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REVIEW ARTICLE

Liquid Phase Microextraction for Analysis of Mycotoxins in Food Samples: REVIEW

Ali. M.A. Alsharif[1,2*], Tan.Guan Huat[1], Choo Yeun Mun[1], Abubakar Lawal[1,3]
[1]Department of chemistry, faculty of science, university of Malaya, Malaysia
[2]Arab Centre for desertification and development of saharian societies, Murzuk, Libya
[3]Department of Pure and Industrial Chemistry, Umaru Musa Yar'adua University Katsina, Nigeria
Email: alshariiiif@yahoo.com, alshariiiif.mohamed9@gmail.com.
***Corresponding author:**Ali. M.A. Alsharif

ABSTRACT
Mycotoxins are secondary metabolite compounds that grow on foodstuffs or animal feeds and are capable of causing disease and death in humans and other animals. In this review, the authors discuss about the new innovative sample pretreatment methods for the extraction and clean-up of mycotoxins and different analytes in the food samples. Extensive efforts to miniaturize liquid-liquid extraction were carried out. These efforts resulted in the innovation of solvent microextraction methods that is considered as the green extraction methods. The principle of liquid phase microextraction method (LPME) is based on the reduction of the volume ratio of the solvent to aqueous phase. LPME techniques has been effectively used for the extraction of target analytes from various sample solutions. It is comprised of a number of techniques that can be divided into three main categories: single-drop microextraction (SDME), hollow fiber liquid phase microextraction (HF-LPME), and dispersive liquid-liquid microextraction (DLLME). The LPME has diverse application approach ranging from SDME to HF-LPME. However, DLLME is an exception, because of a range of application for different mycotoxin producing species. Compared to the other techniques, DLLME is characterized by the simplicity of its operation, rapidity, low cost, good recovery, and high enrichment factor, which makes it as to be one of the most widely used LPME techniques for the analysis of mycotoxins.
Keywords: *Mycotoxins, green chemistry, liquid phase microextraction, single drop microextraction, dispersive liquid-liquid microextraction, hollow fiber liquid phase microextraction*

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INTRODUCTION

Mycotoxins are naturally occurring secondary metabolite compounds produced by the fungi, and commonly found in the food and feed. A secondary toxic compound is used to differentiate them from the primary metabolite compounds that are essential for all living organisms [1]. Mycotoxins are produced by various fungal species belonging to the genus Aspergillus, Penicillium, and Fusarium. Nowadays, hundreds of mycotoxins have already been identified. Based on their occurrence and toxicity the most significant ones are: aflatoxins (AFs), fumonisins (FMs), trichothecenes (TRCs), ochratoxins (OTs), patulin (PAT), and zearalenone (ZEN), and their metabolites. There are many other toxicologically important mycotoxins that have been least studied, such as ergot alkaloids, enniatins (ENs), alternaria toxins, moniliformin (MON), citrinin (CTN), beauvericin (BEA), cyclopiazonic acid, roquefortine C, mycophenolic acid, penitrems, verruculogen, griseofulvin, citreoviridin, etc [2].

Mycotoxins are known to contaminate food, feed or their source raw materials. The exposure to mycotoxins also leads to diseases in the case of humans and livestock. The existence of mycotoxins in food and feed is considered to be a high risk for the human and animal health, due to its diverse toxic effects and extreme heat resistance nature. In order to ensure food quality and health of the consumers, maximum levels of mycotoxin content in various food items and feed have been set by the European legislation [3].

The current mycotoxin analytical techniques include fast screening methods and confirmatory quantification for certain mycotoxins that are available in various food items. This also aims at strategy planning for the development of these methods as well as discovering new methods for the analysis and quantification of the other mycotoxins. In general, the mycotoxins analysis process from any samples involves several detection stages by using the instruments. These several stages are summarized in

sampling, sample preparation, mycotoxin extraction and clean-up, and qualitative and/or quantitative analysis of the mycotoxins [4, 5].

For obtaining the representative samples containing the target mycotoxins, the sampling step that involves sampling plans play a critical role in mycotoxin analysis due to its high heterogeneity [6]. The mycotoxin-sampling plan measures the mycotoxins concentration within a small portion of the bulk lot, which makes it difficult for the precise and accurate determination of the total available mycotoxin concentration within a bulk lot. A mycotoxin-sampling plan is a complicated process defined by a mycotoxin test procedure with a defined accept/reject limit. This consists of several steps such as (1) Firstly, a sample of a given size is taken from the bulk lot, (2) the sample is then comminuted in a mill for reducing its particle size, (3) a subsample is removed for carrying out the extraction process, and (4) the mycotoxin is extracted and subsequent quantification is done. By using the verified mycotoxin test procedures, there exists an uncertainty associated with each step. Because of this variability, the determination of the true mycotoxin concentration in the bulk lot with 100% certainty remains unattainable. The variability is measured by the variance statistic method, and is found to be proportional to the mycotoxin concentration. Such large variability in sampling method is due the presence of a small percentage of contaminated kernels [7].

The basic principles of sample preparation involves separation and enrichment of target analytes from a sample with the complex composition under suitable conditions for the determination of mycotoxins, by using the analytical methods [8, 9]. Although, in the recent years, new analytical instruments have been developed; however, these technologies still fail to directly process the complex samples [10-12]. A sample needs pretreatment before being injected into an analytical equipment to gain reliable results. The objective of sample preparation is to modify the analyte into a form that is consistent with the determination by isolating the target analyte from the matrix and increasing its concentration. A sample may contain high quantities of carbohydrates, proteins, and lipids, and the concentration of the analyte can be kept extremely low. These substances that are normally associated with extraction of the target analyte are called co-extractives. The co-extractives that share similar properties with the target analyte can cause substantial interference in the analysis, for example 5-hydroxymethylfurfural (HMF) in determination of PAT [13].

In general, the extraction methods for any compounds vary depending on the goal of the requested operation. At times, extraction works by digesting the organic material by the action of a strong oxidizing reagent, which can be stimulated by heat, or burn (ash) the organic material at high temperatures to separate an inorganic compound [14]. But with the use of organic solvents, the chemical composition of a sample remains unaltered, and the analyte is separated from the matrix. The theory of solvent extraction methods depends on the use of a water-immiscible solvent to separate an analyte from an aqueous solution based on the solubility of the analyte in the solvent as compared to the water. Ideally, the selectivity of solvent extraction for the target analyte depends on the polarity of the analyte and the solvent used [15, 16]. Most of the extraction methods are presented with both advantages and disadvantages. Certain methods are time-consuming, whereas others require a large quantity of solvents or are incompatible with the instrument. Hence, development of new techniques is necessary to overcome these problems associated with the classical methods [17].

This review presents some of the applications of chromatographic instruments for analysis of mycotoxins in various food samples and greener sample preparation methods. This review broadly describes their basic principle, classification, advantages and disadvantages. It also lays focus on the efficiency of LPME techniques through a comparative analysis of various LPME techniques (SDME, HF-LPME, and DLLME) and a comparison with other methods such as liquid–liquid extraction (LLE), solid-phase extraction (SPE), and solid-phase microextraction (SPME).

Going green for sample treatment methods

Most of the sample preparation methods depend on the selected organic solvent. The solid-phase microextraction (SPME) is excluded from this group because of its solvent-free approach. The SPME method presents a disadvantage of high running cost, which limits its widespread application [18]. The selection of organic solvent is a critical step in achieving efficient extraction. This depends on several factors such as good affinity for the target analyte, immiscibility in water, low volatility, stability during the extraction, and compatibility with chromatography instruments [19]. An ideal sample preparation method is easy to use, inexpensive, and fast; in addition, it needs only a small volume of organic solvent or is solvent-less to decrease the risk of toxicity and hazardous wastes, as well as low-cost, and compatible with most analytical instruments [11, 12]. To reduce the drawbacks of such methods and their impact on the environment, developments have emerged in two separate directions. The first direction is the employment of miniaturization as a developed sample preparation method. This route has resulted in the development of two common methods, i.e., SPME and LPME [11, 20, 21]. SPME technique is based on

analyte partitioning between the extracting phase immobilized on a fused-silica fiber and the matrix. After equilibrium is reached at a well-defined time, the absorbed compounds are thermally desorbed [22]. The desorption occurs by exposing the fiber into the injection port of a gas chromatograph or redissolved in an organic solvent, respectively, when coupled to HPLC or when combined with CE [10]. The second direction is to find more environmental-friendly solvents for extraction (green chemistry). First example of such greener methods is supercritical water extraction (SWE), which involves changing the properties of water by increasing its temperature up to 650 K under enough high-pressure; as a result, the polarity of water is reduced. However, the extraction yields of this method are little with subsequent solvent evaporation and incompatibility with thermally unstable compounds [18].

The second example is the use of ionic liquids (ILs), which are more environmental friendly because of their low volatile nature, as well as their low toxicity as compared to the organic solvents [23]. ILs represented a novel class of solvents that are widely used in the field of chemistry. The difference between the ILs and classical solvents include: 1) ILs has a negligible vapor pressure; 2) ILs are not degradable by high temperature, tunable viscosity, and miscibility with water and organic solvent; 3) ILs have good extractability for various organic compounds and metal ions. It includes a group of non-molecular solvents that are liquid at (or near) room temperature. Because of the poor ion coordination, these solvents are called room-temperature ionic liquid (RTIL) [23]. The negligible volatilities over the midrange temperatures, low flammability, and high stability are all the green properties of IL and support its use [24, 25]. Several other properties extend the use of RTILs in different fields of research, including the extraction methods. These properties are: (1) high electrical conductivity, (2) enlarged electrochemical window, (3) miscibility with a wide range of organic solvents, (4) good extractability for many different, organic or inorganic, and organometallic compounds, and (5) high viscosity [24, 25].

The third example is the use of non-ionic surfactants in cloud-point extraction (CPE). CPE is a clean technology that accounts for 4% to 12% surfactant volumes of the liquid sample. CPE with surfactants as solvents is employed in isolation of organic pollutants, such as chlorophenols, heavy metals, and polychlorinated biphenyls (PCBs) [26]. This technique has been used in extraction of several compounds such as polycyclic aromatic hydrocarbons [27], polychlorinated compounds [28], chlorophenols [29], hydroxyaromatic compounds [30], and vitamins (vitamins A and E) [31].

The last example is the use surfactants in coacervative extraction (CAE), which is a valuable strategy for replacement of organic solvent in an analytical extraction process [23, 32]. The coacervates are liquids that are immiscible with water, and are made of surfactant aggregates, such as reverse and aqueous micelles, and vesicles. Coacervation can be divided into simple and complex type. The coacervation is induced by a dehydrating agent, namely temperature, pH, electrolyte or a non-solvent for the macromolecule. The unique structures of coacervates comprises of vesicles and reversed micelles of alkyl carboxylic acids, and possess high solvation properties for a variety of organic compounds that enable separation of compounds with different degrees of polarity [33, 34]. The advantages of CAE includes low toxicity, low volatility, and, in certain cases, biodegradability [35]. In 2005, the coacervates were used for the first time as a solvent in LPME approaches. L´opez-Jim´enez et al. [34], used vesicular coacervates as a solvent in single-drop microextraction combined with HPLC as a method for analysis the chlorophenols in different water samples (wastewater, superficial water from the reservoir and groundwater), and the detection limits ranged from 0.1–0.3 g L−1 and the recoveries were in the range of 79 and 106% at 5–20 g L−1 spiked level.

Chromatographic systems for mycotoxins analysis

The different chromatographic methods with difference in the sensitivity and accuracy have been developed and used for different purposes in the mycotoxin analysis that includes high-performance liquid chromatography (HPLC) with UV or fluorescence detection (FD), thin-layer chromatography (TLC), gas chromatography (GC) based on flame ionization detector (FID) and electron capture detector (ECD). The qualitative and quantitative determination of mycotoxins have been more accessible by using liquid chromatography-mass spectrometry (LC-MS or LC-MS/MS) and gas chromatography-mass spectrometry (GC-MS or GC-MS/MS) techniques [36].

The TLC is a technique used for the separation, purity assessment, and identification of the organic compounds. There are two techniques of TLC. The first one is called one-dimensional, in which one side of the plate is vertically placed in a solvent tank. The capillary action active on the solvent moves up the plate to reach the other edge. After the removal of the plate from the solvent, the separated spots are visualized by UV, fluorescence, MS, or other techniques [37]. Pittet and Royer [38], have used a one-dimensional technique for the determination of Ochratoxin A in green coffee. The second technique is called 2-dimensional, in which the plate is dried after the first-development and rotated 90°, and developed in another solvent. In most of the studies, TLC has been considered as a commonly used separation method of mycotoxins from the samples by use of several solvents. It has also been considered

as an AOAC method, and the method of choice to quality and quantify aflatoxins at low levels of concentrate [39].

The HPTLC is a developed and improved version of TLC techniques and has been successfully applied to aflatoxins analysis. This development has improved the separation within a shorter time by a reduction in the layer thickness and particle size of the stationary phase [40]. Toteja et al. [41] have used HPTLC to determine aflatoxin B1 after extraction from the rice samples with water/chloroform and silica gel column cleanup.

The over pressured-layer chromatography (OPLC) is a forced-flow technique, using an external pressure on the chromatoplate sealed on the edges, and a pump system for passing the mobile phase into the stationary phase. The advantages of the OPLC method includes the requirement of less mobile phase, use of the off-line method and allowing faster examination with the possibility of parallel analysis. The OPLC methods were developed for the measurement of aflatoxin (B1, B2, G1, and G2) contamination in various foodstuffs such as maize, wheat, peanut, fish meat, rice, sun-flower seeds, and red paprika [42].

The GC analysis is a technique used to partition the analytes between the liquid stationary and gas mobile phase. The scientific researchers have widely used GC for the qualitative and quantitative analysis of mycotoxins in food samples because of the suitability of use of GC for the analysis of thermostable, non-polar, semi-polar, volatile, and semi-volatile compounds [5]. Derivatization has been used to increase the volatility of the mycotoxins, and improve their responses to GC detection system [5, 43]. Due to the Trichothecenes, mycotoxins are not strongly absorbed in the UV range, due to their non-fluorescence, and show diverse polarity [44, 45], and derivatization process has also been used for their analysis [46]. The GC-MS method was considered as the routine approach for the determination of many mycotoxins (Ochratoxin A, trichothecenes, patulin, citrinin, and Zearalenone) [47, 48] although this approaches (GC and GC-MS) have some drawbacks that are summarized as follows: (a) requirement to carry out the derivatization of analytes prior to the analysis of the samples; (b) The majority of mycotoxins are smaller in size, nonvolatile and polar molecules that requires breaking of the hydrogen bridges for its acquiescence to the GC–MS analysis; (c)for mycotoxins detection with the GC–ECD, brominating or fluoroacylating agents are used for taking advantage of the specificity of the detector [49, 50]. Also, problems such as double peaks of analytes can appear as a result of the incomplete derivatization [44].

The GC-MS or GC-MS/MS have been applied to determine the different kinds of mycotoxin in various food samples, for example trichothecenes in wheat grain [51] and bee pollen [52], trichothecenes groups A and B in grains [53], in harvested corn [54], simultaneous determination of trichothecenes and Zearalenone in cereals [48], and Type-B trichothecenes in wheat [46]. For more polarmycotoxins such as PAT and citrinin, only a few GC methods are published, which mostly employ derivatization or direct analysis based on MS. For example, detection of PAT and 5-hydroxymethylfurfural (HMF) in apple juice [55] and citrinin in Monascus by GC-MS [56], and PAT in apple and quince products by GC-MS[57].

The HPLC is widely used as a qualitative and quantitative method for mycotoxin analysis in food [58]. The difference between the GC and HPLC methods is well stated. The HPLC technique separates a mixture of compounds by relative affinity of the compounds for a stationary (column) and a mobile phase (one solvent or mixture). Depending on the physical and chemical features of the target analytes, the compounds are eluted from the column pass through a detector that helps to determine the specific compounds in the original sample, which was injected onto the column. Derivatization (pre-column or post-column derivatization) is sometimes needed to improve the sensitivity of mycotoxin detection. For example, on-line electrochemical bromination using a “Kobra” cell is a powerful procedure to enhance fluorescence before passing through the detector in the analysis of aflatoxins [59, 60].

During the purification step for the extract, sometimes there is the formation of certain substances that have similar retention times to the target analytes, thereby leading to false positives or misidentification. An example of such interference is HMF during a determination of PAT in apple juice. However, HPLC conditions can be easily modified to avoid such problems [61, 62]. Also, nutmeg has often caused problems during the analysis of aflatoxins because of a large number of volatile compounds that are naturally present [63]. Moreover, the injection of relatively “dirty” samples drastically shortens the column life that may lead to broader peaks if residues are build up in the injector or column [63]. HPLC applied for determination a lot of mycotoxins for example ; aflatoxins in noodle samples[64], cereals and nuts[65].

Liquid chromatography coupled with mass spectrometry (LC-MS) or tandem mass spectrometry (LC-MS/MS) is a most powerful tool to avoid the problems related to the HPLC method for the detection and identification of mycotoxin [66, 67]. The different ionization sources are employed for LC/MS and LC-MS/MS, such as atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) interfaces coupled with single or triple quadrupole mass spectrometers [66, 67]. Ion-trap instruments have also been utilized for the determination of mycotoxins, but compared to triple quadrupole

instruments that exhibit disadvantages like lower limits of detection, poor calibration linearity, and lower measurement repeatability [66]. LC/MS methods have been applied for single mycotoxins and multimycotoxins [68, 69]. For developing an LC-MS/MS method for the analysis of multiple mycotoxins, seems to be challenging due to their different physicochemical properties. Although APCI has been mentioned to give good results for the problematic trichothecene mycotoxins, however, ESI is commonly applied for multi-class or multi-residue mycotoxins methods [4, 5].

For the analysis of multimycotoxins, different applications of LC with MS or MS/MS have been reported, for example: (a) UHPLC–MS/MS for analysis of 56 fusarium, Alternaria, Penicillium, Aspergillus, and Claviceps mycotoxins in a wide range of animal feed samples [70]; (b) LC/MS/MS method for the simultaneous determination of deoxynivalenol, aflatoxins (B1, B2, G1, G2), zearalenone, ochratoxin A, T-2 and HT-2 toxins in cereals samples [71], (c) UHPLC-MS/MS method were developed for the for the determination of 10 mycotoxins, namely ochratoxin A, beauvericin, citrinin, enniatin A, A1, B1, and aflatoxin B1, B2, G1, G2, found in the eggs at trace levels [72]; (d) LC-ESI-MS/MS method was developed for the simultaneous determination of 16 essential toxic mycotoxins, such as aflatoxins B1, B2, G1, and G2, ochratoxin A, beauvericin, enniatins A, A1, B, and B1, fumonisin B1, B2, and B3, diacetoxyscirprenol, HT-2, and T-2 toxin, in the dried fruits [73]; ;(e) LC-ESI-QTOF-MS/MS for analysis mycotoxins trichothecenes type-A and type-B in cereal samples[74];(f) measure of aflatoxins levels B1,B2, G1, and G2 in cereals and peanut products [75]. multi-analyte LC–MS/MS method for the analysis of 23 mycotoxins in different sorghum samples [76] and 30 mycotoxins in animal feed and meat ,eggs, and milk by LC-MS/MS as Multi-mycotoxin analysis method [77].

Liquid Phase Microextraction techniques

LPME techniques seem to be a promising tool for analysis different compounds in complex samples due to its unique properties of easy sample cleanup, low limits of detection, low price, and more environmental friendly approach than other methods. This review focuses on the newly developed LPME-based techniques and their applications to determine the different kinds of mycotoxins present in the food samples. The conceptions, classification, and applications of LPME techniques for mycotoxins detection has been discussed in this paper.

SDME is a newly developed method that uses 1.3 μL of an immiscible organic solvent suspended in the form of a watery drop. This method has been reported by Liu and Dasgupta, which was then named as drop-in-drop method [79]. At the same year, Jeannot and Cantwell developed a new technique, in which a microdrop of an organic solvent was suspended at the end of a Teflon rod immerged in an aqueous sample solution and stirred by the magnetic stirrer. After the extraction, the rod was removed from the sample solution aided by a microsyringe, and an aliquot of the organic drop was injected into a GC for further analysis [80]. Newer techniques were introduced by He and Lee [81], such as the static and dynamic modes of SDME. In the static mode, 1 μL of the solvent drop was suspended on the microsyringe needle tip that was immersed in an aqueous sample solution. In the dynamic mode, a microsyringe was used as a micro-separator funnel. An aqueous sample was first withdrawn into the microsyringe containing the solvent and subsequently pushed into the aqueous solution. This whole process was repeated multiple times (usually 20 times). The remaining solvent was injected directly into a GC. When the solvent was withdrawn into the microsyringe, it formed a thin film on the inner wall, and later the analyte in the aqueous sample rapidly formed a partition in the film. There was subsequent diffusion of the analyte into the bulk organic solvent on the expulsion of the aqueous portion from the microsyringe [81].

Both the static and dynamic modes are presented with certain advantages and disadvantages. The static mode provides better reproducibility, but suffers from limited enrichment and demands longer extraction time. The dynamic mode provides higher enrichment in a shorter period as compared to the static mode, but its disadvantages include low reproducibility and repeatability because of the manual operation [81].

Direct immersion (DI) approach of the SDME techniques is a process that is conducted in a static mode and the basic principle is based on the suspension of a single drop of solvent from the tip of a microsyringe needle that is immersed in an aqueous sample solution. DI-SDME could be performed via two modes. First, the analyte is directly injected to the GC system. Second, the analyte is injected into an HPLC system after redissolving it in a suitable solvent. The drawback of this method is related to the stirring speed; the suspended drop is unstable, and the option of the acceptor phase remains limited for the water-miscible solvents [10, 12, 82]. This mode can also encounter a problem at high stirring speeds, where air bubbles can be formed in the biological samples such as plasma [83].

In head space (HS) SDME, non-volatile matrix interference is introduced, and only volatile, and semi-volatile compounds are extracted in this mode. The analyte is diffused among three phases: aqueous phase, headspace, and solvent drop. The aqueous phase mass transfer is the rate determining step in the extraction process [10, 84-86]. As the droplet does not come in direct contact with the sample, the HS-

SDME has enabled the use of an organic solvent as the acceptor to provide excellent cleanup for samples with complicated matrices [12, 82]. The disadvantages of this method include the need for vapor pressure, low viscosity solvent, and compatibility with the GC system. Furthermore, if the solvent is miscible with water, then the drop size may increase during the sampling process that consequently results in falling of the drop from the needle [83].

Liu and Lee [87], reported a new technique called continuous flow (CF) SDME, which relies on continuous refreshing of the surface of the immobilized organic drop that is used as the extract solvent marked by a constant flow of sample solution that is delivered by the pumping system. The extraction solvent drop is held at the outer tip of a polyether ether ketone connecting tube by a microsyringe, and is immersed in a continuously flowing sample solution. This tube acts as a fluid delivery system and solvent holder. The solvent drop size can be controlled by an HPLC injection valve. In addition, this method can prevent the introduction of undesirable air bubbles and achieve a high enrichment factor. The effectiveness of this method contributes to both diffusion and molecular momentum resulting from the mechanical forces. To achieve reliable results, the limit parameters such as solvent, volume, the flow rate of the sample solution, extraction time, pH, and the salt concentration are important for the study [87]. He and Lee [88], applied CF-SDME–HPLC for the extraction and determination of the commonly used pesticides, such as fensulfothion, simazine, etridiazole, bensulide, and mepronil. All the pesticides used in their study showed good linearity between 25 ng mL−1 to 250 ng mL−1 (R2 ranged from 0.9879 to 0.9999). The limit of detection was 4 ng mL−1 for all analytes. The problems in this technique are associated with the need for a peristaltic pump to offer an extra filtration [88].

The directly suspended droplet (DSD) SDME is a technique in which the aqueous sample is filled in a vial containing a stir bar, which is adjusted to the required speed to cause a gentle vortex. The solvent drop is added on the top surface of the aqueous sample, and the single droplet is vortexed at or near the center of rotation. The mass transfer is believed to increase as an effect of the rotation of the droplets on the surface of the aqueous phase. This method provides greater flexibility of operation solvent volume and stirring speed as compared to other SDME techniques [89].

DSD-SDME is an uncomplicated technique that prevents cross-contamination. In this method, a very short time is needed to attain equilibrium, and addition of supporting materials is not necessary. Collection of the microdrop is one of the disadvantages of this method. The entry of a small quantity of water into the syringe can lead to the problem in the instruments. This problem can be avoided by using a solvent with a melting point of 10°C to 30°C (near room temperature) that floats on the surface of the aqueous solution. Following stirring for a specific period, the sample solution is transferred into an ice bath. After the solidification, the solvent droplet is placed in a small vial; after melting, the solvent is used in the analysis of the target analyte [90].

The second technique of LPME uses membrane extraction method. Depending on the analytical applications, the membrane techniques can be classified into two types: first is a permeable membrane technique, in which the selectivity membrane process is based on the pore size and its distribution. Second is a non-permeable membrane technique, which is completely solid or involves impregnating the membrane pore with liquid [91].

This review focuses on the separation techniques involving a porous membrane impregnated with liquid. Most of the solvents in microextraction techniques come in direct contact with the sample. Sometimes, the sample, especially biological samples, may contain multiple compounds that may cause certain interference during the determination stage (co-extraction). This co-extraction may also affect the extraction efficiency of the compound. The use of porous membrane extraction as a development technique may reduce this interference, thus providing high effective clean-up and enrichment factor [92].

In 1999, Pederssen-Bjergaard and Rasmussen introduced a new LPME concept. They used a low-cost, disposable permeable hollow fiber (HF) made of polypropylene to prepare the sample for CE analysis. The solvent was impregnated in fiber porous by dipping the membrane in the solvent for several seconds. The accessed organic solvent inside the lumen was removed by flushing air. The next stage involved addition of the acceptor phase solution inside the lumen. Finally, the HF was immersed in the sample solution. The non-porous membrane was separated between the two aqueous phases. One of these phases, which contained the target analyte, was named as the donor phase, whereas the other that received the target analyte, and was involved in concentrating and transferring the analyte into an instrument, was named as the acceptor phase. By using this technique, a large number of samples can be prepared simultaneously, and cross-contamination and their effects can be eliminated. This technique is renamed as the supported liquid membrane (SLM) technique [93]. For this method, the solvent must fill the pores in the wall, immiscible with water, possess low volatility, strongly immobilized in the pores, provide appropriate extraction selectivity, and not cause any damage to the instruments [94, 95].

MMLLE compliments to the SLM technique, in which polypropylene porous hollow fiber impregnated with organic solvent was used to separate the aqueous sample (donor phase) and organic solvent that was a same organic solvent filled in the pores hollow fiber and into the lumen hollow fiber (acceptor phase). In general, different physical models of SLM and MMLLE modules, mostly flat, spiral and tubular are used. Depending on the membrane surface area to its volume ratio, which should be high to get large enrichment factors, the tubular modules have a highest factor followed by the spiral module and lowest for the flat module [96]. In general, the researchers have used two kinds of modules such as the flat or hollow fiber modules [97].

DL-LPME is one of the LPME techniques developed by Rezaee et al. [98]. DL-LPME was originally developed for water samples. This method has also been applied on other sample types, such as soil and foodstuff, either as a pretreatment technique or in combination with other techniques. The principle of the technique is dependent on the different affinities of the analytes to the aqueous sample and organic extract. DL-LME is performed by adding a small volume of the organic solvent with dispersion solvent into the aqueous sample, thus creating a turbid solution. After centrifugation, the sediments are collected at the bottom of the sample vessel [98]. The measurement of analytes in the settled layer can be performed by the analytical techniques. The dispersive solvent functions by aiding in extracting the target analyte from the aqueous samples [98, 99]. The dispersive liquid must be miscible in both the extraction solvent and aqueous sample. The most dispersive liquids used are methanol, ethanol, acetonitrile, and acetone, because of their miscibility in both the phases. The extraction solvent has to possess the following properties: capability to form small droplets in the sample, low solubility in water, compatibility with the desired analytical instrument, ability to collect the analytes, and larger density than that of the sample. Halogenated hydrocarbons, such as chlorobenzene, carbon disulfide, carbon tetrachloride, and chloroform, are mostly used in the solvent extraction method. The simplicity of the operation, rapidity, low cost, good recovery, and high enrichment factor prove advantageous to the extraction process [83].

Numerous researchers have added certain modifications to this method such as: Shokoufi et al. [100] combined fiberoptic-linear array detection spectrophotometer with DL-LME to preconcentrate and determine cobalt and palladium in water, and Xu et al. reported a new technique that involved solidification of the solvent droplet (SFO-DLLME); this technique provides double enrichment factor compared to other techniques [101].

Applications of LPME for mycotoxins analysis

In general, many reviews articles are published about SDME as one of the LPME methods has diverse utilization for extraction of a variety of compounds (pesticides , organic pollutants, clinical and pharmaceutical compounds)in different kinds of samples (biological samples ,foods, and environmental samples [10, 102-107]. However, as per our knowledge, there have been no previous studies in relation to the application of SDME for extraction of mycotoxins in any of the samples.

Although of high efficiency of Hollow Fiber Liquid-Phase Micro-Extraction (HF-LPME) and overcome its disadvantages by doing some modifications on the HF-LPME strategies which resulted in; efficiency improvement, decreasing time and as an eco-friendly approaches that provide a better enrichment factor, higher recovery, low detection limit and higher extraction throughput by utilization low toxic solvent (Ionic Liquid) or forcing drive for extraction , and a wide range of applicability for various analytes in the food samples. However, as per our knowledge, only four reports related to mycotoxins extraction and pre-concentration has been found in the case of four food matrix (wine, beer, milk, and soya juice). The first one was performed by Gonzalez-Penas et al. [108], they determined the Ochratoxin A (OTA) content in wine via HF(2)LPME along with HPLC and fluorescence detector. Many parameters have been investigated to optimize the procedure such as best extraction solvent, length of a hollow fiber, stir speed, pH, and salt concentration. OTA was separated from wine by 1-octanol loaded in the pores of the HF, and then in the acceptor phase. The same solvent was used in the pores (1-octanol) filled in the lumen of HF as acceptor phase. The recovery of this method was 77%, and the limit of detection (LOD) was 0.2 ng/mL [108].

In the second study, Romero-González et al. [109] used HF (2) LPME combined with LC-MS/MS to determine Ochratoxin A and T-2 toxin in wine and beer, respectively. The target analyte was extracted from the aqueous sample (donor phase) to the 1-octanol (SLM) as a solvent immobilized in the pores of HF. Subsequently, the target analyte was adsorbed by the aqueous solution consisting of a mixture of acetonitrile and water. After optimization of the different affecting factors, the relative recoveries were higher than 70%, with good linearity ($R2 > 0.993$) and LOQ (0.02–0.09 μg/L). In addition, the relative standard deviations (RSD) was always lower than 12%, whereas the intra-day precision was lower than 21% [109]. An automated hollow fiber liquid-phase microextraction (HF-LPME) coupled with liquid chromatography/tandem mass spectrometry method was developed for the extraction and

determination of aflatoxin M1 (AFM1) in milk samples. The enrichment factor (EF) reached 48, and the limits of detection (LOD) and quantification were 0.06 and 0.21 g kg−1, respectively with recoveries ranging from 61.0% to 106.7% [110]. The new approach was eco-friendly because of some characteristics such as low organic solvent consumption and no usage of chlorinate solvents. In addition, it was a cheaper and easier means with no requirement for centrifugation. Furthermore, this new technique had great potential for use in automated systems. This new method called HF-DLLME was introduced in 2015 by Simão et al. [111]. They applied HF-LPME combined with DLLME for the extraction of aflatoxins(B1,B2,G1,and G2) in soybeans juice for analysis by HPLC. The linear range varied from 0.03 to 21 μg L^{-1}, with R^2coefficients ranging from 0.9940 to 0.9995. The LOD ranged from 0.01 μg L^{-1} to 0.03 μg L^{-1} and the limit of quantification (LOQ) ranged from 0.03 μg L^{-1} to 0.1 μg L^{-1} while the recovery ranged from 72% to 117% with accuracy ranging between 12% and 18% [111].

Different mycotoxins have been studied in diverse food samples after being separated by the DLLME technique, such as PTA in apple juice, [13, 112], zearalenone in beer sample [113, 114], OTA in wine and malt beverage [115-119], aflatoxins, fumonisins, trichothecenes, ochratoxin A, citrinin, sterigmatocystin, and Zearalenone in milk and dairy products [120-122], aflatoxins and ochratoxin A in cereals and cereal products [123-127], AFTs B1, B2, G1, and G2 in edible oil [128], and raisin samples [129] as shown in Table (1). Most of the food samples have been analyzed using DLLME coupling to liquid chromatography, except one that has been coupled to GC technologies [126]. Most of the solvents used in DLLME are immiscible with water and compatible with GC. The use of DLLME–GC is related to its variable applications in many areas. At times, suitable derivatization reactions are used with DLLME to simplify the procedure and reduce the analysis time. The derivatization depends on polarity, thermally labile, and volatility of the target compounds [130].

The challenges associated with DLLME technique is the correct selection of a solvent mixture. The sediment phase volume increases with the increase in the solvent volume and decrease in the pre-concentration factor. Thus, the optimal volume must ensure high pre-concentration factors and a sufficient volume of the sediment phase for further analysis after the centrifugation. It is necessary to attain a low extractant phase to sample ratio, and a high distribution coefficient to achieve high pre-concentration factors and extraction efficiencies [130]. Chloroform is the most commonly used extraction solvent in the mycotoxins analysis. The necessity in selecting the disperser solvent is its miscibility in both the phases (extraction solvent and the aqueous phase). The most common disperser solvents used are acetonitrile and methanol. The volume of the disperser solvent directly affects the formation of the cloudy solution consisting of water along with the disperser and extraction solvents, the degree of dispersion of the extraction solvent in the aqueous phase, and the extraction efficiency. A change in the volume of the sediment phase is observed due to the variations found in the volume of the disperser solvent. Thus, it is necessary to change the volumes of the disperser and the extraction solvents simultaneously to achieve a constant volume in the sediment phase [130].

The factors, such as pH and ionic strength, play an important role in LLE efficiency. For the ionizable compounds, the DLLME efficiency could be modulated by an aqueous phase pH adjustment; the ionized form is soluble in water and poorly extracted by the organic phase, whereas the unionized form is easily transferred into the DLLME extractant. The first DLLME was performed to eliminate the hydrophobic matrix interferences, while the targeted analyte remained in their ionized form in the aqueous phase that is considered to be advantageous. In the second DLLME, the analyte was subsequently recovered by the change in the pH to shift the dissociation equilibrium from the ionized to unionized form.The pH-controlled DLLME (pH-DLLME) is presented by Campone et al. [127], as a selective sample preparation method for the analysis of ionizable analytes in complex matrices. The hydrophobic matrix interferences in the raw methanol extract were removed by the first DLLME method performed at pH 8 for the reduction of the solubility of OTA in the extractant. The pH of the aqueous phase was then adjusted to two, and the analyte was extracted and concentrated by the second DLLME. The method offered additional advantages for DLLME, primarily a higher selectivity and an extension to the analysis of extremely complex matrices [127].

Soares Emídio et al. [131], introduced an environmental friendly method for determination of the estrogenic mycotoxins (zearalenone, zearalanone, α-zearalanol, β-zearalanol, α-zearalenol, and β-zearalenol) in environmental water samples. They used low-toxic solvents (highly toxic chlorinated solvents are not required) dispersive liquid–liquid microextraction and liquid chromatography–tandem mass spectrometer. This method seemed to be economical and rapid with a high extraction efficiency, low LODs, good repeatability, and simple set-up. According to the RSDs, the precision was found to be better than the repeatability and intermediate precision that accounted for only 13%. The average range of recoveries of the spiked compounds was from 81 to 118%. The method such as LOD and LOQ, considering a 125-fold pre-concentration step, were valued at 4–20 and 8–40 ng L−1, respectively [131].

In several studies, RTILs have been used as extraction solvents to replace the typical organic solvents in DLLEM that has found applications in analyzing pesticides in water samples [113, 124], and synthetic food colorants in soft drinks and confectioneries [125]. Lai et al. [118], presented the ionic liquid-based dispersive liquid–liquid microextraction (IL-DLLME) method in combination with LC and a FD for the analysis of Ochratoxin A in rice wines. At first, the rice wine samples were diluted to 18% alcohol with deionized water, and then with the ionic liquid [HMIM][PF6] at room temperature, which was dispersed in ethanol and was introduced into the microextraction for OTA analysis [118]. The enrichment factors were approximately 30. A good linearity was obtained with a correlation coefficient (r) of 0.9998, and a limit of detection of 0.04 μg L^{-1} under the optimized experimental conditions. The recoveries ranged from 75.9% to 82.1% with an RSD below 10.4% [118].

Mostly, the DLLME has been applied directly to the water samples, for example, the organic compounds such as organochlorine and organophosphorus pesticides, and substituted benzene compounds [126], triazine herbicides [112], organophosphorus flame retardants and plastizicers [114], and bisphenol A [116] In addition, it can also be combined with other sample treatments to improve the selectivity of the sample preparation process and/or the achieved LOQs for the complex matrices, for example solid phase extraction (SPE) [133, 134] and liquid-liquid extraction (LLE) [129].

The HMF is considered the most common interference in the determination of PAT in apple juices and products derived from it[13]. In addition, HMF is found to be at two or three times higher concentration than that of PAT[135], which may lead to a serious problem in determination of PAT . The micellar electrokinetic chromatography (MEKC) is the preferred electrophoretic mode for the analysis of PAT that leads to the separation of HMF, which is the main interference in apple juice [136]. The satisfactory limits of quantification can also be achieved by methods such as capillary electrophoresis (CE) and HPLC that exhibits certain advantages that includes their ability to use a smaller volume of organic solvent and produce less volume of waste. MEKC technique in combination with DLLME is considered to be an environmental friendly alternative in determining PAT, which is marked by reduction in the consumption of organic solvent in both the steps (sample treatment and determination) of the method mentioned above that is in agreement with the new trends related to the green analytical chemistry [13]. Liquid chromatography technologies were the common instruments utilized with LPME approaches(HF-LPME and DLLME) for the determination of mycotoxins with only one exception that it utilized gas chromatography technologies [126].

Efficiency of LPME methods for separated different compounds

To estimate the efficiency of LPME, some researchers performed comparison studies among LPME methods (SDME, HF-LPME, and DLLME) and compared LPME with different other sample extraction methods like LLE, SPE, and SPME. Sarafraz-Yazdi and Es'haghi have compared HF-LPME with SDME through Aniline derivatives analysis in Water by HPLC. The results of this comparison showed better RSD for HF-LPME than for SDME whereas recovery was higher for SDME. They attributed that to the HFME memory effect, i.e. retention of analyte molecules in the pores of the hollow fiber (HFME), whereas for SDME, the extraction medium was new every time. LOD was 1.5–3.5 for SDME and 1.0–2.5 μg L^{-1} for HF-LPME. The LOD for HF-LPME was slightly better than those obtained for SDME, thus reflecting that HFME enabled high enrichment of analytes and consequently had high sensitivity. However, the SDME technique accompanies certain disadvantages like drop instability, time-consuming, tedious steps and more importantly, the low sensitivity and precision of this method. Also there is a need for filtration of the sample when utilized in SDME for the extraction of complex matrixes [137].

To estimate the efficiency of HF-LPME in pesticide field, Xiong and Hu have critically compared HF-LPME and DLLME for the analysis of OPs in different sample matrices (water, soil, and beverage samples) through Gas Chromatography- Flame photometric detectors (GC-FPD). The following results were obtained from the analysis of the spiked samples: the recovery was 81.7–114.4% with RSDs of 0.6–9.6% obtained for HF-LPME, and the recovery was 78.5–117.2% with RSDs of 0.6–11.9% obtained for DLLME. While analyzing non-complicated samples such as water sample, DLLME showed some advantages like less extraction time and high suitability for batches of simultaneous sample pretreatment. In addition, a higher extraction capacity was obtained by DLLME than the HF-LPME mode. But in separated Ops from soil and beverage samples which are more complicated than water, HF-LPME was found to be more robust and sensitive as compared to the DLLME method. For this reason, DLLME needs to undergo some extra steps such as applied filtration and dilution for the sample to reduce the coextractant. Moreover, the HF-LPME demonstrated repeatability better than that of DLLME [138].

For evaluating the efficiency of LPME in separation of drugs, a comparative study of dispersive liquid–liquid microextraction and hollow fiber liquid–liquid–liquid microextraction was used for the determination of narcotic drugs in water and biological fluids by HPLC. Simultaneously the results were compared with other previous studies for the same compounds. The inter-day precisions of the methods

were determined by performing three consecutive extractions each day over a period of three working days. The intra-day RSDs ranged between 1.7 and 6.4%, and inter-day RSDs varied from 14.2% to 15.9% for DLLME. For HF-LLLME intra-day precision varied from 0.7% to 5.2%, and inter-day precision were between 3.3% and 10.1%.The results demonstrated that HF-LLLME had better inter- and intra-day RSDs than DLLME. The values of the squared correlation coefficient (R2) were relatively very close. The results indicated that EFs were between 275 and 325 for DLLME and ranged from 190–237 for HF-LLLME. In addition, the highest EFs for DLLME led to lower LOD as compared to the HF-LPME. LOD for DLLME was between 0.4 and 1.9 μg/L and between 1.1 and 2.3 μg/L for HF-LLLME. It is clear that DLLME can provide more analyte enrichment than HF-LLLME. This can be attributed to the large surface area between the extraction solvent and the aqueous sample in DLLME method. When compared with methods like SPE–GC–MS and SPME–GC–MS, the LODs for both methods (DLLME and HF-LPME) were a little higher. However, HF-LPME methods are sensitive enough to determine these drugs in the biological samples [139].

Meng et al. [140] performed another comparative study between HF-LPME with DLLME technique for the determination of drugs of abuse in biological samples by GC-MS. No significant differences were found between the analytical data of spiked urine and blood samples after HF-LPME extraction and ultrasound-assisted low-density solvent dispersive liquid-liquid microextraction, (UA-LDS-DLLME). Typical chromatograms were obtained for the spiked biological samples after the HF-LPME and UA-LDS-DLLME extraction. The LOD ranged from 0.5 to 5 ng/mL for HF-LPME and 0.5 to 4 ng/mL for UA-LDS-DLLME. It was clear that the UA-LDS-DLLME was slightly more sensitive than the HF-LPME, thus reflecting that UA-LDS-DLLME enabled high enrichment of analytes. The recovery of 79.3 – 98.6% with RSDs of 1.2 – 4.5% was obtained for HF-LPME, and the recovery of 79.3 – 103.4% with RSDs of 2.4 – 5.7% was obtained for DLLME. It was found that the repeatability of HF-LPME was better than UA-LDS-DLLME, because the impurities could be easily coextracted by the tiny droplets of organic extractant and resulted in worse repeatability in the former case. However, when the extraction time was used as one of comparative factor, the UA-LDS-DLLME was found to have an excellent timing of 3 min as compared to 15 min for HF-LPME. This was attributed to the large surface area between the extraction solvent and the aqueous sample in UA-LDS-DLLME method. Initially, the surface areas between the extraction solvent and sample solution were infinitely large. Therefore, the UA-LDS-DLLME had higher extraction efficiency than the HF-LPME. There were less impurity peaks after the HF-LPME extraction than UA-LDS-DLLME [140]. This comparison of results among the LPME techniques denoted that the disposable nature of the hollow fiber eliminates the possibility of sample carry over and ensures high reproducibility in HF-LPME. In addition, the pores in the walls provide some selectivity to the hollow fiber membrane by preventing high molecular weight materials to reach the acceptor phase (organic or aqueous solution). This gives HF-LPME advantage over the other LPME techniques.

SDME method was compared with modified acetone-partition extraction procedure (APE) method for the separation and analysis of multiclass pesticides in tomatoes. SDME exhibited good analytical characteristics by reporting similar to 138 times lower LODs as compared to APE. The enrichment factors of the SDME procedure ranged from 0.7 to 812 whereas, the concentration factors for SDME ranged from <0.1 to 52. Relative recoveries ranged from 67 to 90% for SDME and from 90 to 120% for APE. Matrix effects assessment performed for both the methods indicated that SDME is a more selective sample preparation method than APE [141].

Lin et al. performed a comparison of HF-LPME with the LLE and SPE methods for the determination of pyrethroid metabolites in urine samples. The LOD of HF-LPME was lower than LLE because of some matrix interference while using LLE, which was reflected in the complicated noise signal. In addition, the HF-LPME method consumed only 8 μL extracting solvent (1-octanol) and one tenth of the derivatizing agent used in LLE and SPE methods within 15 min to achieve the extraction and derivatization obtained within 2–4 h in the LLE and SPE methods [142].

Frenich et al. [143] compared SPME with HF-LPME for the simultaneous extraction of different pesticides in drinking water using Gas chromatography–mass spectrometry (GC-MS). They concluded that SPME was the best technique as it was simple, highly automatable and did not require much equipments. LOD of SPME was lower than HF-LPME. The LODs values varied between 0.1 ng/L to28.8 ng/L with SPME and between 0.2 ng/L to47.1ng/L for HF-LPME. In addition, SPME showed better sensitivity than HF-LPME for most of the pesticides, except for sulfotep and clodinafop-propargyl. This can be further explained by taking into account the fact that the whole extract is injected in SPME, while only 10 μL was analyzed in HF-LPME. SPME recoveries ranged from 70.2% to 113.5%, while in HF-LPME, they ranged from 70.0% to 119.5%.However, HF-LPME correctly recovered 56 compounds while SPME recovered 77 compounds out of a total of 77pesticides that spiked in the sample. Intra-day precision (RSD) ranged from 2.1% to 19.4% for the SPME and 4.3% to 22.5% for HF-LPME, while inter-day precision (RSD) ranged from 5.2% to

23.9% and 8.4% to 27.3% for SPME and HF-LPME, respectively [143]. Nine samples of fortified wine ranging from 0.4–3 ng/ml, and one sample of white wine from a inter laboratory study, were assayed and quantified by LPME and immunoaffinity column (IAC) procedures. The results obtained for both the methods were similar. Moreover, a lineal relationship was obtained when representing the results obtained from the IAC process versus those obtained from the LPME process. Further, this was proved by the good correlation coefficient obtained (r = 0.99), a slope close to 1 (0.98) (confidence interval 95%: 0.85–1.12) and an intercept value near 0 (−0.04 ng/ml) (confidence interval 95%: 0.26–0.18 ng/ml) [108].

Yang et al. performed a comparison among the DLLME, SPE, MAME, and SPME methods for the separation of OPPs in soil samples. The result showed that the LODs for SPE, microwave-assisted micellar extraction (MAME), and SPME (2970-9490, 200–95000, 500 pg/g respectively**)** and the volumes of the organic solvent required in both SPE and MAME (30.0, 10.0 mL) were higher than DLLME (2mL). The % RSDs for MAME method were lower than the DLLME method and the RSDs for both SPE–GC–NPD and SPME–GC–FPD (4.0–20.0%, 1.95–12.2% respectively) were higher than the DLLME method (2.0–6.6%). All of these results gave DLLME an advantage over the other methods. Also DLLME is a simple, rapid, and environmentally friendly method [144].

Table 1: Applications of DLLME techniques in mycotoxins analysis

Analytes	Matrix	System	DS	ES	LOD	Ref
AFB1, AFB2, AFG1 and AFG2	Cereal products	HPLC-FID	MeOH	CHCl3	0.01–0.17 g kg^{-1}	[123]
AFM1	Milk samples	LC-MS/MS	Acetonitrile	Chloroform	0.6 ng kg^{-1}	[120]
AFM1	Milk samples	SMES	MeOH/water	MeOH/Water	13 ng L-1	[121]
Zearalenone	Beer samples	LC-MS		Toluene	0.44 mg kg-1	[113]
AFB1, AFB2, and OTA	Rice samples	HPLC	MeCN	CHCl3	0.06–0.5 g/kg	[124]
Deoxynivalenol	Wheat Flour	HPLC	Acetonitrile	CHCl3	125 µg/kg	[125]
T-2, HT-2, DON, NIV,	Grain & mixed feed	GC	Acetonitrile	Dichloromethane	0.01–5 mg/kg	[126]
Different mycotoxins	Milk thistle	LC-MS/MS	MeCN	Chloroform	0.45- 459 g kg^{-1}	[122]
OTA	Wine	HPLC	Acetonitrile	Chloroform	5.5 ng L^{-1}	[115]
OTA	Malt beverage	HPLC	Acetone	Chloroform	0.1 ng/ml	[117]
PAT	Apple juice	HPLC	Acetonitrile	Chloroform	8-40 µg/L	[112]
Zearalenone	Beer	TLC, HPLC	Acetonitrile	Chloroform	0.12 pg Ml^{-1}	[114]
Estrogenic mycotoxins	Water	LC-MS/MS		Bromocyclohexane	4–20 ng L^{-1}	[131]
AFB1, AFB2, AFG1 & AFG2	Edible oils	HPLC	Acetonitrile	Chloroform	1.1×10^{-4} to 5.3×10^{-3} ng mL^{-1}	[128]
OTA	Wine samples	LC-MS/MS	Acetone	CHCl3	0.005 $ngmL^{-1}$	[116]
Estrogenic mycotoxins	Water	MEKC–MS	Acetonitrile	Chloroform	0.04–1.10 µg /L	[132]
OTA	Rice wines	HPLC	Ethanol	[HMIM][PF6]	0.04 µg L^{-1}	[118]
AFB1 , AFM1	Milk & dairy products	HPLC	Acetonitrile	Chloroform	0.01 - 0.1 µg/kg	[133]
PAT	Apple juice	HPLC	Propanol	Chloroform	0.6 µg/L	[13].
OTA	Raisin samples	HPLC	Methanol	CHCl3	0.7 µg kg^{-1},	[129]
OTA	Cereals	HPLC	Methanol	$CCl_4 + C_2H_4Br_2$	0.019 µg/kg^{-1}	[127]
OTA	Various foods& wine	HPLC	Methanol	[C6MIm][PF6]	5.2 ng/L	[119]

Aflatoxins Blue 1(AFB1), Aflatoxins Blue 2(AFB2), Aflatoxins Green 1(AFG1), Aflatoxins Green 2(AFG2), Aflatoxins Milk 1(AFM1), Flame ionization detector (FID),Gas chromatography (GC), High-performance liquid chromatography (HPLC), Liquid chromatography-mass spectrometry tandem mass spectrometry (LC-MS/MS), Limit of detection (LOD), Micellar electrokinetic chromatography (MEKC),Ochratoxin A (OTA).

CONCLUSION

LPME are newly devised microextraction techniques with the most desirable property of reducing the volume of organic solvent needed for extraction. All LPME techniques can be utilized effectively for the extraction of target analytes from various sample solutions. For this reason, LPME is classified under "greener" chemistry methods. It has several advantages like, reduced extraction time compared to the other conventional LLE techniques, lower cost, good enrichment factors, high recovery rate, low detection

limits, and high sample throughput. The LPME techniques have been divided into three major modes – SDME, DLLME, and HF-LPME, with each group having a variety of modifications. SDME is a simple, quick, low-cost, and environmentally friendly technique but it has some limitations, including low extraction efficiency and poor reproducibility. DLLME is found to be one of the most widely used LPME techniques applied for the analysis of mycotoxins. Most of the solvents used in DLLME are immiscible with water and compatible with GC. The used of DLLME–GC is related to its variability of applications in many areas. Sometimes, suitable derivatization reactions are used with DLLME to simplify the procedure and reduced the analysis time. Compared to other techniques, DLLME greatly enhances the extraction efficiency and results in reduced time. Overall, DLLME has various advantages such as efficacy, simplicity, versatility, and accuracy, as well as low impact on the environment, shorter analysis time, and relatively low-cost.

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