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Recent developments in sample preparation techniques combined with high-performance liquid chromatography: A critical review

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ABSTRACT

This review article compares and contrasts sample preparation techniques coupled with high-performance liquid chromatography (HPLC) and describes applications developed in biomedical, forensics, and environmental/industrial hygiene in the last two decades. The proper sample preparation technique can offer valued data for a targeted application when coupled to HPLC and a suitable detector. Improvements in sample preparation techniques in the last two decades have resulted in efficient extraction, cleanup, and preconcentration in a single step, thus providing a pathway to tackle complex matrix applications. Applications such as biological therapeutics, proteomics, lipidomics, metabolomics, environmental/industrial hygiene, forensics, glycan cleanup, etc., have been significantly enhanced due to improved sample preparation techniques. This review looks at the early sample preparation techniques. Further, it describes eight sample preparation technique coupled to HPLC that has gained prominence in the last two decades. They are (1) solid-phase extraction (SPE), (2) liquid-liquid extraction (LLE), (3) gel permeation chromatography (GPC), (4) Quick Easy Cheap Effective Rugged, Safe (QuEChERS), (5) solid-phase microextraction (SPME), (6) ultrasonic-assisted solvent extraction (UASE), and (7) microwave-assisted solvent extraction (MWASE). SPE, LLE, GPC, QuEChERS, and SPME can be used offline and online with HPLC. UASE and MWASE can be used offline with HPLC but have also been combined with the online automated techniques of SPE, LLE, GPC, or QuEChERS for targeted analysis. Three application areas of biomedical, forensics, and environmental/industrial hygiene are reviewed for the eight sample preparation techniques. Three hundred and twenty references on the eight sample preparation techniques published over the last two decades (2001–2021) are provided. Other older references were included to illustrate the historical development of sample preparation techniques.

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1. Introduction

Analytical chemistry's history has documented that an analytes' accurate determination at the trace level without any pretreatment step is challenging. With all the technological advances in instrument development, instrumentation cannot handle samples with complex matrices. High-performance liquid chromatography (HPLC) methods covered in this review often require sample preparation steps due to real samples' complex matrices. The sample preparation step has always been crucial in the analytical process steps, and during the last two decades or so, it has come of age. Today, several sample preparation techniques exist that could perform three basic steps: (i) sample/analyte transformation into a form suitable for measurement; (ii) simplifying the matrix; and (iii) preconcentration to improve detection limit. Based on recent development trends, sample preparation techniques can achieve these three steps. With developments in biological therapeutics [1–3], proteomics [4,5], lipidomics [6–9], metabolomics [10–12], glycans cleanup [13,14], untargeted analysis [14,15], applications are expanding to cover aqueous and solid sample matrices containing non-volatile analytes. When sample preparation techniques are hyphenated, they have provided a powerful analytical tool capable of excellent simultaneous extraction efficiency, cleanup, and preconcentration.

Recent trends have seen sample preparation techniques developed for offline and automated online coupling to HPLC and a suitable detector. We have focused this review on eight sample preparation techniques. They are solid-phase extraction (SPE), liquid-liquid extraction (LLE), gel permeation chromatography (GPC), Quick Easy Cheap Effective Rugged, Safe (QuEChERS), solid-phase microextraction (SPME), ultrasonic-assisted solvent extraction (UASE), and microwave-assisted solvent extraction (MWASE). This review will later discuss the principles/concepts and applications for each of these sample preparation techniques. It is noted that selecting a sample preparation technique solely de-

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Table 1
Advantages and disadvantages of SPE, LLE, GPC, QUEChERS, UASE, MWASE, SBSE, and SPME.

SP Technique	Advantages	Disadvantages	Coupling to HPLC	Refs.
SPE	simplicity, and convenience, very selective, practical with a variety of matrices, many sorbent choices, less consumption of organic solvents, ability to interface with different instrumentations, high sample throughput, high recoveries, and reproducibility.	greater complexity or difficulty to master, lengthy method development, costly, no optimum sorbent for all applications, matrix constituents can be absorbed, limited selectivity or sensitivity.	offline and online	[42]
LLE	high selectivity of separation, high production capacity, low energy consumption, easy continuous operation, inorganic salts easily removed, short method development time, low cost.	difficult to automate, labor-intensive, utilize a large volume of toxic organics, emulsion formation, poor sample throughput, poor reproducibility, and loss of sensitivity	offline and online	[33,40,95]
GPC	good extraction efficiency for large molecules, favorable transfer kinetics, time-saving	cannot extract small molecules.	offline and online	[105,108]
QuEChERS	high recoveries for a wide range of analytes, high sample throughput, speed, environmental friendliness, inexpensive, rugged, efficient cleanup.	cannot extract large molecules.		[108]
UASE	simple, inexpensive, reproducible, high extraction yield, improve mass transfer, less extraction time, low energy consumption, low solvent consumption, non-destructive, easily coupled with other extraction techniques		offline	
MWASE	short extraction time, simple operation, no organic solvent, high selectivity, versatile & efficient extraction	difficult to optimize, energy consumption.	offline	[120]
SBSE	simplicity, high sorption capacity, robustness, excellent extraction efficiency	a limited spectrum of analyte polarities for the available stationary phases, strong matrix effects, and the need for heightened control of extraction conditions.	offline and online	[16,17]
SPME	simple, fast, solvent-free, non-exhaustive extraction technique, reproducible	fiber breakage, bleeding from conventional coated fibers, sample carry-over problems, pH instability. Note that these drawbacks have been overcome by introducing sol-gel, MIP, and electrochemical-assisted techniques for manufacturing SPME fibers.	offline and online	[145,155]

pends on a specific objective/problem to be handled. However, no matter which path the sample preparation follows, the ultimate goal is to achieve the most accurate, precise, selective, sensitive, and robust analytical method. Ultimately, knowledge of the various sample preparation techniques helps the analyst reach the separation's targeted goal.

Table 1 compares/contrasts the eight sample preparation techniques covered in this review. Each has unique advantages and disadvantages, and all of them have been reported in the literature in several configurations. The sample preparation approach of stir bar sorptive extraction (SBSE) [16–18] is worth mentioning. It was developed as a novel sample preparation technique in 1999 [19], and it operates on similar principles to SPME. It differs from SPME in that it uses a magnetic stir bar instead of a fiber. The stir bar has a magnetic rod with a glass jacket, and polymers are coated onto the glass jacket with a specific thickness greater than that used for SPME. The higher extraction phase thickness in SBSE results in higher extraction efficiency than SPME. Since its introduction, applications have grown to cover environmental analysis [20–22], food [23–25], biological samples [26], to name a few. In Fig. 1, we show a timeline of the significant progress since the SBSE introduction. Fig. 2 compares traditional methods and novel methods for preparing stir bar coatings. Fig. 3 shows the preparation steps for new novel coatings [27–29]. Developments and applications of SBSE are the subjects of another review. This review attempts to describe eight sample preparation techniques in use today that have been combined with HPLC and a suitable detector and provided insights into their advantages and disadvantages for their targeted applications. We also provided a section for microextraction-based methods. Methods developed for online and offline sample preparation approaches, ideal for analysis with gas chromatography (GC) coupled to mass spectrometry (MS), and other detection methods are the subject of another review.

2. Sample preparation basics

In most chemical analyses, the sample collected will not be suitable for direct examination and must be converted into a form suitable for analysis. The sample may present itself as a mixture of the analyte, interference, and a matrix. Converting any sample into a format ideal for measuring the analyte is referred to as sample preparation. Sample preparation is performed to modify the sample to make it amenable to detailed chemical analysis or improvement. Sample preparation is still tedious and manually intensive for many applications, indicating the tremendous time analysts put into these procedures. Sample preparation has had a profound influence on total analysis time and the quality of the data that will result. The process may involve several other aspects, such as precipitation, digestion, or preconcentration. These are all critical steps to successful chemical analysis, but their incorporation is specific to a sample and analyte to be determined. In some investigations, the extraction approach becomes part of the sample analysis, and their incorporation or exploitation may determine the success of the analytical method. When a sample is not amenable to analysis even after it has been purified, derivatization is usually employed. The derivatization process will allow the analyte to be converted to a format containing functionality detectable by the instrument of choice. This review will address online, and offline sample preparation approaches suitable for HPLC analysis with MS and other detection methods.

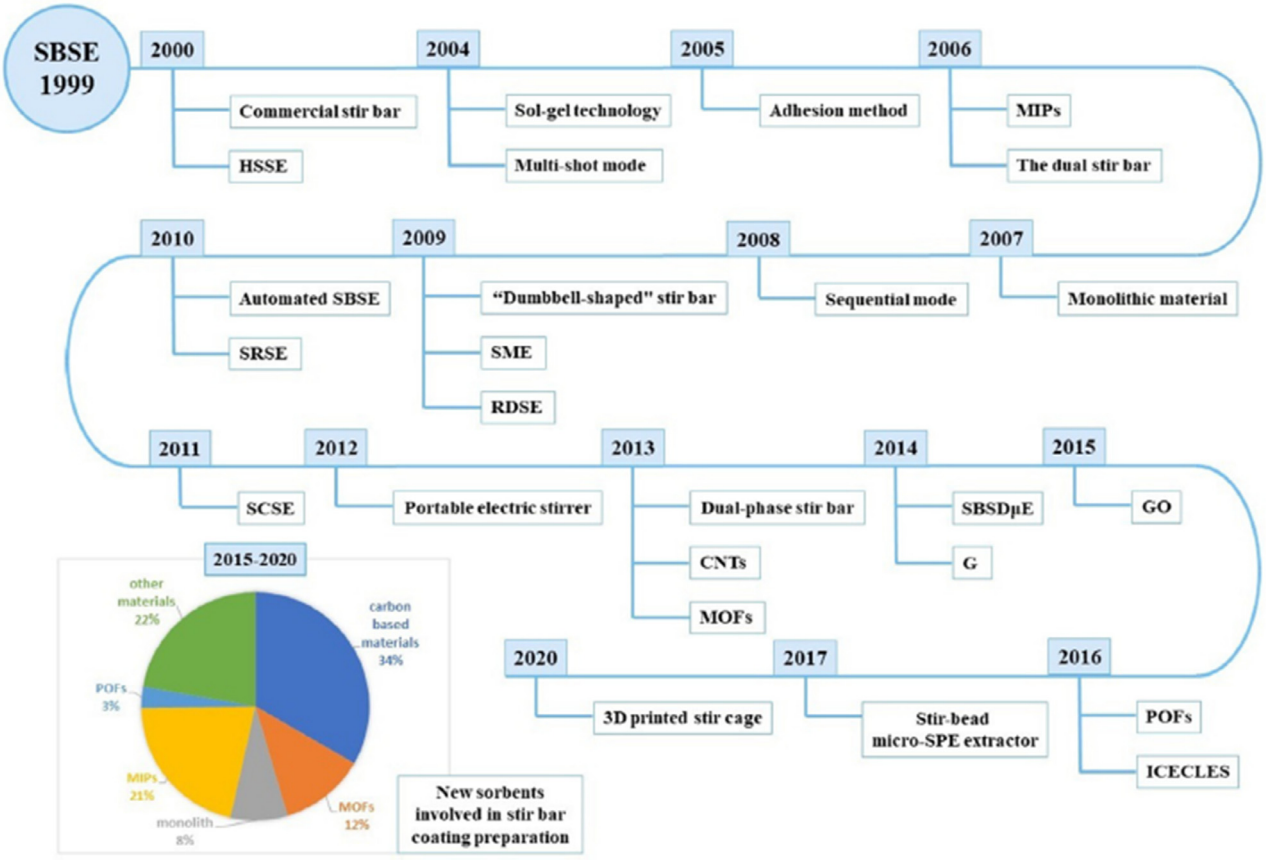

Fig. 1. Timeline for major progress of SBSE, along with the percentage of different coating materials used for SBSE reported in 2015-2020,. J. Chromatogr. A (2021) 1637:461810. Copyright (2021) Elsevier [Ref. 18].

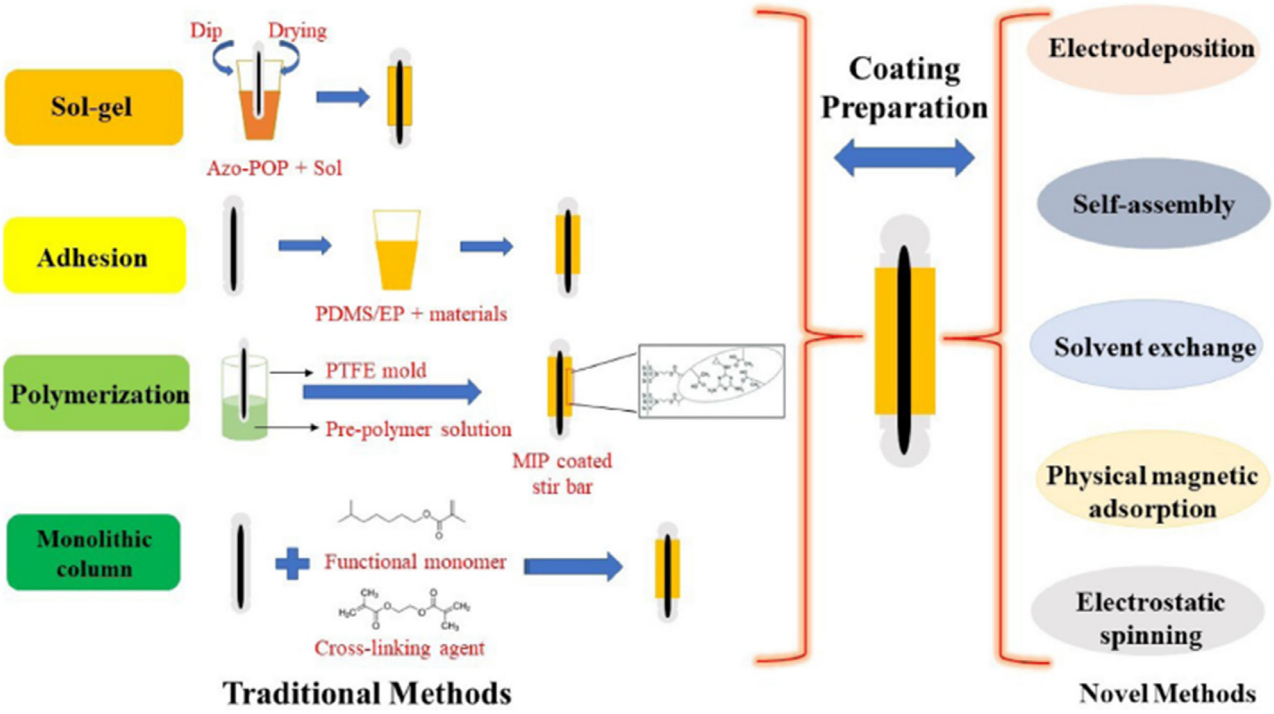

Fig. 2. Coating preparation of stir bar for traditional and novel methods,. J. Chromatogr. A (2021) 1637:461810. Copyright (2021) Elsevier [Ref. 18].

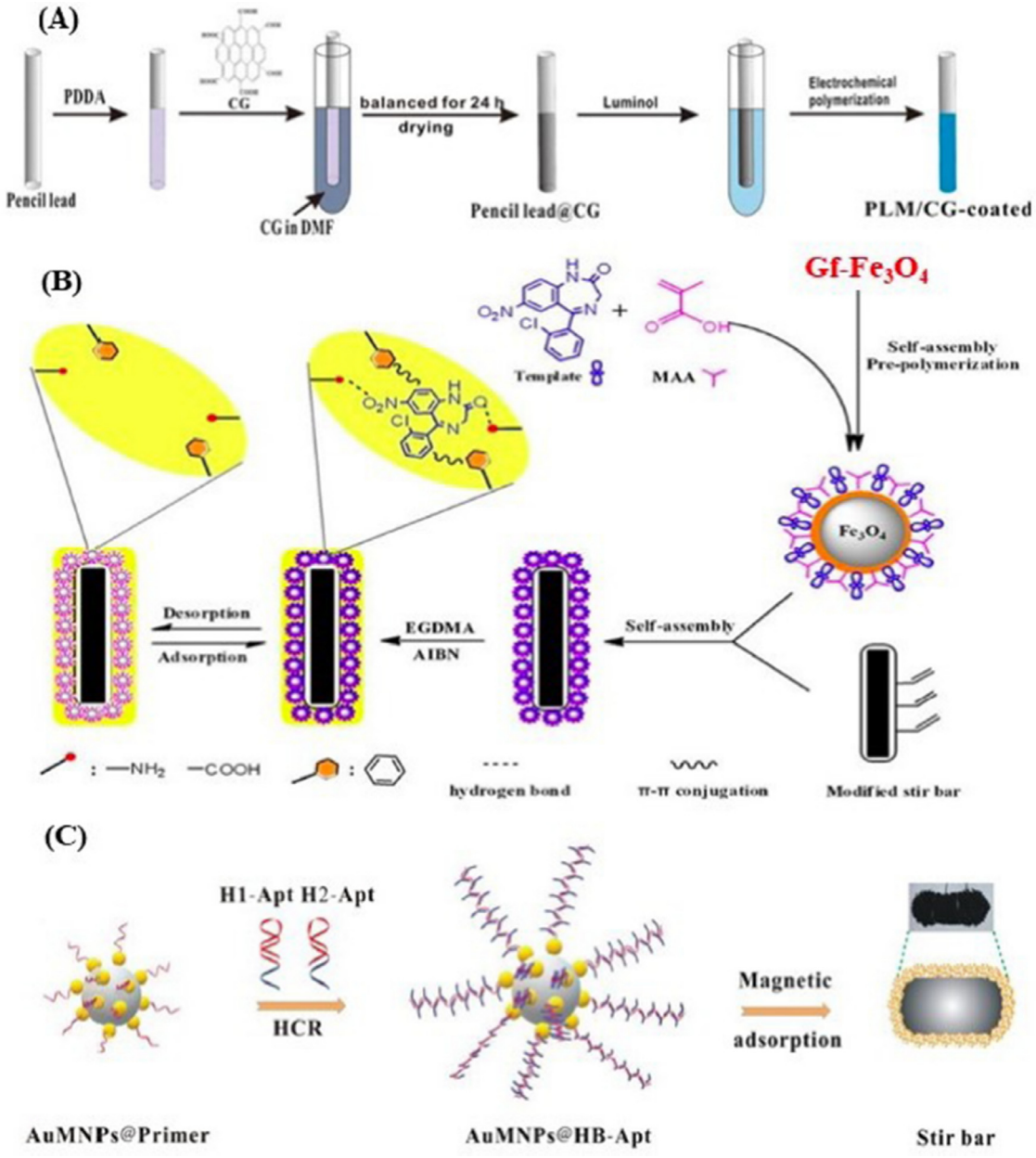

Fig. 3. New methods for coating preparation: the preparation of a polyluminol coating by electrodeposition (A) [ref. 21], the gf-Fe_3O_4 NPs and MIPs-MSB (B) [Ref. 22], and Au MNPs- HB-Apt coated stir bar by physical magnetic adsorption (C) [Ref. 23]. J. Chromatogr. A (2021) 1637:461810. Copyright (2021) Elsevier [Ref. 18].

3. Early sample preparation techniques

It is no doubt that analytical separation and detection was the area given significant attention in the past, while sample preparation remains in the shadow. It was not until susceptible analytical systems were developed that analysts realized that sample preparation was an essential part of the analytical method. Even when an excellent state-of-the-art analytical technique is applied, any mistake in collecting and processing a sample could lead to a substantial error in the final result. In the history of sample preparation, two techniques, namely, liquid-liquid extraction (LLE) and solid phase extraction (SPE), have been considered the oldest and most commonly used approaches to target trace amounts of analytes [30–33]. SPE was first introduced back in 1951 by Braus et al. [34]. Fig. 4 shows the first carbon filter that paves the way for SPE development. The work conducted at the US Public Health Service (Cincinnati, OH, USA) packed 1200–1500 g granulated activated carbon in an iron cylinder to isolate organic compounds from filtered surface waters.

The carbon filters were used to sample six water plants, transported back to the lab, air-dried, and extracted with diethyl ether with a Soxhlet extractor. They separate the organic extract into five groups and identify the trapped chemicals. The carbon filter work continued under Rosen et al. [35]. In their experiment, they identify petroleum refinery waste in surface water. They pumped several thousand gallons of surface water through carbon filters, extracted the trapped components with chloroform, fractionated, and measured the petroleum pollutants with column absorption chromatography and infrared spectroscopy [35]. The results revealed low ppm concentrations of petroleum contaminants in surface waters. Rosen et al. continued their work on carbon filters by developing a method to monitor and detect various water insecticides.

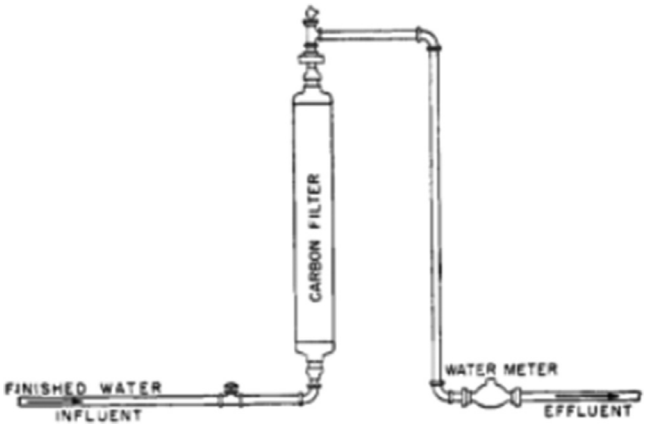

Fig. 4. The first carbon filter used for sampling filtered water for trace quantities of organic pollutants that pave the way for SPE development,. Anal. Chem. 1951; 23:1160-1164. Copyright (1951) American Chemical Society [Ref. 34].

The filter used active carbon, and the trapped pesticides were extracted with chloroform and analyzed with absorption chromatography and infrared spectroscopy [36]. What was unique in this study is that they examine the absorptions process's efficiency and the recovery of chlorinated pesticides and found the method satisfactory [36]. Their pesticide work on carbon filter work led to DDT detection in five large rivers at concentrations below those toxic to aquatic life. Another publication in 1973 [37] imitate the SPE approach, but several other problems encountered at the time hampered the progress of heterogenous activated carbon becoming an efficient carbon filter method [38].

Oak Ridge National Laboratory first introduced Liquid-liquid extraction (LLE) to analyze rare earth in the 1950s. Chemical potential drove the separation that leads to the transfer. As perhaps the earliest separation technique used in analytical chemistry [39,40], LLE helps extract and isolate an analyte from a complex mixture to simplify its analysis. In some instances, LLE can enhance selectivity by separating the analyte from a matrix of interfering compounds. It is also helpful for improving selectivity by concentrating the analyte from a large sample volume.

Historically, LLE and SPE have been considered the oldest and most commonly used sample preparation methods for organic analytes [32,33]. Over the years, analysts have recorded several advantages and disadvantages for these two sample preparation techniques. Table 1 summarizes the advantages and disadvantages of SPE and LLE.

4. Modern sample preparation techniques

Today, various sample preparation techniques for offline and online coupling to HPLC are coupled to a suitable detector. The most common are SPE, LLE, gel permeation chromatography (GPC), Quick Easy Cheap Effective Rugged, Safe (QuEChERS), solid-phase microextraction (SPME), ultrasonic-assisted solvent extraction (UASE), and microwave-assisted solvent extraction (MWASE) techniques. Each is briefly described below, along with its salient features and applications. Several well-documented reviews of sample preparation techniques relate to HPLC-MS [31–33,38,40–45]. Unfortunately, there is not enough time in the short review to detailed all method development and validated strategies related to sample preparation. Our goal, therefore, is to compile with few selected examples, including microextraction techniques, over the last two decades to demonstrate the analytical power of method development and validation strategies relevant to isolation, separation, identification, and determination of substances in several fields.

4.1. Solid-phase extraction (SPE)

The drive to significantly reduce solvent consumption in chemical analyses was the main driving force in searching for a simplified, automated, and miniaturized sample preparation technique. SPE is one sample preparation technique that has played a crucial role in sample pretreatment and is now available for coupling offline or online to an HPLC and a suitable detector. Its developmental progress has been remarkable. Since it was introduced back in 1951 [34], significant development has been achieved in both the adsorption process and the versatility of sorbent materials able to trap different analytes. These developments have made SPE an attractive sample preparation alternative now designed with microgram levels of sorption material that could achieve high recovery rates and enrichment with a significant reduction in the total organic solvents used. Fig. 5 is a schematic representation that documents the milestone in the development of SPE [42]. The significantly small size of sorbent materials that utilize minimal organic solvents today for SPE has improved green chemistry approaches in preparing samples for analysis.

Over the years, efforts have been made to develop and characterize new formats of advanced sorbent materials that have improved target analytes' selectivity or specificity. These materials have also been shown to have a high sorptive capacity and enhance physicochemical and mechanical stability. Sorbent materials developed over the years include cartridges [46–48], disks [49–55], pipette tips or in-syringe SPE [56–58], multi-well SPE plates [59].

To focus on the SPE technique's future, we have discussed briefly below some selective novel and advanced sorbent materials available to SPE. The applicability of SPE is primarily dependent on the trapping medium used in the extraction column. Recently, these media have aroused sample preparation researchers to develop materials with high cleanup and efficiency for dealing with trace analysis in complex matrices [42]. The few selected example materials below demonstrate the analytical power of SPE, which has promoted green chemistry incorporation.

Nanoparticles (NPs) materials have been used in several analytical chemistry fields. These materials have unique behavior, their particle size exists at the nanoscale level, and they can be easily miniaturized [60,61]. Several advantages have been noted in the literature for these particles. These include easy derivatization procedures, a high sample-to-volume ratio, easiness of surface modification, and unique thermal, electronic, and mechanical properties [60,62,63]. The important sorbent group of this category is carbon and magnetic nanoparticles and electron nanofibers (NFs).

Many materials with nanoparticle characterization have been investigated for their capability to act as sorbent materials for SPE. A few examples of these include carbon nanomaterials [64–67], graphene and graphene oxide [68–70], fullerenes [67,71], carbon nanotubes [72,73]. Other researchers have investigated sorbents for SPE that included dendrimers [71,74,75], restricted access materials (RAMs) based sorbents [76–79], aptamer-based sorbents [80–82], cyclodextrin based sorbents [83–85], and molecular imprinted polymer (MIP)-based sorbents [86–90]. The most recent SPE development is dispersive solid-phase extraction (d-SPE), introduced in 2003 [91]. Its introduction has attracted growing attention due to its remarkable simplicity, short extraction time, and low requirement for solvent expenditure, accompanied by high effectiveness and wide applicability. The d-SPE technology that requires a meager amount of sorbent and solvent has paved the way for SPE to be viewed as a more environmentally friendly method. Most of the sorbents mentioned here have already been applied to d-SPE [92]. A more extensive review of SPE sorbents, their production, advantages, and disadvantages have been discussed elsewhere [31,38,42,75].

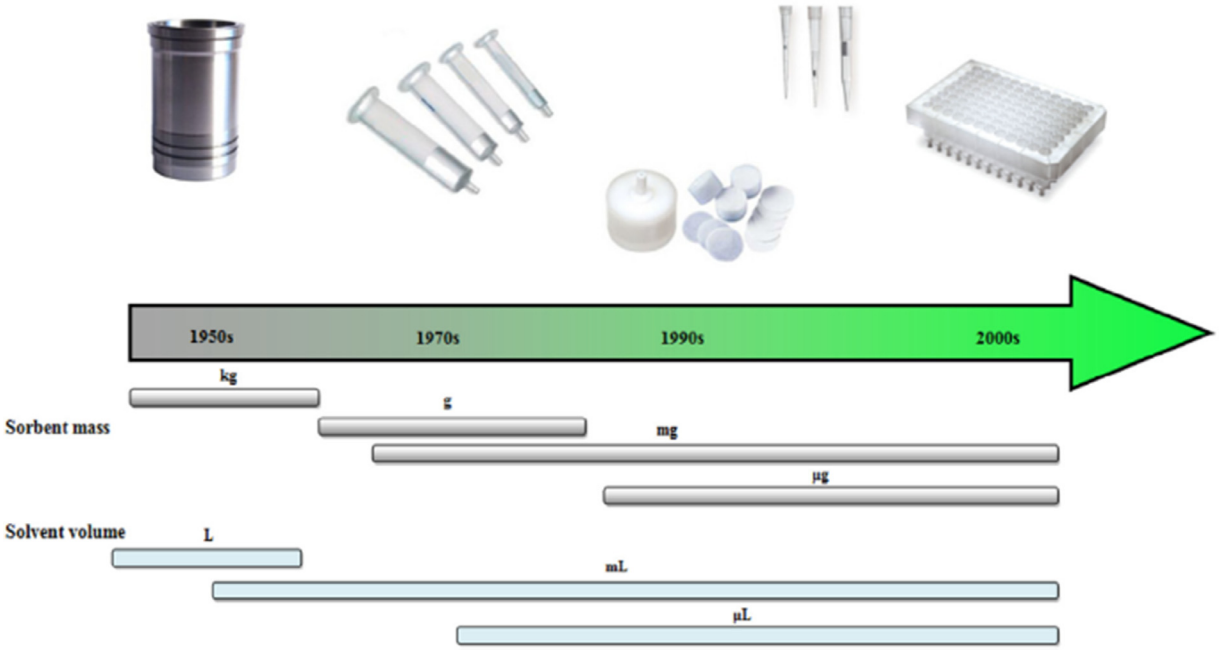

Fig. 5. SPE developmental milestone that contributed to the gree nature of sample preparation steps,. Trends Anal. Chem. 2016; 27:23–43. Copyright (2016) American Chemical Society [Ref. 42].

4.2. Liquid-liquid extraction (LLE)

LLE, as discussed earlier, has played an essential role in sample preparation development, despite several drawbacks, which include large sample volume, the formation of emulsions, manual handling, and lack of analyte-specific workflow optimizations. The theory, operation modes, and LLE advantages have been discussed elsewhere [33,40]. The pressing issue for LLE is its competitiveness with other sample preparation techniques. Thus, research has continued to look for new ways to miniaturize and automate the sample preparation technique because of its simplicity. The dispersive liquid-liquid microextraction (DLLME) technique is one miniaturization form of LLE that attracts the most attention when it was introduced in 2006 [93]. The DLLME approach is rapid, simple, inexpensive, efficient, achieves a good preconcentration factor, and requires microlitre volumes of low- and high-density solvents to extract many water-based samples. Based on this success in miniaturization, several other reviews were published [94–97]. Since the development of DLLME, there was a push by analytical chemists to automate the process. Success in automation became real when DLLME's analytical steps were integrated inside a syringe [98–100]. Today, automation has been achieved with LLE [101–103], increasing the throughput process of LLE and significantly reducing solvents' exposure without sacrificing data quality**.** Fig. 6 shows an image of the current version of a micro-LLE syringe suitable for integrating with different instrumentations.

4.3. Gel permeation chromatography (GPC)

Gel permeation chromatography (GPC), also known as size exclusion chromatography (SEC) or gel filtration chromatography (GFC), is a controlled separation technique that separates molecules based on hydrodynamic molecular size or volume [104,105]. GPC operates with a porous material as the stationary phase and a liquid as a mobile phase making it suitable for interfacing with liquid chromatography. It is a technique that can be applied offline or online with HPLC and has been widely used to separate and purify macromolecules [106,107]. The analytical chemistry community can view GPC as an adequate sample cleanup strategy in sample preparation. It has also been combined with QuEChERS [108] and d-SPE [109] to effectively remove the majority matrix co-extractives.

4.4. Quick easy cheap effective rugged, safe (QuEChERS)

Initially was introduced in 2003 [91] for monitoring multi-class pesticides from fruits and vegetables. The original method that was later validated [110] extracted a wide range of compounds from non-polar to very polar pesticides. The scientific community quickly adopted this sample preparation approach. According to the PubMed search engine, approximately 1918 articles focused on QuEChERS covering a wide range of applications when writing this review. There is enough evidence to conclude that QuEChERS is user-friendly, has high throughput, reduced sample amounts, and solvents, thus meeting green chemistry standards [111–113]. It has also been applied to HPLC in offline and online formats. As an effective sample preparation technique, QuEChERS works by dispersing salts from extracts to isolate and clean up a wide range of analytes from a complex matrix in a two-step process: (i) an extraction step operates on partitioning via salting-out extraction. Thus, an equilibrium between an aqueous and an organic acetonitrile layer is promoted, followed by (ii) a d-SPE (introduced in Section 4.1) step involves further cleanup using several combinations of porous sorbents and salts to remove matrix interfering substances [113]. In Step 2, a small amount of extract and sorbent is used to allow the reduction or elimination of additional centrifugation, filtration or precipitation steps [114,115]. Fig. 7 is an overview of the QuEChERS's essential features and their advantages over other extraction methods.

4.5. Ultrasonic-assisted solvent extraction (UASE)

Ultrasonic assisted extraction (UASE) is an innovative sample preparation approach that uses ultrasound waves to extract numerous compounds from a diversified matrix. When ultrasound waves propagate through a sample, it causes an implosion of bub-

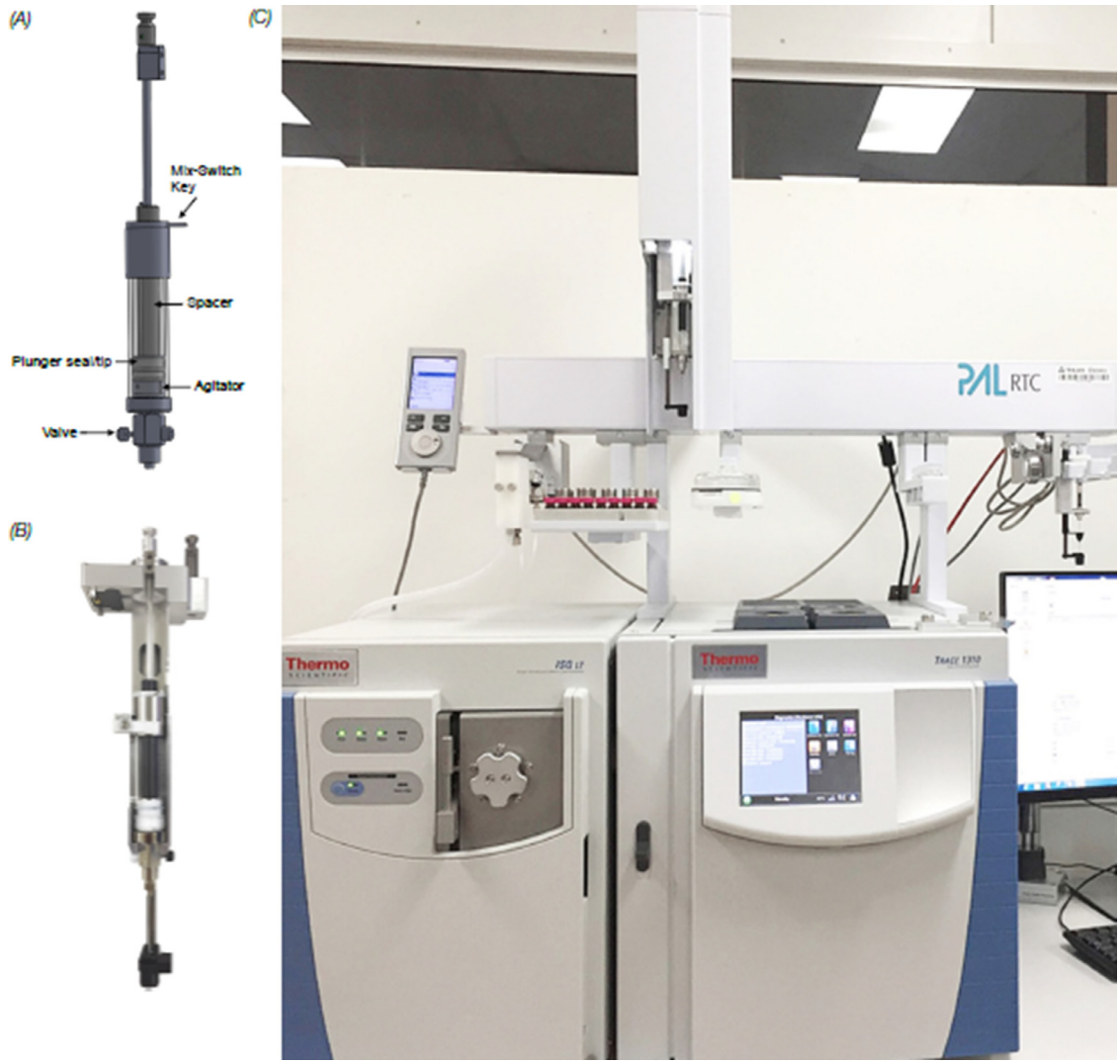

Fig. 6. Fully automated micro-LLE system. (a) the current version of a micro-LLE syringe, (B) the current version of the micro-LLE syringe on a PAL tool, and (C) the automated micro-LLE system. Copyright (2021) Trajan Scientific and Medical Technical Poster (Part #: TP-0236-G) [Ref. 103].

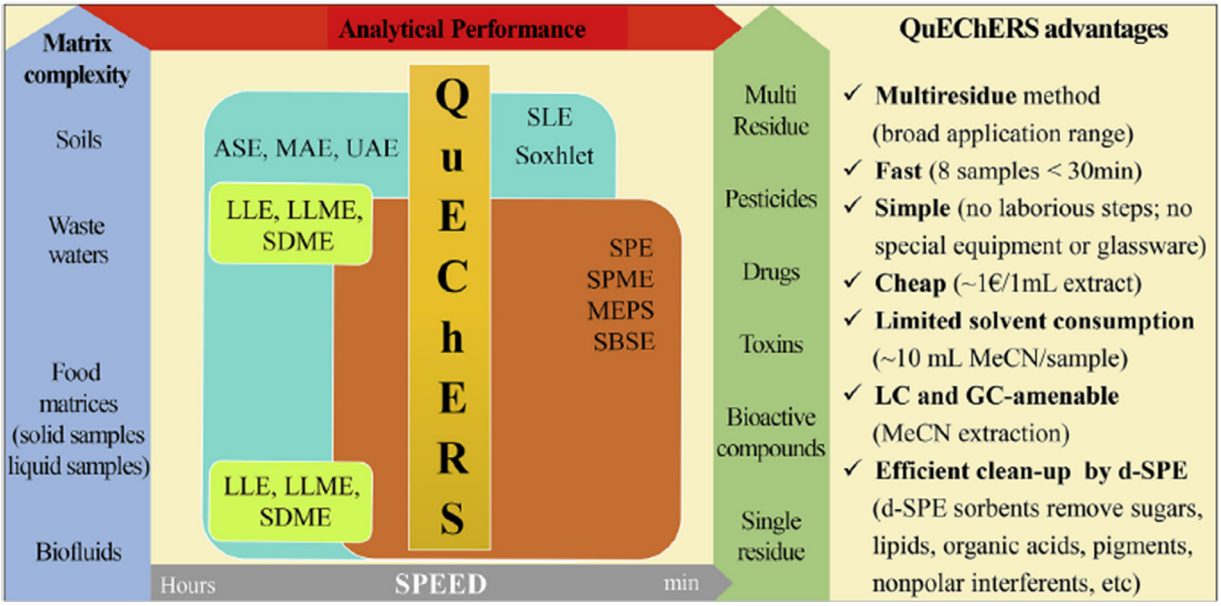

Fig. 7. Overview of QuEChERS features and advantages over other extraction methods. Anal. Chimi. Acta (2019) 1070:1-28. Copyright (2019) American Chemical Society [Ref. 113].

bles (an acoustic cavitation process). Cavitation induces macroturbulence, high-velocity interparticle collisions, and perturbation in the sample's particulate nature. As a result, a solute can quickly be converted to a solvent [116–119]. The first recorded citation of the sample preparation technique was back in 1952 [117], but it became more popular in 2006 [120]. UASE is a clean extraction technique and has offered a unique offline sample preparation option for HPLC. It has several advantages, such as its simplicity, effectiveness, and inexpensive. However, its most significant advantage is that it provides an increased extraction yield and accelerated kinetics compared to other conventional extractions [118].

4.6. Microwave-assisted solvent extraction (MWASE)

MWASE has gained significant attraction in the last 15–20 years owing to its greener and efficient extraction capacity [119]. MWASE is a conventional offline sample preparation technique that uses microwave energy non-ionizing radiation to heat a sample, thereby improving the solvent's dispersion while accelerating the compounds' partitioning from a liquid or solid sample into the solvent [121]. The use of this conventional technique was cited for the first time in 1975 [122], and the first application patent that extracted natural products with MWASE was filed in 1995 [123]. Several advantages have been documented for this sample preparation technique. These include reduced extraction time and solvent consumption, high sample throughput, and the added possibility of efficient internal diffusion extraction. With growing interests in green technology, MWASE is among the most promising sample preparation methods for extracting valuable compounds from a diversified matrix [124,125].

4.7. Microextraction based techniques

In any analytical measurement where the analyte is determined, microextraction techniques are an essential part of the determination. Thus, the choice of microextraction method can be very effective in analyte measurement. The popular microextraction techniques coupled with HPLC are liquid-phase microextraction (LPME) [126]. It has emerged as a new attractive alternative for sample preparation. LPME is a miniaturized version of the conventional LLE in which the amount of organic solvents is significantly reduced. Not surprisingly, LPME has been performed in different modes, including DLLME (discussed earlier), single-drop microextraction (SDME) [127–133], hollow-fiber liquid-phase microextraction (HF-LPME) [134–142], and solidified floating organic drop microextraction (SFODME) [143,144].

In HF–LPME, extraction, concentration, and sample cleanup are combined in a single step. A hollow fiber membrane can preserve the acceptor phase from the interference of the sample solution. Two-phase and three phases are the two main types of HF-LPME. HF-LPME is particularly applicable to the analysis of complex samples due to the porous HF as both carriers protect the acceptor phase and micro-strainer, which purify the sample. Two of its significant advantages are its tolerance to a wide pH range and compatibility with multiple instrumentations. SFODME, on the other hand, is a simple, fast, and inexpensive LPME in which a small volume of an extraction solvent with a melting point near the room temperature (10–30 °C) and a density lower than that of water is floated on the surface of an aqueous solution containing an analyte. The aqueous phase is agitated to induce convection in the organic drop. At this stage, you transfer the lipophilic analyte to the organic phase. After equilibrium is reached, the floated extractant droplet is easily collected by solidifying it at a low temperature.

An effective, efficient, and high throughput microextraction technique that has shown success with HPLC for untargeted analysis is SPME [145]. As with other microextraction techniques, several drawbacks are associated with SPME, mainly when applied to HPLC. Drawbacks reported have included fiber breakage, coating stripping, bending of the syringe needle, sample carryover, requirement to condition the SPME fiber, additional instrument modifications, to name a few [146]. These drawbacks have been overcome with the development of hollow fiber solid-phase microextraction (HF-SPME) [147–150], magnetic dispersive solid-phase microextraction (MDSPME) [151,152], in-tube solid-phase microextraction [153,154], ultrasonic-assisted magnetic solid-phase microextraction (UAMSPME) [155,156], and microwave-assisted extraction-hollow fiber-liquid/solid-phase microextraction (MAE-HF-L/SPME) [157]. Fig. 8 shows a schematic of the MAE-HF-L/SPME extraction process designed for pharmaceuticals and personal care products [157].

Ultrasound-assisted microextraction techniques have also been developed. In a method known as ultrasound-assisted emulsification microextraction (USAEME), a microvolume of water-immiscible extraction solvent is dispersed into a sample aqueous solution by ultrasound-assisted emulsification without using any dispersive solvent [158–160]. This technique usually results in a short extraction time even at room temperature. The introduction of USAEME overcome two disadvantages encountered with DLLME. The disadvantages overcome are (i) using a dispersive solvent that could decrease the partition of analytes into the extraction solvent, and (ii) using halogenated environmentally unfriendly hydrocarbons. Table 1 summarizes the advantages and disadvantages of all sample preparation techniques discussed in Section 4.

5. Selected HPLC applications

Applications developed for sample preparation techniques have been tremendous, and it would be impossible to review them all in this brief report. We have, however, categorize studies of sample preparation techniques with HPLC relevant to the isolation, separation, and determination of compounds in biomedical, forensic, and environmental/industrial hygiene analysis. Some representative examples published over the last decade are summarized below to provide the reader with an appreciation of the possible breadth of applications.

5.1. Biomedical applications

One of the primary reasons for continued research in sample preparation methods is that even with considerable analytical instrumentation development, sample preparation is still considered the analytical process's bottleneck. Because of the tedious and time-consuming pretreatment procedures required, combining SPE sorbents have proved helpful in biomedical applications. Combining RAM and MIP [161,162] SPE sorbents to get RAM-MIP was sufficient to extract 2-methoxy estradiol from rat plasma samples [163]. This study concluded that RAM-MIP was satisfactory and reproducible in the pretreatment of biological fluids. One advantage of RAM-MIP combined SPE sorbents is the possibility of cleanup and enrichment in a single step and separating both large and small molecules. MIP sorbents combined with HPLC-UV were also applied to analyze trace levels 3,4-methylenedioxymethamphetamine (MDMA) in plasma samples [164] and carvedilol in serum samples [165]. Fig. 9 shows the basic principles behind MIP operation as a sorbent [42]. One of the most promising materials emerging in biomedical applications as sorbents for SPE and HPLC is diamond-like carbon (DLC) [166–169]. DLC has superior tribological and mechanical properties with corrosion resistance, biocompatibility, and hemocompatibility. DLC materials with various atomic bond structures and compositions are used in orthopedic, cardiovascular, and dental applications [166]. While MIP as SPE sorbents has been shown to increase selectivity, when MIP is combined

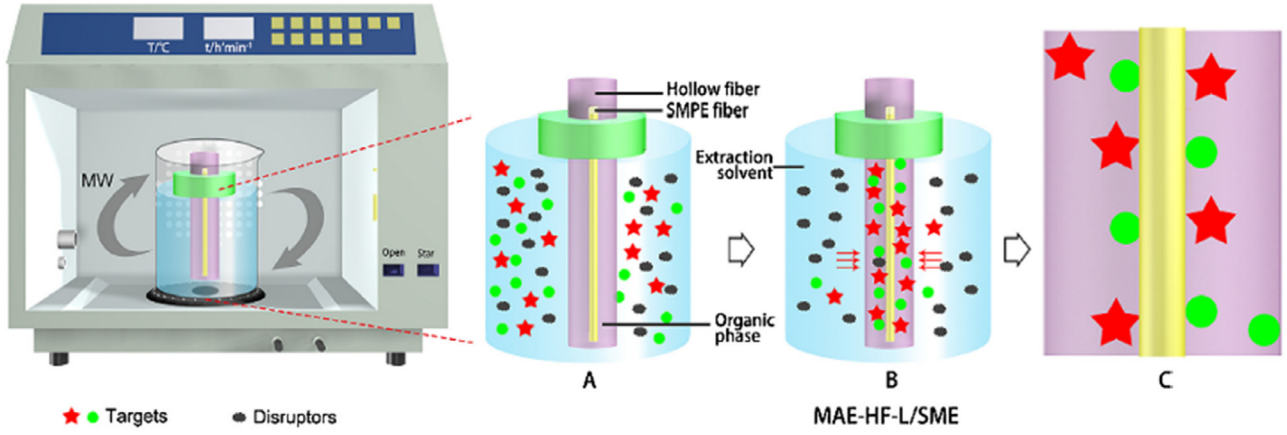

Fig. 8. (A) Schematic diagram of extraction process of 54 pharmaceuticals and personal care products, (B) targets enter the organic phase from the aqueous phase, and (C) targets adsorb to the SPME fiber from the organic phase. J. Chromatogr. B 1051 (2017) 41-53. Copyright (2021) Elsevier [Ref. 157].

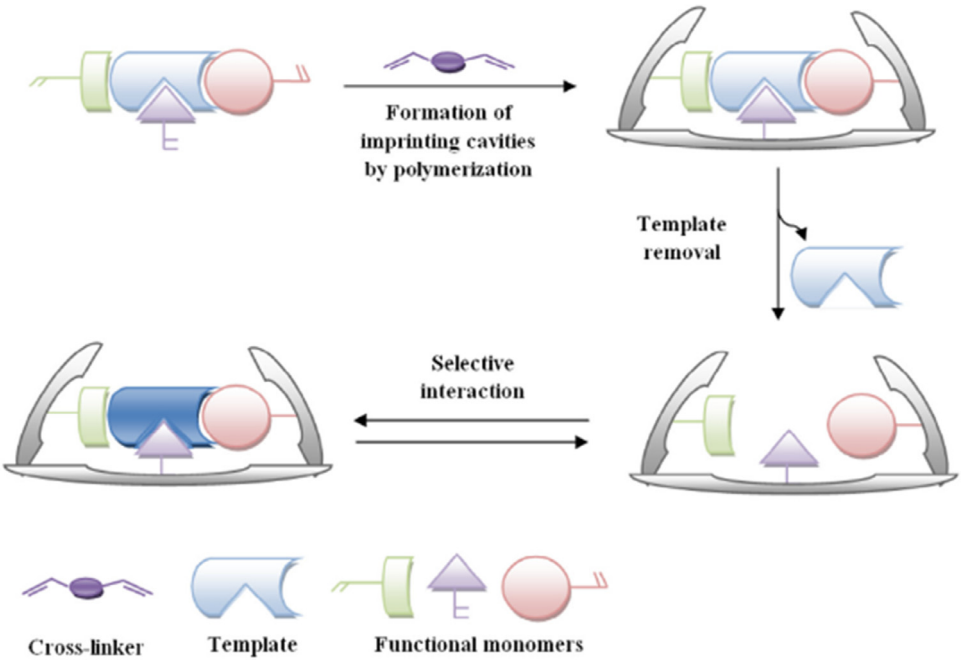

Fig. 9. Basic principles of molecular imprint sorbents. Trends Anal. Chem. 2016; 27:23–43. Copyright (2016) American Chemical Society [Ref. 42].

with magnetic nanoparticles, the resulting sorbent improves selectivity and preconcentration [170]. The resulting MMIP sorbent was applied to enrich cocaine and its metabolites in urine samples before HPLC-MS/MS analysis. The results obtained show excellent preconcentration factors, and the LOQ of the method was lower than cut-off values for cocaine in urine for confirmation analysis [170]. A scheme for the possible interaction mechanism between magnetic nanoparticles and MIP resulting in MMIP is shown in Fig. 10. Drug analysis in biological samples is a routine task in the clinical-medical and even forensic fields. SPE followed by UHPLC-MS/MS was applied to identify and quantitate forty-two drugs belonging to different chemical classes [171] and reported as the first automated online SPE coupled to any HPLC instrument. Fig. 11 shows the set-up for the first automatic online SPE UHPLC-MS/MS configuration. A later review has documented several online SPE systems coupled to HPLC [172]. Fig. 12 shows a standard online SPE-LC system for one and two-pump systems [172].

The 96-well plate SPE extraction system has become a worldwide standard work-horse platform for development and discovery studies and high throughput bioanalysis [173]. This system and other SPE cartridges followed by UPLC-MS/MS have been applied to the detection of aldosterone from human plasma [174], antibiotics in animal tissues/sewage effluent [175,176], and quantitating active metabolites of Vitamin D intending to evaluate the risks and therapies for multiple diseases [177]. Dispersive micro solid-phase extraction (d-μ-SPE) is an SPE technique that exhibits some advantages (such as convenience for efficiency and recovery, short time requirement, and reduced solvent consumption) over the traditional SPE technique. d-μ-SPE doped with magnetic nanoparticles followed with HPLC analysis was used to analyze benzodiazepines [178], bisphosphonates [179], and other acidic and basic drugs [180] in biological fluids. The need to integrate extraction, preconcentration effect and small sample size in a single step makes packed fiber SPE coupled to HPLC-ECD or HPLC-MS/MS an attractive approach for analyzing DNA and RNA in the human urine sample [181–184].

This review will focus on selected biological applications for DLLME. Analysis of biological matrices has become a severe challenge to analytical chemists mainly because of low target an-

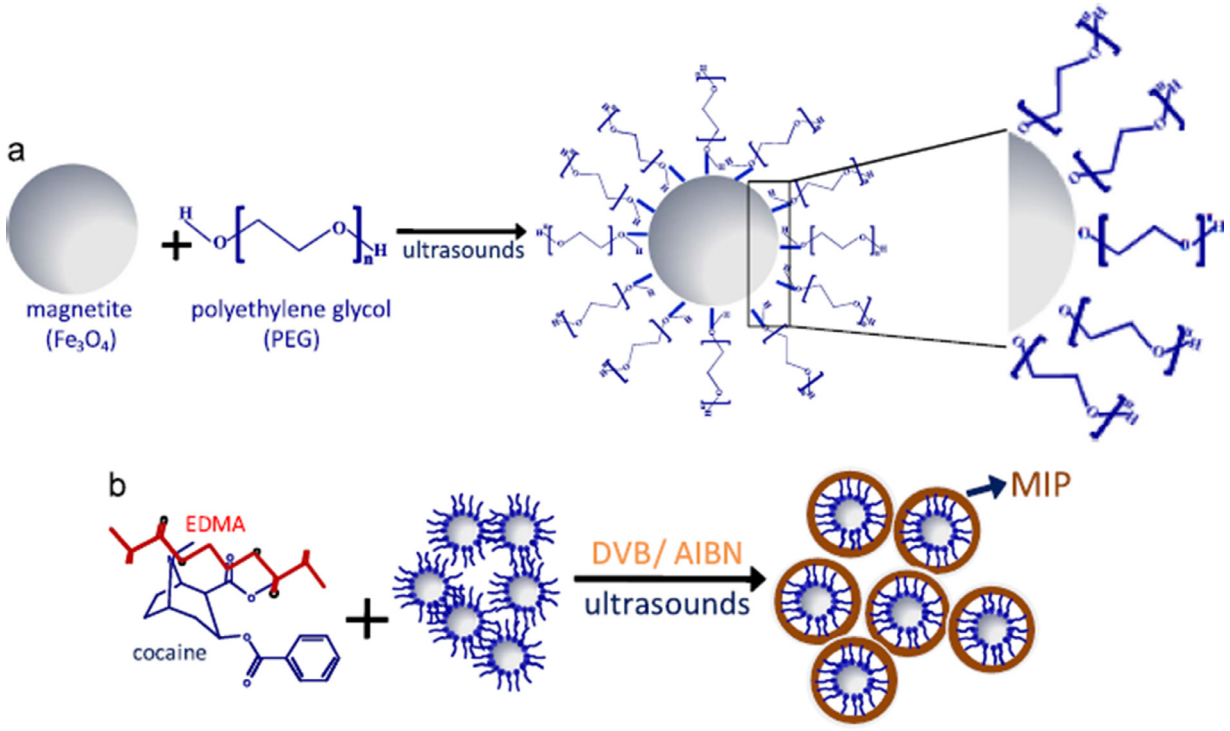

Fig. 10. Schematic representation of binding mechanism between magnetite nanoparticles and PEG (a) and MMIP preparation (b). Talanta (2016) 147:641-649. Copyright (2016) American Chemical Society [Ref. 170].

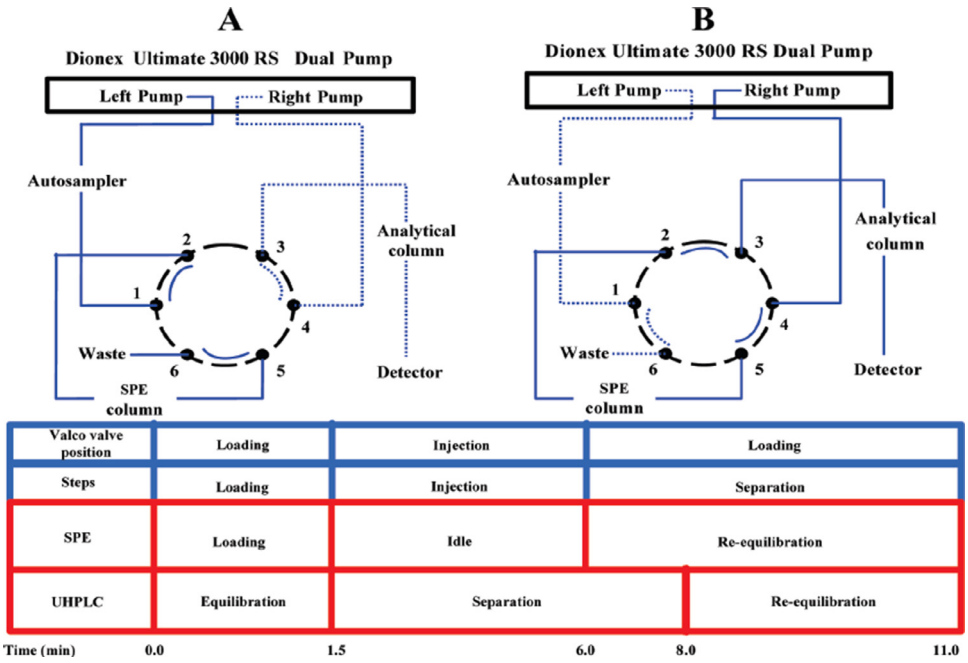

Fig. 11. The instrumental configuration of online SPE using a Valco valve position, where A is loading and B is injection. The system set up for online SPE consists of three steps: loading, injection, and separation. Anal. Chem. (2010) 82:5636–5645. Copyright (2010) American Chemical Society [Ref. 171].

alytes concentrations. Since DLLME was developed [93], different matrices have been successfully analyzed and shown to be economical and environmentally friendly sample preparation techniques. DLLME has been combined with HPLC-UV or HPLC-MS/MS for analysis of malathion or chlorpyrifos in urine samples [185,186], antiretroviral drugs in biological samples [187], monitoring of Felodipine, Ramipril, and Metoprolol (hypertension treatment drugs) in plasma samples [188], determination of estrogen in human urine [189], and determination of emodin and its metabolites, tetrahydropalmatine, and tetrahydroberberine in urine samples [190,191].

Recently, most biomedical applications are based on gel electrophoresis (GE) combined with HPLC. GPC is not as sensitive as GE for the detection of molecular size heterogeneity. GPC requires a larger sample quantity than GE experiments. Since sample preparation has moved towards reduced sample size, it is not surprising

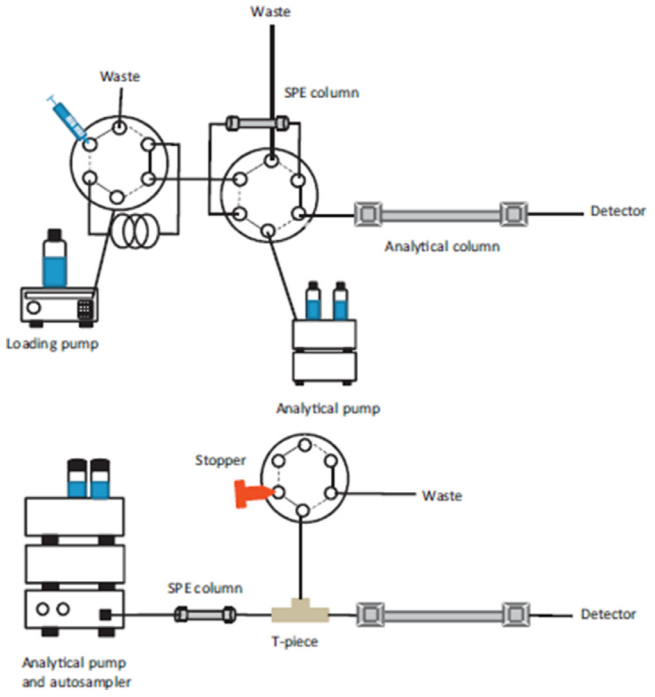

Fig. 12. Common online SPE-LC systems. Top: two-pump system. Bottom: one-pump system. J. Pharm. Biomed. Anal. (2014) 87:120– 129. Copyright (2010) Elsevier Ref. [172].

that most analytical chemists are choosing GE over GPC in biomedical applications. In recent years, proteomics techniques have advanced tremendously in life and medical sciences to detect and identify proteins in body fluids, tissue homogenates, and cellular samples to understand biochemical mechanisms leading to different diseases. HPLC combined with laser-induced fluorescence was developed for profiling proteins in body fluids to discriminate normal and malignant samples responsible for cancer [192,193]. Proteomic research involving microvesicles has been documented to improve biological understanding in basic research and translational biomarker discovery. GE combined with HPLC-MS/MS was used to profile proteins in saliva microvesicles. The pilot study was documented as a non-invasive valuable tool for the early detection of different diseases [194]. In another study, GPC-HPLC and high-temperature sodium dodecyl sulfate-polyacrylamide GE have been recommended as part of a toolkit for early drug development to maintain drug stability [195]. Offline-gel electrophoresis has been combined with LC-selected reaction monitoring-MS to enhance data quality and sensitivity when monitoring animal tissues' peptides [196]. Other studies have used GPC-HPLC to profile lipoproteins in beagle dogs [197] and SEC-RP 2D-LC to directly analyze free drug and related small molecule impurities in antibody-drug conjugates without any sample preparation required [198]. This study helped gain insights into antibody-drug conjugates degradation mechanisms.

QuEChERS was mainly developed for multi-residue pesticide analysis but was also introduced to various analytes and matrices, including biological fluids. QuEChERS extraction and cleanup combined with LC-MS/MS or UPLC-MS/MS have been developed for detecting lipids in human blood plasma and urine sample [199], investigate the presence of mycotoxins and their metabolites in human breast milk [200,201], and determination of steroids adulterated in liquid herbal medicines [202].

UASE and MWASE gained increasing interest over the last few decades [203]. As discussed earlier, these are green and fast extraction techniques growing globally for analyzing medicinal plants [204]. Different extraction techniques that included UASE and MWASE when combined with HPLC were used to determine bioactive diterpenoids in different extracts of Andrographis paniculata (an erect herb in India with a history of treating hepatitis and acute infections of the gastrointestinal tract, respiratory organs, and urinary systems) [204]. In other studies, UASE and other extraction methods with the intent to cover a vast polarity range were combined with UPLC-HRMS to profile the complete chemical component and biological activity of Sideritis sipylea Boiss [205]. It was reported that Sideritis sipylea is an endemic plant of the Mediterranean basin distributed in the Greek islands of the North Aegean Sea. It is considered an endangered species because of its uncontrolled collection from its original habitat. Sideritis sipylea has over 320 subspecies and has been demonstrated to have anti-inflammatory, antimicrobial, antifeedant, antihyperglycemic, anti ulcerative, gastroprotective, spasmolytic, and bone-remodeling properties [206,207]. The chromatogram of three extracts from Sideritis sipylea studied in negative mode ESI UPLC-HRMS shows the detection of hydroxycinnamic acid derivatives, phenylethanoid glycosides, flavonoids flavonoid-7-O-di glycosides, and flavonoid acetyl glycosides [205].

As one of the relatively new extraction techniques with unique advantages over conventional extractions, MWASE plays a significant role in biomedical applications. It has been combined with HPLC-MS/MS or UHPLC-q-TOF-MS for therapeutic drug monitoring of fluoroquinolones for tuberculosis patients [208] and for detecting polyphenolic compounds in hawthorn leaves [209]. A series of publications of biomedical significance have compared advanced extraction techniques coupled to HPLC-MS/MS. UASE and MWASE were among the successful extraction techniques from an economic perspective, being inexpensive, efficient, and straightforward for profiling bioactive compounds in different matrices [210,211]. Analysis of iridoid glycosides and oligosaccharides has posed challenges for analytical chemists. The challenges are the hydrophilic nature of these compounds, similar chemical structures, and the absence of chromophore and fluorophore groups. The fourth challenge of polarity difference is presented when these compounds are present in Radix Rehmanniae as ingredients. MWASE combined with HILIC-UHPLC-TQ-MS/MS has been developed to simultaneously analyze iridoid glycosides and oligosaccharides in Radix Rehmanniae [212]. The method was reported to exhibit excellent performance with simple sample preparation, short analysis time, high selectivity, and sensitivity.

5.2. Forensic applications

Applying the full range of science to questions of interest in a legal system concerning either criminal or civil action is what the analytical chemist will refer to as forensic chemistry. One area in which sample preparation techniques continue to improve is the detection of illicit and therapeutic drugs. The number of illegal drugs consumed is steadily increasing, especially with the recent emergence of opioids, and drug lists must be continuously updated. The widespread increase in unlawful and therapeutic drugs is evidenced by the rise in more recent analysis screening methods. Most importantly, analytical processes need to be constantly updated to keep up with the constant emergence of new uncontrolled analogs. Recent developments in sample preparation techniques have had a direct influence in achieving better results in forensic applications.

When a drug comes in contact with fluids in the human body, it can quickly be metabolized to water-soluble compounds and eliminated through urination or sweat. Factors that influence how quickly the drug is metabolized include the type of drug, dose, matrix, and individual metabolism. The drug can still be detected in its original form or its metabolites in plasma, sweat, urine, and

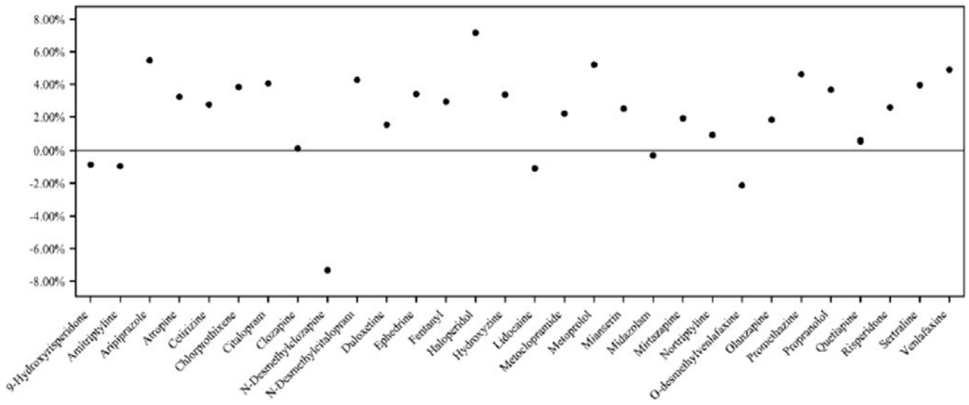

Fig. 13. Difference between the slopes derived from calibration curves in brain and blood for 30 analytes. The difference is calculated as $(slope_{brain} - slope_{blood})/slope_{blood}$. Drug Test Anal. (2018) 10:1147-1157. Copyright (2018) John Wiley & Sons, Ltd [Ref. 218].

hair [171]. Sample preparation techniques have played a vital role in drug detection and forensic applications. The PubMed search engine returned 163 publications with SPE combined with HPLC analyses for forensic samples over the last decade. Our review has focused on selected SPE publications from this list. A mixed-mode cation exchange SPE cartridge combined with UPLC-MS/MS method was reported as a sensitive method for analyzing fentanyl and nor-fentanyl in biological samples [213]. Asthma and preterm labor drugs such as Clenbuterol, salbutamol, and ractopamine are misused β_2-agonists. Misuse of these drugs has resulted in some accidental poisoning in humans, making them necessary for these drugs to be detected in body fluids. SPE without the complex deproteinization step combined with UHPLC-MS/MS and isotopic dilution was developed as a simple and sensitive method for detecting these drugs in milk [214]. In recent years, hair has become the third most crucial biological matrix used for drug testing (after blood and urine). SPE followed by hydrophilic interaction liquid chromatography-tandem mass spectrometry (HILIC-MS/MS) or MMIP combined with UHPLC-MS/MS has been developed to analyze cocaine and its metabolites in hair and urine samples [215,170]. SPE-UHPLC-MS/MS has also been developed for quantifying fentanyl and twenty-two of its analogs in whole blood, urine, or hair samples [216,217]. In 2010, the first automated online SPE for HPLC was introduced [171]. Several other articles were published to validate this approach [172].

In forensic toxicology work, whole blood concentration is the primary post-mortem specimen used to provide drug concentrations for comparison to literature values. There is usually a problem in some traumatic injuries where no blood is available. Thus, other post-mortem specimens, such as tissues, must provide the same result as whole blood to help interpret the cause of death. A fully automated SPE followed by UHPLC-MS/MS method has been developed to quantify frequently encountered pharmaceuticals and metabolites in post-mortem blood and brain tissue [218]. The authors further report that when the internal-standard approach is incorporated, the total number of samples required per analysis is lowered without compromising the quality of the analytical results and reducing forensic laboratories' workload. Fig. 13 shows the relative difference between the slopes in the brain and blood for each analyte. The majority of the analytes showed a slightly steeper curve in brain homogenate than in blood, while 7 of the 30 analytes had a flatter curve [218]. Among new psychoactive substances that have been routinely detected in forensic casework are synthetic cannabinoids. However, the analysis of cannabinoid metabolites in urine samples necessitates a sensitive, selective, and specific analytical approach. Automated SPE by LC-ESI-MS/MS, including stability testing, was developed to analyze 61 phases one urinary synthetic cannabinoid metabolites [219–221]. Besides the differentiation between the intake of a synthetic cannabinoid, the validation results show the study was specific and selective with good recovery and sensitivity [219].

Other studies have used MIP-μ-SPE followed by HPLC-MS/MS for cannabinoids analysis in plasma and urine samples [222]. Fig. 14 represents the synthesis of the MIP material and the MIP-μ-SPE procedure [222]. Amphetamine is another illegal drug classified as a central nervous system stimulant [223], and its growing consumption is of concern worldwide [224]. Amphetamine is also a doping substance and an abused drug in sports, making its detection a vital test in most clinical and criminal laboratories. A novel polymeric magnetic nanoparticle (PMNP) SPE sorbent that combines magnetic cores and polymeric shells was synthesized specifically to extract amphetamine from urine samples [225]. The technology was interfaced with HPLC-UV for the selective detection of amphetamine in biological urine samples. Fig. 15 demonstrates the synthesis scheme for the novel PMNP. Fig. 16 (a–d) shows the FT–IR spectra, X-ray diffraction pattern, vibrating sample magnetometry, size, zeta potential, and SEM images for the synthesized PMNP material [225]. Other magnetic SPE adsorbents, namely magnetic graphene oxide nanoparticles, combined with HPLC, have been developed as a new sample pretreatment technique for extracting amphetamine and methadone from urine samples [226]. SPE was also combined with UHPLC-MS/MS to extract and detect α-solanine and α-chaconine in post-mortem blood samples [227].

Another SPE sorbent that has been synthesized for extracting psychoactive drugs from urine samples is magnetic graphene oxide (GO) [228]. The developed sorbent exhibited excellent extraction efficiency through π- π interactions for urine samples. GO-Fe_3O_4 was coupled with UHPLC-MS/MS for a sensitive, rapid, and simple method for determining psychoactive drugs [228]. Fig. 17 represents the schematic synthetic steps for GO-Fe_3O_4. An ionic liquid carbon-coated magnetic nanoparticles were recently used as an adsorbent in a mixed hemimicelle magnetic dispersive SPE method. The extraction was followed with HPLC-UV-vis to determine tramadol in biological urine samples [229]. Tramadol is an opioid pain medication used to treat mild pain and could be abused due to its euphoric effect on the central nervous system [230]. While SPE combined with HPLC has successfully detected drugs in biological matrices, other types of forensic samples have also been analyzed with this approach. A dual-sorbent SPE followed with LC-HRMS was used to extract selectively and detect multiple classes of explosives in wastewater. The developed method was also capable of the enhanced removal of matrix interferences from various sample types [231].

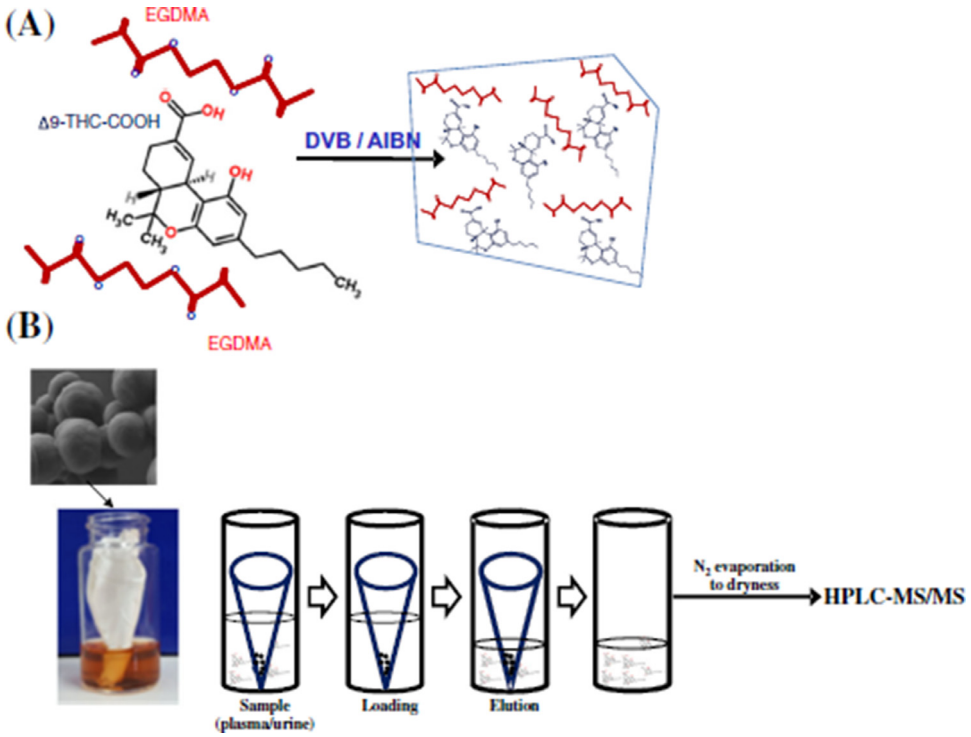

Fig. 14. Schematic representation of MIP synthesis (A) and MIP-μ-SPE procedure (B). Anal. Bioanal. Chem. (2017) 409:1207-1220. Copyright (2017) Springer [Ref. 222].

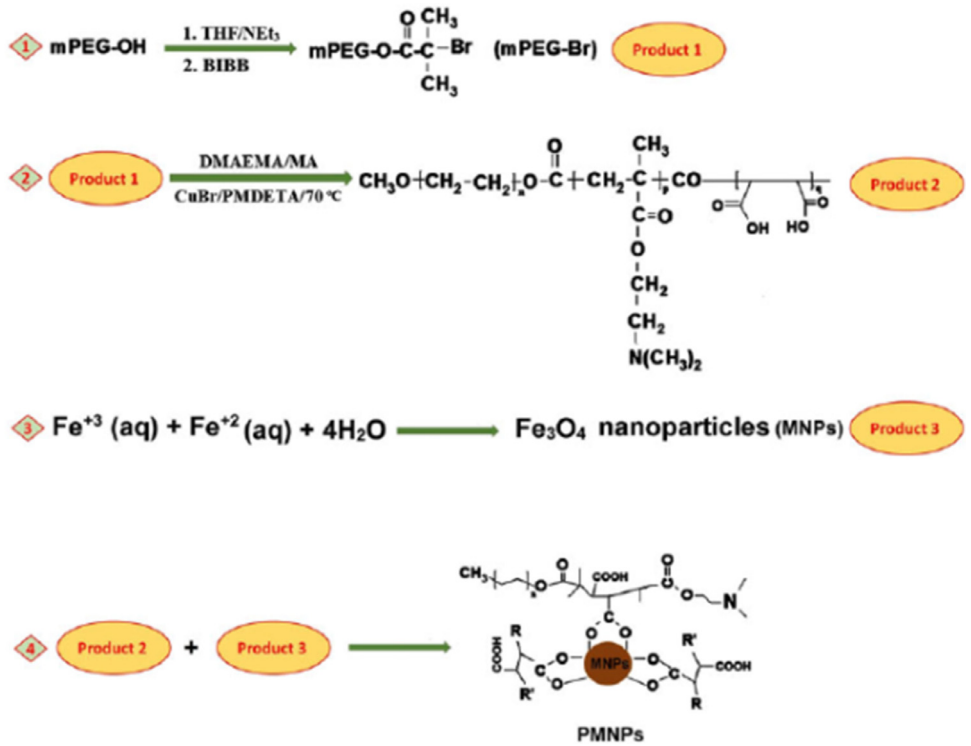

Fig. 15. The sequence synthesis steps of PMNPs. Drug Test. Anal. (2018) 10:832-838. Copyright (2018) John Wiley & Sons, Ltd [Ref. 225].

As mentioned earlier, DLLME, combined with other microextraction techniques, development of alternative solvents, and automation, is the new trend in LLE [232]. Diazinon has been reported as one of the most common causes of occupational, clinical, and forensic organophosphate poisoning globally [233]. Current methods for the detection of diazinon are time-consuming and too expensive for routine analysis. Recently, a DLLME-HPLC-DAD method shown to be accurate and sensitive for forensic toxicology application has been used to determine diazinon in human urine samples [234]. Analysis of abused drugs in biological samples is mainly hampered by the complexity of the matrices, low compound concentrations, and the small sample size available for analysis. DLLME was designed as a green sample preparation technique that is environmentally friendly. When combined with HPLC and

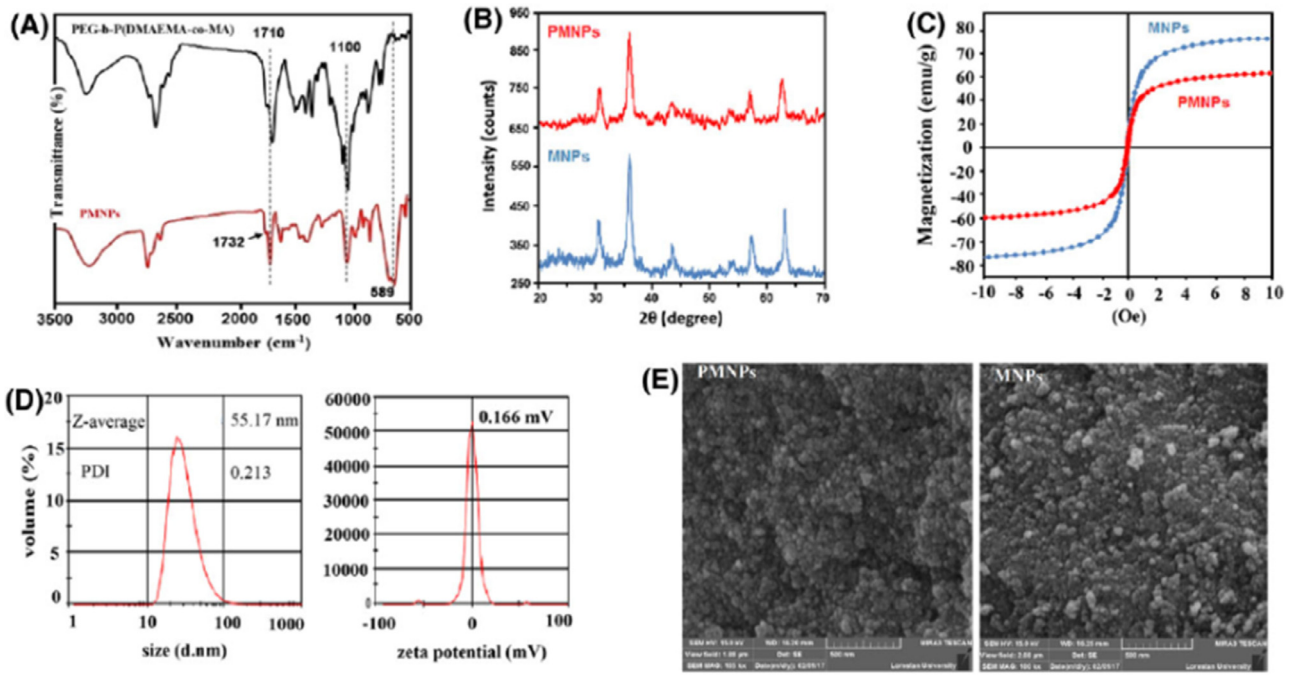

Fig. 16. (a). Fourier transform infrared spectroscopy spectrums of PEG-b-P(DMAEMA-co-MA) block copolymer and poly magnetic nanoparticles (PMNPs), (b). X-ray diffraction pattern of PMNPs and MNPS, (c). vibrating sample magnetometry of PMNPs and MNPs, (d). size and zeta potential of PMNPs, and (e). SEM images of MNPS and MNPs. Drug Test. Anal. (2018) 10:832-838. Copyright (2018) John Wiley & Sons, Ltd [Ref. 225].

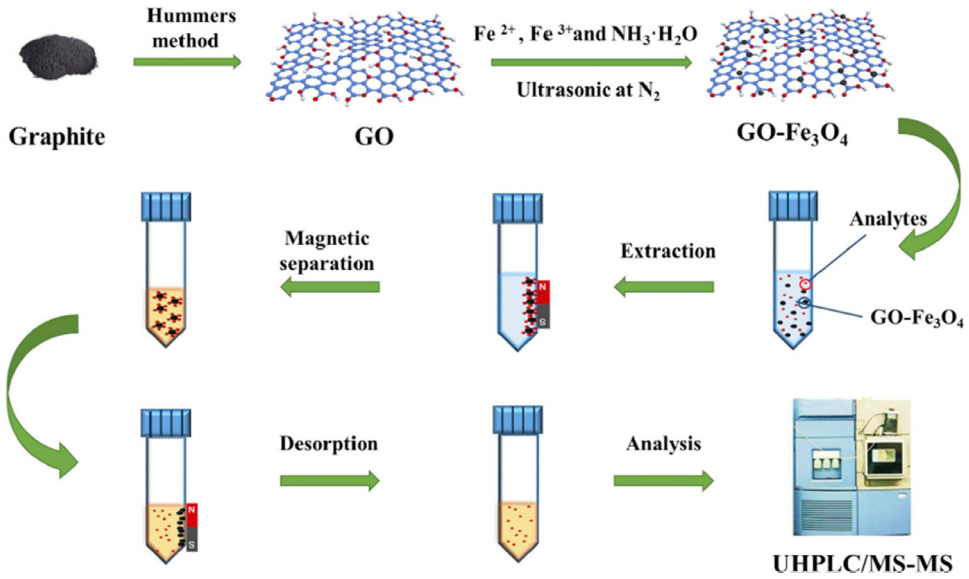

Fig. 17. Schematic illustration of the GO-Fe_3O_4 and MSPE procedure synthesis to analyze the eight psychoactive drugs. Talanta (2020) 206:120212. Copyright (2020) Elsevier [Ref. 228].

a suitable detector, it has been prosperous for analysis of cocaine adulterants in human urine [235], drugs of abuse in human plasma [236,237], hair [238], urine [239], oral fluids, or blood [240,241], and tricyclic antidepressants in urine samples [242]. A well-known poison that has affected animals and humans is anticoagulant rodenticide. Reported human poisoning and suicide cases involving anticoagulant rodenticide have occurred in several incidents. Thus, a sensitive and rapid analytical method to determine anticoagulant rodenticide in animal or human organs is necessary. Among methods that have been developed, LLE pretreatment followed by UHPLC-MS/MS was used to quantitate six anticoagulant rodenticides in dog feces [243].

An ultrasound-assisted low-density solvent DLLME combined with UHPLC-MS/MS was recently developed to determine nine anticoagulant rodenticides in urine samples [244]. DLLME extractions followed by UHPLC-MS/MS have also been used to determine abused drugs in human hair [245] and new psychoactive substances in whole blood [246]. Suvorexant is a novel sedative/hypnotic drug approved for the treatment of insomnia. It has significant forensic importance and potential for abuse due to its hypnotic and depressant effects on the central nervous system. DLLME followed by ultrasound-assisted back extraction, and UHPLC-MS/MS assay was developed and validated to determine suvorexant in urine samples [247]. LLE for forensic applications

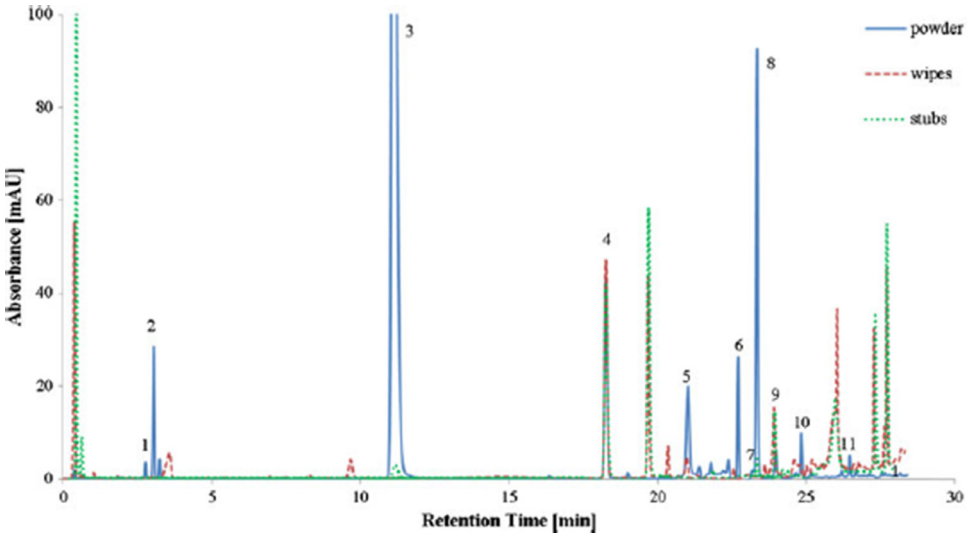

Fig. 18. Overlayed example chromatograms of smokeless powder before shooting (40 S&W, Winchester, Australia; blue line) and the gunshot residues collected from the hands of a shooter after discharge using a 22 Glock pistol collected using wipes (red dashed line) and GSR stubs (green dotted line). 1 = 1,2-dinitroglycerine; 2 = 1,3-dinitroglycerine; 3 = nitroglycerine; 4 = 2-naphthol (IS); 5 = diethyl phthalate; 6 = methyl centralite; 7 = N-nitroso diphenylamine; 8 = diphenylamine; 9 = 2-nitroso diphenylamine; 10 = ethyl centralite; 11 = dibutyl phthalate. Anal. Bioanal. Chem. (2016) 408:2567-2576. Copyright (2016) Springer [Ref. 248] (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

demonstrated flexibility such that it has been applied to the analysis of gunshot residues. LLE was applied to two lifting protocols, namely swabbing and tape lifting, from hands followed by UHPLC-UV-vis and UHPLC-MS/MS to detect explosives from gunshot residue. Fig. 18 are overlayed example chromatograms of smokeless powder before shooting, and the gunshot residues collected from the hands of a shooter after discharge using a 22 Glock pistol collected using wipes [248].

Regarding drug analysis with chromatography techniques, QuEChERS has been good at reducing matrix effect and ion suppression. There have been some critical forensic application papers for QuEChERS combined with HPLC in the last decade. QuEChERS combined with d-SPE and followed by HPLC-MS/MS has been used to extract benzodiazepines in biological fluids [249], disulfoton, and five metabolites in whole human blood [250], and the simultaneous identification of psychoactive drugs and metabolites in headache patients [251]. The liver is a body tissue that is preferred for analysis whenever blood is unavailable. However, the liver may contain lipids that can contribute to the matrix effect and be problematic for HPLC instrumentation [252]. QuEChERS is ideal for this problem, and because it combines the advantages of LLE and SPE, it is suitable for tissue analysis. A QuEChERS method was developed at the microscale level combined with UHPLC-MS/MS to determine different human liver drugs [253]. Other work has modified QuEChERS and d-SPE into a rapid and convenient one-pot caking extraction method to analyze various types of drugs and metabolites in a small amount of whole blood specimen. The modification allows for easier layer separation, emulsion formation avoidance, and user-friendly quick sample processing [254].

When combined with LC-MS, it allows for simultaneous extraction and detection of drugs and metabolites of forensic interests in whole blood specimens [254]. Modified QuEChERS and LC-MS have also been used as an analytical approach to investigate fatal poisoning cases in which several new designer cathinone were considered the cause of death [255] or identification and quantitation of predominant metabolites of AB-CHMINACA in an authentic human urine specimen obtained from an abuser [256]. The drug strychnine is an alkaloid with fatal poisoning properties. Poisoning from strychnine results in muscular contractions and death through asphyxiation. Intentional or accidental poisonings with strychnine occur mainly in small animals, especially dogs and occasionally cats. The detection of strychnine is primarily through the liver or stomach contents. However, due to significant matrix effects, especially for dead animals, these detections can be problematic. The use of the second-generation fragment as an analyte signal can eliminate this problem. QuEChERS combined with HPLC-MS^3 has been developed to determine strychnine in dead animals' livers [257.258]. The developed method resulted in improved repeatability, reproducibility, and signal-to-noise ratio.

Very few publications have developed UASE for forensic applications. However, ultrasonic-assisted-DLLME (UA-DLLE) combined with UHPLC-MS/MS has been developed and validated as an approach to eliminate false positives for determining drugs in oral fluids [259] or suvorexant in urine [247]. Recent reviews have documented HPLC, UPLC, and UHPLC hyphenated techniques to analyze cannabinoids [260] or COVID-19 antiviral drugs in biological fluids and tissues [261].

5.3. Environmental/industrial hygiene applications

One area where the sample preparation techniques discussed in this review have been extensively investigated is environmental samples. Environmental waters (mainly wastewaters and surface waters) have become one of the main routes through which pollutants are introduced into the environment. Given that these compounds pose a threat to the environment even at low concentrations, the development of sensitive analytical methods to analyze concentrations in the different environmental compartments is essential. The detection of phthalate esters [262], nitrosamines [263], chlorophenols [264,265], estrogen mimics [266], and drugs of abuse [267] in wastewaters and surface waters has been investigated with SPE-LC-MS/MS. Researchers have shown that combining two or more SPE sorbents is a promising approach to retaining pollutants of different polarities in environmental water samples [268–270]. Antibiotics and their quinoline derivatives can be detected in wastewater using SPE-UPLC-MS/MS or SPE-DLLME-UHPLC-MS/MS. These hyphenated techniques offer a simple, rapid, sensitive, and reliable multi-residue method [271–273]. Examples

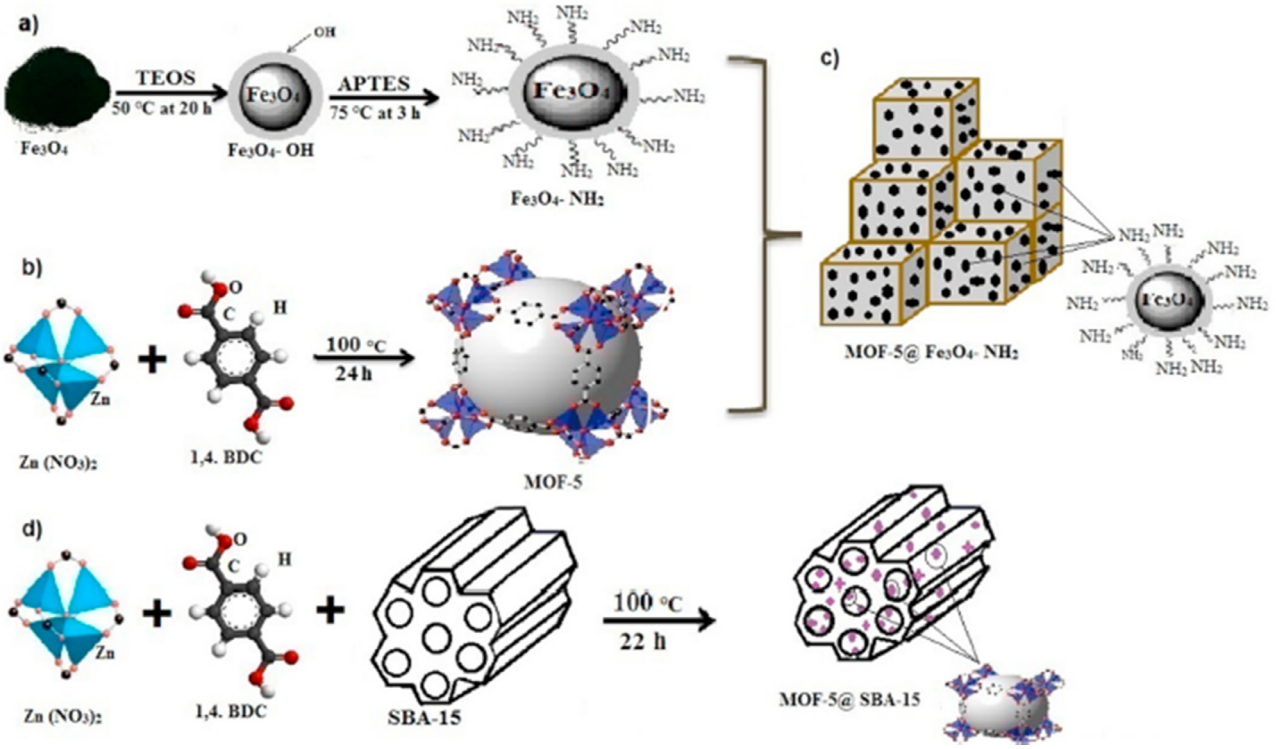

Fig. 19. Schematic illustration of a) Fe_3O_4-NH_2, b) MOF-5, c) MOF-5@ Fe_3O_4-NH_2, and d) MOF-5@ SBA-15 synthesis processes. J. Chromatogr. B (2019) 1114-1115:45-54. Copyright (2019) Elsevier [Ref. 289].

of SPE applications with HPLC-MS/MS are extensive, and these methods are helpful for the analysis of a vast array of pollutants. For example, the study of non-steroidal anti-inflammatory drugs in water samples can be conducted with a facile d-μ-SPE combined with HPLC [274]. The analysis of sub-ng/L levels of estrogens, androgens, endocrine-disrupting compounds, veterinary antibiotics, and benzotriazole UV stabilizers in surface water and wastewater can also be accomplished with fully automated online SPE and HPLC-MS/MS or SPE-UHPLC-MS/MS [275–279]. Among important hazardous pollutants is mercury. Mercury can accumulate in human body tissue and cause substantial neurotoxicity. The best way to analyze environmental mercury is through hyphenated techniques. Dithizone-functionalized SPE or magnetic SPE based on sulfur-containing functional magnetic polymer has been hyphenated with HPLC-ICP-MS for analyzing speciated mercury on water samples [280,281]. Both approaches demonstrated a great potential for real-world sample analysis of speciated mercury in complex matrices. Other uniques SPE approaches combined with HPLC-MS/MS have been developed for environmental research. They include a fluoro-functionalized paper-based SPE to analyze perfluorinated compounds [282] and an SPE disk extraction combined with UHPLC-TOFMS to analyze psychopharmaceuticals in industrial wastewater and groundwater with suspended organic particulate matter [283]. Other novel SPE applications combined with HPLC have determined X-ray contrast media in environmental water samples [284], analyze sulfonamides in water samples [285], cyanotoxins in reservoirs [286], and monitor fluoroquinolones in water and food samples [287].

Protecting people in the workplace from exposure to pollutants (VOCs, particulate matter, etc.) [288] has been a primary goal for industrial hygienists. One problematic biomarker of environmental and occupational exposure to styrene is mandelic acid. Mandelic acid is generated in the metabolic pathway after exposure to styrene and ultimately excreted from the body through urination. Styrene exposure usually occurs in manufacturing unit workplaces. Detection of mandelic acid in urine samples of patients exposed to styrene has been successful when microextraction by packed sorbents (MEPS) is combined with other SPE sorbents. A two-hybrid metal-organic framework including MOF-5@ Fe_3O_4-NH_2 and MOF-5@ SBA-15 [289] and MIP [290] were combined with MEPS followed with HPLC to detect mandelic acid in urine samples. The resulting hyphenated interfaces of MOF-MEPS-HPLC-UV-vis [289] and MIPMEPS-HPLC-UV-vis [290] result in a sensitive, reusable, fast, inexpensive, user-friendly environment-friendly technique for the extraction and analysis of mandelic acid from liquid biological samples. Fig. 19 illustrates the hybrid metal-organic framework's synthesis pathway, and Fig. 20 is the MEPS procedure scheme [289]. Pharmaceuticals, recently recognized as emerging pollutants of concern and designed to have biologic activity and, once in the environment, can provoke undesired effects in non-target organisms and become contaminants potentially hazardous, persistent, and ubiquitous, are also suitable for detection with SPE-HPLC-MS/MS [291].

Most DLLME-HPLC applications developed for environmental analysis have mainly focused on water samples. Improved DLLME techniques have been developed for the detection of fullerene C_{60} nanoparticles [292], the determination of diphenyl ether herbicides [293], the determination of copper [294], a salting-out LLE approach for monitoring cytotoxins in water [295], and detection of triazines in wastewater [296]. Endocrine-disrupting chemicals have emerged as a public health threat due to their potency to interfere with several aspects of the endocrine system [297]. A challenging task for analytical chemists has been detecting these compounds. However, ultrasound-assisted in-situ derivatization DLLME coupled with UHPLC-MS/MS has provided a suitable simultaneous determination of multiple endocrine-disrupting compounds in real samples. The developed method demonstrated high sensitivity, speed, and good sample cleanup ability [297].

QUEChERS combine with d-SPE has been highly successful for analyzing food samples [298-–308], including pollutants contam-

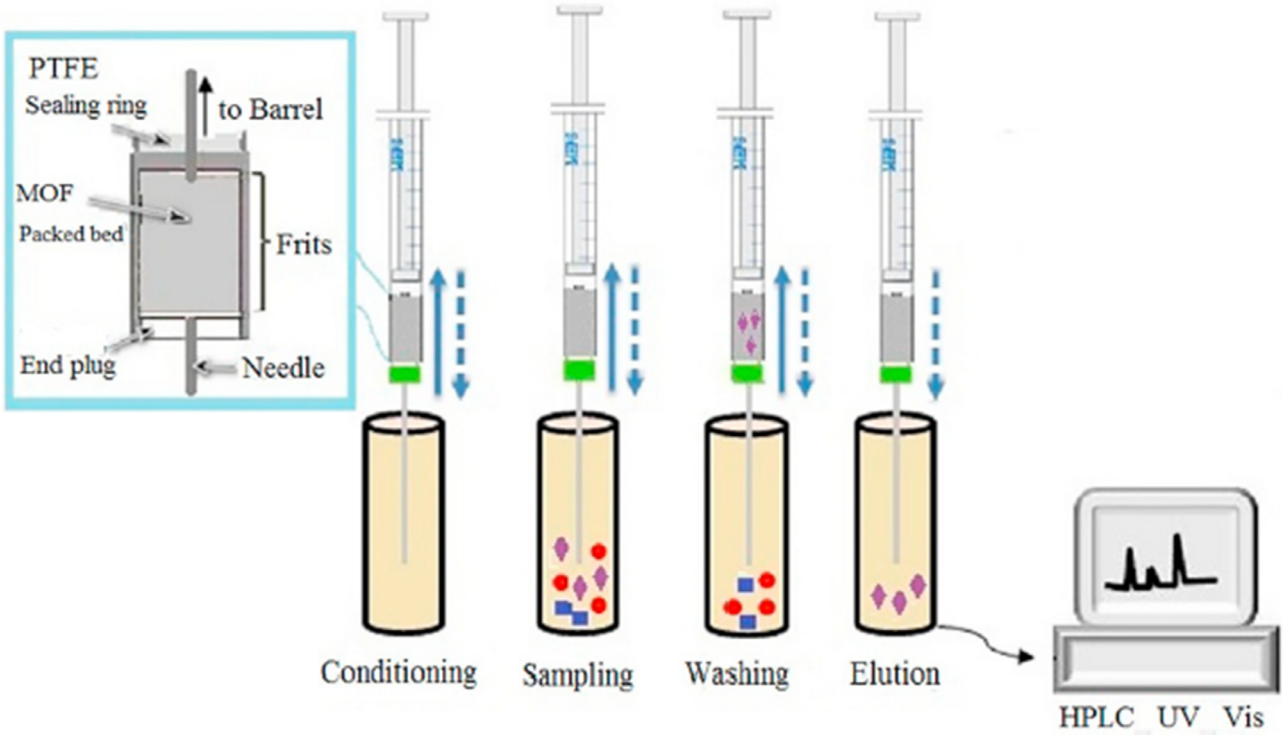

Fig. 20. Scheme of MEPS procedure. J. Chromatogr. B (2019) 1114-1115:45-54. Copyright (2019) Elsevier [Ref. 289].

Table 2
Example recent applications of sample preparation techniques coupled with HPLC (2019-2021).

SP Technique	Matrix	Analyte	Detection System(s)	LOD Range	Reference
SPE	biological specimen, water, soil, food	nucleotides, perflorinated compounds, 1,2-ethanedithiol, chaconine, drug metabolites, antiviral drugs	HPLC-DAD, HPLC-MS/MS, HPLC-ICP-MS, HPLC-FLD, UHPLC-MS/MS, HPLC-UV	0.04-5.00 ng/L	[150,278,277] [223,215,185]
LLE	water	cyanotoxins, phthalates, C_{60}, pharmaceuticals, triazines	UHPLC-MS/MS, UHPLC-DAD, HPLC-UV	0.02-3.4 µg/L	[292,144,290] [140,141,295]
GPC					
QuEChERS & UASE	sediments	PAHs	HPLC-UV, HPLC-FLD	0.00108-0.314 ng/g	[316]
UASE	plant extracts	flavonoids	UPLC-HRMS	-	[205]
MWASE	plant extracts	polyphenolic compounds	UHPLC-q-TOF-MS	26.5-37.7 ng/mL	[209]
SPME	plastic, water, biological specimen, food	estrogen, E. coli, fluoroquinolines, PAHs	HPLC-DAD, HPLC-MS, HPLC-FLD	< 0.20 µg/L	[152,144,283,153]

ination on vegetables and other food products. There have been a few publications, however, purely dedicated to environmental analysis. Other studies have combined SPE/d-SPE and QuEChERS to analyze fungicide in wine samples by HPLC-DAD and LC-QqQ-MS [309]. For direct environmental applications, QuEChERS combined with HPLC-MS/MS or UHPLC-MS/MS have been applied to novel psychoactive drugs in wastewater [310], herbicides in corn ecosystems [311], pesticides in insect samples [312], drugs, toxins, and other substances in animal feed [313], and mycotoxins in animal feed [314].

The majority of UASE and MWASE have been combined with other sample preparation techniques to maximize efficiency. UASE has been combined with titanium-based SPE to determine polycyclic aromatic hydrocarbons [315] and ionic liquid to analyze fungicides [316]. MWASE combined with other extraction techniques has been developed to analyze auxins in plants [317], chlorophenols and PAHs in soils and sediments [318,319], and phenolic acids and flavonoids in raw propolis [320]. Combining two or more sample preparation techniques can achieve extraction and cleanup to solve several drawbacks with commonly used procedures. Table 2 summarizes recent applications (2019-2021) and reported detection limits for sample preparation techniques coupled to HPLC.

In summary, improvements documented with sample preparation techniques in the last decade lead to a wide variety of applications and have significantly enhanced the power of the sample preparation technique.

6. Sample preparation for HPLC instruments in the future

Given the ease with which several sample preparation techniques have been successfully interfaced and automated with HPLC instruments and the value-added to the data obtained, it will not be surprising to see recent miniaturization in sample preparation trends continues. In this respect, the design of selective extractant phases that could isolate target analytes of different polarities is essential. Analyzing complex mixtures in different matrices has demanded an improvement in modern analytical methods to monitor residue and contaminants. Advancements in cost, miniaturization, and sustainability are gaining importance. The trend has cre-

ated a powerful analytical tool for fundamental investigations and a robust and practical method to analyze complex mixtures. One approach that leads to improvements in complex mixture analysis is the combination of sample preparation techniques or combinations/development of sorbents, as in SPE. That has lead to satisfactory extraction efficiency, cleanup as well as excellent preconcentration capacity. In the future, microscale sample preparation techniques that can be combined and automated are promising. Developments in sample preparation techniques have enhanced several applications. Applications such as biological therapeutics [1–3], proteomics [4,5], lipidomics [6–9], metabolomics [10–12], glycan cleanup [13,14], untargeted analysis [14,15], analysis techniques for blood [216,218,227], to name a few, are growing in popularity. Application advances will lead to better diagnostic tools, more effective cures for diseases, and better nutrition for the world's population. Improvements in miniaturization, selectivity, and automation of sample preparation techniques are essential for high-throughput analysis in analytical chemistry. One might logically conclude that combining different existing sample preparation techniques or developing handheld or smartphone-based strategies is the way to increase sample preparation efficiency and reduce the sample volume, making sample preparation more sustainable.

Declaration of Competing Interest

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

CRediT authorship contribution statement

A Bakarr Kanu: Conceptualization, Investigation, Writing – review & editing, Methodology, Writing – original draft, Funding acquisition.

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