OVERVIEW OF MIXED-MODE ION-EXCHANGE MATERIALS IN THE EXTRACTION OF ORGANIC COMPOUNDS

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Abstract

Mixed-mode ion-exchange materials, including silica-based, polymer-based and other supports, have been applied in sample treatment with different techniques, mainly solid-phase extraction, but also other microextraction techniques such as solid-phase microextraction, stir bar sorptive extraction and microextraction by packed sorbent. These materials are widespread because they conveniently combine capacity (through the reversed-phase interactions in the material backbone) and selectivity (through the specific ion-exchange interactions).

This review provides an overview of the advances and applications of mixed-mode ion-exchange materials for the extraction of organic compounds from complex matrices in environmental, food and biological samples. We summarise the different approaches used to prepare these materials and discuss the extraction protocols applied and the types of compounds and samples analysed based on different selected examples.

Keywords

Mixed-mode ion-exchange materials; silica-based; polymer-based; ion-exchange interactions; reversed-phase interactions; organic compounds; solid-phase extraction; solid-phase microextraction; stir-bar sorptive extraction; microextraction by packed sorbent.

1. INTRODUCTION

One of the remaining challenges for analytical chemistry is to develop analytical methods for determining target and non-target organic compounds in complex samples of different origins, such as environment, food or biological tissues and fluids. Hyphenated chromatography-mass spectrometry techniques have become well established for achieving this aim. Nonetheless, sample treatment still plays an important role in the analytical methods since it not only helps to enrich the compounds and so achieve lower detection limits, but also to clean up the sample matrix.

Among the different extraction techniques, for liquid samples or for liquid extracts from solid samples already extracted, the most widely applied are sorptive extraction techniques, mainly solid-phase extraction (SPE) and its modifications. However, considerable progress has been made in microextraction techniques, such as solid-phase microextraction (SPME), stir bar sorptive extraction (SBSE) and microextraction by packed sorbent (MEPS), among others. The main reason for this is the versatility of materials available that cover different types of interactions [1,2]. Choosing the appropriate material during sample treatment is the key point in sample treatment since it determines the type of interactions and retention with the compounds, and, eventually, it can significantly affect the selectivity and capacity of the whole analytical method.

To date, a number of materials have been reported and most of them have been commercialised. In SPE, silica-based modified with groups such as C_{18}, C_8, CN, phenyl or NH_2 were the first to be introduced. However, they have some drawbacks, including instability at extreme pH, the presence of residual silanols and the low retention of polar compounds. Later, carbon-based sorbents, including graphitised carbon black (GCB) and porous graphitic carbon (PGC), appeared. However, their high retention involved some elution problems with some compounds. Polymer-based sorbents based on hydrophobic polystyrene-divinylbenzene (PS-DVB) improved the disadvantages of the previous sorbents. Gradually, different polymer sorbents have been developed to accommodate high capacity by means of preparing hypercrosslinked structures that enhance the specific surface area (SSA) and/or introduce hydrophilic moieties [3]. In recent years, other developments in sorbent technology for exploiting capacity have emerged, including carbon nanomaterials, and metal-organic frameworks, among others [1,4].

To improve selectivity, molecularly imprinted polymers (MIPs) that have specific cavities in shape and chemistry were designed to selectively interact with the target analyte and/or structurally related compounds, but remove all other compounds including interferences [5].

For the other microextraction techniques, few types of materials are only available, except in the case of MEPS, which usually sources its materials from SPE materials. In SPME, the commercially available coatings are mainly polydimethylsiloxane (PDMS), polyacrylate (PA), carbowax (CW), carboxen (CAR), DVB and combinations of them. Different in-house prepared materials appeared later to cover the retention of a broad group of compounds with suitable capacity [6,7]. For SBSE, for years PDMS was the only commercially available coating. Later, EG-Silicone and PA phases appeared and different research groups developed other hydrophilic phases in order to improve the extraction of the more polar compounds [6,8]. Phases have also been discreetly developed based on MIP technology and have been applied to both SPME and SBSE [5,6].

Although capacity and selectivity can be achieved separately, it is of great interest to combine them in a single material. With this aim, in recent years research into material technology is focusing on developing mixed-mode ion-exchange materials [4,9]. These materials are mainly based on either the silica or polymeric phase in which ionisable functional groups specifically designed to interact with ionic species have been introduced. Therefore, there are ion-exchange interactions (specific) between the ionic moiety and the ionic or ionisable compounds and reversed-phase interactions (unspecific) between the phase backbone and the rest of the compounds. SPE is also the technique that most applies mixed-mode materials, although in recent years some applications of this kind of material in other extraction techniques have been developed.

It should be noted that purely ion-exchange materials such as those based on amorphous silica modified with ion-exchange groups are not considered to be mixed-mode ion-exchange materials since these materials only interact through the ion-exchange interactions and not through the reversed-phase interactions that emerge in the material network. Therefore, these ion-exchange materials have a poor capacity to retain organic compounds, and are thus mainly applied to retain inorganic species, such as metals, or to clean up matrices from (ionic) interferences and rinse out target compounds [10].

In this review, we present and critically discuss the use of mixed-mode ion-exchange materials in sample treatment. The synthetic approach and the main properties of each material are presented. We then evaluate their application to extract different types of organic compounds

from complex matrices of different origins, including environmental, biological and food samples.

2. FUNDAMENTALS

Mixed-mode ion-exchange materials can be classified into four groups depending on the ionic moiety attached to them. These groups are based on the combinations of either strong or weak and cationic or anionic. The extraction protocol should be adapted accordingly in order to exploit the ionic-exchange interactions and promote selectivity during the extractions.

Strong cation exchange (SCX) materials are usually functionalised with sulfonic groups (pK_a < 1), which remain negatively charged independently of the pH conditions. This group establishes cation-exchange interactions with the protonated (basic) compounds in the sample. In contrast, strong anion-exchange (SAX) materials that are functionalised with quaternary amines remain positively charged and establish anion-exchange interactions with deprotonated (acidic) compounds in the sample. The common feature of these strong ion-exchange materials is that the material remains charged regardless of the pH, and the interactions with the analytes can be promoted or disrupted depending on the chargeability of the compounds in the different extraction steps. Figure 1 summarises the recommended protocol for each of the four types of ion-exchange materials. For instance, in the recommended protocol for SCX, loading the sample at pH 3 ensures the protonation of the basic compounds (common pK_a > 6) so that they can establish ionic interactions with the sulfonic group in the material. During the washing step, the aqueous-based solution removes the most water-soluble compounds attached to the material by reversed-phase interactions; while, the organic solvent-based washing removes all non-protonated compounds attached by reversed-phase interactions. Thus, ideally, after this type of washing step, only those compounds (basic) attached to the material by ionic-exchange interactions are still (specifically) attached. During the elution step, the basic additive (NH_4OH) ensures the deprotonation of the basic analytes, and although the material is still in its ionic form, the ionic interactions between them are disrupted. Finally, the basic analytes elute thanks to the elution strength of the organic solvent.

Weak cation-exchange (WCX) materials are usually modified with carboxylic acid or any weak acidic group (pK_a < 4) that is negatively charged at neutral or basic pHs (above its pK_a). This group establishes cation-exchange interactions with the protonated (basic) compounds in the sample. In the case of weak ion-exchange materials, however, the chargeability of both the material and the compounds can be switched depending on the pH. During the elution step

(Figure 1), the acidic additive ensures the protonation of the weak acid moiety (carboxylic acid) of the material rather than switching the chargeability of the compounds. As the material is transformed into its neutral form, it can no longer establish ionic interactions with the compounds, which elute thanks to the elution strength of the organic solvent. Weak anion-exchange (WAX) materials are modified with either primary, secondary or ternary amines (weak cation groups) (pK_a > 6). This cationic group promotes ion-exchange interactions with the deprotonated acidic compounds (pK_a < 4) in the sample under neutral conditions, when both moieties are in their charged form.

Using this recommended protocol (Figure 1) favours the specific ionic interactions between the mixed-mode ion-exchange materials and the compounds, and these interactions are not disrupted unless the pH is changed. This allows solvents of high elution strength to be used during the washing step, which favours selectivity when mixed-mode ion-exchange materials are used in the extraction techniques. Nonetheless, most studies do not follow a protocol that fully exploits the ion-exchange interactions, and therefore, selectivity is not promoted in these methods.

3. SOLID-PHASE EXTRACTION

Mixed-mode ion-exchange materials are most used in SPE because they were first introduced for this technique, and they are continuously developed and applied for SPE. As there are numerous materials available, in this section we cover and present mixed-mode ion-exchange materials prepared on silica-based materials and polymer-based materials separately. In another subsection, we also present other types of supports, like carbon.

3.1 SILICA-BASED MATERIALS

Mixed-mode ion-exchange silica-based sorbents combine both ion-exchange moieties and alkyl chain groups so that they can simultaneously deliver ionic interactions and reversed-phase interactions, respectively. Several commercial brands provide these types of sorbents. For instance, the Isoute series from Biotage offers Isolute HCX (SCX), HCX-Q (WCX) and HAX (SAX). In particular, Isolute HCX combines C_8 alkyl chains (non-polar) and $-SO_3^-$ moieties (SCX), and Isolute HCX-3 combines C_{18} alkyl chains with $-SO_3^-$ moieties. In Isolute SCX-2, the bare silica (-OH) is functionalised with the SCX moieties, and therefore, it is not classified as a mixed-mode sorbent. Similar sorbent phases are commercialised by other brands, such as Discovery DSC-MCAX, which combines C_8 alkyl chains with benzene sulfonic acid from Sigma-Aldrich; and the Bond Elut series with Certify (SCX) and Certify II (SAX), which both combine C_8 alkyl chains with the respective ionic moiety, for example. Table 1 shows selected examples of the

application of mixed-mode ion-exchange silica-based sorbents. For example, Bond Elut Certify II (C_8 and SAX moieties) was used for extracting an antihistaminic drug (hydroxyzine) and its major metabolite (cetirizine) from whole blood samples. During the SPE protocol, the authors used different elution solvents depending on the analyte. That is, for the elution of cetirizine, which has a carboxylic acid functionality, they needed acetic acid (HAc) as an additive since this compound is bound with WAX interactions with the sorbent [11].

Apart from the commercially available sorbents, different research groups have developed in-house sorbents that are functionalised with different types of ion-exchange moieties than the commercial sorbents. Table 1 shows examples of the application of these in-house sorbents. A ternary mixed-mode silica sorbent with octamethylene, carboxyl and amino groups has been prepared [12]. After careful optimisation of the SPE protocol, the sorbent was applied to extract a group of drugs (with basic, acidic or neutral character) from human serum samples. The authors concluded that the retention mechanisms of this multi ion-exchange sorbent were too complicated and electrostatic repulsion of groups of similar ionic behaviour might arise during the retention. Moreover, they found that hydrophobic interactions played the dominant role in retaining the neutral and acidic compounds, and cation-exchange interactions played the main role for basic compounds [12].

Different authors have developed mixed-mode ion-exchange silica-based sorbents by functionalising with ionic liquids (ILs) to obtain sorbents with SAX features [13–16]. Nevertheless, when most of them were applied to SPE, the protocol did not include an exhaustive washing step to exploit the ion-exchange interactions. More details on this are shown in Table 1. As an example, Vidal et al. [13] prepared three IL-functionalised silica sorbents and applied them to extract a group of organic acids, amines and aldehydes. The results showed that SAX interactions were predominant, but reversed-phase interactions also played a role in the retention.

Although ion-exchange silica-based sorbents have been used in several applications, these materials have some drawbacks, as already mentioned in the Introduction. Some of these drawbacks have been solved with the introduction of organic-inorganic hybrid materials. These materials have unique features because the inorganic unit (thermally stable and robust) is combined with the organic one (large sorption capacity and strong binding affinity toward the target analytes). In addition, it has high flexibility for tuning its structure and properties depending on its starting units and synthesis [17]. Thus, it is also feasible to obtain ion-exchange materials with organic-inorganic hybrid material as a core. For instance, Zheng et al.

[18] prepared a hybrid silica monolith that exhibits reversed-phase and SCX interactions. It was successfully applied to the on-line micro-SPE extraction of a group of sulfonamides from milk. Moreover, the performance of the silica monolith was compared before (only reversed-phase interactions) and after (reversed-phase and cation-exchange interactions) oxidation, and it was found to have a much higher extraction efficiency after oxidation. In another study [19], ampholine was chemically immobilised on hybrid organic-inorganic silica material. This material displays carboxylic acid and amine moieties that involved WCX and WAX interactions as well as reversed-phase interactions thanks to the structure of ampholine. Thus, when this sorbent was applied to extract a group of acidic and basic compounds from beverage samples (cola drink), some of the analytes' unexpected retention behaviours were attributed to the repellence between charges. Nevertheless, the results obtained were similar to those achieved separately with Oasis WAX (retention of acidic compounds) and Oasis WCX (retention of basic compounds) [19]. Table 1 details some other examples of organic-inorganic hybrid materials with ion-exchange moieties.

In addition, mesoporous silica is gaining research interest among the different approaches with inorganic-based materials because it has some outstanding features, such as high SSA (ca. 600 m^2/g), large pore volume, well defined pore-size distribution and modifiable surface properties [20]. Examples of bare mesoporous silica materials are MCM41 (Mobile Composition Matter Nº 41), SBA (Santa Barbara amorphous) KIT-6 (Korea Advanced Institute of Science and Technology-6) or HMS (hexagonal mesoporous silica), among others. Moreover, mesoporous silica can be modified with functional groups, and also onto other substrates, such as graphene (G) or magnetic nanoparticles (MNPs) [21]. These features make these materials very versatile. Thus, when an ionic moiety is put into place during functionalisation, the material becomes a mixed-mode ion-exchange material that has a framework with exceptional morphological properties. Examples of this can be found very recently in the literature. However, some of the studies are focused on extracting inorganic species or removing compounds rather than being used as part of an extraction technique [21–23].

Nonetheless, some applications of mesoporous silica material used to extract organic compounds have been reported [24–27] and some examples are shown in Table 1. Very recently, Casado et al. [25] functionalised mesoporous silica (HMS) with different proportions of octacyl and quaternary ammonium groups (HMS-C_8-NH_4^+) to obtain three different materials with reversed-phase and SAX retention mechanisms. These three materials were successfully applied in the dSPE to extract a group of polyphenols from juice samples. Finally, the selected HMS-C_8-NR_4^+ material with the highest amount of NR_4^+ groups provided the best

recoveries, which was attributed to the optimum compromise between reversed-phase and SAX interactions [25]. However, the proposed protocol did not include a washing step. Another mesoporous silica material (KIT-6) was functionalised with dendrimers (great functionalisation) to obtain a material for SPE that combines reversed-phase with anion-exchange interactions. This sorbent was selectively applied to extract a group of acidic drugs from urine. These selective interactions were promoted during the SPE protocol, which included a washing step that consisted of 5 mL of 5% MeOH in 25 mM phosphate buffer followed by 1 mL of ethyl acetate [28].

Alternatively, other authors have functionalised silica coated onto MNPs (SiO_2@Fe_3O_4), as for instance, the functionalisation with 3-aminopropyltriethoxysilane (APTES) to obtain a material (APTES@SiO_2@Fe_3O_4) that displays amino groups. This magnetic material was readily employed in dSPE to extract two chlorophenoxyacetic acids from environmental water samples. During the optimisation of the elution step, NH_4OH was added to break down the cationic interactions between the sorbent (amino-based) and the analytes (acidic). However, the authors did not mention the optimisation of the washing step, which was described to consist of 2 mL of water [29]. It should be noted that an organic-based washing step would benefit the removal of interferences bound to the sorbent through reversed-phase interactions. More examples of these composite materials with ion-exchange features can be found in Table 1.

3.2 POLYMER-BASED MATERIALS

Mixed-mode ion-exchange polymeric materials are prepared by incorporating ionic moieties into the polymeric backbone. They can be introduced by functionalising the polymer with an ionic group or by copolymerising with a monomer that already contains this ionic group. These mixed-mode ion-exchange polymeric sorbents also display both ion-exchange interactions and reversed-phase interactions. Similarly, the ionic groups can be categorised as SCX (sulfonic acid), SAX (quaternary amine), WCX (carboxylic acid) or WAX (primary, secondary or ternary amine). The polymeric backbone that governs the reversed-phase interactions can be macroporous (crosslinked polymers mainly obtained by suspension polymerisation that has an SSA up to 800 m^2/g) or hypercrosslinked (presents permanent porosity that leads to an SSA up to 2000 m^2/g as a consequence of its synthetic procedure). Thus, depending on the polymer morphology (macroporous or hypercrosslinked) and the polarity of the backbone (hydrophobic or hydrophilic), the retention of the mixed-mode ion-exchange polymeric sorbents is enhanced compared to that of the silica-based sorbents.

There are several commercially available mixed-mode ion-exchange polymeric sorbents, and as far as we know, all of them are based on previously commercialised polymeric macroporous sorbents, further modified with an ion-exchange group. Oasis HLB (polyvinylpyrrolidone-divinylbenzene, 800 m^2/g) from Waters has been further modified with sulfonic acid moieties to deliver SCX interactions in the Oasis MCX, and with dibutylmethylamine to obtain Oasis MAX (SAX interactions). In addition, Oasis WCX is obtained via oxidation of the intermediate chlorinated resin to obtain a resin functionalised with carboxylic acid. Oasis WAX is obtained by introducing piperazine groups into the Oasis HLB skeleton. Phenomenex supplies Strata series (PS-DVB copolymer functionalised with pyrrolidone moieties, 800 m^2/g) that is functionalised with the different ion-exchangers (i.e. Strata-XC, Strata-XA, Strata-X-WC and Strata-X-WA). Similarly, other brands also offer polymeric sorbents modified with different ionic moieties to deliver the respective SCX, SAX, WCX and WAX sorbents, such as the Bond Elut Plexa series (hydroxylated PS-DVB, 550 m^2/g) from Agilent Technologies, the Evolute family (hydroxylated PS-DVB, no information of SSA) from Biotage, Chromabond HR (PS-DVB, 1000 m^2/g) from Macherey-Nagel and the Cleanert family (functionalised PS-DVB, 600 m^2/g) from Bonna-Agela Technologies. Table 2 gives an overview of the applications in which commercial mixed-mode ion-exchange polymeric sorbents are included. Out of all of these options, the Oasis series is the most wide spread, which might be because it has been available for longer and has achieved excellent results. Therefore, more examples that use this series are found in the literature and accordingly in Table 2.

A study has compared the performance of the mixed-mode SCX and SAX polymeric sorbents from the Oasis and Bond Elut Plexa brands for extracting a group of β-blocker drugs (basic amino and alcohol functional groups) from urine samples [30]. The protocol applied in each case was the appropriate one (Table 2), and as expected, the mixed-mode SCX sorbents (Oasis MCX and Bond Elute Plexa PCX) provided the best results because, as the authors point out, the cationic-exchange interactions were exploited. Moreover, the performance between brands was similar in all the instances [30]. In another study [31], Oasis MAX was compared to C_{18} and Oasis HLB to evaluate the cleaning efficiency in the extraction of a group of eight monoalkyl phthalate esters (carboxylic acid in its structure) in porcine tissues, including liver, lung, heart, muscle, among others. Oasis MAX attained higher recoveries, especially for those compounds that showed lower recovery with the other sorbents. In addition, it was demonstrated that the extraction with Oasis MAX under basic loading conditions yielded improved recoveries.

The performance of Oasis WCX and Oasis MCX was compared for the extraction of a group of cathinones from river and sewage waters. Oasis WCX was selected since it provides better recoveries and lower matrix effect (ME) [32]. For the extraction of a similar group of cathinones from urine, Oasis MCX outperformed Oasis WCX in terms of recoveries and ME [33]. These results could be attributed to the competition of the urea present at a high concentration in urine for the active carboxylic sites in the sorbent, which disable the interactions with the target compounds [33]. Other studies that also dealt with urine samples, applied clean-up protocols that were slightly different from the recommended ones (Fig 1). For example, Strata-XL-A (SAX) and Strata-XL-C (SCX) were evaluated for extracting stanozol metabolites (basic anabolic steroids) from urine samples (containing interfering compounds of weak acidic character). After evaluating the two approaches, Strata-XL-A (rinsed with water/MeOH (90/10, v/v)) yielded higher recoveries and lower ME than Strata-XL-C (rinsed with pure MeOH). These unexpected results may be attributed to the large ionic interferences present in urine, which were effectively rinsed using water [34]. In another study, which used Oasis WCX to effectively retain cationic surfactants, the authors decided to wash with 6 mL of water plus 3 mL of 0.5% trifluoroacetic acid (TFA) in water in order to effectively wash the (inorganic) cations retained in the cartridge that could cause artefacts if they were injected into the MS detector [35]. Thus, depending on the application, aqueous-based washing can be more effective than organic-based washing. Therefore, it is highly advisable to optimise the SPE protocol specifically for each type of compound and matrix.

The pH should always be optimised in the different steps of the SPE protocol in order to fully exploit the selective ionic interactions. For example, for the extraction of sesamol (weak acidic compound) from sesame oil using Cleanert PAX (mixed-mode polymeric SAX sorbent), the authors paid a lot of attention to the ionic interactions established during the extraction because the sample (oil) was dissolved in organic solvent and in this media only the ionic interactions could be maintained. Thus, the loading was optimised under basic pH conditions, the washing under neutral pH conditions, and the elution under acidic conditions [36].

In contrast, in some studies, neither the protocol applied nor the compounds selected were suitable for exploiting the selective ion-exchange interactions. For instance, a multi-residue method based on SPE followed by LC-MS/MS was developed for the simultaneous determination of 24 pharmaceuticals and personal care products (PPCPs), endocrine disrupting chemicals (EDCs) and artificial sweeteners (ASs). During the optimisation of the SPE, Chromabond HR-X (mixed-mode polymeric SCX) was selected from among five sorbents (including polymeric, WAX and silica-based functionalised with C_{18}) because it provided the

best recoveries for all the studied compounds (%R >75%). Nonetheless, most of the target analytes were not able to establish cationic interactions with the sorbent and the protocol applied was not suitable [37].

In other studies, the mixed-mode ion-exchange polymeric sorbents are merely used as a clean-up cartridge [31,38–41]. In the extraction of three antiviral drugs from processed products, chicken tissues and eggs, the authors first extracted the target compounds from the solid samples using Quechers extraction with acidified ACN. After the extraction, the 10 mL of ACN extract was loaded directly onto an Oasis MCX cartridge. This cartridge was washed and the retained antiviral drugs were eluted (see Table 2 for details on the SPE protocol). After applying this clean-up, the target analytes were quantitatively recovered (80-92%) and the ME was lower than ± 5% [41]. Different extraction strategies have been tested in the determination of metronidazole from water, sediments and fish tissues. In sediments, Strata-XC was applied to purify the sediment extracts and it was demonstrated that the extraction method was much more efficient when the SPE conditions (Table 2) were adjusted so that the ion-exchange interactions between the sorbent and the compound were promoted [38].

Mixed-mode ion-exchange polymeric sorbents have also been connected in series to another SPE cartridge in order to exploit complementary features, which is often the clean-up of the sample matrix [39,42,43]. Evolute WAX (Biotage) was connected in series after Oasis HLB to eliminate the interferences from sewage samples, and not to retain the target compounds (a group of fluoroquinolones). Although the recoveries found using the single cartridge (Oasis HLB) were similar to those with the dual approach (Oasis HLB and Evolue WAX), the combination of cartridges helped reduce the ME [42]. Oasis MAX and Oasis MCX in series were also well-suited for the complete extraction of a group of micropollutants that had both acidic and basic properties. This dual approach outperformed the different approaches tested that consisted of single cartridges (SCX, SAX, WCX and WAX) or tandem approaches (combinations of neutral sorbent, SCX and SAX) all from the Oasis and Strata brands [43], because with the suitable protocol, Oasis MAX selectively enriches the acidic compounds, whereas Oasis MCX selectively enriches the basic compounds.

In addition, different in-house mixed-mode ion-exchange polymeric sorbents have been prepared. Table 2 lists some examples of these sorbents and their applications. For example, glycidylmethacrylate-ethylenglycoldimethacrylate (GMA-EDMA) was sulfonated to obtain a SCX sorbent that was evaluated for extracting a group of alkylate-purine adducts from human urine. In this study, the authors optimised the different parameters involved in the SPE

protocol. Among them, different solutions for washing out proteins and salt from urine samples were studied. They found that the best washing solution combines 3 mL of 2% formic acid in H_2O with 3 mL of MeOH/H_2O (50/50, v/v). The formic acid content could ensure the cationic interaction between the analytes and the sorbent, whereas the addition of MeOH washes off the weakly polar compounds and the undissociated acidic compounds [44](10264).

In another study, vinylbenzyl chloride-EDMA (VBC-EDMA) was functionalised with trimethylamine (TEA), imidazole, piperidine and pyrrolidine to obtain four mixed-mode sorbents with anion-exchange capabilities, which were evaluated for the extraction of a group of acidic and basic pharmaceuticals from tap and river water. Finally, the sorbent functionalised with imidazole provided the best results and was applied for analysing environmental water samples [45]. N-vinylimidazole (VIm) was also used as a monomer in the preparation of the copolymer with DVB [46] and EDMA [47]. It was then exploited as a SAX sorbent for the selective extraction of a group of acidic NSAIDs [46] or acidic oil degradation products [47] from environmental waters. In addition, the modification of polymeric sorbents with ILs (called polymeric ILs –PILs) has been reported. Most of these ILs are based on imidazolium derivatives, for example, N-methylimidazole-based ILs were attached to VBC-DVB [48,49] or a GMA-EDMA [50] polymer or N-butylimidazole was attached to a chlorinated styrene-DVB polymer [51] to deliver the respective mixed-mode anion-exchange polymeric sorbents. Alternatively, PILs can be prepared by copolymerisation of two ILs. For instance, N-vinyl-3-(2-methoxy-2-oxyl ethyl) imidazolium chloride ([VMIm]Cl) was copolymerised with 1,4-butanediyl-3,30-bis-l-vinylimidazolium dibromide (BVDB) to obtain a crosslinked polymer that delivers anion-exchange interactions with the cationic compounds. This sorbent was then used in the SPE of curcumin from its plant extract. During the sorption experiments it was demonstrated that both ion-exchange and H-bonding interactions arose during extraction [52]. Table 2 provides more examples of the application of PILs.

It has already been attempted to prepare mixed-mode ion-exchange polymeric sorbents that have dual functionality. For instance, different sorbents that contain different proportions of N,N-dimethylaminoethanesulfonic acid attached to GMA-EDMA polymers have been prepared. Later, the retention behaviour of these sorbents was evaluated under HILIC conditions (Table 2) towards a group of nucleobases (including acidic, basic and neutral compounds) in ultrapure water. After this evaluation it was found that in order to elute the acidic compounds (ionically retained through ternary amine groups) and basic compounds (ionically retained through sulfonic groups) an ionic aqueous solution was necessary rather than water alone [53]. Thus, it was demonstrated that this sorbent displays both cationic and anionic moieties.

Hypercrosslinked polymers have also been functionalised with different ionic moieties so that different mixed-mode ion-exchange polymeric sorbents that cover SCX [54], SAX [55,56], WCX [57] and WAX [58] with enhanced capacity features (thanks to the high SSA displayed) emerged. Figure 2 shows the chemical structure of these mixed-mode ion-exchange polymeric sorbents. For instance, for the preparation of the mixed-mode sorbent modified with SCX groups, the hypercrosslinked polymer (HXLPP) obtained via the Friedel-Craft reaction of the precursor based on VBC-DVB prepared by precipitation polymerisation was modified with different percentages of lauroyl sulfate. Finally, the HXLPP-SCX modified with 50% of lauroyl sulfate had the highest ion-exchange capacity (IEC) and largest SSA (1370 m^2/g), and showed the best features as a SPE sorbent when it was used for the extraction of a broad group of licit and illicit drugs from environmental samples [54]. A similar strategy was adopted to functionalise the HXLPP-WAX with ethylenediamine (EDA) or piperazine [58]. In contrast, HXLPP-SAX was functionalised with dimethylbutylamine (DMBA) before the hypercrosslinking because of the steric impediments of DMBA to react with the free chlorine groups [55]. This HXLPP-SAX was evaluated for the extraction of a group of pharmaceuticals from environmental samples. A similar HXLPP-SAX sorbent functionalised with trimethylamine (TMA) was applied to solid-phase extract a group of fluoroquinolones from milk [56]. In both studies, parallel experiments were performed using commercially available sorbents such as Oasis MAX [55,56] and SampliQ SAX [55], and similar or even better results were achieved with the in-house prepared HXLPP-SAX sorbents. To develop the HXLPP-WCX sorbent, the carboxylic moiety was introduced in the precursor monomer (methacrylic acid - MAA) used in the terpolymer MAA-VBC-DVB, which was further hypercrosslinked. HXLPP-WCX was successfully applied in the SPE, after the extraction protocol was carefully optimised, to extract a group of pharmaceuticals from environmental samples [57].

Composite materials based on a polymeric backbone have also been developed. For example, two SAX macroporous sorbents based on 2-(diethylamino)ethyl methacrylate (DEAEMA)-DVB-SiO_2 composites, which were then functionalised with different proportions of diglycidyl ether derivatives followed by quaternisation with TEA [59] or N,N-dimethylethanolamine (DMEA) [60], were prepared and evaluated for extracting a group of NSAIDS (including basic and acidic features) from effluent wastewater [59] and urine [60] samples. Both the reversed-phase and anion-exchange interactions were explored when the prepared sorbents were characterised and evaluated. As an example, Figure 3 shows a schematic illustration of these interactions and the disruption mechanisms between ibuprofen (as the model acidic compound) and the hyperbranched sorbent functionalised with DMEA [60].

In a more sophisticated approach, a polyamidoamine dendrimer was functionalised with magnetite (Fe_3O_4) nanoparticles to obtain a sorbent that displays WAX features due to the presence of primary and secondary amines in the dendrimer. Then, the sorbent was applied in the dSPE to extract a group of acidic compounds of the NSAID family. However, although the elution was optimised, the selectivity of the sorbent was not fully exploited because a washing step was not applied before elution [61].

3.3 MISCELLANEOUS MATERIALS

Different forms of carbon materials, such as carbon nanotubes (multiwallet carbon nanotubes-MWCNTs) and graphene oxide (GO), have the common feature that their surface chemistry is easily functionalised with different functional groups by introducing the rich chemistry of the –OH and –COOH groups onto the surface by oxidation [62]. There are different examples in the literature that functionalise these carbon-based materials with ion-exchange moieties; however, only a few of these examples have been exploited as mixed-mode ion-exchange sorbents since in most cases this ionic group is introduced only to avoid the aggregation of these carbon materials in aqueous solution [63,64]. Table 3 provides examples in which carbon materials are functionalised with ion-exchange moieties and shows their applications as mixed-mode ion-exchange materials.

To prevent aggregation, G/CNTs were functionalised with EDA [63] or G sheets functionalised with p-phenyl-SO_3H [64]. In contrast, Zhong et al. [65] exploited the prepared carboxylated-GO sorbent for the selective extraction of a group of sulphonamides from cosmetic products and prevented it from aggregating by suspending it with polyvinylchloride to obtain a composite material. Moreover, the performance of the prepared sorbent was compared to the sorbents from Oasis MCX and Oasis WCX. In general, the prepared sorbent provided better recoveries than the Oasis WCX sorbent, and similar recoveries to the Oasis MCX sorbent, which the authors attributed to several functional groups present in the carboxylated-GO. Later, in another study [66], the same authors prepared an amino-functionalised GO composite with PS-DVB (to prevent aggregation) for the selective extraction of a group of perfluorinated alkyl acids from human serum. During the elution step, 1% of NH_4OH in MeOH was used to break the ionic interactions between the target compounds and the sorbent [66]. However, a washing step to rinse out the interferences bonded by unspecific interactions was not applied.

There are some studies that coat a carbon-based material, such as G or CNTs, onto the surface of magnetic NPs. In addition, in some studies, these nanocomposites have been functionalised

with ion-exchange moieties such as 2-aminobenzotiazole [67], aminopyridimine [68] or some immidazolium-based ILs [69].

Layered double hydroxides (LDHs) are nanomaterials 2D structured on hydroxide layers consisting of positively charged metals (combining trivalent and divalent metal cations) separated by an interlayer region containing anions to maintain the charge neutrality. Due to this configuration, LDHs are promising materials for enriching anions thanks to their excellent anion exchange capacity, large SSA and porosity [70]. Figure 4A shows how the inorganic anions in the LDH structure are replaced by the anionic target compounds during the extraction. However, the application of LDHs as a sorbent in extraction techniques is less common than their use for directly removing anions from aqueous samples since the strong ionic interactions between LDHs and the anions are difficult to disrupt. This limitation could be solved by developing dissolvable LDHs (dissolved in TFA solutions at pH<4) for dSPE. This would mean that the elution step would not be necessary and would ensure that all the analytes would be present in the acidic media (Figure 4B). However, by doing so, the LDHs cannot be reused, which could make this process wasteful and time-consuming. In addition, the LDHs can be co-precipitated again by adding basic solution. Under these conditions, metal cations and the anionic analytes form new intercalated LDHs (Figure 4B) [71,72]. Table 3 shows some representative examples of the application of LDHs for extracting organic compounds. For instance, 5 mg of LDH based on Ni-Fe cations with NO_3^- as interlayer anions was used for the dSPE of haloacetic acids from drinking water. After the extraction, 100 µL of 8% TFA in water was added to the sorbent to dissolve, and an aliquot of this solution containing the analytes was injected directly into the LC-MS/MS [72]. To the best of our knowledge, no washing step was applied in any of the reported studies.

Other emerging materials such as metal-organic frameworks (MOFs) (structures formed by self-assembly of metal ions and organic ligands via coordinative bonds) have also been presented as sorptive materials in the extraction of different inorganic ions, and to a lesser extent, of organic compounds that also have anionic moieties [1,73]. In any case, the interaction mechanisms are not based on purely ionic interactions, but rather they are attributed to the unsaturated metal cation sites in MOF that facilitate the ability to coordinate the anions in the compounds with the open metal sites. Then, at some point, MOFs might also be considered as mixed-mode ion-exchange materials; however, to the best of our knowledge they have not been exploited as this yet.

4. SORPTIVE MICROEXTRACTION TECHNIQUES

Although SPE is the extraction technique most used for liquid samples, other techniques are also available, such as SPME, SBSE, MEPS, and bar adsorptive microextraction (BAμE), among others, as stated in the Introduction. In recent years, mixed-mode materials have also been applied to these techniques, although clearly to a lesser extent than in SPE. In the following section we cover the use and application of mixed-mode materials in these techniques, which in most cases corresponds to in-house synthesised materials.

4.1 SPME

SPME is a widely established technique and is applied in several fields. Several fibre coatings are commercially available, although none of them have mixed-mode ion-exchange properties. Mixed-mode ion-exchange materials based on silica or polymer have been used. The silica based C_{18}/SCX with propylsulfonic acid [74–77] and benzenosulfonic acid [78,79] are the most used, as can be seen in Table 4. In most cases, the authors use a prototype of mixed-mode SPME from Sulpelco, which, to the best of our knowledge, has not been commercialised as yet. This coating has mainly been used to extract basic drugs [75,77,79] from biological samples.

Apart from the prototype used, some authors have prepared their own fibres using several procedures. One of these consists in immobilisation of commercially available SPE sorbents using a Loctite 349 adhesive on stainless steel wire [78,80]. A variety of mixed-mode ion-exchange sorbents, both silica- and polymer-based, have been used, such as Clean Screen Dau (C_8 and benzenosulfonic acid) or mixed-mode Oasis or Strata series sorbents, among others.

Another fibre preparation procedure consists in chemically bonding dimethyloctadecyl [3-(trimethoxysilyl) propyl] ammonium chloride and 3-(trimethosysilyl)-propanamine, the gel precursors, on an anodized Ti wire [81]. The authors report a high mechanical strength and strong adhesion of the mixed-mode coating due to the anodised Ti wire having uniform TiO_2 nanotube arrays. The authors compared the results of this fibre with PA, PDMS and C_{18}-functionalised and NH_2-funcitonalised fibres for the extraction of perfluooctane sulfonate and perfluorooctanoic acid from river water, and found better results with the mixed-mode fibre.

Although all the examples described so far used SPME fibre, mixed-mode ion-exchange materials have also been developed in in-tube SPME [82], which overcomes the shortcomings of conventional silica fibres in terms of fragility and poor flexibility. To do this, a 10 cm PEEK tube, was first etched with sulphuric acid, then stepwise functionalised with dopamine and GO, which was in-situ immobilised. The authors applied this new material to extract quaternary alkaloids from herbs and plasma.

SPME fibre tips have also been tested with a C_{18}-SCX sorbent to extract amphetamine-type stimulants and synthetic cathinones, although the authors obtained better results with a PDMS-DVB fibre tip [83].

Apart from the different coatings used, the thickness and length of the coating are critical parameters in SPME. In terms of thickness, the prototype from Supelco was 45 µm thick, while the sorbent on Ti wire was approximately 5 µm thick. Different lengths of this prototype (coating lengths of 4, 7 and 15 mm) were evaluated for an *in vivo* SPME of biomarkers from tissue samples. The best results were obtained with a 7 mm length taking into account sensitivity and reproducibility [84].

All applications refer to direct immersion-SPME. As regards to the protocol used, in most cases the sample pH is not adjusted and, in biological fluids, the pH corresponds to 7.4 [74,76], which ensures the ion-interaction with basic compounds. In some cases, however, the sample pH was adjusted to 2 [81] to ensure the ionisation of the coating. The washing step is only applied in some cases [79,85] and only water is used, mainly to eliminate salts. For the elution step, a mixture of MeOH, ACN or water is used in most cases, and is adjusted at acidic or basic pH to disrupt the ionic interactions and favour the desorption of the retained compounds [76,78].

Some studies have compared the results obtained with mixed-mode coatings with other coatings commonly used in SPME. For instance, Duckovic et al. [80] evaluated 42 different SPME coatings (including mixed-mode both silica and polymer-based coatings) for the extraction of 36 metabolites from human plasma. The results showed that both mixed-mode and PS-DVB coatings are suitable for retaining the majority of metabolites. Another study [79] evaluated the effect of haematocrit on the SPME recoveries and tested a biocompatible SPME fibre coated with C_{18} and benzenesulfonic acid (prototype of Supelco) and a hydrophilic lipophilic balance (HLB) phase. The authors mentioned that the attachment of macromolecules is usually observed in the case of mixed-mode ion-exchange coating under aggressive agitation conditions and long extraction times. Therefore, a lower agitation speed had to be used (400 rpm), while for HLB, 1500 rpm was used. Different effects were observed depending on the analyte's characteristics and extraction parameters. While for some compounds no haematocrit effect was observed for any of the coatings, for others, the effect was observed only when a mixed-mode ion-exchange coating was used; and, another group of compounds found a great influence for both coatings.

As can be seen in Table 4, mixed-mode ion-exchange SPME coatings have been applied to extract several analytes from biological samples, not only by direct immersion [75,80] but also by *in vivo* sampling [85], which is quite advantageous in biological samples. An example in the environmental field is the extraction of perflurooctane sulfonate and perfluoroctanoic acid from a SAX mixed-mode coating [81].

4.2 SBSE

SBSE was developed to increase the amount of extraction phase, which results in higher amount of analytes being extracted from the samples. Although it was developed in 1999, there are still few commercially available phases, and these only include PDMS, EG-silicone and PA. PDMS is the most widely used. However, several in-house coatings have been developed [86], most of which introduce polar groups into their structure or ILs, which significantly improves the retention of polar compounds. These coatings are mainly polymeric, although there are also coatings based on PDMS combined with MWCNTs [87] or even PDMS/MOFs prepared by sol-gel approach [88].

Some of these coating can involve mixed-mode ion-exchange interactions; however, in most cases, the experimental conditions do not make it possible to exploit these types of interactions and they are used as a polar coating. This is the case of the stir bar based on MAA-DVB used to extract a group of polar pharmaceuticals in complex water samples [89].

Examples of the mixed-mode ion-exchange coatings in SBSE are shown in Table 5. As can be seen, most coatings are polymeric although one based on amino modified MWCNTs/PDMS has been described. They have not only been applied to water samples but also to urine and honey samples, and in all cases the extract has been analysed by LC.

Regarding polymeric coatings, Huang et al. [90] developed a monolithic material prepared in situ by copolymerisation of methacrylic acid-3-sulfopropyl ester potassium salt (MASE) and DVB, and evaluated different ratios of MASE and DVB to extract basic compounds. They applied it to extract a group of quinolones from water. Under the optimum extraction conditions, pH 5, both the reversed-phase interactions and cation-exchange interactions between the sulfonic groups in the monolithic material and amino groups in quinolones were enhanced. For the desorption, the authors used MeOH/water at pH 1.3 (80/20, v/v), which is not the most suitable protocol. The same stir bar material was also applied to extract nitroimidazole residues in honey [91]. This material extracted the compounds more efficiently than PDMS or poly(vinylpyrine-co-ethylene dimethacrylate) monolith stir bars.

Another monolithic stir bar based on VIm-EDGMA was prepared and the monomer, crosslinker and porogen compositions were optimised [92]. The best material was applied to extract perfluoroalkyl acids, and both the reversed-phase and ion-exchange interactions were exploited by adjusting the extraction pH to 3 and desorbing with MeOH containing 0.4% ammonia. The authors compared the performance of the new stir bar with the commercial ones, EG-silicone and PDMS, and better extraction efficiency and faster extraction dynamics were obtained with the mixed-mode stir bar.

Another example is the stir bar coated with MWCNTs/PDMS modified with 4,4'-diaminodiphenylmethane (DDM) [87]. The sol-gel technique was employed to prepare the MWCNTs-DDM/PDMS coating and the capillary glass bar containing an iron wire previously treated with NaOH was immersed vertically into the prepared sol solution for 24 h at 60 °C. Figure 5 shows a diagram of the process for preparing MWCNTs-DDM. These stir bars were applied to extract phenolic compounds at pH 4, which enables mixed-mode interactions, and desorption was carried out with MeOH/1mM NaOH (8/2) in order to disrupt the ionic interaction.

A mixed-mode ion-exchange polymer was recently applied in a hybrid approach developed by Grau et al. [93]: stir bar sorptive dispersive microextraction. This technique combines the principles of SBSE and dSPE in such a way that at a low stirring rate the magnetic material stays on the surface of the stir bar, whereas at a high stirring rate the material is completely dispersed into the sample. Once stirring ceases, the magnetic material containing the target analytes is retrieved by the stir bar without requiring an additional magnetic field. In this case, the sorbent material consists of a magnetic composite made of $CoFe_2O_4$ MNPs embedded into a mixed-mode WAX polymer, Strata-X-AW. This material was used to extract triphenyl phosphate (TPP) and its metabolite diphenylphosphate (DPP) in urine samples. In this case, the TPP was retained by means of hydrophobic and π-π interactions and the DPP by additional WAX interactions.

BAμE can also be considered a modification of SBSE. This technique is based on floating sampling technology and the bar is prepared by coating polyethylene hollow cylinder tubes with adhesive films, followed by covering them with powdered sorbents (0.5-2.5 mg). Different sorbents have been used, among them Oasis WAX and Oasis-MAX. For instance, a mixture of the two sorbents provided the best results for the extraction of NSAIDs from urine and water samples when the sample was extracted at pH 5.5, in which the NSAIDs are fully ionised, promoting the ion exchange interactions [94].

4.3 MEPs

MEPS is a miniaturised SPE that can be performed in both off-line and on-line mode connected to a GC or LC system without any modification. In this technique, a small amount of sorbent (1-4 mg) is directly packed into a small cartridge that it placed between the body and the needle of a syringe. Therefore, MEPS can be adapted to existing SPE methods simply by scaling the volumes. The type of sorbents used in MEPS can be the same as the one in SPE.

The MEPS technique has been extensively used in bioanalysis for a variety of samples, such as plasma, urine, oral fluid and blood, among others [95], shown in Table 6. The complexity of these kinds of samples, which require a clean-up step, together with the limited sample volume available, make MEPS a very attractive microextraction technique in bioanalysis.

MEPS syringes with several sorbents are commercially available from SGE, mainly made from silica or DVB, which are modified or functionalised to obtain different retention properties. Among these, C_8/SCX (80/20), which is a mixture of 80% C_8 and 20% SCX with a phenylsulphonic acid group, provides mixed-mode interactions and has been widely used in bioanalysis [96–100]. This mixed-mode sorbent has also been compared with C_8 and C_{18} sorbent for the extraction of 10 drugs of abuse C_8/SCX performed better for all the drugs except morphine and methadone, which showed slightly better extraction using a C_{18} phase [97]. The protocol applied includes a washing step of MeOH/H_2O (10/90, v/v) to eliminate some interferences from the sample, and the elution solvent contains NH_4OH to neutralise the compounds and disrupt the ion-exchange interactions.

Two other mixed-mode sorbents, Oasis MCX and Clean Screen DAU (C_8/SCX with benzenesulphonic group), together with C_8 and ENV+ sorbents, have also been evaluated for extracting cocaine and its metabolite. The highest extraction efficiency was obtained with C_8/SCX [101]. In this study the eluted fraction from MEPS was analysed by direct analysis in real-time (DART) and mass spectrometry using a time-of-flight analyser.

Although most of the sorbents used in this technique are commercial SPE sorbents, a recent study describes an in-house sorbent [102] and applies it in a modified set up using a spinal syringe connected to a syringe pump. The authors used Ni-Fe LDH nanostructures in MEPS. This type of material, which has been used in SPE as previously described, combines high SSA and a high anion exchange capacity. The authors determined NSAIDs from urine with satisfactory results.

Table 6 shows the conditions under which MEPS was applied and we can see that in most cases the sample is pre-treated and the MEPS technique is used as clean-up, as previously mentioned. The pH of the loading and elution steps was optimised in most cases in order to enhance the ionic interactions. In most examples a washing step is included based on water and a low percentage of MeOH. The solvent and pH were optimised for the elution conditions. For instance, Ares et al. [96] tested different elution solvents: 0.1% formic acid in H_2O/ACN (90/10, v/v), MeOH, dichlormethane/isopropanol/NH_4OH (78/20/2, v/v), 5% NH_3 in ACN and 5% NH_3 in MeOH. Better results were obtained with the ternary solution. They also optimised the washing solvent by changing the pH and % of MeOH. Although 0.1% formic acid proved to be the best washing solvent for most drugs, for morphine, the best results were obtained with H_2O/MeOH (90/10).

Although different sorbents have been already applied in MEPs, it is feasible that much others (similar to SPE) would be successfully exploited in MEPs.

5. CONCLUSIONS

Mixed-mode ion-exchange materials have been increasingly used in different extraction techniques to exploit both types of interactions to favour the retention of the target compounds as well as to clean up the sample.

They have been successfully prepared on supports such as silica-based, polymer-based or other emerging materials, including carbon nanomaterials or MOFs.

These mixed-mode materials have been widely applied to SPE to extract several types of organic compounds from different complex samples, including environmental, food and biological samples. Moreover, they have been progressively included in microextraction techniques, such as SPME, SBSE and MEPS, with successful results, although a clean-up step is not used in the extraction protocol as much as in SPE.

It can be anticipated that the field of mixed-mode ion-exchange materials will be extended in the future to other supports, extraction techniques and applications.

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FIGURE CAPTIONS

Figure 1. Recommended SPE protocols for each type of mixed-mode ion-exchange material.

Figure 2. Structure of four mixed-mode ion-exchange polymeric sorbents with a hypercrosslinked network.

Figure 3. Schematic illustration of the interactions (a) and disruption (b) mechanisms between the target analyte (ibuprofen) and the composite material (SiO_2@DEAEMA-DVB) functionalised with dimethylethanolamine (DMEA) that has reversed-phase and SAX interactions. Reproduced from [60] with the permission of Elsevier.

Figure 4. Schematic representation of LDH and its anion-exchange mechanisms (a), and the dissolvable and co-precipitations mechanisms (b). In this illustration, phthalic acid is an example of an analyte. Reproduced from [103] with the permission of the American Chemical Society.

Figure 5. Preparation process of MWCNTs-DDM. Reproduced from[87] with the permission of Springer.

Table 1. Commercial and in-house prepared mixed-mode ion-exchange SPE sorbents prepared on silica.

		SPE sorbent	Analytes	Sample	SPE conditions	% Recovery	Determination technique	Ref.
Commercially available	**SAX**	Bond Elut Certify II (C_8 + SAX) (Agilent Technologies)	Hydroxyzine cetrizine	Whole blood	Off-line SPE (? mg) L: 1mL blood → 5 mL acetate buffer 0.1M, pH4 W: 3 mL H_2O E (hydro.): 2 mL DCM/IPA/NH_4OH (85/15/3, v/v/v) E (cetrizine): 2 mL DCM/IPA/HAc (85/15/3, v/v/v)	87-118	GC-MS	[11]
	SAX	Isolute HAX (C_8 + SAX) (Biotage)	Sugammadex (type cyclodextrin)	Urine, plasma	96-well SPE plate L: 0.2 mL urine/ 0.25 mL plasma W: 0.5 mL H_2O/MeOH (95/5, v/v) + 0.5 mL H_2O/MeOH (25/75, v/v) E: 1 mL 20% HCOOH in EtAc (urine) E: 0.5 mL 5% HCOOH in MeOH (plasma)	29-46	LC-MS/MS	[104]
In-house prepared	**SAX**	Si-C_{18}/-SAX	Aristolochic acids	Herbs	Off-line SPE (20 g) L: 100 g herbs → 2 L 5mM K_2HPO_4/MeOH (50/50, v/v) W: 5 mL H_2O + 5 mL MeOH E: 7 mL 5% HCOOH in MeOH	67-105	LC-UV	[105]
	WCX/WAX	Si-COOH/-NH_2	Acidic, neutral and basic drugs	Human serum	Off-line SPE (500 mg) L: 2 mL pH 3-6 or 6-11 W: 3 mL MeOH/20 mM phosphate buffer (5/95, v/v) E: 2 mL MeOH + 2 mL 5% HCOOH in MeOH	90-100	LC-UV	[12]
IL	**SCX/SAX**	Si-IL (1-Alkyl-3-(propyl-3-sulfonate) imidazolium)	Organic acids, amines & aldehydes	Atmospheric aerosol water	Off-line SPE (100 mg) L: 0.5 mL W: 1 mL H_2O E: 0.5 mL 10% HAc in H_2O (acids) 0.5 mL 10% HAc in MeOH (amines)	87-110	LC-MS GC-MS	[13]

	SAX	Si-IL (N-methyl imidazolium)	Sulfonylurea herbicides	Surface water	L: 250 mL W: 5mL MeOH/H_2O (2/8, v/v) E: 10 mL ACN	54-100	LC-UV	[15]
Hybrid Organic-Inorganic	**SCX**	Si-C_8-SO_3^-	Sulfonamides	Milk	on-line µSPE (monolith) L: 1 mL pH 2.5 W: 0.08 mL 0.2% HCOOH in H_2O E: 0.15 mL mobile phase (ACN/20 mM NH_4Ac, 24/76, v/v)	40-92 (RR)	LC-UV	[18]
	WAX	Si-ampholine	Acidic & basic compounds	Beverage samples	Off-line SPE (50 mg) L: 10 mL pH 4-6 (acids), pH 6 (basics) W: 1 mL H_2O/MeOH (50/50, v/v) E: 1 mL H_2O/MeOH (50/50, v/v) pH 11(acids) 1 mL H_2O/MeOH (50/50, v/v) pH 1 (bases)	84-110	LC-UV	[19]
	WAX	Si-tris(2-aminoethyl) Amine-3-phenoxybenzal-dehyde)	Chlorophenols	Tap and surface water	dSPE (10 mg) L: 20 mL pH 8 W: - E: 0.5 mL 1% HAc MeOH	89-110	LC-UV	[106]
	SCX	Si-C_8-SO_3^-	Sulfonamides	Milk	on-line µSPE (monolith) L: 1 mL pH 2.5 W: 0.08 mL 0.2% HCOOH in H_2O E: 0.15 mL mobile phase (ACN/20 mM NH_4Ac, 24/76, v/v)	40-92 (RR)	LC-UV	[18]
Mesoporous	**SCX**	**SBA-15-C_{18}-SO_3^-** SBA-15-C_8-SO_3^-	Veterinary drugs	Meat	Off-line SPE (200 mg) L: 2 g →10 mL ACN/5% TCA in H_2O (50/50, v/v) W: 5 mL acetate buffer E: 2 mL ACN + 2 mL MeOH + 2 x 2 mL 3% NH_4OH in MeOH	70-100	LC- MS/MS	[24]

	SAX	HMS-C_8-SAX	Polyphenols	Juice	dSPE (50 mg) L: 5 mL pH 9 W: - E: 6 mL MeOH/H_2O (95/5, v/v) pH 9	70-100	LC- MS/MS	[25]
	WAX	SBA-15-NH_2	NSAIDs	Tap, river, wastewater	Off-line SPE (500 mg) L: 500 mL pH 7-8 W: 4 mL 25 mM phosphate buffer/MeOH (50/50, v/v) E: 3 mL 1% HAc hexane/EtAc (75/25, v/v)	85-114	LC-UV	[26]
composites	**WAX**	CB[6]-NH_2@SiO_2@Fe_3O_4 (Curcubit [6] uril)	Salvianolic acids	Natural plant water	MSPE (1 mg) L: 1 mL pH 5.5 W: - E: 1 mL 1% HAc in MeOH/H_2O (60/40, v/v)	95-106 RR	LC-UV	[107]
	WAX	APTES@SiO_2@Fe_3O_4 (3-aminopropyl-triethoxysilane)	Chlorophenoxy-acetic acids	Well and surface water	MSPE (30 mg) L: 25 mL pH 5 W: 2 mL H_2O E: 3 x 2 mL 1% NH_4OH in MeOH	80-100	LC-UV	[29]

ACN: Acetonitrile; APTES: 3-aminopropyltriethoxysilane; DCM: Dichloromethane; dSPE: Dispersive SPE; E: Elution; EtAc: Ethyl acetate; Fe_3O_4: magnetite; GC: Gas chromatogrpahy; HAc: Acetic acid; HCOOH: Formic acid; HMS: Hexagonal mesoporous silica; IL: Ionic liquid; IPA: Isopropanol; L: Loading; LC: Liquid chromatography; MeOH: Methanol; MS: Mass spectrometry: MS/MS: Tandem mass spectrometry; MSPE: Magnetic SPE; NH_4OH: Ammonium hydroxide; SAX: Strong anionic exchange; SBA: Santa Barbara Amorphous; SiO_2: Silica; SPE: Solid-phase extraction; SCX: Strong cationic-exchange; UV: Ultraviolate detector; W: Washing; WAX: Weak anionic-exchange; WCX: Weak cationic-exchange.

Table 2. Commercial and in-house prepared mixed-mode ion-exchange SPE sorbents prepared on polymers.

		SPE sorbent	Analytes	Sample	SPE conditions	% Recovery	Determination technique	Ref.
Commercially available	**SCX**	Oasis MCX (Waters)	Antiviral drugs	Processed products, chicken tissue, eggs	Off-line SPE (500mg) L: 5 g → 10 mL ACN acidified extract W: 6 mL 5% NH_4OH in MeOH/H_2O (40/60, v/v) E: 10 mL 5% NH_4OH in MeOH	80-92	LC-MS/MS	[41]
		Oasis HLB, MAX, **MCX** (Waters) **Bond Elut** Plexa, PAX, **PCX** (Agilent)	B-blockers	Urine	Off-line SPE (60 mg) L: 1 mL pH 3 W: 1 mL 2% HCOOH in MeOH E: 3 x 0.5 mL 2% NH_4OH in MeOH	79-89	LC-UV	[30]
		Strata-X-C (Phenomenex) Oasis HLB C_{18}	Cysteine	Saliva, human serum, pharmaceutical preparations	Off-line SPE (30 mg) L: 1 mL 0.1 M HCl W: 0.5 mL 0.1 M HCl + 0.5 mL MeOH E: 2 x 0.5 mL 5% NH_4OH in MeOH	93-97	LC-DAD	[42]
		Strata-X-C (Phenomenex) Supelco-NH_2	Metronidazole	Sediment	Off-line SPE (200 mg) L: L: 5 g → 15 mL 0.1 M HCl aq. W: 3 mL 0.1 M HCl + 3 mL MeOH E: 3 mL 5% NH_4OH in MeOH	89-97	LC-MS/MS	[38]
	SAX	Oasis MAX (Waters)	Gamma-hydroxybutyric acid (GHB)	Hair	Off-line SPE (500mg) L: 25 mg → 3.5 mL pH 7 W: 3 mL 0.03%NH_4OH in H_2O + 3 mL MeOH E: 3 mL 5%HAc in MeOH	80	LC-MS	[108]
		Tandem Oasis MAX-MCX	Micropollutants and its TP from ozonization	Tap, surface and WW	Off-line SPE (100mg) L: 1000 mL (MAX) W: 2 mL 5% NH_4OH aq. E: 6 mL 2% HCOOH in MeOH/EtAc (70/30, v/v) L: 1000 mL (MCX)	90-110	LC-MS/MS	[43]

					W: 2 mL 2% HCOOH aq. E: 6 mL 5% NH_4OH in MeOH/EtAc (70/30, v/v)			
		Strata XA Oasis MAX NVI-EDMA	Acidic oil degradation products	Harbor water	Off-line SPE (150mg) L: 300 mL W: 10 mL MeOH+ 2 mL H_2O + 3 mL THF E: 2 mL 0.2% HAc MeOH + 2 mL 1% HAc in MeOH + 2 mL 2% HCOOH in MeOH	74-92	GC-MS	[47]
		Cleanert PAX (Bonna Angela)	Sesamol	Sesame oil	Off-line SPE (500mg) L: 0.5 g → 20 mL basic EtOH W: 5 mL EtOH pH 7 E: 5 mL MeOH pH 2	88-106	LC-UV	[36]
	WCX	C_{18} + **Oasis WCX** Oasis HLB Oasis MCX (Waters)	Aminoglycosides	Milk	Off-line SPE (500 mg) L: 2 g → 15 mL 12% TCA aq → C_{18} W: 6 mL H_2O E: 5 mL 40% HCOOH in MeOH	72-88	LC-MS/MS	[39]
		Oasis WCX Oasis MCX (Waters)	cathinones	River, EWW, IWW	Off-line SPE (500 mg) L: 500 (river), 250 (EWW) & 100 (IWW) mL pH 7 W: 10 mL MeOH E: 5 mL 5% HCOOH in MeOH	54-86	LC-HRMS	[32]
	WAX	**Oasis WAX** Oasis HLB, Strata X, Isolute ENV+, Oasis MCX, Oasis WCX, Oasis MAX, Strata-XL-AW	Cytostatic drugs	Surface, EWW and IWW	Off-line SPE (500 mg) L: 100 mL pH 10 W: - E: 6 mL MeOH + 6 mL 5% HCOOH in MeOH	85-116 (except FU 29%)	LC-MS/MS	[109]
		Oasis WAX (Waters)	14 synthetic dyes	Jelly and gummy candy	Off-line SPE (60 mg) L: 1 g → 10 mL H_2O W: 1 mL 2% TFA in H_2O + 1 mL MeOH E: 2 mL 2% NH_4OH in MeOH	86-99	LC-DAD	[110]

		Oasis WAX Oasis HLB, Oasis MAX,	PFSAs, PFCAs, PFPAs	Fish, vegetables, amended soil	Off-line SPE (200 mg) L: 0.5 g → 7 mL H_2O pH 7 W: 1 mL 2% HCOOH in H_2O + 1 mL H_2O/MeOH (95/5, v/v) E: 4 mL 2.5% NH_4OH in acetone	80-120	LC-MS/MS	[40]
In-house prepared	**SCX**	GMA-EGDMA-SO_3^-	Alkylated purine adducts	Human urine	Off-line SPE (30 mg) L: 2 mL pH acid W: 3 mL 2% HCOOH in H_2O + 3 mL MeOH/H_2O (50/50, v/v) E: 4 mL 5% NH_4OH in MeOH	90-105	LC-MS/MS	[44]
		Sulfonated HEMA/DVB AMPSA/HEMA/PETRA	Drugs	EWW and IWW	Off-line SPE (200 mg) L: 50 mL (EWW) and 25 mL (IWW) pH 3 W: 5 mL MeOH E: 3 mL 5% NH_4OH in MeOH	39-98	LC-MS/MS	[111]
	SAX	VBC-DVB-IL (methylimidazolium)	Pharmaceuticals	Tap, river, EWW	Off-line SPE (500 mg) L: 1000 (tap, river), 250 (EWW) mL pH 7 W: 20 mL MeOH E: 10 mL 5% HCOOH in MeOH	63-100	LC-UV	[48,49]
		GMA-EDGMA-IL (methylimidazolium)	Caffeine, theophiline	Green tea	Off-line SPE (200 mg) L: 1 g → 0.2 mL H_2O W: 2 mL H_2O E: 2 mL ACN/H_2O (80/20, v/v) + 2 mL 10% HAc in ACN	87-91	LC-UV	[50]
		VBC-EGDMA func TEA **Imidazole** Piperidine Pyrrolidone	Estrogens + NSAIDs	Tap and river	Off-line SPE (30 mg) L: 200 mL pH 7 W: 1mL H_2O + 15 min drying E: 4.5 mL MeOH + 4.5 mL 2% TFA in MeOH	53-94	LC-UV	[45]
		HXLPP-SAX (trimethylamine)	Fluoroquinolones	Milk	Off-line SPE (150 mg) L: 1 g → 0.2 mL H_2O W: 3 mL ACN +3 mL MeOH/H_2O (75/25, v/v) E: 3 mL 10% HAc in MeOH	86-118	LC-UV	[56]

		HXLPP-SAX (dimethylbutylamine)	Drugs	River and EWW	Off-line SPE (200 mg) L: 500 (river) and 100 (EWW) mL pH 7 W: 10 mL MeOH E: 10 mL 10% HCOOH in MeOH	60-90	LC-UV	[55]
	WCX	MAA-EGDMA (methacrylic acid)	Sulfur and nitrogen mustard	Organic matrix (i.e. diesel)	Off-line SPE (50 mg) L: 1 mL organic matrix W: 1mL hexane E: 1 mL EtAc	75-98	GC-MS	[112,113]
		HXLPP-WCX (methacrylic acid)	Pharmaceuticals	River and EWW	Off-line SPE (200 mg) L: 500 (river) and 250 (EWW) mL pH 7 W: 2 mL 2% NH_4OH in MeOH E: 5 mL 2% TFA in MeOH	54-90	LC-UV	[57]
	WAX	HXLPP-WAX (EDA and piperazine)	NSAIDs	River and EWW	Off-line SPE (200 mg) L: 500 (river) 250 (EWW) mL pH 7 W: 4 mL MeOH E: 2 mL 2% NH4OH in MeOH/ACN (25/75, v/v)	77-101	LC-UV	[58]
composites	**SAX**	SiO_2@DEAEMA-DVB func TEA 2-diethylaminoethyl methacrylate (DEAEMA)	Drugs	EWW	Off-line SPE (200 mg) L: 500 mL pH 7 W: 3 mL 10% HAc H2O E: 9 mL MeOH + 3 mL 1% HCOOH in MeOH	82-101	LC-UV	[59]
		SiO_2@DEAEMA-DVB func dimethylethanolamine (DMEA)	NSAIDs	Urine	Off-line SPE (200 mg) L: 3 mL W: 5 mL MeOH/50 mM NaAc aq (5/95, v/v) + 5 mL MeOH E: 4 mL 1% HCOOH in MeOH	85-104	LC-UV	[60]

In bold, the sorbent selected when different sorbents are compared.

ACN: Acetonitrile; AMPSA: 2-Acrylamido-2-methylpropane sulfonic acid; DAD: Diode array detector; DEAEMA: 2-diethylaminoethyl methacrylate; DVB: Divinylbenzene; E: Elution; EDA: Ethylenediamine; EGDMA: Ethyleneglycol dimetracrylate; EtAc: Ethyl acetate; EtOH: Ethanol; EWW: Effluent wastewater; FU: 5-Fluorocil; GC: Gas chromatogrpahy; GMA: Glycidyl methacrylate; HAc: Acetic acid; HCl: Chlorhydric acid; HCOOH: Formic acid; HEMA: Hydroxyethylene dimethacrylate; HRMS: High resolution MS; HXLPP: Hypercrosslinked sorbent prepared by precipitation polymerisation; IL: Ionic liquid; IWW: Influent wastewater; L: Loading; LC: Liquid chromatography; MeOH: Methanol; MMA: Methacrylic acid; MS: Mass spectrometry: MS/MS: Tandem mass spectrometry; NH_4OH: Ammonium hydroxide; NSAIDs: Non-steroidal anti-inflamatori drugs; PFAAs: Perfluoroalkyl acids; PFCAs: Perfluorinated carboxylic acids; PFSAs:

Perfluorosulfonic acids; PETRA: Petraerythritol triacrylate; SAX: Strong anionic exchange; SCX: Strong cationic-exchange; SiO_2: Silica; SPE: Solid-phase extraction; TCA: Trichloroacetic acid; TEA: Triethylamine; TFA: Trifluoroacetic acid; UV: Ultraviolate detector; VBC: Vinylbenzyl chloride; W: Washing; WAX: Weak anionic-exchange; WCX: Weak cationic-exchange.

Table 3. In-house prepared mixed-mode ion-exchange SPE sorbents prepared on carbon and LDHs materials.

		SPE sorbent	Analytes	Sample	SPE conditions	% Recovery	Determination technique	Ref.
Carbon-based	**WAX**	MWCNTs-PDDA	Nerve agents	Ultrapure water	Off-line SPE (12 mg) L: 20mL blood W: - E: 3 mL 0.1 M HCl aq + 3 mL 0.1 M HCl in MeOH	89-112	GC-MS	[114]
		GO-NH_2/PS-DVB	PFAAs (perfluoroalkyl acids)	Serum	Off-line SPE (500 mg) L: 500 µL serum + 0.1 mL HCl + 4 mL H_2O W: - E: 3 mL 1% NH_4OH in ACN	90-96	IC-MS	[66]
	WCX	GO-COOH/PVC	sulfonamides	Cosmetic cream	Off-line SPE (150 mg) L: 0.2 g → 5 mL 0.1M NH_4Ac W: 1 mL 0.1M NH_4Ac + 2 mL hexane + 2 mL H_2O E: 2.5 mL 1% NH_4OH in MeOH/acetone (50/50, v/v)	90-102	IC-UV	[65]
composites	**WAX**	GO@Fe_3O_4@PABT	NSAIDs	Urine	MSPE (16 mg) L: 5 mL pH 3.1 W: - E: 0.12 mL 40% HAc in ACN	85-90	LC-UV	[67]
LDHs	**SAX**	Ni-Fe-LDH (NO_3^-)	Haloacetic acids	Drinking water	dSPE (5 mg) L: 10 mL pH 6 W: - E: 0.1 mL 40% TFA in H_2O	200-300 EF	LC-MS/MS	[72]
		Mg-Al-LDH (NO_3^-)	Aromatic acids	Urine and sport drinks	dSPE (3 mg) L: 10 mL pH 7 W: - E: 0.1 mL 8% TFA in H_2O	81-128	LC-UV	[103]

ACN: Acetonitrile; dSPE: Dispersive SPE; DVB: Divinylbenzene; E: Elution; EtAc: Ethyl acetate; Fe_3O_4: Magnetite; GO: Graphene oxide; HAc: Acetic acid; HCl: Chlorhydric acid; IC: Ion Chromatography; L: Loading; LC: Liquid chromatography; LDH: Layered double hydroxides; MeOH: Methanol; MS: Mass spectrometry: MS/MS: Tandem mass spectrometry; MSPE: Magnetic

SPE; MWCNTs: Multiwalled carbon nanotubes; NH_4Ac: Ammonium acetate; NH_4OH: Ammonium hydroxide; NSAIDs: Non-steroidal anti-inflamatori drugs; PABT: Polyaminobenzothiazole; PDDA: Polydiallyldimethyl ammonium; PFAAs: Perfluoroalkyl acids; PFCAs: Perfluorinated carboxylic acids; PFSAs: Perfluorosulfonic acids; PS: Polystyrene; PVC: Polyvinylchloride; SAX: Strong anionic exchange; SCX: Strong cationic-exchange; SiO_2: Silica; SPE: Solid-phase extraction TFA: Trifluoroacetic acid; UV: Ultraviolate detector; W: Washing; WAX: Weak anionic-exchange; WCX: Weak cationic-exchange.

Table 4. Examples of applications of mixed-mode ion-exchange coatings in SPME.

	Coatings	Analytes	Sample	Protocol	Determination technique	Ref.
SCX	C_{18}/SCX (propylsulfonic acid) 45 µm	Amphetamine	Standard solutions	E: 1.5 mL sample pH 7.4, 2 h. D: 120 µL ACN/H_2O pH 11, 15 min	LC-UV	[74]
		Amitriptyline, amphetamine	Biological samples	E: n.r. pH 7.4 D: 120 µL ACN/H_2O (9/1) pH 11, 15 min	LC-MS	[75]
		Pharmaceutical and illicit drugs	Standard solutions	E: 1.5 mL sample pH 7.4, 2 h. D: 120 µL ACN/H_2O (9/1) 0.1% NH_3, 15 min 120 µL ACN/H_2O (9/1) 0.1% TFA	LC-UV; LC-FD	[76]
		Diazepam and amitriptyline	Pork muscle	E: 5 mL, 2 h D: 120 µL ACN/H_2O (9/1) 0.1% NH_3, 15 min	LC-UV	[77]
SCX	C_{18}/SCX (benzenosulphonic acid) 45 µm	Pharmaceutical and illicit drugs	Blood	E: 1200 µL, 90 min W: H_2O, 3 steps (5 s each) D: MeOH/ACN(4/1) 20 min	LC-MS/MS	[79]
		D-phenylalanine, L-tryptophan, cholic acid, deoxycolic acid	Lung and liver tissues	E: directly to tissue (30 min liver and 30 min lung) W: H_2O D: MeOH/H_2O (1/1) 90 min	LC-HRMS	[84]
SCX	Several sorbents C_{18} and C_8 with benzenosulphonic acid	36 metabolites	Human plasma	E: 300 µL 5 min D: 250 µL ACN/H_2O (1/1)	LC-MS HILIC-MS	[80]
SCX	SPME-biocompatible mixed-mode In-vivo	Doxorubicin	Lung tissue	E: 15 g, 20 min W: H_2O (10 s) D: 300 µL of ACN/MeOH (8/2) with HCOOH, 60 min	LC-MS/MS	[85]
SAX	Ti- APTES and C_{18}-TMOS, 5 µm	Perfluoroctane sulfonate and perfluoroctanoic acid	River water	E: 20 mL pH 2, 60 min D: 100 µL MeOH, 15 min	LC-MS	[81]
WCX	Peek tube funcionalized with polydopamine and GO	Quaternary alkaloids	Herb and plasma	E: 5 mL pH 6 D: LC mobile phase, ACN/ NH_4Ac pH3 (2/4)	LC-MS	[82]

SAX **SCX** **WAX** **WCX**	C_{18}-benzenesulphonic acid (B), C_8-B, MAX, MCX, WCX, WAX	Dopamine, serotonin, gamma aminobutyric acid, glutamine	Artificial cerebrospinal fluid, rat brain tissue	E: n.r., 1 h. D: 180 µL H_2O/ACN (3/2) with 0.1% HCOOH	LC-MS	[78]

n.r. not reported

ACN: Acetonitrile; APTES: 3-aminopropyltriethoxysilane; D: desortpion; E: extraction; FD: Fluorescence detector; GO: Graphene oxide;; HAc: Acetic acid; HCOOH: Formic acid; HILIC: Hydrophilic interaction LC; HRMS: High resolution MS; LC: Liquid chromatography; MeOH: Methanol; MS: Mass spectrometry: MS/MS: Tandem mass spectrometry; NH_4Ac: Ammonium acetate; NH_4OH: Ammonium hydroxide; SAX: Strong anionic exchange; SCX: Strong cationic-exchange; SPME: Solid-phase microextraction TFA: Trifluoroacetic acid; TMOS: tetramethylorthosilicate; UV: Ultraviolate detector; W: Washing; WAX: Weak anionic-exchange; WCX: Weak cationic-exchange.

Table 5. Examples of different in-house mixed-mode ion-exchange coatings in SBSE.

	Material	Analyte	Sample	Protocol	Determination technique	Reference
SCX	Poly(MAA-3-sulfopropyl ester potassium salt-DVB)	Quinolones	Wastewater	E: 100 mL pH 5, 60 min D: 3 mL MeOH/H_2O pH 1.3 (80/20), 40 min	LC-DAD	[90]
		Nitroimidazole	Honey	E: 100 mL pH 5, 180 min D: 3 mL MeOH/H_2O pH 2 (90/10), 60 min	LC-DAD	[91]
WAX	Amino modified MWCNTs/ PDMS	Phenols	Water	S: 10 mL H_2O pH 4, 30 min D: 100 µL MeOH/1mM NaOH (8/2), 25 min	LC-UV	[87]
WAX	VIm-EGDMA	PFAAs	Water	E: 10 mL of MeOH/ H_2O (1/1) at pH 3, 60 min W: H_2O D: 300 µL MeOH containing 0.4% NH_3 (V/V), 10 min	LC-MS/MS	[92]
WAX	Magnetic composite made of $CoFe_2O_4$ magnetic nanoparticles embedded into a mixed-mode weak anion exchange polymer, Strata-X-AW	Triphenylphosphate and diphenylphosphate	Urine	E: 25 mL urine, 5 min W: H_2O D: 0.5 mL MeOH with 0.02 M NH_3, 5 min	LC-MS/MS	[93]

D: Desorption; DAD: Diode array detector; DVB: Divinylbenzene; E: Extraction; EGDMA: Ethyleneglycoldimetracrylate; LC: Liquid chromatography; MAA: Methaacrylic acid; MeOH: Methanol; MS: Mass spectrometry: MS/MS: Tandem mass spectrometry; MWCNTs: Multi-wallet carbon nanotubes; NaOH: Sodium hydroxide; NH_3: Ammonia; acetate; PDMS: Polydimethylsiloxane; PFAAs: Perfluoroalkylacids; SAX: Strong anionic exchange; SCX: Strong cationic-exchange; SBSE: Stir bar sorptive extraction; UV: Ultraviolate detector; VIm: 1-vinylimidazole; W: Washing; WAX: Weak anionic-exchange; WCX: Weak cationic-exchange.

Table 6. . Examples of different mixed-mode ion-exchange sorbents used in MEPS.

	Material	Analytes	Sample	Protocol	Determination technique	Ref.
SCX	C_8/SCX (80/20) (phenylsulphonic acid) 4 mg	19 new psychoactive drugs and two metabolites	Oral fluid	L: 100 µL pretreated oral fluid (pH 9) W: 50 µL MeOH/H_2O (10/90, v/v) E: 90 µL DCM/IPA/NH_4OH (78/20/2, v/v)	LC-MS/MS	[96]
		10 drugs of abuse and metabolites	Plasma	L: 10x100 µL (300 µL pretreated plasma and 200 µL phosphate buffer (pH 8)) W: 150 µL MeOH/H_2O (10/90, v/v) E: 200 µL DCM/IPA/NH_4OH (78/20/2, v/v)	LC-FD	[97]
		Olanzapine, Chlorpromazine and oxidation products	Rat brain microdialysates	L: 50 µL microdialysate sample mixed with 150 µL phosphate buffer pH 2.5 W: 100 µL 5% HAc and 100 µL MeOH/H_2O (10/90, v/v) E: 50 µL H_2O (10/90, v/v) 5% NH_4OH in 80% MeOH	Capillary LC-UV	[98]
		6 opiates: Tramadol, codeine, morphine, 6-acetyl codeine, 6-monoacetylmorphine and fentanyl	Hair	L: 9x150 µL of hair extract W: 3x50 µL 3.36% HCOOH E: 8x100 µL 2. 36% NH_4OH in MeOH	GC-MS/MS	[99]
		Ketamine Norketamine (metabolite)	Urine (U) Plasma (P)	L: 250 µL urine or plasma diluted with 250 µL H_2O (U) or 7 mL phosphate buffer (P). W: 250 µL of 5.25% HAc and 100 µL 5% MeOH in water (U). 100 µL 0.1% HAc and 100 µL 10% MeOH (P) E: 100 µL 6% NH_4OH in MeOH (U), 100 µL 3% NH_4OH in MeOH (P)	GC-MS/MS	[100]
SCX	C_8/SCX 2 mg	Antidepressants: Setraline, mirtazapine, fluoxetine, citalopram, paroxeinte	Plasma	L: 250 µL diluted plasma pH 4 µL W: 50 µL MeOH/H_2O (5/95) E: 150 µL H_2O pH 4.5/ MeOH (55/45, v/v)	LC-UV	[115]
SCX	Clean Screen DAU (C_8/SCX, benzenesulphonic) Oasis MCX	Cocaine and its metabolites	Human urine	L: 250 µL urine/phosphate buffer (1/1, v/v) W: 250 µL H_2O E: 100 µL DCM/IPA/NH_4OH (79.5/20/0.5, v/v)	DART-TOF	[101]

SAX	Ni-Fe- LDHs nanoparticles 8 mg	NSAIDs: naproxen, diclofenac, ibuprofen, mefenamic acid	Urine	L: 9 x 250 µL urine pH 4.5 W: 2 x 150 µL 0.1% HCOOH in MeOH/H_2O (5/95, v/v) E: 2 x 150 µL 0.1% HCOOH in MeOH/H_2O (95/5, v/v)	LC-UV	[102]

DART: Direct analysis real time; DCM: Dichloromethane; E: Elution; FD: Fluorescence detector; GC: Gas chromatography; HAc: Acetic acid; HCOOH: Formic acid; IPA: isopropanol; L: Loading; LC: Liquid chromatography; MeOH: Methanol; MEPS: Micro extraction by packed sorbents; MS: Mass spectrometry: MS/MS: Tandem mass spectrometry; NH_4OH: Ammonium hydroxide; NSAIDs: Non-steroidal anti-inflamatori drugs; SAX: Strong anionic exchange; SCX: Strong cationic-exchange; TOF: time of flight; UV: Ultraviolate detector; W: Washing.