



Bioanalytical Applications of Microextraction Techniques: A Review of Reviews

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Abstract

Sample preparation is a critical step in the separation of target analytes from complex matrices, which can influence the reliability and accuracy of the resulting analysis. Recent trends in sample preparation techniques are directed toward the automation and online coupling of sample preparation units, miniaturization, high efficiency, low costs, and reducing or eliminating solvent consumption. Microextraction techniques (METs) have all these advantages over conventional extraction methods. Thus, the application of METs in the analysis of different analytes from biological samples has increased significantly in recent years. Over time, many review articles have been written, which focus on the advantages, applications, and advances of these techniques for the analysis of various compounds in biological matrices. This paper presents a review of publications pertaining to the application of different types of METs in the analysis of biological samples along with their different aspects and a discussion of their future.

Keywords Bioanalysis · Microextraction techniques · Review

Introduction

Generally, biological chemistry can be defined as the development and application of chemical measurements in biology, biochemistry, and medical science. The bioanalysis of compounds usually involves identifying the structural properties and by quantification measuring the concentration of analytes within the samples [1]. Target analytes can include chemicals exposed to the environment and their metabolites, drugs, lipids, peptides, proteins, DNA, carbohydrates,

among other compounds [1]. To analyze compounds or their metabolites in living organisms or biological fluids, aspects related to human health, medical research, pharmaceutical research, biochemical research, and occupational exposure assessment must be considered [2, 3]. The bioanalysis of different compounds is a complicated process, for which each step, i.e., in sample preparation and analytical technique, is very important to obtain accurate results [4]. Because biological materials and pharmaceutical products are highly complex mixtures, appropriate sample preparation is critical to analyzing biological samples. This mixtures often contain proteins, salts, acids, bases, and various other compounds that may be similar to the target analyte [4]. In other words, most biological samples are incompatible with the analytical instruments due to their complexity, thus the sample preparation step is essential [2]. Another significant step is sample pretreatment for extremely low concentrations of analytes, which are not detectable by the analytical instrument [5]. The extraction process of target analytes from biological samples is time-consuming, therefore bioanalysis studies require application of proper analytical techniques for trace concentration levels of metabolites present in biological samples [6]. Conventional methods used for bioanalysis of compounds have several disadvantages, including detrimental environmental effects (i.e., using large amounts of

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hazardous organic solvents), problems in coupling to the analytical instruments, and limited selectivity [3, 7, 8]. During the past years, microextraction techniques (METs) have been proposed as an alternative method in response to the problems related to conventional methods for analysis of biological samples [6]. A summary of bioanalytical applications of METs is presented in Fig. 1. Different METs can improve compatibility with analytical instruments, reducing the use of hazardous solvents and removing interference compounds from complex biological samples [9, 10]. Although broadly different METs have known properties in that they are solventless or solvent-minimized, straightforward, fast, low cost, and eco-friendly [11, 12]. To date, numerous studies have reported the successful use of METs to identify various analytes in biological samples [7, 13, 14]. Therefore, for the first time, we presented a comprehensive overview of published review articles related to the application of METs in bioanalysis. In this paper, we considered review articles with the most citations and historically updated. A summary of recent published articles on this subject is depicted in Table 1. The terms searched included “review on developments in the analysis of biological samples”, “critical review of bioanalysis”, “biological monitoring”, “recent developments and applications of METs in biomedical analysis: a review”, etc. This paper covers various topics, such as the general aspects and advanced techniques, METs application for the determination of drugs and specific analytes in

biological samples, in vivo and in vitro studies, and future trends. The critical opinion of the authors of this review is given under “Comments” for each section.

Historical Overview and Principles of METs

METs Based on Solid Phase

METs with a solid-phase basis include solid-phase microextraction (SPME), in-tube SPME, the needle trap device (NTD), thin-film microextraction (TFME), and fabric phase sorptive extraction (FPSE) [3, 11]. Different types of METs based on extraction media are presented in Fig. 2. In the early 1990s, Pawliszyn et al. first proposed SPME as a sample preparation technique of choice for diverse fields including bioanalysis, pharmaceuticals, toxicology, and drug monitoring; this is because it allows the extraction and separation of both volatile and non-volatile analytes from complex matrices [15–17]. In fact, this technique allows a number of analytical steps such as sampling, preconcentration, separation, and sample introduction into analytical instruments to be carried out in a single step [15]. Additional advantages of SPME over traditional techniques include its simplicity, its compatibility with a variety of analysis instruments, the possibility of automation, its solvent-free nature, and the commercial availability of coating materials [18, 19].

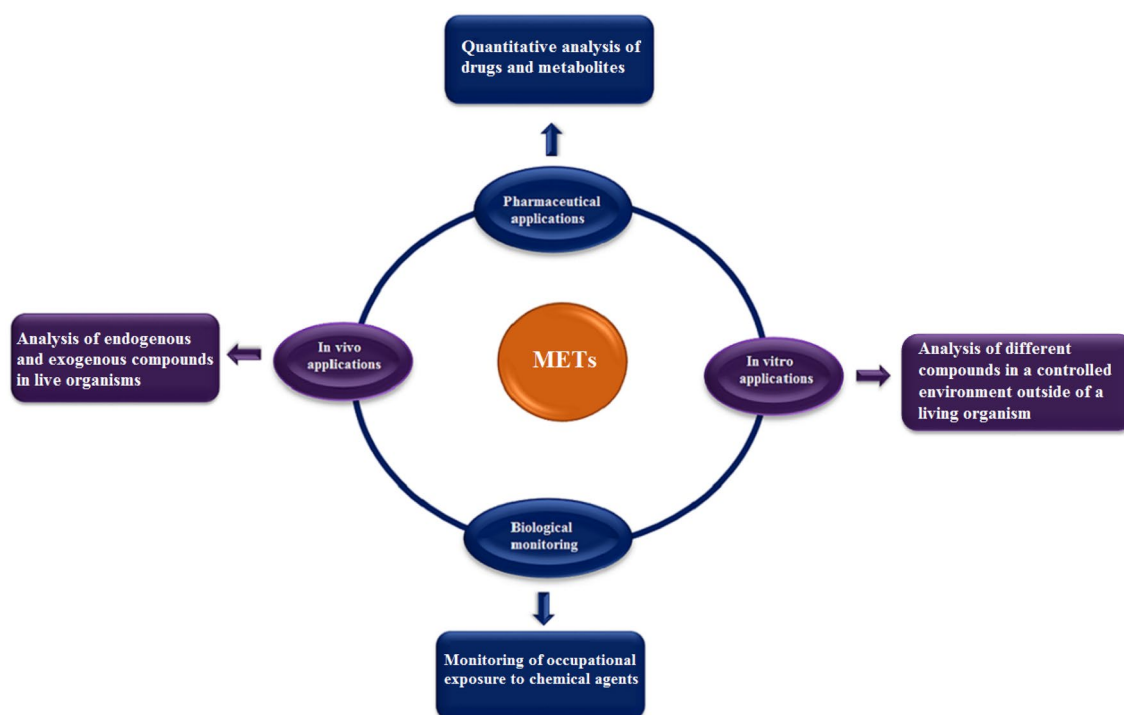


Fig. 1 Applications of microextraction techniques in bioanalysis

Table 1 Recent published articles that reviewed the applications of METs in bioanalysis

Extraction phase	METs	Applications of METs in bioanalysis	References
Solid phase	SPME	Extraction of endogenous substances from biological sample (feces, saliva, blood/ serum, breath, urine, cell culture medium, plants, animal tissue, bacteria and fungus, and insect)	[67]
	SPME	Bioanalysis of drugs	[79]
	SPME	Bioanalysis of drugs	[81]
	SPME, In-tube SPME	Biomedical analysis	[83]
	SPME	Bioanalysis of drugs	[82]
	SPME	In vivo and in vitro sampling of analytes in plants	[88]
	SPME	In vitro and in vivo metabolites analysis	[90]
	SPME	In vitro and in vivo analysis of various metabolites	[91]
	SPME, In-tube SPME, NTD	Biological monitoring of occupational exposure to chemical agents	[3]
	SPME	Biological monitoring of occupational and environmental exposure to chemical agents	[99]
Liquid phase	SPME	Analysis of biological VOCs	[92]
	SPME	VOCs analysis as potential biomarkers of cancer	[100]
	LPME	Pharmaceutical applications	[77]
	DLLME	Pharmaceutical and biomedical applications	[78]
	LPME	Bioanalysis of drugs	[69]
	HF-LPME	Pharmaceutical and biomedical analysis	[80]
	LPME	Bioanalysis of drugs	[82]
	LPME	Determination of small-molecule drugs in biological samples	[84]
	SDME, HF-LPME, DLLME	Biological monitoring of occupational exposure to chemical agents	[3]

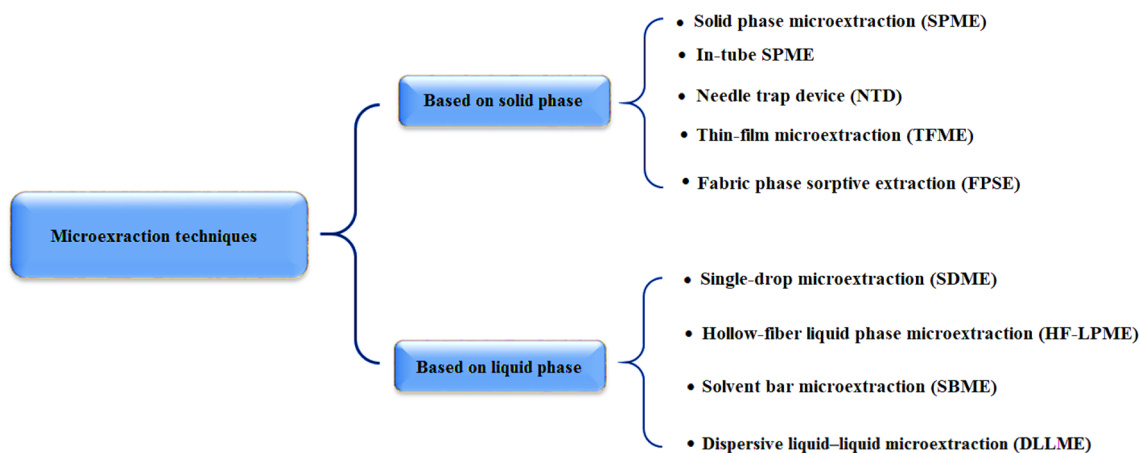


Fig. 2 Different types of microextraction techniques

In 1997, in-tube SPME was introduced by Pawliszyn et al. [19, 20]. This technique is generally applied in combination with high-performance liquid chromatography (HPLC), which can lead to increased sensitivity due to utilizing an open tubular column in the extraction phase [19, 21, 22]. However, SPME have some drawbacks such as fiber fragility, equilibrium-based extraction, limited sorption capacity, the use of expensive coated fibers, the impossibility of active sampling, and memory effects [11]. In response to these problems, Pawliszyn et al. developed the NTD technique,

in which a stainless steel needle is packed with a suitable extraction phase (sorbent) and used for the sampling and analysis of target analytes in different matrices [23, 24]. This technique has all the advantages of SPME and some additional ones such as active sampling, loading larger amounts of sorbent, and protection of the extraction phase inside the stainless steel shield [25, 26]. After sampling, the NTD is disconnected from the sampling pump and placed into the injection port of a gas chromatograph (GC). Subsequently, the target analytes are desorbed from the extraction media

via thermal desorption and transported by a carrier gas to the GC column for analysis [3, 27, 28]. The NTD technique has been successfully applied to the analysis of a wide range of analytes [3, 27, 29]. Thin-film microextraction (TFME) is one of the techniques used to improve sensitivity. In this process, a sheet of flat film with a high surface area-to-volume ratio is used as the extraction phase [30], and the volume of the extraction phase increases while the thickness of the coating remains fixed. Thus, the time required to extract the analytes is reduced [31, 32]. In this technique, reducing the thickness of the extraction phase shortens the equilibrium extraction time. In addition, when the extraction phase has a large surface area, the speed of the extraction is increased [33, 34]. Overall, TFME can be classified into two categories, i.e., (1) thermally desorbed TFME and (2) solvent-desorbed TFME. The thermally desorbed TFME can be used with instruments to allow the introduction of the analytes in the gas phase and solvent-desorbed TFME can be used in analytical instrumentation when dealing with liquid samples [35, 36].

Another technique, which is known as fabric phase sorptive extraction (FPSE), was developed by Kabir et al. in 2014. This technique overcomes two important drawbacks of all sorptive extraction techniques, i.e., (1) low sample capacity and (2) longer analysis time [37, 38]. The application of this technique requires several steps, the first of which is placing the sol-gel sorbent-coated FPSE media in an appropriate solvent to clean contamination from the material; subsequently, the media are rinsed with deionized water to remove any organic solvent residue. Then, the sample solution is transferred into a vial and the FPSE media are introduced into the vial. Then, the FPSE media is removed from the vial and placed in another vial that contains the eluting solvent. Subsequently, the sample must be centrifuged and filtered before it is injected into the analytical apparatus [39, 40]. Due to the advantages provided by the sol-gel-derived microextraction sorbents and the hydrophilic property of the cellulose fabric substrate, the consumption of solvent is minimized in this highly sensitive, efficient technique which is capable of extracting target analytes from complex matrices. One of the main advantages of FPSE is its ability to directly extract both polar and nonpolar analytes from aqueous samples [37, 39, 41]. Generally, the advantages of the FPSE technique can be noted as follows: the sample preparation is simple and inexpensive, created by introducing the FPSE media into the sample matrix; the sample preparation is efficient because of sonication and magnetic stirring, thus reducing the sample preparation steps and the potential for errors in sample preparation; the sample preparation has a high preconcentration factor; and so on [42]. The FPSE technique has successfully extracted and preconcentrated many analytes in different samples such as biological samples [43].

METs Based on Liquid Phase

METs with a liquid-phase basis include (Fig. 2) single-drop microextraction (SDME), hollow fiber liquid-phase microextraction (HF-LPME), solvent bar microextraction (SBME), and dispersive liquid-liquid microextraction (DLLME) [44–46]. The SDME technique was introduced for organic compound analysis by Jeannot et al. in 1996 [47–50]. In this technique, a small drop of solvent is suspended from the tip of a syringe and then submerged into an aqueous sample; relative to conventional methods, the volume of extraction solvent is greatly reduced [47, 49, 51]. This technique has numerous applications for bioanalytical studies, but also faces some disadvantages, the main one being the instability of the solvent drop and the risk of drops falling into the solution during the extraction process [49, 52]. In 1999, Pedersen et al. introduced HF-LPME, in which the extraction phase is contained within a porous hollow polypropylene fiber, thus not in direct contact with the sample matrices; this prevents loss of the extraction phase in the sample [53, 54]. Therefore, the hollow fiber LPME technique is a more stable and reliable alternative to LPME; however, both SDME and HF-LPME share drawbacks such as slow kinetics and the use of holders [53]. The solvent bar microextraction (SBME) technique was introduced in response to those problems. In this technique, solvent bar is prepared by filling the interior of a short length of porous polymer fiber membrane with extraction solvent. The bar is then added to the sample and suspended in solution by stirring [55–57]. This process leads to increase in the mass transfer of target analytes from the sample into the extraction phase. This also enables the reduction of microextraction experiments as well as reduction in the cost and the time of the analysis, compared to common HF-LPME. SBME has successfully determined a wide range of organic substances such as metals, food, and medical chemicals. SBME also can be used in the two-phase or in the three-phase mode: in the two-phase mode, an organic solution fills the fiber pores and in the three-phase mode, an organic solution saturates the pores and separates the extraction phase from the sample [56, 58, 59]. The DLLME is an environmentally friendly extraction technique, which is based on the use of a dispersive extraction solvent applied directly into the sample. That is, a dispersing solvent is used to disperse the extractant phase, which forms a cloud solution and increases the interface surface area [60, 61]. Next, phase separation is carried out by centrifugation and then the droplet floating inside the sample solution is extracted with a syringe for analysis [60–62]. This technique provides advantages such as simplicity, reduced equilibration time, and higher efficiency, which led to DLLME being a widely used technique [62–64]. Overall, in all METs, the extraction process is based on transmission of the target analytes from the sample

into the extraction phase (whether liquid or solid) [3, 65]. All of these techniques have the potential for automation and consequent reduction in analysis time and all display suitable sensitivity, extraction efficiency, and selectivity [3, 65]. Thus, METs are in line to meet the requirements of modern green analytical chemistry [65, 66].

General Reviews

Despite considerable advances in developing analytical instruments to determine the analytes in biological samples, pretreatment of samples is essential to eliminate interfering compounds from complex matrices. To date, a wide range of review articles have provided a general overview of METs and their applications in bioanalysis [13, 14, 67–69]. Gonzalez et al. described general developments in METs, with the main goal to highlight new developments of MET in bioanalysis. This review explained the main METs, particularly SPME, SDME, HF-LPME, and DLLME. The review also covered future trends of METs in bioanalysis and microextraction methods such as nanoextraction systems and microchip devices for analysis of biological samples [2]. In another study, Kabir et al. reviewed METs used in analytical and bioanalytical samples preparation. The aim of this review was to report on the METs applied in quantitative analysis of complex matrices to reduce analysis time, solvent consumption, and use of non-toxic solvents in line with green analytical chemistry [7]. Mills et al. reviewed the applications of the headspace SPME technique to analyze biological fluids and materials. This review presented the background of the techniques and fibers used, extraction conditions, and derivatization methods and separately discussed the applications of SPME with different biological matrices such as urine, blood, breast milk, hair, breath, and saliva. The review included the analysis methods for drugs, metabolites, solvents, chemicals materials, anesthetics, pesticides, and organometallics, along with specific examples. In addition, this review investigated the potential of SPME in the analysis of biological samples and the development of new devices coupling with HPLC [22]. Lucena et al. also reviewed the applications of LPME-related techniques in bioanalysis and presented a general overview of the historical and principles of LPME techniques and essential trends such as descriptions of extraction modes and solvent [70]. Namera et al. reviewed recent trends in the miniaturization and automation of extraction techniques for biological analysis. These techniques' advantages and disadvantages for biological analysis and their applications in the extraction of analytes from biological matrices were also discussed [71]. Lee et al. considered the applications of HF-LPME, with a special focus on bioanalytical chemistry. They looked at new trends in LPME, particularly electromembrane extraction, in

which analytes are extracted through the supported liquid membrane by the application of electrical potentials [10].

Another review focused on applications and new advances of SPME technique in bioanalytical and clinical analysis. In this article, SPME analysis of biological matrices such as urine, tissues, blood and blood fractions was discussed. Different calibration strategies were employed and advantages and limitations of SPME, concerning the analysis of complex biological matrices, were described. Accordingly, beneficial information about the future prospects of this technique in bioanalysis applications was presented [72]. The application of SPME in determination of biomarkers was reviewed by Hamidi et al. A wide range of complex biological matrices like plasma, blood, urine, and exhalation gases can be studied by tracing of biomarker molecules. However, suitable sample preparation methods should be applied for quantification of biomarkers, which can support reproducible and accurate data. In this review, recent progress of microextraction methods for analysis of biomarkers was surveyed. Consequently, the general concepts of microextraction methods and the applications of each studied biomarker, along with a discussion of their future prospects, were described [73].

Comments Sample preparation techniques during recent decades have trended toward miniaturization and automation, resulting in METs being added to analytical systems. However, many challenges can be encountered during the application of these techniques, including capillary clogging and poor sample cleanup during in-tube SPME techniques associated with the analysis of complex samples with high protein contents, such as blood and plasma. Thus, the development of new extraction techniques, including both solid and LPME techniques, remains necessary for bioanalytical applications, such as the analysis of small volumes of plasma, oral fluids, and urine samples. Further studies should focus on the improvement of these techniques, by synthesizing and employing novel materials, with higher surface areas and extraction capacities. The development of nanotechnological methods is likely to be useful in this field.

Reviews Focused on Pharmaceutical Applications

Overall, quantitatively determining the drugs and metabolites in different biological samples (e.g., serum, plasma, urine, blood, and tissue) is essential for therapeutic drug monitoring, forensic toxicological analysis, drug abuse screening, drug metabolism investigation, biomarkers, and drug development studies [74, 75]. In addition, identification of metabolites and their structures in biological matrices clearly has major roles in drug discovery and development of pharmaceutical compounds [76]. Due to the low drug

concentrations and the complex sample matrix, measuring drugs in biological fluids requires a sample preparation step, which has spurred the emergence and development of a wide range of METs in drugs bioanalysis [2]. Huang et al. conducted a 5-year review of the development and applications of SPME in the determination of endogenous substances. They provided a comprehensive overview of different aspects, including the design of SPME devices and applications, emerging instruments, and strengths and weaknesses of SPME in endogenous substances analysis [67]. Seidi et al. reviewed the pharmaceutical applications of different LPME techniques and discussed the principles and history of these techniques and the influence of experimental parameters, along with commercialization, automation, and future trends. In addition, the repeatability, sample cleanup, extraction efficiency, and automation possibilities of LPME techniques such as SDME, HF-LPME, and DLLME in pharmaceutical applications were investigated [77]. Mansour et al. considered the pharmaceutical and biomedical applications of DLLME, focusing on the principles, experimental variables, and extraction solvents used and the different parameters affecting extraction efficiency. The authors also discussed the applications of different DLLME modes in pharmaceutical bioanalysis [78]. Bjergaard et al. examined the applications of three-phase, two-phase, and carrier-mediated LPME for drug extraction with biological samples such as plasma, whole blood, urine, and breast milk. The extraction principles and future trends of this sample preparation technique were also discussed [69]. Ansaria et al. reviewed the progress, challenges, and trends in trace determination of drugs using the molecularly imprinted solid-phase microextraction (MI-SPME) technique. They focused on the applications and configurations of MI-SPME for trace determination of drugs, which can increase sensitivity and selectivity. This review included MIPs such as SPME fiber coatings, MIP and in-tube SPME, monolithic MIP fibers for SPME, sol-gel MIP and SPME, membrane MIP, and other MIP-SPME techniques used in drug analysis. The discussion also concerned the advantages of these techniques and the possibilities to improve the absorption and extraction of a variety of analytes using these techniques [79]. Another article reviewed applications of membrane-based extraction techniques such as HF-LPME with a special focus on pharmaceutical and biomedical analysis. The principles, advantages, and drawbacks of membrane-based extraction techniques were also described [80].

Moein et al. reviewed the applications of SPME technique and its related techniques for analysis of pharmaceutical in biological samples. The developments of microextraction sample preparation methods including fiber SPME, and microextraction in packed sorbent for analysis of drugs in biological fluids were discussed. In

addition, the use of new extraction media such as monolithic sorbents and MIPs in these techniques was presented [81]. Kataoka reviewed developments and applications of METs in drug analysis. This review focused on METs and their characteristics for drug analysis in biological samples. Overall, the headlines of the surveyed review articles can be classified into two main categories including LPME and SPME techniques. For each category, the studied analytes, samples, and biological matrices were comprehensively discussed [82]. In another report, the applications and advances of SPME techniques in biomedical analysis were reviewed by Kataoka et al. In this review, the developments of different SPME configurations like fiber SPME and in-tube SPME for biomedical analysis were presented and discussed. Moreover, the applications of these techniques in different areas such as pharmaceutical studies, forensic science, clinical diagnostic analysis, and environmental and occupational exposure assessment were discussed. Additionally, the future trends concerning the SPME techniques in biomedical analysis were described [83]. Recent advances in the LPME techniques for quantification of small-molecule drugs in biological samples, with specific focus on the mass spectrometry (MS) as a detection system, were reviewed in another study [84].

Comments Biological samples are complex matrices containing various compounds, such as proteins, salts, and organic compounds, with properties similar to target analytes. Therefore, the appropriate preparation of biological samples is essential for the isolation of analytes from troublesome matrices, such as tissues, blood, and urine, prior to analysis. The development of new techniques that improve the extraction process is expected in the future. During LPME techniques, the application of safer extractants and dispersers is very important for increasing green analytical aspects. The automation of the extraction process not only decreases potential sources of error during analyses but also saves time. The use of new selective sorbents in different types of SPME techniques can enhance both the selectivity and sensitivity of METs used during drug analyses. For example, the use of polypyrrole (PPy) during ion exchange interactions may facilitate selective drug analyses at plasma levels. Restricted access material (RAM) sorbents can divide plasma samples into two fractions, based on molecular weight, including a protein matrix and a drug fraction. The recognition and application of immunosorbents have led to METs with very low quantification limits. In the future, the improved integration of sample preparation techniques within analytical instruments may result in the wider use of automated online pharmaceutical analyses. In addition, future studies should focus on the improved selectivity, sensitivity, and capability of METs to extract large molecules.

Reviews Focused on In Vivo and In Vitro Studies

In vivo and in vitro studies represent basic methods for the assessment of the human health risks posed by a wide range of chemicals. In vivo studies refer to any studies that utilize whole, live microorganisms during toxicological experiments, including the examination of the toxic effects of varying exposure conditions [85]. These effects can include acute toxicity, subacute toxicity, and chronic toxicity. In contrast, in vitro studies refer to those studies conducted using dissociated organs or cells, which can often be performed more quickly and economically than in vivo experiments [86]. One primary advantage of in vitro studies is the ability to utilize human cells, which removes the potential confounding factor of species differences when assessing human toxicity [86]. To date, many review articles have focused on the applications of different types of METs during in vivo and in vitro studies. Zhang et al. reviewed in vivo sampling techniques, with a specific focus on SPME, outlining the challenges and opportunities associated with SPME in freely moving fish. The spatial and temporal resolution and technical parameters associated with SPME, such as sampling times and probe dimensions, were also examined. Additionally, the ability to perform in vivo monitoring of endogenous compounds using SPME was investigated, which result in future applications of this technique in the burgeoning field of metabolomics [68]. Musteata et al. reviewed recent developments and future perspectives regarding the application of SPME for assessing live biological samples. They focused on recent advances and future trends in the development of SPME methods for the analysis of both endogenous and exogenous compounds in live organisms, with a specific emphasis on animals. Moreover, this review addressed both the development of in vivo methods and their applications. The development section discussed extraction techniques, the selection of extraction phases, calibration procedures, the determination of free concentrations, and automation. The application section discussed the sampling of insect volatile emissions, in vivo drug analysis, and the sampling of volatiles emitted by humans [87]. Zhu et al. reviewed the applications of in vivo and in vitro SPME techniques for the analysis of organic compounds in different plant organs, including fruits, flowers, leaves, stems, roots, and seeds, and in the whole plant. The future perspectives and applications of SPME for plant analyses, especially in vivo sampling approaches, were also described. This study also discussed how to apply SPME techniques during in vivo sampling, providing a powerful method for plant analyses [88]. Vuckovic et al. reviewed the technological developments associated with

SPME and the increasing application of this sample preparation technique to the field of bioanalysis. This review discussed the introduction of various new biocompatible coating phases that are suitable for bioanalysis and the development of sampling interfaces, which permit the application of in vivo SPME during a wide range of analyses, including pharmacokinetics, bioaccumulation, and metabolomics studies. This review summarized how these new developments have translated into applications for the determination of unbound and total drug concentrations in complex matrices, such as whole blood, with no requirements for sample pretreatment, and the distribution of drugs in various compartments [89]. Another article reviewed the application of SPME techniques during both in vitro and in vivo studies for the analysis of metabolites after the ingestion of herbal and pharmaceutical agents, foods, and other nutrients [90]. In addition, recent progress in the applications of SPME during the in vitro and in vivo analyses of various metabolites and drugs during clinical and pharmaceutical studies was reviewed by Roszkowska et al. [91]. Advances and new developments in the analysis of biologically volatile organic compounds (VOCs) were reviewed by Zhang et al. In this review, the authors describe biological VOCs characteristics and developments in the sampling, analysis, and corresponding bio-information distillation methods for biological VOCs. The SPME technique is described as a sampling method used for the analysis of VOCs in biological samples. In addition, they discussed the combination of some suitable sampling and bio-information distillation techniques for the study of biological VOCs and the future frontier of this field [92]. In another paper, the current challenges in VOCs analysis as potential biomarkers of cancer were reviewed by Schmidt et al. They reviewed the application of extraction techniques such as SPME that have been applied in studies of potential volatile biomarkers of cancer in the exhaled breath of patients and in cancer cells, tissues, or biological bodily fluids [93].

Comments METs, especially SPME techniques, have many advantages, including simplicity, high speed, high selectivity, reduced solvent consumption, automation, and compatibility with different analytical instruments, and have been widely used for the analysis of various compounds, both in vivo and in vitro. However, certain technical challenges, including issues associated with sensitivity and quantification, must be overcome. The efficiency and sensitivity of SPME techniques primarily depend on the extraction phase. The selection of the appropriate extraction phase can facilitate the application of SPME techniques, in vivo. To determine the quantities that can be obtained by SPME techniques during in vivo sampling, appropriate calibration methods must be applied. Costs represent another challenge associated with in vivo SPME techniques. Moreover,

the application of SPME techniques to *in vivo* and *in vitro* studies must be validated for their abilities to extract target compounds from matrices with high concentrations of macromolecules and cells. More studies must be performed to address the existing shortcomings associated with these techniques. Future research should focus on the applications of these techniques in soft tissues, including the automation and utilization of specific extraction phases.

Reviews Focused on Biological Monitoring of Occupational Exposures

Generally, biological monitoring is defined as the assessment of human exposure through the determination of the presence of chemical agents or their metabolites in living organisms or biological fluids [94]. Biological monitoring can provide more information than environmental monitoring, because it covers all the routes of exposure to compounds. Thus, biological monitoring can be lead to improvements in the assessment of occupational exposures [95–97]. As mentioned earlier, the sample preparation process is very important when analyzing complex biological samples such as tissues, blood, and urine. In response to the problems associated with the conventional methods used to prepare samples, many reports have focused on the application of METs in biological monitoring [8, 98]. The application of METs in occupational exposure assessments was reviewed by Jalili et al. In this review article, the authors addressed the historical and principles of METs, the extraction media used in METs, and existing occupational exposure assessment methods. The application of METs in biological monitoring was also discussed, including its benefits and role in assessing occupational exposure. Additionally, examples of the application of different types METs in the biological monitoring of various compounds were described [3]. The use of breath air analysis as a biomarker in the biological monitoring of occupational and environmental exposures to chemical compounds was reviewed by Amorim et al. In this paper, the authors addressed the principles of exposure biomarkers for exhaled air analysis, the use of exhaled air as an exposure biomarker, biological exposure limits, sampling techniques and breath analysis, and the use of the SPME technique in the analysis of exhaled air [99].

Comments Biological monitoring represents an important step in the accurate assessment of occupational exposures. METs provide a significant opportunity to improve the biological monitoring of occupational exposures because these techniques exhibit good sensitivity and selectivity during biological analyses. However, most studies validate these techniques under laboratory conditions and less commonly validate their use for real and occupational samples. Future

studies should investigate the potential applications of METs for the biological monitoring of occupational exposures.

Concluding Remarks

In this study, we reviewed articles that address the application of different types of METs for the sampling and analysis of various compounds in biological samples. As mentioned in previous sections, biological samples have complex matrices that can disrupt the analysis of analytes of interest. Several factors such as the type of analyte and sample matrix, efficiency and time required for analysis, repeatability, and costs of the method are key points in the selection of a suitable sample preparation method. Today, it is established that METs represent a powerful method for sample preparation in the analysis of biological fluids and substances. In recent years, the use of these techniques for the extraction and enrichment of analytes in biological materials has significantly increased. The use of METs as a sample preparation method can lead to an excellent extraction of analytes from biological samples. These techniques make possible automation, miniaturization, traceability, reduced analysis time, and high efficiency analysis. In addition, METs can now be interfaced with many instrumental analytical instruments such as GC–MS, HPLC–MS, and inductively coupled plasma MS, which further broadens their application for the extraction of different compounds. The exploitation of this features opens up new possibilities and applications in a variety of areas, including pharmaceutical, occupational exposure assessment, and *in vivo* and *in vitro* studies, to name a few. Undoubtedly, exciting developments in METs for the analysis of target analytes from biological samples will continue in the future. The development of more sensitive and selective phases can lead to further miniaturization of these techniques. Furthermore, automating sample preparation to speed up these methods and improving their precision and cost effectiveness is expected. However, challenges in the development of these techniques remain. For example, more attention must be paid to the quality control methods used in the manufacture and choice of extraction media. This is because there are a number of reproducibility problems with respect to their analysis, which can originate from variable surface properties of the extraction media. Moreover, the identification of safer and low-toxicity extraction solvents could increase the green aspects of METs (LPME techniques). Therefore, more research must be conducted to uncover all the advantages and limitations of these techniques.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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