



Novel in-house mixed-mode ion-exchange materials for sorptive phase extraction techniques

Joan Carles Nadal, Francesc Borrull, Rosa Maria Marcé*, Núria Fontanals

Department of Analytical Chemistry and Organic Chemistry, Universitat Rovira i Virgili, Sescelades Campus, Marcel·lí Domingo 1, Tarragona 43007, Spain

ARTICLE INFO

Keywords:

Mixed-mode ion-exchange
Complex samples
Solid-phase extraction
Solid-phase microextraction
Stir bar sorptive extraction
Ionisable compounds

ABSTRACT

Mixed-mode ion-exchange materials have been implanted in different sorptive extraction techniques as they combine capacity and selectivity in a single material. They are a good option for concentrating ionic (or ionisable) compounds from complex samples using an appropriate washing step that simplifies the sample matrix. Research into the development of in-house mixed-mode ion-exchange materials is therefore a field of scientific interest. These materials are developed with the aim to improve the features of both the core and the ionic moieties attached. The study of the optimal extraction protocol to exploit the ionic interactions between the material and the target compounds is a key point in method development.

This review is an overview of the preparation, characterisation, evaluation and application of in-house mixed-mode ion-exchange materials. It mainly covers the technique of solid-phase extraction; however, the latest advances in solid-phase microextraction, stir bar sorptive extraction and other emerging microextraction techniques are also presented. Examples of different applications that cover the extraction of different compounds in several types of samples are also illustrated.

Introduction

Trace analysis of organic contaminants is always challenging due to the complexity and diversity of the sample matrices. In spite of the recent advances in analytical instrumentation, especially in chromatography and mass spectrometry (MS), analysing complex samples requires sample treatment before the chromatographic analysis. By including a sample treatment, the complexity of the extract is simplified to make it easier to separate the target analytes from other components [1]. Several treatment techniques have been used in the past decades to extract organic compounds from different types of samples. For liquid samples, although solvent extraction techniques have been miniaturised to achieve high enrichment factors, minimise solvent consumption and reduce waste, sorptive extraction techniques are the preferred extraction techniques. The most commonly used sorptive extraction techniques are solid phase extraction (SPE) followed by solid-phase microextraction (SPME) or stir bar sorptive extraction (SBSE), but other techniques such as fabric phase sorptive extraction (FPSE), stir bar sorptive-dispersive microextraction (SBSDME), rotating disk sorptive extraction (RDSE), disposable pipette extraction (DPX), capsule phase microextraction (CPME) and stir-cake sorptive extraction (SCSE), amongst others, have recently been developed [2–8].

The selectivity and capacity of the sorptive extraction techniques are mainly determined by the material, and a wide variety of them

have been exploited. In SPE, the first materials were silica-based, which are usually modified with C_{18} to be used to extract apolar compounds. Nevertheless, they show limited recovery for polar and ionisable compounds [9]. Later on, carbon-based sorbents were introduced, although their high retention hinders the elution of analytes. Polymer-based sorbents were developed to improve the properties of the previous materials. The first one was based on polystyrene-divinylbenzene; however, its hydrophobic character is a limitation to trapping the most polar compounds [10]. New generations of polymeric materials, namely hydrophilic polymer sorbent and hypercrosslinked polymers, emerged to enhance capacity [11]. To promote selectivity, molecularly imprinted polymers were synthesised to extract selectively target analytes [12]. In addition, other emerging materials, such as metal-organic frameworks, magnetic materials, nanomaterials, etc., have been developed [13,14].

For other microextraction techniques, materials based on polydimethylsiloxane (PDMS) were the first to be introduced in both SPME and SBSE; however, they lack retention for the most polar compounds. Other materials have gradually appeared to solve this drawback, such as polyacrylate (PA), carbowax (CW) and carboxen (CAR) for SPME; and ethyleneglycol-Silicone and PA for SBSE [15].

The need to combine in a single material an improvement of capacity and selectivity towards ionisable compounds evidences the interest in developing novel sorbents, such as mixed-mode ion-exchange sorbents. These are developed by incorporating ionic functional groups

* Corresponding author.

E-mail address: rosamaria.marce@urv.cat (R.M. Marcé).

in a hydrophobic and/or hydrophilic base. Depending on the properties of the material, the ionisable analytes can establish either ionic interactions with the ionic groups of the material and hydrogen bonding, dipole-dipole or Van der Waals forces with the skeleton [16,17]. The materials to prepare the mixed-mode ion-exchange sorbent are silica- and polymer-based, and most commonly are the polymeric ones [18,19]. Moreover, there are different types of mixed-mode ion-exchange materials that have different properties depending on the functional groups attached to the resin: strong anion-exchange (SAX), strong cation-exchange (SCX), weak anion-exchange (WAX) and weak cation-exchange (WCX). On one hand, strong ion-exchangers are charged throughout the pH range and comprise sulfonic acids or quaternary amines, and are cationic or anionic exchangers, respectively. On the other hand, weak exchangers tune their ionisation state in accordance with the pH, since they are functionalised with carboxylic acids or tertiary, secondary or primary amines, and are cationic or anionic exchangers, respectively.

It is crucial to select the appropriate SPE protocol to achieve good results when using mixed-mode ion-exchange sorbents. For instance, the common SPE protocol for SCX sorbents uses an acidic (pH 2-3) sample so that the basic analytes are in their protonated form, and uses a basic elution medium (normally 3–5% NH_4OH in MeOH) to break any ionic interactions between the analytes and the sorbent, neutralising the basic analytes. Conversely, in the general SPE protocol for SAX sorbents, the sample is always loaded at pH 7-9 to deprotonate the acidic compounds and establish ionic interaction with the quaternary amine groups of the sorbent. The elution of the acidic compounds is performed at acidic pH to protonate the compounds and disrupt the ionic interaction. In the case of WAX or WCX, the recommended protocol uses a neutral pH to load the sample so that both the functional groups of the sorbent and the analytes are in ionic form. As an elution solution, normally an acidified organic solution is employed for WCX sorbents to neutralise the carboxylic acid groups of the sorbent; and a basic elution solution in organic solvent is used for WAX sorbents to neutralise the amine groups of the sorbent. These are general protocols, but they should be optimised depending on the pK_a of the analytes and the sorbents.

Mixed-mode ion-exchange sorbents can be either universal or very selective. They can be universal because numerous compounds can be extracted from samples due to the enhanced retention towards ionic compounds given by the presence of ionic functionalities. In addition, their selectivity can be increased towards ionic analytes if the compounds retained through other type of interactions are rinsed from the sorbents using washing steps with organic solvents to disrupt these interactions [16,17,20].

Although several commercial mixed-mode ion-exchange sorbents have been developed, in recent years different *in-house* sorbents have been prepared. This review will focus on the synthesis, characterisation and application of *in-house* mixed-mode ion-exchange materials to different sorptive techniques, being the SPE the most used, in different types of samples.

Solid-phase extraction

There is an increasing amount of mixed-mode ion-exchange materials due to the challenging need to improve the SPE sorbents. Although commercial mixed-mode ion-exchange sorbents, based on Strata-X, Oasis, Discovery and the Bond Elut series, amongst others, are available and have been studied by the analytical chemistry community [21–25], the necessity to enhance their capacity and selectivity properties has led to the development of *in-house* mixed-mode ion-exchange sorbents. Various materials are applied as *in-house* sorbents for SPE, most commonly silica and polymer based materials. This section is divided into mixed-mode cation-exchange, mixed-mode anion-exchange material and zwitterionic sorbent sections. Each section covers the preparation, characterisation, evaluation and application of each type of material. **Table 1**

details the different *in-house* mixed-mode ion-exchange materials used in SPE, their optimal conditions and their applications.

Mixed-mode cation-exchange sorbents

Mixed-mode cation-exchange sorbents contain sulfonic acid or carboxylic acid moieties as functional groups anchored to the backbone, and have a SCX or WCX character, respectively. There are diverse synthetic methods for obtaining *in-house* mixed-mode cation-exchange. Regarding the polymeric backbone, traditional polymerisation methods, such as precipitation polymerisation (PP) [26–28], bulk polymerisation [27], dispersion polymerisation [28] and non-aqueous dispersion polymerisation [28] are mainly used to prepare polymer-based mixed-mode materials. These can be prepared by copolymerisation followed by a second step of functionalisation to incorporate the functional group, or by copolymerisation with a monomer that already contains the functional group. Studies that apply these *in-house* materials as SPE sorbents for the extraction of analytes in complex matrices are presented in **Table 1**. For instance, Gilart et al. [29] prepared two different cation-exchange polymeric materials employing different polymerisation approaches. One was prepared by copolymerisation of the two monomers, 2-hydroxyethyl methacrylate (HEMA) and divinylbenzene (DVB), followed by a post-sulfonation with H_2SO_4 to obtain a SCX polymer. The monomers gave the polymer hydrophilicity due to the ester and hydroxyl groups in the HEMA and also allowed π - π interactions due to the aromatic rings in the DVB. The other material was prepared by the copolymerisation of three monomers: 2-acrylamido-2-methylpropane sulphonic acid (AMPSA), HEMA (functional monomers) and pentaerythritol triacrylate (PETRA) (cross-linker). HEMA and PETRA provided hydrophilicity to the material, and AMPSA provided an ionic character since it contains a secondary amide group and a sulfonic acid in its structure. The materials had different ion-exchange capacities, 0.84 mmol g^{-1} for the AMPSA/HEMA/PETRA sorbent and 2.05 mmol g^{-1} for the HEMA/DVB sorbent. The last of these is the material with the most ion-exchange sites and surface area to keep the analytes strongly retained. This was confirmed by the high recoveries of the analytes when wastewater samples were extracted.

The sulfonation process to develop a SCX material was carried out beforehand mainly using alkyl sulfates, such as acetyl sulfate and lauroyl sulfate [28,31], but these methods have many drawbacks. Acetyl sulfate has a low cation-exchange capability, implying a limited number of functional groups that can be introduced through the sulfonation reaction. Although lauroyl sulfate has shown to be a better sulfonating reagent, it needs to be freshly prepared before the sulfonation process by using chlorosulfonic acid, a very toxic chemical, and there are some issues for obtaining and working with it. Another sulfonation method is to use concentrated H_2SO_4 , which is much simpler than using alkyl sulfate reagents. Moreover, using H_2SO_4 does not involve sulphonating or highly toxic reagents. H_2SO_4 has been successfully applied for the sulphonation of conventional methods, such as PP [27,28,30].

Silica-based mixed mode ion-exchange materials are generally prepared in a single step by means of adding the reagent with an ionic moiety into the solution mixture. The procedure involves the previous activation of the silica with NaOH and/or HCl, followed by a polycondensation of the monomers via sol-gel technology. The sol-gel process offers high permeability, high mechanical strength, and good organic solvent tolerance. For instance, Zheng et al. [32] developed a hybrid silica monolith functionalised with octyl and thiol moieties in a single step with the sol-gel approach. After oxidation using H_2O_2 to yield sulfonic acid groups, the mixed-mode ion-exchange silica monolith provided a hydrophobic and SCX character and was evaluated by μ -SPE to extract sulphonamides (amphoteric compounds) from milk samples. The sample matrix was adjusted to pH 2.5 since sulphonamides exist in protonated forms at acidic pH and they could interact with the sulfonic acid groups of the silica monolith via cation-exchange interactions. This material exhibited a good extraction capacity (recoveries ranging from

Table 1
Examples of application of SPE *in-house* mixed-mode ion-exchange materials.

Type	Coating	Analytes	Sample	Conditions	Washing	% Recovery	Determination technique	Ref.
SCX	HXLPP-SCX sulphonated with H ₂ SO ₄	Pivotal purine metabolites	Human serum	L: 1 mL with HAc (0.13%) E: 3 mL of 5% NH ₄ OH in MeOH	3 mL of H ₂ O + 3 mL of MeOH	91–103	LC-UV	[27]
SCX	HXLPP-SCX and HXLNAD-SCX functionalised with sulphonic groups	Drugs	EWV and IWW	L: 250 mL at pH 3 E: 5 mL of 5% NH ₄ OH in MeOH	5 mL of MeOH	75–100	LC-MS/MS	[28]
SCX	Sulphonated HEMA/DVB AMPSA/HEMA/PETRA	Drugs	EWV and IWW	L: 50 mL (EWV) and 25 mL (IWW) pH 3 E: 3 mL of 5% NH ₄ OH in MeOH	5 mL of MeOH	39–98	LC-MS/MS	[29]
SCX	GMA-EGDMA-SO ₃ ⁻	Alkylated purine adducts	Human urine	L: 2 mL pH acid E: 4 mL of 5% NH ₄ OH in MeOH	3 mL of 2% HCOOH in H ₂ O+3 mL MeOH/H ₂ O (50/50, v/v)	90–105	LC-MS/MS	[30]
SCX	Si-C ₈ -SO ₃ ⁻	Sulphonamides	Milk	L: 1 mL pH 2.5 (5 mM phosphate buffer) E: 0.15 mL of mobile phase (ACN/20 mM NH ₄ Ac, 24/76, v/v)	0.08 mL of 0.2% HCOOH in H ₂ O	40–92	LC-UV	[32]
SCX	Sulphonic acid-functionalised covalent organic frameworks anchoring Ni particles	Benzimidazoles	Vegetables, fruits and juices	L: 10 mL acidic aqueous sonicated for 2 min E: 3 mL ACN/NH ₄ OH (95:5, v/v) for 2 min	2 mL of H ₂ O + 2 mL of MeOH	80–115	LC-UV	[31]
SCX	SBA-15-C ₁₈ -SO ₃ ⁻ , SBA-15-C ₈ -SO ₃ ⁻	Veterinary drugs	Meat	L: 2 g→10 mL ACN/5% TCA in H ₂ O (50/50, v/v) E: 2 mL ACN + 2 mL MeOH + 2 × 2 mL 3% NH ₄ OH in MeOH	5 mL of acetate buffer	70–100	LC-MS/MS	[33]
WCX	HXLPP-WCX (MAA)	Basic pharmaceuticals	River water	L: 1000 mL at pH 7 E: 5 mL of 2% TFA in MeOH	2 mL of 5% NH ₄ OH in MeOH	54–92	LC-UV	[26]
WCX	Maleic acid-DVB	Basic pharmaceuticals	River, EWV and IWW	L: 250 mL (river) or 100 mL (EWV) or 50 mL (IWW) at pH 7 E: 5 mL of 15% HCOOH in MeOH	5 mL of MeOH	57–89	LC-MS	[34]
SAX	Mesoporous silica SBA-15 functionalised with 3-[2-(2-aminoethylamino)ethylamino]propyl-trimethoxysilane and phenyl glycidyl ether	NSAIDs	Tap and river and WW	L: 500 mL at pH 7.2–7.8 E: 3 mL 1% HAc in hexane/EtOAc (3:1)	4 mL of MeOH/25 mM pH 7 phosphate buffer (1:1, v/v)	81–111	LC-UV	[9]
SAX	SiO ₂ @DEAEMA-DVB func TEA-(DEAEMA)	Drugs	EWV	L: 500 mL pH 7 E: 9 mL MeOH + 3 mL 1% HCOOH in MeOH	3 mL of 10% HAc H ₂ O + 9 mL MeOH	82–101	LC-UV	[20]
SAX	HXLPP-SAXa and HXLPP-SAXb (TEA)	Acidic pharmaceuticals	River and EWV	L: 100 mL at pH 7 E: 10 mL of 10% HCOOH in MeOH	10 mL of MeOH	60–90	LC-UV	[35]
SAX	HXLPP-SAX (TEA)	Fluoroquinolones	Milk	L: 1 g→0.2 mL H ₂ O E: 3 mL of 10% HAc in MeOH	3 mL of ACN + 3 mL of MeOH/H ₂ O (75/25, v/v)	86–118	LC-UV	[36]
SAX	VBC-EGDMA func TEA, Imidazole, Piperidine, Pyrrolidone	Estrogens and NSAIDs	Tap and river	L: 200 mL at pH 7 E: 4.5 mL of MeOH + 4.5 mL 2% TFA in MeOH	1 mL of H ₂ O+15 min drying	53–94	LC-UV	[37]
SAX	SiO ₂ @DEAEMA-DVB func DMEA	NSAIDs	Urine	L: 3 mL E: 4 mL of 1% HCOOH in MeOH	5 mL of MeOH/50 mM NaAc aq (5/95, v/v) +5 mL of MeOH	85–104	LC-UV	[38]
SAX	Bi-functionalised hexagonal mesostructured silicas with C ₈ and NR ₄ ⁺ groups	Polyphenols	Fruit and vegetables based HPP juice	L: 5 mL at pH 9 stirred for 20 min at 300 rpm E: 6 mL of MeOH/water (95/5,v/v) at pH 1		70–101	UHPLC-MS/MS	[69]
SAX	Periodic mesoporous organosilica with (styryl-methyl)bis(triethoxysilylpropyl)ammonium chloride (PMO-STPA) and with bis(3-triethoxysilylpropyl)amine (PMO-TEPA)	Phenoxy acid herbicides	River and EWV	L: 750 mL E: 2 × 4 mL of MeOH at pH 5.6 (PMO-STPA) or 1.8 (PMO-TEPA)		78–108	CE-DAD	[70]

(continued on next page)

Table 1 (continued)

Type	Coating	Analytes	Sample	Conditions	Washing	% Recovery	Determination technique	Ref.
SAX	Ionic liquid crosslinked polymer-supported imidazolium trifluoroacetate salt (IL-CF ₃ COO ⁻) and VBC-DVB-IL (methylimidazolium)	Pharmaceuticals	Tap, river and EWW	L: 1000 mL (tap and river) or 250 mL (EWW) pH 7 E: 10 mL of 5% HCOOH in MeOH	20 mL of MeOH	55–101 and 63–100	LC-UV	[71]
SAX	Si-C ₁₈ /-SAX	Aristolochic acids	Herbs	L: 100 g herbs → 2 L of 5 mM K ₂ HPO ₄ /MeOH (50/50, v/v) E: 7 mL of 5% HCOOH in MeOH	5 mL of H ₂ O + 5 mL of MeOH	67–105	LC-UV	[72]
SAX	Si-IL (1-Alkyl-3-(propyl-3-sulphonate) imidazolium)	Organic acids, amines and aldehydes	Atmospheric aerosol water	L: 0.5 mL E: 0.5 mL of 10% HAc in H ₂ O (acids) 0.5 mL of 10% HAc in MeOH (amines)	1 mL of H ₂ O	87–110	LC-MS GC-MS	[73]
SAX, SCX	Methacrylate based resin functionalised with sulphoethylbetaine	Ionic polar solutes (nucleobases, acids and zwitterions)	Standard solutions	L: 10 mL E: 10 mL of H ₂ O/ 0.2% TFA/ 20 mM NH ₄ Ac	2 mL of ACN	4–105	LC-UV	[74]
SAX, SCX	1-Alkyl-3-(propyl-3-sulphonate) imidazolium-functionalised silica	Aromatic amines	EWW, IWW and soil (mineral and humus) samples	L: 500 µL, 6 mL or 10 mL E: 500 µL of H ₂ O	1 mL of hexane	9–97	LC-UV	[75]
WAX	HXLPP-WAX functionalised with 1,2-ethylenediamine and piperazine.	NSAIDs	River and EWW	L: 1000 mL (river) or 250 mL (EWW) at pH 7 E: 2 mL of 2% NH ₄ OH in MeOH:ACN (1:4, v/v)	4 mL of MeOH	77–101	LC-UV	[19]
WAX	Dendrimer aminopropyl functionalised mesoporous silica KIT-6	Acidic drugs	Human urine	L: 3 mL at pH 7 E: 3 mL of 1% HAc in hexane/EtOAc (3:1, v/v)	5 mL 25 mM phosphate (pH 7.0) in 5% MeOH + 1 mL EtOAc	86–114	LC-DAD	[39]
WAX	Silica gel covered with polyaniline	Alkaloids	Roots and shoots of Chelidonium majus	L: 1 mL E: 5 mL of 0.1 M NH ₃ in MeOH	2 mL of H ₂ O/MeOH (1/1, v/v)	97–99	LC-DAD	[40]
WAX	Si-tris(2-aminoethyl) Amine-3-phenoxybenzaldehyde	Chlorophenols	Tap and surface water	L: 20 mL at pH 8 E: 0.5 mL of 1% HAc in MeOH		89–110	LC-UV	[41]
WAX	CB [6]-NH ₂ @SiO ₂ @Fe ₃ O ₄ (Curcubit [6] uril)	Salvianolic acids	Natural plant water	L: 1 mL at pH 5.5 E: 1 mL of 1% HAc in MeOH/H ₂ O (60/40, v/v)		95–106	LC-UV	[42]
WAX	APTES@SiO ₂ @Fe ₃ O ₄ (3-aminopropyltriethoxysilane)	Chlorophenoxyacetic	Well and surface water	L: 25 mL at pH 5 E: 3 × 2 mL of 1% NH ₄ OH in MeOH	2 mL of H ₂ O	80–100	LC-UV	[43]
WAX	Fe ₃ O ₄ @nSiO ₂ @C ₁₈ @NH ₂	Lipophilic marine biotoxins	Shellfish	L: 4 mL at pH 7.0, vortexed for 30 s and shaken for 5.0 min E: 2.0 mL of HCOOH/MeOH (5/95, v/v) for 1 min	2 mL H ₂ O + 2 mL MeOH	83–119	UHPLC-MS/MS	[76]
WAX	Nanocomposite of silica-polydiphenylamine doped with silver nanoparticles	Pesticides	Well water and tap water	L: 50 mL at pH 7 at 4 mL/min E: 500 µL of MeOH at 0.1 mL/min	1 mL of H ₂ O	86–103	GC-MS	[77]
WAX/WCX	Si-ampholine	Acidic and basic compounds	Beverage samples	L: 10 mL pH 4–6 (acids), pH 6 (basics) E: 1 mL of H ₂ O/MeOH (50/ 50, v/v) pH 11 (acids), 1 mL H ₂ O/MeOH (50/ 50, v/v) pH 1 (bases)	1 mL of H ₂ O/MeOH (50/50, v/v)	84–110	LC-UV	[44]
WAX/WCX	HXLPP-WAX/WCX	Acidic and basic compounds	River and EWW	L: 100 mL at pH 6 E: 5 mL of 5% NH ₄ OH in MeOH	1 mL of MeOH	32–88	LC-UV	[45]

(continued on next page)

Table 1 (continued)

Type	Coating	Analytes	Sample	Conditions	Washing	% Recovery	Determination technique	Ref.
WAX/WCX	Ternary mixed-mode Si-COOH/-NH ₂	Drugs	Human serum	L: 2 mL at pH 6 E: 2 mL of MeOH followed by 2 mL of 5% HCOOH in MeOH	3 mL of 5% MeOH in 20 mM phosphate buffer (pH 6). 1 mL of MeOH	92–117	LC-UV	[46]
SAX/WCX and HXLPP-WAX/SCX		Acidic and basic compounds	River and EWW	L: 500 mL at pH 6 E: 5 mL of 5% NH ₄ OH in MeOH		18–105	LC-UV	[47]

ACN: Acetonitrile; AMPSA: 2-acrylamido-2-methylpropane sulphonic acid; APTES: 3-aminonia propyltriethoxy silane; CE: Capillary electrophoresis; DAD: Diode array detector; DEAE/MA: 2-diethylaminoethyl methacrylate; DMEA: dimethylethanolamine; DVB: Divinylbenzene; E: Elution; EGDMA: Ethylene glycol dimethacrylate; EtOAc: Ethyl acetate; EWW: Effluent wastewater; GC: Gas chromatography; GMA: Glycidylmethacrylate; HAc: Acetic acid; HEMA: 2-hydroxyethyl methacrylate; HXLNAD: Hypercrosslinked sorbent prepared by non-aqueous dispersion polymerisation; HXLPP: Hypercrosslinked sorbent prepared by precipitation polymerisation; IWW: Influent wastewater; L: Loading; LC: Liquid chromatography; MAA: Methacrylic acid; MeOH: Methanol; MS: Mass spectrometry; MS/MS: Tandem mass spectrometry; NaAc: Sodium Acetate; NH₄Ac: Ammonium acetate; NSAIDs: Non-steroidal anti-inflammatory drugs; PE/TRA: Pentaerythritol triacrylate; SAX: Strong anion-exchange; SBA: Silica Santa Barbara Amorphous-15; SCX: Strong cation-exchange; SiO₂: Silica; TCA: Trichloroacetic acid; TEA: Triethylamine; TFA: Trifluoroacetic acid; UHPLC: Ultra high performance liquid chromatography; UV: Ultraviolet detector; VBC: Vinylbenzyl chloride; WAX Weak anion-exchange; WCX: Weak cation-exchange; WW: wastewater.

40 to 92%) and simplified the milk matrix of protein and fat, thus improving sulphonamide determination.

Other networks for developing mixed-mode ion-exchange materials for SPE sorbents, like covalent triazine-based organic frameworks (CTFs), have recently appeared. CTFs are of increasing interest as separation media for chromatography and sample pretreatment due to their uniform and adjustable pore size, effective post-synthetic functionalisation and their stable triazine-benzene structure that allows the materials to endure acid or basic conditions, which is not the case for other porous materials. The CTFs are generally prepared via cyclotrimerisation of 1,4-dicyanobenzene in molten ZnCl₂. In one study [31], the authors generated a SCX sorbent using CTFs. Once the CTFs were synthesised, they were functionalised with chlorosulfonic acid to incorporate the sulfonic acid into the CTF matrix, obtaining CTF-SO₃H. Afterwards, Ni particles were anchored on the CTF support through a magnetising process followed by an *in situ* reduction. This generated a robust magnetic hybrid SPE sorbent (Ni/CTF-SO₃H) with high density and easily accessible ion-exchange sites in a three-dimensional nanospace. The Ni/CTF-SO₃H material showed very good results (recoveries of 80–115%) for the extraction of alkaline benzimidazoles in vegetables, fruits and juices, promoting efficient SCX and reversed-phase interactions, as benzimidazoles contain hydrophobic aromatic rings and protonated nitrogen atoms that interact through both ways with the sorbent.

Regarding the extraction protocol, as mentioned above, the loading conditions for SCX materials involve the sample being adjusted at acidic pH, while the elution conditions use basic additives. Moreover, the washing step is an important process of the SPE to keep in mind. Table 1 details the washing conditions used in the suggested examples. As it can be seen for mixed-mode SCX sorbents, organic solvent, such as MeOH [28,29] and acidified aqueous solution (acidified with HCOOH or HCl) followed by organic solvent [27,30,31] are generally used as washing solutions to remove the compounds retained in the sorbent by reverse-phase interactions (*i.e.* acidic and neutral compounds), keeping the basic compounds still bound to the sorbent by cation-exchange interactions. In a previous study by our research group [28], the HXLNAD-SCX that was applied to extract a group of basic drugs from effluent and influent wastewater, a washing step with 5 mL MeOH was employed to break the reversed-phase interactions and consequently remove the acidic drugs in the washing fraction. Negligible matrix effects (ME) (below 20%), were obtained when 50 mL and 25 mL of effluent and influent sewage water samples were analysed, respectively. This is related to the high selectivity achieved towards the selected analytes. In another example, Hu et al. [30] used 3 mL of 2% HCOOH aqueous solution (pH 2.0) followed by 3 mL of 50% aqueous MeOH solution as washing solutions when extracting by SPE alkylated purine adducts in 2 mL of urine sample using a SCX sorbent (sulphonate functionalised poly(glycidyl methacrylate-divinylbenzene). The acidic aqueous washing solution removed the protein and salt from the urine sample and the organic washing solution was applied to wash off the weakly polar compounds and the undissociated acidic compounds [30]. Some studies only used aqueous-based washing solutions to remove interferents [32,33], and since these washing solutions are weaker than organic-based ones, less interferents are removed from the matrix and, thus, the selectivity is affected.

The synthetic methods to prepare WCX materials are similar to those used for SCX materials. There are fewer studies that prepare and apply WCX materials compared to SCX materials; they are shown in Table 1. In the SPE procedure of the WCX sorbents an acidic pH is not suitable for retaining the basic analytes because the carboxylic acid groups of the sorbent are primarily in their non-ionised form and no ionic interactions are established under this pH. Therefore, sample loading should be at neutral pH so that the carboxylic acid would be in the ionic form. Bratkowska et al. [26] prepared hypercrosslinked polymeric WCX resin by PP with the monomers vinylbenzylchloride (VBC), DVB and methacrylic acid (MAA), acquiring the cation-exchange character by means of the MAA residues. pH 7 was the optimal conditions to load

the samples when a polymeric WCX sorbent was used to extract, in this case, basic pharmaceuticals in 500 mL of river water and 250 mL of effluent wastewater. To elute the basic analytes, an acidic solution, such as 5 mL of 2% trifluoroacetic acid (TFA) in MeOH was found to be the best eluent since acidification protonates the carboxylic acid residues in the sorbent, breaking the cation-exchange interactions. Basified MeOH was used as the washing solution to maintain the desired ionisation state of the analytes and the sorbent [26]. In another study [34], a WCX material was developed by functionalising a mesoporous DVB resin with maleic acid for extracting a group of basic drugs in environmental samples. The functionalisation was carried out through a Diels-Alder reaction with maleic anhydride, and posterior basic hydrolysis generated the carboxyl groups on the polymer surface. A neutral pH was used to load the sample, pure MeOH in the washing step, thus reducing the %ME to values between -30% and 7%, and eluting the analytes with 5 mL of 15% HCOOH in MeOH. The apparent recoveries in 250 mL of river water, 100 mL of effluent wastewater and 50 mL of influent wastewater ranged from 63 to 89%, 62–80% to 57–74%, respectively.

To the best of our knowledge, no *in-house* mixed-mode WCX using silica-based materials has been developed so far.

Mixed-mode anion-exchange sorbents

To prepare mixed-mode anion-exchange sorbents for SPE, similar synthetic procedures to the cation-exchange procedures for functionalising silica and polymeric supports are employed but obviously using different reagents/monomers to obtain the materials with an anion-exchange character. Table 1 shows studies that prepare and evaluate anion-exchange materials applied as SPE sorbents, as well as their SPE protocol conditions. For polymer-based anion-exchange materials, most of the authors chose PP using DVB and VBC as monomers [35,36]. However, Meischl et al. [37] employed PP using VBC and ethylene glycol dimethacrylate (EGDMA) as monomer and crosslinker, respectively, since the incorporation of EGDMA is a suitable tool for interacting with more polar compounds, obtaining high recoveries and enrichment of non-steroidal anti-inflammatory drugs (NSAIDs). The use of VBC made it possible to further functionalise the material through nucleophilic substitution reactions. In this case, the functionalisation was carried out with imidazole, but other authors used dimethylbutylamine (DMBA) [35] or trimethylamine (TMA) [36]. Liang et al. [36] achieved the quaternisation and hypercrosslinking reactions in one single step, reducing the reaction time and simplifying the procedure. In most cases these reactions need two or more steps. Other authors [38] obtained SAX materials by copolymerisation of 2-(diethylamino)ethyl methacrylate (DEAEMA) and DVB generating aminated polyDVB microparticles, which were then functionalised with hyperbranched macromolecules and successive reactions to produce multiple cationic quaternary amines. In this way, a highly branched three-dimensional framework with large mesopores, well-defined particle sizes and a large number of functional groups was developed. The Pickering emulsion polymerisation, used by Huang et al. [20], is another approach for preparing a spherical and porous SAX sorbent. Pickering emulsion is the process in which solid particles are employed to stabilise the emulsion. It requires the self-assembly of the particles at the interface of two immiscible liquids to reduce the interfacial energy of the system. Compared to conventional surfactants, Pickering emulsifier possesses a number of advantages, including the reduced foaming problem and lower toxicity. The reagents 1,4-butanediol diglycidyl ether (BDDE) followed by triethylamine (TEA) were used to functionalise the material.

The recommended SPE protocol for SAX resins suggests loading sample at neutral pH so that the acidic analytes (in their ionic form at this pH) can cationically interact with the quaternary amine of the SAX sorbent. Li et al. [9] applied this protocol and used pH 7.2–7.8 to deprotonate the acidic analytes (a group of NSAIDs) to be retained in the SAX. The eluent, 1% HAC in hexane/EtOAc (3/1, v/v), was used to protonate

the acidic analytes and disrupt the ionic interaction with the resin. All the SPE conditions are presented in Table 1.

As discussed previously for the cation-exchange materials, the washing step, normally using organic solvents, should be included to promote selectivity. In one study [38], described in Table 1, two different washing solutions were used when acidic NSAIDs were extracted in 5 mL of urine sample using a SAX cartridge. Since the interferences were retained either by ionic or reversed-phased interactions, they could be selectively washed off. Therefore, two separate washing solutions were employed: 3 mL of 15% acetic acid in water to remove polar interferences, followed by 5 mL of 5% MeOH in 50 mM NaAc (pH 7.0) to further deprotonate the acidic analytes to enhance interactions with the sorbent; and a second washing with 5 mL of MeOH to remove basic and neutral interferences retained via hydrophobic interaction. The results obtained (%R ranged from 85% to 104%) indicated the excellent ability of the sorbent to selectively extract NSAIDs from complex samples. In another study [20], where a SAX resin was used to extract a group of neutral, acidic and basic compounds from complex environmental water, similar washing solutions (aqueous with acidic additive plus a methanolic one) were also applied; however, the second one was used to elute the neutral and basic compounds and not to remove them.

Metal organic frameworks (MOFs) have recently increased in interest for the analytical community due to their mesmerising structures and unique properties, including high surface areas, good chemical resistance, favourable thermal stability and well-defined pore structures. A study by Li et al. [39] prepared a SAX dendrimer-functionalized mesoporous silica material from a MOF material (KIT-6). The SAX material was evaluated by SPE to extract acid drugs (ketoprofen, naproxen and ibuprofen) from 3 mL of urine sample. Two washing solutions, 5 mL of 25 mM phosphate (pH 7.0) in 5% MeOH and 1 mL of ethyl acetate (EtOAc), were applied. In the loading and the first washing step, high molecular weight matrix components, such as proteins, were size-excluded thanks to the small pore diameter (7.9 nm) of the sorbent. In the second washing step, the neutral matrix interferences were washed off. At the end, most matrix interferences were removed and a very clean extract was obtained. Recoveries were in the range of 86 to 114% for the selected acidic compounds.

Similar methodologies used for SAX sorbents were used for WAX sorbents. Table 1 lists some examples of WAX sorbents and their applications. For instance, Wójciak-Kosior [40] prepared a silica WAX sorbent based on polyaniline by *in situ* polymerisation of aniline on the silica gel resin. The sorbent was applied for the SPE of leaf and root extracts from *Chelidonium majus* to determine alkaline plant metabolites such as benzophenanthridine, protoberberine and protopine alkaloids. The SPE protocol used 2 mL of H₂O/MeOH (1/1, v/v) as a washing solution and 5 mL of 0.1 M of NH₄OH in MeOH as elution solvent. Using optimised conditions, the selected alkaloids attained recoveries over 96%. In another study, Gao and Wei [41] developed a silica-based material with WAX properties functionalised with tris(2-aminoethyl)amine and 3-phenoxybenzaldehyde, introducing amino and phenyl groups attached to the surface of silica. The material was functionalised in two sequential steps by adding the functional molecules to the SiO₂-Cl resin to obtain the mixed-mode ion-exchange material. The retention properties of the material were evaluated with chlorophenols, some of them with an acidic character, in 20 mL of tap, river, wetland and lake water. This demonstrated that the established protocol was applicable to water sample analysis (%R between 89% and 110%).

Our research group [19] prepared two different WAX polymer-based materials based on hypercrosslinked polymer resins modified chemically with 1,2-ethylenediamine and piperazine moieties by PP using VBC and DVB as monomers. Under optimal conditions (see Table 1), the 1,2-ethylenediamine (EDA) functionalised material attained better recoveries (67–109%) than the piperazine material for determining the selected acidic model compounds from river water and effluent wastewater samples. The basic elution solution (2 mL of 2% NH₄OH in 1:4 MeOH:ACN)

ensured the deprotonation of the functional moieties of the sorbent and consequently the elution of the acidic compounds.

WAX materials using magnetic nanoparticles were also prepared and evaluated. For instance, Zhang et al. [42] developed a novel amino-terminated WAX material based on magnetic nanoparticles through cucurbit [6] uril promoted azide-alkyne cycloaddition using 2-azidoethylamine as the functional monomer. The material was synthesised following different steps: preparation of Fe₃O₄ magnetic nanoparticles, incorporation of SiO₂ and modification with NH₂, functionalisation with alkynyl and incorporation of cucurbit [6] uril and 2-azidoethylamine in the alkyne-modified Fe₃O₄ particles. The proposed material was employed as dispersive SPE (dSPE) sorbent to extract salivanic acids in 1 mL of Danshen water extract samples. The recoveries were between 95% and 107% for most compounds. 1 mL of sample solution at pH 5.5 was loaded for 20 min and then the analytes were eluted using 1 mL of 1% HAC in MeOH/H₂O (60/40, v/v) solution at 30 °C for another 20 min. The same synthetic method was used by Ghambarian et al. [43] to prepare Fe₃O₄ silica coated nanoparticles modified with amino groups for the extraction of two chlorophenoxyacetic acids (2-methyl-4-chlorophenoxyacetic acid and 2,4-dichlorophenoxyacetic acid) by dSPE from 25 mL of well and surface water samples with good recoveries.

Zwitterionic sorbents

Zwitterionic materials were developed with the aim of retaining both acidic and basic analytes simultaneously, thus improving the properties of the mixed-mode ion-exchange materials. Some studies have prepared and evaluated zwitterionic materials used as sorbents for SPE [44–47].

Some authors have prepared mixed-mode resins that combine WCX and WAX features. For instance, Jin et al. [46] prepared a ternary mixed-mode silica sorbent with carboxyl and amino groups via a Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) click reaction and a subsequent reduction of the remaining azide to primary amine (WAX character). The incorporation of 10-undecyonic acid conferred a WCX character to the silica network. In this case the sample was loaded at pH 6. In the first elution step, 2 mL of MeOH was chosen to elute the acidic and neutral analytes, retained by reversed-phase interactions. In a second elution, a solution of 2 mL of 5% HCOOH in MeOH was selected to elute the basic analytes because formic acid is able to make the carboxyl groups on the sorbent protonated and breaks the cation-exchange interactions between the analytes and the sorbent. Very good recoveries (all around 100%) were obtained in 2 mL of human serum for all the analytes at three different concentration levels. Nevertheless, in spite of developing a zwitterionic sorbent, only the WCX interactions were exploited.

In other examples, different combinations of hypercrosslinked zwitterionic polymeric materials were synthesised and evaluated by SPE to retain ionisable compounds with acidic and basic properties from river and effluent wastewater samples [45,47]. The zwitterionic materials were synthesised via a three-step procedure: PP of DVB and VBC to give poly(DVB-co-VBC) microspheres; hypercrosslinking of poly(DVB-co-VBC) microspheres to give hypercrosslinked poly(DVB-co-VBC) microspheres (HXLPP); functionalisation of HXLPP with either sarcosine further hydrolysed (HXLPP-WAX/WCX) [45], or quaternised sarcosine groups (HXLPP-SAX/WCX) or taurine moieties (HXLPP-WAX/SCX) [47]. Fig. 1 shows the three different structures of the zwitterionic materials prepared *in-house* and evaluated, the HXLPP-WAX/WCX, HXLPP-SAX/WCX and HXLPP-WAX/SCX. In all materials, pH 6 was selected as the optimal pH to load the sample so that all the acidic and basic analytes and the different functional groups of the sorbent would be in ionic form. Excellent recoveries were attained in all sorbents evaluated for all the compounds (from 80% to 108% when 100 mL of ultrapure water was loaded), except for the strongly acidic analytes (acesulfame and saccharin), which were only retained in the HXLPP-SAX/WCX material, with recoveries of 106% and 108%, respectively. This ability of

the HXLPP-SAX/WCX material to retain the strongly acidic compounds could be attributed to the SAX character of the sorbent, as the other two have a WAX character.

Likewise, Wang et al. [44] evaluated a zwitterionic material that includes both primary and secondary amines, and carboxylic acid groups into a silica resin, to retain acidic and basic compounds. The material was synthesised by chemical immobilisation of ampholine on the surface of the hybrid organic-inorganic silica network. A glutaraldehyde solution in phosphate buffer was added to the silica resin and subsequently, ampholine containing NaCNBH₃ was added on the activated support to generate the carboxylic acid groups. Like other WCX studies, 10 mL of sample was adjusted at pH 6 and different elution conditions were adopted depending on the type of compounds to be eluted. A basic aqueous solution at pH 11 and acidic aqueous solution at pH 1, both in MeOH 50/50 (v/v), were used to elute the acidic and basic compounds, respectively. The average recoveries of the ten analytes obtained when a beverage sample was extracted ranged from 82% to 98%.

Solid-phase microextraction

Although there are several commercially available SPME fibres, none of them contain a mixed-mode ion-exchange coating. However, the need to extract ionisable analytes has led to mixed-mode ion-exchange SPME coatings being developed. As can be seen in Table 2, different *in-house* mixed-mode ion-exchange SPME materials have been developed and evaluated to determine analytes from environmental and biological samples. In this section, we have not included the sections about anionic and cationic materials since less studies have been published compared to SPE *in-house* mixed-mode ion-exchange materials.

In general, *in-house* mixed-mode ion-exchange sorbents for SPME can be developed using various methodologies, such as *in situ* immobilisation [48–53] or sol-gel deposition [54] and they can be polymer- or silica-based.

In-house sorbents on stainless steel fibres can be immobilised *in situ* using adhesives [48,51] via sonification [50,52] by photopolymerisation [49] or even by electro-co-deposition using potentiostatic polymerisation [53]. Adhesives such as Loctite 349 impruv and Kasil 1 were used to immobilise a thin film of extraction phase on a flat stainless steel blade. The metal blades were dipped into the adhesives under a UV lamp while rotating to ensure all sides of the coatings were exposed to the UV lamp [51]. In other cases, polydopamine was used as an adhesive for further incorporation of the functional groups [48]. Sometimes an etching pre-treatment with sulphuric acid [48] or concentrated nitric acid [51] or both [52] is necessary before the functionalisation to improve adhesion and porosity of the stainless steel wire. *In situ* photopolymerisation needs a UV crosslinker for the covalent bonding of the monomer on the stainless steel wire. For instance, Cudjoe and Pawliszyn [51] compared different *in-house* SPME fibres by applying two different adhesives (Loctite 349 impruv and Kasil 1) to commercially available SPE particles: polymeric SCX, SAX, WCX and WAX; silica Discovery DPA-6S; C₁₈ + B (C₁₈ with benzenesulphonic); C₈ + B (C₈ with benzenesulphonic); C₁₈; silica Clean Screen DAU and GHB and silica Chromabond for the quantitative LC-MS/MS analysis of four polar neurotransmitters in two biological matrices, cerebrospinal fluid and rat brain tissue, shown in Table 2. For the synthesis of the fibres, the metal blade was dipped into the adhesive, and subsequently rotated in the pile of particles. The mixed-mode sorbents (C₁₈ + B; C₈ + B; MCX); MAX); WCX; WAX) were able to extract all four neurotransmitters in quantitative amounts, showing multiple interaction modes, whereas the rest of the sorbents did not extract all target compounds because they did not interact with analytes through ionic interactions. Comparing the mixed-mode coatings, those with stronger ion-exchange properties performed better in the extraction of the polar neurotransmitters (see Fig. 2). There were no considerable differences between the silica and polymer-based supports, meaning that the extraction efficiency of the sorbent was not dependent on the type of base support.

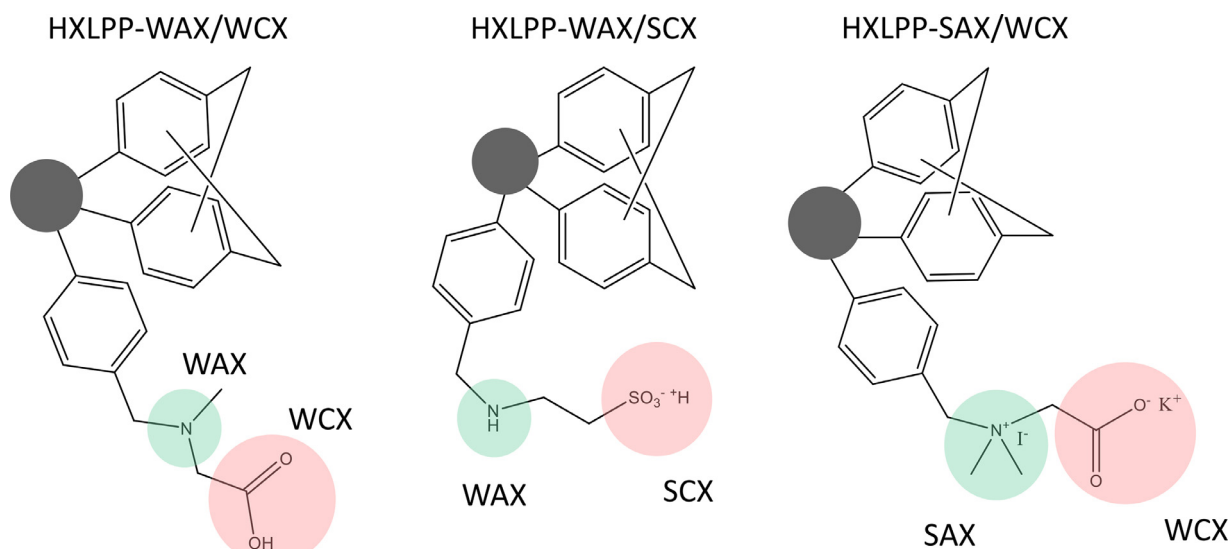


Fig. 1. Structures of 3 different zwitterionic polymeric materials: HXLPP-WAX/WCX, HXLPP-SAX/WCX and HXLPP-WAX/SCX.

Table 2
Examples of application of SPME mixed-mode ion-exchange materials.

Type	Coating	Analytes	Sample	Conditions	% Recovery	Determination technique	Ref.
SCX	C ₁₈ /SCX (benzenesulphonic acid)	Pharmaceutical and illicit drugs	Blood	E: 1200 μ L 90 min W: H ₂ O, 3 steps (5 s each) D: MeOH/ ACN (4/1) 20 min	80–150	LC-MS/MS	[55]
SCX	Several sorbents C ₁₈ and C ₈ with benzenesulphonic acid	36 polar metabolites	Human plasma	E: 300 μ L 5 min D: 250 μ L of ACN/ H ₂ O (1/1)	0–45	LC-MS HILIC-MS	[78]
WCX	Graphene oxide and polydopamine modified etched PEEK tube	Quaternary alkaloids	Herb and plasma	E: 5 mL at pH 6 at the rate of 40 mL h ⁻¹ D: ACN/20 mM NH ₄ Ac at pH = 3 (20/40, v/v)	95–103	LC-MS/MS	[48]
WAX	Hollow fibre membrane-coated polymeric ionic liquid functionalized with 1-(3-aminopropyl)-3-(4-vinylbenzyl)imidazolium 4-styrenesulphonate and 1,6-di(3-vinylimidazolium) hexane as IL-crosslinking agent.	Estrogens	Milk	E: 30 mL at 800 rpm at 70 °C for 40 min D: 500 μ L of ACN shaking for 4 min.	86–112	LC-UV	[50]
WAX	Graphitic carbon nitrides modified hollow fibre (G-CNs-HF)	Uric acid	Urine and serum	E: 1 mL in ultrasonic bath at 20 °C for 30 min D: 100 μ L of BSTFA at 80 °C for 45 min	81–122	GC-MS	[52]
SCX and SAX	C ₁₈ benzenesulphonic acid (B), C ₈ -B, MAX, MCX, WCX, WAX	Neurotransmitters	Artificial cerebrospinal fluid, rat brain tissue	E: 50 ng/mL, 1 h D: 180 μ L of H ₂ O/ ACN (3/2) with 0.1% HCOOH 1 h rotated at 800rpm	20–85	LC-MS	[51]
WAX and SAX	Ti-APTES and C ₁₈ -TMOS	PFASs	River water	E: 20 mL at pH 2 for 60 min D: 100 μ L of MeOH for 15 min	91–102	LC-MS	[54]

ACN: Acetonitrile; APTES: 3-ammonia propyl triethoxy silane; BSTFA: N,O-bis(trimethylsilyl)-trifluoroacetamide; D: Desorption; DAD: Diode array detector; E: Extraction; GC: Gas chromatography; HILIC: hydrophilic interaction liquid chromatography; IL: Ionic liquid; L: Loading; LC: Liquid chromatography; MeOH: Methanol; MS: Mass spectrometry; MS/MS: Tandem mass spectrometry; NH₄Ac: Ammonium acetate; PEEK: Polyether ether ketone; PFAs: perfluoroalkyl acids; SAX: Strong anion-exchange; SCX: Strong cation-exchange; TMOS: Tetramethoxyorthosilicate; UV: Ultraviolet detector; W: Washing; WAX Weak anion-exchange; WCX: Weak cation-exchange.

Zhang et al. [49] used the vinyl polyhedral oligomeric silsesquioxane (POSS) as a crosslinker for bonding the guanidyl-functionalised L-cysteine (G-Cys) as a monomer on the thiolated stainless steel fibre. The thiol functionalised stainless steel fibre was dipped into the polymerisation solution and pulled out quickly so that a thin layer of hybrid coating was formed. Then it was placed into the UV crosslinker for *in situ* pho-

topolymerisation to complete the chemical bonding between thiol and vinyl. Electrochemical techniques normally need the presence of an electrolyte for the electropolymerisation of the polymers. However, in the study by Behzadi and Mirzaei [53] the potentiostatic polymerisation of poly(o-anisidine) and graphene oxide nanosheets (GONSs) was carried out without any supporting electrolyte. The carboxylic acid and

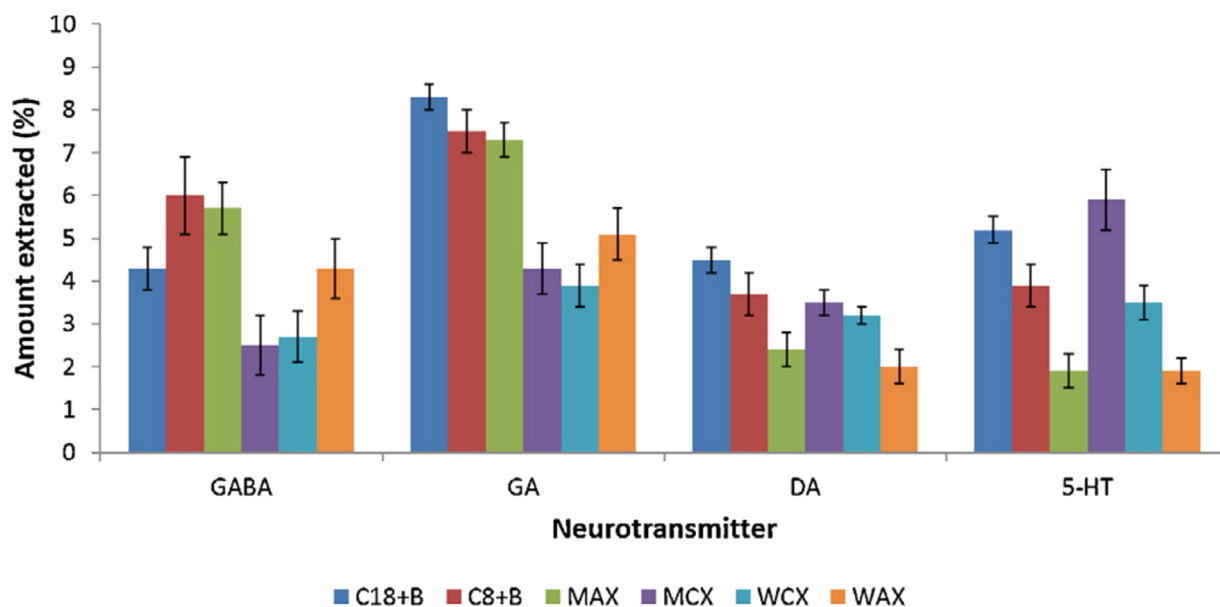


Fig. 2. Comparison of the extraction efficiency of the proposed SPME coatings (polymer-based MAX, MCX, WCX and WAX; silica-based $C_{18}+B$ and C_8+B) for the extraction of neurotransmitters in cerebrospinal fluid. Reprinted from [51] with permission from Elsevier.

hydroxyl groups in GONSs can act as the necessary electrolyte. In other cases, graphene oxide nanosheets have been demonstrated to be suitable material for incorporating the functional groups into the stainless steel fibres [48,53].

As previously mentioned, sol-gel technology is a well-known method for preparing organic-inorganic hybrid materials, synthesising polymer or composite materials under extraordinarily mild conditions. The sol-gel process makes it possible to incorporate additives, such as nanoparticles, into the first stage of the sol preparation without inhibiting the formation of the silica network. Silica has been reported to be a suitable supporting matrix for immobilising noble metal nanoparticles and avoiding their aggregation. For instance, Chen et al. [54] prepared a mixed-mode SPME fibre with SAX character by sol-gel deposition of a mixed-mode coating to an anodised Ti wire support for the extraction of perfluorooctane sulphonate and perfluorooctanoic acid from river water. The mixed-mode coating was composed of 3-(trimethoxysilyl)-1-propanamine and dimethyloctadecyl [3-(trimethoxysilyl) propyl] ammonium chloride. The SPME fibre was prepared by covalently bonding the designed mixed-mode coating to a Ti wire, with TiO_2 nanotube arrays on the surface, through the sol-gel process. The target analytes were extracted at pH 2, as both analytes are mainly present as anions at this pH and the coating is more positively charged in a more acidic solution. Therefore, a higher extraction efficiency is achieved in a more acidic solution. The authors compared the extraction efficiency of the selected anion-exchange material to commercially available coatings, such as PDMS, PA, and C_{18}/NH_2 -functionalised fibres (see Fig. 3). They found that when the *in-house* anion-exchange coating was used, the extraction efficiency was 4 and 55 times higher than the commercial PDMS and PA, respectively. This significant improvement can be attributed to the cooperative effects of hydrophobic and ionic interaction originated from the functional groups of the mixed-mode coating, which leads to strong adsorptions toward the acidic analytes.

As seen in the SPE section, pH has a crucial influence on achieving a good ionic interaction between the analytes and the coating. Moreover, the ionic state of the analytes and the charge of the fibre coating are pH-dependent. As pointed out in the introduction, different sample and elution pH conditions have been reported depending on the functional group incorporated into the mixed-mode ion-exchange material, as seen in Table 2. Desorption can be achieved by liquid desorption (LD)

[50,54] or thermal desorption (TD) [49,52], and the last one is limited to the further GC analysis.

For LD, the influence of pH is shown in the study by Wang et al. [48], who developed an mixed-mode WCX coating to extract quaternary alkaloids in 5 mL of herb and plasma samples by SPME. They selected pH 6 as the optimal pH to load the sample and pH 3 as the optimal pH value to desorb the analytes. The authors observed that the extraction efficiency of the WCX coating decreased as the elution pH increased.

For those with TD, increasing the desorption temperature led to a decrease in the partition coefficient of the targets between the coating and the gaseous phase, minimising the desorption time and carry-over. However, excessive temperature can damage the coating and result in a shortened lifetime. For instance, some authors chose 280 °C as the optimal temperature to desorb acidic compounds when an anion-exchange mixed-mode sorbent was used [49], although lower temperatures (80 °C) have also been used [52]. The temperature also obviously depends on the stability of the fibre.

SPME is an equilibrium-based extraction procedure and therefore a time-dependent process. As can be seen in Table 2, in most cases the equilibrium time was reached at 30–40 min, and then the peak areas remained steady with a longer extraction time [49,50,52]. In other cases, the equilibrium time was longer, 60 min [54].

Another important extraction parameter is the addition of salt. For ionic compounds, increasing the ionic strength of the sample solution can usually improve its activation state in water, and thus increase the solubility in water. For positively charged coatings, such as the SAX mixed-mode coating mentioned previously [54], increasing the ionic strength tends to screen the electrostatic attraction between the negatively charged analytes and the surface due to the electrical double layer compression, and consequently no salt is added to the sample.

When mixed-mode ion-exchange SPME coatings are used, few methods include a washing step. Reyes-Garcés et al. [55] introduced a washing step consisting of three consecutive washes of 1500 μ L of nanopure water for 5 s each for determining pharmaceuticals and illicit drugs in blood using a SCX sorbent. In this way, the presence of proteins, salts, and other interferences that could affect the instrumental analysis are easily avoided. The rest of the extraction conditions are presented in Table 2.

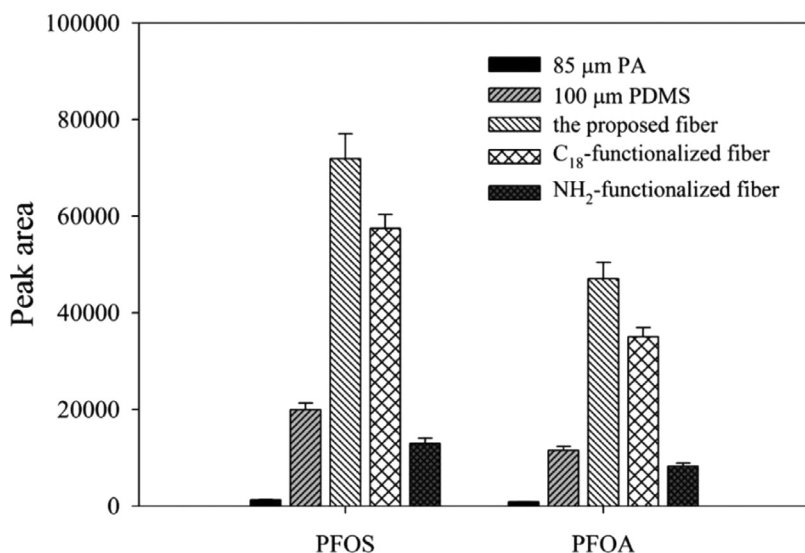


Fig. 3. Comparison of the extraction efficiencies of the selected SPME fibre to commercially available PDMS, PA, and C₁₈/NH₂-functionalised fibres for the extraction of perfluorooctane sulfonate and perfluorooctanoic acid. Reprinted from [54] with permission from Elsevier.

Important parameters are the stability and robustness of the materials, evaluated by performing several extractions or testing the materials in different extraction solvents or temperatures. For instance, Feng et al. [50] reported a decrease in peak areas of 22–27% in the 50th–70th extractions compared to the first 20 extractions when the SPME fibre was applied. Chen et al. [54] tested the robustness of the fibre by dipping it into organic solvents, such as MeOH, ACN, acetone and n-hexane. The authors observed no losses in the extraction efficiency after exposing it to these organic solvents overnight. The SPME fibre's great robustness towards organic solvents can be attributed to the chemical bonding between the mixed-mode coating and the anodised Ti wire. At very high temperatures the fibres can be unstable. For instance, a weight loss of about 20 wt% was observed at 380 °C in the study by Zhang et al. [49], implying the decomposition of the monomer covalently bonded on the surface of the fibre. However, despite the high stability of the fibres, for metabolomic applications the authors suggest using the biocompatible SPME fibres only once to avoid carry over due to the traces of metabolites from previous extractions remaining in the coating.

Stir bar sorptive extraction

Although commercially available SBSE materials, such as PDMS for the extraction of non-polar compounds and EG-silicone for polar compounds, have been used for SBSE applications, new *in-house* mixed-mode ion-exchange materials have been developed to improve the retention of ionic or ionisable compounds. *In-house* mixed-mode materials are mainly developed using two different techniques: sol-gel technology [56] or one pot polymerisation [56–59]. Examples of these materials applied in SBSE are presented in Table 3.

Sol-gel is employed to prepare SBSE surface coating materials taking advantage of their properties. Using this synthetic method, OH-PDMS is added to the sol-gel mixture due to its ability to lengthen the silica network (increasing the surface area of the coating material), distribute the stationary phase uniformly, and reduce the coating layer fragility, preventing the cracking of the coating layer [56]. Hu et al. [56] developed a WAX coating with amino ionic functional groups for SBSE based on multi-walled carbon nanotubes-4,4'-diaminodiphenylmethane/polydimethylsiloxane for the extraction of seven phenols in lake water, which were then determined using HPLC-UV. The mixed-mode ion-exchange material was synthesised by sol-gel technology. The pretreated bars were immersed vertically into the sol solution containing all the reagents. However, since the sample was loaded at pH 4, no ionic interactions were established but hydrophobic, π - π and intermolecular hydrogen bonds between 4,4'-diaminodiphenylmethane and phenols. The LD solvent, MeOH/1 mM NaOH (8/2), was selected

to neutralise the amino moieties of the coating, disrupting the interactions between the phenols and the coating (%R of 79–123% in the water sample and 71–119% in the soil sample).

In one pot polymerisation, the reaction is carried out successively in only one reactor, where all the reactants are included. It is implemented due to its simplicity, simple workup and short reaction time. For instance, in the study by Huang et al. [59] a SBSE with SAX monolithic coating was prepared by *in situ* copolymerisation of DVB and 2-(methacryloyloxy)ethyltrimethylammonium chloride, whose quaternary amines provide the ionic character to the material. The developed material displays SAX interactions with the selected analytes, inorganic anions such as Br⁻, NO₃⁻, PO₄³⁻ and SO₄²⁻, since it contains quaternary ammonium groups in the monolith structure. Hence, 50 mL of commercial purified water samples was loaded and NaOH aqueous solvent was the suitable desorption solvent, reaching recoveries of 70–93% for all the anions in all water samples analysed. In this study the SAX monolithic coating was not exploited as mixed-mode material since only ionic interactions are present between the analytes and the coating. Another example was recently presented by our research group [60], in which a polytetrafluoroethylene (PTFE)-based magnet was coated with a weak anion exchanger monolith (glycidyl methacrylate-EGDMA polymer further modified with EDA). Later, this SBSE-EDA was successfully applied under optimal conditions (10 mL of ultrapure water adjusted to pH 6 stirred at 600 rpm for 180 min; elution with 3 mL ACN containing 5% NH₄OH in the ultrasonic bath for 20 min) to extract a group of acidic compounds with recoveries ranging from 37% to 74%.

Recently, magnetic materials, mentioned previously, such as functionalised nanoparticles, or composite materials made of nanoparticles embedded in polymeric sorbents, have gained popularity in SBSE as they can be recovered by applying a magnetic field. In addition, stir bars made with magnetic nanoparticles have lower extraction times and acquire more versatility than the commercial stir bars. Some examples of *in-house* mixed-mode ion-exchange stir bar devices based on magnetic materials are shown in Table 3. Wang et al. [61] employed a novel covalent modification method for the *in situ* immobilisation of aluminium-based MOF (MIL-68) onto a poly(ether ketone) (PEEK) tube by bonding with benzoic acid groups. They applied this to extract three parabens at pH 6, including methyl paraben, ethyl paraben and propyl paraben from cosmetics, sunscreen and day cream. However, once again the MIL-68@PEEK material is not used as ion-exchange mixed-mode coating, since at pH 6 the selected parabens are protonated and could not establish ionic interactions with the coating.

Ghani et al. [62] prepared *in situ* Zn-Al layered double hydroxide (LDH) on the surface of a nanoporous anodised aluminium bar to be

Table 3
Examples of application of SBSE mixed-mode ion-exchange materials.

Type	Coating	Analytes	Sample	Conditions	% Recovery	Determination technique	Ref.
SCX	Poly (MAA-3-sulphopropyl ester potassium salt-DVB)	Quinolones	WW	E: 100 mL at pH 5, stirred at 400 rpm at r.t. for 60 min D: 3 mL of MeOH/water at pH 1.3 (80/20, v/v) for 40 min at 400 rpm	64–73	LC-DAD	[58]
SCX	Poly(MAA-3-sulphopropyl ester potassium salt-co-DVB)	5-nitroimidazole-based drugs	Honey	E: 100 mL at pH 5, stirred at 300 rpm for 3 h at r.t. D: 3 mL of MeOH/water at pH 2 (90/10, v/v) stirred for 1 h	71–114	LC-DAD	[63]
SAX	Poly(2-(methacryloyloxy) ethyltrimethylammonium chloride-co-DVB)	Inorganic anions	Commercial purified water	E: 50 mL at pH 8 stirred at 400 rpm for 2.5 h at r.t. D: 3 mL of 10 mM NaOH at 400 rpm at r.t. for 3 h	70–90	IC-CD	[59]
WAX	Poly(1-vinylimidazole-ethyleneglycol dimethacrylate)	Perfluoroalkyl acids	Surface water samples	E: 10 mL at pH 3, stirred at 800 rpm for 60 min D: 300 μ L of MeOH containing 0.4% NH ₄ OH (v/v) under sonication for 10 min	80–122	LC-MS/MS	[57]
WAX	MOFs of aluminium-based functionalised with 4-aminobenzoic acid immobilised onto PEEK tube	Parabens	Cosmetics and rabbit plasma	E: 20 mL at pH 6 stirring at 300 rpm for 2 h D: 250 μ L of MeOH by vortex for 10 min.	75–102	LC-MS/MS	[61]
AXE	Zn-Al layered double hydroxide	Organic acidic compounds	Grape juice and non-alcoholic beer	E: 10 mL at pH 7, stirred at 200 rpm for 20 min (25 °C) D: 50 μ L of 10 mM NaOH MeOH sonicated for 2 min.	90–95	LC-DAD	[62]

ACN: Acetonitrile; CD: conductivity detector; DAD: Diode array detector; DVB: Divinylbenzene; E: Extraction; D: Desorption; IC: ion chromatography; L: Loading; LC: Liquid chromatography; MAA: Methacrylic acid; MeOH: Methanol; MOFs: metal organic frameworks; MS/MS: Tandem mass spectrometry; PEEK: Polyether ether ketone; r.t.: room temperature; SAX: Strong anion-exchange; SCX: Strong cation-exchange; WAX: Weak anion-exchange; WCX: Weak cation-exchange; WW: Wastewater.

applied in the SBSE of three organic acidic compounds, including p-hydroxybenzoic acid, 3,4-dihydroxybenzoic acid and quercetin from 10 mL of commercial and natural white and red grape juice, cranberry juice and non-alcoholic beer samples. A porous anodised aluminium bar was electrochemically prepared and used as nanoporous substrate for *in-situ* growth of LDH. The incorporation of LDH gave the stir bar attractive properties such as high anion exchange capacity, compositional flexibility and biocompatibility. The target analytes were desorbed by LD employing 50 μ L of MeOH containing 10 mM NaOH, and good recoveries were obtained.

The SBSE conditions are shown in Table 3. It can be seen that low agitation speeds of 200–400 rpm were preferred for most of the studies [58,59,61–63], considering that a higher speed would cause abrasion loss of the coating. The studies by Hu et al. [56] and Yao et al. [57] are exceptions since the robustness of the stir bars made it possible to submit them to 700–800 rpm. Most of the authors reported an extraction time between 1 h and 2.5 h necessary for the stir bars to reach equilibrium, except Ghani et al. [62] whose stir bars were based on Zn-Al LDH and required only 20 min.

The desorption step is generally carried out by LD or TD. As in SPME, the desorption of thermal-sensitive and polar compounds from the coating is usually performed by LD. The desorption solution is chosen to obtain an effective and strong elution of the compounds, using the minimal volume for entirely immersing the stir bar in the desorption tube. Another reason to select the suitable desorption solvent concerns the chromatographic behaviour. The solvent should be compatible with the mobile phase and column used for the analysis. If not, an evaporation to dryness followed by a reconstitution with a more compatible solvent is necessary [57,63]. Acetone, MeOH and/or ACN in acidic or basic medium are the preferred desorption solvents used in an LD [56–58,61–63]. For instance, when WAX material is used as coating, normally the desorption solvent is basified with NaOH or ammonia to neutralise the functional groups of the coating (amine groups) and therefore disrupt the ionic interactions between the acidic compounds and the sorbent [56,57,59,62].

An acidic medium was introduced to the desorption organic solvent for strong cation-exchangers [58,63]. For instance, Huang et al.

[63] performed an SBSE to determine nitroimidazoles in 100 mL of honey employing a SCX stir bar based on poly(methacrylic acid-3-sulphopropyl ester potassium salt-co-divinylbenzene) monolithic material with sulphonic groups (see Table 3). When the optimal desorption solvent, MeOH:H₂O (pH 2) (90:10), is used, recoveries from 71% to 114% were attained for the selected analytes in real honey samples. Tests with 100% MeOH as desorption solvent showed that MeOH disrupts the hydrophobic interactions between coating and analytes; however, if there is no acidified water in the desorption solvent, the extraction efficiencies decreased, as the ionic interactions were not disrupted and the nitroimidazoles were not completely eluted.

Many types and sizes of *in-house* stir bars are obtained depending on the synthetic method. Rods of around 0.1–0.5 μ m of thickness are obtained when sol-gel technology is used, while thicker rods (1 mm) are obtained when *in situ* polymerisation methods are used. They can be reused several times (more than 25–50 extractions) without losing their efficiency, which supports their good stability and proper mechanical fulfilment to prevent their degradation and facilitate their bonding to the glass layer that covers the magnetic rod.

In terms of extraction conditions, most authors reported sample loading pH values between 6 and 8 [59,61,62] for mixed-mode anion-exchange materials. However, Yao et al. [57] chose pH 3 to extract perfluoroalkyl acids from river and lake water samples using a WAX stir bar based on poly(1-vinylimidazole-ethyleneglycol dimethacrylate) monolith (poly(VI-EGDMA)), because at weak acidic pH the imidazole groups of the coating are in an ionic state, as well as the perfluoroalkyl acids. The SBSE conditions are described in Table 3. Regarding strong cation-exchangers, as mentioned in the introduction section, the loading solution is normally acidified to pH 2–3 to protonate the basic analytes, although a value of 5 has also been used depending on the analytes [58,63].

As can be seen in some of the examples shown, successful mixed-mode ion-exchange stir bars have been developed. However, in some applications, the extraction and desorption conditions are not suitable for exploiting the mixed-mode ion-exchange interactions and a washing step was not included in any of the examples, which also limits the selectivity of the method. Therefore, a lot of research can be conducted to

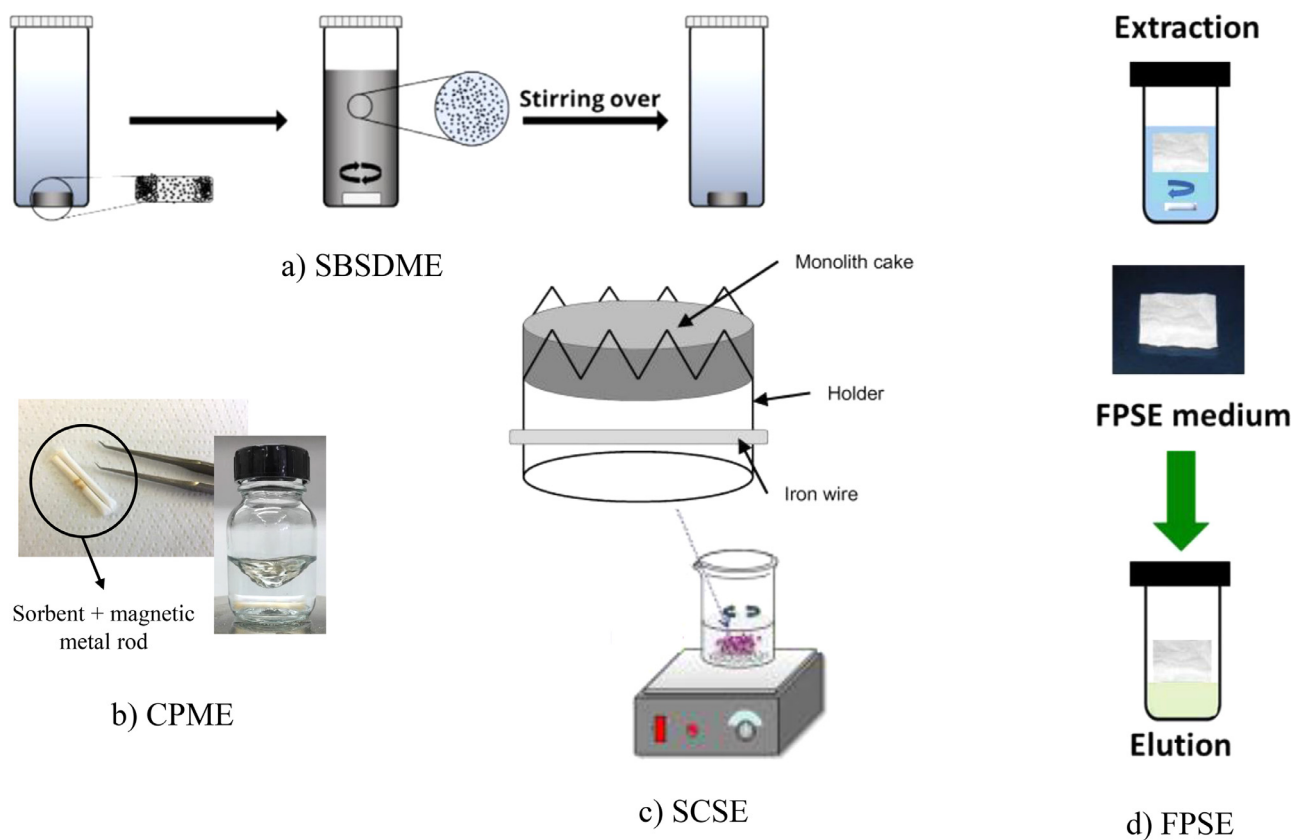


Fig. 4. Schematic configuration of some emerging techniques: (a) SBSDME, reprinted from [79] of Elsevier.; (b) CPME; (c) SCSE; (d) FPSE, reprinted from [80] of MDPI.

improve the development and application of mixed-mode ion-exchange SBSE.

Other techniques

Mixed-mode ion-exchange materials have been used in other microextraction techniques, mainly based on modifications of the previously described microextraction techniques, such as stir bar sorptive-dispersive microextraction (SBSDME) [64] or the more recent stir extraction formats, such as capsule phase microextraction (CPME) [65] and stir-cake sorptive extraction (SCSE) [66], or fabric phase sorptive extraction (FPSE) [67]. Fig. 4 shows the schematic configuration of these emerging techniques. For instance, SBSDME unifies the principles of SBSE and dispersive solid-phase extraction (dSPE) using a neodymium stir bar coated with a magnetic material as the extraction device. As magnetic materials can be recovered by applying a magnetic field, composite materials made of nanoparticles embedded in polymeric sorbents have been widely applied in microextraction techniques. In the study by Grau et al. [64], a magnetic composite made of CoFe_2O_4 magnetic nanoparticles embedded in a mixed-mode WAX sorbent (Strata-X-AW) was used as coating to extract triphenyl phosphate (TPP) and diphenyl phosphate (DPP) in urine samples. A wet chemical co-precipitation method was used to prepare the magnetic nanoparticles, which were then inserted into the polymeric resin. CoFe_2O_4 magnetic nanoparticles were preferred to the classical Fe_3O_4 due to their higher chemical stability. As expected, DPP ($\text{pK}_a=1.12$) was the only analyte to establish WAX interactions with the sorbent, as TPP is not ionisable. Similar results were obtained when loading at a pH below 9, as the amines of the sorbent and DPP are both in ionic state.

Huang et al. [66] prepared a new monolithic sorbent for SCSE from poly(allyl thiourea-co-divinylbenzene) (ATDB) by *in-situ* polymerisation to provide the ATDB-SCSE device. The novel material, which presents

primary and secondary amines as functional groups, was used to extract phenols in different types of water, such as tap, lake and reservoir water. Similar to the study by Grau et al. [64], the extraction of phenols improved when the pH was increased from 3 to 8, and then decreased when the pH was increased further. This is due to the competition between the hydroxyl groups in the sample and phenol groups of the analytes to interact with the activated amino groups of the coating, weakening the anion-exchange interactions. This demonstrates that the amino groups of the sorbent conferred a WAX character to the ATDB-SCSE device.

Another new microextraction technique is the CPME, which consists of two fused porous polypropylene membranes, one accommodates the sorbent and the other encapsulates a magnetic metal rod. In one CPME study [65], the authors prepared two mixed-mode ion-exchange materials combining C_{18} with sulphonic moieties (SCX) and C_{18} with quaternary amines (SAX) using sol-gel technology to retain selectively basic and acidic analytes, respectively. First the tubular membranes were prepared, then the monolithic sorbent was developed *in situ* inside the membrane using the sol-solution. During extraction, for the material with an SCX character, pH 5 was selected to load the sample, while for the SAX, it was pH 7. Regarding the desorption conditions, MeOH containing 5% HCOOH was selected for the material with a C_{18} and SCX character, and MeOH containing 5% NH_4OH for the other material with a C_{18} and SAX character. Under these conditions, each material provided suitable retention and selectivity.

Mixed-mode ion-exchange materials have also been used in FPSE [67,68]. Agadellis et al. [67] prepared a mixed-mode strong cation-exchange membrane to determine four tetracycline antibiotic residues (oxytetracycline, tetracycline, chlortetracycline, doxycycline) in milk, after protein precipitation, by HPLC-UV. The membrane, coated on 100% cellulose cotton, contained propyl sulfonic acid, (strong cation-exchanger) and C_{18} . The material was synthesised using the sol-gel technique. The use of a mixed-mode material was essential for this study

since the structure of tetracyclines present both positive and negative charge centres at different solution pH values, and for this reason the determination of tetracyclines makes it a major challenge. At lower pH values tetracyclines exist mainly as cation, and at higher solution pH values they exist mainly as anionic species. At the natural pH of milk (6.7–6.9), tetracyclines mostly exist as zwitterions due to the simultaneous ionisation of both cationic and anionic functional groups. Zwitterionic FPSE materials were also prepared and evaluated [68] for the extraction of five triazine herbicides (simazine, atrazine, prometryn, terbuthylazine and propazine) from fruit juice samples to be analysed by HPLC-DAD. The novel zwitterionic membrane was prepared by combining C₁₈, propyl sulfonic acid (strong cation-exchanger), and propyl-N,N,N-trimethylammonium chloride (strong anion-exchanger) in a sol-gel siloxane network, chemically coated on 100% cotton cellulose fabric substrate. Triazines exist in neutral state in juice samples, while a large number of ionic species, mainly organic acids and bases, are present in ionic state as interferents of the matrix. The zwitterionic material could efficiently help cleaning all the acidic interferences from fruit juices thanks to their ability to retain the ionic species present in the fruit juice sample through the ionic functional groups attached to the material. By this way, the concentration of ionic species of the matrix is reduced, enabling the retention of neutral triazines by the C₁₈ groups of the material.

Thus, these examples evidence that mixed-mode ion-exchange is spreading through a broad range of sorptive extraction techniques.

Conclusions

New *in-house* mixed-mode ion-exchange materials have been developed mainly for SPE but they are also gaining importance for other sorptive extraction techniques. Precipitation polymerisation, sol-gel technology and *in situ* immobilisation are the main synthetic approaches for creating the basis that is further functionalised with ionic moieties.

Zwitterionic materials recently appeared with the purpose of extracting acidic and basic compounds simultaneously, and are mainly applied in SPE.

These *in-house* mixed-mode ion-exchange materials were successfully applied to selectively extract acidic and basic analytes from complex samples when optimal extraction protocols that take into account the pHs in the different steps are applied. However, it should be mentioned that promising mixed-mode ion-exchange materials have been developed but in some cases not used at the optimum conditions to exploit the potential of these materials.

One of the future trends in *in-house* mixed-mode technology is to apply it to emerging extraction techniques, so that the mixed-mode ion-exchange materials extend the application field of the techniques. Furthermore, mixed-mode ion-exchange materials will be applied in the future to other extraction techniques and supports and will expand the application field to other kinds of samples and analytes.

Declaration of Competing Interest

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

Acknowledgments

This research was funded by MCIN/ AEI /10.13039/501100011033 (Projects: PID2020-1145876B-I00 and RED2018-102522-T). J.C. Nadal is also grateful to Universitat Rovira i Virgili (URV) for his PhD grant (2017PMF-PIPF-49).

References

[1] B.H. Fumes, M.R. Silva, F.N. Andrade, C.E.D. Nazario, F.M. Lanças, Recent advances and future trends in new materials for sample preparation, *TrAC Trends Anal. Chem.* 71 (2015) 9–25, doi:10.1016/j.trac.2015.04.011.

[2] I. Racamonde, R. Rodil, J.B. Quintana, B.J. Seira, A. Kabir, K.G. Furton, R. Cela, Fabric phase sorptive extraction: a new sorptive microextraction technique for the determination of non-steroidal anti-inflammatory drugs from environmental water samples, *Anal. Chim. Acta* 865 (2015) 22–30, doi:10.1016/j.aca.2015.01.036.

[3] J. Moreda-Piñeiro, A. Moreda-Piñeiro, Recent advances in combining microextraction techniques for sample pre-treatment, *TrAC Trends Anal. Chem.* 71 (2015) 265–274, doi:10.1016/j.trac.2015.02.025.

[4] K. Delinska, P.W. Rakowska, A. Kloskowski, Porous material-based sorbent coatings in solid-phase microextraction technique: recent trends and future perspectives, *Trends Anal. Chem.* 143 (2021) 116386, doi:10.1016/j.trac.2021.116386.

[5] A.B. Kanu, Recent developments in sample preparation techniques combined with high-performance liquid chromatography: a critical review, *J. Chromatogr. A* 1654 (2021) 462444, doi:10.1016/j.chroma.2021.462444.

[6] M. He, Y. Wang, Q. Zhang, L. Zang, B. Chen, B. Hu, Stir bar sorptive extraction and its application, *J. Chromatogr. A* 1637 (2021) 461810, doi:10.1016/j.chroma.2020.461810.

[7] P. Richter, A. Arismendi, M. Becerra-herrera, The fundamentals, chemistries and applications of rotating-disk sorptive extraction, *Trends Anal. Chem.* 137 (2021) 116209, doi:10.1016/j.trac.2021.116209.

[8] L.S. Machado, F.Q. Soares, R.O. Martins, R.A. Bernardo, A.T. Cardoso, M.A. Ruggiero, D. Rabelo, P. Sérgio, A.R. Chaves, Polypyrrole monolithic extraction phase: from conventional to miniaturized sample preparation techniques, *J. Chromatogr. A* 1651 (2021) 462260, doi:10.1016/j.chroma.2021.462260.

[9] Y. Li, C. Huang, J. Yang, J. Peng, J. Jin, H. Ma, J. Chen, Multifunctionalized mesoporous silica as an efficient reversed-phase/anion exchange mixed-mode sorbent for solid-phase extraction of four acidic nonsteroidal anti-inflammatory drugs in environmental water samples, *J. Chromatogr. A* 1527 (2017) 10–17, doi:10.1016/j.chroma.2017.10.051.

[10] Y. Wen, L. Chen, J. Li, D. Liu, L. Chen, Recent advances in solid-phase sorbents for sample preparation prior to chromatographic analysis, *TrAC Trends Anal. Chem.* 59 (2014) 26–41, doi:10.1016/j.trac.2014.03.011.

[11] N. Fontanals, R.M. Marcé, F. Borrull, Materials for solid-phase extraction of organic compounds, *Separations* 6 (2019) 56, doi:10.3390/separations6040056.

[12] A. Azizi, C.S. Bottaro, A critical review of molecularly imprinted polymers for the analysis of organic pollutants in environmental water samples, *J. Chromatogr. A* 1614 (2020) 460603, doi:10.1016/j.chroma.2019.460603.

[13] L. Li, Y. Chen, L. Yang, Z. Wang, H. Liu, Recent advances in applications of metal-organic frameworks for sample preparation in pharmaceutical analysis, *Coord. Chem. Rev.* 411 (2020) 213235, doi:10.1016/j.ccr.2020.213235.

[14] T. Zhou, G. Che, L. Ding, D. Sun, Y. Li, Recent progress of selective adsorbents: from preparation to complex sample pretreatment, *TrAC Trends Anal. Chem.* 121 (2019) 115678, doi:10.1016/j.trac.2019.115678.

[15] E. Carasek, L. Morés, J. Merib, Basic principles, recent trends and future directions of microextraction techniques for the analysis of aqueous environmental samples, *Trends Environ. Anal. Chem.* 19 (2018) e00060, doi:10.1016/j.teac.2018.e00060.

[16] N. Fontanals, F. Borrull, R.M. Marcé, Mixed-mode ion-exchange polymeric sorbents in environmental analysis, *J. Chromatogr. A* 1609 (2020) 460531, doi:10.1016/j.chroma.2019.460531.

[17] N. Fontanals, F. Borrull, R.M. Marcé, Overview of mixed-mode ion-exchange materials in the extraction of organic compounds, *Anal. Chim. Acta* 1117 (2020) 89–107, doi:10.1016/j.aca.2020.03.053.

[18] D. Bratkowska, R.M. Marcé, P.A.G. Cormack, F. Borrull, N. Fontanals, Development and application of a polar coating for stir bar sorptive extraction of emerging pollutants from environmental water samples, *Anal. Chim. Acta* 706 (2011) 135–142, doi:10.1016/j.aca.2011.08.028.

[19] N. Fontanals, P.A.G. Cormack, D.C. Sherrington, Hypercrosslinked polymer microspheres with weak anion-exchange character. Preparation of the microspheres and their applications in pH-tunable, selective extractions of analytes from complex environmental samples, *J. Chromatogr. A* 1215 (2008) 21–29, doi:10.1016/j.chroma.2008.10.124.

[20] C. Huang, Y. Li, J. Yang, J. Peng, J. Jin, J. Wang Dhanjai, J. Chen, Preparation of a reversed-phase/anion-exchange mixed-mode spherical sorbent by Pickering emulsion polymerization for highly selective solid-phase extraction of acidic pharmaceuticals from wastewater, *J. Chromatogr. A* 1521 (2017) 1–9, doi:10.1016/j.chroma.2017.09.021.

[21] S. Pascual-Caro, N. Fontanals, F. Borrull, C. Aguilar, M. Calull, Solid-phase extraction based on cation-exchange sorbents followed by liquid chromatography high-resolution mass spectrometry to determine synthetic cathinones in urine, *Forensic Toxicol.* 38 (2020) 185–194, doi:10.1007/s11419-019-00508-8.

[22] S. Triñanes, M.C. Casais, M.C. Mejuto, R. Cela, Selective determination of COXIBs in environmental water samples by mixed-mode solid phase extraction and liquid chromatography quadrupole time-of-flight mass spectrometry, *J. Chromatogr. A* 1420 (2015) 35–45, doi:10.1016/j.chroma.2015.10.004.

[23] J. Janda, K. Nödler, H.J. Brauch, C. Zwiener, F.T. Lange, Robust trace analysis of polar (C2-C8) perfluorinated carboxylic acids by liquid chromatography-tandem mass spectrometry: method development and application to surface water, groundwater and drinking water, *Environ. Sci. Pollut. Res.* 26 (2019) 7326–7336, doi:10.1007/s11356-018-1731-x.

[24] M. Antonelli, B. Benedetti, C. Cavaliere, A. Cerrato, C.M. Montone, S. Piovesana, A. Lagana, A.L. Capriotti, Phospholipidome of extra virgin olive oil: development of a solid phase extraction protocol followed by liquid chromatography–high resolution mass spectrometry for its software-assisted identification, *Food Chem.* 310 (2020) 125860, doi:10.1016/j.foodchem.2019.125860.

[25] A.C. Isaguirre, R.A. Olsina, L.D. Martínez, A.V. Lapiere, S. Cerutti, Development of solid phase extraction strategies to minimize the effect of human urine matrix effect

- on the response of carnitine by UPLC-MS/MS, *Microchem. J.* 129 (2016) 362–367, doi:10.1016/j.microc.2016.07.018.
- [26] D. Bratkowska, R.M. Marcé, P.A.G. Cormack, D.C. Sherrington, F. Borrull, N. Fontanals, Synthesis and application of hypercrosslinked polymers with weak cation-exchange character for the selective extraction of basic pharmaceuticals from complex environmental water samples, *J. Chromatogr. A* 1217 (2010) 1575–1582, doi:10.1016/j.chroma.2010.01.037.
- [27] Y. Xu, J. Liu, H. Zhang, M. Jiang, L. Cao, M. Zhang, W. Sun, S. Ruan, P. Hu, Hypercrosslinked strong cation-exchange polymers for selective extraction of serum purine metabolites associated with gout, *Talanta* 151 (2016) 172–178, doi:10.1016/j.talanta.2016.01.014.
- [28] N. Fontanals, N. Miralles, N. Abdullah, A. Davies, N. Gilart, P.A.G. Cormack, Evaluation of strong cation-exchange polymers for the determination of drugs by solid-phase extraction-liquid chromatography-tandem mass spectrometry, *J. Chromatogr. A* 1343 (2014) 55–62, doi:10.1016/j.chroma.2014.03.068.
- [29] N. Gilart, P.A.G. Cormack, R.M. Marcé, N. Fontanals, F. Borrull, Selective determination of pharmaceuticals and illicit drugs in wastewaters using a novel strong cation-exchange solid-phase extraction combined with liquid chromatography-tandem mass spectrometry, *J. Chromatogr. A* 1325 (2014) 137–146, doi:10.1016/j.chroma.2013.12.012.
- [30] K. Hu, G. Zhao, J. Liu, L. Jia, F. Xie, S. Zhang, H. Liu, M. Liu, Simultaneous quantification of three alkylated-purine adducts in human urine using sulfonic acid poly(glycidyl methacrylate-divinylbenzene)-based microspheres as sorbent combined with LC-MS/MS, *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* 1081–1082 (2018) 15–24, doi:10.1016/j.jchromb.2018.02.028.
- [31] W. Zhao, X. Wang, J. Guo, Y. Guo, C. Lan, F. Xie, S. Zong, L. He, S. Zhang, Evaluation of sulfonic acid functionalized covalent triazine framework as a hydrophilic-lipophilic balance/cation-exchange mixed-mode sorbent for extraction of benzimidazole fungicides in vegetables, fruits and juices, *J. Chromatogr. A* 1618 (2020) 460847, doi:10.1016/j.chroma.2019.460847.
- [32] M.M. Zheng, G.D. Ruan, Y.Q. Feng, Hybrid organic-inorganic silica monolith with hydrophobic/strong cation-exchange functional groups as a sorbent for micro-solid phase extraction, *J. Chromatogr. A* 1216 (2009) 7739–7746, doi:10.1016/j.chroma.2009.08.085.
- [33] N. Casado, D. Pérez-Quintanilla, S. Morante-Zarceo, I. Sierra, Evaluation of bi-functionalized mesoporous silicas as reversed phase/cation-exchange mixed-mode sorbents for multi-residue solid phase extraction of veterinary drug residues in meat samples, *Talanta* 165 (2017) 223–230, doi:10.1016/j.talanta.2016.12.057.
- [34] N. Fontanals, J. Zohar, F. Borrull, S. Ronka, R.M. Marcé, Development of a maleic acid-based material to selectively solid-phase extract basic compounds from environmental samples, *J. Chromatogr. A* 1647 (2021) 462165, doi:10.1016/j.chroma.2021.462165.
- [35] D. Bratkowska, A. Davies, N. Fontanals, P.A.G. Cormack, F. Borrull, D.C. Sherrington, R.M. Marcé, Hypercrosslinked strong anion-exchange resin for extraction of acidic pharmaceuticals from environmental water, *J. Sep. Sci.* 35 (2012) 2621–2628, doi:10.1002/jssc.201200451.
- [36] X. Liang, P. Hu, H. Zhang, W. Tan, Hypercrosslinked strong anion-exchange polymers for selective extraction of fluoroquinolones in milk samples, *J. Pharm. Biomed. Anal.* 166 (2019) 379–386, doi:10.1016/j.jpba.2018.12.047.
- [37] F. Meischl, C.G. Kirchner, S.E. Stuppner, M. Rainer, Comparative study of substituted poly(4-vinylbenzyl chloride/ethylene glycol dimethacrylate) sorbents for enrichment of selected pharmaceuticals and estrogens from aqueous samples, *J. Hazard. Mater.* 355 (2018) 180–186, doi:10.1016/j.jhazmat.2018.05.016.
- [38] C. Huang, Y. Li, J. Yang, J. Peng, J. Tan, Y. Fan, L. Wang, J. Chen, Hyperbranched mixed-mode anion-exchange polymeric sorbent for highly selective extraction of nine acidic non-steroidal anti-inflammatory drugs from human urine, *Talanta* 190 (2018) 15–22, doi:10.1016/j.talanta.2018.07.033.
- [39] Y. Li, J. Yang, C. Huang, L. Wang, J. Wang, J. Chen, Dendrimer-functionalized mesoporous silica as a reversed-phase/anion-exchange mixed-mode sorbent for solid phase extraction of acid drugs in human urine, *J. Chromatogr. A* 1392 (2015) 28–36, doi:10.1016/j.chroma.2015.03.003.
- [40] M. Wójciak-Kosior, I. Sowa, S. Dresler, J. Kováčik, M. Staniak, J. Sawicki, S. Zielińska, R. Świeboda, M. Strzemiński, R. Kocjan, Polyaniline based material as a new SPE sorbent for pre-treatment of Chelidonium majus extracts before chromatographic analysis of alkaloids, *Talanta* 194 (2019) 32–37, doi:10.1016/j.talanta.2018.10.009.
- [41] L. Gao, Y. Wei, Fabrication of a novel hydrophobic/ion-exchange mixed-mode adsorbent for the dispersive solid-phase extraction of chlorophenols from environmental water samples, *J. Sep. Sci.* 39 (2016) 3186–3194, doi:10.1002/jssc.201501299.
- [42] Q. Zhang, D.D. Zhou, J.W. Zhang, D. Gao, F.Q. Yang, H. Chen, Z.N. Xia, Amino-terminated supramolecular cucurbit [6]uril pseudorotaxane complexes immobilized on magnetite@silica nanoparticles: a highly efficient sorbent for salivarianic acids, *Talanta* 195 (2019) 354–365, doi:10.1016/j.talanta.2018.11.086.
- [43] M. Ghambarian, M. Behbahani, A. Esrafilii, H.R. Sobhi, Application of a dispersive solid-phase extraction method using an amino-based silica-coated nanomagnetic sorbent for the trace quantification of chlorophenoxyacetic acids in water samples, *J. Sep. Sci.* 40 (2017) 3479–3486, doi:10.1002/jssc.201700572.
- [44] T. Wang, Y. Chen, J. Ma, M. Chen, C. Nie, M. Hu, Y. Li, Z. Jia, J. Fang, H. Gao, Amphiphilic-functionalized hybrid organic-inorganic silica material as sorbent for solid-phase extraction of acidic and basic compounds, *J. Chromatogr. A* 1308 (2013) 63–72, doi:10.1016/j.chroma.2013.08.025.
- [45] J.C. Nadal, K.L. Anderson, S. Dargo, I. Joas, D. Salas, F. Borrull, P.A.G. Cormack, R.M. Marcé, N. Fontanals, Microporous polymer microspheres with amphoteric character for the solid-phase extraction of acidic and basic analytes, *J. Chromatogr. A* 1626 (2020) 461348, doi:10.1016/j.chroma.2020.461348.
- [46] S. Jin, Y. Qiao, J. Xing, Ternary mixed-mode silica sorbent of solid-phase extraction for determination of basic, neutral and acidic drugs in human serum, *Anal. Bioanal. Chem.* 410 (2018) 3731–3742, doi:10.1007/s00216-018-1037-3.
- [47] J.C. Nadal, S. Dargo, F. Borrull, P.A.G. Cormack, N. Fontanals, R.M. Marcé, Hypercrosslinked polymer microspheres decorated with anion- and cation-exchange groups for the simultaneous solid-phase extraction of acidic and basic analytes from environmental waters, *J. Chromatogr. A* 1661 (2022) 462715, doi:10.1016/j.chroma.2021.462715.
- [48] C. Wang, W. Zhou, X. Liao, W. Zhang, Z. Chen, An etched polyether ether ketone tube covered with immobilized graphene oxide for online solid phase microextraction of quaternary alkaloids prior to their quantitation by HPLC-MS/MS, *Microchim. Acta* 184 (2017) 2715–2721, doi:10.1007/s00604-017-2262-8.
- [49] N. Zhang, X. Lei, T. Huang, L. Su, L. Zhang, Z. Xie, X. Wu, Guanidyl-functionalized polydihydroxyoligomeric silsesquioxane porous hybrid polymer coating for specific solid phase microextraction of phthalate esters in foodstuff, *Chem. Eng. J.* 386 (2020) 124003, doi:10.1016/j.cej.2019.124003.
- [50] J. Feng, M. Sun, Y. Bu, C. Luo, Hollow fiber membrane-coated functionalized polymeric ionic liquid capsules for direct analysis of estrogens in milk samples, *Anal. Bioanal. Chem.* 408 (2016) 1679–1685, doi:10.1007/s00216-015-9279-9.
- [51] E. Cudjoe, J. Pawliszyn, Optimization of solid phase microextraction coatings for liquid chromatography mass spectrometry determination of neurotransmitters, *J. Chromatogr. A* 1341 (2014) 1–7, doi:10.1016/j.chroma.2014.03.035.
- [52] Y. Sun, J. Chen, H. Qi, Y. Shi, Graphitic carbon nitrides modified hollow fiber solid phase microextraction for extraction and determination of uric acid in urine and serum coupled with gas chromatography-mass spectrometry, *J. Chromatogr. B* 1004 (2015) 53–59, doi:10.1016/j.jchromb.2015.09.025.
- [53] M. Behzadi, M. Mirzaei, Poly(*o*-anisidine)/graphene oxide nanosheets composite as a coating for the headspace solid-phase microextraction of benzene, toluene, ethylbenzene and xylenes, *J. Chromatogr. A* 1443 (2016) 35–42, doi:10.1016/j.chroma.2016.03.039.
- [54] C. Chen, J. Wang, S. Yang, Z. Yan, Q. Cai, S. Yao, Analysis of perfluorooctane sulfonate and perfluorooctanoic acid with a mixed-mode coating-based solid-phase microextraction fiber, *Talanta* 114 (2013) 11–16, doi:10.1016/j.talanta.2013.04.018.
- [55] N. Reyes-Garcés, M.N. Alam, J. Pawliszyn, The effect of hematocrit on solid-phase microextraction, *Anal. Chim. Acta* 1001 (2018) 40–50, doi:10.1016/j.aca.2017.11.014.
- [56] C. Hu, B. Chen, M. He, B. Hu, Amino modified multi-walled carbon nanotubes/polydimethylsiloxane coated stir bar sorptive extraction coupled to high performance liquid chromatography-ultraviolet detection for the determination of phenols in environmental samples, *J. Chromatogr. A* 1300 (2013) 165–172, doi:10.1016/j.chroma.2013.05.004.
- [57] X. Yao, Z. Zhou, M. He, B. Chen, Y. Liang, B. Hu, One-pot polymerization of monolith coated stir bar for high efficient sorptive extraction of perfluoroalkyl acids from environmental water samples followed by high performance liquid chromatography-electrospray tandem mass spectrometry detection, *J. Chromatogr. A* 1553 (2018) 7–15, doi:10.1016/j.chroma.2018.04.014.
- [58] X. Huang, N. Qiu, D. Yuan, Q. Lin, Preparation of a mixed stir bar for sorptive extraction based on monolithic material for the extraction of quinolones from wastewater, *J. Chromatogr. A* 1217 (2010) 2667–2673, doi:10.1016/j.chroma.2009.09.072.
- [59] X. Huang, J. Lin, D. Yuan, A new anionic exchange stir bar sorptive extraction coating based on monolithic material for the extraction of inorganic anion, *J. Chromatogr. A* 1217 (2010) 4898–4903, doi:10.1016/j.chroma.2010.05.063.
- [60] J.C. Nadal, M. Catalá-Icardo, F. Borrull, J.M. Herrero-Martínez, R.M. Marcé, N. Fontanals, Weak anion-exchange mixed-mode materials to selectively extract acidic compounds by stir bar sorptive extraction from environmental waters, *J. Chromatogr. A* (2022) 462748.
- [61] C. Wang, W. Zhou, X. Liao, X. Wang, Z. Chen, Covalent immobilization of metal organic frameworks onto chemical resistant poly(ether ether ketone) jacket for stir bar extraction, *Anal. Chim. Acta* 1025 (2018) 124–133, doi:10.1016/j.aca.2018.04.056.
- [62] M. Ghani, *In-situ* growth of zinc-aluminum-layered double hydroxide on nanoporous anodized aluminum bar for stir-bar sorptive extraction of phenolic acids, *Microchem. J.* 147 (2019) 1173–1179, doi:10.1016/j.microc.2019.04.052.
- [63] X. Huang, J. Lin, D. Yuan, Simple and sensitive determination of nitroimidazole residues in honey using stir bar sorptive extraction with mixed mode monolith followed by liquid chromatography, *J. Sep. Sci.* 34 (2011) 2138–2144, doi:10.1002/jssc.201000880.
- [64] J. Grau, J.L. Benedité, J. Serrano, A. Segura, A. Chisvert, Stir bar sorptive-dispersive microextraction for trace determination of triphenyl and diphenyl phosphate in urine of nail polish users, *J. Chromatogr. A* 1593 (2019) 9–16, doi:10.1016/j.chroma.2019.02.014.
- [65] J.C. Nadal, F. Borrull, K.G. Furton, A. Kabir, N. Fontanals, R.M. Marcé, Selective monitoring of acidic and basic compounds in environmental water by capsule phase microextraction using sol-gel mixed-mode sorbents followed by liquid chromatography-mass spectrometry in tandem, *J. Chromatogr. A* 1625 (2020) 461295, doi:10.1016/j.chroma.2020.461295.
- [66] X. Huang, Y. Wang, D. Yuan, X. Li, S. Nong, New monolithic stir-rod-sorptive extraction for the determination of polar phenols by HPLC, *Anal. Bioanal. Chem.* 405 (2013) 2185–2193, doi:10.1007/s00216-012-6301-3.
- [67] E. Agadellis, A. Tartaglia, M. Locatelli, A. Kabir, K.G. Furton, V. Samanidou, Mixed-mode fabric phase sorptive extraction of multiple tetracycline residues from milk samples prior to high performance liquid chromatography-ultraviolet analysis, *Microchem. J.* (2020) 159, doi:10.1016/j.microc.2020.105437.

- [68] N. Manousi, V. Alampanos, I. Priovolos, A. Kabir, K.G. Furton, E. Rosenberg, G.A. Zachariadis, V.F. Samanidou, Exploring sol-gel zwitterionic fabric phase sorptive extraction sorbent as a new multi-mode platform for the extraction and pre-concentration of triazine herbicides from juice samples, *Food Chem.* 373 (2022) 131517, doi:10.1016/j.foodchem.2021.131517.
- [69] N. Casado, D. Pérez-Quintanilla, S. Morante-Zarcelero, I. Sierra, Bi-functionalized mesostructured silicas as reversed-phase/strong anion-exchange sorbents. Application to extraction of polyphenols prior to their quantitation by UHPLC with ion-trap mass spectrometry detection, *Microchim. Acta* 186 (2019) 1–13, doi:10.1007/s00604-019-3267-2.
- [70] J. Valimaña-Traverso, S. Morante-Zarcelero, D. Pérez-Quintanilla, M.Á. García, I. Sierra, M.L. Marina, Cationic amine-bridged periodic mesoporous organosilica materials for off-line solid-phase extraction of phenoxy acid herbicides from water samples prior to their simultaneous enantiomeric determination by capillary electrophoresis, *J. Chromatogr. A* 1566 (2018) 146–157, doi:10.1016/j.chroma.2018.06.042.
- [71] N. Fontanals, S. Ronka, F. Borrull, A.W. Trochimczuk, R.M. Marcé, Supported imidazolium ionic liquid phases: a new material for solid-phase extraction, *Talanta* 80 (2009) 250–256, doi:10.1016/j.talanta.2009.06.068.
- [72] J. Wei, Z. Guo, P. Zhang, F. Zhang, B. Yang, X. Liang, A new reversed-phase/strong anion-exchange mixed-mode stationary phase based on polar-copolymerized approach and its application in the enrichment of aristolochic acids, *J. Chromatogr. A* 1246 (2012) 129–136, doi:10.1016/j.chroma.2012.03.047.
- [73] L. Vidal, J. Parshintsev, K. Hartonen, A. Canals, M.L. Riekkola, Ionic liquid-functionalized silica for selective solid-phase extraction of organic acids, amines and aldehydes, *J. Chromatogr. A* 1226 (2012) 2–10, doi:10.1016/j.chroma.2011.08.075.
- [74] T. Tsukamoto, A. Yamamoto, W. Kamichatani, Y. Inoue, Synthesis of novel sulfobetaine-type adsorbents and characteristics of their adsorption of polar solutes in hydrophilic SPE, *Chromatographia* 70 (2009) 1525–1530, doi:10.1365/s10337-009-1378-3.
- [75] L. Vidal, O. Robin, J. Parshintsev, J.P. Mikkola, M.L. Riekkola, Quaternary ammonium-functionalized silica sorbents for the solid-phase extraction of aromatic amines under normal phase conditions, *J. Chromatogr. A* 1285 (2013) 7–14, doi:10.1016/j.chroma.2013.02.003.
- [76] F. Xu, F. Liu, C. Wang, Y. Wei, Reversed-phase/weak anion exchange magnetic mesoporous microspheres for removal of matrix effects in lipophilic marine biotoxins analysis by ultrahigh-performance liquid chromatography coupled to tandem mass spectrometry, *Food Chem.* 294 (2019) 104–111, doi:10.1016/j.foodchem.2019.05.031.
- [77] H. Bagheri, S. Banihashemi, Sol-gel-based silver nanoparticles-doped silica - polydiphenylamine nanocomposite for micro-solid-phase extraction, *Anal. Chim. Acta* 886 (2015) 56–65, doi:10.1016/j.aca.2015.06.012.
- [78] D. Vuckovic, J. Pawliszyn, Systematic evaluation of solid-phase microextraction coatings for untargeted metabolomic profiling of biological fluids by liquid chromatography-mass spectrometry, *Anal. Chem.* 83 (2011) 1944–1954, doi:10.1021/ac102614v.
- [79] V. Vázquez-Gomis, J. Grau, J.L. Benedé, D.L. Giokas, A. Chisvert, A. Salvador, Fundamentals and applications of stir bar sorptive dispersive microextraction: a tutorial review, *Anal. Chim. Acta* 1153 (2021) 338271, doi:10.1016/j.aca.2021.338271.
- [80] A. Kabir, V. Samanidou, Fabric phase sorptive extraction: a paradigm shift approach in analytical and bioanalytical sample preparation, *Molecules* 26 (2021) 865, doi:10.3390/molecules26040865.