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Current trends on microextraction by packed sorbent – fundamentals, application fields, innovative improvements and future applications

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MEPS, the acronym of microextraction by packed sorbent, is a simple, fast and user- and environmentally-friendly miniaturization of the popular solid-phase extraction technique (SPE). In fact, it has been widely shown that MEPS can easily replace SPE for most, if not all, previous applications. It can attain this with obvious gains in sample and solvent usage, which is greatly reduced without compromising the extraction efficiency. Furthermore, MEPS can be operated with semiautomatic electronic syringes, making it very reliable and versatile, particularly to handle very low and very high sample volumes. This review will focus on the strengths and weaknesses of this technique and the different MEPS architectures commercially available in the context of the MEPS applications reported in the last five years. Additionally, innovative improvements will be highlighted, particularly those related with new applications and recent MEPS configurations and sorbents, such as the controlled directional flow or the innovative μSPEed variant.

Introduction

In recent years, extraction procedures in the microliter range with low reagent and sample volume requirements gained increasing relevance. The work of Abdel-Rehim (2004),[1] describing the miniaturization of conventional solid phase extraction (SPE) in packed bed devices, particularly syringes, is usually described as one of the triggers for this trend. This format, MEPS (microextraction by packed sorbent), is essentially represented by the commercial presentation, in which a small amount of the sorbent, usually 1–4 mg, is either inserted into the syringe barrel (BIN – barrel insert and needle) as a plug or between the needle and the barrel as a cartridge (Fig. 1). This format provides a selective medium suitable for sampling under a wide range of different conditions and target analytes.[2] Furthermore, it can be easily interchanged between the manual mode using a Hamilton syringe, the semi-automatic version driven by the eVol® electronic syringe, or fully automatic autosamplers (Fig. 1). In contrast, many reports involving in-house devices similar to original μSPE proposed by Abdel-Rehim (2004)[1] are essentially proof of concept devices designed to accommodate custom sorbents. Regardless of the presentation format, in technical terms, a fundamental difference between MEPS and commercial SPE, is that the packing is integrated directly into the syringe and not in a separate column. So, MEPS can handle small sample volumes (~10 μL) as well as large volumes (>1000 μL) without compromising the extraction efficiency. Beyond the obvious enrichment factor, this approach for sample preparation has several additional advantages, involving much lower solvent and sample requirements, easy and fast operation and a minimal cost of analysis, particularly when compared to conventional SPE.[3] Previously, different reviews introduced MEPS and spanned its potential in microextraction as a more efficient and greener alternative to SPE and other forms of microextraction.[1,2,4–8] Meanwhile, other studies focused on MEPS applications in particular topics, such as bioanalysis[3,4,7,9] and medical diagnosis,[10] and more recently, Vlckova *et al.* (2016) explored specifically the development of MEPS-UHPLC-MS/MS methods for the clinical analysis of statins.[11] In this review, we will critically assess the MEPS applications reported in the last five years in the context of the different MEPS architectures used. This will certainly contribute to unveil and broaden the range of applications for MEPS and particularly for its recent and innovative μSPEed configuration.

Technical considerations about the MEPS procedure

MEPS is a microextraction approach tailored for liquid samples and so additional sample pre-treatment can be

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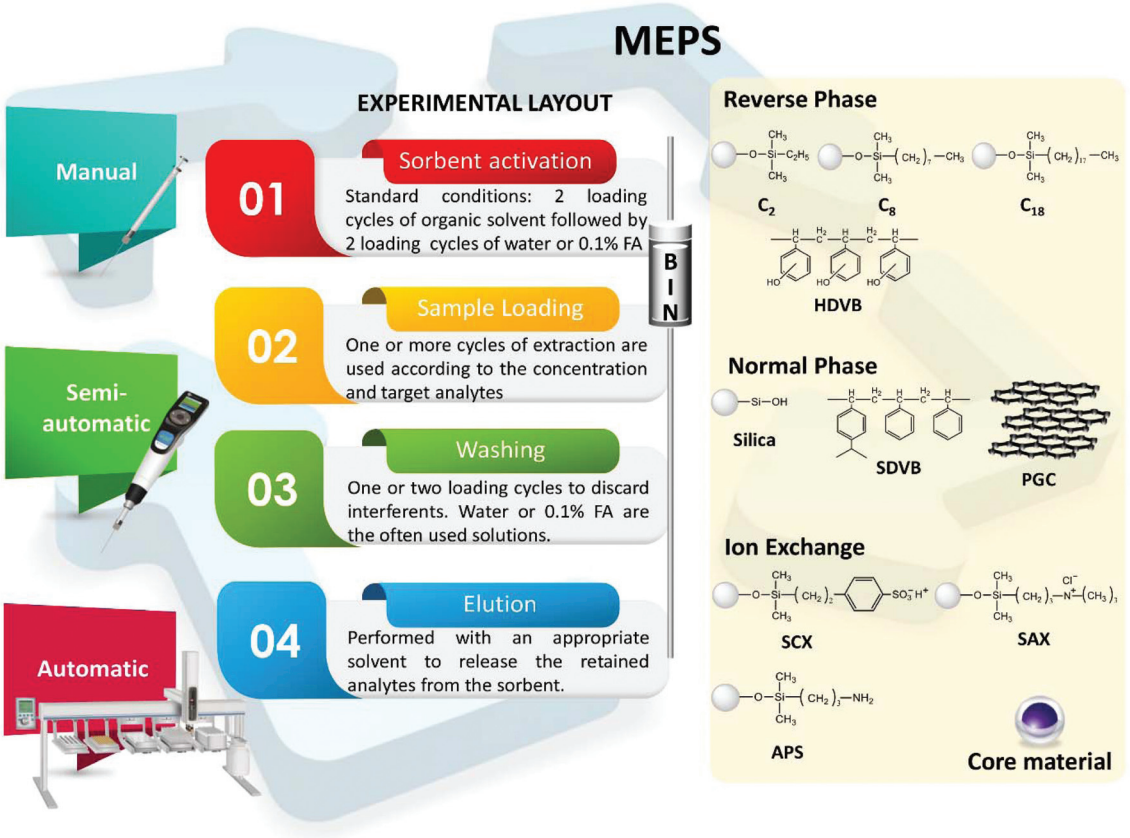

Fig. 1 Experimental layout of the MEPS procedures, highlighting the MEPS formats available (manual, semi-automatic and automatic), a short description of the different operation steps (activation, sample loading, washing and elution), and the main sorbents commercially available and chemistry involved in the interaction with target analytes (reverse and normal phase and ion exchange).

necessary under certain conditions. This is the case of solid samples, for which a dissolution or extraction with a broad solvent like MeOH can be particularly helpful to transfer the target analytes to the liquid phase before its processing with MEPS. But complex liquid matrices may also require pre-treatment procedures to avoid sorbent clogging and extend its reusability. Furthermore, this is also crucial to the extraction and concentration of low-abundance analytes, therefore ensuring high sensitivity and selectivity. Sample dilution to decrease the viscosity, precipitation and filtration with selective filters to remove matrix interferents are often reported for such cases. At a different level, pH adjustment may be required to modulate the interaction of the target analytes with the sorbent, particularly when using ionic exchange sorbents. Other generic sample pre-treatment procedures used previously to MEPS include sample homogenisation using vortex or ultrasound and centrifugation. In this context, the critical evaluation of sample pre-treatment techniques[12] or the review devoted to the extraction of veterinary antibiotics from environmental waters may be particularly relevant for some readers.[13] The MEPS procedure usually follows the conventional 4-step SPE: conditioning of the stationary phase, sample injection, washing and elution (Fig. 1). Despite this simplicity, MEPS involves a wide range of optimization steps that allow a fine tuning of the extraction efficiency.[5] The appropriate selection of the sorbent, for instance, is of utmost importance to achieve satisfactory clean-up and analyte recovery. Moreover, depending on the target analytes, some steps can be simplified or skipped. The number of extraction cycles, for instance, can be increased by drawing the sample through the needle into the syringe several times (draw-eject), leading to a higher recovery level that can be optimized for each application.[14] Upon the target analyte retention in the solid phase packed into the BIN, the washing step is usually considered to remove matrix interferents. This is an important part of the MEPS procedure since it is intended to discard unwanted and weakly retained interferents, eventually allowing a significant increase in the extraction efficiency.[14] In most applications reported, this step is performed with the same solvent used to equilibrate the sorbent in the first step.[5] However, this decision should be carefully considered and optimized. The increase of the organic solvent in the washing solution is required for an efficient removal of matrix interferents, but also favours the leakage of the target analytes from the sorbent (elution). The target analytes are eluted in the final step, which should also be critically optimized to allow the release of the analytes from the sorbent in a suitable solvent. Typically, this step is performed with an organic solvent, namely methanol (MeOH),

isopropanol (IPA) or acetonitrile (ACN), pure or mixed with acidic or basic solutions (0.1–3%), and the maximum amount of analyte should be eluted with the minimum volume of the solvent possible.[14] The small solvent volume used in this step allows a considerable enrichment factor and a direct injection into the chromatographic systems. Furthermore, it also facilitates the on-line integration of the extraction and a consequent gain in terms of high-throughput and cost per analysis.[3,4] Hence, MEPS can be used as a fully automated and miniaturized sample preparation procedure connected online with chromatographic devices (GC and LC) coupled to mass spectrometry without any or minimum modification of the existent hardware configurations.[10] These facts are particularly important for the clinical environment, given the limited sample volumes available and the fast and high-throughput requirements. Beyond significant advantages in terms of speed and simplicity, MEPS may also reduce the carry-over and matrix effects that often affect the analysis of complex matrices. Moreover, the sorbent can be used for up to 100 extractions or more, depending on the matrices and target analytes involved (for some watered samples, MEPS can be used more than 400 times), whereas a SPE column is designed to be used once.[3] Since its development, numerous sorbent materials were made commercially available for MEPS. These sorbents are essentially the traditional silica matrices (unmodified silica, C_2, C_8 and C_{18}), the functionalized strong and weak cation and anion exchange C_{18} versions (SCX, SAX) and mixed sorbents (C_8/SCX). More recently, the polymeric sorbent, polystyrene-divinylbenzene copolymer (PV-DVB), modified or functionalized to meet different retention abilities and target analytes, became available (Fig. 1). A detailed review about the properties of these sorbents has been provided by Pereira *et al.*[6] As MEPS has a simple design, there is a very significant number of custom sorbents reported for MEPS, including restricted access materials (RAM) and molecular imprinted polymers (MIPs). However, these sorbents are not commercially available and so their use is still limited to proof of concept applications. But MEPS, like every sample extraction approach, presents some drawbacks, the most relevant being those associated with sorbent clogging and the consequent cavitation process. This is often reported in complex matrices with high protein and lipidic contents, resulting in poor recoveries and repeatability.[15] Nevertheless, depending on the affinity of the selected sorbent to the target analytes, this problem can be greatly minimized by diluting the sample and performing several loading steps. This strategy has, however, an obvious cost of time.

The MEPS architectures

MEPS can be operated in different modes, the manual syringe being the format most often reported among the three types commercially available. Its simplicity, low-cost and easy design and operation are certain factors behind such popularity.[6] As already mentioned, the experimental layout involved in a MEPS procedure is very simple (Fig. 1), but can be highly repetitive. Often, different steps (sorbent conditioning, sample loading, washing, elution, sorbent reconditioning) are repeated to optimize the extraction. In these cases, the minimization of user intervention using the semiautomatic (e-Vol®) or automatic (autosamplers) MEPS architectures is critical to mitigate the experimental errors arising from the repetitive operation steps. As reviewed by Pereira *et al.*,[6,9] the semiautomatic and automatic versions of MEPS are very user-friendly, provide full customization of the extraction procedures and allow greater precision and higher automation, being more reliable than the manual versions. Overall, these features are particularly relevant to the pharmaceutical and clinical environments.[10] Despite the higher costs of the semiautomatic and fully automatic MEPS architectures in comparison with the manual MEPS, the easy interchange between the three formats will certainly favour the former ones, leaving the manual MEPS mainly for small scale and exploratory projects.

Application fields: from pharmaceutical and clinical analysis to food composition

MEPS has been widely employed in different fields of research, encompassing clinical, forensic toxicology, and environmental and food analysis applications. This approach has been successfully applied for the extraction of a very broad range of analytes from different matrices. Considering only the last five years, MEPS applications cover the most diverse matrices, such as biological samples (urine, saliva, plasma or blood), water and wastewaters and several foods and beverages. Regarding the target analytes, a broad range of examples has also been reported involving different drugs (pharmaceuticals, drugs of abuse, pesticides, environmental contaminants, *etc.*) and bioactive compounds. These and other MEPS applications reported in the last five years in different fields of research will be discussed in more detail in the following sections.

Pharmaceutical and clinical analysis

New drugs are continuously being developed to be used in different aspects of our lives, particularly during disease treatment, and also to prevent or mitigate its development. This certainly demands equivalent analytical requirements to verify the effects these drugs may have in our health and environment and understand their therapeutic and toxic effects.[16,17] In this context, analytical research plays a crucial role in assessing the quality of the pharmaceutical products, providing mandatory information about their purity, safety and metabolic fate in the biological samples in which they may be present.[18] Parameters such as peak plasma drug concentration, clearance and bioavailability, for instance, must be known before a new drug can be approved. To measure these parameters, it is essential to know the levels of drug metabolites in the body fluids. In turn, this will allow the optimization of pharmacotherapy and will provide the basis for wider studies on patient compliance, bioavailability, pharmacoki-

netics and genetics, organ function and influence of co-medication.[17] There are nevertheless, at least three points which are crucial in the selection of the most suitable extraction procedure. Firstly, the complexity of the biological samples and the eventual presence of interfering elements (*e.g.* salts, acids, bases, proteins, and many organic compounds), which can mask or interfere with the compounds of interest and limit the direct analysis of the target analytes.[17,19] Also, the concentrations in which the pharmaceuticals are generally found in our body and fluids justify an initial stage of preconcentration and purification of the target analytes prior to their analysis.[20,21] Finally, in the pharmaceutical industry, sample preparation is frequently performed off-line and in fact, this is often a limiting step to achieve fast bioanalysis. As the number of samples grows, high-throughput and fully automated analytical techniques become essential.[22] In this context, MEPS has gained popularity as an attractive and powerful sample-preparation approach suitable to fulfil these three challenges.[5] In fact, this technique has been successfully used in the extraction of a wide variety of drug analytes, such as antidepressants,[23] antibiotics,[24] anti-inflammatories,[25] antidiabetics,[26] antipsychotics,[27] and antiepileptics,[28] among others, from several biological matrices.[23] As can be observed in Table 1, the silica-modified materials (C_8 and C_{18}) are the MEPS sorbents most often reported in pharmaceutical and clinical applications. This is related to their ability to retain a wide range of compounds with different properties in a single sample extraction procedure.[6] For this reason, in most MEPS applications reported in the literature, the C_{18} sorbent was selected without a comprehensive comparison of the efficiency of the remaining MEPS sorbents available. This includes pharmaceutical and clinical analysis reports on the extraction of different antibiotics,[29] antifungics,[30] cardiac drugs[31] or the putative biomarker 4-hydroxynonenal.[32] There are some studies, however, which involved the appropriate comparison of several MEPS sorbents and experimental conditions to support the definition of the best extraction conditions. Szultka *et al.*,[24] for instance, showed that among five sorbents, C_2, C_8, C_{18}, M1 and pure silica (Sil), the C_8 sorbent presented better selectivity and higher recovery for linezolid, while C_{18} showed the best performance for amoxicillin extraction. Similarly, Ferrone *et al.*[29] assayed the polymerics polystyrene divinylbenzene (SDVB) and the highly crosslinked PSDVB (HDVB), as well as Sil, C_2 and C_{18}, in the extraction of the antibiotics meropenem, linezolid, and levofloxacin. They also found that C_{18} was the best sorbent for the simultaneous extraction of the target analytes. These two examples show that the physicochemical properties of the analytes must be carefully considered when selecting the MEPS sorbent.[7] Despite the wide application of C_{18}, there are certainly many reports involving MEPS extraction whose analytical performance could be even better if a more extensive sorbent assay has been performed. This is particularly relevant if we remember that the polymeric sorbents present a higher loading capacity and lower selectivity, which make them particularly suitable for multiple residue extraction (reviewed by Pereira *et al.*).[6] These sorbents became commercially available only in recent years and certainly this fact contributes to their less use than the silica counterparts. Following the MEPS extraction, most methods reported so far are coupled with a liquid chromatography analysis often complemented with an MS detection. This combination is an excellent analytical tool for the screening and determination of pharmaceutical drugs and their metabolites in biological samples. It is particularly suitable for drug metabolism studies, analysis and identification of impurities and degradation products, as well as the isolation and characterization of potential drug substances from natural synthetic sources.[33,34] Ultimately, the use of tandem MS/MS in the MEPS/LC configuration creates a new standard in analytical performance and opens an avenue for broader applications.[35,36] Meanwhile, the performance of MEPS has already been challenged with on-line LC-MS assays of drugs and metabolites in different biological samples.[34] These on-line sample pre-treatment processes greatly speed up the analyses and were described for the first time by Moein *et al.*[37] The authors reported the extraction and screening of sarcosine as a putative prostate-cancer marker in human plasma and urine samples, using DMIP-MEPS followed by LC-MS/MS. The results reported clearly showed that, despite the simplicity of the sample preparation procedure, the on-line MEPS approach enabled good selectivity and high sensitivity. Additionally, this work is also a good example of the development of promising sorbents, namely, molecularly-imprinted polymers (MIPs), exhibiting highly specific recognition abilities for target molecules.[5,37,38] These materials have proven to be useful in many fields of chemistry or biology, mainly as selective sorbents for SPE.[39–41] The LC-MS/MS configurations used are, nevertheless, very expensive and they are not available in many laboratories. For most routine analysis, cheaper configurations involving, for instance, UV detection, fit for the purpose, retrieving enough analytical performance, were used. The enrichment factor that MEPS allows, contributing to a very significant improvement of the detection and quantification limits of several compounds, is obviously determinant for such achievement.[6] This comparison involving the use of MS *versus* UV detection can be clearly observed in the reports of Szultka *et al.*[24] and Ferrone *et al.*[29] Both groups proposed MEPS approaches for the extraction and quantification of different antibiotics in human plasma, but Szultka *et al.*[24] used MS detection and reported ten times more sensitivity (Table 1). Nevertheless, the merit of the work reported by Ferrone *et al.*[29] is that the MEPS/UHPL-PDA methodology proposed was still useful for the therapeutic drug monitoring of the selected antibiotics and consequent critical evaluation of the dosage regimen given to the patients. This simplified configuration, MEPS/UHPLC-PDA, has also been reported by Alves *et al.*[23] and Gonçalves *et al.*[27] for the analysis of antidepressants and antipsychotics in urine, respectively.

The analysis of different aminated products in human samples, such as biogenic amines and several non-polar heterocyclic amines, constitutes a valuable source of metabolic information about several biological processes, including

Table 1 Recent applications of MEPS in pharmaceutical and clinical analyses

Drug class (analytes)[ref]	Matrix (sample volume, μl)	MEPS sorbent/type	Analytical performance					
			Methodology	Linear range (ng ml^{-1})	Elution solvent* (V, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Agonists								
BAM8-22, BAM22-8[44]	Plasma (50)	C_8/custom	LC-MS/MS	20–3045 (nmol l^{-1})	95% MeOH (0.25% NH_4OH)	—/20nM	3–14	85
Amines								
Biogenic amines (12 low molecular weight and hydrophilic molecules with a wide range of polarities)[43]	Plasma (100), urine (50)	APS/eVol®	HILIC-MS	10–2000	MeOH (0.1% FA) (3 × 50)	2–5/10–20	<3.6 <3.2	84–104
Biogenic amines (γ-amino butyric acid, cadaverine, ornithine, putrescine, spermidine)[42]	Urine (500)	C_{18}/online	PTV-GC-MS	0–40	EtOH (20)	0.18–2.70/0.17–9	<15	90–113
Analgesics and anti-inflammatories								
Dexamethasone, dexamethasone disodium phosphate[45]	Aqueous humor (50)	C_{18}/eVol®	LC-MS/MS	0.5–150	MeOH	—/0.5–0.7	4–16	91–119
NSAIDs (non-steroidal anti-inflammatory drugs)								
Acetylsalicylic acid, diclofenac, ibuprofen, ketoprofen, naproxen[46]	Urine (20)	C_{18}/eVol®	UHPLC-UV	5–20 000	ACN (pH 8.0) (20)	1.07–16.2/ 3.21–48.7	0.503–9.27	89–107
Fenbufen, flurbiprofen, furprofen, ibuprofen, indomethacin, indoprofen, ketoprofen[47]	Plasma, urine (85)	C_{18}/eVol®	HPLC-PDA	1–10 000	95% MeOH : (0.1% NaOH)	30/f100	0.07–11.1; 0.59–10.8	—
Carprofen, fenbufen, flurbiprofen, ibuprofen, indomethacin, indoprofen, ketoprofen[48]	Human dialysates	C_{18}/custom	UHPLC-DAD	25–15 000	MeOH : 1% NaOH (95 : 5)	8–10/25–33	0.10–7.69	94–100
Several NSAIDs (7) and FLQs (4)[25]	Urine (180)	C_{18}/manual	UHPLC-PDA	100–10 000	MeOH (8 × 25)	1.07–16.2/ 3.21–48.7	<20	89–107
Antibiotics								
Amoxicillin, linezolid[24]	Plasma (50)	Sil, C_2, **C_8**, **C_{18}**, M1/ manual	LC-MS/MS	1–50 000	MeOH	0.1341–0.1407/ 0.3814–0.4249	0.24–6.83	70
Levofloxacin, linezolid, meropenem[29]	Plasma	Sil, C_2, C_8, **C_{18}**, SDVB, HDVB/ manual	UHPLC-PDA	10–30 000	MeOH (150)	—/10–20	≤9.76	92–98
Ciprofloxacin, levofloxacin[49]	Sputum (cystic fibrosis patients)	C_{18}/eVol®	HPLC-PDA	50–2000	MeOH (20)	—/50	1.75–11.1	—
Ulifloxacin[50]	Plasma, urine (50)	C_{18}/eVol®	UHPLC-PDA	20–10 000	MeOH (150)	—/20	0.49–6.74	95
Antidepressants								
Agomelatine[51]	Plasma, saliva (50)	C_8/manual	HPLC-FLD	0.5–25	MeOH	0.15/—	3.40–4.53	90–99
Citalopram, clomipramine, fluoxetine, imipramine, mirtazapine, paroxetine, sertraline[52]	Plasma (200)	Monolithic/manual	LC-MS/MS	5–850	MeOH : ACN (100)	—/0.05–100	0.4–14.3	—
Clomipramine, desmethylclomipramine, fluoxetine, norfluoxetine[23]	Urine (500)	C_{18}/eVol®	UHPLC-PDA	100–5000	MeOH : ACN (80 : 20)	68–87/100	3.0–8.5	84–99
Citalopram, fluoxetine, paroxetine, sertraline[53]	Plasma (400)	M1 manual	CE-DAD	20–500	55% MeOH/P buffer (50 mmol l^{-1}, pH 4.5)	—/20–30	2.9–8.7	—

Table 1 *(Contd.)*

			Analytical performance				
Drug class (analytes)[ref]	Matrix (sample volume, μl)	MEPS sorbent/type	Methodology	Linear range (ng ml^{-1})	Elution solvent* (*V*, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Fluoxetine, norfluoxetine, paroxetine[54]	Plasma (500, patients with depression)	C_{18}/manual	LC-FLD	5–750	MeOH (1% FA) (5 × 200)	—/—	≤13.6	59–77
O-Desmethylvenlafaxine, venlafaxine[55]	Plasma (100)	C_{18}/manual	LC-FLD	10–1000	MeOH	—/10–20	1.3–5.1	72–83
Antidiabetics (chlorpropamide, glimepiride, gliclazide)[26]	Plasma (100)	C_{18}/manual	HPLC-DAD	100–50 000	70% ACN	—/100–1000	0.8–11.3	37–72
Antidyslipidemics								
Multistatin analysis (7 clinically relevant statins, their interconversion products and metabolites)[11]	Serum (50)	C_8/manual	UHPLC-MS	0.1–1000	ACN : $NH_4CH_3CO_2$ (0.01 M, pH 4.5) (5 : 95) (100)	—/10	0.3–19.2	79–119
Antiepileptics/anticonvulsants								
Carbamazepine; carbamazepine-10,11-epoxide; licarbazepine; lamotrigine; oxcarbazepine; phenytoin, phenobarbital[56]	Plasma (100)	C_{18}/manual	HPLC-DAD	100–40 000	MeOH (2 × 30)	10–90/100–400	0.6–17.7	57–98
Carbamazepine, dexamethasone, naproxen[57]	Urine (100)	Polymer network/ manual	HPLC-DAD	4.2–500	MeOH	1.3–1.5/4.2–5.0	1.3–7.4	—
Carbamazepine, lamotrigine[52]	Plasma (200)	Monolithic/manual	LC-MS/MS	0.5–10 500	MeOH : ACN (100)	—/0.05–100	0.2–14.4	—
Lamotrigine[58]	Rat plasma and brain (100)	C_{18}/eVol®	HPLC-DAD	0.100–20 000	MeOH (2 × 30)	—/10–500	1.0–8.6	68–87
Zonisamide[28]	Plasma (100)	C_{18}/manual	HPLC-DAD	200–80 000	ACN	—/200	1.5–13.3	63–65
Antifungics								
Imidazole and triazole drugs (12)[30]	Plasma (150), urine (200)	**C_{18}**/manual	HPLC-DAD	20–5000	MeOH (8 × 25)	7–70/20–200	1.47–13.4	—
Antihypertensives and antiarrhythmics								
Amiodarone, desethylamiodarone[59]	Plasma (100)	C_{18}/manual	HPLC-DAD	1–10 000	MeOH : FA (95 : 5) (100)	20/100	0.94–5.16	59–68
Metoprolol enantiomers[60]	Plasma, saliva (100)	C_4, C_8, C_{18}, polysorbate/manual	LC/MS	2.5–500	IPA (200)	0.5–1.5/—	2.25–4.56	93–97
Acebutolol, metoprolol[61]	Plasma	Carbon-XCOS/ online	LC-MS/MS	10–2000 (nM)	MeOH (0.1% FA)	10/— (nM)	4.4–14.4	80–90
Antipsychotics								
9-Hydroxyrispiridone, clozapine, norclozapine, rispiridone[27]	Urine (500)	C_{18}/eVol®	UHPLC-PDA	100–5000	MeOH : ACN : H_2O (2 × 500)	52–55/100	2.65–18	76–96
Clozapine, chlorpromazine, haloperidol, olanzapine, quetiapine[52]	Plasma (200)	Hybrid silica monoliths/manual	LC-MS/MS	0.5–1550	MeOH : ACN (100)	—/0.05–10	0.2–13.9	—
Chlorpromazine, clozapine, cyamemazine, haloperidol, levomepromazine, olanzapine, quetiapine[62]	Plasma (250)	M1/manual	GC-MS/MS	0.8–1000	MeOH : NH_3 (95 : 5) (200)	0.2–1.0/1000	0.24–10.67	62–92
Ziprazidone[63]	Plasma (100)	C_2/manual	HPLC-UV	1–500	MeOH	0.3/1.0	3.0–4.1	92–95
Antivirals (entecavir)[64]	Plasma (50)	PGC/eVol®	HILIC-UHPLC-MS/MS	0.1–100	75% ACN (100)	0.15–0.3/0.5–1.0	0.9–17.4	80–106
Anxiolytics (clonazepam, diazepam)[52]	Plasma (50)	PGC/eVol®	HILIC-UHPLC-MS/MS	5–850	MeOH : ACN (100)	—/0.05–0.10	1.5–13.5	—
Cardiacs								
Acylcarnitines, carnitine[31]	Urine (100)	C_2, C_8, C_{18}, M1, **C_2 + M1**/eVol®	HILIC-UHPLC-MS/MS	0.1–500	ACN (C2), 20 mM pyridine/ACN (M1)	0.1/—	0.8–9.4	—
Aliskiren, prasugrel, rivaroxaban[65]	Urine (200)	C_8/manual	UHPLC-MS/MS	0.0005–1000	MeOH (100)	—/0.005–0.0005	0.96–7.12	98–100

Table 1 *(Contd.)*

Drug class (analytes)[ref]	Matrix (sample volume, μl)	MEPS sorbent/type	Analytical performance: Methodology	Linear range (ng ml^{-1})	Elution solvent* (*V*, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Aliskiren, enalapril, enalaprilat[66]	Plasma and urine (50)	C_8/eVol®	UHPLC-MS/MS	0.01–500	MeOH (100)	—/0.01	0.3–9.6	75–93
Betaxolol[67]	Urine	C_{18}/online	SIC-FLD	5–400	ACN: 0.5% triethylamine (pH 4.5) (30 : 70)	1.5/5	1–4	100–108
Local anaesthetics								
Bupivacaine, lidocaine, mepivacaine, ropivacaine[68]	Plasma, urine (100)	MIPs/manual	LC-MS/MS	5.0–2000 (nM)	60% (MeOH/0.25% NH_4OH)	1.0/5.0 (nM)	0.7–14.0	60–80
Lidocaine, prilocaine, ropivacaine[69]	Plasma, saliva	Reduced graphene oxide/manual	LC-MS/MS	5–2000 (nM)	MeOH : FA (90 : 10) (2 × 100)	2.0–4.0/5.0 (nM)	2.39–19.14	95–106
Putative disease biomarkers								
5-Hydroxymethyluracil; 8-hydroxy-2′-deoxyguanosine; malondialdehyde, uric acid[70]	Urine (50)	C_8/eVol®	UHPLC-PDA	0.5–250 000	0.01% FA (5 × 50), 20% MeOH /0.01% FA (3 × 50)	0.05–720/ 0.23–2310	1.0–8.3	91–104
5-Hydroxymethyluracil; 8-oxo-7,8-dihydro-2′-deoxyguanosine[71]	Urine (250)	C_8/eVol®	UHPLC-PDA	0.5–5000	MeOH (0.01% FA) (90)	0.05–40/0.23–130	0.9–8.3	64–102
4-Hydroxynonenal[32]		C_2, C_8, **C_{18}**, M1 and SIL/manual	HPLC-UV	30–500 (nM)	ACN (100 150)	4.5/9.0 (μM)	1.30	47–89
Eicosanoids[72]	Urine (250)	C_2, C_8, C_{18}, Sil, M1, PEP, VAX, **RAX**, RCX, PGC, HLB-DVB/eVol®	UHPLC-PDA	0.1–300	MeOH (2 × 50)	0.04–1.12/ 0.10–2.11	1.29–10.43	>95
Sarcosine[37]	Plasma (100), urine (100)	DMIP/online	LC-MS/MS	3.0–10 000	80% ACN (100)	—/1.0–3.0	2.9–7.1	87–89
Preservatives (benzyl-, butyl-, ethyl-, methyl- and propyl-parabens)[73]	Urine (200)	C_{18} /manual	UHPLC-MS/MS	0.5–50	80% MeOH (50)	—/0.5	4.3–15	—
Others (AZD6118, candidate drugs against cognitive disorders)[74]	Dog plasma	M1/eVol®	UHPLC-MS/MS	20–25 000 (nM)	60% (MeOH/3% NH_4OH) (50)	—/—	1.9–3.2	—

Legend: * – elution solvent composition is indicated in v/v ratios and these are discriminated only when they are not equivalent among the components of the mixtures used; ACN – acetonitrile; APS – aminopropyl silane MEPS sorbent; CE – capillary electrophoresis; CLC – capillary liquid chromatography; DAD – diode array detector; DMIP – dummy molecularly imprinted polymer; EtOH – ethanol; FA – formic acid; FLD – fluorescence detection; GC – gas chromatography; HDVB – highly crosslinked polystyrene divinylbenzene; HILIC – hydrophilic interaction chromatography; HPLC – high performance liquid chromatography; LODs – limits of detection; LOQs – limits of quantification; M1 – mixed-mode C8/SCX MEPS sorbent; MeOH – methanol; MEPS – microextraction by packed sorbent; MIPs – molecularly imprinted polymers; MS – mass spectrometry; MS/MS – tandem MS; NSAIDs – non-steroidal anti-inflammatory drugs; PDA – photodiode array detector; PGC – porous graphitic carbon MEPS sorbent; PTV – programmable temperature vaporization; SCX – strong cation exchange MEPS sorbent; SIC – sequential injection chromatography; Sil – silica MEPS sorbent; SDVB – polystyrene divinylbenzene; Si-G – graphene supported on aminopropyl silica; UHPLC – ultra performance liquid chromatography; UV – ultraviolet detection; VAX – polymeric DVB partially functionalized with quaternary amine groups (Verify® AX); μPESI – micropillar array electrospray ionization chip.

pathological conditions. Regarding this, it is very interesting to verify that different biogenic amines extracted from plasma and urine using MEPS were analysed using distinct approaches such as HILIC-MS, PTV-GC-MS and CLC-MS.[42,43] This is also indirect evidence of the wide compatibility of MEPS with different analytical methodologies. These reports highlight the broad usage and potential of MEPS extraction in the analytical layout supporting pharmaceutical and clinical analysis. For an extended analysis, please follow Table 1.

Pesticides and environmental contaminants

The use of pesticides in modern agriculture is an indispensable measure to protect crops from diseases and pests, therefore ensuring their economic viability.[75,76] Pesticide usage, however, is not limited to industrial applications, being nowadays also widespread in homegrown applications. For this reason, there are more than 1100 active compounds registered and available in the European Union (EU) markets![77] However, pesticides are simultaneously harmful to the environment (*e.g.* soils, surface and ground waters) and potentially dangerous to human health.[76,78] Compounds such as atrazine, metribuzin and bifenthrin can cause endocrine disruption,[78] and chronic exposure to different pesticides may result in genotoxic, mutagenic and carcinogenic events,[79,80] as well as congenital malformations and degenerative diseases at the beginning of embryonic development.[81–83] Organochlorines (OCPs) and organophosphorus (OPPs), for instance, are widely known as environmental contaminants.[77,84] In fact, OCPs are one of the most persistent organic pollutants (POPs) present in the environment, and their monitorization and control is important not only for the protection of the environment, but also for human health.[77] In this context, different methods using MEPS coupled to GC-MS have been reported to analyse several OCPs (Table 2). Taghani *et al.*, for instance, proposed nanodiatomite[77] and carboxyl-purified multiwalled carbon nanotubes (CNTs)[84] as sorbents for the preconcentration of several OCPs (Table 2). In turn, Kaur *et al.*[75] used the C_{18} MEPS sorbent to extract endosulfan and its metabolites in tap water. Endosulfan is a broad-spectrum chlorinated cyclodiene insecticide widely applied to cereals, fruits and vegetables and its quantification was achieved with good analytical performance (good linearity, lower limits of detection (LODs) and quantification (LOQs) and high recoveries).[75] OPPs appeared as substitutes to other pesticides, mainly OCPs. Their application increased in agriculture to control insects and pests due to their lack of bioaccumulation in ecosystems. Nevertheless, OPPs are still toxic to humans and potentially mutagenic and carcinogenic.[80,85] Diazinon, for instance, due to its wide use in agriculture, became a major environmental contaminant, namely aqueous matrices, and its monitorization is therefore very important. Accordingly, several authors customized different MEPS sorbents to achieve suitable methods to extract this and other OPPs. Taghani *et al.*,[86] for instance, used nanoperlite, while Saraji *et al.*[80] used a new porous composite of nanoclay and polysiloxane. These reports attained an excellent analytical performance in water sample analysis, but Santos *et al.*[85] raised the challenge by reporting a MEPS/GC-MS/MS approach to determine OPPs in whole blood. Synthetic pyrethroids are being adopted to replace toxic OPP insecticides and persistent OCPs. Once again, their impact on human health and the definition of safety limits is still a matter of debate. In this context, Klimowska and Wielgomas[87] proposed a fast MEPS followed by large volume injection-gas chromatography-mass spectrometry (MEPS-LVI-GC-MS) for the determination of pyrethroid metabolites in human urine. At another level, the prevalence of several environmental contaminants in air, soil, sediments and water, such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyl (PCBs), brominated diphenyl ethers (BDEs), phthalate esters (PEs), nonylphenols, bisphenols, steroid hormones, and nitro and musk compounds, among others, has generated increasing public concerns, since most of these compounds promote mutagenic and carcinogenic events, even when present at trace levels. For this reason, the release of such contaminants to the environment should be closely monitored. Certainly with this goal in mind, Quinto *et al.*[88] reported an optimized MEPS/GC-MS procedure to accurately quantify PAHs in aqueous samples. BDEs are flame retardants that have been classified as POPs by the Stockholm Convention (http://chm.pops.int/TheConvention/ThePOPs/TheNewPOPs/tabid/2511/Default.aspx). To assay the presence of such compounds in sewage sludge, Martínez-Moral *et al.*[89] reported a method based on selective pressurized liquid extraction followed by MEPS/GC-MS/MS. A similar application was developed by Naccarato *et al.*[90] to extract a specific class of BDEs, the organophosphate ester flame retardants (OPFRs), from environmental waters. The authors assayed several MEPS cartridges and solvents and reported divinylbenzene (DVB) and acetonitrile as the best sorbent material and elution solvent, respectively. Phthalate acid esters (PAE) are extensively used in consumables, household and personal care products (PCP), generating a 6.0 million tons annual production worldwide.[91] Due to their potential risks to the environment and human health, PAEs have been placed in the priority pollutant list issued by the EU and the United States Environmental Protection Agency (USEPA).[92] To target these compounds, Amiri *et al.*[92] synthesized nanohydroxyapatite (HAP) and used it as an efficient MEPS sorbent for the PAE extraction from water samples. Currently, increasing attention is also being paid to the monitorization and control of musk compounds commonly used as additives in many products, as PCPs and detergents. Due to their extensive use, musk products have become emerging organic contaminants (EOCs) and have already been detected in diverse environmental matrices. Caballero-Díaz *et al.*,[93] for instance, combined MEPS with surface-enhanced Raman spectroscopy (SERS) for the determination of musk ketone (MK) in river water samples. The MEPS/LVI-GC-MS is, nevertheless, the most popular approach for this application. Cavalheiro *et al.*,[94] for instance, proposed it for the simultaneous determination of nitro and polycyclic musk compounds in estuarine and wastewater samples. Aromatic amines are another chemical group classified as environmental water pollutants due to their toxicity,

Table 2 Recent applications of MEPS in environmental analysis

Environmental contaminant classes (analytes)[Ref]	Matrix[Ref] (sample volume, μl)	MEPS sorbent/type	Analytical performance					
			Methodology	Linear range (ng ml^{-1})	Elution solvent* (*V*, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Aromatic amines (Azo dye derivatives)[95]	Textiles (200 mg)	PEP/eVol®	GC-MS	0.040–989	1-Propanol (60)	0.040–42/0.13–139	<15	1–96
BDEs (BDE-3, -10, -28, -47, -99, -100, -154)[89]	Water (100)	C_{18}/autosampler	GC-MS/MS	0.06–1.2 (ng g^{-1})	*n*-Hex (100)	0.0004–0.003/0.0007–0.006	<7	92–102
Chlorophenols (2-chlorophenol; 2,4-dichlorophenol; 2,4,6-trichlorophenol and 4-chloro-3-methylphenol)[101]	Soil (20 g)	C_{18}/autosampler	GC-MS	1–12 (μg kg^{-1})	EtAc (10)	0.118–0.894/0.353–2.683 (μg kg^{-1})	<10	13–23
Chlorobenzenes (12 derivatives)[96]	Water (1.75 ml)	C_{18}/autosampler	PTV-GC-MS	0.0003–500	Hex : acetone (25)	0.0003–0.07/0.001–0.2	<12	26–81
Dinotefuran[106]	Water, artificial saliva (200)	MIPs/—	HPLC-DAD	—	IPA (200)	—/—	<8.70	89–92
Endocrine disrupting chemicals (EDCs)								
Aldicarb, dimethoate, propazine, terbutryn[97]	Urine (1), tap water (1), soil (2 g)	C_{18}/manual	HPLC-UV	1–500	MeOH (30)	0.05–0.58/0.175–1.98	<6.3	81–98
Benzyl, butyl, ethyl, methyl and propyl parabens	Water[99] (3.6)	Si-G/manual	HPLC – UV	0.2–20	ACN : MeOH	0.06–0.09/0.2–0.3	1.5 to 19.2	82–119
	Urine[73] (0.4)	C_{18}/manual	UHPLC-MS/MS	0.5–50	80% MeOH	—/0.5–50	<15	—
Mandelic acid[107,108]	Urine (800)	MIPs/manual	HPLC-UV	15–2000	EtOH-acetic acid (80 : 20) (2 × 100)	60/200	3.4–6.6	88
HAAs (dibromo-, dichloro-, monobromo-, monochloro-, trichloroacetic acid)[100]	Water (2.5)	C_{18}/autosampler	PTV-GC-MS	0.36–300	MTBE (20)	0.36–1.2/1.2–3.6	4.2–14	83–117
Musk compounds								
Cashmeran, celestolide, galaxolide, musk ambrette, musk ketone, musk mosken, phantolide, tonalide, traseolide[94]	Water (5.5 ml)	C_{18}/autosampler	LVI-GC-MS	0.005–2.5	Acetate : *n*-hex (25)	0.005–0.084/—	<13.2	75–135
Musk ketone[93]	River water (500)	C_{18}/manual	SERS	50–1000	MeOH (10)	20/50	15.2	47–63
Nitroexplosives[109]	Plasma and urine (0.05), water (0.1)	C_{18}/manual	GC-MS	—	MeOH (30)	0.014–0.828/0.046–2.732	2.3–4.9	78–99
OCPs (organochlorines)								
Aldrine, heptachlor, hexachlorobenzene[77]	Water (10 ml)	Nano-diatomite/custom	GC-MS	0.1–40	DCM (100)	0.02–0.13/—	3.5–11.1	78–108
Alachlor, aldrine, heptachlor, hexachlorobenzene, metolachlor[84]	River water (10 ml)	CNTs/custom	GC-MS	0.1–25	MIBK (100)	0.02–0.16/—	3.3–8.5	81–118
Endosulfan isomers and derivatives (α-endosulfan, β-endosulfan, endosulfan ether, endosulfan lactone, endosulfan sulfate)[75]	Water (750)	C_{18}/manual	GC-MS	1–500	MeOH (30)	0.0038–0.0045/0.0125–0.035	<4.4	88–98
OPFRs (organophosphate flame retardants)[90]	Water (2 ml)	SDVB/eVol®	GC-MS/MS	0.0027–10	ACN (3 × 20)	0.0027–0.107/0.01–0.2	<20	69–120
OPPs (organophosphorus)								
Azynphos-ethyl, chlorfenvinfos, chlorpyrifos, diazinon, parathionethyl, quinalphos[85]	Whole blood (100)	C_{18}/manual	GC-MS/MS	500–50 000	MeOH (4 × 110)	—/500–2500	<15	61–77
Diazinon[80]	Water (2 ml)	Nanoclay/custom	CD-IMS	0.2–20.0	MeOH (25)	0.07/0.20	5–12.3	95–106

Table 2 *(Contd.)*

Environmental contaminant classes (analytes)[Ref]	Matrix[Ref] (sample volume, μl)	MEPS sorbent/type	Analytical performance					
			Methodology	Linear range (ng ml^{-1})	Elution solvent* (*V*, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Diazinon, ethion, malathion[86]	Water (10 000)	Nano-perlite/ custom	GC-MS	0.4–35.0	DCM (100)	0.07–0.38/—	2.8–8.9	81–103
PAHs (polycyclic aromatic hydrocarbons)[88]	Water (4.5 ml)	C_8/autosampler	GC-MS	0.001–1	MeOH (25 × 50)	Draw-eject: 0.0005–0.002/ 0.0016–0.0062 Extract-discard: 0.0002–0.0008/ 0.0008–0.002	0.5–14.2	98–122
PCBs (28, 52, 101, 118, 138, 153, 181)[102]	Bovine serum (100)	C_8/manual	GC-MS	2–200	EtAc (50)	0.06–0.53/0.20–1.77	<5.72	60–91
Pyrethroids[87]	Urine (500)	C_{18}/eVol®	LVI-GC-MS	0.05–25	HFIP/DIC/hex (1 : 2 : 97) (2 × 40)	0.06–0.08/—	<14	92–124
VOCs[99]	Water (0.5)	C_{18}/ autosampler	PTV-GC-MS	0.2–20	ACN : MeOH	0.02–1.72/—	1.5–19.2	—
***trans*, *trans*-Muconic acid** (index for benzene exposure)[110]	Urine	MIPs/custom	HPLC-UV	15–2000	EtOH/acetic acid (80 : 20)	15/50	3.4–6.6	90

Legend: * – elution solvent composition is indicated in v/v ratios and these are discriminated only when they are not equivalent among the components of the mixtures used; BDEs – brominated diphenyl ethers; CD-IMS – corona discharge ion mobility spectrometry; CE – capillary electrophoresis; CLC – capillary liquid chromatography; CNT/PDPA – carbon nanotubes/ polydiphenylamine; CNTs – carbon nanotubes; DAD – diode array detector; DIC – diisopropylcarbodiimide; EDCs – endocrine disrupting chemicals; EtAc – ethyl acetate; FID – flame ionization detector; FLD – fluorescence detection; GC – gas chromatography; HAAs – haloacetic acids; hex – hexane; HDVB – highly crosslinked polystyrene divinylbenzene; HFIP – 1,1,1,3,3,3-hexafluoroisopropanol; HPLC – high performance liquid chromatography; LODs – limits of detection; LOQs – limits of quantification; LVI – large volume injection; MeOH – methanol; M1 – mixed-mode C8/SCX MEPS sorbent; MEPS – microextraction by packed sorbent; MIPs – molecularly imprinted polymers; MS – mass spectrometry; MS/MS – tandem MS; MTBE – methyl *tert*-butyl ether; OCPs – organochlorines; OPFRs – organophosphate ester flame retardants; OPPs – organophosphorus; PANI – polyaniline; PAEs – phthalate esters; PAHs – polycyclic aromatic hydrocarbons; PANI – polyaniline; PCBs – polychlorinated biphenyls; P buffer – phosphate buffer; PDA – photodiode array detector; PEP – polar enhanced polymer MEPS sorbent; PTV – programmable temperature vaporization; SCX – strong cation exchange MEPS sorbent; Sil – silica MEPS sorbent; SDVB – polystyrene divinylbenzene; Si-G – graphene supported on aminopropyl silica; UHPLC – ultra performance liquid chromatography; VOCs – volatile organic compounds; UV – ultraviolet detection.

carcinogenicity and persistence (highly soluble in water). Dyes, pesticides and pharmaceuticals are obtained using aromatic amines and so these compounds may be released into the environment directly through industrial discharges, or indirectly through the degradation of, for instance, azo dyes and pesticides.[95] This fact led the EU to classify aromatic amines as priority pollutants that should be monitored regularly in surface waters.[95] In this context, Sánchez *et al.*[95] proposed a MEPS/GC-MS method to assay the water contamination with aromatic amines from azo dyes used in the textile industry. Related with this, Noche *et al.*[96] developed a fully automated method based on MEPS-PTV/GC-MS for the determination of chlorobenzene congeners[96] in water samples. These compounds have been widely used for many decades for industrial and domestic applications (as solvents, degreasing agents and pesticides), but unfortunately they also constitute an important source of environmental contamination. Endocrine Disrupting Chemicals (EDCs) are compounds that mimic human hormones and can block their receptors in our bodies. Depending on the exposition levels, this interference can disrupt the normal activity of the endocrine system leading to its malfunctioning.[97] Although EDCs are usually found at low concentrations in the aquatic environment, their ability to initiate estrogenic activity even at trace levels led the EU to classify these hormone-like chemicals as hazardous. Thus, their monitorization and control in environmental samples is crucial and for this purpose several analytical methods have been purposed. Among these, Kaur *et al.*[97] coupled MEPS with HPLC-UV to detect EDCs (pesticides) in biological and environmental samples. Parabens are esters of *p*-hydroxybenzoic acid widely used as preservatives in foodstuffs, cosmetics and pharmaceutical drugs. Recently, they were proposed as emerging contaminants due to their weak endocrine disrupter potential.[98] In this context, several MEPS approaches have already been described to extract parabens from environmental waste waters. With this aim, Fumes *et al.*[99] proposed a MEPS/HPLC-UV approach using graphene supported on aminopropyl silica through covalent bonds (Si-G) as a MEPS sorbent. In turn, Jardim *et al.*[73] used the C_{18} MEPS sorbent combined with UHPLC-MS/MS for the simultaneous determination of five parabens in human urine samples. As by-products of drinking water disinfection, the accumulation of haloacetic acids (HAAs) in the human body is potentially carcinogenic. This has led the USEPA to establish a maximum contamination level (MCL) of 60 μg l^{-1} for the sum of HAA concentrations in drinking water.[100] In this context, Ferreira *et al.*[100] proposed a novel analytical method based on *in situ* aqueous derivatization followed by MEPS/GC-MS for the determination of five HAAs in drinking and swimming pool water. As shown in Table 2, the use of MEPS in environmental analysis is very popular for water matrices, a fact that is certainly related with the low complexity and viscosity of the samples, therefore requiring less processing steps. Nevertheless, there are some interesting applications involving the extraction of different environmental contaminants in more complex samples, as textiles,[95] soils,[101] blood,[85,97] or serum.[102] There are also several examples reporting MEPS approaches to detect pesticides and other environmental contaminants in food matrices, such as wheat flour,[103] honey[104] or corn.[105] These and other examples will be considered in more detail in the section specifically dedicated to food composition and quality (Table 4).

Forensic analysis and drugs of abuse

Detection of drugs and related substances may be a very challenging task, requiring highly sensitive and selective analytical techniques. In a forensic context, this is extremely important, since a positive result for the presence of a drug may have legal implications for the examinee's life or freedom.[111] In this sense, forensic drug chemistry and toxicology have a fundamental role during a criminal investigation. In this context, forensic chemists analyse samples of unknown materials, including powders, liquids and stains, to determine the chemical identity or characteristics of the compounds in the sample. In turn, forensic toxicologists are concerned with the detection and quantification of drugs and other toxic substances in biological specimens to aid medical or legal investigation of death, poisoning and drug use.[112,113] In both cases, forensic scientists employ a wide variety of analytical tools, ranging from commercial kit-based immunoassays to sophisticated instrumental techniques (*e.g.* GC-MS, LC-MS/MS, and MALDI-TOF/MS) to detect, identify and quantify the presence of drugs in several types of matrices.[114–116] MEPS, due to its ability to combine sample extraction, concentration and clean-up in a single device,[6] reducing the sample volume to the microliter level, gains particular relevance in forensic toxicology. A key reason for this fact is that very often several exams need to be performed on a very limited sample amount and MEPS is particularly tailored to cope with this limitation.[117] Furthermore, MEPS can be easily combined with chromatographic techniques, such as GC-MS and LC-MS/MS, constituting therefore an excellent tool for the screening and determination of drugs and their metabolites in biological and other complex samples.[112] A brief literature review on the last five years shows that MEPS has been successfully applied to the extraction of drugs of abuse, such as amphetamines,[118] cocaine and its metabolites,[119] opioids,[120,121] and cannabinoids,[120,122] as well as several classes of new psychoactive substances,[123,124] from biological samples. Interestingly, MEPS has also been used to extract benzodiazepines, a class of drugs commonly used in drug-facilitated crimes, from several types of beverages.[125,126] Table 3 summarizes the most recent applications of MEPS for the determination of drugs and their metabolites in a forensic context. The broad range of applications included in that table clearly reflect the advantages of MEPS and its suitability for toxicology assays. In the analysis of drugs of abuse, silica-based sorbents containing C_{18} or C_8 groups and mixed-mode C_8/SCX (M1) are the most commonly used sorbents. In general, the versatility of C_8 and C_{18} bonded silica sorbents combines good retention capacity with high recoveries, making these sorbents very attractive for drug analysis. On the other hand, M1 selectivity is more suitable to

Table 3 Application of MEPS for forensic drug analysis

Drug class (analytes)[Ref]	Matrix (sample volume, μl)	MEPS sorbent/ type	Analytical performance					
			Methodology	Linear range (ng ml^{-1})	Elution solvent* (V, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Anaesthetics (ANAEs)								
Ketamine[129]	Fruit juices (400)	M1/ manual	Q-TOF	—	—	—/—	—	—
Ketamine, norketamine[127]	Plasma, urine (250)	M1/ manual	GC-MS/MS	10–250/ 10–500	MeOH (50)	5/10	<15	63–101
Benzodiazepines								
Bromazepam, chlordiazepoxide, clobazam, clonazepam, flunitrazepam, flurazepam, lorazepam, oxazepam[126]	Beverages (300)	C_{18}/eVol®	UHPLC-UV	2.5–125	ACN (3 × 100)	860–1750/ 2070–5830	<2.78	21–102
Chlordiazepoxide, diazepam, lorazepam, medazepam, oxazepam[125]	Grappa drink (300)	C_{18}/eVol®	UHPLC-UV	1–100	ACN (3 × 100)	500/2000	<12	61–92
Cannabinoids								
11-Hydroxy-THC, 11-nor-9-carboxy-THC, cannabidiol, cannabinol, THC[130]	Oral fluid (125)	C_{18}/ manual	LC-MS/MS	0.02–1.0	MEOH (2 × 25)	0.008–0.12/ 0.020–0.40	<1.16	50–105
11-Hydroxy-THC, 11-nor-9-carboxy-THC, THC[122]	Plasma (250)	M1/ manual	GC-MS/MS	0.1–30	10% NH_4OH/MeOH (6 × 100)	1/1	<14.25	53–78
Cocaine and metabolites (COC)								
Benzoylecgonine, cocaine, ecgonine methyl ester[119]	Urine (200)	M1/ manual	GC-MS	25–1000	MeOH (1% NH_4OH) (4 × 100)	—/25	<11.4	15–83
Miscellaneous								
New psychoactive substances (PHEs, PIPs, SCANs, SCATs)[123]	Oral fluid (90)	C_{18}/ manual	UHPLC-MS/ MS	0.015–200	MeOH	0.005–0.850/ 0.015–2.600	<25	31–96
Amphetamine (AMPH), methadone (OPI)[131]	Urine (100)	C_8/ manual	MS/MS	20–5000; 5–5000	MeOH (0.1% FA) (50)	1.5–6.0/5.0–20.0	<17.1	92–107
Illicit drugs and metabolites (AMPHs, ANAEs, COCs, OPIs)[121]	Oral fluid (120)	C_{18}/ manual	LC-MS/MS	0.5–200	MeOH (5 mM FA) (5 × 20)	0.2–10/0.5–30	<15	18–102
Several drugs of abuse (COCs, OPIs, SCATs)[120]	Plasma (300)	M1/eVol®	UHPLC-PDA	50–10 000	DCM : IPA : NH_4OH (78 : 20 : 2) (200)	5–25/10–50	<11	80–105
New psychoactive substances (alkaloids, COCs, OPIs, SCATs)[128]	Oral fluid (300)	M1/eVol®	UHPLC-MS/ MS	0.5–500	DCM/IPA/NH_4OH	—/0.5–1.0	<13.7	75–125
Salvinorin A (*Salvia divinorum*)[132]	Urine (200)	C_{18} /manual	GC-MS/MS	20–1000	MeOH : ACN (7 : 3) (50)	5/20	<15	71–80

Legend: * – elution solvent composition is indicated in v/v ratios and these are discriminated only when they are not equivalent among the components of the mixtures used, ACN – acetonitrile, AMPHs – amphetamines, ANAEs – anaesthetics, COC – cocaine; DART – direct analysis in real time; EtAc – ethyl acetate; FA – formic acid; GC – gas chromatography; hex – hexane; IPA – isopropanol; LODs – limits of detection; LOQs – limits of quantification; MS – mass spectrometry; MS/MS – tandem MS; MeOH – methanol; MEPS – microextraction by packed sorbent; MIBK – methyl isobutyl ketone; M1 – mixed-mode C8/SCX MEPS sorbent; OPIs – opioids; PDA – photodiode array detector; PIP – piperazine; PHEs – phenethylamines; THC – tetrahydrocannabinol; Sil – silica MEPS sorbent; SCANs – synthetic cannabinoids; SCATs – synthetic cathinones; UHPLC – ultra performance liquid chromatography; UV – ultraviolet detection.

extract basic compounds from aqueous solutions, such as drugs and their metabolites from physiological fluids, and for this reason, mixed-mode sorbents have been gaining popularity over the reversed phase sorbents.[6] Apart from the nature of the sorbent, the nature of the sample matrix has an important influence on MEPS performance.[5] Generally, biological samples like blood, urine, oral fluid and other complex samples should be processed before being loaded into the MEPS device.[5] Urine, the most commonly used matrix to assay the presence of drugs of abuse, is typically diluted with deionized water[124,127] or buffer solutions[119] prior to the microextraction. Blood and plasma samples are preferential samples to assess the short-term use of drugs of abuse, and the analysis of these specimens by MEPS involves deproteination and dilution of the sample (to reduce the viscosity) before microextraction. Because proteins may cause significant interference, ACN and MeOH are commonly used to precipitate proteins.[120,122] Oral fluid has also become a valuable biological specimen for toxicological analysis, particularly in the cases where driving under the influence of drugs is investigated.[121] Oral fluid provides information on the recent drug use and sample collection is relatively easy and non-invasive, and can be performed under supervision. Nevertheless, some issues, such as varying viscosity, pH, sample availability, and potential external contamination, should be considered.[121] Often the oral fluid sample is diluted or pre-treated before microextraction to discard potential interferents, such as proteins, food debris and air bubbles.[128] Eventually, this procedure can affect the analytical performance of the methodology and so, in such cases, the number of extraction cycles can be increased to favour the enrichment of the target analytes. The same strategy is usually applied for plasma or urine samples. Taking into consideration the reports using MEPS for drugs of abuse analysis (Table 3), the number of extraction cycles for plasma samples can vary from 10 up to 26 cycles with sample volumes ranging from 250 to 300 μl. This high number of aspirations is justified because plasma samples are typically diluted at least 20 times to prevent the obstruction of MEPS cartridges.[127] For urine samples, the number of extraction cycles is lower, varying from 5 to 8 cycles, with sample volumes ranging from 100 to 200 μL, while for oral fluid 5 to 6 cycles with a sample volume from 90 to 300 μL are enough to achieve the best extraction efficiency. It should be noted that a controlled sample flow, generally between 10 and 20 μL s^{-1}, allows a better interaction between the analyte and the sorbent. This feature is obviously more accurate when MEPS is performed using the semiautomatic eVol® syringe, autosamplers or online systems. Finally, it is worthwhile to refer to the applications in which MEPS was directly coupled to the mass detector, therefore greatly simplifying the analytical layout by skipping the chromatographic separation. This approach was applied with success to the detection of the rave drug ketamine in fruit juices.[129]

Food composition

Over the years, MEPS has been successfully used to extract a wide range of analytes in different biological matrices (such as blood, plasma, urine) and in water (reviewed elsewhere).[3,5,9] Many of these analytes are the same or very similar to the ones found in foodstuffs and so MEPS was started to be used in food-related applications. Since Anizan (2010)[133] reported MEPS extraction followed by GC-MS for steroid profiling in cattle (using urine samples), more than 30 studies had been published on the application of MEPS to food matrices. These reports are essentially related with the assessment of food quality under different conditions. The characterization of food composition in bioactive molecules, such as phenolics,[134–136] is often reported. A second application refers to the evaluation of food integrity by assessing the presence of molecules that result from food contamination, such as pesticides, or degradation, such as compounds resulting from bacterial or fungal spoilage.[137–139] The excessive usage of veterinary drugs to increase productivity is also studied.[102,133,140–143] Finally, the presence of contaminants and pesticides in food composition is another very relevant MEPS application (Table 4).[78,91,103,105,144,145] Regarding this, Capoferri *et al.*[103] obtained custom MIPs to use as MEPS sorbents for the extraction of the OPP dimethoate in wheat flour, while Andrade *et al.*[105] used the same strategy to extract the herbicides atrazine, simazine, simetryn, ametryn, and terbutryn in corn samples. More recently, another two custom MEPS sorbents, one obtained with packed hybrids of gold nanoparticles and layered double hydroxide nanosheets (Au/LDH),[146] and the other a metal–organic framework MIL-101(Cr),[147] were reported to allow even better analytical performance for triazine extraction from maze and corn, respectively. MEPS is often used in the targeted analysis of a limited number of analytes. However, several examples show that this extraction approach is robust enough for multiresidue analysis, as reported by Salami and Queiroz[104] and Di Ottavio *et al.*[144] In these studies, MEPS was used to verify the presence of 22 pesticides in honey[104] and 25 pesticides and fungicides in wheat flour.[144] More recently, MEPS is also being used to define signatures to certify the authenticity of certain food products, notably beverages. This is achieved through the comprehensive analysis of their volatile and semi-volatile profiles.[148] In fact, as shown in Table 4, beverage composition, particularly wine, is a popular MEPS application. As already mentioned, this trend is easily understood, as the matrix is already in the liquid form, therefore facilitating the extraction of the target analytes with minimum sample pre-treatment. Another interesting MEPS application in food research relates with the assessment of food intake through the analysis of the presence of different dietary metabolites in plasma and urine. This is particularly relevant to show the internalization of certain antioxidants to plasma, namely phenolic compounds, following the ingestion of different foodstuffs rich in these compounds, often known as functional foods. This has been elegantly used to find the presence of olive biophenols, caffeic acid, oleuropein and tyrsol, in rat plasma following the ingestion of olive oil.[149] To perform this assay the authors developed a new MEPS sorbent, a carbon nanoporous adsorbent (CMK-3), and the extraction was followed by a LC-UV analysis. A similar assay was performed

Table 4 Application of MEPS related with foodstuff analysis

Target analytes (foodstuff)[Ref]	Matrix (sample volume, μl)	MEPS sorbent/type	Analytical performance					
			Methodology	Linear range (ng ml^{-1})	Elution solvent* (V, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Food composition								
5-Hydroxymethyl-2-furaldehyde, 2-furaldehyde, 2-furylmethanol, 2-furyl methyl ketone and 5-methyl-2-furaldehyde[151]	Sugarcane honey (1.5 ml)	C_2, C_8, C_{18}, M1, PEP, PGC, RAX, **RCX**, Sil/eVol®	UHPLC-PDA	100–17 800	ACN (3 × 500)	10.1–234.4/30.6–737.7	2.1–5.6	92
5-Hydroxymethyl-2-furaldehyde, 5-methyl-2-furaldehyde, 2-furaldehyde and 2-furylmethyl ketone[152]	Madeira wine (600)	C_2, **C_8**, C_{18}, M1, PGC, RAX, RCX, Sil/eVol®	UHPLC-PDA	40–700 000	95% MeOH (200)	0.0045–0.1293/0.0149–0.9505	—	74
5-Hydroxymethyl-2-furfural, 2-furfural, furyl methyl ketone and 5-methyl-2-furfural[153]	Madeira wine (600)	**C_8**/eVol®	UHPLC-PDA	—	MeOH (200)	—/—	—	—
Bioactive phenolic compounds[134]	Methanolic extract of argan leaves (100)	C_2, C_8, C_{18}, **M1**/eVol®	LC-DAD-MS/MS	0.3–100	MeOH (500)	0.3/0.1	<3.7	87
Isoanthohumol and xanthohumol[135]	Beers (500)	C_2, C_8, **C_{18}**, M1, Sil/eVol®	UHPLC-PDA	1–5000	ACN (250)	0.4–1.0/0.9–3.0	0.4–1.6	67
Ellagic acid[136]	Pomegranate and grape juice (2.5 ml)	Functionalized SB_A-15/custom	HPLC-UV	500–100 000	ACN (6 × 80)	0.8/—	—	97
Hydrocarbon, ester, alcohol and fatty acid (*Solanaceous* plant species)[154]	*Solanaceous* plant cuticular waxes (50)	Sil/eVol®	GC-FID GC-MS	—	Petroleum ether (50); DCM:15% acetone (2 × 50)	—/—	—	—
Senkyunolide A and ligustilide (bioactive compounds)[155]	*Rhizoma chuanxiong*	C_{18}/manual	VSMC/CMC-MEPS-GC-MS	250–4000	MeOH (1 ml)	—/—	—	—
Volatile profile (multi-VOC analysis)[148]	"Sweet" and "hard" ciders (500)	C_{18}/manual	GC-MS and GC-FID	40–300 000	DCM (25)	0.02–2.34/0.04–4.69	1.9–5.9	—
Food quality markers								
Benzylbutyl phthalate, dibutyl phthalate, dicyclohexyl phthalate, diethyl phthalate and dipropyl phthalate[91]	Carbonated drinks, perfumes and creams (500)	C_{18}/manual	GC-MS	0.5–500	MeOH (30)	0.003–0.015/0.009–0.049	1.3–2.7	88
Ethyl carbamate[137]	Madeira wine (300)	C_2, **C_8**, C_{18}, M1, Sil/eVol®	GC-MS	5–400	DCM (100)	1.5/4.5	5.0–7.0	97
Ochratoxin A (OTA)[138]	Red, white and rosé wines (350)	C_{18}/eVol®	HPLC-FLD	0.02–3.0	ACN : 0.2% Acetic acid (90 : 10) (2 × 25)	0.08/0.24	3.8–4.5	90
Sotolon[139]	Red, white and fortified wine (750)	C_2, C_8, C_{18}, M1, **PEP**, PGC, RAX, RCX, Sil/eVol®	UHPLC-PDA	10 000–100 000	50% MeOH (100)	0.45–2.51/1.49–8.36	0.4–5.6	81
Dietary compounds								
Olive biophenols (caffeic acid, oleuropein, tyrsol)[149]	Plasma (200)	CMK-3/eVol®	HPLC-UV/VIS	0.005–2	ACN (100)	0.25–4.7 (μM)/0.82–15.7 (μM)	<2.5	84–106
Diet-derived phenolic acids[150]	Plasma	**C_{18}**/online	GC-MS/MS	—	ACN (360)	—/—	>15	10–120
Environmental contaminants (pesticides)								
Ametryn, atrazine, bifenthrin, carbofuran, metribuzine, tebuthiuron[78]	Sugarcane (250)	C_{18}/manual	GC-MS	2.0–1000	EtAc (30)	0.2–1.5/2–10	3.9–15.9	72–107

Table 4 *(Contd.)*

Target analytes (foodstuff)[Ref]	Matrix (sample volume, μl)	MEPS sorbent/type	Analytical performance					
			Methodology	Linear range (ng ml^{-1})	Elution solvent* (V, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Ametryn, atrazine, simazine, simetryn, terbutryn[105]	Corn (1000)	MIPs/manual	LC-ESI-ToF	10–80	ACN : 0.1% acetic acid (70 : 30) (1 ml)	3.3/10 (ng g^{-1})	0.4–12.1	92–102
Clofentezine[145]	Milk and juice samples	Polythiophene dendrimer/custom	HPLC-UV	1–10 000	MeOH (400)	0.2/—	5–9.2	93–98
Dimethoate[103]	Wheat flour (250)	MIPs/manual	UHPLC-MS/MS	22.9–229.3	ACN (3 × 100)	—/—	0.7–2.7	60
Pesticides (multiresidue analysis)[104]	Honey (3 g)	C_8, **M1**, SAX, SCX, Sil/manual	GC-MS	2–100	EtAc (20)	—/10 (ng g^{-1})	2.0–15.0	82–114
Pesticides and fungicides (multiresidue analysis)[144]	Wheat flour (250)	HDVB/manual	UHPLC-MS/MS	0.0001–250	ACN (3 × 100)	0.30–5.00/ 0.75–15.00	2.0–13.0	19–98
Triazine herbicides	Maize[146]	Au/LDH/custom	HPLC-DAD	2.5–300	EtAc (400)	35–108 (pg g^{-1})	0.99–2.88	—
	Corn[147]	MIL-101(Cr)/custom	HPLC-MS	2.0–200	ACN (2 ml)	0.01–0.12/ 0.04–0.35 (ng g^{-1})	<9.11	—
Veterinary drug usage								
Polychlorinated biphenyls (28, 52, 101, 118, 138, 153 and 180)[102]	Bovine serum (100)	C_{18}/custom	GC-MS	2–200	EtAc (2 × 50)	0.06–0.53/ 0.20–1.77	1.90–5.66	60
Ractopamine[141]	Porcine muscle and urine (1000)	**C_{18}**, **M1**/eVol®	HPLC-UV	0.01–2	95% MeOH : 0.2% NH_4OH (300)	0.003/0.010	3.9–7.6	82
Tetracycline residues[143]	Milk	Graphene/custom	UHPLC-MS/MS	15–110	MeOH (100)	—/50–900	2.1–8.8	87–118

Legend: * – elution solvent composition is indicated in v/v ratios and these are discriminated only when they are not equivalent among the components of the mixtures used; Au/LDH – packed hybrids of gold nanoparticles and layered double hydroxide nanosheets; DAD – diode array detector; FLD – fluorescence detection; HDVB – highly crosslinked polystyrene divinylbenzene; HPLC – high performance liquid chromatography; LODs – limits of detection; LOQs – limits of quantification; M1 – mixed-mode C8/SCX MEPS sorbent; MEPS – microextraction by packed sorbent; MS – mass spectrometry; MS/MS – tandem MS; MIL-101(Cr) – metal–organic framework (MOF)-based catalyst, chromium hydroxide number 101; PDA – photodiode array detector; PEP – polar enhanced polymer MEPS sorbent; PGC – porous graphitic carbon MEPS sorbent; R(A/C)X – polymeric DVB partially functionalized with quaternary amine groups or sulfonic acid groups, respectively; SAX – strong anion exchange; SCX – strong cation exchange; Sil – silica MEPS sorbent; SVOCs – semi-VOCs; VSMC/CMC – vascular smooth muscle cells/cell membrane chromatography; UHPLC – ultra high performance liquid chromatography; UV – ultraviolet detection; μECD – microelectron-capture detector.

with gerbil (desert rats) fed with calafate, an edible Patagonian dark blue berry rich in phenolic acids.[150] In this case, however, the authors used a MEPS-GC-MS/MS experimental layout to screen 40 dietary phenolics previously derivatized. This strategy aimed to obtain the complete metabolic snapshot that follows the ingestion of calafate extract by mammals.

Comparison with other microextraction techniques

In the sample preparation procedure, the extraction step has a critical influence on the analytical performance of the methodology proposed to analyse a given analyte. The conventional extraction approaches, such as liquid–liquid extraction (LLE) and solid phase extraction (SPE) showed good responses for a large number of target analytes in different sample matrices.[2,86,107,128,156,157] However, the traditional extraction techniques are mostly time consuming and require large amounts of organic solvents and samples.[86,107,156,157] To minimize these drawbacks, different strategies have been proposed, such as the use of ultrasound in the sample processing and extraction steps,[80,92,107,126] or different forms of conventional LLE and SPE miniaturization.[126,156,158,159] In terms of liquid–liquid microextraction (LLME), methodologies like SDME (single drop microextraction)[158–160] or DLLME (dispersive liquid–liquid microextraction)[126,161,162] have been reported as good alternatives to the traditional protocols, presenting several advantages, such as a drastic solvent reduction and a great preconcentration factor.[126,158–162] Nevertheless, such approaches involve experimental protocols and manipulation of the extraction devices that require some specific skills.[163] In contrast, the microextraction approaches involving SPE miniaturization are more simple and prone to automation, while also allowing a significant solvent and sample reduction. In this context, several methodologies, such as SPME,[164–166] SBSE,[167,168] and MEPS[2,80,107,157] have been widely reported in the literature for the extraction of a great range of analytes in different fields of application. Several of these reports included extensive comparisons with the literature about MEPS efficiency against other extraction approaches for the same target analytes. This is the case of the initial work of Abdel-Rehim,[1] reported in 2004, that clearly pointed that MEPS allows similar or better extraction efficiency than conventional methodologies for the extraction of several anaesthetics.[1] This was also previously shown for different antiepileptic drugs,[169,170] or NSAIDs.[171] In this section, however, we will mainly focus on the comparisons in recent reports involving microextraction techniques, such as DLLME,[126,172,173] HF-LPME,[87,100] SDME,[109,174] μSPE[175–180] and SPME,[1,109,133,181,182] that already incorporate significant technological improvements by comparison with more conventional techniques, such as LLE[1,87,183] and SPE (Table 5).[1,87,109,120,183] These comparisons of MEPS applications with other extraction approaches would be more meaningful if the same experimental conditions were involved but unfortunately this is not available so far for many applications. Apart from small variations in the experimental protocols used, often the matrices used were not the same, nor the analysis that followed the extraction procedure. Therefore, the comparison between different extraction approaches for the same target analytes was simplified to the analytical performance level (limits of detection and quantification, precision and recovery). Accordingly, the examples shown in Table 5 involve target analytes from different applications including several classes of pharmaceutical drugs, drugs of abuse, pesticides, environmental contaminants and bioactive compounds. Overall, it is shown that the analytical performance obtained with MEPS is, at least, in the same range as other methodologies reported in the literature. This certainly makes the adoption of this approach more advantageous at different levels, as previously demonstrated. There are, nevertheless, some examples whose performance may be more interesting in favour of other extraction approaches. Sánchez *et al.*,[95] for instance, compared the extraction efficiency of MEPS (using the HyperSep™ Retain™ PEP sorbent) with salting-out-assisted liquid–liquid extraction (SALLE), both combined with GC-MS for the determination of aromatic amines formed from azo dyes in textiles. Based on the results obtained, low LODs and less interfering compounds from the matrix were achieved using MEPS, whereas SALLE showed the highest recovery rates and lower time for extraction and preconcentration of the target analytes. Regarding the analytical performance, good results were achieved for all target analytes, in terms of linearity, LOD and recovery. NSAIDs are pain-relieving therapeutic agents widely used in the human population. Their administration is so massive that there are growing concerns about the side effects of NSAIDs on human health, as well as on the environment.[184] Therefore, there are abundant reports in the literature involving different methodologies to quantify NSAIDs in biofluids (mainly plasma and urine) and environmental waters. Table 5 presents a comparative analysis of MEPS and SPE extractions followed by liquid chromatographic separation. As can be observed, MEPS extraction using commercial C_{18} sorbents[25,46–48] retrieves equivalent analytical performance to SPE approaches using custom MIP sorbents.[185] Moreover, both approaches are compatible with the less expensive DAD detection for the quantification of NSAIDs in the biological fluids. This makes MEPS a suitable approach for the extraction of NSAIDs from biological fluids and eventually to monitor the presence of these drug residues in the environment. In this last case, however, the use of MS/MS detection will be necessary to attain the required analytical performance of such analysis.

Innovative improvements and future applications

Since its introduction by Abdel-Rehim, in 2004,[1] MEPS has gone through several improvements mainly affecting its technical configuration and sorbents. These were made commercially available for MEPS by simple downscale of the SPE equivalents commercially available, firstly the silica-based sorbents and later the polymeric versions. As already mentioned, a review of the chemistries and properties of the different sorbents com-

Table 5 Comparison between MEPS and other extraction methods

Class (analytes)[Ref]	Sample matrix	Methodology: Extraction (sample volume, μL)	Methodology: Analysis	Analytical performance: Linear range (ng ml^{-1})	Elution solvent* (V, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Antibiotics								
Levofloxacin, linezolid and meropenem[186]	Human plasma	MEPS	HPLC-PDA	10–30 000	MeOH (150)	4.0–7.0/10–20	<10.5/<10.8	92–97
Cefepime, ciprofloxacin, linezolid, meropenem, moxifloxacin and piperacillin[187]	Human plasma	PP	HPLC-MS/MS	50–4 000 000	—	50–500	<6.8/<10.9	—
Ofloxacin (FLQs)[175]	Urine, plasma	UA-dM-μSPE	Spectrofluorimetry	1–500	—	0.21/—	<2.5	98–101.5
Antidepressants								
Citalopram, fluoxetine, paroxetine and sertraline[53]	Human plasma	MEPS (400)	NACE	10–500	MeOH : P buffer (50 mmol l^{-1}, pH 4.5) (55 : 45) (150)/ACN (50)	—/20–30	—/2.9–8.7	92–101
		SBSE (800)	NACE			—/10–25	—/2.9–12.6	95–101
Citalopram and sertraline[176]	Urine, plasma	dM-μSPE	HPLC-UV	2–800	MeOH	0.6–0.7/2	<9.2	94–96.4
Aromatic amines[95]	Environmental water samples	MEPS	GC-MS	0.040–989	1-Propanol (60)/ EtAc (750)	0.040–42/0.13–139	—/<15	1–96
		SALLE				0.10–3.7/0.35–12	—/<11	26–98
Antipsychotics (ziprasidone)[63]	Human plasma	MEPS (100)	HPLC-UV	1–500	MeOH (500)	0.3/1.0	3.0–3.1/ 3.3–4.0	92–95
		SPE (250)	HPLC-UV			0.2/0.5	3.2–3.5/ 3.7–4.4	90–91
Benzodiazepines								
Bromazepam, chlordiazepoxide, clobazam, clonazepam, flurazepam, flunitrazepam, lorazepam, oxazepam[126]	Beverages	MEPS (300)	HPLC-UV	2500–250 000	ACN : FA (90 : 10) (3 × 100)	1050–1660/ 2070–5530	0.14–3.43/ 0.78–2.78	14–103
		DLLME (1000)			—	860–1750/2180–5830	0.88–5.82/ 1.02–4.21	38–102
		UA-DLLME (1000)			—	—	0.55–2.27/ 0.53–2.02	24–102
Chlordiazepoxide, diazepam, lorazepam, medazepam, oxazepam[125]	Alcoholic grappa drink	MEPS (300)	UHPLC-UV	500–2000	ACN : FA (90 : 10) (3 × 100)	500/2000	0.5–12/1.1–200	61–92
Chlorobenzene derivatives	Water samples[96♣]	MEPS (1750)	PTV-GC-MS	0.0003–500 (MEPS)	Hex/acetone (25)	0.0003–0.07/ 0.001–0.2	2.4–8.0/ 2.8–12.0	26–81
		LLE (500)	GC-MS	—	—	0.000005–0.00001/—	—/—	39–73
		SPE (200)	GC-MS			0.010–0.045/—	1.6–13.3/—	62–98
		SPME (5000)	GC-MS			0.003–0.006/—	1.2–8.2/—	92–108
		LPME (4000)	GC-MS			0.020–0.050/—	1.6–17.9/—	83–105
		SDME (10 000)	GC-MS			0.003–0.031/—	2.1–13.2/—	82–107
	Water samples[174]	MHS-SDME (20 000)	GC-MS	0.05–5	—	0.004–0.008/—	3–18/—	82–114
Drugs of abuse								
SCATs and other drugs of abuse and metabolites[120]	Human plasma	MEPS (200)	UHPLC-PDA	50–10 000	DCM : IPA : NH_4OH (78 : 20 : 2) (200)	10–25/10–50	0.9–13.8/ 1.2–13.8	80–105
		SPE (1000)	UHPLC-PDA			—/—	—/—	—
SCAN, SCAT and PHEs[177]	Whole blood	μSPE (100)	LC-MS/MS	—		—/0.25–5		21–70
Antivirals (entecavir)[64]	Plasma	MEPS (50)	UHPLC-MS/MS	0.5–100	ACN:5 mM $NH_4CH3COOH$ pH4.0 (75 : 25) (100)	0.15/0.50	0.9–3.6/ 2.9–17.4	95–106
		PP-SPE (500)	UHPLC-MS/MS	—	ACN: 5% NH_4OH (95 : 5) (1000)	0.3/1	1.1–4.1/ 2.3–6.3	80–106

Table 5 *(Contd.)*

		Methodology		Analytical performance				
Class (analytes)[Ref]	Sample matrix	Extraction (sample volume, μL)	Analysis	Linear range (ng ml^{-1})	Elution solvent* (*V*, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Haloacetic acids (dibromoacetic acid, dichloroacetic acid, monobromoacetic acid, monochloroacetic acid, trichloroacetic acid)	Tap water and swimming pool water[100♣]	MEPS (2500)	PTV-GC-MS	0.36–300	MTBE (20)	0.36–1.2/1.2–3.6	4.2–9.8/9.4–14	83–117
		HF-LPME (10 ml)	GC-ECD	—	—	0.5–3/—	5.0–12.0/—	97–109
		HS (25 ml)	GC-ECD			0.02–1.10/—	15–21.3/—	68–103
		SBME (1000)	GC-MS			0.02–1.0/—	5.8–9.2/—	92–98
		SDME (30 ml)	GC-MS			0.01–0.20/—	5.1–8.5/ 8.8–12.36	83–98
		HS-SPME (10 ml)	GC-ITMS			0.01–0.45/—	3–7.9/7.9–10.3	—
	Swimming pool water[178]	μSPE	UPLC-UV	1–150	NaH_2PO_4 buffer	0.008–0.01/ 0.025–2.16	0.03–7.40	110
Nitroexplosives (2,4,6-trinitrophenyl-*N*-methyl-nitramine; 2,4,6- trinitrotoluene and its metabolites)[109♣]	Environmental (river water) and biological samples (human blood and urine)	MEPS (50)	GC-MS	—	MeOH (30)	0.014–0.828/ 0.046–2.732	—/2.3–4.9	78–99
		MEPS	HPLC-UV	—	—	0.062–0.099/—	3.5–5.6/—	82–96
		SPME (25–35 ml)	HPLC-UV			1.0–10.1/—	10.2–27.2/—	67–122
		SPE (25–35 ml)	HPLC-UV			0.03–0.29/—	3.1–13.12/—	76–100
		SPME (20 ml)	HPLC-UV			0.17–0.93/—	1.3–2.7/ 1.7–3.3	86–99
		SPME (5 ml)	GC-MS			0.03–1.10/—	2.0–8.9/—	86–114
		SDME (5 ml)	GC-MS			0.08–1.3/—	4.3–9.8/—	82–102
NSAIDs (non-steroidal anti-inflammatory drugs)								
Acetylsalicylic acid, diclofenac, ibuprofen, ketoprofen, naproxen[46]	Urine	MEPS (20)	HPLC-PDA	5–20 000	ACN (pH 8.0) (20)	1.07–16.2/3.21–48.7	0.503–9.15/—	89–107
Fenbufen, flurbiprofen, furprofen, ibuprofen, indomethacin, indoprofen, ketoprofen[47]	Plasma, urine	MEPS (85)	HPLC-PDA	100–10 000	95% MEOH : 0.1% NaOH (8 × 20)	30/100	—/—	—/—
		SPEs	HPLC-PDA	100–10 000	MEOH (1 ml)	—	—/—	45–87
Carprofen, fenbufen, flurbiprofen, ibuprofen, indomethacin, indoprofen and ketoprofen[48]	Human dialysates	MEPS	UHPLC-DAD	25–15 000	95% (MEOH : 1% NaOH) (200)	8–10/25–33	—/—	94–100
Several NSAIDs (7) and FLQs (4)[25]	Urine	MEPS (180)	UHPLC-PDA	100–10 000	MeOH (8 × 25)	30/100–1000	0.70–14.9/ 0.22–13.5	—
Diclofenac, ibuprofen, ketoprofen and naproxen[185]	Urine	MIP-SPE	UHPLC-DAD	1000–50 000	MeOH (1 ml)	—/20–30	—/—	89–112
Ibuprofen, diclofenac, ketoprofen and mefenamic acid[179,188]	Water samples	d-μSPE (15 ml)	HPLC-UV	0.8–500/1–1000	IPA	0.21–0.51/0.71–1.70	1.2–5.1	85.1–106.4
Phenolic acids (40 dietary phenolic acids)[150]	Rodent plasma	MEPS	GC-MS	—	ACN (4 × 90)/EtAc (700)	—/—	<5/—	<70
		LLME					10–20/—	80–120
Pyrethroid metabolites[87♣]	Human urine	MEPS (500)	GC-MS	0.05–25	HFIP/DIC/hex (1 : 2 : 97) (2 × 40)	—/0.06–0.08	2–14/3–14	92–124
		LLE (2500)		—	—	0.02–0.08/—	0.7–6.6/ 4.3–10.8	81–104
		SPE (HLB, 2000)				0.05–0.1/—	1.2–9.3/ 1.7–13.9	74–114
		SPE (C_{18}, 3000)				0.002–0.019/ 0.007–0.062	4.8–14.6/—	87–121
		HF-LPME (5000)	GC-ECD			1.6–12/—	5.0–12.0/—	—

Table 5 *(Contd.)*

		Methodology		Analytical performance				
Class (analytes)[Ref]	Sample matrix	Extraction (sample volume, μL)	Analysis	Linear range (ng ml^{-1})	Elution solvent* (*V*, μl)	LOD/LOQ (ng ml^{-1})	RSD (%)	Recovery (%)
Triazine herbicides	Maize[146]	MEPS	HPLC-DAD	2.5–300	EtAc (400)	—/35–108 (pg g^{-1})	1.0–6.9/ 4.6–7.8	91.5–101
	Corn[147]	MEPS	HPLC-MS	2.0–200	ACN (2 ml)	0.01–0.12/0.04–0.35 (ng g^{-1})	0.10–14.6	73–107
	Oilseed[173]	MSPD-DLLME	UFLC-UV	8–1000	50% EtAc (1.5 ml)	1.20–2.72 3.99–9.06 (ng g^{-1})	<7.7	86–106
	Soybean[189]	NPSMAE	HPLC-DAD	5–513	MeOH (2 ml)	1.56–2.00 (ng g^{-1})	<6.7	91–107
	Water[190]	SUPRAS-MNP	HPLC-UV	300–250 000	MeOH (60)	300–500	4.6–6.5	90–105
	Rice[191]	SPE	HPLC-UV	5–1000	diethyl ether (3 ml)	0.71–1.08 2.67–3.64 (ng g^{-1})	<8.45	89–100
	Orange juice[192]	SPE	GC-MS	0.1–1000	MeOH (200)	0.03–0.6	3–11.4	75–125
	Juices[180]	dM-μSPE	HPLC-DAD	—	—	0.23–1.6/0.76–5.3	1.9–5.4	98.2–99.4
	Waste water[181]	VAdM-SPME	HPLC-DAD	—	—	2.0–5.3/6.1–15.7	5.8–10.2/ 3.8–6.3	97.6–101.5
Tetracycline residues	Milk	MEPS[143]	HPLC-MS/MS	15–110	MeOH (6 × 100)	0.03–0.21/0.05–0.9	—/—	—
	Milk	LLE[193]	HPLC–MS/MS	15–110	EtAc (6 ml)	—/5 (μg kg^{-1})	—/13.0–29.0	—
	Milk, eggs	FIL-NOSM[194]	HPLC-UV	0.5–500	—	0.08–1.12/— (μg kg^{-1})	1.0–3.7/ 1.1–5.7	94–102
	Infant foods	SALLE[195]	UHPLC-MS/MS	15–110	ACN (3.2 ml)	0.05–0.14/0.16–0.48	3.7–7.3/ 5.8–11.3	89–97
	Beef	DLLME[172]	HPLC-MS/MS	25 000–200 000	MeOH : DCM (5 : 1) (1.2 ml)	2.0–3.6/7.4–11.5	—/—	80–105
	Animal tissue	SPE[196]	HPLC-MS/MS	0.2–500	MeOH : EtAc (10 ml)	0.5–4.0/2–10	<10/<14	54–102
	Honey[182]	MF-SPME	HPLC-MS/MS	0.005–100 (μg kg^{-1})	—	0.007–0.017 (μg kg^{-1})	5.0–9.5/ 3.6–10.0	70.5–111.0
Carnitine, acylcarnitines	Urine	MEPS (100)[31]	UHPLC-MS/MS	0.1–500	C2–ACN (100)	0.1/—	—/—	—
		Evaporation (50)[197]	CE		M1–20 mM pyridine in ACN (100)	1.6/—	1.5–10.2/ 2.6–21.0	—
	Human sera, rat tissue[198]	SLE (15 μL serum, 10 mg tissue)	UHP-HILIC-MS/MS	5–600	ACN : MeOH (3 : 1) (65 150)	0.5–5/—	1.2–29.3/ 1.2–36.3	>88

Legend: * – elution solvent composition is indicated in v/v ratios and these are discriminated in the table only when they are not equivalent among the components of the mixtures used; ♣ – comparative data reported in the literature; ASE – accelerated solvent extraction; CE – capillary electrophoresis; DAD – diode array detector; DART – direct analysis in real time; DCM – dichloromethane; DI – direct injection; DLLME – dispersive liquid–liquid microextraction; dM-μSPE – dispersive magnetic solid phase microextraction; DSLE – dispersive solid–liquid extraction; ECD – electron capture detector; EtAc – ethyl acetate; FIL-NOSM – functionalized ionic liquid-based nonorganic solvent microextraction; FLQ – fluoroquinolones; GC – gas chromatography; HF-LPME – hollow-fibre liquid-phase microextraction; HPLC – high performance liquid chromatography; IPA – isopropanol; ITMS – ion trap mobility spectrometry; LLE – liquid–liquid extraction; LODs – limits of detection; LOQs – limits of quantification; MALLE – non-porous membrane-assisted liquid–liquid extraction; MEPS – microextraction by packed sorbent; MF-SPME – monolith fibre solid-phase microextraction; MHS-SDME – magnetic headspace single-drop microextraction; MIPs – molecularly imprinted polymers; MISPE – molecular imprint SPE; MS – mass spectrometry; MS/MS – tandem MS; MSPD – matrix solid-phase dispersion; NACE – non-aqueous capillary electrophoresis; NPD – nitrogen phosphorus detector; NSAIDs – non-steroidal anti-inflammatory drugs; NPSMAE – non-polar solvent microwave assisted extraction; PDA – photodiode array detector; PHEs – phenethylamines; PP – protein precipitation; PTV – programmable temperature vaporization; Q-TOF – quadrupole time-of-flight mass spectrometry; RSD – relative standard deviation; SALLE – salting-out-assisted liquid–liquid extraction; SBME – stir bar microextraction; SBSE – stir bar sorptive extraction; SCANs – synthetic cannabinoids; SCATs – synthetic cathinones; SDME – single-drop microextraction; SPE – solid-phase extraction; SPME – solid-phase microextraction; SUPRAS-MNP – supramolecular solvent-magnetic nanoparticles; UA-dM-μSPE – ultrasound assisted dispersive magnetic micro solid-phase extraction; UA-DLLME – ultrasound assisted dispersive liquid–liquid microextraction; UHPLC – ultra performance liquid chromatography; UHP-HILIC – ultra-high performance hydrophilic interaction liquid chromatography; UV – ultraviolet detection; VAdM – vortex-assisted dispersive magnetic extraction.

mercially available for MEPS can be found elsewhere.[6] There is, nevertheless, a significant number of MEPS applications using custom sorbents, such as graphene[69,143] and other nanomaterials,[80,145–147,199,200] as well as molecularly imprinted polymers (MIPs)[106–108,110] and imprinted interpenetrating polymer networks (IPNs),[57] that are not commercially available. These sorbents were shown to provide better selectivity, but their limited production and packing in home-made syringes, such as 1 mL glass insulin injection syringes,[77,84,86] or similar low-volume syringes, limit their use in the manual MEPS mode. An exception to this are the polymer monoliths[201] and the poly(ethylene glycol) functionalization of monolithic poly(divinyl benzene)[202] sorbents that Candish *et al.* packed in the MEPS BINs to be compatible with the semiautomatic eVol® syringe. An on-line MEPS architecture using custom sorbents was also reported by Abdel-Rehim *et al.* for the extraction of sarcosine from biological fluids[37] and beta-blockers from plasma.[61] However, these applications require some skills and customizations to interface MEPS with the LC-MS/MS configurations described that are not easy to implement for routine use. At the instrument level, the first commercial MEPS format available was manually driven through a Hamilton-type syringe. This configuration is simple and fast to operate, but it is not very prone to automatization. Moreover, it is too much exposed to experimental errors that inevitably arose from repetitive operation steps performed by the human subjects. The electronic syringe eVol® was a breakthrough in MEPS extraction, allowing a significant automation of the experimental procedure which became very close to what an autosampler can offer, but for one tenth of the price. The eVol® is a hand-held dispensing system for controlled positive displacement with in-built and intuitive programming functions. This is very convenient as it allows an easy customization of repetitive procedures. Furthermore, it is particularly useful for MEPS extractions which involve many repetitive operation steps of loading and dispensing of solvents, samples and washing solutions, eventually using different aspirating and dispensing velocities. The indicative number of operation steps can vary from 8 up to 20 steps or more, depending on the volume of the sample loaded by the cycle of extraction, the number of washing steps and even the elution process. Elution can include two successive steps to increase the target analyte recovery or even previous drying steps with air. In this way, eVol®-MEPS extraction is more reliable than manual MEPS, exhibiting better reproducibility and repeatability. Finally, the online and fully automatic MEPS approaches using autosamplers are still very expensive and in the last five years only two applications using this format were reported.[42,67] In MEPS operation, the samples and solvents are loaded and discarded through the same channel. This may be particularly critical for target analytes with weak interactions with the sorbent. These analytes can be partially eluted and lost during the sample withdrawal and washing steps. And whilst in some cases it is possible to skip the washing step, for most applications this strategy will compromise the specificity of the method. To overcome this, a two-way valve laterally incorporated into the barrel of the syringe, designated controlled directional flow (CDF), was described by Candish *et al.*[201–203] This CDF, represented in Fig. 2B, permits an independent flow path for the sample and solvents, which gives a better control over the direction of liquid flow. This allows, for instance, the loading of the elution solvent directly from the top of the sorbent bed, therefore reducing the possibility of dilution, carryover and any other contamination made during the bidirectional flow. The same principle applies for the washing solution, minimizing the target analyte loss during this step. The advantages of this CDF-MEPS architecture were shown by Candish *et al.*[203] for the rapid screening of codeine metabolites in urine. This includes a very significant carryover effect reduction in comparison with traditional MEPS (1% for CDF MEPS and 65% for conventional MEPS), while conserving satisfactory analytical performance (recovery >89% for 50 μL sample, matrix effects <42%, linearity $r^2 > 0.99$, and LODs < 5 ng mL^{-1}). The same researchers used the CDF-MEPS approach to assay new sorbents and their protein clean-up properties, namely polymer monoliths[201] and the poly(ethylene glycol) functionalization of monolithic poly(divinyl benzene).[202] The CDF-MEPS was also used by Elmongy *et al.*[60] to extract metoprolol enantiomers from human plasma and saliva. In this case, the CDF path was used as the inlet to load the samples. More recently, a new improvement to MEPS was introduced in the market by EPREP company (Victoria, Australia). This variant, named μSPEed extraction, represents a major upgrade by including several important modifications to MEPS extraction. As can be observed in Fig. 2C, the μSPEed cartridge architecture contains an efficient pressure-driven one-way check valve. This allows an ultra-low dead volume connection and a single way flow path through the sorbent bed in every step of the extraction protocol. In this way, the aspiration can be achieved only by means of vacuum when the plunger is pulled back, and therefore, does not have to pass the bed but bypasses the sorbent. Essentially this a more elegant and efficient operation mode than the CDF-MEPS because the entire system is incorporated into a single cartridge, not requiring additional tubes and fittings. Another very relevant modification in μSPEed is concerned with the use of smaller sorbent particles (3 μm or smaller) in a small cartridge, instead of the 50 μm diameter particles normally used in traditional MEPS. These small particles, which are available in the equivalent MEPS chemistries, offer a higher surface area, therefore favouring a more efficient separation. For this reason, μSPEed cartridges resemble a short (<1 cm long) sub 2 μm liquid chromatography column. The high-pressure fitting of the μSPEed, which is plug and play and not screw type as in MEPS, is also more advantageous, allowing an easy rejection of the used cartridge. This is particularly relevant for the use of autosamplers as μSPEed cartridges can be switch or discarded without any operator intervention. Furthermore, unlike MEPS BINs, μSPEed cartridges are made in polypropylene and so they are less expensive and suitable to single use protocols. Both these features are particularly tailored for applications in which a single use of the sorbent is mandatory for safety, quality control or regu-

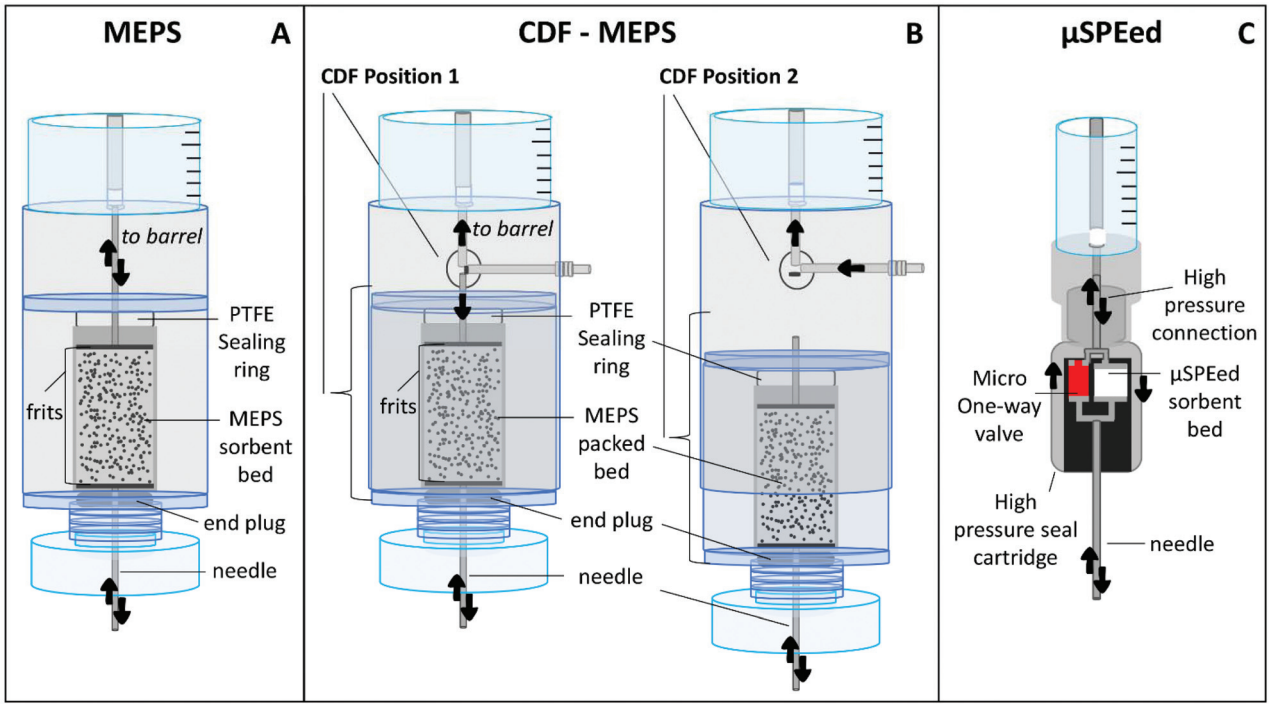

Fig. 2 Overview of different MEPS formats currently available: (A) original MEPS architecture with a two-way flow, (B) CDF-MEPS architecture with a lateral flow tube allowing a second injection path, and (C) µSPEed architecture, with a pressure-driven one-way valve originating a single direction and flow path.

latory reasons. This is the case, for instance, of clinical applications involving biological fluids and high throughput analysis. The µSPEed design also allows a constant, high pressure (up to 1600 psi) and single direction flow through the small particle size sorbent, retrieving more efficient extractions of the target analytes. Consequently, better performance can be attained in the following analytical procedures. The simpler and cheaper design of µSPEed cartridges will certainly facilitate the assay of custom and more efficient sorbents, as well as their faster incorporation into the commercial supply chains. Finally, it should also be noted that µSPEed cartridges can be operated using the standard eVol® syringe or the new eXact[3] Digital Syringe Driver (EPREP). This second syringe is more potent and can cope with much higher backpressures, what can be very advantageous for the extraction of more complex samples that often cause sorbent clogging. However, unlike the cordless eVol®, the eXact[3] requires a continuous power connection to operate. Meanwhile, the potential of µSPEed extraction has been already shown in three different applications. Porto-Figueira *et al.*[204] reported the good analytical performance of this new approach in the analysis of phenolic compounds in teas by UHPLC-PDA. In turn, Alexandrou *et al.*[205] demonstrated that µSPEed was faster and cheaper than traditional methods, attaining similar recovery rates for the determination of four common trihalomethane disinfection by-products in water. Moreover, the authors obtained this result using 1000 times less sample and 200 times less elution volumes. Also noteworthy is the report by Pandohee and Jones[206] that used the µSPEed cartridges for on-column derivatisation of short-chain fatty acids in olive oil previously to the extraction procedure. This strategy unveils a whole new range of applications, where different chemical reactions, particularly derivatisations before the target analyte extraction, can be easily performed. Such achievement will streamline very significantly long, laborious, repetitive, and cumbersome experimental layouts. At a different level, it should also refer to a major simplification of the experimental layout involving MEPS. This is the case of the direct coupling of MEPS to the detection system, therefore skipping the chromatographic separation. This remarkable shortening of the analytical path was already described for the analysis of opiates from urine samples using ESI-MS[203] and for the detection of the rave drug ketamine in fruit juices using Q-TOF analysis.[129]

Conclusions

As a sample microextraction approach, MEPS is being successfully used in different fields of research. This is certainly related with its easy operation mode and broad properties of the sorbents commercially available. It is striking, however, that this usage is excessively focused on the C_{18} sorbent and remaining silica and the more effective polymeric sorbents are still marginally used. Overall, and taking into consideration the reports involving MEPS published in the last five years, its adoption as a preferential extraction approach seems to be

somehow limited. The number of reports using MEPS, with an average of around 20 reports per year, is far below the ones involving SPE or SPME. This suggests that eventually the interest in MEPS is being hindered by some limitations, such as the costs, reusability and automation possibilities. The commercialization of μSPEed, with a more efficient and flexible design, cheaper and easier to incorporate in high-throughput analysis, has the potential to overcome the problems identified and allows a wider use of microextraction in forensic, clinical, and pharmaceutical analyses. The innovative μSPEed architecture also facilitates the packing of new materials, and consequently the transition of promising proof of concept applications to the commercial circuits will be favoured. Finally, the use of μSPEed as a reaction vessel for different biochemical reactions will be a breakthrough in the simplification of several experimental layouts covering the most diverse research applications, particularly the clinical, pharmaceutical and metabolomics analyses.

Abbreviations

ACN	Acetonitrile
AMPHs	Amphetamines
ANAEs	Anaesthetics
APS	Aminopropyl silane MEPS sorbent
ASE	Accelerated solvent extraction
BDEs	Brominated diphenyl ethers
CD-IMS	Corona discharge ion mobility spectrometry
CDF	Controlled directional flow
CE	Capillary electrophoresis
CLC	Capillary liquid chromatography
CNTs	Carbon nanotubes
CNT/PDPA	CNTs/ polydiphenylamine
COC	Cocaine
DAD	Diode array detector
DART	Direct analysis in real time
DI	Direct injection
DIC	Diisopropylcarbodiimide
DLLME	Dispersive liquid–liquid microextraction
DMIP	Dummy molecularly imprinted polymer
ECD	Electron capture detector
EDCs	Endocrine disrupting chemicals
EtAc	Ethyl acetate
EtOH	Ethanol
FA	Formic acid
FID	Flame ionization detector
FIL-NOSM	Functionalized ionic liquid-based nonorganic solvent microextraction
FLD	Fluorescence detection
FLQ	Fluoroquinolones
GC	Gas chromatography
HAAs	Haloacetic acids
HDVB	Highly crosslinked polystyrene divinylbenzene
hex	Hexane
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HF-LPME	Hollow-fibre liquid-phase microextraction
HILIC	Hydrophilic interaction chromatography
HPLC	High performance liquid chromatography
IPA	Isopropanol
ITMS	Ion trap mobility spectrometry
LLE	Liquid–liquid extraction
LODs	Limits of detection
LOQs	Limit of quantification
LVI	Large volume injection
M1	Mixed-mode C8/SCX MEPS sorbent
MALLE	Non-porous membrane-assisted liquid–liquid extraction
MeOH	Methanol
MEPS	Microextraction by packed sorbent
MIBK	Methyl isobutyl ketone
MIPs	Molecularly imprinted polymers
MISPE	Molecular imprint SPE
MS	Mass spectrometry
MS/MS	Tandem MS
MSPD	Matrix solid-phase dispersion
MTBE	Methyl *tert*-butyl ether
NACE	Non-aqueous capillary electrophoresis
NPD	Nitrogen phosphorus detector
NSAIDs	Non-steroidal anti-inflammatory drugs
NPSMAE	Non-polar solvent microwave assisted extraction
OCPs	Organochlorines
OPFRs	Organophosphate ester flame retardants
OPIs	Opioids
OPPs	Organophosphorus
PAEs	Phthalate esters
P buffer	Phosphate buffer
PAHs	Polycyclic aromatic hydrocarbons
PANI	Polyaniline
PCBs	Polychlorinated biphenyls
PDA	Photodiode array detector
PEs	Phthalate esters
PEP	Polar enhanced polymer MEPS sorbent
PGC	Porous graphitic carbon MEPS sorbent
PHEs	Phenethylamines
PIP	Piperazine
PP	Protein precipitation
PTV	Programmable temperature vaporization
Q-TOF	Quadrupole time-of-flight mass spectrometry
R(A/C)X	Polymeric DVB partially functionalized with quaternary amine groups or sulfonic acid groups, respectively
RSD	Relative standard deviation
SALLE	Salting-out-assisted liquid–liquid extraction
SAX	Strong anion exchange
SBME	Stir bar microextraction
SBSE	Stir bar sorptive extraction
SDME	Single-drop microextraction
SCANs	Synthetic cannabinoids
SCATs	Synthetic cathinones
SCX	Strong cation exchange MEPS sorbent
SDVB	Polystyrene divinylbenzene

SERS	Surface-enhanced Raman spectroscopy
SIC	Sequential injection chromatography
Sil	Silica MEPS sorbent
Si-G	Graphene supported on aminopropyl silica
SPE	Solid-phase extraction
SPME	Solid-phase microextraction
SVOCs	Semi-VOCs
SUPRAS-MNP	Supramolecular solvent – magnetic nanoparticles
THC	Tetrahydrocannabinol
UA-DLLME	Ultrasound assisted dispersive liquid–liquid microextraction
UHPLC	Ultra performance liquid chromatography
UHP-HILIC	Ultra-high performance-hydrophilic interaction liquid chromatography
UV	Ultraviolet detection
VAX	Polymeric DVB partially functionalized with quaternary amine groups (verify AX)
VAMD	Vortex-assisted magnetic dispersive
VOCs	Volatile organic compounds
VSMC/CMC	Vascular smooth muscle cells/cell membrane chromatography
μECD	Microelectron-capture detector
μPESI	Micropillar array electrospray ionization chip

Conflicts of interest

The authors have no conflict of interest to declare.

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