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Review Article

Application of hollow fiber liquid phase microextraction and dispersive liquid–liquid microextraction techniques in analytical toxicology

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ABSTRACT

The recent developments in hollow fiber liquid phase microextraction and dispersive liquid–liquid microextraction are reviewed. Applications of these newly emerging developments in extraction and preconcentration of a vast category of compounds including heavy metals, pesticides, pharmaceuticals and abused drugs in complex matrices (environmental and biological matrices) are reviewed and discussed. The new developments in these techniques including the use of solvents lighter than water, ionic liquids and supramolecular solvents are also considered. Applications of these new solvents reduce the use of toxic solvents and eliminate the centrifugation step, which reduces the extraction time.

1. Introduction

There is no doubt that reliability, precision and accuracy of the results of any analytical procedure are strongly dependent on the sample preparation method, especially when trace and ultratrace levels of the analytes in complex matrices (biological and environmental) should be analyzed. Indeed, sample preparation is often thought to be the most critical step in the whole analytical procedure because its steps account for one-third of the errors generated by the analytical method [1]. The traditional sample preparation technique is liquid–liquid extraction (LLE). Despite extensive use of this method over the years it has important disadvantages. The LLE method is tedious, time consuming and uses large amount of toxic solvents [2]. In order to overcome these drawbacks, a great number of efforts have been made to develop new extraction techniques. The final goal of these efforts is to develop simple,

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rapid and inexpensive techniques that consume the minimum volume of toxic solvents and have the ability of automation. The efforts of different researchers in this area have resulted in the invention and development of new extraction techniques known as liquid-phase microextraction (LPME). The LPME is a solvent-minimized sample pretreatment procedure of LLE, in which only several microliters of solvent is required to concentrate analytes from various samples rather than hundreds of milliliters needed in traditional LLE. The other advantages of LPME are simplicity of operation, rapidity, low cost, high recovery and high enrichment factor [3]. The LPME can be divided into three main modes [4]: (1) single-drop microextraction; (2) hollow-fiber liquid phase microextraction (HFLPME); and (3) dispersive liquid–liquid microextraction (DLLME). Among these modes of LPME, HFLPME and DLLME have received much attention because of their benefits.

In this review, the recent developments including the use of ionic liquids and supramolecular solvents in HFLPME and DLLME and applications of HFLPME and DLLME in the extraction and preconcentration of different analytes from complex matrices (environmental and biological) are discussed.

2. HFLPE

HFLPME is a mode of LPME that uses a porous polypropylene hollow fiber for immobilization of organic solvent in the pores of hollow fibers. This technique was introduced by Pedersen-Bjergaard and Rasmussen [5]. The main components of this technique are: (1) donor phase that usually is an aqueous sample containing the analytes of interest; (2) porous polypropylene hollow fiber for immobilization of organic solvent in its pores; (3) organic solvent that is immobilized in the pores of the hollow fiber; and (4) acceptor phase that usually is an organic, acidic or basic solution that fills the inside of the hollow fiber lumen.

From a practical point of view, a short piece of a porous hollow fiber is dipped in the organic solvent in order to immobilize solvent in its pores. Thus, a thin layer of organic solvent is formed within the wall of the hollow fiber. In the next step, the lumen of the hollow fiber is filled with an appropriate acceptor solution and then the hollow fiber is placed into the sample vial containing the sample donor phase. Extraction takes place from the donor phase into the organic layer on the walls of the hollow fiber and then into the acceptor phase inside the lumen of the hollow fiber.

2.1. *Different modes of HFLPME*

According to the type of acceptor phase and solution agitation, HFLPME is classified into different modes. (1) Two phase HFLPME: in this mode the acceptor solution is the same organic solvent immobilized in the pores of the hollow fiber. This mode is usually used for the extraction of analytes with a solubility in an organic solvent immiscible with water. (2) Three phase HFLPME: in this mode, the acceptor phase is an acidic or alkaline aqueous solution. The analytes are extracted from an aqueous sample, through the thin film of organic solvent and then into an aqueous acceptor solution. This extraction mode is limited to basic or acidic analytes with ionizable functions. In this mode of HFLPME, the pH adjustment plays a central role. For acidic analytes, the pH of the donor phase should be adjusted into the acidic region to suppress the ionization of analytes and keep them in their neutral form to be dissolved more effectively in organic solvent. The acceptor phase in this case should be an alkaline solution to guarantee the ionization of analytes and their extraction into the acceptor phase [6]. The situation for basic analytes is the reverse. The donor phase (sample matrix) is an alkaline and the acceptor phase is an acidic solution. (3) Static mode: in this mode of HFLPME, extraction speed is enhanced by stirring the sample solution usually using a magnetic stirrer. (4) Dynamic mode: in this mode, using the syringe plunger, small volumes of the aqueous sample are repeatedly pulled in and out of the hollow fiber [7]. Dynamic HFLPME improves extraction speed, as compared with static systems but operation in the dynamic mode complicates instrumentation and adds experimental parameters that have to be optimized and controlled [4]. Different steps of HFLPME are shown in Figure 1.

2.2. *Parameters affecting the extraction efficiency of HFLPME*

Different parameters affect the efficiency of HFLPME, including type of hollow fiber materials, type of organic solvent, extraction time, pH of donor and acceptor phases, temperature and salt addition.

2.2.1. *Selection of hollow fiber materials*

To achieve better results of HFLPME, the hollow fiber should be slightly hydrophobic so that the micropores in the hollow fiber can be impregnated with the organic extraction solvent. Polyethersulfone and polyvinylidene fluoride are usually used for extraction [8]. From the view of atom orbitals sulfur atom has d orbitals that can accommodate the valent electrons to form complex polar resonance structures. On the contrary, the fluorine atom in the structure of polyvinylidene fluoride has stronger nucleophilicity [8].

2.2.2. *Type of organic solvent*

The type of extraction solvent is an important factor that has a great effect on the extraction efficiency. Ideally, organic solvent in HFLPME should be nonvolatile, immiscible with water, strongly immobilized within the pores of the hollow fiber, be able to provide high solubility for the target analytes, and should be compatible with the instrumental analysis system. Solvents such toluene, chloroform, 1-octanol and *n*-hexyl ether are usually used as organic solvents in HFLPME. Recently application of ionic liquids [9–12] and supramolecular solvents [13,14] as an efficient solvent for extraction in HHLPME has increased.

2.2.3. *Effect of the pH of donor and acceptor phases*

The pH of the donor and acceptor phases plays a major role in extraction efficiency, especially when the target analytes have ionizable functional groups. The pH of donor phase should be adjusted to a level that guarantees the neutrality of analytes and consequently reduces their solubility in the sample

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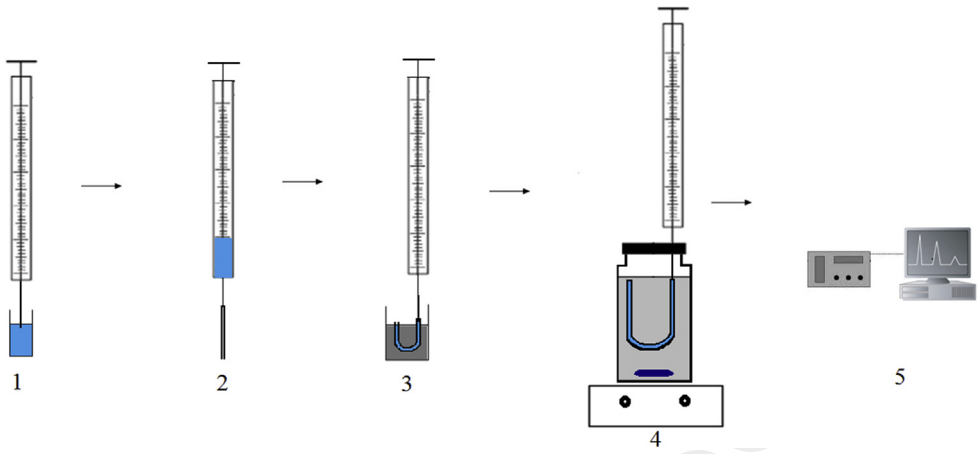

Figure 1 – Different steps of hollow fiber liquid phase microextraction: (1) filling the syringe with acceptor phase; (2) filling the hollow fiber lumen with acceptor phase; (3) bending the hollow fiber into the U shape and its insertion into the aqueous sample; (4) agitation with stirring; and (5) instrumental analysis.

solution. In contrast, the pH of the acceptor phase should be at a level that guarantees the ionization of analytes. Therefore, for acidic analytes, the donor and acceptor phases are acidic and basic solutions, respectively. The situation for basic analytes is the reverse where the donor and acceptor phases are basic and acidic solutions, respectively. It is believed that the pH of the acceptor phase should be at least 2–3 units different from the pKa values of the analytes, to insure the appropriate extraction [15].

2.2.4. *Effect of sample and organic solvent volume*

Sample and solvent volume are two other important factors affecting the extraction efficiency in HFLPME. Indeed, increasing the phase ratio between sample and organic solvent volume would increase the preconcentration factor of analytes to some extent [16].

2.2.5. *Effect of temperature*

Temperature obviously affects the extraction efficiency in two ways. On the one hand, temperature affects the mass transfer rates of analytes, and on the other hand, temperature affects the partition coefficients between the organic and aqueous phases [16]. When the temperature increases, the mass transfer rates of analytes increases, but the partition coefficients decrease. Depending on the dominating factor, the extraction efficiency would either increase or decrease. It should be mentioned that elevated temperatures may have an adverse effect on the extraction efficiency due to the organic solvent evaporation, increasing the solubility of organic solvent in the aqueous phase and formation of air bubbles adhering to the hollow fiber [16,17].

2.2.6. *Extraction time in HFLPME*

As for any other extraction technique, extraction time is a crucial parameter in HFLPME and should be as short as possible. The typical extraction times in HFLPME are in the range of 30–60 minutes. At first, it was thought that the mass transfer across the boundary layer at the donor phase and organic solvent was the rate-limiting step in HFLPME [18] but new findings showed that the mass transfer through the organic solvent layer is the rate-limiting step in HFLPME [19]. Moreover, it is believed that the structure of the hollow fiber has a strong effect on the transfer of analytes through the immobilized organic solvent. Therefore, in order to speed up HFLPME, use of thinner membranes and low viscous organic solvents has been recommended [19].

2.2.7. *Effect of stirring speed*

Sample agitation played an important role in enhancing extraction efficiency. In the static mode of HFLPME, agitation of the sample solution is performed using a stirring bar. Stirring the sample solution enhances the mass transfer in the aqueous phase and consequently reduces the extraction time to attain a thermodynamic equilibrium. Thus, the equilibrium between the aqueous and organic phases can be achieved more rapidly by stirring the aqueous sample. However, when the stirring speed is around 1400 rpm, the stirring bar inclines to rotate at random, which results in poor reproducibility [16]. In the dynamic mode, solution agitation is performed using a syringe plunger. In this case, a small volume of the aqueous sample is repeatedly pulled in and out of the hollow fiber using the syringe plunger. This method improves extraction speed, as compared with static systems but operation in the dynamic mode complicates instrumentation and adds experimental parameters that have to be optimized and controlled [4].

2.2.8. *Effect of ionic strength*

The salting-out effect has been commonly used in LLE, SPME and LPME. Generally salt addition causes an enhancement in extraction because of the salting-out effect [20]. In HFLPME, by addition of a salt to the sample solution, different results may be observed. In some cases, salt addition improves the extraction efficiency [21,22]. However, in some instances the extraction efficiency decreases by addition of salt [6,23,24]. These anomalous effects of salt addition could be explained

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using the following phenomena. First, the dissolution of salt (usually NaCl) in water might change the physical properties of the Nernst diffusion film and reduce the rate of diffusion of the target analytes into the extraction solvent. Second, the addition of salt could lead to an increase in the ionic strength of the solution and then decrease the solubility of the target analytes in the aqueous phase and enhance their partitioning into the organic phase. Third, the addition of salt could also affect the phase ratio. The first and third factors could lead to a decrease in extraction efficiency, while the second factor could lead to an increase. Depending on the dominant factor, the extraction efficiency would either increase or decrease [16].

2.2.9. *Applications of HFLPME*

Determination of methylmercury in human hair and sludge samples was performed using two- and three-phase LPME and graphite furnace atomic absorption spectrometry [25]. In both modes of HFLPME, toluene was used as the organic solvent. In three-phase mode, the acceptor phase was 4% thiourea in 1M HCl. One of the advantages of this method is that it differs between organic and inorganic mercury. Methylmercury was extracted into the organic phase while inorganic mercury remained as a free species in sample solution. The enrichment factor of three-phase LPME (240) was greater than that of two-phase LPME (50). The limit of detection (LOD) of the three-phase mode was lower than that of the two-phase mode, while their relative standard deviation values were similar (11% and 13%, for two and three phases, respectively).

A homemade hollow fiber-protected headspace liquid phase microextraction was used for simultaneous derivatization and extraction of free cyanide in human urea and saliva [26]. The acceptor phase contained Ni(II)-NH_3 (as derivatization agent), sodium carbonate and ammonium pyromellitate (as internal standard), which was held within a hollow fiber membrane, affixed to a syringe needle and immersed in the headspace of sample container. The cyanide formed a stable $Ni(CN)_4^{2-}$ complex that was determined by capillary electrophoresis (CE). Under the optimized condition, an LOD of 0.01 μg/mL was obtained, which was high enough for determination of cyanide in biological matrices.

Determination of gabapentin, an anticonvulsant drug, in human urine and plasma was performed using three-phase HFLPME and high-performance liquid chromatography (HPLC)-UV [27]. Before determination, the gabapentin was derivatized in order to increase its absorption characteristics. Dihexyl ether, 2.0 mol/L HCl and borate buffer with pH 9.1 were organic solvent, acceptor and donor phases, respectively. Under the optimized conditions, preconcentration factor 95 and detection limit 0.2 μg/L were obtained.

HFLPME in combination with HPLC was used for determination of three aconitum alkaloids (aconitine, hypaconitine and mesaconitine) in urea [17]. The analytes were extracted from the aqueous donor phase with pH 11.0 into the 1-octanol as organic solvent and then into the acidified aqueous solution with pH 3.0. The stirring speed was 800 rpm and temperature was set at 40°C. The optimum volume of acceptor phase was 9 μL. Enrichment factors of 98–228-fold within the 60 minutes of extraction were achieved.

Three-phase HFLPME in combination with HPLC using diode array and fluorescence detector was applied for the determination of eight widely used fluoroquinolones including: marbofloxacin, norfloxacin, ciprofloxacin, danofloxacin, enrofloxacin, gatifloxacin, grepafloxacin and flumequine in environmental water and urine [22]. Central composite design, a chemometrics method, was used in order to optimize the extraction parameters (pH of donor and acceptor phases and stirring time). At the optimized condition, 1-octanol was used as organic solvent between a 2 mol/L Na_2SO_4 aqueous solution (pH 7) as donor phase and aqueous solution (pH 12) as acceptor phase.

Determination of amphetamine-type stimulants (amphetamine, methamphetamine, fenproporex, 3,4-methylenedioxymethamphetamine and 3,4-methylenedioxyamphetamine) in human hair samples was performed using three-phase LPME and gas chromatography/mass spectrometry (GC/MS) [28]. The hair samples were decontaminated with dichloromethane followed by alkaline hydrolysis. Dihexyl ether was used as organic solvent. Since the analyzed amphetamines had pKa values ranging from 9.41 to 9.90 and the conditions used to digest hair samples (NaOH 1 mol/L) made the donor phase in alkaline mode, the pH of the donor phase was not changed for HFLPME. The acceptor phase was 0.1 mol/L HCl. The optimum extraction time was 45 minutes at the stirring rate of 1000 rpm. The addition of salt to the sample solution did not cause a marked improvement in the efficiency of extraction. However, the precision improved by addition of 10 mg salt. The amphetamine was preconcentrated effectively and detection limits (0.01–0.05 ng/mg) were below the cut-off value stabilized by the society of hair testing.

Yamini et al [13] developed an HFLPME method based on the supramolecular solvents constructed of vesicles of decanoic acid for extraction of halogenated amines from water samples. The appropriate properties of supramolecular solvent including the capability of solubilizing solutes with a wide polarity range and the ability to achieve high preconcentration factors, mainly arising from the mixed-mode mechanisms and multiple binding sites that they can provide, make these solvents good alternatives to conventional organic solvents. The parameters influencing the extraction efficiency were optimized using two different optimization methods: one variable at a time and the Box–Behnken design. Calibration curves were linear in the range of 1.0–100 μg/L. LOD was in the range of 0.05–1.0 μg/L.

The other applications of HFLPME in different matrices are reported in Table 1.

3. DLLME

DLLME was introduced by Assadi and co-workers in 2006 as a new LLE technique for determination of polyaromatic hydrocarbons [50]. This technique generally is based on a ternary component solvent system including extraction solvent, disperser solvent and an aqueous sample. In DLLME, when an appropriate mixture of extraction and dispersive solvents is injected into an aqueous sample containing the analytes of interest, a cloudy solution is formed. When the cloudy solution is centrifuged, the extraction solvent is normally sedimented at the bottom of the tube (if the density is above that of water) and removed with a microsyringe for later

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Table 1 – Application of HFLPME in different matrices.

Analyte	Sample matrix	Type of HFLPME	Organic solvent	Acceptor phase	LOD[a]	Linear range	Refs
Pb, Ni	Water	Two phase	[C6MIM][PF6]	[C6MIM][PF6]	0.02,0.03	0.04–2.0	[29]
Se	Vegetable, fruit	Two phase	Toluene	Toluene containing N-octyl acetamide	0.08	0.2–5	[30]
Se(IV)	Urine, plasma, natural water	Two phase	1-Octanol	1-Octanol	0.02–0.1	0.05–100	[31]
Organomercury	Biological	Three phase	Bromobenzene	L-Cysteine	0.03–0.14	0.1–25.0	[32]
Methylmercury	Human hair	Two and Three phase	Toluene	4% thiourea in 1 mol/L HCl	0.1–0.4	1–40	[25]
Hg	Water	Three phase	Toluene	0.05 mol/L ammonium iodide	0.06	0.2–3.0	[33]
Anti-inflammatory drugs	Urine	Two phase	1-Octanol	1-Octanol	0.03–0.07	0.08–400	[34]
Bisphenol A	Water	Three phase	n-Octanol	NaOH	0.2	0.5–200	[8]
Hg	Fish, rice	Three phase	Propylbenzoate	H_2SO_4	0.012	0.2–30	[35]
Inorganic Sb	Water	Two phase	1-Octanol	1-Octanol	1.1	5–50	[36]
Fungicides	Orange juice	Three phase	2-Octanone	HCl	0.1	0.1–0.10	[37]
Pentazocine	Urine, plasma	Three phase	n-Octanol	Acetic acid	2.0	10–500	[38]
Sulfonamides	Honey	Static	1-Octanol:1-pentanol(55/45)	Carbonate buffer	5.1–27.4	16–500	[39]
Tricyclic antidepressant drugs	Water	Three phase	n-Dodecane	Methanol	0.08–0.2	0.2–1000	[40]
Pesticides	Cucumber	Two phase	Chloroform	Chloroform	0.01–0.31	0.05–500	[41]
Organophosphorus pesticides	Baby food	Two phase	1-Octanol	1-Octanol	0.01–04	0.04–10	[42]
Phenothiazine	Urine	Two phase	Toluene	Toluene	1.4–203.4	10–7000	[23]
Mitiglinide	Urine, plasma	Three phase	1-Octanol	NaOH	1.38	5–1000	[43]
Fluoxetine, norfluoxetine	Plasma	Three phase	*n*-Hexyl ether	HCl	5	5–500	[44]
Tramadol	Urine, plasma	Three phase	n-Dodecane	Acetonitrile	0.08	0.1–400	[21]
Organophosphorus pesticides	Fish	Two phase	o-Xylene	o-Xylene	2.1–4.5	20–500	[45]
Dinitrophenols	Plasma	Three phase	Dihexyl ether	Sodium hydrogen carbonate	0.05–0.1 ppm	0.06–0.6 ppm	[46]
Pb	Soft drink	Two phase	Toluene	Toluene	0.007	0.024–1.0	[47]
Polycyclic aromatic hydrocarbons	Organic aerosol	Two phase	n-Undecane	n-Undecane	0.1–15 ppt	16.6–1333 ppt	[48]
Pesticides	Industrial and fresh orange juice	Two phase	Toluene and ethyl acetate (85:15, v/v)	Methanol and acetone (50:50,v/v)	0.003–0.35 ppm	0.01–10 ppm	[49]

[a] LOD and LDR units are ppb except those specified. HFLPME = hollow fiber liquid phase microextraction. LOD = limit of detection.

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instrumental analysis. The advantages of DLLME are simplicity of operation, rapidity, low cost, high recovery, high enrichment factor and short extraction time [50]. Since the initial introduction of DLLME, several modifications have been applied to this technique including: use of solvents with a density lower than that of water [51–54]; extraction without the need for centrifugation [55]; use of ionic liquids as extraction solvent [56–59]; and recent application of supramolecular solvent as extraction solvent [60]. The extraction efficiency of DLLME is influenced by several factors (e.g., types and volumes of extraction and disperser solvents, extraction time, sample amount, pH, and salt addition). Different steps in DLLME are shown in Figure 2.

3.1. *Effect of type and volume of extraction solvent*

The extraction solvent has a great effect on the extraction efficiency. The extraction solvent should be miscible with disperser solvent and has low solubility in water. The ability for extraction of the compounds of interest and low solubility in water are the other important factors in selection of an appropriate extraction solvent [50]. Since the extraction solvent in DLLME is centrifuged and sedimented as a separate phase at the end of the extraction process, the extraction solvent should have a distinct density from water. In many studies of DLLME, the solvents used had higher density than water. Solvents such as chlorobenzene, carbon tetrachloride, tetrachlorethylene and carbon disulfide are frequently used extraction solvents in DLLME [61]. However, because of the toxic nature of these solvents they are generally hazardous to laboratory personnel and the environment. Therefore, the new developments in DLLME have focused on the use of solvents with less toxicity and solvents with densities lower than water [62]. Kocúrová et al published a useful review about the use of solvents lighter than water as extraction solvent in DLLME [63].

The enrichment factor (EF) in DLLME is influenced by the volume of extraction solvent. Indeed, with the increase in extraction solvent volume, the final organic phase obtained by centrifugation is increased, resulting in a decrease in the concentration of the target analyte in the organic phase, and therefore, EF will decrease. Thus, the optimal extracting solvent volume should ensure both high EF and enough volume of the sedimented phase for the subsequent analysis after centrifugation.

3.2. *Effect of the type and volume of disperser solvent*

The dispersive solvent plays a key role in DLLME since it helps extraction solvent to form fine droplets in aqueous samples. Disperser solvent should be soluble in extraction solvent and be miscible in water, thus enabling the extraction solvent to be dispersed as fine particles in aqueous phase to form a cloudy solution. Acetone [64], methanol [65] and acetonitrile [66] can be used as disperser solvents. After the formation of cloudy solution, the surface area between the extracting solvent and the aqueous sample becomes large, so the equilibrium state is achieved quickly and, therefore, the extraction time is short. Indeed, the short extraction time is the main advantage of DLLME. The degree of the dispersion of the extraction solvent in aqueous phase and subsequently, the extraction efficiency, is directly affected by the volume of disperser solvent. Variation in disperser solvent volume changes the volume of the sedimented phase. Usually, 0.5–1.5 mL of disperser solvent is used. The suitable volume of disperser solvent for cloudy solutions depends on the volume of both aqueous phase and extracting solvent. In DLLME, the important factors affecting the volume of sedimented phase are: (1) solubility of extracting solvent in water; (2) sample solution volume; (3) disperser solvent volume; and (4) extracting solvent volume [67]. Low volumes of disperser solvent do not disperse the extraction solvent properly, and therefore, cloudy solution cannot be formed completely. Conversely, at high volumes, the solubility of analytes in water increases by increasing the volume of disperser solvent, thus, the extraction process is incomplete [68]. As mentioned before, the disperser solvent should be soluble in the extraction solvent and miscible in water, thus enabling the formation of fine droplets of the extraction

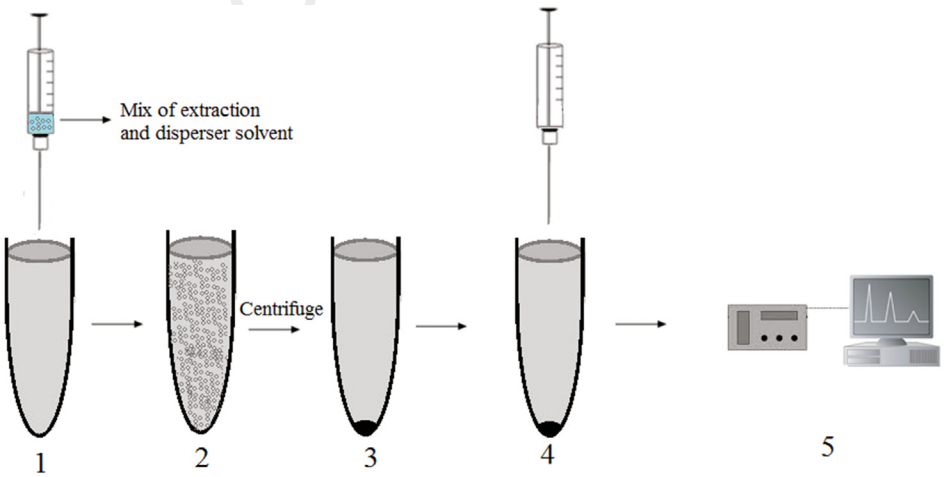

Figure 2 – Different steps of dispersive liquid–liquid phase microextraction: (1) rapid injection of a mixture of disperser and extraction solvent into the aqueous solution; (2) formation of a cloudy solution; (3) sedimentation of the extraction solvent after centrifugation; (4) removal of sedimented phase; and (5) instrumental analysis.

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solvent in the aqueous phase. Indeed, the degree of dispersion of the extraction solvent in the aqueous phase and the final volume of sedimented extraction solvent, and subsequently, the extraction efficiency is directly affected by the type and volume of disperser solvent. Variation in disperser solvent changes the volume of the sedimented phase. Solvents such as acetone, methanol and acetonitrile with volumes of 0.5–1.5 mL are usually used as dispersive solvents.

3.3. *Effect of extraction time*

In DLLME, the extraction time is defined as the time between injecting the mixture of extraction and centrifugation [69]. After the formation of a cloudy solution, the surface area between the extracting solvent and the aqueous sample becomes large, so the equilibrium state is achieved quickly and, therefore, the extraction time is short [67]. The results obtained from many investigations showed that the extraction is accomplished in a short time after the formation of a cloudy solution and the equilibrium state is achieved quickly [70–72].

3.4. *Applications of DLLME*

An ultrasound-assisted DLLME combined with UPLC-diode array detector method was used for the determination of seven benzodiazepines (alprazolam, bromazepam, clonazepam, diazepam, lorazepam, lormetazepam and tetrazepam) in human plasma samples [73]. The influences of extraction parameters were optimized using an asymmetric screening design, and 2 mL methanol, 250 μL of chloroform, 2 minutes ultrasonic shaking and pH 9 were selected as optimal conditions. The optimized method exhibited a good precision level, with relative standard deviation values < 8%.

DLLME and CE with UV detection were used for the chiral separation and determination of the multiple illicit drugs (heroin, DL-methamphetamine, DL-3, 4 methylenedioxymethamphetamine and DL-ketamine) in banknotes, kraft paper, plastic bags and silver paper [74]. Chloroform and isopropyl alcohol were selected as extractant and disperser solvents, respectively. The organic phase, which contained the target analytes was centrifuged, evaporated to dryness, reconstituted in lidocaine hydrochloride aqueous solution (internal standard) and introduced by electrokinetic injection into CE.

Combination of electromembrane extraction and DLLME followed by GC/flame ionization detection was developed for determination of tricyclic antidepressants (TCAs) in untreated human plasma and urine samples [75]. Response surface methodology was used for optimization of experimental extraction parameters. The results indicated a matrix effect for urine and plasma samples in comparison with neat solutions, so the match matrix method was used for drawing working calibration curves, and no carry-over appeared at the retention time of the investigated TCAs (S/N < 3).

Halogenated organic compounds in water samples were determined using GC/electron-capture detection orGC/MS after DLLME extraction [62]. Acetone and 2-dodecanol were used as disperser and extractant solvents, respectively. After centrifugation for 5 minutes at 6000 rpm, the glass tube was transferred into a beaker containing crushed ice; the organic solvent was solidified in 5 minutes. The solidified solvent was melted quickly at room temperature and was injected into the gas chromatograph for analysis.

The (DLLME-SFO) technique was used for the determination of duloxetine in human plasma samples by HPLC with fluorescence detection [76]. 1-Undecanol was used as an extractant. After precipitation of the protein, using a mixture of zinc sulfate solution and acetonitrile, duloxetine in an alkaline sample solution was quickly extracted into 50 μL 1-undecanol (extractant solvent). The disperser solvent was not used because the small amount of remaining acetonitrile, which acted as a protein-precipitating reagent, was also used as a disperser, therefore, organic solvent consumption was reduced as much as possible. The emulsion was centrifuged and fine droplets were floated on top of the sample solution. The floated droplets were solidified in an ice bath and easily transferred. At the optimized condition, a preconcentration factor of 98 was obtained.

The combination of DLLME with CE and time-of-flight mass spectrometry was evaluated for screening 30 toxicological compounds (amphetamines and their derivatives, opiates, cocaine and its metabolites and pharmaceuticals) in urine samples [77]. A Plackett– Burmann design was used to investigate the effects of seven factors on the extraction efficiency. The experimental factors were: the volume of 1M NaOH used for pH adjustment, volume of the solvent mixture, ratio between the dispersing and extraction solvent volumes, presence of agitation, extraction time, centrifugation speed, and centrifugation time. Dichloromethane and isopropanol were selected as the extraction and dispersing solvents, respectively. Results of the experimental design revealed that the solvent mixture volume and extraction time had a strong effect on the preconcentration factor with positive and negative effects, respectively. The other examined factors had a positive effect on the extraction of some compounds and negative effect on the preconcentration factor of the other compounds.

DLLME followed by HPLC-UV were used for determination of opium alkaloids (morphine, codeine, papaverine and noscapine) in human plasma [78]. 1-Undecanol and acetone were used as extractant and disperser solvents, respectively. The optimized condition for extraction were: pH 9, addition of 1% (w/v) NaCl and extraction time of 30 seconds.

DLLME combined with HPLC-UV was used for the determination of three psychotropic drugs (amitriptyline, clomipramine and thioridazine) in urine samples [79]. The determination was performed on a C_8 column. The extraction parameters were optimized and finally 20 μL CCl_4 as extraction solvent, 0.5 mL of acetonitrile as disperser, pH 10, and extraction time of 3 minutes were considered as optimum extraction conditions. The method was successfully applied to real urine samples.

Ionic liquid-dispersive LLME combined with micro-solid phase extraction and HPLC were developed for determination of TCAs in water samples [80]. Twenty microliters of 1-hexyl-3-methylimidazolium tris(pentafluoroethyl)trifluorophosphate and 200 μL methanol were used as extractant and dispersive solvents, respectively. After this, a micro-solid phase extraction device, containing a novel material zeolite imidazolate framework 4, was added to the sample solution and 1 minute of

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Table 2 – Different applications of DLLME in different matrices.

Analyte	Sample matrix	Extraction solvent	Disperser solvent	LOD[a]	LDR	Refs
Pesticides	Banana	[C6MIM][PF6]	Methanol	1.8134.1	0.01–6.83	[65]
Neonicotinoid insecticides	Grains	$CHCl_3$:CH_2Cl_2 (1:1, v/v)	Acetonitrile	0.002–0.005 ppm	0.02–4.5 ppm	[81]
Triazophos and carbaryl pesticides	Water and fruit juice	Tetrachloroethane	Acetonitrile	0.0012–0.016	0.1–1000	[82]
Organophosphorus pesticides	Soil and marine sediment	CCl4	Acetonitrile	0.001–0.009 ppm	0.02–8.3 ppm	[83]
Bisphenol A, 4-n-nonylphenol, 4-tert-Octylphenol	Water	[C8MIM][PF6]	—	0.23–0.48	1–300	[84]
chloramphenicol and thiamphenicol	Honey	1,1,2,2-tetrachloroethane	Acetonitrile	0.1, 0.6	3–2000	[85]
Trace fungicides	Environmental water	Toluene	Methanol	0.026–0.071	0.1–200	[86]
N-Methylcarbamate insecticides	Water	$CHCl_3$	Acetonitrile	0.1–0.5	0.001–10 ppm	[87]
Acetanilide herbicides	Water, green tea	Chlorobenzene	Acetone	0.01–0.03	0.1–50.0	[88]
Pesticide residues	Greenhouse tomato	CCl_4	Acetonitrile	0.0027–0.25 ppm	0.01–6.0 ppm	[89]
Organophosphorus pesticides residues	Tomato	Chlorobenzene	Acetone	0.1–0.5	0.5–1000	[90]
Neonicotinoid insecticides	Cucumber	$CHCl_3$	Acetonitrile	0.8–1.2	2.7–200	[91]
Organochlorine pesticides	Honey	Chloroform	Acetonitrile	0.02–0.15	0.1–20	[92]
Aluminum	Water	1-Undecanol	Acetone	0.8	1.0–250.0	[93]
Multiclass pesticides	Water	Trichloroethane	Acetonitrile	0.1–50.0 ppt	0.08–40.0	[94]
Organophosphorus pesticides	Water	Chlorobenzene	Acetone	0.2–1.5 ppt	1–10,000 ppt	[95]
Carbamate pesticides	Water	Toluene	Acetonitrile	0.001–0.050	0.005–20	[96]
Benzimidazole fungicides	Agricultural products		Acetonitrile	0.1–0.5	0.1–500	[97]
Polycyclic aromatic hydrocarbons	Environmental water	n-Hexane	Acetone	3.7–39.1 ppt	0.05–50	[98]
N-Methylcarbamates		Toluene	Acetonitrile	1–144 ppt	4.7–10,000 ppt	[99]
Organochlorine pesticides	Aqueous samples	Dodecyl acetate	Water containing 1 mg/L Tween 80	0.5–5.0 ppt	1–10,000 ppt	[100]
Rhodium	Water, rose flower leaves	2-(5-bromo-2-pyridylazo)-5-diethylamino phenol	—	0.37	4.0–500.0	[101]
Polycyclic aromatic hydrocarbons	Water	Propionic acid	1-Bromo-3-methylbutane	0.0003–0.0078	0.01–10.0	[102]
Pb	Environmental water	Carbon tetrachloride	Ethanol	0.95 ppt	0.01–100	[103]
Macrolide antibiotics	Urine	1-Dodecanol	Methanol	10–40	0.025–4.0 ppm	[104]
Psychotropic drugs	Urine	CCl_4	Acetonitrile	68.0–165.0	0.02–6.0 ppm	[79]
Salmeterol	Dried blood spot	Methanol	1-Butyl methylimidazolium	0.3–1.0	1.0–5.0	[105]
Palladium	Water	CCl_4	Ethanol	2.4 ppt	0.1–5	[106]
Hg, CH_3Hg	Environmental water	Methyltrioctylammonium thiosalicylate	—	0.03–0.4	0.5–100	[107]
As, Sb	Water	CCl_4	Methanol	0.01–0.05	0.05–5.0	[47]
7-Aminoflunitrazepam	Urine	Dichloromethane	Isopropyl alcohol	0.025	0.05–2.5	[108]
Pyrethroid insecticides	Fruit juice	Chloroform	Methanol	2.0–5.0	2.0–1500.0	[109]

[a] LOD and LDR units are in ppb except those specified. LOD = limit of detection.

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vortex-assisted extraction was performed. After 5 minutes of sonication-assisted desorption, 10 μL desorption solvent was injected into an HPLC system for analysis. The calibration curves were linear in the range of 1–1000 μg/L.

Shemirani and Jafarvand used reversed micelles of decanoic acid dispersed in tetrahydrofuran–water as supramolecular solvent to extract malachite green in textile industry wastewater [60]. By application of this method, disadvantages of DLLME such as extraction capability of only hydrophobic analytes and using toxic and hazardous organic solvents as the extraction solvent, and disadvantages of coacervation-based extraction method such as tedious, labor-intensive and time-consuming stirring procedures have been avoided. In this technique THF plays a double role, and not only acts as disperser solvent but also causes self-assembly of decanoic acid. Under the optimized condition, a linear range of 18–256 μg/L and LOD of 4 μg/L were obtained.

The other applications of DLLME in different matrices are listed in Table 2.

4. Conclusions

Because of the useful benefits of HFLPME and DLLME, their application in the extraction and preconcentration of various types of analytes in different matrices is growing. The major advantages of HFLPME and DLLME are consumption of low volumes of organic solvents and short extraction times. Although these techniques use a small amount of organic solvents, new efforts and developments are based on the use of solvents with low toxicity such as ionic liquids and supramolecular solvents. The use of these solvents results in reduction of the whole analysis time.

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