Review

Metal-Organic Frameworks in Bioanalysis: Extraction of Small Organic Molecules

Natalia Manousi [1,*] , Orfeas-Evangelos Plastiras [1] , Natasa P. Kalogiouri [1] , Constantinos K. Zacharis [2] and George A. Zachariadis [1,*]

[1] Laboratory of Analytical Chemistry, Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece; orfeplas@hotmail.com (O.-E.P.); kalogiourin@chem.auth.gr (N.P.K.)
[2] Laboratory of Pharmaceutical Analysis, Department of Pharmaceutical Technology, School of Pharmacy, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece; czacharis@pharm.auth.gr
* Correspondence: nmanousi@chem.auth.gr (N.M.); zacharia@chem.auth.gr (G.A.Z.)

Abstract: The quantitative determination of xenobiotic compounds, as well as biotics in biological matrices, is generally described with the term bioanalysis. Due to the complexity of biofluids, in combination with the low concentration of the small molecules, their determination in biological matrices is a challenging procedure. Apart from the conventional solid-phase extraction, liquid-liquid extraction, protein precipitation, and direct injection approaches, nowadays, a plethora of microextraction and miniaturized extraction techniques have been reported. Furthermore, the development and evaluation of novel extraction adsorbents for sample preparation has become a popular research field. Metal-organic frameworks (MOFs) are novel materials composed of metal ions or clusters in coordination with organic linkers. Unequivocally, MOFs are gaining more and more attention in analytical chemistry due to their superior properties, including high surface area and tunability of pore size and functionality. This review discusses the utilization of MOFs in the sample preparation of biological samples for the green extraction of small organic molecules. Their common preparation and characterization strategies are discussed, while emphasis is given to their applications for green sample preparation.

Keywords: sample preparation; metal-organic frameworks; extraction; MOFs; bioanalysis; biological samples; small molecules

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1. Introduction

Bioanalysis is a term generally used to describe the quantitative determination of xenobiotics (i.e., exogenous chemical compounds, such as drugs and their metabolites) and biotics (i.e., endogenous compounds such as biomarkers) in biological matrices. As a result, bioanalysis is of high importance for drug discovery, since it provides crucial information regarding drug absorption, distribution, metabolism, and elimination [1]. In bioanalytical studies, conventional biofluids, such as urine, human plasma, serum, and whole blood, are usually analyzed [2]. However, other alternative matrices like oral fluid [3], keratinized matrices namely hair and nail clippings, dry blood spots and cerebrospinal fluid can be also examined. Hair and nails can provide information on chronic exposure and they can be obtained through non-invasive methods under supervision in order to prevent adulteration or substitution. Moreover, compared to the conventional samples, the collection of dried blood spots is simple and requires only a small amount of blood [2,4,5].

The predominant separation technique that is typically used for the determination of small organic molecules in biosamples is high performance liquid chromatography (HPLC). Next to universal detectors, tandem mass spectrometers (MS/MS) are widely used for the high-throughput quantitative determination of drug and metabolites in complex matrices samples, since they provide high sensitivity. Moreover, the application of ultra-high performance liquid chromatography (UHPLC) with small particles (<2 μm) can

provide a further improvement in speed, resolution, and sensitivity compared to the conventional HPLC technique [6]. Other examples of analytical instrumental techniques that have been successfully employed in the determination of small organic molecules are gas chromatography (GC) [7] and capillary electrophoresis (CE) [8].

Typically, an analytical method consists of two main parts, the sample preparation of the biological fluid and the detection of the target analyte [9]. The determination of small molecules in biological samples is a demanding procedure since they are complex samples that often contain proteins, inorganic salts, acids, bases, phospholipids, and other organic compounds that might exhibit similar chemical or physical properties with the target analytes. In addition to the sample complexity, the analytes often exist in low concentration and a preconcentration step might be required [2,10].

Conventional sample preparation techniques include solid-phase extraction (SPE), liquid–liquid extraction (LLE), direct injection and precipitation of proteins. These techniques are commonly employed for bioanalytical sample preparation to enable the accurate and sensitive determination of small organic molecules. However, these conventional sample preparation approaches (i.e., LLE and SPE) exhibit many fundamental drawbacks, such as large consumption of organic solvents and requirement for high quantity of sample. Moreover, these techniques are composed of time-consuming and complicated steps, while automation is complicated [11,12]. Aiming to overcome these disadvantages, various sample preparation techniques have been developed [13]. In the early 1990s, Pawliszyn and Arthur [14] introduced a green extraction technique named solid-phase microextraction (SPME). Since then, attention has been paid to microextraction techniques that overcome the drawbacks of the conventional sample preparation approaches. A few years later, Liu and Gasgupta [15] introduced liquid-phase microextraction (LPME). Until today, a plethora of miniaturized extraction techniques have been also developed, including dispersive solid-phase extraction (d-SPE) [16], magnetic solid-phase extraction (MSPE) [17], fabric phase sorptive extraction [18], matrix solid-phase dispersion [19], stir bar sorptive extraction (SBSE) [20], stir rod sorptive extraction [21] and pipette tip solid-phase extraction (PT-SPE) [22]. These examples of microextraction and miniaturized extraction techniques comply with the guidelines of Green Analytical Chemistry by reducing the amount of sample needed and the consumption of hazardous organic solvents [23]. Examples of the aforementioned techniques are presented in Figure 1. Moreover, aiming to enhance the sensitivity and the selectivity of the sample preparation, many novel adsorbents have been synthesized and evaluated. Typical examples of novel sorbents that have been successfully utilized in microextraction and miniaturized extraction approaches include carbon-based materials, including carbon nanotubes [24], graphene [25], and graphene oxide (GO) [16], molecularly imprinted polymers (MIPs) [26], metal-organic frameworks (MOFs) [27], and covalent organic frameworks [28].

MOFs are a class of novel crystalline materials that exhibit structures formed from the coordination between multidentate organic groups and metal ions [29]. Compared to other solid-phase extraction sorbents, MOFs exhibit superior surface area, satisfactory thermal and mechanical stability, as well as tunability of pore size and functionality [30,31]. Moreover, MOFs can be modified with chemical groups that uniquely affect the overall selectivity and sensitivity of the extraction process [29,31]. Due to their interesting physical and chemical properties, MOFs have been employed in different scientific fields, including gas separation, gas storage, and catalysis [32]. Currently, MOFs are used in biomedical applications for various purposes, e.g., as nanocarriers for drug delivery, and various functionalization approaches can be adopted to prepare MOFs with therapeutic agents [33]. Apart from their applications in drug carrying substrate for drug delivery, MOFs are also utilized as contrast agents in magnetic resonance imaging [34]. MOFs have been also employed for the biosensing of biological markers. The applications of MOFs for the detection of biomarkers were recently discussed by Mendes et al. [35]. In the field of analytical chemistry, these materials have been employed as adsorbents in sample preparation [31], as stationary phases for GC, HPLC, and capillary electrochromatography [36], as well

as column coatings for chiral separations [37]. Until now, MOFs have been utilized in multiple microextraction and miniaturized extraction techniques. Numerous publications regarding MOFs applications in sample preparation [27,31,38–44] have been reported in the last decade. The applications of MOFs as sorbents for the extraction of biomacromolecules has been extensively discussed by Ma et al. [39]. However, to the best of our knowledge the applications of MOFs as sorbents for the extraction of small organic molecules for bioanalytical purposes, as well as the common preparation/characterization approaches to design MOFs that can be used in bioanalysis have not been sufficiently discussed. Herein, we discuss the applications of MOFs and their different sub-families such as zeolitic-imidazole frameworks (ZIFs) in bioanalysis regarding the extraction of small organic molecules. Common preparation and characterization strategies that are employed to design MOFs will be also discussed, while emphasis is placed on their applications for green microextraction and miniaturized extraction techniques.

Figure 1. Examples of green extraction techniques utilizing MOFs as adsorbents. PT-SPE: Pipette tip solid-phase extraction, SPME: Solid-phase microextraction, EME: Electromembrane extraction, d-SPE: dispersive solid-phase extraction, SBSE: Stir bar sorptive extraction, MSPE: Magnetic solid-phase extraction.

2. Preparation and Characterization Strategies for MOFs

The proper selection of the constituents of MOFs plays an important role in the designation of the material, since the metal ions and the ligand connectivity are responsible for the generation of a particular crystal structure with specific characteristics (e.g., pore size and widow) [45]. Currently, the most common metal ions used in MOFs include Zn(II), Co(II), Cu(II), Fe(III), and Zr(IV), while the most common organic linkers used in MOFs include terephthalic acid (1,4-benzenedicarboxylic acid), trimesic acid (benzene-1,3,5-tricarboxylic

acid), or 2-methylimidazole [38]. Other examples of organic linkers used in MOF preparation are fumaric acid, ethanedioic acid, propanedioic acid, 1,2-benzenedicarboxylic acid, 1,3-benzenedicarboxylic acid, 4H-imidazole, 1H-1,2,3-triazole, 1H-1,2,4-triazole, 4,4′-bipyridine and 4,4′-azopyridine [46]. The chemical structures of common organic linkers used in MOF synthesis are shown in Figure 2.
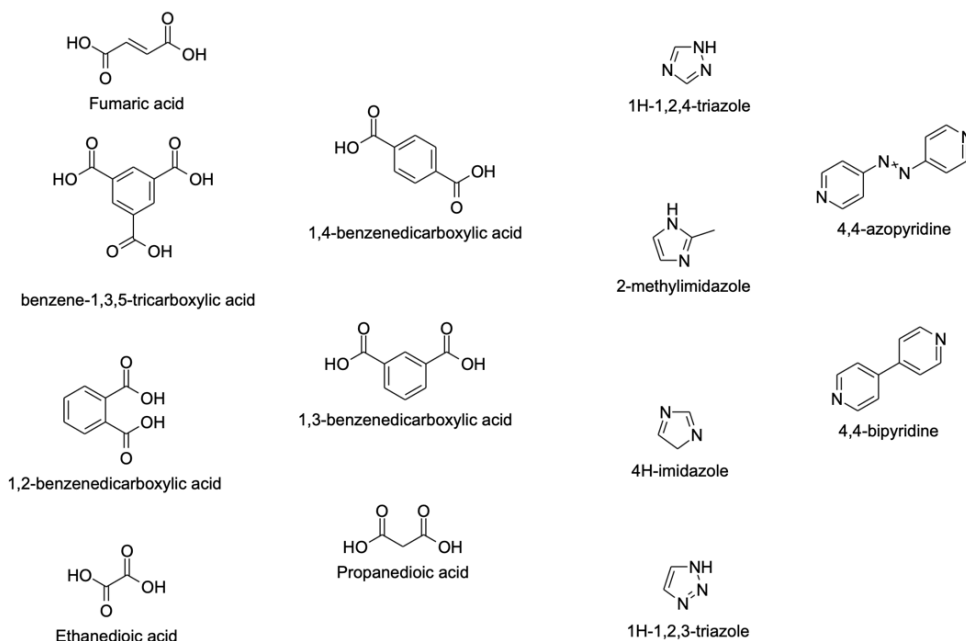

Figure 2. Examples of the chemical structure of common organic linkers used in MOF preparation.

As metal centers, the utilization of low-toxicity metals, such as Mg, Ca, Mn, Fe, Al, and Zr, is preferable in terms of green considerations during MOF preparation. In this aspect, the safety of the metal salts must be also taken into consideration since there are metals such as metal nitrates that exhibit risk of explosion. As for the organic linkers, typically the use of low-cost carboxylic acids (e.g., fumaric acid, terephthalic acid etc.) is preferred, while the selection of tailored linkers can be a choice in order to prepare MOFs with higher surface areas [45].

An important consideration during the design of MOFs as adsorbents for sample preparation is their stability. As a result, when MOFs are used in extraction techniques, they must be stable both during adsorption and during desorption of the target analytes [38]. Moreover, MOFs may exhibit strong affinity towards small organic compounds. Therefore, this must be taken into account to avoid the selection of MOFs that may lead to incomplete desorption of the target analyte. These are also two important factors for the reusability of the MOF sorbent, since incomplete elution and/or collapse of structure during sample preparation could significantly limit the application of the material. In order to increase the stability, and thus the reusability of MOFs, the use of additives (e.g., graphite oxide and nanoparticles etc.) and/or the deposition of the MOF on substrates (e.g., fibers, textiles etc.) can be employed [38,47]. Finally, since MOFs have proven to be good catalysts, it is crucial to select MOFs that do not pose potential reactivity and thus, they do not lead to the degradation of the target analytes [47]. In order to overcome some of those limitations and to enhance the extraction efficiency of the sorbent, the functionalization of MOFs can be employed [38].

There are various synthetic routes for the preparation of MOF materials. Among them, the most common method is the solvothermal approach, in which the metal salt and the organic linker are typically mixed in an organic solvent and heated in an autoclave for a certain time span near (or above) the boiling temperature the solvent [45,46]. The solvothermal method can be used to form nanoscale morphologies at high yields, while it can also

provide better crystallinity. This approach requires special instruments (e.g., autoclaves) to obtain the desired conditions of temperature and pressure [46]. An interesting and environmentally friendly alternative to the solvothermal method, is the hydrothermal method in which water is used as a solvent. Recently, an increasing number of MOF materials were synthesized through the hydrothermal method under atmospheric pressure [45]. Other alternative synthetic methods include the mechanochemical approach, the electrochemical approach, the micro-microwave assisted method, as well as sonochemical methods [45,48]. Compared to the solvothermal technique, the microwave-assisted synthesis of MOFs can produce MOFs in much shorter time [46]. Regarding the mechanochemical approach, the preparation of MOFs is performed with the assistance of mechanical energy with small amounts (or without) of solvents. As a result, it is an environmentally friendly method for MOF preparation. Figure 3 shows the common synthetic routes for the preparation of MOFs, as well as techniques for their characterization.

Figure 3. Common synthetic routes for MOFs (above) and characterization techniques (below). TEM: Transmission electron microscopy, SEM: Scanning electron microscopy, TGA: Thermogravimetric analysis, XRD: X-ray diffraction, BET: Brunauer–Emmett–Teller surface area, DSC: Differential scanning calorimetry, FT-IR Fourier transform infrared spectroscopy.

In order to study the structure of MOFs, a variety of characterization techniques is available. Fourier transform infrared spectroscopy (FT-IR) is a characterization technique that serves as a significant tool for the characterization of the functional groups of MOFs. FT-IR spectra are composed of specific peaks that provide useful information regarding the structure of MOFs. The morphology of MOFs can be characterized by transmission electron microscopy (TEM) and scanning electron microscopy (SEM). The former technique produces images by scanning the surface with a focused beam of electrons, while in the latter approach, the electron beam is transmitted through the specimen to provide an image. Finally, thermogravimetric analysis (TGA) can provide information regarding the structure of the material by determining the relationship between the mass loss and the temperature change of a MOF [49]. Figure 4 shows an example of an SEM micrograph, a TEM micrograph, an FT-IR spectrum, and a TGA curve image of a MOF material.

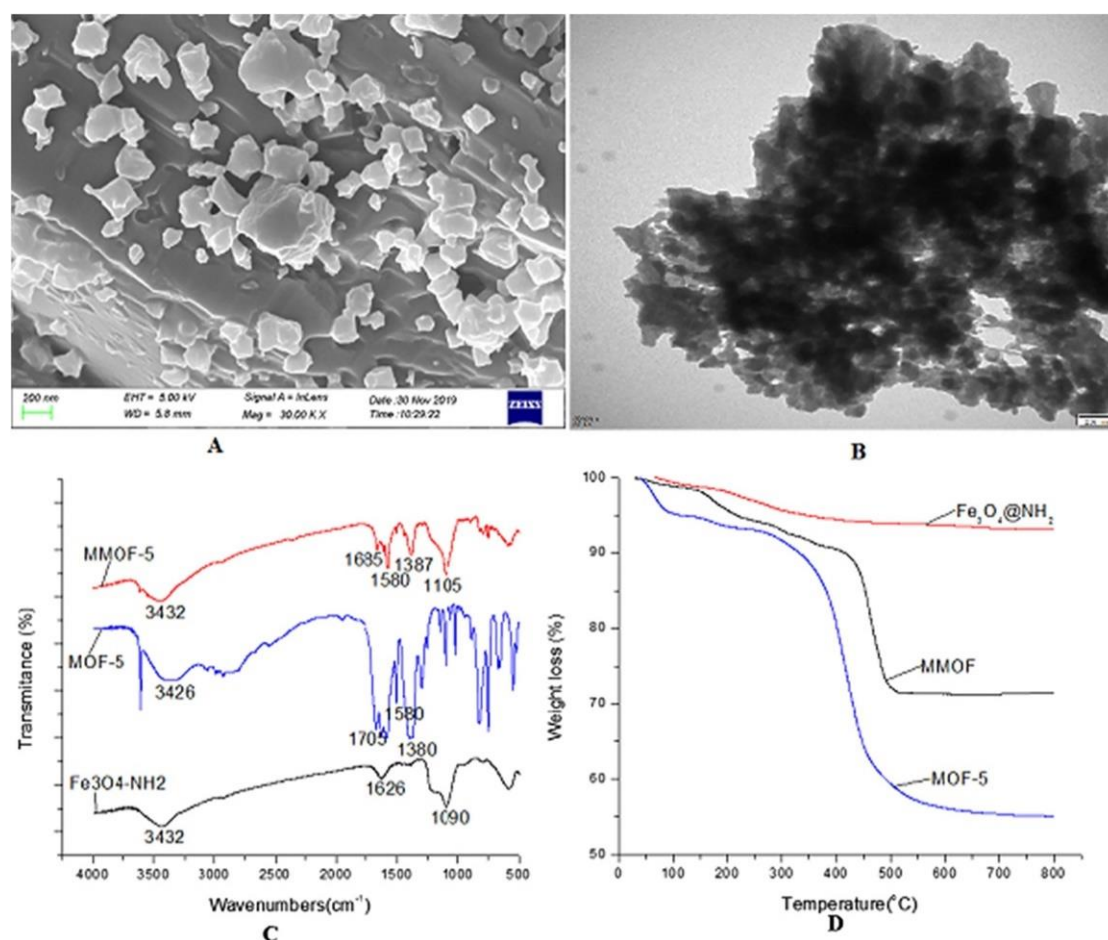**Figure 4.** Example of a SEM micrograph (**A**), a TEM micrograph (**B**), an FT-IR spectrum (**C**) and a TGA curve image (**D**) of a MOF material. Reproduced with permission from [50]. Elsevier. Copyright Elsevier, 2020.

Other characterization techniques for MOF materials include Brunauer–Emmett–Teller (BET) surface area, differential scanning calorimetry (DSC) and X-ray diffraction (XRD). DSC is a thermoanalytical technique that is able to measure the difference between the amount of heat that is needed to enhance the temperature of a material in comparison to that of a reference sample. This technique can be employed for inorganic or organic species to support corroboration of the structure of the as-synthesized material. BET can be used to study the specific surface area of the material, in combination with its pore size distribution, thus providing information for the surface and pore characteristics of the material. Finally, XRD for single-crystalline materials, or powder X-ray diffraction for cases when appropriate single crystals cannot be obtained, are two other important characterization techniques to study the chemical structure of MOF [16,49].

3. Bioanalytical Applications

Until now, many MOFs have been employed for the sample preparation of biological samples. Typical examples of the most common MOFs that have been evaluated in bioanalysis include MOF-5 synthesized from a zinc salt and benzene-1,4-dicarboxylic acid, MIL-100(Cr) synthesized from a chromium salt and benzene-1,3,5-tricarboxylic acid, MIL-101(Cr) synthesized from a chromium salt and benzene-1,4-dicarboxylic acid, MIL-101(Fe) synthesized from an iron salt, and benzene-1,4-dicarboxylic acid, MIL-53(Al) synthesized from aluminum salt and benzene-1,4-dicarboxylic acid and UiO-66 synthesized from a zirconium salt and benzene-1,4-dicarboxylic acid [51–53]. MOFs can exhibit good affinity towards small organic molecules. Thus, high adsorption efficiency can be observed through various mechanisms, including π–π interactions between the delocalized π-electron system

of the target analytes and the aromatic rings, the sorbents, and hydrophobic interactions. A further increase of the affinity towards the target analytes can be achieved through functionalization of the MOF sorbent [38].

ZIFs are a subfamily of MOFs synthesized from Zn^{2+} or Co^{2+} and imidazole linkers which are also used as extraction sorbents. ZIFs combine the benefits of zeolites and MOFs. The most common zeolitic imidazolate framework that has been evaluated in sample preparation is ZIF-8. This material can be synthesized from zinc nitrate hexahydrate 2-methylimidazole and it exhibits interesting characteristics including high surface area and permanent porosity [54,55]. It has been reported that unlikely with other zeolitic imidazole frameworks, ZIF-8 has exceptional chemical and thermal stability in aqueous alkaline solutions and water [56]. ZIF-7 is another common zeolitic imidazole framework that has been evaluated in bioanalytical applications [53].

3.1. Dispersive Solid-Phase Extraction

Dispersive solid-phase extraction is one of the most common extraction techniques used for the sample preparation of biological samples. In d-SPE, the sorbent is dispersed into the sample to adsorb the target analytes. After extraction, the sorbent is retained by a mechanical process, such as centrifugation. This technique is favored by the contact between the sorbent and the target analytes. As a result, one of the major advantages of this technique is its high extraction efficiency. Moreover, d-SPE is a simple and rapid sample preparation approach that avoids potential limitations of the conventional SPE process, such as channeling or blocking of cartridges or [57,58].

Rocío-Bautista et al. [59] evaluated three different MOFs (HKUST-1, MOF-5 and MIL-53(Al)) for the vortex-assisted d-SPE of parabens from environmental waters, cosmetic creams, and human urine samples. Vortex irradiation was chosen to avoid problems due to the non-uniform energy dispersion and due to temperature increase. Among the examined materials, HKUST-1 provided the best performance and was finally chosen. Due to the application of vortex irradiation, rapid extraction (around 5 min) was achieved.

MIL-53(Al) has been used as adsorbent for the extraction of estrogens and glucocorticoids from water and urine samples by dispersive micro-SPE prior to their determination by UPLC-MS/MS. Compared to MIL-101(Cr), MIL-100(Fe), and UiO-66(Zr) that were also studied, MIL-53(Al) provided better adsorption efficiency, as well as more significant binding ability towards the target analytes. Extraction of the target analytes took place due to hydrophobic effects among the phenyl rings of MOFs and the steroid ring system of the target analytes. Intermolecular hydrogen bonds between the carboxylic groups of MOFs and hydroxylic groups of hormones and π–π interactions between phenyl rings of MOFs and estrogens could also occur [60].

Other examples of MOFs that have been employed as d-SPE sorbents include the zirconium-based MOF UiO-66-NH_2 [61] with 2-aminoterephthalic acid as linkers and ZIF-67 [62]. In the former case, the adsorbent was used for the extraction of sialic acids from serum samples. In the latter case, the sorbent was synthesized from cobalt nitrate hexahydrate and 2-methylimidazole and employed for the extraction of buprenorphine from plasma and urine [61]. A ZIF-8 derived carbon porous has been also applied for d-SPE of methamphetamine from urine samples [63]. The sorbent was prepared by the carbonization of the precursor MOF at 800 °C under nitrogen steam for 8 h. The reported method enabled the rapid and cost-effective determination of methamphetamine.

3.2. Magnetic Solid-Phase Extraction

Magnetic solid-phase extraction is a form of d-SPE, that utilizes a magnetic sorbent which is added to an aqueous sample to adsorb the target analytes. Following the adsorption step, an external magnet is employed to remove the adsorbent and the sample solution is discarded. Afterwards, elution from the sorbent takes place by the addition of an appropriate solvent, the sorbent is isolated with the assistance of the magnet and the eluent is analyzed by an instrumental technique. This extraction techniques takes advantage of

the benefits of the d-SPE process, with the ease in separation due to the magnetic properties of the sorbent [64–66].

In order to prepare appropriate MPSE sorbents, magnetization of MOFs is required to enable the possibility of magnetic separation during adsorption and elution steps. To date, there are various methods for the magnetization of MOFs for their utilization as MSPE sorbents. Examples of these approaches include the direct magnetization of MOFs, the in situ growth of magnetic nanoparticles, the single-step MOF coating and the layer-by layer MOF growth. An interesting approach for the fabrication of magnetic sorbents derived from MOF materials is their carbonization under inert atmosphere that results in the formation of magnetic porous carbons [67]. Until now, various MOFs have been employed for the fabrication of MSPE adsorbents for the extraction of small organic molecules from biological fluids.

Magnetic MIL-101(Fe) (Fe_3O_4/MIL-101) has been utilized for the MSPE of six organophosphorus pesticides (OPPs) from urine and hair samples prior to their determination by GC coupled with a flame photometric detector (FPD) [51]. This MOF exhibits resistance to common solvents and to water. Thus, it is a good adsorbent for the sample preparation of aqueous solutions. Prior to the extraction process, urine samples were treated with acetonitrile and acetone for protein precipitation, while hair samples were treated with acetone under ultrasonic radiation. The novel hybrid sorbent exhibited high porosity and high extraction efficiency for the OPPs due to the presence of a large amount of oxygen groups and π-electrons.

Magnetic MIL-101(Cr) (Fe_3O_4@MIL-101) has been used for the extraction of phthalate esters from plasma samples followed by separation and quantification by GC–MS [68]. In this case, the adsorbent was synthesized with the hydrothermal approach and it was decorated with magnetite nanoparticles. The sorbent exhibited good extraction efficiency due to the hydrophobic and π–π interactions among the phthalate esters and the terephthalic acid units of the MOF. Additionally, the coordination interaction among the oxygen atoms of the analytes and chromium metal center of the MOF, as well as the iron metal centers of the magnetite, may be also driving forces for the extraction procedure. The novel MSPE method exhibited rapid extraction dynamics, high extraction capacity and reduced consumption of organic solvents. Moreover, Wang et al. [69] prepared a Fe_3O_4-NH_2@MIL-101(Cr) sorbent by fabricating amine-functionalized magnetite particles with MIL-101(Cr) and used it for the MSPE of monohydroxy polycyclic aromatic hydrocarbons from urine samples from coke-oven workers.

Liu et al. [70] synthesized magnetic UiO-66-OH (Fe_3O_4@UiO-66-OH) using 2-hydroxyterephthalic acid as organic linker and zinc as metal ion. The nanocomposite was employed for the MSPE of diuretics from urine. High adsorption efficiency was observed due to π–π interactions between the delocalized π-electron system of the target analytes and the aromatic rings the sorbents. Other factors that contributed to the extraction efficiency of the sorbent include its high surface, the metal cation–π bonds that were formed through electrostatic attraction, as well as the enhanced dispersibility of the sorbent in the sample that is assisted by the introduction of the hydroxyl group and enhances the adsorption of the target analytes through hydrogen bonding. Magnetic amino-functionalized UiO-66 (Fe_3O_4-SiO_2-NH_2@UiO-66) has been employed for the MSPE of urinary muconic acid from urine samples prior to its determination by HPLC-UV [71]. The introduction of the functional groups (i.e., amino, silica, hydroxyl, and carboxyl groups) of enhanced the selectivity, the chemical stability, and the extraction reproducibility of UiO. The amino group enhanced the anchoring sites in Fe_3O_4-SiO_2 for the target analytes and improves the charge-transfer interaction between the sorbent and the MOFs. As a result, good extraction efficiency was reported.

Safari et al. [72] synthesized the MOF material TMU-10 by mixing cobalt nitrate hexahydrate and 4,4′-oxybisbenzoic acid in dimethylformamide and heating the mixture at 145 °C for 48 h in an autoclave. After functionalization of the prepared MOF with magnetic nanoparticles, the composite material was used as an MSPE sorbent for the extraction of

tricyclic antidepressants from urine and plasma. The proposed sorbent exhibited high magnetization saturation, accessible sites, and specific adsorption affinities.

Other examples of MOFs that have been employed as adsorbents in MSPE approaches for the extraction of small organic molecules from biological samples include MIL-100(Fe) [73], MOF-5 [74] and bio-MOF-1 [75]. In the latter case, a zinc adeninate bio-MOF-1 was incorporated from biomolecules and biocompatible metal cations in order to reduce the potential leaching of toxic metal ions and other harmful constituents. This material was employed for the extraction of benzodiazepines from urine and wastewater samples and adsorption of the target analytes was performed through π–π interactions, electrostatic interaction, and hydrogen bonding [75].

Composite magnetic materials composed of MOFs and GO have been also used in sample preparation. GO is a material rich in oxygen-containing groups which enhance the interaction between the material and organic molecules through strong π-π stacking, hydrophobic interaction and hydrogen bonding [64]. Pourbahman et al. [76] synthesized and used a GO/MOF-74/Fe_3O_4/polytyramine nanoporous composite for the MSPE of prokinetic drugs from human plasma. The surface modification of GO by MOF-74 and polytriamine was found to improve the properties of GO nanosheets, such as surface area-to-volume ratio, adsorption capacity, hydrophobic interactions, and selectivity. Peng et al. [77] developed a magnetic sorbent composed of GO, magnetite nanoparticles and ZIF-8. In this case, the GO nanosheets acted as carriers for the MOF and the nanoparticles. The sorbent was found to be stable and recyclable, however the elution process was relatively slow. Another example of an MOF and GO composite material was proposed by Hua et al. [78]. The researchers prepared a GO-encapsulated magnetic Zr-MOF (GO-Mag@Zr-MOF) sorbent and used it for the MSPE of photosensitizers hematoporphyrin and hematoporphyrin monomethyl ether from human urine samples prior to their determination by ultra-performance liquid chromatography-high resolution mass spectrometry (UPLC-HRMS).

The combination of magnetic MOFs with MIPs for the fabrication of composite nanoparticles has been also proposed. MIPs are synthetic polymeric materials that exhibit high affinity over analytes with analogous molecular structure due imprinted sites complementary to a specific molecule. Thus, MIPs can be employed as adsorbents in sample preparation for the development of highly selective extraction protocols [79]. Asfaram et al. [80] used magnetic HKUST-1 composite as a support for surface imprinting of gallic acid MIP (HKUST-1-MOF-Fe_3O_4-GA-MIP-NPs). The novel sorbent was used for the ultrasound assisted extraction of gallic acid from urine, plasma and water samples and the overall method exhibited rapidity and selectivity.

Finally, porous carbons [81] and carbon nanotubes [82] derived from MOFs have also been employed as adsorbent media for MSPE of small organic molecules from biological samples. An iron-embedded porous carbon material derived from MIL-53(Al) was fabricated and used for the MSPE of sex hormones from water and human urine prior to their determination by HPLC-UV. The MIL-53-C possessed a high surface area and good magnetic behavior. The porous sorbent was prepared from the MIL-53(Al) via direct carbonization at 700 °C for 6 h under nitrogen flow. The novel sorbent exhibited high pore volume, high specific surface area, good magnetism and it was found to be reusable for at least 10 times [81]. Wu et al. [82] prepared magnetic carbon nanotubes with encapsulated cobalt nanoparticles through one-step pyrolysis of ZIF-67. The novel sorbent exhibited nanopores, a high specific surface area, and strong magnetic response. This sorbent was successfully employed for the extraction of flurbiprofen and ketoprofen from human serum.

3.3. Solid-Phase Microextraction

Solid-phase microextraction is a sample preparation technique in which extraction and preconcentration of the target analytes takes place at the outer coating of a fused-silica fiber. There are two basic modes of SPME, i.e., the direct immersion SPME (DI-SPME) and the

headspace SPME (HS-SPME). In the former approach, the fiber is directly immersed into the sample solution containing the target analytes, while in the latter approach the fiber is exposed to the gas phase above the sample. After the extraction step, the analytes can be desorbed either thermally or by the addition of an appropriate solvent [65]. Although there are multiple commercially available SPME fibers, most of them suffer from various limitations (e.g., short lifetime, ease of breakage, swelling in organic solvents etc.) [83]. As a result, the development of novel SPME fiber coatings is at the forefront of research. Until now, MOFs have been successfully utilized to prepare coated SPME fibers [40].

Non-steroidal anti-inflammatory drugs have been extracted from biological fluids and tablet formulation samples by a novel SPME fiber based on a capillary glass tube coated with magnetic copper benzene-1,3,5-tricarboxylate MOF. For the fabrication of the fibers, glass tube capillary fibers were used as substrate and the coating was performed by a sol-gel processing approach. The synthesized fibers showed a stable and reproducible response without interferences from the biological samples [84].

Wu et al. [85] prepared coated SPME fibers on etched stainless-steel wire by the in situ solvothermal growth method for immobilization of MOF-5 and ionic liquid functionalized graphene composite. Ionic liquids (ILs) are an alternative to conventional organic solvents that consist of bulky, non-symmetrical organic cations in combination with different anions (inorganic or organic). ILs are characterized by extraordinary properties, such as a negligible vapor pressure, good thermal stability and viscosity tunability [86]. Graphene exhibits good stability and high specific surface area, while it is rich in π-electrons and thus it is a useful adsorbent in sample preparation. The functionalization of graphene derivatives with ionic liquids can improve the dispersibility of the sorbent. The composite coated fibers exhibited high enrichment capacity for the target analytes (i.e., chloramphenicol and thiamphenicol) since it could interact through π–π and hydrogen bonding interaction. Moreover, high mechanical stability and durability were reported [85].

Chang et al. [87] combined the use of ZIF-8 coated SPME fibers with the use of a ZIF-8 coated capillary as stationary phase for GC column. For the fabrication of the coated fibers, the layer-by-layer deposition method was followed. It was reported that the proposed combination enabled the selective extraction and separation of n-alkanes from complex matrices such as petroleum-based fuel and biological fluids. Moreover, high enhancement factors and wide linear ranges were observed for the target analytes.

MIL-101(Cr) has been also used for the extraction of naproxen and its metabolite from urine samples. For this purpose, the sorbent was placed in a poly(ether ether ketone) (PEEK) tube as micro-trapping device for the online in-tube sorptive extraction prior to the determination of the target analytes by HPLC coupled with fluorescence detection (HPLC-FLD). In-tube SPME, is a variation of SPME in which a small sample volume migrates towards the stationary phase of a capillary tube and the target analytes are extracted, followed by desorption with an appropriate solvent [88]. MIL-101 exhibited good water, high surface area, permanent porosity and open metal sites, thus resulting in good extraction efficiency towards the target analytes. Moreover, urine samples could be directly subjected to analysis without any additional sample pretreatment (e.g., precipitation of proteins). Compared to C_{18}-bonded silica and multi-walled nanotubes, MIL-101 exhibited higher extraction capacity [89].

Lyu et al. [90] fabricated a MIL-53(Al) incorporated polymer monolith for the in-tube microextraction of non-steroidal anti-inflammatory drugs in water and urine samples prior to their determination by HPLC-DAD. Monolithic materials show several benefits for in-tube SPME applications, such as frit-free construction, biocompatibility, as well as simple in-situ preparation with controllable porosity. The novel MIL-53(Al) incorporated monolith was prepared via in-situ polymerization and it exhibited larger surface area than the neat polymer monolith. Urine samples were centrifuged and diluted with a phosphate buffer solution prior to the extraction procedure. The novel monolithic column exhibited high specific surface area and resulted in satisfactory extraction efficiencies. Moreover, reusability of the monolith column for 120 times was reported. Another example of a

MOF-based monolithic column was reported by the Luo et al. [91]. In this case, a NH$_2$-MIL-53(Al)-polymer monolithic column was employed for the online coupling with HPLC for the direct and sensitive determination of estrogens in human urine samples. The novel column exhibited high enrichment capability, good permeability, chemical stability, as well as long lifetime.

An interesting format of SPME is SPME arrow, which was recently introduced. SPME arrow combines the benefits of conventional SPME fiber and SBSE. This technique employs an arrow-shaped tip to provide conservative penetration of septa [92,93]. Due to the robust substrate and the large surface for immobilization of coating, SPME Arrow exhibits high extraction capacity. MOFs have been employed to develop coatings for SPME arrow [93]. Currently, the applications of SPME arrow are mostly focused on the analysis of food and environmental samples. However, their application for the extraction of small organic molecules in bioanalysis is also expected to gain popularity.

3.4. Stir Bar Sorptive Extraction

Stir bar sorptive extraction is a sample preparation technique that was introduced in 1999 by Baltussen et al. [94]. SBSE utilizes a coated stir bar that is inserted into a vial containing the sample and the adsorption of the target analytes is performed under stirring to reach equilibrium. Subsequently, elution of the adsorbed analytes is performed either by adding an appropriate solvent or thermally [20]. Among the advantages of SBSE are the simplicity of the extraction step, its overall good extraction efficiency, the reduced solvent consumption and the possibility to perform solvent-free sample preparation [20]. Currently, PDMS coated stir bars are widely used since they are commercially available, however a lot of research is focused on the development of coated stir bars with high selectivity and sensitivity [95]. MOFs have been successfully utilized to develop coatings for stir bars for the SBSE of small organic molecules from biological matrices.

Wang et al. [96] prepared a SBSE device by in situ immobilization of MIL-68 onto chemical resistant PEEK jacket. For this purpose, the MIL-68 material was prepared through the solvothermal approach from benzene-1,4-dicarboxylic acid and aluminum chloride hexahydrate. Moreover, the PEEK jacket was functionalized and plenty of benzoic acid groups were available to bind with the MOF material. The novel SBSE device was used for the extraction of parabens from cosmetics and rabbit plasma. Under optimum condition, the coated SBSE could extract the analytes within 2 h, while 250 μL of methanol were required for their desorption. The proposed method exhibited good performance characteristics.

Fluorouracil and phenobarbital have been extracted from urine and plasma samples by a SBSE coated with a ZIF derived nanoporous carbon [97]. For this purpose, ZIF-67 was initially prepared from cobalt nitrate hexahydrate and 2 methylimidazole, followed by carbonization at 700 °C under nitrogen flow for 6 h. Subsequently, a borosilicate glass bar containing an iron bar were activated and a silicon glue was employed as adhesive media to prepare the coated bars. Due to the strong adhesion of the sorbent onto the surface of the SBSE bar, good mechanical and chemical stability were observed and the SBSE media were found to be reusable for up to 70 times.

3.5. Pipette Tip SPE

Pipette tip SPE is a miniaturized format of SPE in which the sorbent is usually placed between two frits inside a pipette tip. Extraction of the target analytes is achieved after several repeated aspirating/dispensing cycles to complete. Pipette-tip extraction is a rapid and easy extraction technique that requires low consumption of organic solvents [22,98]. Moreover, other advantages of PT-SPE are its good overall extraction efficiency and the possibility of automation. However, only a small number of commercially available tips are currently available [99]. MOFs have been successfully employed as adsorbents for PT-SPE in bioanalysis. An important consideration for the utilization of MOFs in PT-SPE methods is the minimal back-pressure during sample and solvent aspiration [98,100].

Kahka et al. [98] evaluated an amino-functionalized UiO-66 (UiO-66-NH$_2$) as sorbent for the PT-SPE of carbamazepine from urine and water samples prior to their determination by HPLC-UV [98]. The amino-functionalized MOF was prepared from zirconium chloride and 2-aminoterephthalic acid. Due to the amino functionality on organic linker, the novel sorbent exhibited good performance and selectivity towards carbamazepine. For this purpose, an aliquot of 5 mg of the sorbent was placed into a 20 μL pipette-tip which was further attached to 100 μL variables sampler. Extraction of the target analyte was achieved by aspirating the same sample solution in five aspirating/dispensing cycles, while elution was performed by aspirating different aliquots of the eluent for seven cycles. The developed PT-SPE combined the benefits of PT-SPE technique (e.g., rapid extraction and ease in operation) with robustness and large adsorption capacity of the novel MOF.

The same authors also proposed the utilization of a tantalum MOF as adsorbent for the PT-SPE of nicotine from saliva, urine and wastewater samples prior to their determination by HPLC-UV [100]. For the preparation of the novel sorbent, tantalum(V) chloride and benzene-1,3,5-tricarboxylic acid were employed, and the material was prepared through a microwave assisted reverse micelle procedure. The highest extraction efficiency was observed when 5 mg of the sorbent was placed into a 20 μL pipette tip. Extraction of nicotine was achieved by aspirating and dispensing the sample over the sorbent for 15 cycles, while 20 draw/eject cycles were required for the elution step. The proposed method provided high enrichment factors and low organic solvent consumption.

3.6. Other Extraction Techniques

MOFs have been also tested for the sorption of isopropanol and acetone in exhaled breath samples followed by their determination by GC coupled with flame ionization detector (GC-FID) [53]. These compounds are established biomarkers for diabetes. Three different MOFs, i.e., MOF-5, ZIF-7, and UiO-66, were examined as adsorbents in packed tubes. UiO-66 was found to be the most suitable MOF, due to its high surface area and its porous structure. Acetone and isopropanol were able to enter the main cavities of UiO-66, resulting in strong van der Waals interactions among the methyl groups in their structure and the aromatic rings in the ligands. Moreover, the O-atoms of the carbonyl group of acetone were able to donate electrons to the zirconium cation, resulting in higher adsorption efficiency compared to isopropanol. After the extraction step, thermal desorption of the analytes was performed and the developed method provided low LODs, long lifetime, and satisfactory reproducibility.

UiO-66, amino-functionalized UiO-66 (UiO-66-NH$_2$), and magnetic UiO-66-NH$_2$@Fe$_3$O$_4$-SiO$_2$ have been evaluated as adsorbents for the micro-extraction by packed sorbent (MEPS) of trans-muconic acid from urine samples followed by determination by HPLC-UV [101]. MEPs is as a miniaturized mode of SPE, in which conditioning, loading, washing and elution steps are performed at a microliter syringe instead of a SPE cartridge. Among the benefits of MEPs technique is the lower consumption of organic solvent, its simplicity and its low cost [101,102]. Among the three examined UiO-66 derivatives, the magnetic sorbent exhibited the highest sensitivity (in terms of detection limits), while all of the three examined materials showed good extraction performance.

MOF enhanced electromembrane extraction (EME) has been also utilized for biosamples' analysis. EME is an alternative to the LPME that is based on migration of charged species in an electric field. Due to the application of voltage, ionizable compounds are transported from an aqueous solution to an acceptor phase (Figure 5). Among the advantages of EME are the speed of the extraction, the low cost, the utilization of disposable extraction units, and the negligible organic solvents consumption [103]. Fakhari et al. [104] used a MIL-101(Cr) in a supported liquid membrane. This approach was successfully employed for the extraction of basic drugs from biological fluids.
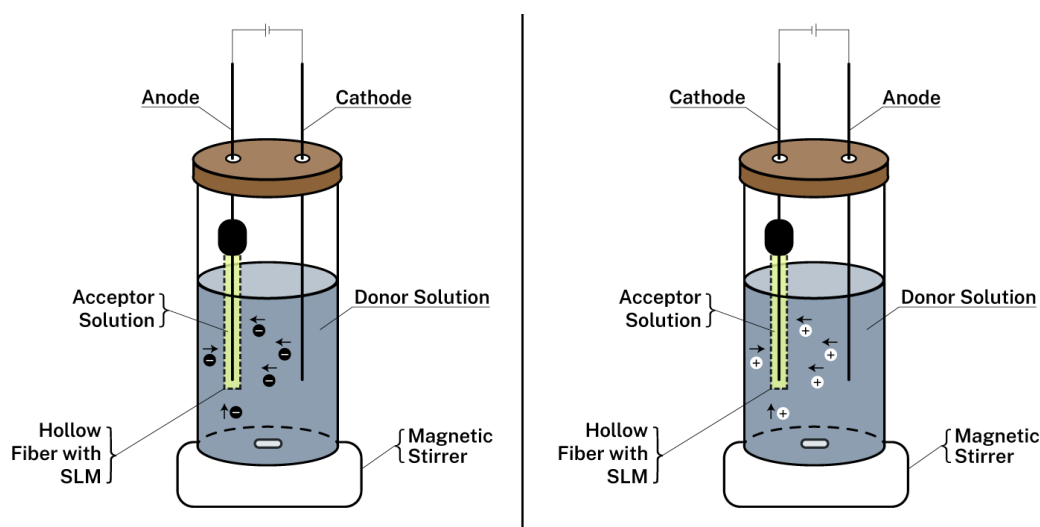
Figure 5. Main elements of the EME technique for the extraction of anions (left) and cations (right). SLM: Supported liquid membrane.

Gao et al. [105] developed a vortex-assisted membrane extraction based on MOF mixed-matrix membrane for the determination of estrogens in human urine. For this purpose, MIL-53(Al) was embedded in a polyvinylidene difluoride. For the sample preparation, the membrane was immersed into the sample solution and the target analytes were adsorbed within 15 min under sonication. The proposed membranes exhibited durability, a large-area, stability, and flexibility, while they were found to be reusable for at least 20 times.

Extraction by nanofibers doped with MOFs has been also proposed for the sample preparation of biological samples. Arabsorkhi et al. prepared a polyacrylonitrile doped with a copper benzene-1,3,5- tricarboxylate MOF composite nanofibrous material (Cu-BTC/PAN) via electrospinning [106]. The novel sorbent was used for the solid-phase extraction of trace tetracycline antibiotic. For the sample preparation, the composite material was added into the aqueous sample solution and removed by forceps after adsorption. Elution was performed in a different vial with acetonitrile. It was observed that the incorporation of the MOF material into the polyacrylonitrile nanofibers resulted in a significant increase of their specific surface area and porosity. Methyl-modified MOF-5/polyacrylonitrile composite nanofibers have been used for the SPE of estrogenic drugs from urine samples [107]. In this approach, the nanofibers were prepared via electrospinning and they were packed into the mini-disc cartridges to be used as SPE devices. More recently, Amini et al. [108] prepared electrospun nanofibers of polyacrylonitrile and a Ni-MOF 74 (PAN/Ni-MOF-74) and used them as sorbents for the spin-column micro-solid-phase extraction (SC-µSPE) of atenolol and captopril from biological fluids.

The applications of MOFs in bioanalysis are summarized in Table 1.

Table 1. Applications of MOFs in the determination of organic compounds in biological samples.

Analyte	Sample Matrix	MOF Sorbent	Analytical Technique	Sorbent Amount (mg)	Extraction Recovery (%)	LODs (ng mL^{-1})	Reusability	Ref.
			d-SPE					
Parabens	Water, urine and cosmetics	HKUST-1	HPLC-DAD	150	-	0.1–0.6	-	[59]
Estrogens and glucocorticoids	Water, urine	MIL-53(Al)	UHPLC-MS/MS	8	-	0.005–1.8	≤10 times	[60]
Sialic acids	Serum	UiO-66-NH$_2$	HPLC-FLD	8	-	0.11–0.16	≤8 times	[61]
Buprenorphine	Urine, plasma	ZIF-67	HPLC-UV	10	96.2	0.15	-	[62]
Methamphetamine	Urine	ZIF-8 derived carboxylated carbon porous	HPLC-UV	40	-	10	≤8 times	[63]
			MSPE					
Phthalate esters	Human plasma	Fe$_3$O$_4$@MIL-101(Cr)	GC-MS	15	-	0.15×10^{-3}	-	[68]
Monohydroxy polycyclic aromatic hydrocarbons	Urine	Fe$_3$O$_4$-NH$_2$@MIL-101(Cr)	HPLC-FLD	0.5	-	0.016–0.042	≤10 times	[69]
OPPs	Human urine, hair	Fe$_3$O$_4$/MIL-101(Fe)	GC-FPD	20	>76.8	0.21–2.28	≥10 times	[51]
Diuretics	Urine	Fe$_3$O@UiO-66-OH	HPLC-UV	10	90.3–103.0	0.08–0.23	-	[70]
Urinary muconic acid	Urine	Fe$_3$O$_4$-SiO$_2$-NH$_2$@UiO-66	HPLC-UV	20	96–98	0.001	≤times	[71]
Tricyclic antidepressants	Urine, plasma	Fe$_3$O$_4$@TMU-10	HPLC-UV	5	57.33–66.66	2–4	≥5 times	[72]
Dopamine, epinephrine and norepinephrine	Urine, serum	Fe$_3$O$_4$@MIL-100(Fe)	HPLC-UV	22	91.4–103.4	0.22–0.36	≥6 times	[73]
Colchicine	Root of colchicium extracts and plasma	MOF-5(Zn)-Fe$_2$O$_4$	HPLC-UV	2.5	-	0.13	-	[74]
Benzodiazepines	Urine, wastewater	Bio-MOF-1	HPLC-MS	15	84.1–94.4	0.71–2.49×10^{-3}	≤10 times	[75]
Prokinetic drugs	Plasma	GO/MOF-74/Fe$_3$O$_4$/polytyramine	HPLC-UV	15	88.0–90.0	0.4–1.1	≤15 times	[76]
Atorvastatin and simvastatin	Urine	Composite sorbent of ZIF-8, Fe$_3$O$_4$ and GO	HPLC-DAD	25	-	0.116–0.387	≥7 times	[77]
Hematoporphyrin and hematoporphyrin monomethyl ether	Urine	GO-Mag@Zr-MOF	UPLC-HRMS	5	>98	0.036–0.042	≤8 times	[78]
Gallic acid	Urine, plasma and water	HKUST-1-MOF-Fe$_3$O$_4$-GA-MIP-NPs	UV-Vis	1.6	98.13 (average)	1.377	≥6 cycles	[80]
Sex hormones	Urine	MIL-53(Al) derived carbon	HPLC-UV	15	>94.6	0.1–0.3	≥10 times	[81]
Profens	Serum	Carbon nanotubes derived from ZIF-67	HPLC-UV	20	-	0.60×10^{-3}	≥10 times	[82]

Table 1. *Cont.*

Analyte	Sample Matrix	MOF Sorbent	Analytical Technique	Sorbent Amount (mg)	Extraction Recovery (%)	LODs (ng mL^{-1})	Reusability	Ref.
			SPME					
NSAIDs	Serum, plasma, urine, tablet	Magnetic Copper 1,3,5-tricarboxylate MOF	HPLC-UV	-	94.0–102.0	0.03–0.05	≥110 times	[84]
Chloramphenicl and thiamphenicol	Milk, honey, urine, serum	MOF-5	GC-FID	-	-	14.8–19.5 × 10^{-3}	≤150 times	[85]
n-alkanes	Petroleum-based fuel and human serum	ZIF-8	GC-MS	-	-	0.46–1.06 × 10^{-3}	-	[87]
Naproxen and its metabolite	Huma Urine	MIL-101(Cr)	HPLC-FLD	-	>85.3	11–34 × 10^{-3}	-	[89]
NSAIDs	Urine	MIL-53(Al)	HPLC-DAD	40	77.3–104	0.12–0.24	≤120 times	[90]
Estrogens	Urine	NH$_2$-MIL-53(Al)	HPLC-UV/FLD	-	75.1–120	0.002–0.040	-	[91]
			PT-SPE					
Parabens	Cosmetics and rabbit plasma	MIL-68	HPLC-MS/MS	-	-	0.001–0.002	-	[96]
Fluorouracil and phonobarbital	Urine and plasma	ZIF-67	HPLC-UV	-	-	0.21–1.4	≤70 times	[97]
			SBSE					
Carbamazepine	Urine	UiO-66-NH$_2$	HPLC-UV	5	-	0.05	≥8 times	[98]
Nicotine	Saliva, urine and wastewater	Tantalum MOF	HPLC-UV	5	92.8–111.3	0.7	≤11 times	[100]
			Others					
Trans-muconic acid	Urine	UiO-66 (1), UiO-66-NH$_2$ (2), UiO-66-NH$_2$@Fe$_3$O$_4$-SiO$_2$ (3)	HPLC-UV	≈3	86.0 (1), 95.0 (2), 98.5 (3)	0.005 (1), 0.005 (2), 0.003 (3)	≤70 times	[101]
Basic drugs	Urine, plasma	MIL-101(Cr)	CE-UV	-	66–95	0.61–2.7	-	[104]
Estrogens	Urine	MIL-53(Al)	HPLC-FLD	-	80.5–91.8	0.005–1.0	≥20 times	[105]
Tetracycline	Human plasma	Copper 1,3,5-tricarboxylate MOF	HPLC-UV	10	>90	2.4	≥12 times	[106]
Estrogenic drugs	Urine	Methyl modified MOF-5	HPLC-UV	5	85.6–94.8	0.02	≤15 times	[107]
Atenolol and captopril	Urine, plasma	Ni-MOF-74	HPLC-DAD	15	77.5–87.5	0.13–0.15	≥50 times	[108]
Acetone, isopropanol	Exhaled breath	UiO-66	GC-FID	50	89.1–106.7	0.79–0.84	≥120 times	[53]

4. Conclusions

Unequivocally, MOFs are an interesting choice of sorbents that enrich the analytical toolbox for the extraction of small organic molecules from biological samples. Due to their superior characteristics these materials have been successfully utilized with many sample preparation techniques. (e.g., MSPE, d-SPE, SPME, PT-SPE, etc.). Moreover, MOFs have been proven to be suitable sorbents for the enrichment of a wide variety of chemical compounds (e.g., antibiotics, antidepressants, endocrine disrupting compounds, etc.) from complex biological sample matrices (e.g., plasma, urine, exhaled breath, etc.).

Future perspectives in the field of sample preparation of biological samples with MOFs include the further enhancement of the stability of these sorbents in aqueous environment. Improved sorbent stability can lead to sorbent reusability and recyclability that complies with the terms of Green Analytical Chemistry while it significantly reduces the total analysis cost. Additionally, further evaluation of more MOFs and functionalized MOF nanocomposites coupled with various extraction techniques (e.g., d-SPE, MSPE, SBSE, PT-SPE) is of high importance, since an almost unlimited combination of metal ions, ligands, and other functional groups can be employed to prepare highly efficient adsorbents. Therefore, it is important to develop more sorbents for the accurate and selective extraction of various target analytes from biological samples. Moreover, the development of on-line extraction techniques that can decrease the sample consumption, the usage of organic solvents, as well as the required sample preparation steps should be also explored.

Finally, the application of MOFs for the sample preparation of alternative biosamples is another interesting future perspective regarding the exploration of MOFs. Until now, these materials have been widely employed for the sample preparation of common biological samples, such as urine, blood plasma, and blood serum. However, since MOFs are found to be suitable sorbents for these matrices, they could be potentially used for the extraction of small organic molecules from alternative samples, such as saliva, nails, hairs, vitreous humour, etc.

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