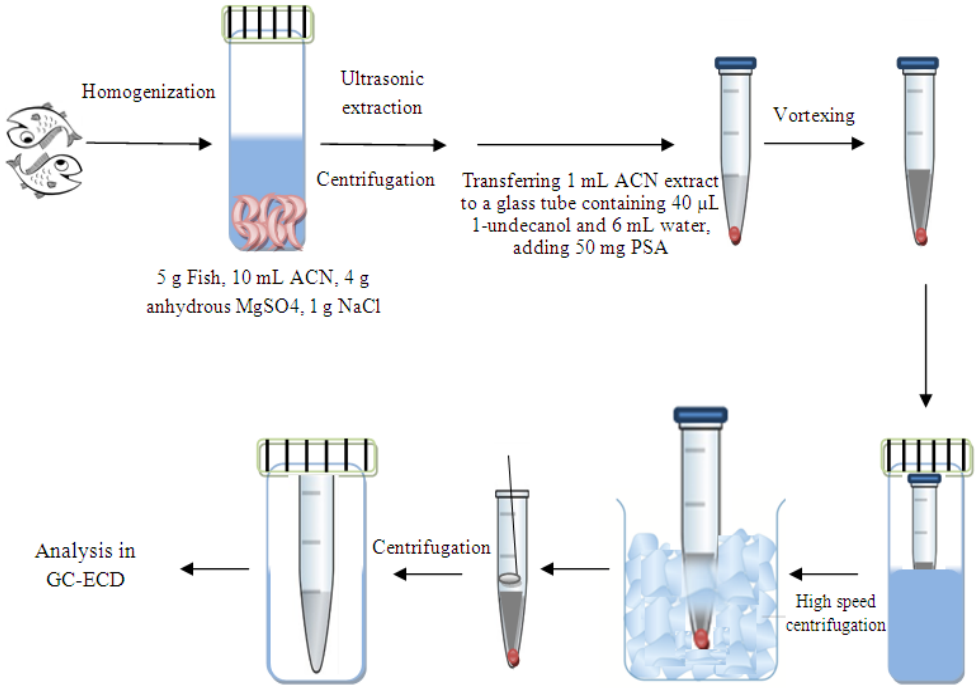


Figure 6. The combination of QuEChERS-DLLME (SFOD) [47].

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

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

4. Comparison and scope of combined extraction methods

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

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

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

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

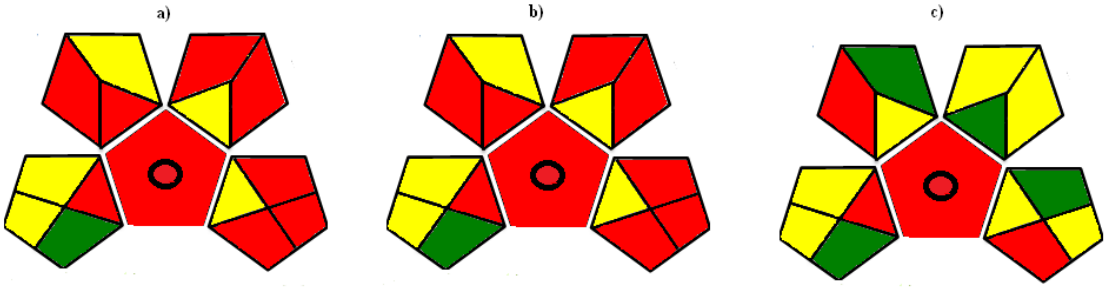
5. Green Analytical Chemistry and combined extraction methods

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

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

In order to present the differences in the green nature of selected procedures [52, 53, 54] based on LLE (Procedure 1 [52]), UAE (Procedure 2 [53]) and UAE-DLLME (Procedure 3 [54]) for target compound determination in oil samples, a Green Analytical Procedure Index (GAPI) and Analytical Eco-Scale were applied. GAPI is a “green” assessment tool of analytical methodologies which rates analytical methods against amount and type of waste, environmental hazard and chemical health, and energy requirements [55]. This tool presents information on the entire analytical protocol, from sampling, through sample preparation to final determination. The second tool named Analytical Eco-Scale, is a tool based on penalty points (PPs) which are subtracted from a base of 100. Penalty points are assigned for each reagent/ chemical compound relating to the amount, chemicals utilization, occupational hazards, high energy consumption, and generation of waste [56]. In the case of analytical procedures comparison, this one in assigned as greener and more 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 that the other two methodologies. This is mainly
557 because an microextraction instead of extraction at macro scale is performed, thus less
558 reagents/solvents is 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 that 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 6th 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].

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6. Conclusion and future recommendations

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

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

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

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

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

Issue	**Conventional methods**		**Enhanced extraction techniques**	
	Soxhlet	***Extraction with mechanical agitation***	***Microwave-assisted***	***Ultrasound-assisted***
Force of driving	Heat	Solvent contact	Microwave power	Acoustic cavitation
Sample size	1-30 g	1-30 g	1-10 g	1-30 g
Extraction time	6-24 h	Several hours	3-30 min	10-60 min
Solvent amount	150-500 mL	50-500 mL	10-40 mL	50-200 mL
Power amount	High	High	High	Moderate
Advantages	Not use of sophistical equipment	Not use of sophistical equipment	Fast. Easy to handle. Moderate use of solvent.	Safe (atmospheric pressure and ambient temperature). Easy to handle. Moderate use of solvent. Reproducible.
Limitations	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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931 ***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) $\times 10^{-6}$	[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^{2+}	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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974 ***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	Internal standard	4	Acetone: 1 mL	4
8 mL	4	Dichlorometane: 70 mL	6	Toluene: 100 µL	3
Internal standard	0	n-hexane: 20 mL	16		
Saline solution: 50 mL	0				
Dichloromethane: 20 ML	6				
Acetonitrile: 1 mL	8				
	Σ 42		Σ42		Σ7
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
Total PPs: 54 **Score:** 46		**Total PPs:** 53 **Score:** 47		**Total PPs:** 14 **Score:** 86	