Liquid Phase Microextraction Techniques Combined with Chromatography Analysis: A Review

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Sample pretreatment is the first and the most important step of an analytical procedure. In routine analysis, liquid–liquid microextraction (LLE) is the most widely used sample pre-treatment technique, whose goal is to isolate the target analytes, provide enrichment, with cleanup to lower the chemical noise, and enhance the signal. The use of extensive volumes of hazardous organic solvents and production of large amounts of waste make LLE procedures unsuitable for modern, highly automated laboratories, expensive, and environmentally unfriendly. In the past two decades, liquid-phase microextraction (LPME) was introduced to overcome these drawbacks. Thanks to the need of only a few microliters of extraction solvent, LPME techniques have been widely adopted by the scientific community. The aim of this review is to report on the state-of-the-art LPME techniques used in gas and liquid chromatography. Attention was paid to the classification of the LPME operating modes, to the historical contextualization of LPME applications, and to the advantages of microextraction in methods respecting the value of green analytical chemistry. Technical aspects such as description of methodology selected in method development for routine use, specific variants of LPME developed for complex matrices, derivatization, and enrichment techniques are also discussed.

Keywords: Liquid phase MicroExtraction, gas chromatography, liquid chromatography, derivatization, large volume injection

1. Introduction

Sample pre-treatment is the first and the most important step of an analytical procedure. In gas chromatography (GC) and liquid chromatography (LC) analysis, sample preparation is frequently considered the bottleneck of the entire analytical method. The main reasons to perform an extraction are to obtain a more concentrated sample, to eliminate interfering substances and to improve detection limits for specific compounds. In the past two decades, substantial efforts have been made to adapt the existing extraction methods and develop new approaches to save time, labor and materials [1]. Analytes' isolation from the matrix and their preconcentration are important aspects of this process. Several sample preparation methods have been accomplished for this purpose. The methods proposed for separation and pre-concentration including: liquid–liquid extraction (LLE) [2], coprecipitation [3], solid-phase extraction (SPE) [4–6], and cloud-point extraction (CPE) [7].

LLE is the oldest isolation technique in analytical chemistry. This operation mode is time-consuming, requires large volumes of sample and solvents, and is quite expensive and labor intensive. SPE in comparison with LLE is simpler to operate; it provides a higher enrichment factor and is easily automated, but uses amounts of solvents still relatively large [8]. To overcome these drawbacks, new sample preparation techniques have been developed over the last decades. Solid-phase microextraction [9–11] and liquid phase microextraction (LPME) [12] are recently renewed miniaturized sample preparation techniques that have been used in several applications. Modern trends in analytical chemistry lean towards the simplification and miniaturization of sample preparation, as well as the minimization of the organic solvent used.

The introduction of LPME allowed three milestones to set in green analytical chemistry (GAC). These 3 GAC operating modes have nowadays become commonly used techniques. They are as follows: i) the use of one solvent drop for extraction proposed by Liu and Dasgupta and Jeannot and Cantwell in the mid-1990s [13–15] resulted in the development of single-drop microextraction (SDME); ii) the use of supported liquid membranes by Audunsson [16] and hollow fibers by Thordarson et al. [17] and Pedersen-Bjergaard et al. [18] as solid support and protection for the extraction solvent resulted in supported liquid membrane extraction (SLME) and hollow-fiber liquid-phase microextraction (HF-LPME), respectively; and iii) the use of a ternary solvent system by Rezaee et al. [19] that contained the aqueous sample, an extraction solvent, and a dispersion solvent to promote the formation of solvent droplets, which is denoted as dispersive liquid–liquid microextraction (DLLME).

The use of these techniques is extensive in water samples, but unfortunately, the application of DLLME (or its variants) on biological samples is more complicated [20]. In complex samples, it is more difficult to obtain a separated floating organic drop due to the interaction of the matrix components with the organic solvents [21]. Therefore, researchers in the field

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developed ad hoc methods to determine the target analytes in specific matrices, such as rice [22], meat [20, 23], cheese [24], milk [25], wine [26], urine [27], honey [25], and plasma [1].

Thus, miniaturized methods of LLE have been developed to reduce the amount of organic solvents and substitute chlorinated solvents with more environmentally friendly solvents [28]. In recent years, new solvents such as deep eutectic solvents (DESs) based on ionic liquids (ILs) have been introduced to further improve the efficiency of LPME operating modes [29–32].

It is difficult to differentiate and distinguish amongst all the published microextraction techniques, because their principles or practical implementation are similar or differ only in a few details. We thus decided to classify the many apparently different operating modes in three main groups based on the first distinction made above. Therefore, we distinguished i) SDME-based operating modes, ii) supported liquid membranes and hollow-fiber microextraction modes, and iii) basic DLLME and its variants.

The aim of this review is to report on the state-of-the-art liquid-phase microextraction techniques used in column chromatography, with an emphasis on the description of the systems currently available on the market and the fully automated ones, given the recent upswing in the availability and range of automation techniques. Attention was paid to the classification of the LPME techniques and to their historical contextualization in applications in the most varied matrices through derivatization and enrichment techniques in respect of GAC principles.

2. Literature Search Criteria, Overview of the Results, and Classification of the Liquid Phase MicroExtraction (LPME) Techniques

Much literature has been produced since the 90s concerning LPME techniques. We could find about 4.000 papers on the Scopus database (Elsevier, Amsterdam, Netherlands). We organized the papers in three main groups, using structured search strategies based on two concepts: (1) the technique names (both full name and acronym) and their technical setup, (2) the keywords and acronyms liquid–liquid microextraction, LLME, liquid-phase microextraction, LPME. We used Boolean operators AND/OR to obtain correct and comprehensive results. As time frame for our research, we selected the period from 1975 to January 2019. No document-type restrictions were applied.

DLLME is the technique on which more peer-reviewed publications were produced with about 2.200 results; HF-LLME and SDME techniques resulted second in line according to the number of publications, with about 500 scientific papers each. Last, with 140 publications, was the microporous-membrane liquid–liquid extraction (MMLLE) technique.

The papers were also divided by subject area. The main research areas for LPME techniques are chemistry, biochemistry, genetics and molecular biology, chemical engineering, and environmental science. The above results are represented graphically in Figure 1.

In the following, the three groups of techniques are reviewed in order of relevance as evidenced by the number of

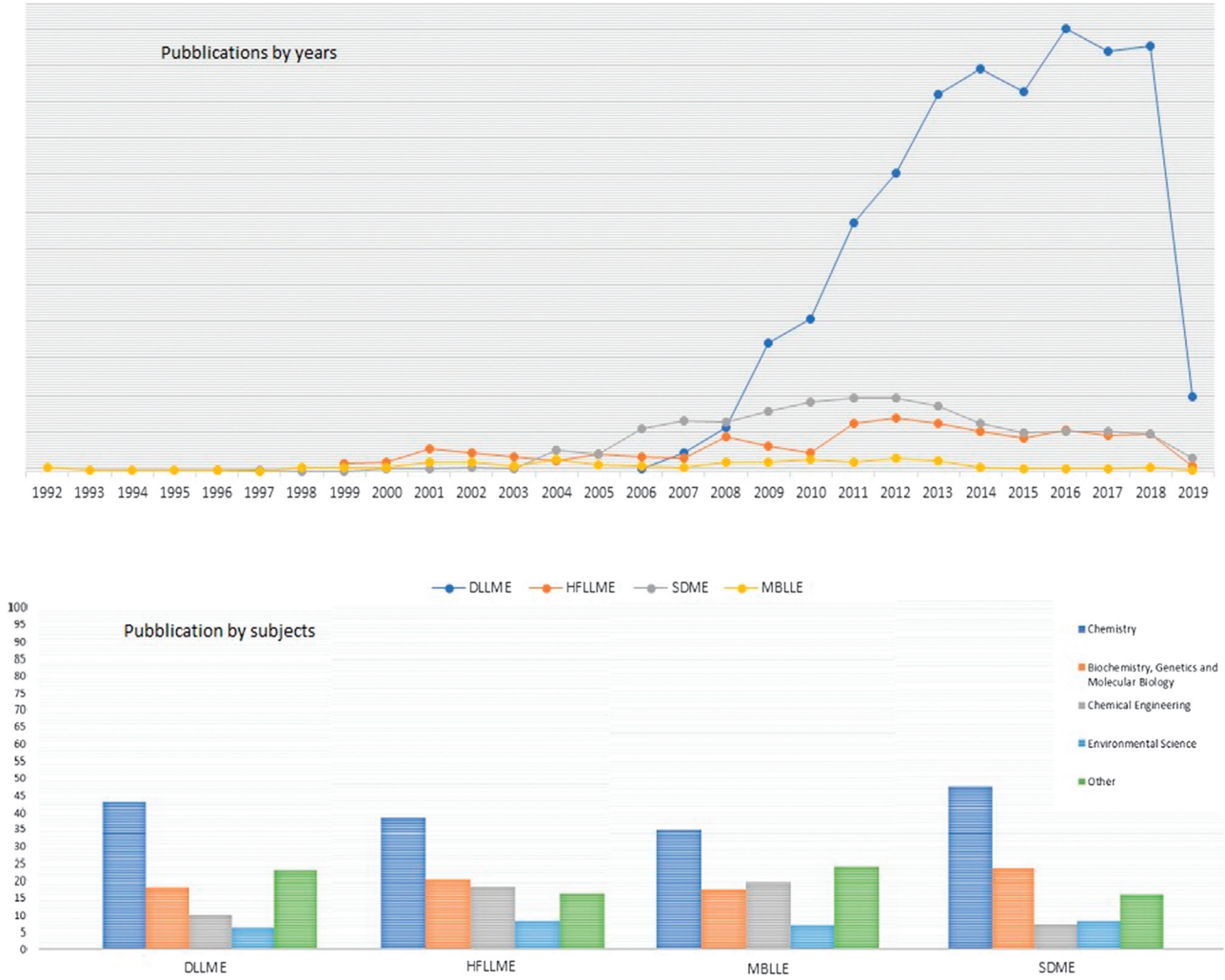


Figure 1. Scientific paper about LLME divided by years and by subjects

Table 1. Application and possible tools combination of the three LLME techniques

		Dispersive-Liquid Liquid MicroExtraction	Membrane-based Microextraction	Single Drop MicroExtraction
n° phases	2	✓	✓	✓
	3	✓	✓	✓
	4	✓		
Extraction	Low Density Solvent	✓		✓
	High-density solvent	✓		✓
	Alcohol assisted	✓		
	Ionic Liquids	✓	✓	✓
	Deep Eutectic Solvents	✓		✓
	Supramolecular solvents	✓	✓	✓
	Liquid anion exchanger	✓		
	Biosorption- based	✓		✓
	Cloud Point	✓		
	Switchable Solvents	✓		
Dispersion	Ultrasound-assisted emulsification	✓	✓	✓
	Vortex assisted	✓		
	Microwave assisted	✓	✓	✓
	Supercritical fluid	✓		
	Subcritical water	✓		
	Accelerated solvent	✓		
	Magnetic stirring	✓	✓	
	Airflow	✓		
	Robotic up-down shaking	✓		
	Pulsed flow	✓		
	Single-step vigorous solvent injection	✓		
	Repeated aspiration/injection	✓		

papers published, i.e., DLLME, HF-LLME and SDME, and MMLLE.

In addition, three LPME sampling modes could be recognized based on the number of immiscible phases concerned. These are two-, three-, [33, 34] and four-phase [23, 35–37] LPME modes; for the latter mode, an auxiliary solvent is provided to adjust the density of the extraction phase. Table 1 shows the possible applications and tools that have already been used in previous scientific productions, which will be analyzed in the following paragraphs.

3. Dispersive Liquid–Liquid Microextraction

To increase the extraction efficiency of LPME, Rezaee et al. developed dispersive liquid–liquid microextraction (DLLME) in 2006 [19]. In the basic DLLME experiment, a few microliters of a water-immiscible organic solvent (extraction solvent) are mixed with a water-miscible solvent (dispersive solvent), and the mixture is rapidly injected into an aqueous sample to form a homogenous cloudy solution by manual or mechanical shaking.

The induced dispersion leads to a significant increase in the contact surface between the extractant and the sample, which markedly increases the extraction efficiency. Actually, DLLME can be also regarded as an extension of the homogeneous liquid–liquid extraction (HLLE) technique first reported by Murata and Ikeda in the late 60s of the past century [38]. HLLE is based on the phenomena of phase separation from a homogeneous solution. The surface area of the interface between the two phases (aqueous and organic) initially can be considered to be infinitely large. Consequently, vigorous shaking or mixing is not necessary. HLLE is a simple and powerful preconcentration method that reduces reagent consumption, extraction time, cost of analysis, and the exposure to organic solvents. Murata and Ikeda illustrated the use of a water–propylene carbonate system; this technique was based on the properties of propylene carbonate, the solubility of which increases remarkably in water with temperature, and above 70 °C, it results in a homogeneous solution. Since the first reports in the 1970s [38, 39], a multitude of approaches have been described using different ways to overcome the saturation point and to promote droplet formation inside the sample.

3.1. DLLME Theory. In DLLME, 2 organic solvents (the extraction and the dispersive solvents) are mixed together before being injected into the aqueous sample. By manual shaking, a cloudy solution is formed due to the formation of fine droplets of the organic extractant dispersed in the sample volume. A wide variety of organic solvents can be used as organic extractants. The characteristics of these organic extractants depend on the selected DLLME operating mode. However, the extractants show common features:

i. (i) They must have low water-miscibility; otherwise, no phase separation or partitioning takes place.
ii. (ii) The organic solvent must be able to dissolve the analyte of interest. Organic solvents with higher partition coefficients (K) are preferable. Although partition coefficient data are not available for all solutes in different solvents, the reported K_{ow} for octanol–water system can be used as an indication of the lipophilicity of the analyte. K_{ow} can be either predicted or experimentally determined from the equation:

$$K_{ow} = C_{oct,eq}/C_{w,eq} \quad (1)$$

where $C_{oct,\ eq}$ is the equilibrium concentration of the analyte in the octanol layer and $C_{w,\ eq}$ is the equilibrium concentration of the analyte in water. Partition coefficients for the analyte–liquid phase system can be found on databases of physical–chemical data [40–44] or can be computed starting from the octanol–water partition coefficient (K_{ow}) and Henry's constant (K_H) values for a given analyte.

When log K_{ow} < 1.8 and the analyte solubility is >150 mg/mL, carrier-mediated LPME was found to be the most favorable technique, wherein an ion-pair reagent was added to the sample solution [45].

iii. (iii) The organic solvent should be dispersible after manual or mechanical shaking with or without the aid of an organic disperser.
iv. (iv) The selected solvent should be compatible with the following steps in the analytical method; otherwise, it has to be evaporated, and the sample reconstituted in an appropriate solvent. This extra evaporation step may affect

the precision of the extraction method, besides the time and effort required to do it.

v. (v) The organic solvent should be available at a reasonable price, in order to maintain the total cost of the analytical method within acceptable limits.

Enrichment factors (EF) and recoveries (ER%) were used to represent, respectively, the ratio of analyte concentration in the organic phase to the analyte concentration in the sample solution and the extraction performance during the optimization of different experimental parameters. The enrichment factor (EF) [46, 47] is defined as the ratio of the analyte concentration in the organic-rich phase to that in the bulk phase; Eq. (1) has been used for calculation of the enrichment factor:

$$\mathrm{EF} = C_1/C_0 \tag{2}$$

where C_1 is the analyte concentration in the organic-rich phase after phase separation, and C_0 is the initial concentration of analyte expressed in μg/L.

The ER% has been defined as the ratio of the slope of the calibration graph for the method response to that of the calibration graph of the method response for a reference standard solution prepared in water without pre-concentration [48, 49].

$$ER\% = (C_{\mathrm{ES}} \times V_{\mathrm{ES}}/C_0 \times V_0) \times 100\% \tag{3}$$

where C_{ES}, C_0, V_{ES}, and V_0 are the analyte concentration in the extraction solvent obtained from the calibration graph of the direct injection of the aqueous standard solution, the initial concentration of the analyte in the sample, the volume of the collected organic extraction solvent, and the volume of the sample, respectively.

3.2. Advantages and Limits of DLLME. Detailed reviews of the analytical applications have been published [50, 51].

The advantages of DLLME are simplicity of operation, rapidity, low cost, relatively high enrichment factor (EF), and extraction recovery (ER%). Typically, only microliters of the extraction solvent are used, which lead to reduced solvent consumption, low-level waste generation, and low level exposure of the operators to toxic solvents. Additionally, shorter extraction times and higher preconcentration factors (often >100) with a high reproducibility (often ≤5%) compared to LLE can be achieved [41].

DLLME suffers from 3 limitations: i) the use of halogenated solvents, which are toxic; ii) the need for mechanical agitation of the sample, which is recommended for the minute dispersion of the organic solvents in the aqueous sample; and iii) the need for centrifugation after dispersion, which is time-consuming and makes the entire procedure difficult to automate. Automation of the extraction procedures is particularly important in LPME and DLLME due to the nature of these processes, which require strict control of all the steps during extraction.

3.2.1. The Use of Extraction and Dispersive Solvents. In the last decade, a remarkable effort was made to overcome the abovementioned limitations of DLLME. To widen the range of extractants used in DLLME, solvents lighter than water, such as toluene, xylene, and octanol were tried in low density solvent-DLLME (LDS-DLLME) [52]. Liang et al. proposed the technique named high-density solvent-based solvent de-emulsification dispersive liquid–liquid microextraction (HSDDLLME), which involves the use of chloroform (extraction solvent) and acetone (dispersive solvent). A de-emulsification solvent (acetonitrile) was then injected into the aqueous emulsion, which is thus rapidly cleared into 2 phases [53].

To further facilitate the extractant transfer after the microextraction process, solidification of organic drop was proposed [54]. Organic solvents with melting point in the range of 10–25 °C such as 1-undecanol, 1- and 2-dodecanol, and *n*-hexadecane have been used as extraction solvents in the DLLME variant named solidification of floating organic droplets (SFOD-DLLME) [55, 56].

A less toxic and environmentally friendly technique is based on alcoholic-assisted DLLME (AA-DLLME). In this variant, the use of alcoholic solvents for both extraction and dispersive solvents in the DLLME procedure showed improved applicability for the determination of polycyclic aromatic hydrocarbons in environmental water samples prior to LC analysis [57].

New types of green extraction solvents have also been introduced in the use such as ionic liquids (IL) [30, 58–60], and their future via the deep eutectic solvents (DESs) [36], supramolecular solvents (SUPRAs) [35], biosorption (bio)-based DLLME by the use the surfactants as dispersive solvents (surfactant-assisted [SA]-DLLME) [61] or as a extraction solvent (cloud-point [CP]-DLLME) [54], and switchable solvents (SS) [23, 37, 62] have led to the development of new LPME techniques.

Complex matrices such as food and biological treated with ordinary DLLME often provide extracts which contain the target analytes together with high levels of impurities, which can interfere or cause false positives in chromatographic separations. In order to solve these application problems, some researchers have proposed a DLLME extraction technique exploiting also one back extraction solvent (BES). In this operating mode, after DLLME, the polar analytes are back-extracted from the organic solvent into the aqueous solution, and then separated and determined. This approach could lower the matrix effect to a certain extent and greatly expanded the applicability of DLLME. Melwanki et al. first used the BES-DLLME technique to determine clenbuterol in urine samples with LC [63]. They first carried out the DLLME with tetrachloroethylene as an extractant and then back-extracted the analyte from tetrachloroethylene into a 1% formic acid solution in water prior to analysis.

Sun et al. reported a method for the determination of highly substituted hydrophobic chlorophenols in red wine by DLLME–capillary electrophoresis (CE). The authors first extracted the chlorophenols from the sample by DLLME with diethyl carbonate as the extractant, and then the extractant phase was diluted 8 times with 100 mM NaCl solution containing 25% (*v*/*v*) isopropanol and 37% (*v*/*v*) ACN before analysis [64].

3.2.2. The Solvent Dispersion Step. The solvent dispersion step is crucial in DLLME. If the distribution for the dispersion solvent between the organic phase and the sample is not properly controlled, the inherently non-homogeneous system may lead to errors in the determination of the analytes. The distribution for the dispersion solvent in the sample may be altered primarily by the sample salinity but also by any other cause that may affect the analyte solubility in the phases created in the sample. The altered analyte solubility of course will affect the extraction efficiency and, consequently, the analytical recoveries [65]. Additional concerns in method development are needed for an appropriate dispersion solvent and the dispersion-solvent-to-sample volume ratio [66]. To overcome the issue regarding efficient mixing of the dispersion solvent in the sample, several means of dispersion have been developed in order to control with high precision the kinetic energy administered. Extraction solvent dispersion was accomplished by ultrasound-assisted emulsification–microextraction (USAEME) [67], vortex-assisted mixing (VA) [68, 69], microwave-

assisted extraction (MAE) [70–72], supercritical-fluid extraction (SFE) [73], subcritical-water extraction (SWE) [74], accelerated solvent extraction (ASE) [75], magnetic stirring [76], airflow [77], robotic up-and-down shaking [78, 79], pulsed flows [80], single-step vigorous solvent injection [81], and repeated aspiration/injection as in air-assisted DLLME (AADLLME) [82]. Effervescence-assisted DLLME has also been proposed. This technique involves the in situ generation of bubbles of CO_2 by adding a mixture of sodium carbonate [83, 84] or sodium hydrogen carbonate [85] and an acid to assist the dispersion of the extraction solvent, removing a need for the dispersive solvent.

Although at first, it may seem redundant to mention so many similar means of agitation of the sample, e.g., magnetic and vortex stirring, we included all these techniques in this review in agreement with the judgment of Michal Alexovič who emphasized that the choice of any one of these methods for sample dispersion implies significant differences in the options of method automation [86]. In addition, all the dispersive modes reported also differ based on their dispersion efficiency depending on many factors related to the sample and analytes chemistry.

3.2.3. The Phases Separation Step. Centrifugation is commonly used to separate the phases after extraction. The application of the centrifugal force is the first-hand obvious approach used to break the emulsion and help separate the two phases apart. However, since centrifugation is a time-consuming step, researchers have also devised other means for phase separation.

Other approaches adopted to terminate the dispersion in the sample not only do accelerate the extraction process, but also can make automation easier.

Centrifugeless modes of DLLME were reported [86–88]. Additional modifications to DLLME methods include the use of a solvent, which causes phase separation of the emulsion [89]. Other authors reported on the addition of $AlCl_3$ to the sample in order to promote phase separation by disruption of the interfacial tension at the droplets surface [90]. The removal of the extractant solvent (1-octanol) by using bare Fe_3O_4 magnetic nanoparticles has also been reported. The Fe_3O_4 magnetic nanoparticles in acetic acid provide the recovery of the extractant solvent thanks to the interaction between the polar surface of the nanoparticles and the alcohol functional group of the solvent [84].

Hydrophobic magnetic nanoparticles that can interact with the extraction phase and can be separated by applying a magnet were proposed to eliminate the centrifugation step [91].

In order to skip the centrifugation step, Chen et al. introduced the solvent-terminated DLLME (ST-DLLME) technique in 2010 [92, 93]. In ST-DLLME, an amount of the dispersing solvent is added to the cloudy mixture to break the emulsion and induce phase separation in the sample. The plain addition of water to the cloudy mixture of sample/extractant/disperser may break the emulsion, but at the same time increases the volume of the sample, and this may affect the equilibrium concentration leading to unpredictable errors. Therefore, this approach is generally not the most viable option [93]. The number of organic solvents tested as demulsifiers in ST-DLLME is still limited, and references are there for studies which evidence needs an update [94–96]. Other methods of demulsification were reported involving nitrogen floatation [97], agitation-induced termination [98], pH change [99], salting-out effect [100], and temperature change [101]. It appears clearly that a comparison of the demulsification efficiency for the different techniques reported would be very important to select the most effective procedure in method development. However, at the current state of the art, a fair comparison between the efficiencies of the different techniques reported is still debatable since the data published are not enough for the purpose.

4. Membrane-Based Microextraction

An innovative alternative to HF-LLME and SDME, which can further improve the capabilities of these LPME techniques and minimize some of their main shortcomings, is the use of a polymeric membrane, which serves as a support for the extracting solvent and as an interface between the donor and acceptor phases. To make a clear-cut classification and not to confuse mixed mode techniques such as HF-LLME with proper membrane-based techniques, we decided to classify membrane-based microextraction techniques only as the completely non-porous membrane techniques, where the membrane forms a separate phase (polymeric or liquid) between the donor and acceptor solutions. The microporous-membrane liquid–liquid extraction (MMLLE) technique belongs to this category.

In MMLLE, several different extraction solvents have been used with the aim to improve the technique greenness. Also, in this case, ILs [102] and SUPRAs [103] were adopted. Moreda-Piñeiro et al. [104] and Lambropoulou [105] proposed, respectively, USAEME, MAE, and magnetic stirring to upgrade the extraction capability of membrane-based microextraction techniques.

4.1. Microporous-Membrane Liquid–Liquid Extraction (MMLLE). A novel set of non-porous membranes (Membrane-Assisted Solvent Extraction, MASE) has been recently designed for analytical purposes by Gerstel GmbH & Co. KG. (Mülheim an der Ruhr, Germany) in collaboration with the Environmental Research Centre (UFZ, Leipzig, Germany) as an alternative configuration. These membranes, which can be used in automated operation have a pore size of 0.2 μm and a thickness of 30 μm. The liquid sample is placed into a vial; a special conical membrane is inserted, and the vial is capped. The rest of the procedure is completely automated by an *xyz* autosampler, including solvent addition, vial heating and agitation, solvent extract withdrawal and final injection for either GC or LC analysis.

4.2. Hollow Fiber (HF)-LLME. Hollow fiber liquid–liquid microextraction (HF-LLME) was first introduced by PedersenBjergaard et al. in 1999 [18]. In this technique, the target analytes are first extracted from a few mL of an aqueous sample into a thin water-immiscible organic phase (made of 1-octanol in the original work of Pedersen-Bjergaard) inside the pores of a polypropylene HF and then into a small volume of acceptor solution contained inside the same HF.

HF-LLME combines isolation, purification, and concentration of the analytes in a single step [106].

A 96-well position HF-LLME system combined with an auto-injector integrated in a conventional HPLC–UV system was developed and used for the analysis of trace levels of drugs in different biological samples [107].

HF-LLME may also be carried out in a dynamic mode (DHF-LLME). In the two- or three-phase mode, a micro-syringe is filled with a few mL of a water-immiscible organic solvent. A small piece of porous HF (1–2 cm) is soaked in the same organic solvent to fill the pores, and subsequently, that piece of HF is attached to the needle of the microsyringe. The syringe needle and the piece of HF are placed in an aqueous sample, and during extraction, small volumes of the aqueous sample are repeatedly pulled in and pushed out of the HF, using a syringe plunger. During withdrawal of the aqueous sample, a thin film of organic solvent builds up in the HF and

extracts analyte from the sample, whereas during sample expulsion, this thin film recombines with the bulk organic phase in the syringe. During this recombination, the portion of analyte extracted in the current cycle is trapped in the bulk organic solvent. After extraction, which includes many repeated cycles, a portion of the bulk organic solvent is subjected to chromatographic analysis [108, 109].

In 2004, Jiang and Lee proposed a technique of ME named solvent bar microextraction (SBME) as an alternative extraction method derived from HF-LLME [110].

SBME involves the use of a short length HF sealed at both ends impregnated with organic extracting solvent. This system forms a "solvent bar" that can be tumbled freely in the sample solution under magnetic stirring. The free movement of the "solvent bar" in the stirred aqueous sample solution considerably increases the transfer of analytes from the sample into the extraction solvent, improving the extraction efficiency. SBME can provide a high analyte enrichment of the extract with excellent sample clean-up at the advantage of low-cost disposable consumables. SBME was applied successfully to the analysis of biopharmaceuticals [111], bovine milk [112], and estuarine water samples [113].

A low-cost and efficient LPME variant, termed ballpoint-tip-protected liquid-phase microextraction (BT-LPME), was recently proposed. The BT-LPME device has a bullet-shaped BT that possesses a hollow cavity of about 12 mL of volume for solvent storage, and an opening tail for solute extraction 16-mm long. Magnetic-field-induced BT spinning promotes the extraction process of organic analytes from aqueous samples. The efficiency of the system was demonstrated, testing river, surface, and tap water samples for the presence of 5 polycyclic hydrocarbon congeners, evidencing the experimental conditions of optimal use [114].

5. Single Drop Microextraction (SDME)

Single-drop microextraction (SDME) has been introduced in use since 1996, and it is one of the oldest existing LLME techniques [14].

SDME is a preconcentration non-exhaustive technique utilizing a small volume of an organic solvent (typically one drop) immersed in an aqueous sample in which it is immiscible, creating a two-phase heterogeneous system. The drop of organic solvent can also be positioned at the interface of the aqueous sample headspace, thus creating a three-phase heterogeneous system.

SDME is operated in 2 modes: static SDME [14, 15] and dynamic SDME [115, 116].

Basically, in SDME, the organic phase which captured the analytes is collected using a syringe and directly introduced into the analytical apparatus for analyte determination. Headspace and direct immersion SDME are applicable for multiresidue analyses; the technique is simple, cost-effective and time-saving, and can be fully automated [117]. A distinct advantage of SDME over other LPME techniques is that only a common laboratory syringe is required for its application. In contrast, the limitations of the original SDME procedure were due to partial solubility of the organic solvents adopted in water, limited extraction drop volume, and analyte losses due volatility and drop dislodgement [118].

Advances in the development of more effective variants of the basic SDME procedure have been reported regularly and included continuous flow microextraction (CFME) [119], drop-to-drop solvent microextraction (DDSME) [120], directly suspended droplet microextraction (DSDME) [121], solid-drop LPME [122], and solidification of floating organic drop by freezing after extraction [123]. All these variants of SDME may be classified into the group of two-phase SDME-based methods in which a liquid sample and an acceptor solvent can be recognized.

Over the years, for SDME, in addition to classic applications with low-density solvent LDS [124] and high-density solvent (HDS) [125], different and greener extraction solvents have been proposed such as ionic liquids (ILs) [30, 126], deep eutectic solvents (DESs) [30, 113], and supramolecular solvents (SUPRAs) [104].

In order to enhance the SDME extraction yield in specific application, recently, the extraction was proposed to be assisted by different kinetic processes, such as MAE and USAEME, as reported in [104].

6. Robotics Automation

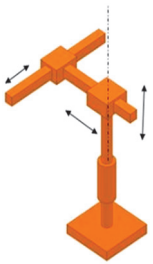
Complete automation of analytical processes save time, reduce costs, and make any procedure more precise, controllable, and applicable for routine analysis. Robotic arms are commonly classified according to their geometric coordinate system or configuration. The most prevalent of these are: Cartesian (rectangular), cylindrical, polar (spherical), and revolute (anthropomorphic). These designs permit the arm at least 3 degrees-of-freedom.

Commercially available Cartesian *xyz* robotics systems ensure on-line full automation. These 3-axis autosamplers used for sample injection into LC and GC instruments already include sample preparation. Dedicated accessory instruments are available for automating some types of sample cleanup and extraction as part of LC and GC injection. The robotic change of tools enables unattended 24/7 operation, even for multistep workflows and thereby greatly increases the productivity of labs. At the same time, process safety is optimized since all operations become traceable. Transferring repetitive or dangerous manual tasks to a robot improves safety. The product lines of commercially available, fully-automated miniaturized techniques center on 3-axis autosampler systems. In the last 10 years, on-line *xyz* autosamplers have proliferated, thus contributing to the increase in the usage of hyphenated techniques in analytical chemistry.

CTC Analytics AG (Zwingen, Switzerland) was the first company to offer commercial three axis autosamplers for GC; A200S, the first GC liquid autosampler, was released on the market in 1986. Subsequently, CTC Analytics produced the PAL system platform in 1998, expanded it into the HTX PAL offering an extended *x*-range in 2003, and brought out its PAL RTC, RSI, and LSI systems between 2012 and 2014. Basically, this Swiss company made history with its *xyz* autosamplers. Other front-end for on-line automation LPME solutions, all of which are based on CTC Analytics' instruments, are nowadays produced by Leap Technology Inc. (Trajan Scientific and Medical, Ringwood Victoria, Australia), Chromtech Analytical Instruments (Bad Camberg, Germany), Gerstel GmbH & Co. KG (Mülheim an der Ruhr, Germany), Da Vinci Laboratory Solution B.V. (Rotterdam, The Netherlands), Anatune Ltd. (Cambridge, United Kingdom), and Axel Semrau (Sprockhövel, Germany). These autosamplers injecting into LC valves using the loop overfill method, or GC performing LVI, are equipped with what is necessary to completely run the LPME: robotic tool change, bottom sensing, vortex mixer, centrifugation, weighed with balance, all through a traceability given by a barcode reader (Table 2).

Guo and Lee proposed a fully automated DLLME system by the use of a modified vial for Cartesian autosampler [127]. The system proposed is also interesting from the point of view of the data analysis software: Da Vinci Laboratory Solution propose DryLab as LC method development and optimization

Table 2. Versatility of different automation systems coupled with LLME techniques. *The Thermo Scientific F5 and Chrombot are robotic arms that could be applied in the preparation of the sample only by using *ad hoc* tools and supports

Company	Instrument	Geometric coordinate system	GC	LC	Barcode Reader	Wash Station	Weight scale	Evaporation Station	Centrifuge	DeCapper	Agitator	Dilutor	Solvent Module	Vortex Mixer	Chemometrics
CTC Analytics AG	PAL RTC, RSI, and LSI	 Cartesian autosampler	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	
Chromtech Analytical Instr.	PAL RTC, RSI, and LSI		✓	✓	✓	✓			✓		✓	✓	✓	✓	
Axel Semrau	PAL RTC, RSI, and LSI		✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓
Leap Technology Inc	PAL RTC, RSI, and LSI		✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	
Gerstel GmbH & Co. KG	MultiPurpose MPS		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Da Vinci Laboratory Solution B.V.	MultiPurpose MPS		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Anatune Ltd	MultiPurpose MPS		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Chromtech Analytical Instr.	Chrombot *	Revolute robotic arms													
Thermo Fisher Scientific	Thermo Scientific F5*	 Polar robotic arms													
Andrew Alliance S.A.	Andrew system	 Cylindrical robotic arm		✓		✓						✓	✓		
SOTAX AG	APW and TPW			✓	✓	✓	✓		✓		✓	✓	✓	✓	

software. The DryLab software predicts chromatograms under a wide range of experimental conditions. Other remote-control tools were proposed by Axel Semrau, which introduced the Chronos system for analytical system controls, while Gerstel GmbH proposed the Maestro software.

The best known cylindrical robotic arm was the Zymate by Zymark Corp: this consisted of a cylindrical coordinate arm with interchangeable hands and a variety of work-stations interfaced to a custom controller. In 2008, SOTAX AG (Aesch, Switzerland) acquired the Zymark brand and product lines from Caliper Life Sciences (now part of PerkinElmer). All remaining Zymark product lines were rebranded to SOTAX AG in 2014, namely APW and TPW models.

Recently, 2 robotic arms have been introduced to the market: i) ChromBot (Chromtech Analytical Instruments), a laboratory revolute robot orientates itself both in the dimensions, as well as in the speed of movement on the human arm (load capacity of up to 500 grams), and ii) Andrew system (Andrew Alliance S.A., Vernier, Switzerland), an automated liquid handling polar robot that uses Gilson pipettes and can be used for many applications such as LPME. Thermo Scientific F5 (Thermo Fisher Scientific, Waltham, MA, USA) 6-axis anthropomorphic revolute robot is designed for laboratory automation: ±0.02 mm repeatability at full and 5 kg payload.

Other systems have been proposed to increase analytical productivity using LPME: robotic approaches based on flow, batch, flow-batch, in-syringe [86, 128], and designed homemade extraction vessels [52, 82].

7. Derivatization Procedures

Polar organic compounds (POCs) are analytes which contain one or more functional groups such as hydroxyl, thiol, amine, carbonyl, and carboxyl groups. Their determination is a problem area in analytical chemistry. Bad peak shape, poor retention, adsorption on the column, or poor separation is usually encountered in the common chromatographic techniques. Therefore, chemical derivatization is performed, because it can modify the structure of the compound, and thus change its behavior in the analytical system.

In GC–mass spectrometry (MS), POCs are normally derivatized in order to reduce their polarity and facilitate volatilization and ionization. The electron impact mass spectra obtained for most of the more common derivatives are generally reproducible and well documented in mass spectra commercial libraries making them suitable for library matching.

In LC/MS–MS, derivatization and library matching are still in a development phase of advancement. However, chemical derivatization can increase the sensitivity and specificity of LC/MS–MS methods for POCs and provides additional structural information.

There are many GC derivatization methods, which can produce suitable volatile and stable derivatives. One of the most used derivatization methods is silylation because there are several silylating agents available. The different silylating agents are flexible reactants, are able to simultaneously transform several different chemical groups with quantitative yields in very short times, and work under rather easy-to-handle conditions. However, silylation has two drawbacks [129, 130]. First, silylating reagents and silyl derivatives are susceptible to hydrolysis; thus, in situ aqueous derivatization is not feasible. Aqueous samples require a pretreatment, consisting generally in an extraction and drying, which complicates the experimental procedure. Secondly, aqueous samples can generate byproducts, which can interfere with the target analytes in the course of the chromatographic separation. A few studies reported that silylation of polar organic compounds in aqueous matrices using a large excess of silylating reagents could overcome these obstacles [131]. However, these methods are inapplicable for trace analysis. The first attempt for direct silylation using hexamethyldisilazane (HMDS), and bis(trimethylsilyl)trifluoroacetamide (BSTFA) was developed to improve the detection limits of polar metabolites such as lactate, alanine, glycerol, succinate, and glucose in aqueous solutions of pathogenic protozoa [132].

Analytical procedure based on SDME combined with in-syringe BSTFA derivatization and GC/MS was developed for determination of some phenolic acids in fruits and fruit juices. The analytes were extracted from 3 mL of sample solution using 2.5 μL of hexyl acetate. The extracted phenolic acids were derivatized inside the syringe barrel using 0.7 μL of BSTFA before injection into the GC–MS [133].

A combination of headspace (HS)-SDME and GC was used for determination of iodine in milk powder or urine. The derivative obtained from the reaction between iodine and butanone in acidic media was extracted into a micro-drop and determined by GC with electron capture detector (GC-ECD) [134].

Pentafluorobenzyl bromide (PFB-Br) is a versatile derivatization agent. It has been widely used in liquid and gas chromatography and MS since several decades. PFB-Br reacts with the target molecule through a classical nucleophilic substitution mechanism of reaction, which involves the bromide ion as a leaving group. The bromide ion is substituted by wide a spectrum of nucleophiles in aqueous and non-aqueous systems to form electrically neutral derivatives. These products are soluble in most organic solvents, and they are generally thermally stable, volatile, strongly electron-capturing, and ultraviolet light-absorbing derivatives. For the last 10 years, PFB-Br has been applied in the LPME [135].

In 2017, Tsai et al. developed a multistep derivatization procedure named tandem microwave-assisted derivatization (tMAD), to alkylate the polar groups of two model bithiolic compounds containing multiple polar groups (i.e., cysteine and homocysteine that contain also amine and carboxylic groups), using 3,4,5-trifluorobenzyl bromide (Br-TFB) as a derivatizing agent. In the first step of the procedure, the strong nucleophilic groups of the analytes were derivatized in an aqueous solution; then, the intermediate derivatives were extracted and the derivatizing reagent was resumed into the non-aqueous medium using salting-out assisted liquid–liquid extraction. The weak nucleophilic groups of the analytes were derivatized in an aprotic reaction system that reduced the polarity and improved the volatility, thermal stability, separation ability, and sensitivity of the analytes prior to GC–MS analysis [136].

To transform urinary organic acids into their methyl esters, Liebich et al. proposed trimethyloxonium tetrafluoroborate (TMO) as a derivatizing reagent; after derivatization, the methyl ester is extracted with few μL of chloroform and subsequently analyzed by GC–MS. TMO has the advantage that the organic acids can be transformed into their methyl ester derivatives directly in the urine [137].

In 2015, Ammazzini et al. proposed a single-step derivatization with triethyloxonium tetrafluoroborate (TEO) to obtain ethyl derivatives of thiocyanate from salivary samples and subsequently extract it with SDME from the HS [138]. TEO has been recently introduced in the field of analytical chemistry as derivatizing agent for inorganic anions. It is a water-soluble reagent able to perform ethylation directly in aqueous media and at room temperature; aqueous solutions of TEO, however, are not stable because they undergo rapid hydrolysis.

Recently, Takeuchi et al. proposed the 2,2-dimethoxy-propane (DMP) as a derivatizing agent to determine organic

acids: DMP acted as dehydration and derivatization reagent; in the presence of HCl, the organic acids were directly methylated with DMP and can be analyzed by GC–MS. The advantages of using DMP are that extraction and evaporation procedure are not needed [139].

Chiang et al. presented a gas chromatographic method for the simultaneous extraction of amphetamine and methylenedioxyamphetamine by derivatization with pentafluorobenzaldehyde (PFBAY) – added to the extraction solvent – using HS HF-LPME [140].

The *O*-2,3,4,5,6-(pentafluorobenzyl)hydroxylamine hydrochloride (PFBHA) derivatizing agent was shown to be an excellent extraction, concentration, and derivatization medium for HSSDME coupled to GC–MS analysis of aldehydes [141].

An analytical workflow is described for GC–MS based metabolomic profiling of protic metabolites, particularly amino-carboxylic species in biological matrices. The sample preparation is carried out directly in aqueous samples and uses simultaneous in situ heptafluorobutyl chloroformate derivatization and DLLME [142].

8. Phase Transfer Catalysis (PTC)

PTC has been a well-established technique in the synthesis of organic chemicals for more than three decades. Wittig et al. demonstrated in 1947 the value of utilizing tetramethylammonium cations paired with trityl and fluorenide ions for alkylation in dry alcohol solution, and the PTC application in analytical chemistry has been overviewed by Fiamegos and Stalikas [143].

Basically, in PTC, one reactant is lipophilic and the other being hydrophilic. Each reactant is dissolved in the appropriate solvent (normally one phase is water, whereas the other is usually an organic solvent). Then, a phase-transfer catalyst is added to promote the transport of one reactant into the other phase.

PTC has been employed as a tool for the simultaneous extraction, preconcentration, and derivatization/reaction in the analysis of primarily organic, and to a lesser extent, inorganic compounds. Concerning LPME, two such applications have been reported [120, 144].

9. LC and GC Large Volume Injection

Sample analysis by large-volume injection (LVI) in combination with liquid chromatography–tandem mass spectrometry (LC–MS–MS) consists in the direct introduction of large sample volumes (for example, 200–2000 μL) into an LC system for separation and subsequent detection. The primary advantages of LVI compared to traditional off-line or on-line sample preparation techniques, such as SPE or LLE, include decreased sample preparation, greater analyte mass introduced for detection (that is, increased sensitivity), and less solvent and solid waste [145]. In the late 1970s and early 1980s, the Single analytical Column LVI technique (SC-LVI), which consisted of simply injecting a large volume of sample into an analytical column, was proposed [146]. This technique has the obvious advantage of the simplicity and velocity, but this advantage is balanced by the amount of dirt that can be loaded on the column and into the instrumental apparatus with the natural consequences of rapid column damage/clogging and instrument contamination/carry-over. Starting from the early 1990s, Elbert A. Hogendoorn et al. published a series of papers dealing with the analysis of a variety of pesticide residues in a range of environmental samples [147, 148] and of drugs and metabolites in biological fluids [149–151] using the so-called coupled-column or column switching-LVI technique (CC-LVI). Between the 1990s and the 2000s, LCs coupled to MS emerged, but the capacity of the vacuum systems permitted only low mobile phase flow rates; low LC flow rates required lower LC column diameters and low injection volumes. Therefore, with the emergence of the first LC/MS systems, the development and application of LVI methods took a step backward. Limits of detection (LOD) were confined by the restricted injection volumes that were compatible with the narrow-bore columns used. With the advent of commercial mass spectrometers fitted with multiple-stage vacuum systems and with more efficient atmospheric pressure ionization sources, higher LC flow rates, larger column diameters, and larger injection volumes were made possible. An increasing number of publications have since appeared in the scientific literature that describe the feasibility and implementation of LVI for use with LC–MS for injecting volumes of environmental samples as large as 100 mL [152–155].

As regards the issue of improving the sensitivity of GC analysis by using LPME, an additional preconcentration step is required to lower the detection limits [156]. Among the various options available for sample preconcentration, large volume injection (LVI) is very convenient for GC analyses as it can be automated and carried out on-line. The currently available LVI methods include various injection modes, namely, programmed-temperature vaporizing (PTV) solvent split, on-column injection (OCI), direct sample introduction (DSI)/difficult matrix injection (DMI), splitless overflow/concurrent solvent recondensation (CSR), AT-column, through oven transfer adsorption–desorption (TOTAD), and stomach-shaped insert liner.

10. Assessment of Method Greenness

The evaluation of analytical methods in the context of green chemistry is difficult because of the complexity of sample matrices, the diversity of analytes and analytical methods, and the special analytical criteria that need to be considered like LOD, and precision. Thus, the presence of methods and tools to calculate and provide an answer to whether an analytical procedure can be regarded as green or not is necessary. Tools such as Analytical Eco–Scale (AES) [157], National Environmental Methods Index [43], Green Analytical Procedure Index (GAPI) [158], and greenness metrics [159, 160] have been proposed to assess the greenness of analytical methods.

Examples of the application of NEMI and AES have started to appear recently, such as the evaluation of the greenness of a UPLC method for the determination of caffeine and theobromine in commercial teas [161]. In addition, an interesting review concerning the future perspectives of introducing the concepts of green chemistry at the higher education degree has been recently published [162].

11. Conclusion

Analytical methods based on traditional LLE have been shown to suffer from drawbacks such as the use of large volumes of hazardous organic solvents and samples. These methods produce high amounts of toxic chemical waste and are time consuming, expensive, environmentally unfriendly, tedious, and laborious. Compared with conventional LLE and SPE, LPME techniques are more attractive due to their effective clean-up ability, high enrichment ratios, and small consumption of consumables. LPME is a simple and cheap tool and requires small volumes of organic solvents. Complete automation of these processes saves time, work, reduces overhead costs, and makes LPME more applicable for routine analysis.

Abbreviations

AA-DLLME: air-assisted dispersive liquid–liquid microextraction or alcoholic-assisted dispersive liquid–liquid microextraction
AS: auxiliary solvent
ASE: accelerated solvent extraction
BES: back extraction solvent
BT-LPME: ballpoint tip-protected liquid-phase microextraction
CE: capillary electrophoresis
CP-DLLME: cloud-point dispersive liquid–liquid microextraction
CPE: cloud-point extraction
DE: demulsification efficiency
DES: deep eutectic solvent
DHF-LLME: dynamic mode hollow fiber liquid–liquid microextraction
DLLME: dispersive liquid–liquid microextraction
EF: enrichment factor
ER: extraction recovery
GAC: green analytical chemistry
GC: gas chromatography
HDS: high density solvent
HDS-DLLME: high density solvent dispersive liquid–liquid microextraction
HF-LLME: hollow fiber liquid–liquid microextraction
HF-LPME: hollow fiber liquid-phase microextraction
HLLE: homogeneous liquid–liquid extraction
IL: ionic liquid
LC: liquid chromatography
LDS: low density solvent
LDS-DLLME: low density solvent-dispersive liquid–liquid microextraction
LLE: liquid–liquid extraction
LPME: liquid phase microextraction
MAE: microwave assisted extraction
MASE: membrane assisted solvent extraction
MMLLE: microporous-membrane liquid–liquid extraction
RP: reversed-phase
SBME: solvent bar microextraction
SDME: single drop microextraction
SFE: supercritical fluid extraction
SFOD: solidification of floating organic droplets
SFOD-DLLME: solidification of floating organic droplets-dispersive liquid–liquid microextraction
SLME: supported liquid membrane extraction
SPE: solid-phase extraction
STDLLME: solvent terminated-dispersive liquid–liquid microextraction
SUPRA: supramolecular solvent
SWE: subcritical water extraction
USAEME: ultrasound-assisted emulsification-microextraction
VA: vortex assisted

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