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SAMPLE PREPARATION

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Microextraction using packed sorbent as an effective and high-throughput sample extraction technique: Recent applications and future trends.

Abstract

In the last decade, several developments, particularly in the liquid chromatography and hyphenated techniques fields, have allowed researchers to reach analytical limits that are becoming very close to the single molecule level. Sample preparation, however, despite being a key step in the analytical methodology, did not track these developments and very few approaches able to cope with these stringent analytical requirements were developed. One such approach is microextraction by packed sorbent (MEPS), a sophisticated and miniaturized form of solid phase extraction that has reduced to the microliter scale every step of the sample extraction methodology including sample volume and solvent usage. Simultaneously, the amount of extraction phase used was also reduced and, more importantly, the sorbent is reusable dozens of times which significantly lowers the cost of analysis versus other solid-phase extraction approaches. In this review, we will update the state-of-the-art of the MEPS technique, focusing on the trends and applications reported since 2010 and future perspectives and developments that in our view will further improve the high-throughput potential and applications of this sample preparation methodology.

Keywords

Microextraction by packed sorbent (MEPS) • eVol • Sample preparation • Solid phase extraction (SPE)

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1. Introduction

In the last decade, several technological improvements have led to a fast evolution in several analytical tools used in many different fields of research. The ultra-high pressure liquid chromatography (UHPLC) technology developed by Waters (Waters Corporation, Milford, USA) is probably the most remarkable development in the chromatographic field, creating a new standard in liquid chromatography (LC) which is amongst the most widely used techniques in sample analysis. More or less concomitantly, the detection methodologies used in conjunction with LC (ie. mass-spectrometry (MS)) have also made extensive progress in lowered detection limits. However, during these technological breakthroughs sample preparation, which is one of the most time-consuming and laborious steps in analytical procedures, seems to have been forgotten as a key process in the analytical methodology [1]. Sample preparation is the "bottleneck" of dozens of reference methodologies using fast and high-throughput sample analysis and detection procedures, which are currently coupled with cumbersome, low efficiency and unreliable sample preparation approaches [2]. In fact, sample preparation represents an essential step in the analytical process greatly influencing the reliability and accuracy of the results in addition to increasing the time and cost of analysis. Therefore, the choice of the suitable sample preparation technique should be carefully considered according to several factors including matrix complexity and polarity of the target analytes.

Sample preparation techniques are generally classified as liquid-liquid (LLE) or solid-phase extractions (SPE) depending on the nature of the sorbent phase used to extract target analytes. The most often used extraction techniques are shown in Figure 1 and classified according to several parameters including simplicity, speed, low environmental impact, and cost, in addition to characterizing their efficiency in terms of sensitivity and selectivity. Most of the referred techniques are becoming outdated considering that they were developed several decades ago (with the exception of SPME) and, although small improvements have been made they continue to process samples needing significantly higher volumes versus the newly available analytical procedures. Generally, LLE and SPE

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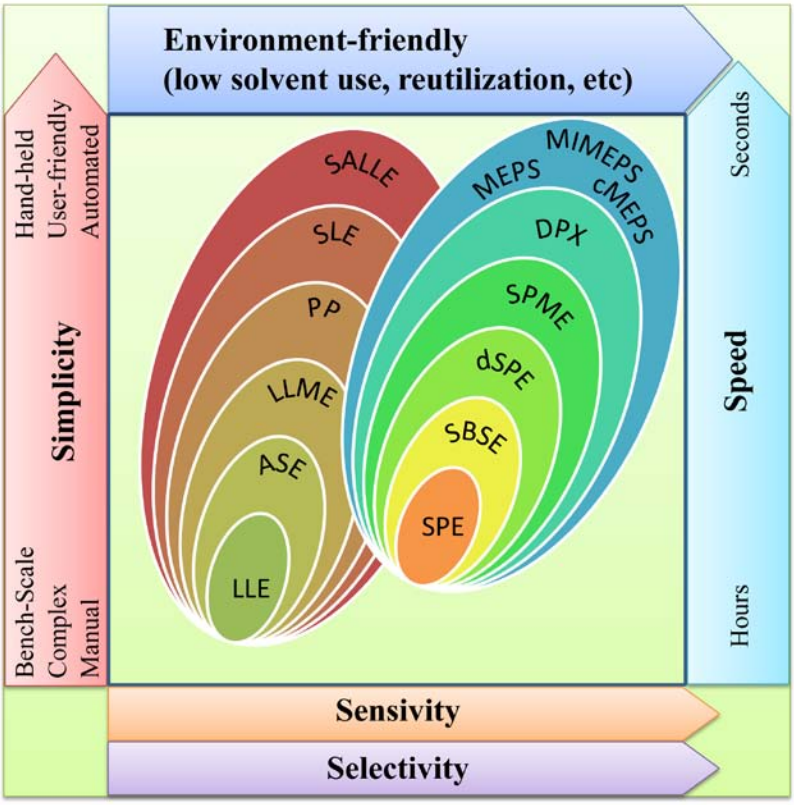

Figure 1. Overview and comparison of the analytical features of liquid-liquid extraction (LLE) and solid-phase extraction (SPE) and their derivative methodologies. Legend: ASE - Accelerated Solvent Extraction (or Pressurized liquid extraction), cMEPS – custom MEPS, DPX - Disposable Pipette Extraction, dSPE – dispersive SPE, LLME - Liquid–liquid microextraction (variants: SDME - single-drop microextraction, HF-LPME - hollow fibre liquid phase microextraction and dispersive liquid–liquid microextraction (DLLME)), MIMEPS – molecular imprint MEPS, PP - Protein precipitation; SALLE - Salting-out assisted LLE, SBSE - Stir bar sorptive extraction, SPME - Solid phase microextraction, SLE - supported liquid extraction.

techniques work within the range of millilitre (mL) of sample, mL of solvents and milligrams (mg) of extraction phase, while newer techniques including gas chromatography (GC), UHPLC and the several hyphenated detection techniques currently require microliters (µL) of sample, with even smaller volumes required with the rise of nano-LC technology [3]. Therefore, the difference between the sample preparation volume range and sample volume needed for analysis is increasing and not converging.

The recent trends in sample preparation include miniaturization automation, high-throughput performance and on-line coupling with analytical instruments which leads to a reduction in solvent volume and time [4]. This clearly indicates that more advanced extraction techniques need to be developed. In this context, micro-extraction by packed sorbent (MEPS) has emerged as a powerful technique. MEPS is a miniaturized SPE technique developed in 2004 by Abdel-Rehim et al. at AstraZeneca, Sweden [5] and made commercially available by SGE (SGE Analytical Science, Melbourne, Australia). It combines sample extraction, concentration and clean-up in a single device composed by two parts: the MEPS syringe and the MEPS cartridge, also known as barrel insert and needle (BIN) (Figure 2). The BIN contains the MEPS packed bed, a solid support that retains the target analytes when the sample passes through the bed.

The simple design of MEPS, resembling a short LC column in a syringe [6], presents several advantages when compared with other sample preparation techniques. The most important benefit is the ability to inject the target analytes directly into an LC or GC system without the need for concentration steps usually associated with analyte losses. This feature is particularly important to handle low sample volumes, such as for biological fluids where the sampling process is usually invasive and painful (*e.g.* blood, plasma). As a miniaturized SPE, MEPS uses low sorbent masses (1-4 mg) that are able to very quickly and efficiently process a wide range of sample volumes (from µL to mL). Given the low sorbent mass, the extraction solvent volume is also greatly reduced. Additionally, the sorbent bed is not disposable as compared to single-use SPE cartridges and can be reused up to 100 times depending on the nature of the sample processed [5,7,8]. Finally, the recovery and sensitivity parameters for most MEPS applications are excellent, as further described below (see section 5). Overall these MEPS properties create a high-throughput and efficient sample extraction technique, being much more environment-friendly and less expensive than any SPE or LLE approaches commercially available. The disadvantage of MEPS is that it is unable to process viscous or highly concentrated samples that need to be previously diluted and fully dissolved in the solvent otherwise the BIN can be easily blocked.

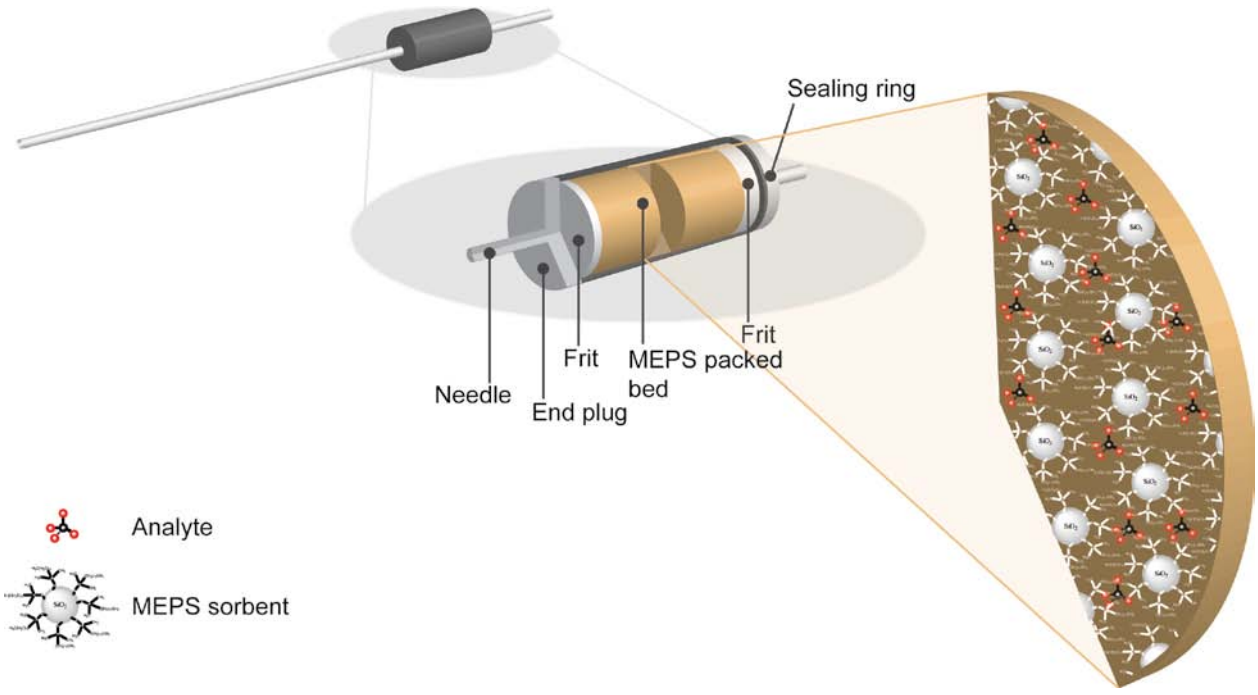

Figure 2. Overview of the MEPS BIN (barrel insert and needle). The sorbent is packed and properly sealed inside the barrel to avoid leakage. When the sample is loaded through the BIN, the analytes will be selectively retained in the sorbent and separated from remaining sample matrix.

2. Experimental overview

Typical MEPS is a simple and straightforward methodology that can be performed in four sequential steps. These steps only take a few minutes from sample loading to analytes elution for most samples with the exception of complex matrices such as plasma/serum and whole blood samples that are pre-treated by dilution in ratios of 1:4 and 1:20, respectively, and centrifuged prior to MEPS [9]. An outline of a typical sampling process is shown in Figure 3. Briefly, after sorbent conditioning with appropriate solvents, usually methanol followed by water (step A), the sample is drawn through the needle into the syringe once or several times (depending on experimental optimization) allowing the retention of the target analytes in the sorbent (step B). This is followed by a washing step to remove matrix interferences most often using acidic water (step C). Finally, the target analytes are eluted using an appropriate elution solvent, usually an organic solution (methanol, acetonitrile, etc.) to a receptor vial or directly into the LC or GC injector [10] (step D).

The conditioning step allows the sorbent activation when it is used for the first time or its clean up and regeneration for a new sample extraction cycle, which is an advantage over traditional SPE which has single-use sorbent cartridges. In the MEPS experimental layout the solvents and sample are loaded from the bottom of the column which allows both solvents and sample to pass through the extraction phase twice for each syringe cycle and optimization of experimental conditions will help reduce unspecific retention of analytes to the sorbent allowing an excellent sample concentration and clean-up, as well as high analytical recovery and sensitivity [11]. MEPS can be optimized for any of the four steps of the generic experimental layout (Figure 3), particularly in the sample loading

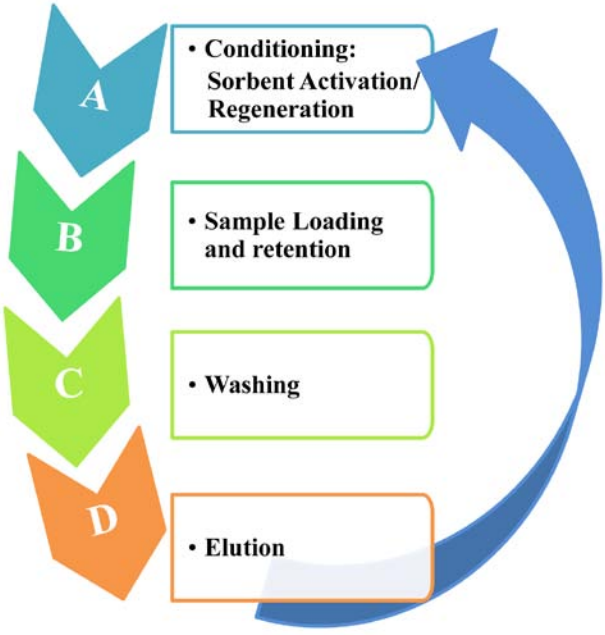

Figure 3. Overview of the four steps involved in most of MEPS applications. The step A corresponds to the sorbent activation whenever the device is used for the first time and to the device regeneration between extractions cycles (remember that MEPS is reusable up to 100 times or more, if the matrix is not very saturated or complex, reviewed in [8]). The sample is loaded in the step B (its volume, pH, temperature, dilution, etc., can be optimized), washed (step C) and finally eluted in a tenth of the initial sample volume loaded in B. Then, the device is regenerated and is ready for a new extraction cycle.

step that can involve several cycles and different sample volumes and dilutions. However, the high number of optimization possibilities may be experimentally challenging and cumbersome for some compounds with poor recoveries, particularly if simultaneously extracting analytes with very different chemistries.

3. MEPS formats

MEPS is commercially available in off-line and on-line formats (Figure 4). The simplest and most often reported format is the manual MEPS where the BIN containing the desired sorbent and the MEPS syringe is manually operated via a Hamilton-type syringe. This was the first commercially available format and is the most widely used in the scientific community. The semi-automatic MEPS version (eVol-MEPS) (Figure 4) was recently introduced by SGE and Thermo Fisher Scientific and is a major breakthrough for method development since it is more reliable than the manual MEPS. The eVol couples a digitally controlled and programmable electronic drive and an XCHANGE® enabled analytical syringe allowing greater precision and higher automation possibilities to the MEPS extraction process. This improvement is achieved by the minimization of user intervention and by the accuracy of the electronic pipette which provides customizable and precise flow volumes and velocities allowing for repeatable extraction of target analytes. Figure 5 shows two examples of a custom method used to perform a MEPS extraction of a urine sample [12,13]. The third form of MEPS is the fully automatic MEPS that can be easily achieved using the same MEPS XCHANGE® syringes on autosamplers (eg. CTC Analytics, Zwingen, Switzerland). This coupling allows the interface of MEPS with LC-MS or GC-MS, thus providing a completely automated MEPS/LC-MS or MEPS/GC-MS system [7,14]. In fact, this was the first format described for MEPS in the determination of local anaesthetics in human plasma samples using GC-MS [15]. Using this platform online with the following analytical systems (either LC or GC), the user need only load the samples to be processed and input the method to be used. Therefore, the user intervention in the whole procedure is reduced to the minimum, facilitating the development of regulated methodologies between different laboratories. In experimental terms, a new method using MEPS can be easily developed and optimized using the semiautomatic eVol system and then smoothly transferred to the fully automatic platform as the sorbent configurations used are the same, being only operated by a different device. This is possibly the fastest and most efficient method development system for throughput analysis currently available and its applications, as we will see later in this review, are continuously growing in all fields of analytical chemistry.

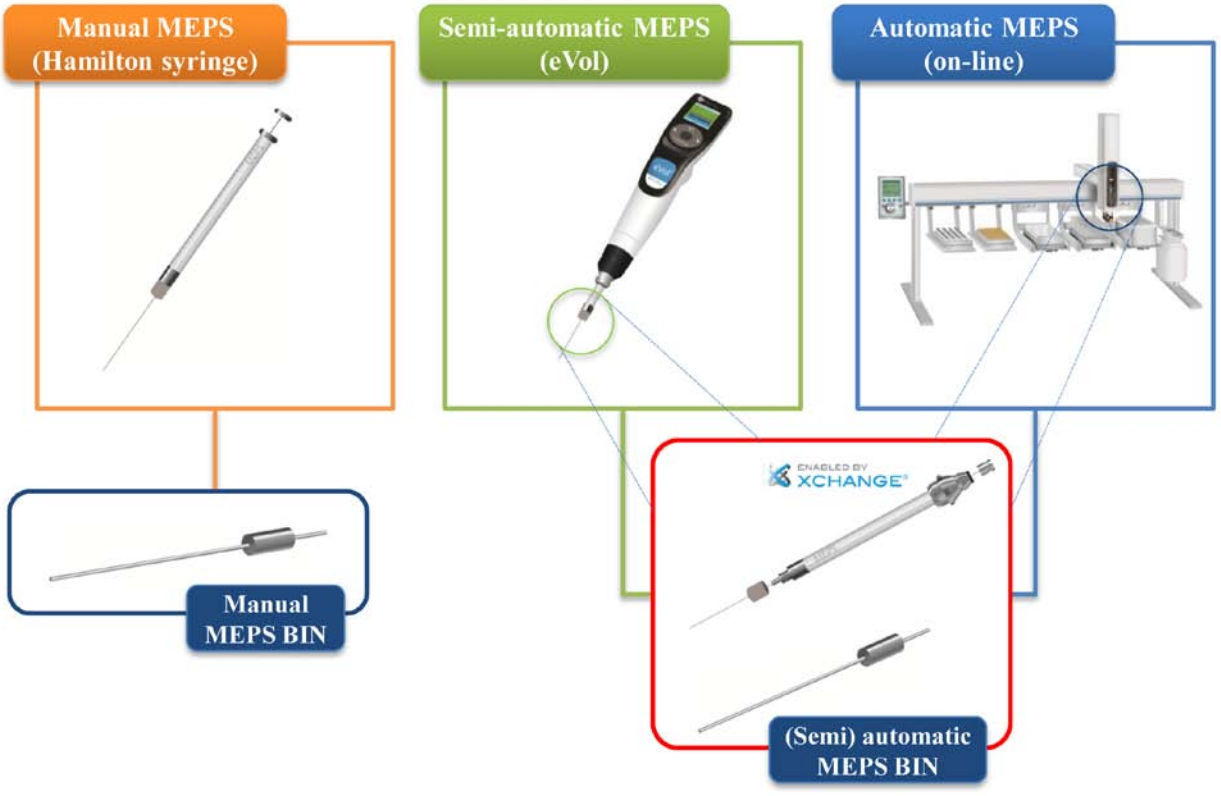

Figure 4. MEPS formats commercially available: manual (Hamilton syringe), semi-automatic (eVol) and on-line (several configurations available by CTC Analytics, for instance). The first MEPS BINs available are still indicated for the manual MEPS and compatible with the semi-automatic and automatic formats. However for the last two formats, new fibres containing higher diameter particles were designed to minimize cavitation and blockage of the BIN by complex matrices.

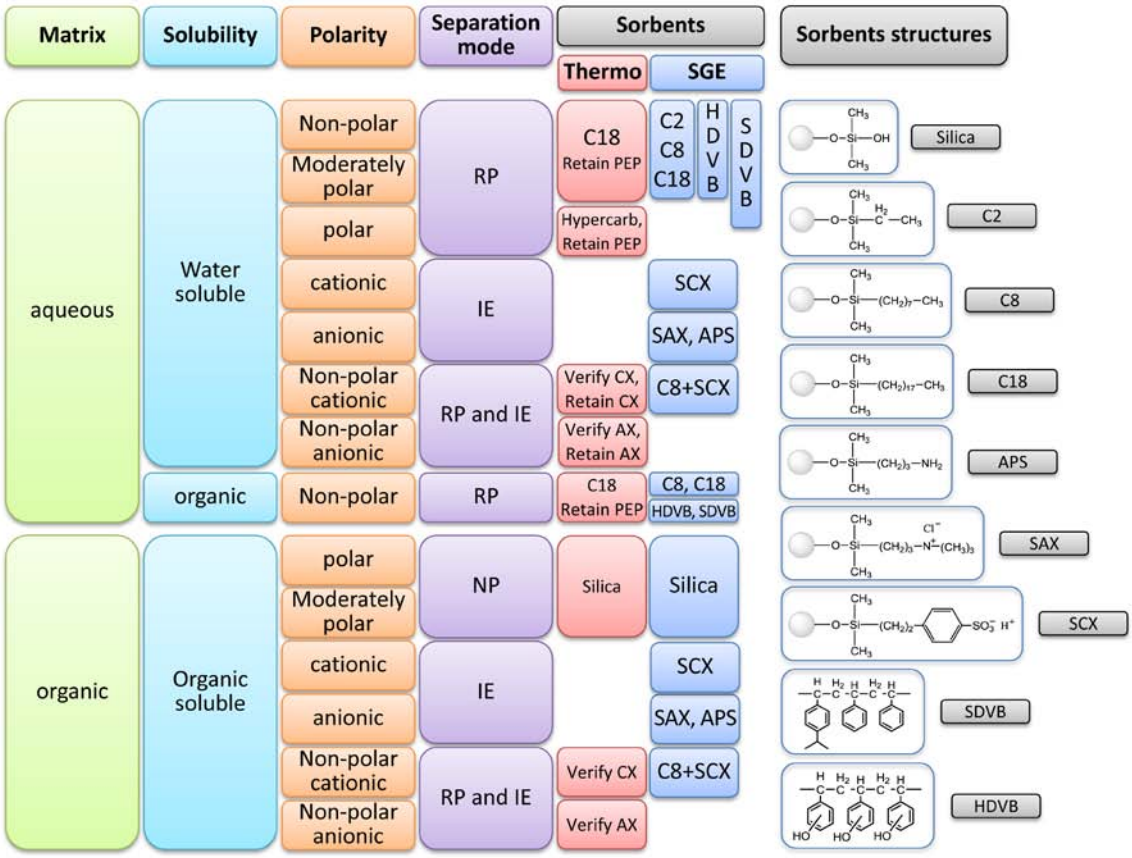

Figure 5. Simplified chart for selection of the commercial MEPS sorbents according to several chemical parameters, namely the properties of the matrix, the solubility and polarity of the target analytes and the separation mode used. The fibres in the red boxes are sold by Thermo Fisher Scientific, while the ones in the blue boxes are sold by SGE. Some simplified chemical structures of the sorbents are also presented. Legend: APS – aminopropyl silane, DVB – divinylbenzene, IE – ion exchange, NP – normal phase, RP – reversed phase, SAX – strong anion exchange, SCX – strong cation exchange.

4. Sorbent selection

A critical parameter in MEPS extraction is the choice of the sorbent since analytes are retained by the sorptive material through different forms of reversible interactions (hydrophobic, polar and ionic) (reviewed in [16]). Sorbent selection will determine the efficiency of the methodology (*e.g.* selectivity and affinity) as it is dependent on the strength of the interaction between the target analytes and the sorbent used in the MEPS BINs. A wide range of sorbents designed with different properties are commercially available (Table 1), making MEPS extraction suitable for reversed phases (extraction of hydrophobic analytes or polar organic analytes from aqueous matrices), normal phases (extraction of polar analytes from non-polar organic solvents), mixed mode and ion exchange chemistries (extraction of charged analytes from aqueous or non-polar organic samples).

Commercially available sorbent choices have increased considerably with the introduction of several options by Fisher Thermo Scientific, which re-designed several extraction phases from their solid-phase extraction portfolio to use with MEPS. These sorbents were adapted to MEPS utilization by the reduction of sorbent particle size and some properties extrapolated from the analogous SPE sorbent particles. Notably, different polymeric sorbents were made available by the two suppliers allowing a wide range of sorbents available to use with MEPS. It should be noted that specific sorbents, particularly those from SGE, are only available for certain MEPS formats (manual, eVol or on-line) and applications (LC or GC). For example, although we can use the MEPS BINs designed for manual MEPS in the eVol, these BINs, unlike the remain formats, do not contain larger sorbent particles to minimize the flow resistance during the semi-automatic extraction and this can be a critical issue in complex or saturated samples. Additionally, it will be very important for MEPS success as an extraction technique if suppliers provide more and detailed information about the properties of the new sorbents that they are commercializing.

Generically, MEPS sorbents are based in silica particles or polymeric phases which are modified to obtain different chemical properties resulting in a large portfolio of specificities for target analytes. As a result, currently there are more than a dozen

Table 1. Overview of the MEPS sorbents properties. The different suppliers sorbents were classified according to their backbone (silica-based or polymeric polystyrene DVB), being modified (mod) or not (unmod) with different alkyl side chains (silica sorbents) or higher crosslinking (polymeric sorbents) and being functionalized with different properties (amino groups - APS, SAX; sulfonic groups – SCX; urea groups – Retain PEP). The blue boxes sorbents are commercialized by SGE, the red ones by Thermo Fisher Scientific and the orange boxes by both suppliers. IE – ion exchange, NP – normal-phase, RP – reversed phase.

Sorbent type		Name	Chemistry	Properties
Silica	Unmod	Silica	NP	• highly polar sorbent retaining polar analytes (as those that contain amino groups from non-polar matrices)
	modified	C2	RP	• fairly non-polar sorbent (short chain length of functional group) • alternative to C8 and C18 if analytes are retained too strongly
		C8		• less retentive than C18 for non-polar compounds • lower carbon loading than C18
		C18		• highest hydrophobic and least selective sorbent • extremely retentive for non-polar compounds, retaining most organic analytes from aqueous matrices • suitable for the simultaneous extraction of analytes with diverse structures
	Functionalized	SCX	Mixed-mode (RP, IE)	• **S**trong **C**ation e**X**change: silica bonded benzene ring offering mixed-mode capabilities (hydrophobic interactions) • very low pKa (<1.0) due to H^+ counter ion from the benzene sulfonic acid • excellent capacity; suitable for weakly basic compounds
		SAX		• **S**trong **A**nion e**X**change: remains charged at all pH levels due to the quaternary amine bonded to silica • selectivity can be modified by changing the counter ion with the appropriate buffer during conditioning • suitable for weakly acidic compounds
		APS		• very polar silica-bonded aminopropyl phase used as an ion-exchanger in both normal-phase and ion-exchange applications • allows the rapid release of very strong anions such as sulfonic acids that may be retained irreversibly on SAX
		M1 (C8+SCX)		• dual retention mechanisms broadens retention for a range of neutral, basic, acidic and zwitterionic compounds • higher selectivity for basic compounds from biological fluids
		Verify CX (C8+SCX)		
		Verify AX (C8+SAX)		• non-polar and cationic characteristics for improved analysis of acidic drugs of abuse and metabolites from biological matrices (including THC and its metabolites) and moderately polar to non-polar and ionized and charged compounds
Carbon		Hypercarb	RP	• 100% porous graphitic carbon material • **retention of extremely polar** compounds • recommended for **pesticides extraction** from different matrices
Polymeric polystyrene DVB	Unmod	SDVB	RP	• hydrophobic polystyrene-divinylbenzene copolymer; **highly retention of non-polar** compounds; **poor retention of polar** compounds
	mod	HDVB		• highly cross-linked polystyrene divinylbenzene copolymer (PS-DVB); hydrophobic polymeric sorbent offering 100% reversed phase interaction
	Functionalized	Retain PEP	Mixed-mode (RP, IE)	• polymeric PS-DVB **modified with urea functional groups** to give balanced retention of polar and non-polar analytes. • ideal for a wide range of applications, such as **drugs and metabolites in biological fluids**
		Retain-CX	Mixed-mode (NP, IE)	• polymeric PS-DVB **material partially functionalized with sulfonic acid groups** to give balanced retention of basic and non-polar analytes. • ideal for the retention of a wide range **of drugs of abuse, including basic and neutral drugs**
		Retain-AX		• polymeric PS-DVB **material partially functionalized with quaternary amine groups** to give balanced retention of acidic and non-polar analytes. • ideal for the **retention of THC and its metabolites**

sorbents available for consideration of the maximum efficiency in a MEPS extraction. This number will certainly increase with the growing interest in MEPS applications.

Silica-based sorbents were the first to be used in MEPS since they are particularly suitable for reversed-phase extractions as the interaction mechanisms are mainly based on hydrophobic interactions (Van der Waals forces) between the analytes and the extraction phase (reviewed in [17]) and secondary interactions such as hydrogen bonding and dipole–dipole forces (hydrophilic or polar interactions) (reviewed in [18]).

They are usually a spherical silica particle with a high pore size, typically 120 Å, which is larger than the conventional SPE pore sizes of 60–80 Å, favouring a high retention capability to MEPS particles since pore size is proportional to the surface area [11]. As the silica surface can be easily modified, different polymers functionalized with various moieties (amines, carboxylic acids, etc.) are attached to silica particles, creating final sorbents with hydrophobicities and retention abilities covering a wide range of interactions from hydrophobic to hydrophilic (C2 to C18, APS, SAX, SCX, etc.) (Figure 5). This occurs because silica itself is hydrophilic and alkaline instable, but the hydrocarbon chains make the surface hydrophobic. Disadvantages of silica sorbents include a narrow pH stability (typically within the range of 2 to 7.5), a poor surface contact with aqueous matrices resulting in low recoveries in extracting polar compounds and the presence of some residual silanol groups (reviewed in [17]).

More recently, carbon and polymeric sorbents have become available for MEPS. Carbon sorbents are not very popular with only a single product commercially available (Hypercarb, Thermo Fisher Scientific) (Table 1). These sorbents have great adsorption capacity and chemical, thermal and mechanical resistance, but a low specific surface area (100 $m^2 g^{-1}$). Moreover, some analytes show excessive or even irreversible retention which is completely undesirable for such a technique [17]. Polymeric sorbents are based on the poly (styrene-divinylbenzene) (PS-DVB) polymer which is robust with a high surface contact area obtained through the introduction of functional moieties or by increasing the specific surface area directly. Consequently, they possess an improved retention towards polar compounds as the number of points of interaction between the sorbent and the analyte is significantly increased [17-19]. For example, Fritz et al. (1995), have shown that the SPE recoveries for phenol were 6% with silica sorbent (C18), 91% with the polymeric sorbent PS–DVB and 100% with modified polymeric resins containing carbonyl groups [20]. Polymeric sorbents are also suitable for extractions over an extended pH range and also work at elevated temperatures. Their main disadvantage is a lower selectivity than silica or carbon sorbents. However, as polymeric resins are resistant to organic solvents, these solvents can be used to optimize the extraction conditions and improve selectivity, namely in the conditioning, washing and elution steps (reviewed in [16] and [21]).

Figure 5 shows the chemistries and vendor guidelines for selecting the best commercially available sorbents for each application. It should be noted that different vendor designations may correspond to the same sorbent and these recommendations are merely informative since suitability of sorbents is dependent on analyte hydrophobicity which has unclear boundaries which may be modulated (eg. pH adjustment). Additionally, MEPS is used in the simultaneous extraction of several compounds with different chemical properties, thus, a compromise must be established to achieve the best condition for the whole set of analytes. Finally, it is necessary to highlight that the range of applications of hydrophobic sorbents such as C8 and C18 is much higher than can be depicted from the Figure 5. Alternatively, sorbents as SCX (strong cation exchange) and SAX (strong anion exchange) have a more specific utilization, being more suitable for the extraction or fractionation of complex mixtures.

Unfortunately, unlike SPE that can be adapted to the user and application needs, MEPS BINs are not currently customizable because proprietary instruments are required to pack the sorbent. The reports in the literature (Table 2) that use special sorbents were exceptionally prepared and are not commercially available. These customized sorbents are most often molecular-imprinting polymers (MIPs) prepared for specific target analytes created to improve the analytical performance of the whole methodology.

5. Recent trends and applications

The advantages of MEPS and its suitability for sample preparation are clearly reflected in its applications. Table 2 presents the MEPS applications reported in the literature since 2010. It can be clearly observed that MEPS uses at least ten times less sorbent, sample volume and solvent volume than other extraction techniques, with similar or better analytical performance as indicated by equal or improved LODs. The first reports using MEPS date from almost a decade ago focussing on the extraction and characterization of pharmaceutical metabolites in anaesthetic drugs in plasma [5,15,95-98]. More recently, bioanalyses continue to be the main field of MEPS applications (reviewed in [7,99,100]), however, this technique has been extended for use in the environmental [101-103] and forensics fields, particularly in the screening of drugs of abuse [85,104]. Since 2010 the number of literature reports using MEPS, as well as the range of its applications, has increased considerably as presented in Table 2 which includes the characterization of the target analytes, sorbents and experimental conditions used in addition analytical results. Whenever possible, MEPS was compared with other extraction techniques, generally SPE, regarding its efficiency in the extraction of the same target analytes.

More recently, the electronic pipette eVol was made available to control the MEPS extraction procedure. This is a breakthrough for MEPS generalization as an extraction technique as eVol-MEPS coupling allows a tight control of experimental errors associated to the repetitive handling operations and between user variations such as flow speed which impacts the interaction between analytes and extraction phase.

Regarding the sorbents usage, it can be depicted from the Table 2 that C8 and C18 are the sorbents most often used which is related to their ability to retain a wide range of compounds with different properties in single sample extraction. For this same reason, the more recent and currently developing polymeric sorbents will certainly gain popularity over the generic C8 and C18 silica sorbents.

MEPS miniaturization has allowed for improved detection and quantification limits of several compounds, thus allowing for the use of UV detection in many instances thereby avoiding the expensive MS detection (Table 2). Certainly MEPS will become the standard for quantification of many compounds

Table 2. Comparative list of the literature reports using MEPS as sample preparation methodology since 2010, with works using other sample extraction approaches for the same target analytes. The analytical performance was normalised to a common unit to facilitate the comparison with other techniques. Legend: 1 *Experimental procedure: A – conditioning, B – sample volume loaded, C – washing, D – elution; manual MEPS unless otherwise indicated.* Abbreviations used: *ACN – acetonitrile, CD - coulometric detection, CLC-FLD – capillary liquid chromatography- fluorimetric detection, CMK-3 – carbon-based nanoporous sorbent, DCM – dichloromethane, EA – ethyl acetate, ESI-IMS – electrospray ionization-ion mobility spectrometry, FA – formic acid, GC-FID – gas chromatography coupled to flame ionization detector, GC-MS – gas chromatography-mass spectrometry, H_2O – water, HAc – acetic acid, Hex – hexane, HPLC-ED – high performance liquid chromatography coupled to electrochemical detection, HPLC-UV – high pressure liquid chromatography coupled to ultraviolet detector, IPA – isopropyl alcohol, LC-DAD – liquid chromatography with diode array detection, LC-MS/MS – liquid chromatography-tandem mass spectrometry, LC-UV – liquid chromatography coupled to ultraviolet detector, LLE – liquid-liquid extraction, LOD – limit of detection, LOQ – limit of quantification, LVI-deriv-GC-MS – large volume injection-in-port-derivatization-gas chromatography–mass spectrometry, MDA – Methylenedioxyamphetamine, MeOH – methanol, MISPE - Molecularly imprinted solid-phase extraction, NACE - Non-aqueous capillary electrophoresis, NH_3 – ammonia, NH_4OAc – ammonium acetate, NH_4OH – ammonium hydroxyl, Oasis HLB – hydrophilic-lipophilic-balanced reversed-phase sorbent, PBS – phosphate buffer solution, PDPA/CNT – polydiphenylamine reinforced with carbon nanotube, PNN - Polyaniline nanowires network, PP – protein precipitation, PTV-GC-MS – programmed temperature vaporizer–gas chromatography–mass spectrometry, PVI-GC-MS – large volume injection - gas chromatography-mass spectrometry, SPE – solid phase extraction, UHPLC-MS/MS – ultra high pressure liquid chromatography-tandem mass spectrometry, µPESI-MS/MS – microcapillar array electrospray ionization mass spectrometry, UPLC-PDA – ultra pressure liquid chromatography- photodiode array, VOCs - Volatile organic compounds.*

	Target analytes	Matrix	Stationary phase	Methodology[1]	LOD / LOQ (ng mL^{-1} by default)	Analytical method	Ref.
Life Science / Bioanalysis	8-oxodG and 5-HMUra	Urine	C8	**eVol-MEPS**: A- 100 µL MeOH + 100 µL FA 0.1%; B- 5x50 µL (10x diluted); D- 3×30 µL MeOH 20% in FA 0.1% (v/v)	5-HMUra: 0.05/0.23 8-oxodG: 4.0/130.0	LC-UV	[12]
	Steroids		C18	A- 100 µL MeOH + 100 µL H_2O; B- 3×100 µL; C- 100 µL H_2O + 80 µl Hex; D- 2×90 µL MeOH:EA (30:70, v/v)	5-15/---	GC-MS	[22]
	Non-polar heterocyclic amines			A- 250 µL MeOH + 250 µL H_2O; B- 100 µL; C- 100 µL MeOH 30% v/v; D- 100 µL MeOH 90% v/v	1.6-5.6 /5.5-18.7	CLC-FLD	[23]
	Cotinine		*SPE/LLE*	Two sequential SPE procedures (Florisil followed by OASIS HLB cartridge) and LLE; sample volume - 2.5 mL	0.7/2.4	GC-MS	[2]
			C8	A- 3×100 µL MeOH + 3×100 µL H_2O; B- 10×50 µL; C- 100 µL H_2O; D- 250 µL MeOH	0.8/2.7		
	Biogenic amines			A- 3×250 µL MeOH + 3×250 µL H_2O; B- 500 µL; D- 2×100 µL MeOH	5-50/---	LC-ED	[24]
	Verapamil, propranolol and metoprolol		C2, C8 and C18	A- 50 µL MeOH + 50 µL H_2O; B- 5×200 µL; C- 50 µL H_2O; D- 2×25 µL alkaline MeOH	---/---	µPESI-MS/MS	[25]
	Antipsychotic drugs	Plasma	C8+SCX	B - 100µL HAc 5% + 100µL MeOH 10% , C - 250uL; D- 200µL NH_4OH 5% in MeOH	0.2-1/---	GC-MS/MS	[26]
	BAM8-22 BAM22-8		C8	A- 100 µL MeOH + 100 µL H_2O; B- 3×50 µL; C- 50 µL MeOH 5% v/v; D- 40 µL 0.25% NH_4OH in MeOH 95% v/v	20/--- (nM)	LC-MS/MS	[27]
	Risperidone and 9-hydroxy-risperidone			A- 300 µL MeOH + 300 µL H_2O; B- 10×100 µL (urine and plasma) 10×50 µL (saliva); C- 200 µL H_2O + 200 µL MeOH 30% v/v (urine), 10% v/v (saliva and plasma); D- 500 µL MeOH	0.7-1.0/2-3	LC-UV	[28]
		Urine			1.5-2.0/4-6		
		Saliva			0.7-1.0/2-3		
		Plasma and saliva		A- 3×100 µL MeOH + 3×100 µL H_2O: B- 15×100 µL; C- 100 µL H_2O + 100 µL MeOH 5% v/v; D- 250 µL MeOH	0.17/0.5 (nM)	LC-CD	[29]
		Plasma	*SPE*	Bond Elut Certify SPE	0.5 /---		[30]
		Urine		mixed-mode sorbent (sample volume - 200 µL)	0.2 /--- 1.00 /---	LC-MS/MS	[31]
	Oxcarbazepine and its metabolites	Plasma and saliva	C18	A- 3×100 µL MeOH + 3×100 µL H_2O; B- 10×50 µL; C- 100 µL H_2O; D- 250 µL MeOH	0.015-0.037/0.050-0.125	LC-DAD	[32]
	Pravastatin and pravastatin lactone		C8	**eVol-MEPS**: A- 3×250 µL ACN + 3×250 µL NH_4OAc (0.01 M); B- 50 µL; C- 2×250 µL NH_4OAc+ 250 µL ACN:NH_4OAc (5:95, v/v); D- 100 µL ACN:NH_4OAc (90:10, v/v)	1.5/5 (nM)	LC-MS/MS	[33]
	Lidocaine	Saliva	C8	B- 100 µL; C- 100 µL 0.1% FA; D- 100 µL 0.25% NH_4OH in MeOH 60%	---/5		[34]
	Anaesthetics (lidocaine, ropivacaine and bupivacaine)	Plasma and urine	MIPs	B- 5x100 µL; C- 100 µL 0.1% FA; D- 200 µL 0.25% NH_4OH in MeOH 60%	1.0-5.0		[35]
		Blood	C18	**On-line MEPS**: A- 50 µL MeOH + 50 µL H_2O; B- 50 µL; C- 100 µL H_2O; D- 50 µL MeOH 60% (NH_4OH 0.25%); additional A- 3×250 µL of D + 3×250 µL H_2O	---/10 (nM)		[36]
	Clozapine and derivatives		C8	A- 3×100 µL MeOH + 3×100 µL H_2O; B- 10×150 µL; C- 100 µL H_2O + MeOH 5% v/v); D- 150 µL MeOH:ACN:PBS (20:16:64, v/v/v)	0.08/0.25	LC-CD	[37]
	Immunosuppressive drugs (Cyclosporine A, Tacrolimus, Sirolimus, and Everolimus)			**On-line MEPS**: A- 50 µL MeOH + 50 µL H_2O; B- 6×100 µL; C- 100 µL MeOH 5% v/v; D- 50 µL MeOH:IPA:ACN:H_2O (50:30:10:10, v/v/v /v)	0.15-0.9/0.5-3.0	LC-MS/MS	[38]
			PP/SPE	PP (MeOH/ ZnSO4 1.125M sample precipitation) + On-line SPE	1.15-5.6/1.8-15.4		[39]
	Atorvastatin and its metabolites	Serum	C8	A- 3×100 µL ACN + 3×100 µL NH_4OAc (0.1 M); B- 50 µL; C- 2×100 µL NH_4OAc (0.1 M) + ACN: NH_4OAc (15:85, v/v); D- 100 µL ACN:NH_4OAc (95:5, v/v)	0.03-0.33/0.08-0.66 (nM)		[40]
			SPE	Discovery DSC-18 sorbent (500 µL sample volume)	0.03-0.19/0.09-0.57 (nM)		[41]
	Psychotropic drugs		C8-SCX	A- 250 µL MeOH + 250 µL FA 0.1%; B- 5×50 µL; C- 4×50 µL FA 0.1%; D- 4×100 µL MeOH:H_2O:NH_3 (25%, 95:4:1, v/v/v)	(2.0-5.0 /8.0-17.0)x10	LC-DAD	[42]
			SPE	Bond Elut Certify (mixed bed, C8-SCX) sorbent (1 mL sample volume)	---/---		
	Antiepileptic drugs			Oasis HLB extraction cartridges (0,1 mL sample volume)	8-39/14-65		[43]

	Target analytes	Matrix	Stationary phase	Methodology[1]	LOD / LOQ (ng mL^{-1} by default)	Analytical method	Ref.
Life Science / Bioanalysis	Antiepileptic drugs	Blood and urine	C18	A- 100 µL MeOH + 100 µL H_2O; B- 10×50 µL; C- 50 µL H_2O; D- 30 µL MeOH	(1.8-3.6/5.6-10.8) $x10^{-3}$	GC-MS	[44]
				A- 100 µL MeOH + 100 µL H_2O; B- 10×50 µL; C- 50 µL H_2O; D- 35 µL MeOH	(4.0-59.3/13.2-195.6) $x10^{-2}$	LC-UV	[45]
		Plasma	*SPE*	Oasis HLB extraction cartridges (200 µL; 250 µL sample volume)	5/15		[46]
					25-100/70-300	LC-DAD	[47]
			SBSE	10-mm stir bars coated with 0.5 mm PDMS (1 mL sample volume)	(8.0-12.5) x10/---	LC-UV	[48]
			LLE	---	(6.0-8.0)x10/---		
	Remifentanil		*SPE*	Waters Oasis® SPE cartridges	0.18/0.5	LC-MS	[49]
			C8-SCX	A- 50 µL MeOH + 50 µL H_2O; B- 4×50 µL; C- 100 µL of 5% MeOH in 0.1% FA; D- 50 µL MeOH 90% v/v containing NH_4OH 3%	0.02/0.05	LC-MS/MS	[50]
	Antidepressants			A- 250 µL MeOH + 250 µL H_2O; B- 400 µL; C- 100 µL FA 0.1%; D-150 µL PBS:MeOH (55:45, v/v)	10-25/---	LC-UV	[51]
	Amiodarone and desethylamiodarone		C18	A- 3×100 µL MeOH:FA (95:5 v/v) + 2×100 µL H_2O; B- 100 µL; C- 100 µL H_2O; D - 100 µL MeOH:FA (95:5 v/v)	(2.0-10.0)x10/---	LC-DAD	[52]
			SPE	Oasis HLB extraction cartridges	1.9-2.7/2.5-7.5	LC-MS/MS	[53]
	Antibiotic drugs		C8 and C18	A- 100 µL MeOH 90% v/v + 100 µL FA 0.1%; B- 5×50 µL; C-2×100 µL FA 0.1 %; D- 250 µL MeOH	(2.9-3.9/8.6-9.2)x10	LC-UV	[54]
					0.141-0.134/0.381-0.425	LC-MS/MS	
	Phenolic acids			A- 2×100 µL MeOH + 2×100 µL H_2O; B- 5×100 µL; C- 100 µL acidified H_2O; D- 3×35 µL MeOH	---/---	GC-MS	[55]
	Quinolones	Groundwater and urine	---	---	---/0.091-0.315	LC-UV	[56]
Environment	Pesticides	Honey	C8+SCX	A- 250 µL MeOH + 250 µL H_2O, B- 3g; C- MeOH; D- 20 µL EA	---/2-10 (ng g^{-1})	GC-MS	[57]
		Water	PDPA/ CNT	A- MeOH + acetone +ACN + 4 mL H_2O; B- 7 mL; D- 200 µL Hex	(1.0-10.0)$x10^{-5}$/---		[58]
			PNN	A- 2 mL MeOH + 4 mL H_2O; B- 7 mL; D- 200 µL ACN	0.01-0.3/---		[59]
			Nanofiber	A- 2 mL MeOH + 4 mL H_2O; B- 7 mL; D- 100 µL DCM	0.04-0.1/---	GC-FID	[60]
	Aromatic amines		C18	**eVol-MEPS:** A- 500 µL EtAc + 500 µL H_2O; B- 8×500 µL; C- 500 µL H_2O; D- 100 µL EtAc	(6-350/17-1060)$x10^{-3}$	PTV-GC-MS	[61]
	Ciprofloxacin, norfloxacin, ofloxacin and flumequine		MIP-MEPS	**eVol-MEPS:** A- 15×100 µL MeOH:HAc (50:50, v/v) + 3×100 µL MeOH + 3×100 µL H_2O; B-8×100 µL; : 100 µL MeOH + 100 µL H_2O; D- 2×25 µL MeOH:HAc	(0.5-3.8)$x10^{-3}$/---	LC-MS/MS	[62]
			MISPE	Custom SPE (Sample volume - 500 µL)	(1.1-8.1)$x10^{-3}$/---		
	Phenoxyacid herbicides		Oasis HLB	A- 2×200 µL H_2O + 200 µL MeOH; B- 7×200 µL; C- 100 µL H_2O; D- 20 µL MeOH	(60-90)$x10^{-3}$/---	ESI-IMS	[63]
	Pharmaceutical residues		C18	**On-line MEPS:** A- 250 µL EA + 250 µL H_2O; B- 250 µL H_2O; C- 3×250 µL; D- 25 µL EtAc	3.0-110/---	PTV-GC-MS	[64]
	Estrogenic compounds		MIPs and C18	**eVol-MEPS:** A- 10×100 µL EA:DCM (70:30, v/v) +3×100 µL MeOH 3×100 µL H_2O; B- 800 µL; C- 2×100 µL H_2O; D- 50 µL EtAc:DCM (70:30, v/v)	(1.3-22)$x10^{-3}$/--- (MIP) (0.02-87)$x10^{-3}$/--- (C18)	LVI-deriv-GC–MS	[65]
	Polycyclic aromatic hydrocarbons (PAHs)		C8	**eVol-MEPS:** A- 50µL MeOH +50µL H_2O; B- 4mL; D- 50 µL MeOH	(0.5-1.6/1.8-6.0)$x10^{-3}$	GC-MS	[66]
			SPME	Polydimethylsiloxane (PDMS) fiber (Sample volume - 30 mL)	(40-100)$x10^{-3}$/---		[67]
			SBSE	10-mm stir bars coated with 0.5 mm PDMS (Sample volume - 10 mL)	(0.02-1.2)$x10^{-3}$/---		[68]
			C18	**On-line MEPS:** A- 80 µL MeOH + 100 µL H_2O; B- 40×50 µL; C- 100 µL H_2O; D- 50 µL MeOH	(0.8-8.2/2.5-27.5)$x10^{-3}$		[69]
			SPE	C18 cartridge (Sample volume - 50 mL)	(4.8-35.9/15.8-119.6)$x10^{-3}$		
	Organic pollutants	Wastewater and snow	C18	**eVol-MEPS:** A- 100 µL Hex:EtAc (50:50, v/v) + 3×100 µL MeOH + 3×100 µL H_2O; B- 800 µL; D- 75 µL Hex:EtAc (50:50, v/v)	(0.2-266/0.7-421.6)$x10^{-3}$	LVI-GC-MS	[70]
			SPE	Polar plus® C-18 bonded phase was used as SPE sorbent (Sample volume - 100 mL)	(0.2-736/0.2-2204.1)$x10^{-3}$		
	Macrocyclic musk fragrances	Wastewater	C18	**eVol-MEPS:** A- 25 µL EtAc + 25 µL H_2O; B- 40×100 µL, C- 2×25 µL H_2O; D- 50 µL EtAc	(5-10/10-25)$x10^{-3}$	LVI-GC-MC	[71]
	Parabens, triclosan and methyl triclosan		C18	**On-line MEPS:** A- 50 µL EtAc + 50 µL MeOH + 50 µL H_2O; B- 20×100 µL; C- 2×50 µL H_2O; D- 2×25 µL EtAc	0.02-0.59/---	GC-MS	[72]
	UV filters and polycyclic musk compounds		C8 and C18	**eVol-MEPS:** A- 2×50 µL MeOH + 2×50 µL H_2O; B- 8×100 µL; - 50 µL H_2O; D- 2×25 µL EtAc	34-96/---		[73]
	Chlorobenzenes		C18	**On-line MEPS:** A- 250 µL Hex:Acetone (1:1) + 250 µL H_2O; B- 7×250 µL; C- 250 µL H_2O + 7x250 µL air; D- 25 µL Hex:Acetone (1:1)	0.0006-0.02/0.0006-0.2		[74]
	Ionic liquids		Silica	**Custom MEPS:** A – NaOH 0.1M + H_2O; C- 5mL; D- 250 µL MeOH containing 5 mM CH_3COONH_4 + FA 0.2%	---/20-30	NACE	[75]
	Wine antioxidants	Wine	C8	A- 3 x 100 µL MeOH + 3 x 100 µL H_2O; B- 100 µL; C- 5×100 µL H_2O; D- 250 µL MeOH	(0.02-10/0.05-25)$x10^{-3}$		[76]
	L-ascorbic acid	Ice tea Fruit juices	Silica	C- 300 µL; D- 60 µL MeOH 90% v/v	7200/2400	LC-UV	[77]

	Target analytes	Matrix	Stationary phase	Methodology[1]	LOD / LOQ (ng mL^{-1} by default)	Analytical method	Ref.
Environment	Polyphenols	Wine	*SPE*	Oasis HLB extraction cartridges (Sample volume - 900 µL)	(0.6-58.0/ 1.9-19.4)x10	LC-PDA	[78]
			C8	A- 100 µL MeOH + 100 µL FA 0.1%; B- 5×250 µL; C- 100 µL FA 0.1%; D- 250 µL MeOH 95% v/v	(21.0/68.0)x10		[79]
	(E)-resveratrol				8.5-32.0x10/(2.8-108.0)x10		[80]
	Phenolic acids				(0.1-2.0/0.3-7.0)x10^2		[81]
	Flavonols				6.0-13.0/12.0-42.0		[82]
			SPE	Oasis HLB extraction cartridges (Sample volume - 900 µL)	(1.0-5.9/3.2-19.8)x10		
	VOCs and semi-VOCs		C8	A- 50 µL MeOH + 50 µL FA 0.1%; B- 10×100 µL; C- 100 µL FA 0.1%; D- 250 µL DCM	---	GC-MS	[83]
	Olive Biophenols	Rat plasma	CMK-3	A- 3 × 100 µL MeOH + 3 × 100 µL H_2O; B- 24x200 µL; C- 100 µL H_2O; D- 10x80 µL ACN	0.25-4.7/---	LC-UV	[84]
	Amphetamine and its met derivative	Hair	C18	**On-line MEPS:** A- 100 µL MeOH + 50 µL H_2O; B- 1-5 mg; C- 50 µL MeOH 20%; D- 50 µL MeOH	---/0.20 (ng mg^{-1})	GC-MS	[85]
			SPE/SPME	OASIS HCX extraction followed by SPME (10 mg of Sample)	0.2/--- (ng mg^{-1})		[86]
		blood	*MISPE*	SupelMIP-Amphetamine SPE cartridge	0.4-3/1.25-5		[87]
	MDA- and piperazine- derivatives	Urine	*SPE*	Polymeric reversed phase cartridges Strata X (Phenomenex) (Sample volume - 3 mL)	0.2-3/0.5-9	LC-MS/MS	[88]
	Piperazine derivatives		C8 and C18	A- 5x250 µL MeOH + 4×100 µL H_2O; B- 100 µL; C- 250 µL MeOH 10%; D- 50 µL MeOH	---/0.5x10^3	LC-DAD	[89]
			C8+SCX	A- 5x250 µL MeOH + 4×100 µL H_2O; B- 100 µL, C- 250 µL HAc 1% + 100 µL MeOH 10%, D- 50 µL NH4OH 5% in MeOH	(0.05-0.1/0.1)x10^3		[90]
	Methadone	Hair	*SPE/SPME*	OASIS HCX extraction followed by SPME (10 mg of Sample)	0.13/--- (ng mg^{-1})	GC-MS	[86]
		Blood	C18	A- 3×100 µL ACN + 3×100 µL H_2O; B- 100 µL H_2O + 50 µL ACN 5%; C- 50 µL; D- 2×250 µL ACN	1.2/4	LC-CD	[91]
			SPE	OASIS MCX SPE columns, (Sample volume – 1 mL)	173.64/526.17	GC-MS	[92]
	Opioids		C8	A- 3×100 µL ACN + 3×100 µL H_2O; B- 15×100 µL; c- 2×100 µL H_2O + 50 µL ACN 5%; D- 2×250 µL ACN	0.04-0.9/0.13-3	LC-CD	[93]
		Urine	PS-DBVB	**eVol-MEPS**: 50 µL MeOH + 2×50 µL H_2O; B- 2×50 µL; C- 2×50 µL H_2O; D- 2×50 µL MeOH with FA 0.1% (v/v)	2-5/---	MEPS-ESI-MS	[13]
	Salvinorin A		C18	**A- 5 × 0.25** µL **MeOH + 4 × 0.25** µL H_2O, C- 0.15 µL 8% 2-propanol in 2% FA, D- 50 µl MeOH:ACN (7:3, v/v)	5/---	GC-MS/MS	[94]

with the continuous improvement of sorbent selectivity and the development of novel applications. Another important feature in need of highlighting is the custom-made sorbents reported in several studies, especially those using MIPs prepared for specific analytes. Although this possibility was previously described by Abdel-Rehim [96], their use was for long time restricted. Moder et al. [62,65,70,73] used custom-made MIPS sorbents loaded in the MEPS BINs by SGE for the quantification of several water-based contaminants. This custom form of MEPS using MIPS, considered as MIMEPS in homology to MISPE (solid-phase extraction using MIPs as sorbents), allows a trace enrichment of very low abundance compounds and greatly improves MEPS specificity. However, the commercially available options are generic MIPs designed for classes of compounds rather than being analyte-specific, including fluoroquinolones [105] and amphetamines [87], among many others (reviewed [9]) which are only available in the SPE format (SupelMIP™ from Sigma-Aldrich Biotechnology LP., Inc.). Additionally, Candish et al. [13] recently reported the utilization of eVol-MEPS to infuse extracted analytes directly into the ESI-MS- (electrospray ionization) source, without any additional modifications allowing the possibility of analyzing trace analytes. Moreover, the same report described for the first time a modified MEPS syringe (named controlled directional flow (CDF) MEPS syringe) in which a parallel flow channel is used to insert solvents in the system without disturbing the sorbent with bound analytes allowing for sharp, concentrated sample bands delivered directly to the MS in very small volumes without need for elution optimization. In addition to MEPS miniaturization, several µSPE approaches are continuously being developed using different supports to accommodate small amounts of sorbents that will contact the sample solution. For example, µSPE approaches include needle trap microextraction [106], polypropylene membrane sheet envelopes [107] and the simplest µSPE in pipette tips [108]. The first two techniques, however, are not yet very reliable because extractions are user-dependent and therefore much more prone to experimental errors and variations. Moreover, the range of sorbents commercially available is very limited. The third technique using µSPE in pipette tips is more accurate since there are a high number of different sorbents available and multichannel electronic pipettes can be used to perform consistent and reliable microextractions which are not user-dependent.

6. Future trends

As exhibited in this review, given its potential applications and advantages, MIMEPS will certainly become more widely available for many applications including those related with food control and human health. In our view, as shown in Figure 1, MEPS is one of the best sample extraction techniques in terms of simplicity, speed, selectivity, sensitivity and is environmentally-friendly. Moreover, it allows for easy scale up to meet any high-throughput demands in regulated applications. However, MEPS can certainly be further improved. Starting with its high-throughput capacity, a major improvement in MEPS extraction via online methodologies would be the capacity to duplicate (triplicate, etc) its processing rate. A simple design to fulfil this requirement would be the inclusion of additional modules to control the XCHANGE® enabled analytical syringes, as presented in Figure 6. Additionally, there are specific applications in which very low abundant and low molecular weight analytes are present in complex matrices, usually biological matrices that need to be previously fractionated to allow the trace enrichment of the target analytes. For example, Xu et al. [109] recently described the use of RAM-MIPs followed by HPLC-UV detection of sulfonamides in bovine milk, allowing them to obtain the same analytical performance of reference methods using LC-MS/MS detection [110,111]. RAM (restricted access materials) are generic materials that can fractionate a biological sample into its protein matrix and analyte fraction by means of a molecular-weight cut-off mechanism. Using these RAM materials, the macromolecules are excluded since they interact only with the outer surface of the particle support coated with hydrophilic groups, while the smaller analytes are retained within the pores of the phase (reviewed in [112] and [6]). If these inner pores are filled with MIPs, then only the target analytes can be selectively retained by rinsing of the remaining contaminants. The investigation of new sorbent materials for use in sample extraction is a very dynamic field and certainly improved sorbent phases will be continuously described including multi-wall carbon nanotubes (MWCNT) (reviewed in [113]) and graphene [114-116].

Figure 6. Schematic representation of a prototype from an automatic MEPS device able to extract two samples simultaneously. The prototype possesses two MEPS operating arms that can be operated individually or together, duplicating the efficiency of the methodology.

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