Liquid-phase microextraction

Ali Sarafraz-Yazdi, Amirhassan Amiri

The development of faster, simpler, inexpensive and more environmentally-friendly sample-preparation techniques is an important issue in chemical analysis.

Recent research trends involve miniaturization of the traditional liquid-liquid-extraction principle by greatly reducing the acceptor-to-donor ratio.

The current trend is towards simplification and miniaturization of sample preparation and decreasing the quantities of organic solvents used.

We discuss liquid-phase microextraction with the focus on extraction principles, historical development and performance.

Abbreviations: AAS, Atomic absorption spectrometry; BTEX, Benzene, toluene, ethylbenzene and xylenes; DI, Direct immersion; DLLME, Dispersive liquid-liquid microextraction; DSDME, Directly-suspended droplet microextraction; CE, Capillary electrophoresis; CFME, Continuous-flow microextraction; ECD, Electron-capture detector; EME, Electrokinetic membrane extraction; ETAAS, Electrothermal atomic absorption spectrometry; ETV-ICP-OES/MS, Electrothermal vaporization-inductively coupled plasma optical emission spectrometry/mass spectrometry; FID, Flame-ionization detector; GC, Gas chromatography; GF-AAS, Graphite-furnace atomic absorption spectrometry; HPLC, High-performance liquid chromatography; HFM, Hollow-fiber membrane; HF-LPME, Hollow-fiber liquid-phase microextraction; HS, Headspace; IL, Ionic liquid; LLE, Liquid-liquid extraction; LLLME, Liquid-liquid-liquid microextraction; LPME, Liquid-phase microextraction; MASE, Microwave-assisted solvent extraction; MS, Mass spectrometry; PAHs, Polycyclic aromatic hydrocarbons; PCB, Polychlorinated biphenyl; SDME, Single-drop microextraction; SPE, Solid-phase extraction; SPME, Solid-phase microextraction; SLM, Supported liquid membrane; TD, Thermal desorption; TILDLME, Temperature-controlled ionic liquid dispersive liquid-phase microextraction; THF, Tetrahydrofuran; VOC, Volatile organic compounds; VIS, Visible; UV, Ultraviolet

Keywords: Continuous-flow microextraction (CFME); Directly-suspended droplet microextraction (DSDME); Dispersive liquid-liquid microextraction (DLLME); Electrokinetic membrane extraction (EME); Extraction; Hollow-fiber liquid-phase microextraction (HF-LPME); Liquid-phase microextraction (LPME); Miniaturization; Sample preparation; Single-drop microextraction (SDME)

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1. Introduction

In recent years, the development of fast, precise, accurate and sensitive methodologies has become an important issue. However, despite the advances in the development of highly efficient analytical instrumentation for the end-point determination of analytes in biological and environmental samples and pharmaceutical products, sample pre-treatment is usually necessary in order to extract, to isolate and to concentrate the analytes of interest from complex matrices because most of the analytical instruments cannot directly handle the matrix. A sample-preparation step is therefore commonly required.

Sample preparation can include clean-up procedures for very complex (dirty) samples. This step must also bring the analytes to a suitable concentration level. However, conventional sample-preparation techniques [i.e. liquid-liquid extraction (LLE) and solid-phase extraction (SPE)] have involved drawbacks (e.g., complicated, time-consuming procedures, large amounts of sample and organic solvents and difficulty in automation). Using harmful chemicals and large amounts of solvents causes environmental pollution, health hazards to laboratory personnel and extra operational costs for waste treatment. Ideally, sample-preparation techniques should be fast, easy to use, inexpensive and compatible with a range of analytical instruments, so the current trend is towards simplification and miniaturization of the sample-preparation steps and decrease in the quantities of organic solvents used.

In 1990, Arthur and Pawliszyn [1] introduced a new method termed solid-phase microextraction (SPME). A polymer-coated fiber, on which the investigated compound adsorbs, is placed in the sample or its headspace. SPME has several important advantages compared to the traditional sample-preparation techniques:

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- it is a rapid, simple, solvent free and sensitive method for the extraction of analytes;
- it is a simple, effective adsorption/desorption technique;
- it is compatible with analyte separation and detection by high-performance liquid chromatography with ultraviolet detection (HPLC-UV);
- it provides linear results for a wide range of concentrations of analytes;
- it has a small size, which is convenient for designing portable devices for field sampling; and,
- it gives highly consistent, quantifiable results from very low concentrations of analytes.

Although the use of SPME fibers is increasingly popular, they have significant drawbacks, e.g.:

(i) their relatively low recommended operating temperature (generally in the range 240–280°C);
(ii) their instability and swelling in organic solvents (greatly restricting their use with HPLC);
(iii) fiber breakage;
(iv) stripping of coatings; and,
(v) the bending of needles and their expense [2].

In order to overcome these problems, simple, inexpensive liquid-phase microextraction (LPME) was introduced recently. LPME is a solvent-minimized sample-pretreatment procedure of LLE, in which only several μL of solvent are required to concentrate analytes from various samples rather than hundreds of mL needed in traditional LLE. It is compatible with capillary gas chromatography (GC), capillary electrophoresis (CE) and HPLC.

In LPME, extraction normally takes place into a small amount of a water-immiscible solvent (acceptor phase) from an aqueous sample containing analytes (donor phase). It can be divided into three main categories:

(1) single-drop microextraction (SDME)
(2) dispersive liquid–liquid microextraction (DLLME)
(3) hollow-fiber microextraction (HF-LPME)

We devote this article to discussion of microextraction techniques and performance and conclude with advantages and drawbacks.

2. Single-drop microextraction (SDME)

SDME, using typically 1–3 μL of an organic solvent at the tip of a microsyringe, has evolved from LPME. After extraction, the microdrop is retracted back into the syringe and transferred for further analysis.

In practice, two main approaches can be used to perform SDME:

(1) direct immersion (DI)-SDME
(2) headspace (HS)-SDME

In DI-SDME, a drop of a water-immiscible solvent is suspended directly from the tip of a microsyringe needle immersed in the aqueous sample.

Applications of DI-SDME are normally restricted to medium polarity, non-polar analytes and those whose polarities can be reduced before the extraction. Furthermore, the organic solvents used for DI-SDME are immiscible with water.

In HS-SDME, a microdrop of appropriate solvent is placed in the headspace of the sample solution or in a flowing air sample stream to extract volatile analytes. HS-SDME has similar capabilities in terms of precision and speed of analysis to DI-SDME but has the advantage of a wider variety of solvents to choose from. Unlike in DI-SDME, water can be also used as the solvent in HS-SDME to extract volatile and water-soluble analytes. This significantly enhances the range of extractable analytes as well as the range of analytical methods that can be coupled to SDME. In addition, HS-SDME is found to provide excellent clean up for samples with complicated matrices.

Liu and Dasgupta [3] were the first to report a novel drop-in-drop system where a micro drop of a water-immiscible organic solvent (~1.3 μL) is suspended in a larger aqueous drop.

At the same time, Jeannot and Cantwell [4] introduced a new solvent microextraction technique, where a micro drop (8 μL) of organic solvent was left suspended at the end of a Teflon rod immersed in a stirred aqueous sample solution. After extraction for a certain time, the rod was removed from the sample solution and, with the help of a microsyringe, an aliquot of the organic drop was injected into a GC instrument for further analysis (Fig. 1).

One disadvantage of above methods is that extraction and injection have to be performed separately, using different apparatus. To overcome this problem, Jeannot and Cantwell [5] suggested an alternative drop-based extraction technique. According to this revised protocol, microextraction was performed simply by suspending a 1-μL drop directly from the tip of a microsyringe needle immersed in a stirred aqueous solution. After extraction, the organic phase was withdrawn back into the microsyringe, and then the sample was injected

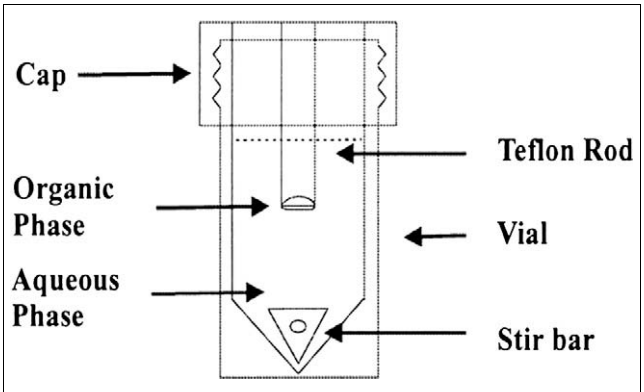

Figure 1. Side view of the solvent microextraction system [3].

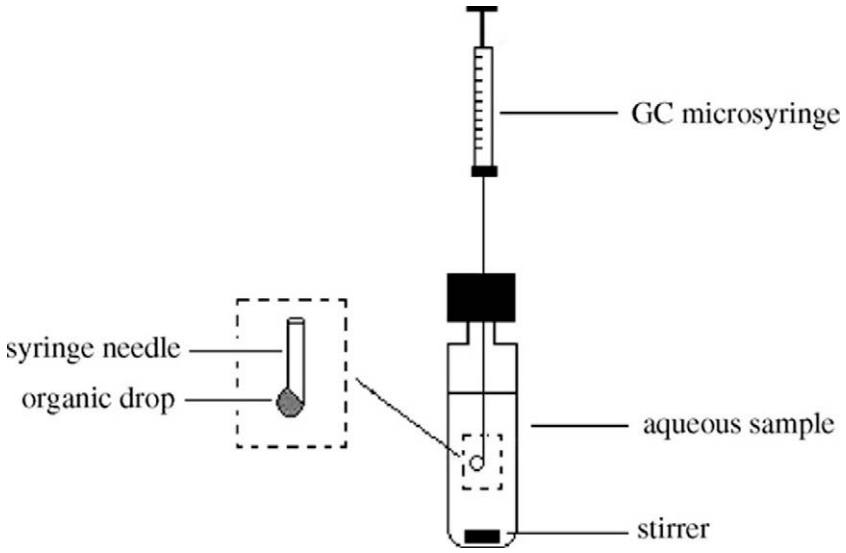

Figure 2. Direct-immersion single-drop microextraction [5].

into a GC system for further analysis (Fig. 2). In this proposed method, the single device is used for extraction and injection, so the operation of microextraction is better.

One disadvantage of DI-SDME is the instability of the droplet at high stirring speeds. Fast agitation of the sample can be employed to enhance extraction efficiency, because agitation permits continuous exposure of the extraction surface to fresh aqueous sample and reduces the thickness of the static layer. Assadi et al. [6] employed some modification of the needle tip, causing its cross section to increase and increasing adhesion force between the needle tip and the drop, thereby increasing drop stability and achieving a higher stirrer speed (up to 1700 rpm).

He and Lee [7] introduced a new solvent microextraction technique (dynamic LPME), using a microsyringe and a GC sample injector (Fig. 3). In dynamic LPME, extraction occurs by withdrawing aqueous sample into a microsyringe already containing solvent. The aqueous phase is then pushed out of the syringe and the process is repeated several times. At the end of this procedure, the remaining solvent is injected into the GC instrument for further analysis.

Extraction in dynamic LPME primarily occurs in the thin organic film formed on the inner side of the microsyringe barrel and needle.

Comparison of static LPME with dynamic LPME for some chlorinated benzenes showed that the two methods are comparable in terms of organic solvent consumption (<2 μL). Static LPME provides better reproducibility but suffers limited enrichment and longer extraction time. Dynamic LPME provides higher enrichment within a much shorter time. But, using manual operation, there were shortcomings in that reproducibility and repeatability deteriorated.

In order to overcome these shortcomings, Hou and Lee [8] used a programmable syringe pump to automate the extraction. Subsequently, Myung et al. [9] controlled the movement of the syringe plunger with a computer, so a computer-controlled syringe device was manufactured to

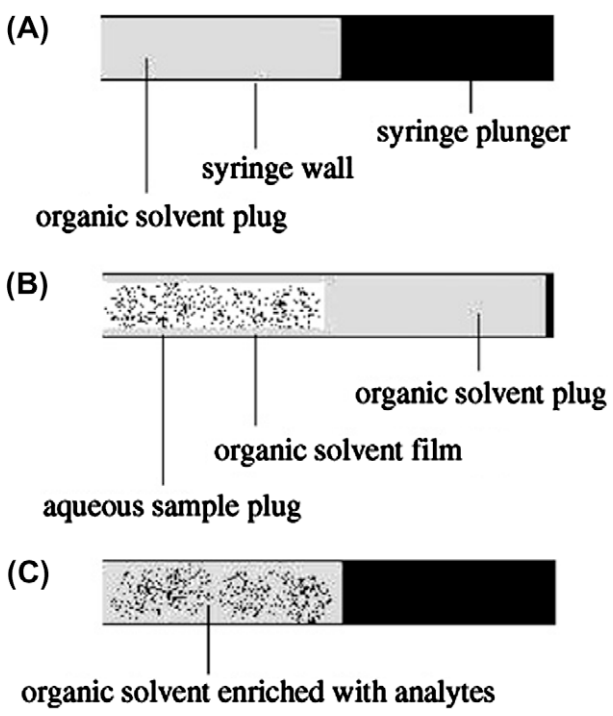

Figure 3. Operation of dynamic liquid-phase microextraction [7].

cope with the problems of the manual operation (e.g., deterioration of validated results, tedious plunge operation and difficulty in controlling plunger speed).

In HS-SDME, an organic solvent suspended at the tip of a microsyringe is placed in the headspace of the sample solution to extract volatile or semi-volatile analytes (Fig. 4). In this mode, the analytes are distributed among three phases (i.e. the water sample, the headspace and the organic drop).

In 2001, the possibility of using a hanging μL solvent drop (HS-SDME) for preconcentration in headspace analysis of volatile organic compounds in an aqueous matrix was reported for the first time [10].

HS-SDME and HS-SPME appear to have similar capabilities in terms of precision and speed of analysis; however, HS-SDME appears to offer two distinct advantages over HS-SPME. First, there is a greater variety of solvents to choose from for HS-SDME, compared to the number of phases currently available for HS-SPME. Second, the cost of μLs of the solvent for HS-SDME is negligible compared to the cost of commercially prepared SPME fibers. However, SPME offers the advantages that there is no solvent peak in the chromatogram, and splitless ''injection'' can be employed.

Compared with DI-SDME, the selection of the extractant for HS-SDME is very flexible and its solubility in the sample solution need not be considered. However, the main limitation on the solvent is that its vapor pressure must be low enough to avoid evaporation during sampling but, at the same time, it must be compatible with GC analysis; furthermore, when aqueous samples have to be analyzed, if the solvent is miscible with water, the drop size may increase, causing the drop to fall from the needle [11].

Subsequently, Shen and Lee [12] introduced manual dynamic HS-LPME that overcomes some limitations of the static microdrop HS-LPME. In comparison to droplet LPME, the dynamic LPME described provides a larger enrichment factor within a shorter analysis time and selection of solvent is more flexible. Because they used a manually-operated extraction system, the precision of the method was relatively poor [e.g., relative standard deviation (RSD) was 5.7–17.7%].

In order to improve ease of the operation and to achieve greater reproducibility in sample extraction, Saraji [13] introduced a semi-automatic dynamic HS-LPME system. A variable-speed stirring motor was used to automate the sample-extraction step.

Ouyang et al. [14] introduced a fully automated HS-LPME technique for dynamic methods, with a CTC CombiPal autosampler. All the operational parameters involved in this process could be precisely and conveniently controlled by the autosampler. Additionally, they devised a kinetic calibration method to correct the matrix effects in applications, and demonstrated it with the analysis of BTEX in orange juice.

Deng et al. [15] used microwave energy for quantitative analysis of paeonol (a bioactive compound) in two traditional Chinese medicines while using HS-SDME. The heating mechanism of the microwave, which can be interpreted as being mainly by dielectric polarization and conduction, is very different from that of conventional heating. Microwaves are directly coupled with the species present in the sample matrix, leading to instantaneous, localized superheating.

Hansson and Hakkarainen [16] combined multiple headspace extraction with SDME. In this method, the extraction process continued until all analytes were re-

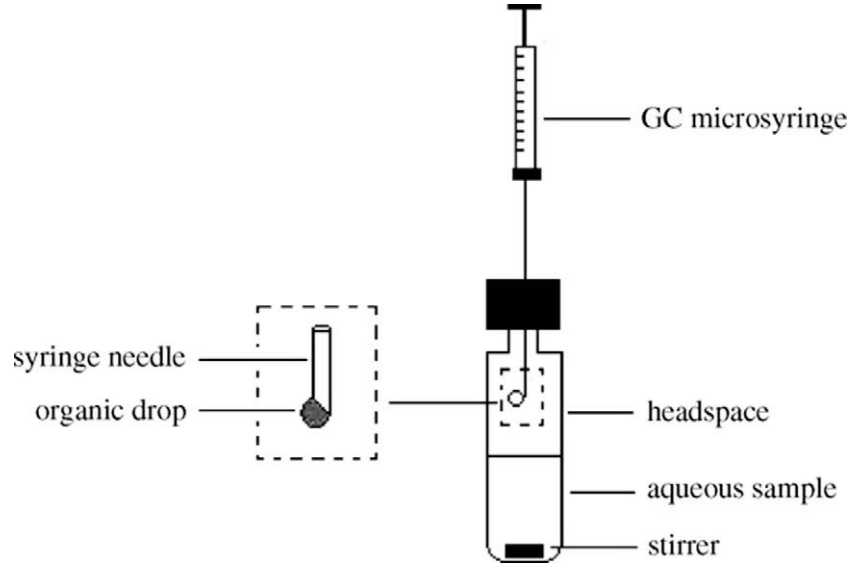

Figure 4. Headspace single-drop microextraction [10].

moved from the sample, thus resulting in complete recovery and elimination of matrix effects.

Zhang et al. [17] introduced the novel headspace microextraction technique termed headspace water-based LPME (HS-WB-LPME). Unlike conventional HS-LPME, instead of high-boiling point organic solvent, water is used as the solvent to extract volatile or semi-volatile ionizable compounds. By combining CE with this extraction technique, the entire analytical process is totally free of organic solvents, so it is environmentally friendly.

Liu et al. [18] used ionic liquids (ILs) as extraction solvents. ILs, which are ionic media resulting from the combination of organic cations and various anions, have been proposed as an alternative to organic solvents due to their low vapor pressure and their high viscosity, which allow the use of larger, more reproducible extracting volumes. IL solvents boast other unique properties, including dual natural polarity, good thermal stability, and miscibility with water and organic solvents. They are also regarded as environmentally-friendly solvents and are easily synthesized or commercially available. Moreover, no evaporation occurs due to their high boiling points. However, this last advantage becomes a drawback if GC is going to be used after SDME, since this lack of volatility dirties the GC system and even blocks the column. This drawback limits the possibilities of the IL-based SDME, since the IL-SDME-GC combination cannot be achieved, even though it could be a useful tool for different analytical purposes.

Valcárcel et al. [19] focused on the use of ILs as extracting media for coupling SDME to GC-MS. For this purpose, a new, removable interface permits direct injection of the extraction medium into the chromatograph. The new interface was built in order to prevent the IL from entering the capillary column while effectively transferring the extracted analytes into the gas chromatograph.

The impossibility of direct injection of an IL droplet from an IL-based SDME in a GC inlet, even filled with glass wool, was clearly demonstrated by Valcárcel and co-workers [19], who showed that IL considerably dirtied the GC system, and even blocked the column, after only three injections. They recommended substituting this removable unit for every 10 μL of IL being injected, requiring 1 h of equilibration time.

Chisvert et al. [20] presented direct use of IL-based SDME prior to GC. The approach is based on the thermal desorption (TD) of the analytes from the IL droplet to the GC system, by using a robust, commercially-available TD system. The proposed approach prevents IL from entering the GC system. It is easy to operate, and makes use of robust commercially-available instrumentation. Moreover, the proposed approach allows larger volumes of IL to be used without the need to disassemble the inlet, thus avoiding equilibration times and increasing the sample throughput within a working day. However, as no extractant reaches the GC system, no solvent delay is necessary in the detection step, thus allowing acquisition from the first moment, which enables highly volatile substances to be determined with small retention times.

Since water-immiscible solvents are generally used in SDME, GC is the preferred technique for the analysis of the extracts.

In general, HPLC is a widely used versatile separation and quantification technology. However, there have been only a few papers reporting the use of this technique following SDME. SDME is more suited for volatile or semi-volatile analytes that are of a relatively more hydrophobic nature, necessitating the use of immiscible extracting solvents. This intuitively disqualifies HPLC from being considered. Moreover, a smaller volume of the extracting solvent is usually chosen taking into consideration stability during SDME with stirring; however, for most HPLC injections, a sample size of more than 2 μL is preferred. It is of course important that the organic extraction phase selected is compatible with the HPLC mobile phase. However, this limits the choice of solvents and is not usually realized, and an extra step of solvent exchange and extract reconstitution is needed before analysis [11].

For ionizable analytes, Ma and Cantwell [21] developed a solvent-microextraction procedure with simultaneous back-extraction (SME-BE), otherwise descriptively referred to here as LPME-BE, to reconcentrate and to purify their target compounds. An LPME-BE system comprises three liquid phases:

- the donor solution where pH is adjusted to deionize the compounds;
- the organic solvent phase; and,
- the acceptor solution, the pH of which is adjusted to ionize the compounds.

The unsupported liquid organic phase is held within a Teflon ring to develop an organic solvent layer, and the microdrop of acceptor phase is suspended in the organic phase directly from the tip of the syringe needle. With the help of stirring, the analytes are extracted from the donor solution into the solvent phase and back-extracted simultaneously into the acceptor phase (Fig. 5).

This system has some drawbacks (e.g., the need to wash the vials after each extraction and the difficulty of positioning the ring). In addition, the layout of the ring must always be constant.

In 2004, Sarafraz et al. [22] made some modifications to the basic three-phase SDME set-up and developed a system in which a simple volumetric flask (5 mL) was used instead of a vial with a sleeve in the form of a ring at the entrance of the vial and/or other superfluous components. Also, because of using a conventional volumetric flask, the interface between the aqueous sample solution and the intermediate organic solvent is limited to a very small area in almost the narrowest part of the neck of the flask. During stirring a vortex appears so the

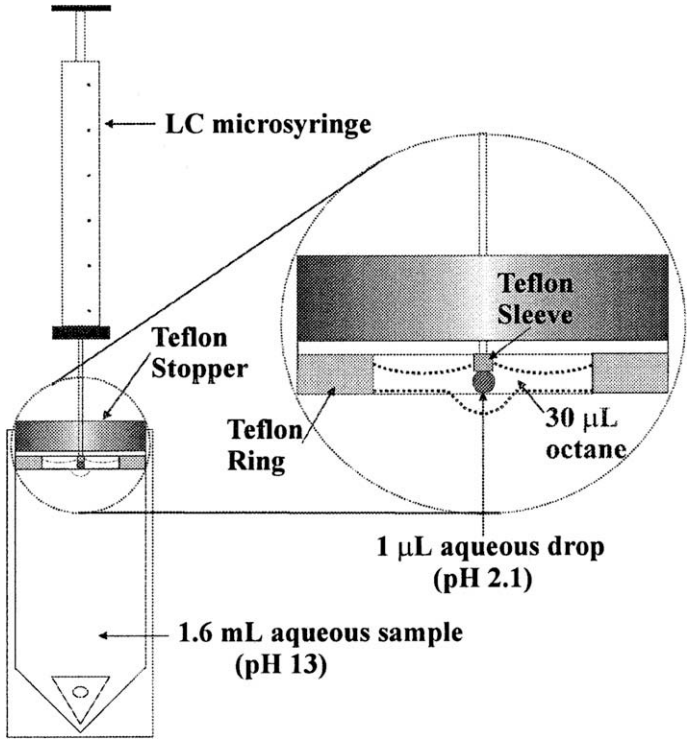

Figure 5. Drop-based microextraction system developed by Ma and Cantwell [21].

surface area increases. The result shows that there is a large increase in mass transfer of the analytes.

SDME (direct and headspace modes) can be easily employed in combination with atomic spectrometry techniques that admit μL samples [e.g., electrothermal atomic absorption spectrometry (ETAAS) and electrothermal vaporization-inductively coupled plasma optical emission spectrometry/mass spectrometry (ETV-ICP-OES/MS)]. ETV is one of the sample-introduction techniques currently employed in plasma atomic emission spectrometry and MS. Compared to conventional pneumatic nebulization sample introduction, it has some merits (e.g., high transport efficiency, low sample consumption, low absolute limit of detection (LOD), and the ability to analyze both liquid and solid samples). HS-SDME has been applied to preconcentration of arsine prior to detection by ETAAS [23].

In recent years, CE has been developed into a highly attractive separation technique for both ionic and neutral compounds. Due to high separation efficiencies, low separation times, low consumption of reagents, and relatively simple method development, CE has been implemented for research and routine analysis (e.g., pharmaceuticals, peptides, proteins, agrochemicals, raw materials, water, and DNA [24]). However, because most CE is performed with UV detection directly on the narrow fused silica capillaries used for separation and because only nL volumes of sample are injected in traditional CE, most concentration LODs obtained in CE are relatively high. Therefore, CE is principally used for compounds present at relatively high concentration levels, while the advantages of the technique are difficult to utilize for trace-analysis applications in connection with biological and environmental samples. To overcome the poor concentration sensitivity of CE, on-column concentration methods (e.g., sample stacking, field-amplified sample injection, large-volume stacking, transient isotachophoresis and sweeping) have been widely used. The advantage of on-column concentration is that no mechanical modification of the column is required and the concentration procedure is relatively simple with little manipulation of buffer and sample systems. However, its application is limited to cases satisfying specific requirements for the run buffer and sample solutions. As an alternative to these techniques, sample-preconcentration methods coupled with CE can be employed.

In 2004, Choi et al. [25] directly combined SDME with CE. They developed an efficient on-line preconcentration method using LPME prior to a CE run. A concentration ratio of three orders of magnitude was obtained for the analyte with 30-min extraction.

3. Continuous-flow microextraction (CFME)

Liu and Lee [26] reported a novel liquid-liquid microextraction technique, which was termed CFME. In this

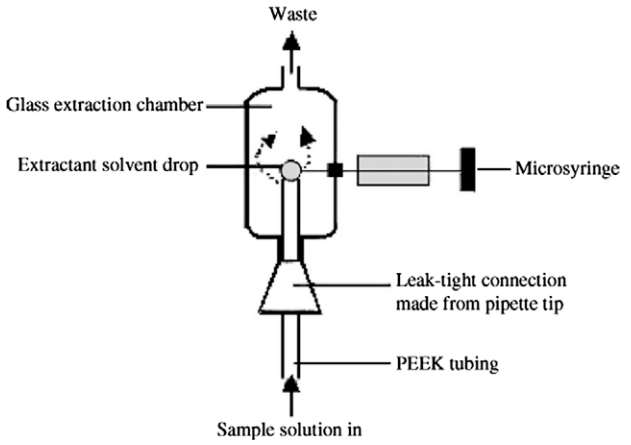

Figure 6. Continuous-flow microextraction [26].

method, the extraction solvent drop is injected into a glass chamber by a conventional microsyringe and held at the outlet tip of a PTFE connecting tube, the sample solution flows right through the tube and the extraction glass unit to waste, the solvent drop interacts continuously with the sample solution and extraction proceeds simultaneously (Fig. 6).

CFME differs from other extraction approaches in that a drop of solvent fully and continuously makes contact with fresh, flowing sample solution. Both diffusion and molecular momentum resulting from mechanical forces contribute to its effectiveness. With the use of an HPLC injection valve, precise control of the solvent drop size could be achieved while introduction of undesirable air bubbles was avoided. Another advantage was that, because of the high preconcentration factor that can be achieved, smaller volumes of aqueous samples were needed for extraction.

Xia et al. [27] made some modification to the basic CFME set-up and developed a recycling-flow system in which the ''waste'' from the chamber was returned to the sample vial. This allowed further reduction in sample size (and unattended operation, since there was no danger of the sample vial running dry).

Hu et al. [28] combined a new method of IL-based cycle flow SDME with ETV-ICP-MS for the determination of trace Co, Hg and Pb with 1-(2-pyridylazo)-2-naphthol (PAN) as both extractant and chemical modifier and 1-butyl-3-methylimidazolium hexafluorophosphate as extraction solvent.

4. Directly-suspended droplet microextraction (DSDME)

LPME based on static microdroplets does have some drawbacks. First of all, the microdroplet can be lost from its support due to gravity, shear force and flow-field turbulence. Also, constrained stirring decreases the extraction efficiency or enrichment factor. The volume of the microdroplet is limited to 5 μL, which results in poor compatibility with some instruments that require larger injection volumes (e.g., HPLC).

In recent years, Lu and co-workers [29] developed DSDME as a new sampling method (Fig. 7). In this method, a stirring bar is placed at the bottom of a vial containing an aqueous sample and rotated at a speed required to cause a gentle vortex. If a small volume of an immiscible organic solvent is added to the surface of the aqueous solution, the vortex results in the formation of a single droplet at or near the center of rotation. The droplet itself may also rotate on the surface of the aqueous phase, increasing mass transfer. Compared with the other LPME techniques based on droplet systems (e.g., SDME), it provides more flexibility in the choice of the operational parameters, especially the amount of the solvent and the stirring frequency.

The possibility of applying larger volumes of organic solvents in this method also makes it a useful technique to match with HPLC in addition to GC.

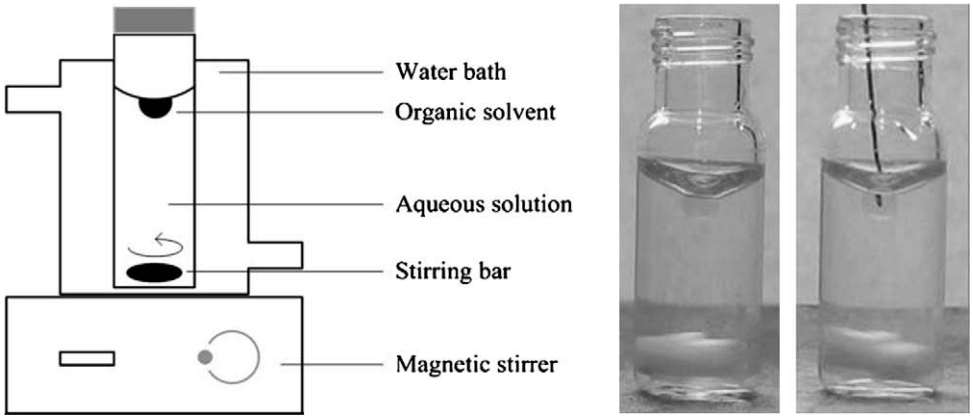

Figure 7. Directly suspended droplet microextraction: (a) the set up; (b) extracting; (c) sampling [29].

In 2008, Sarafraz-Yazdi et al. [30] developed the method and combined DSDME with HPLC for the determination of diclofenac. The same authors also used DSDME with GC with flame ionization detection (GC-FID) for the determination of two tricyclic antidepressant (TCA) drugs, amitriptyline and nortriptyline [31], and BTEX compounds [32].

DSDME is very simple and free from cross contamination, the equilibration time is reached quickly, and supporting materials are not required. The main disadvantage of the method is the difficulty of taking out the small amount of suspended droplet from the solution (<5 μL). Using a microsyringe, exact collection of the microdrop is impossible and some water may be transferred into the syringe, and that can create problems for some instruments (e.g., GC-ECD). To overcome this problem, Yamini et al. [33], introduced a new sampling method based on solidifying the floating organic droplet. In this method, small volume of an organic solvent with a melting point near room temperature (in the range 10–30°C) was floated on the surface of the aqueous solution. The solution was stirred for a prescribed period of time, then the sample was transferred into the ice bath. When the organic solvent was solidified (about 5 min), it was transferred into a small conical vial, and the melted organic solvent was used for determination of the analytes.

5. Dispersive liquid-liquid microextraction (DLLME)

Recently Assadi and co-workers [34] reported DLLME as a new LLE technique that uses μL volumes of extraction solvent along with a few mL of dispersive solvents. In this method, a cloudy solution is formed when an appropriate mixture of extraction and dispersive solvents is injected into an aqueous sample containing the analytes of interest. The hydrophobic solutes are enriched in the extraction solvent, which is dispersed into the bulk aqueous solution. After centrifugation, determination of the analytes in the settled phase can be performed by conventional analytical techniques (Fig. 8).

In DLLME, the dispersive solvent plays a key role that helps extraction solvent form fine droplets in aqueous samples, representing about 97–99% of the total volume of the extraction mixture. Compared to other methods, abundant surface contact between fine droplets and the analyte in DLLME speeds up the mass-transfer processes of analytes from aquatic phase to organic phase, which not only greatly enhances extraction efficiency but also overcomes the problem of the time taken. For low toxicity and low cost, acetone, methanol, ethanol and acetonitrile have generally been used as dispersive solvents. However, they could apply some extraction solvents to form a constant, large volume of sediment when the dosage of extraction solvent is low. Though more costly and noxious than other dispersive solvents, tetrahydrofuran (THF) could constitute larger settled volume, which could provide convenient operation and reduce the volume requirement of toxic, chlorinated extraction solvents. THF as dispersive solvent appears to have more advantages in DLLME.

The advantages of DLLME are simplicity of operation, rapidity, low cost, high recovery, high enrichment factor and very short extraction time (a few seconds). The performance of DLLME was illustrated with the determination of polycyclic aromatic hydrocarbons (PAHs) in water samples by using gas chromatography-flame ionization detection (GC-FID). Subsequently, the same authors also coupled graphite furnace atomic absorption spectrometry (GF-AAS) with DLLME to determine cadmium in water samples [35].

For GC-incompatible analytes, evaporation of the organic extract to dryness and reconstitution of analytes into a suitable solvent prior to HPLC was required. Farajzadeh et al. [36] used this approach for the analysis of antioxidants.

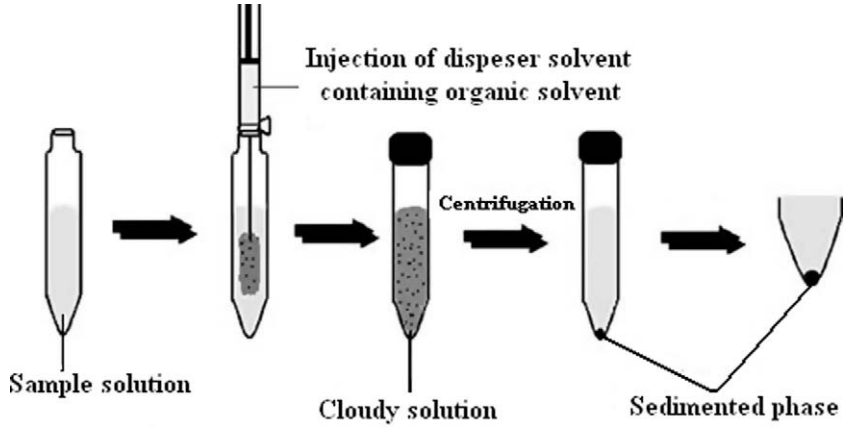

Figure 8. Different steps in dispersive liquid-liquid microextraction [35].

Later, Shemirani et al. [37] combined fiber optic-linear array detection spectrophotometry (FO-LADS) and DLLME for simultaneous preconcentration and determination of palladium and cobalt in drinking water, tap water, river water, seawater and synthetic samples.

Subsequently, Feng et al. [38] demonstrated a new DLLME method based on the solidifying floating organic droplet method (DLLME-SFO). Compared with traditional LPME, the proposed method obtained an enrichment factor about twice that in LPME.

The objective of sample preparation is often not only to isolate the target analytes from the samples and concentrate the analytes, but also simultaneously to reduce or even to eliminate the interferences originally present in the sample to facilitate their determination at low levels. The main disadvantage of DLLME is that it is not a selective extraction method. However, interferences from matrix co-extractives are often present, especially in determination of trace analytes in a complex matrix sample (e.g., soil). This is the main reason that most reported applications of DLLME have focused on simple water samples, so exploration of potential applications of DLLME in more complex matrix samples is desirable. Moreover, DLLME can also be combined with SPE and LLE to improve the selectivity of the sample-preparation process and/or to reduce the limits of quantification (LOQs) achieved for complex matrices.

Assadi et al. have reported the combination of SPE with DLLME for the selective determination of chlorophenols in aqueous samples with various matrices [39]. One of the advantages of such a combination is that it can be used for complex matrix samples. The combination of DLLME with in-syringe back extraction as a selective extraction method for ionizable compounds has also been reported by Fuh et al. [40].

Subsequently, Zhou et al. [41] designed a new extraction method, termed temperature-controlled IL dispersive LPME (TILDLPME). The mechanism was very much like DLLME, but dispersion was realized not by injecting but by dissolving depending on the temperature. Extraction was accomplished during the process of temperature rising and falling. In this method, the sample was heated in water to 80°C after the addition of IL. The IL mixed with the solution entirely at this temperature and thereafter the solution was cooled with ice-water for a certain time. The IL and aqueous phases were separated after centrifugation. This study indicated that TILDLPME can be an excellent, green extraction technique for analyte-species separation and preconcentration.

Zhou et al. [42] introduced IL dispersive LLME (IL-DLLME) method. In this technique, the IL was used instead of the highly toxic, chlorinated solvents that are usually employed as extraction solvents in DLLME. Compared with TILDLPME, IL-DLLME avoids the heating and cooling step, which may lead to degradation of some thermally unstable compounds or other unexpected effects, and significantly reduces the extraction time.

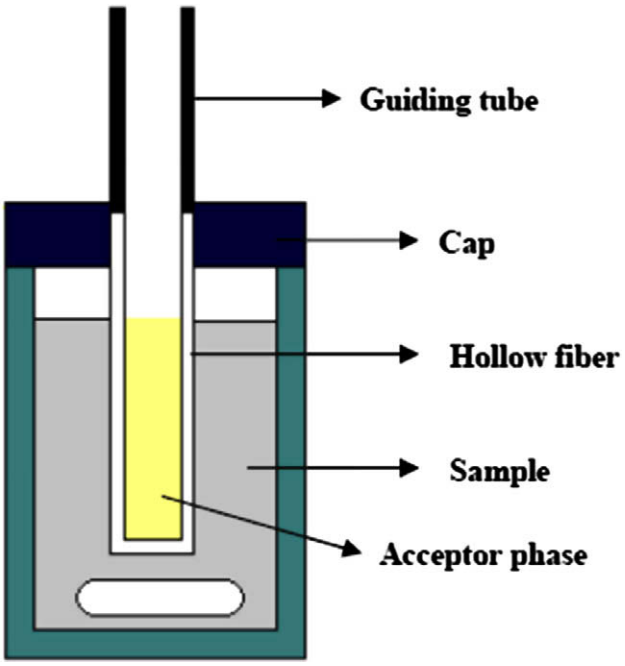

Figure 9. Principle of hollow-fiber liquid phase microextraction [44].

6. Hollow-fiber liquid-phase microextraction (HF-LPME)

Pedersen-Bjergaard and Rasmussen [43] introduced HF-LPME. They used the basic principle of supported liquid membrane (SLM), for the first time, in simple, inexpensive, disposable extraction units for the liquid-liquid-liquid microextraction (LLLME) utilizing polypropylene HFs as the membrane. Fig. 9 illustrates the basic principle of HF-LPME.

The sample vial is filled with the aqueous sample. A short piece of a porous HF may be either a rod with a closed bottom or a u-shape where both ends are connected to guiding tubes. Prior to extraction, the HF is first dipped in the organic solvent for a few times to immobilize solvent in the pores, and excess solvent is removed. The solvent is immiscible with water to ensure that it remains within the pores during the extraction with no leakage to the aqueous sample. The organic solvent forms a thin layer within the wall of the HF. The extraction solvent must be compatible with the HF so that the pores in the wall of the HF can be filled completely.

The acceptor solution then fills the lumen of the HF. This acceptor solution can be an organic solvent (the same as that used for the organic solvent in HF pores),

resulting in a two-phase extraction system, or the acceptor solution may be an acidic or alkaline aqueous solution, resulting in a three-phase extraction system.

In the two-phase LPME system, the target analytes are extracted from the aqueous sample and into the organic solvent (acceptor solution) present both in the porous wall and inside the lumen of the HF. This process may be described by the following equation:

$$A_{sample} \leftrightarrow A_{org} \quad (1)$$

where A represents the target analyte. As discussed in more detail later, two-phase LPME may be applied to most analytes with solubility in an organic solvent immiscible with water substantially higher than in an aqueous medium. The acceptor solution may be directly analyzed with capillary GC, or may be evaporated and reconstituted in an aqueous medium for injection into HPLC or CE.

The extraction solvent must be compatible with the HF so that the pores in the wall of the HF can be filled completely. Also, the extraction solvent must have good affinity for target compounds, be immiscible with water and have low volatility. Finally, the organic solvent should have excellent GC behavior. Successful two-phase LPME requires large distribution ratios for target analytes. Such $K_{org/s}$ (distribution ratio $K_{org/s}$ is defined as the ratio of the concentrations of analyte A in the acceptor and sample phase at equilibrium conditions) values correspond to moderately or highly hydrophobic compounds containing acidic or basic groups, or neutral compounds of similar hydrophobicity.

In three-phase LPME, the analytes are extracted from the aqueous sample, through the organic solvent in HF pores, and further into the aqueous acceptor solution present inside the lumen of the HF.

This process may be described by the following equation:

$$A_{\text{sample}} \leftrightarrow A_{\text{org}} \leftrightarrow A_{\text{acceptor}} \quad (2)$$

This extraction mode is limited to basic or acidic analytes with ionizable functionalities. For extraction of basic compounds, pH in the sample has to be adjusted into the alkaline region to suppress analyte solubility, whereas pH in the acceptor solution should be low in order to promote analyte solubility. In this manner, the basic compounds may be easily extracted into the organic phase and further into the acceptor phase without back-extraction to the organic phase again. By contrast, for acidic analytes, pH in the sample should be low and an alkaline acceptor solution should be utilized within the lumen of the fiber. After extraction, the aqueous acceptor solution is directly compatible with HPLC and CE.

Typically, two-phase LPME has involved the use of toluene or *n*-octanol as the organic phase, whereas, in most cases, three-phase LPME has been conducted with *n*-octanol or dihexyl ether as the SLM. For three-phase LPME, HCl and NaOH have, in most cases, been used to make appropriate pH adjustments in the sample and in the acceptor solution. Common to the published methods is that the analytes are relatively hydrophobic. The extraction efficiency is governed by partitioning of the analyte between the sample matrices and the immobilized solvent and by partitioning between the acceptor phase and the immobilized solvent. Hydrophobic analytes are easily extracted into organic solvents from aqueous sample solutions. In addition, hydrophobic ionic analytes have large solubility differences in acidic and basic aqueous solutions. Consequently, hydrophobic ionic analytes are extracted well into the aqueous acceptor phase.

However, polar analytes have low solubility in water-immiscible organic solvents and small differences in their solubility in acidic and basic aqueous solutions. Polar analytes are, therefore, difficult to extract by three-phase LPME. The ability of LPME to exclude extraction of polar analytes contributes to the selectivity of the method.

In these situations, HF-LPME may be accomplished in a carrier-mediated mode, where a carrier is added to the sample. The carrier, which is a relatively hydrophobic ion-pair reagent providing acceptable water solubility, forms ion-pairs with the analytes followed by the extraction of the ion-pair complexes into the organic phase in the pores of the HF. In the contact region of the organic phase and the acceptor solution, the analytes are released from the ion-pair complex into the acceptor solution, whereas counter-ions present in a very high concentration in the acceptor solution ion-pair with the carrier in the contact area, and the new ion-pair complex are back-extracted into the sample.

The deionized analytes in an aqueous solution are extracted from the sample solution, entering into the organic solvent included in the pores of the HF, and further into the inside of the HF, which holds a small volume of an acceptor solution.

LPME-based methods were found to provide excellent sample clean up by excluding macromolecules from the acceptor phase.

The first report on HF-LPME utilized three-phase extraction with methamphetamine as a model drug [43]. King et al. [44] used two-phase HF-LPME for extracting PAHs from soil.

HF-LPME is carried out in two modes: static and dynamic. In the static mode, extraction speed is enhanced by extensive vibration or stirring of the sample and by careful design of the set-up to minimize diffusion distances of the analytes.

In dynamic mode, a conventional microsyringe with the HF attached to its needle is connected to a syringe pump to perform the extraction. The microsyringe is used as both the microextraction device and the

sample-introduction device for the future analysis. The attached HF served as ''holder'' and ''protector'' of the solvent used for extraction. The solvent is repeatedly withdrawn into and discharged from the HF by the syringe pump. The analytes are extracted from donor samples into the solvent impregnated in the HF, and, subsequently, the organic solvent is injected into instrument. Dynamic LPME was claimed to provide better extraction efficiency and improved reproducibility when compared with the static mode [45].

Dynamic HF-LPME improves extraction speed, compared with static systems, but operation in the dynamic mode complicates instrumentation and adds experimental parameters that have to be optimized and controlled.

Zhao and Lee [46] reported on dynamic HF-LPME for the analysis of two PAH compounds in an aqueous sample. They also compared static HF-LPME and dynamic HF-LPME.

Dynamic HF-LPME was shown to provide good extraction efficiency within extraction times of 10 min, due to the improved kinetics brought about by movement of the solvent. Moreover, with the introduction of semi-automation, reproducibility was ~4%, which was much better than that of manually-operated LPME reported earlier.

Recently, in order to improve ease of operation, Pawliszyn et al. [47] introduced fully automated HF-LPME. All the procedures, including filling the extraction solvent, sample-vial transfer and agitation, withdrawing the solvent to the syringe and introducing the extraction phase into injector, were performed automatically with a commercial CTC CombiPal autosampler and associated Cycle Composer software. The good reproducibility of fully-automated LPME techniques eliminates the need for an internal standard to improve method precision.

Jiang et al. [48] introduced dynamic HF-HS-LPME (DHF-HS-LPME) for the determination of PAHs in a complicated soil matrix. In this method, the extracting solvent is held within an HF, affixed to a syringe needle and immersed in the sample solution, and is moved to-and-fro using a programmable syringe pump. Results indicated that this novel HSME method gave good analyte-enrichment factors, linear range, LODs and repeatability, all of which were evaluated by extracting PAHs from soil samples. This approach was not amenable to less-volatile PAHs or to other high-boiling-point analytes.

The purpose of derivatization varies, depending on the analyte, the matrix of the sample and the analytical method to be applied. Some derivatizations are used in sample clean up or concentration. Much more frequently, derivatization is done to change the analyte properties for the core separation (e.g., GC or HPLC). Typically, the matrix is not affected in these derivatizations.

In GC analyses, the derivatization can be done to obtain better behavior of the analyte in the chromatographic column (e.g., less peak tailing and no decomposition), to modify the separation, to improve thermal stability in the injection port, or to improve delectability. For HPLC and other techniques using a liquid mobile phase, the derivatization is done mainly to enhance detectability, although improvements in separation also may be intended. Derivatization can be applied before or after the core chromatographic process. Pre-column derivatization takes place before the separation and post-column derivatization after it. Basheer and Lee [49] investigated the determination of alkylphenols (APs), chlorophenols (CPs) and bisphenol-A (BPA) in aqueous samples with injection-port derivatization.

Subsequently, Zhang and Lee [50] developed a method for the determination of five carbamate pesticides in water samples using LPME followed by on-column derivatization and GC-MS determination.

Trimethylphenylammonium hydroxide (TMPAH) and trimethylsulfonium hydroxide (TMSH) were used as derivatization reagents for extracts prior to GC-MS analysis as carbamate pesticides are thermally-labile compounds.

Basheer et al. [51] developed a new method by using microwave-assisted solvent extraction (MASE) and LPME using HF membrane (HFM) for extraction of persistent organic pollutants (POPs), including organochlorine pesticides (OCP) and polychlorinated biphenyl (PCB), from marine-sediment samples. Because these POPs have low solubility in water and high affinity to sediments, a higher external energy source is required to extract them from sediment. The main advantage of MASE is that it provides faster, more efficient sample extraction due to direct heat transfer by ionic conduction and dipole rotation.

An interesting variant of HS-LPME was recently published under the name ''liquid–gas–liquid microextraction'' (LGLME) [52]. The aqueous acceptor phase in the channel of the HF was separated from the sample solution by the hydrophobic microporous HF wall with air inside its pores. The analytes (phenols) passed through the microporous HFM by gas diffusion and were then trapped by the basic acceptor solution. After extraction, the acceptor solution was withdrawn into a microsyringe and injected into a CE sample vial for subsequent analysis. By combining CE with this extraction technique, a totally solvent-free analytical procedure was achieved.

7. Electrokinetic membrane extraction (EME)

SLMs have been used in analytical chemistry for extraction and preconcentration of chemical substances before HPLC, GC and CE.

The extraction is based on passive diffusion, and depends on the distribution constants between the SLM (organic solvent) and the sample solution and the acceptor solution, respectively. The mass transfer is promoted by optimal pH conditions on both sides of the SLM (pH gradient). The pH value in the sample solution should suppress analyte ionization, while pH in the acceptor solution should be adjusted to ensure total ionization of the analytes. Extraction is further promoted by strong agitation of the extraction system to reduce the stagnant boundary layer in the vicinity of the SLM and to induce convection in the sample. After extraction, the aqueous acceptor solution can be transferred directly into HPLC and CE.

In addition to pH optimization and strong agitation, optimal LPME also relies on the type of organic solvent used as SLM, the sample volume, the acceptor volume, the vial size, and the surface area of the SLM. Even if optimized LPME is an excellent method for isolating and enriching analytes from complicated matrices, it is a relatively time-consuming process with typical extraction times in the range 15–60 min. Very recently, Pedersen-Bjergaard et al. [53] demonstrated, for the first time, EME (i.e. electrokinetic migration across an SLM as a result of application of an electrical dc potential difference, as illustrated in Fig. 10).

One of the electrodes is placed in the sample solution, while the other electrode is located in the acceptor solution inside the lumen of the fiber. Charged analytes in the sample solution are drawn across the SLM towards the electrode of opposite charge in the acceptor solution. In EME, the electrical field serves as the driving force for the extraction process. The application of an electrical field over the SLM was found to improve extraction speed significantly, and EME was superior to LPME in terms of kinetics. Whereas LPME extractions to a large extent occur only under diffusion conditions,

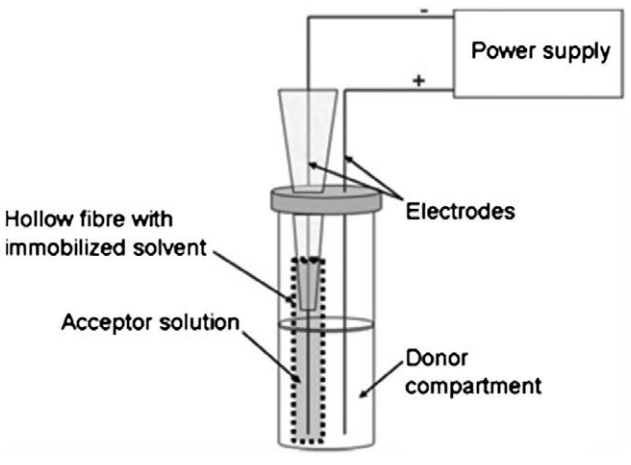

Figure 10. Equipment for electrokinetic membrane extraction [54].

mass transfer in EME always also includes electrokinetic migration in a strong electrical field. The major benefit of EME is significant reduction in extraction times as compared with LPME. With optimized conditions, the extraction time to reach steady state was ~5–10 min in EME.

In the first research [53], several hydrophobic basic drug substances were extracted. Within only 3–5 min, the basic drug substances were extracted to equilibrium, enabling recovery in the range 70–79%.

Compared with using pH gradients (LPME mode) in which equilibrium times were typically in the range 30–60 min, extraction speed in EME was found to be 6–17 times faster [54]. In addition to high extraction speed, mass transfer in EME was found to be strongly compound dependent. This may be utilized to perform highly selective extractions, where the selectivity, to a large extent, may be controlled by extraction time. Especially from small sample volumes, the speed advantage of EME was dramatic compared to LPME, because LPME under diffusion conditions suffers from very poor extraction kinetics As a result, EME may have great potential for extractions in future, especially in miniaturized formats.

Pedersen et al. [55] described and verified a theoretical model for EME, where target analytes are extracted from an aqueous sample, through a thin layer of 2-nitrophenyl octylether immobilized as an SLM in the pores in the wall of a porous HF, and into an acceptor solution present inside the lumen of the HF by applying a difference in electrical potential. The mathematical model was based on the Nernst–Planck equation, and described the flux over the SLM. The model demonstrated that the magnitude of the difference in electrical potential, the ion balance of the system and the absolute temperature influenced the flux of analyte across the SLM. The flux strongly depended on the potential difference over the SLM, and increased potential difference resulted in an increase in the flux. The ion balance, defined as the sum of ions in the donor solution divided by the sum of ions in the acceptor solution, was shown to influence the flux. High ion concentration in the acceptor solution relative to the sample solution was advantageous for high flux. Also, different temperatures led to changes in the flux in EME.

In another work, Lee and co-workers [56] coupled electromembrane isolation (EMI) with CE and UV detection to determine lead (Pb) ions. Very recently, Pedersen-Bjergaard et al. [57] performed EME of basic drugs from 10-μL-sample volumes through an organic solvent (2-nitrophenyl octyl ether) immobilized as an SLM in the pores of a flat polypropylene membrane (25 μm thick), and into 10 μL 10 mM HCl as the acceptor solution. The work investigated, for the first time, miniaturized EME using flat membranes. The set-up used was very simple and required no special instrumentation except a low voltage power supply.

With this simplified system, extractions could easily be performed from sample volumes of the order of 10 μL.

Because knowledge of EME is limited, more work needs to be conducted to understand the exact extraction mechanism, to optimize the extraction of a particular type of analyte, and to demonstrate that the technique provides reliable data for a broad range of analytical applications. EME has also been shown to be highly selective; several experimental conditions can be easily varied to tune the selectivity. Thus, especially in miniaturized analytical systems, we expect EME to be an interesting concept in future, enabling sample preparation to be integrated with final chemical analysis.

8. Comparison of the LPME techniques

Choosing a suitable extraction technique requires consideration of a range of factors, including efficiency of extraction, sample-throughput time, complexity (cost) of equipment, complexity of method development, amount of organic solvent used and range of applicability.

The main tasks to be fulfilled during sample preparation are

(i) analyte preconcentration, allowing low LODs;
(ii) elimination of interferences;
(iii) if needed, analyte conversion, making it more suitable for separation and detection; and,
(iv) providing a robust and reproducible method not sensitive for matrix effects.

SDME was developed as a solvent-minimized sample-pretreatment procedure, which is inexpensive, and, since very little solvent is used, there is minimal exposure to toxic organic solvents [5].

In addition, no preconditioning is required, unlike SPME, where the fiber must be pretreated for efficient extraction. Also, memory effects are avoided. There are perhaps several reasons for the drawbacks of the DI-SDME method, as follows.

(1) First, the volume of the extractant microdrop is small – often no bigger than 5 μL – which confines the amount of analytes extracted and the extraction efficiency.
(2) Second, the microdrop is unstable and easily dislodged from the tip of the microsyringe needle during stirring. The microdrop is suspended on the microsyringe needle by the surface tension, which is relatively low because of the small contact area between the microdrop and the tip of the microsyringe needle, so the stirring velocity cannot be speedy due to the instability of the microdrop, so the extraction often cannot reach equilibrium.
(3) Third, the kind of extractant available is limited, because the extractant in DI-SDME must satisfy certain conditions (e.g., water immiscibility and appropriate density). Otherwise, the extractant microdrop easily floats away or drops from the tip of needle, resulting in a failed experiment.
(4) Fourth, reproducibility is often poor due to the serious dissolution loss of organic extractant, which has a small volume and large contact area with the sample solution.
(5) Furthermore, the technique is not suitable for dirty samples, because particles in the sample affect the extraction by making the drop unstable, and an extra filtration step of the sample solution is usually necessary.
(6) Dynamic SDME involves a tedious operation and precision of the method is not sufficient. Nevertheless the acceptable analytical performance mentioned above, the sensitivity and the precision of SDME methods need further improvement.

HF-LPME overcomes these problems. The disposable nature of the HF totally eliminates the possibility of sample carryover and ensures high reproducibility. In addition, the small pore size prevents large molecules and particles present in the donor solution from entering the acceptor phase, thus yielding very clean extracts. However, HF-LPME tolerates a wide pH range; it can be used in applications that would not be suitable for SPE or SPME. Sample carryover can be avoided because the HFs are inexpensive enough to be single use and disposed of. In cases where a large number of samples need to be prepared by SPE, an equivalent LPME preparation procedure could also be more economical. It has been proved that HF-LPME is very useful for extracting drugs and metabolites from biological matrices and pollutants from environmental samples with simultaneous clean up of the extracts.

Some disadvantages of LPME using HFMs are as follows:

(1) existence of a membrane barrier between the source (sample) phase and receiving (acceptor) phase reduces extraction rate and increases extraction time;
(2) in two-phase LPME, excess solvent is needed for elution of analytes from the lumen and pores of fiber, and this process is also time consuming;
(3) creation of air bubbles on the surface of the HF reduces the transport rate and decreases the reproducibility of the extraction; and,
(4) in real samples (e.g., blood plasma, urine and wastewater), adsorption of hydrophobic substances on the fiber surface may block the pores [33].

To overcome the above problems, other LPME methods (e.g., DLLME) have been developed. Compared to other techniques, DLLME is characterized by very short extraction times, mainly because of the large surface area between the solvent and the aqueous phase. Other advantages are simplicity of operation, low cost, and

high recovery and enrichment factors, offering potential for ultra-trace analysis. However, DLLME also has some drawbacks, including the difficulty of automating and the need to use a third component (disperser solvent) that usually decreases the partition coefficient of the analytes into the extractant solvent. The applications of the method for complex matrices in environmental samples (e.g., urine, whole blood and soil) are very limited.

9. Conclusion

All LPME techniques can be utilized effectively for extraction of target analytes from various sample solutions. The main advantages of the miniaturized systems are high-speed analysis with high efficiency, environmentally-friendly operation due to minimal solvent consumption, and highly selective analysis by systems designed for particular applications. We have reviewed the current literature on LPME coupled with all analytical instruments.

The combination of microscale sample preparation and microscale liquid-phase separation promises good applications in various fields of separation science in future, especially for trace amounts of analytes in complex sample matrices. However, continuous innovations in extraction materials and integrated analytical systems are also needed to find complete solutions to many separation problems.

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