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HIGHLIGHTS

- Microextraction approaches for bioanlysis.
- MIPs and graphene tablets for drug extraction from biological fluids.
- Microextraction by packed sorbent for bioanalytical applications.
- Liquid-phase microextraction based on supported liquid membranes compatible with biological fluids.
- High-performance materials as extractant phases.
- 3D printing in microextraction for bioanalytical applications.

Microextraction approaches for bioanalytical applications: An overview

Mohamed Abdel-Rehim[a,b*], Stig Pedersen-Bjergaard[c], Abbi Abdel-Rehim[d], Rafael Lucena[e], Mohammad Mahdi Moein[f], Soledad Cárdenas[e] and Manuel Miró[g]

[a]*Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, SE 17176 Solna, Sweden.*

[b]*Functional Materials Group, Department of Applied Physics, School of Engineering Sciences, KTH Royal Institute of Technology, SE-164 40 Stockholm, Sweden*

[c]*Department of Pharmacy, University of Oslo, P.O. Box 1068 Blindern, Oslo 0316, Norway.*

[d]*Faculty of Science and Engineering, University of Manchester, Manchester, UK.*

[e]*Departamento de Química Analítica, Instituto Universitario de Investigación en Química Fina y Nanoquímica, Universidad de Córdoba, Campus de Rabanales, Edificio Marie Curie, Córdoba, E-14071, Spain*

[f]*Department of Radiopharmacy, Karolinska University Hospital SE-17176 Solna, Sweden.*

[g]*FI-TRACE Group, Department of Chemistry, University of the Balearic Islands, Carretera de Valldemossa km 7.5, Palma de Mallorca, 07122, Spain*

Corresponding author: Prof. Mohamed Abdel-Rehim

Tel: +46 707108122

Email: Mohamed.abdel.rehim@ki.se; Mohamed.astra@gmail.com

Abstract

Biological samples are usually complex matrices due to the presence of proteins, salts and a variety of organic compounds with chemical properties similar to those of the target analytes. Therefore, sample preparation is often mandatory in order to isolate the analytes from troublesome matrices before instrumental analysis. Because the number of samples in drug development, doping analysis, forensic science, toxicological analysis, and preclinical and clinical assays is steadily increasing, novel high throughput sample preparation approaches are calling for. The key factors in this development are the miniaturization and the automation of the sample preparation approaches so as to cope with most of the twelve principles of green chemistry. In this review, recent trends in sample preparation and novel strategies will be discussed in detail with particular focus on sorptive and liquid-phase microextraction in bioanalysis. The actual applicability of selective sorbents is also considered. Additionally, the role of 3D printing in microextraction for bioanalytical methods will be pinpointed.

Key words: *Bioanalysis; Sample preparation; Microextraction approaches; Nanomaterials; 3D printing*

Contents

1. Introduction

Bioanalysis is a term used for analysis and quantification of analytes (e.g. drugs, metabolites) in biological samples (body fluids or tissues). Bioanalysis is currently involved in many research areas, such as the development of new drugs, forensic analysis, doping control, and identification of biomarkers. Bioanalysis is well established in the pharmaceutical industry to support drug discovery and drug development and it has an invaluable role in toxicokinetic , pharmacokinetic and pharmacodynamics studies.

A bioanalytical method contains three major elements; sample preparation, analyte separation, and detection. With respect to column separation and detection, liquid chromatography-tandem mass spectrometry (LC-MS/MS), and gas chromatography-mass spectrometry (GC-MS) to a lesser extent, are the methods of choice in bioanalysis due to their high selectivity and sensitivity. A sample preparation method is aimed at transferring a complex matrix to a suitable form before injection into the analytical instrument. The usefulness of a sample preparation method [1,2] is: (i) to remove interfering compounds, (ii) to eliminate ion suppression, and (iii) to pre-concentrate the analytes to improve the method's sensitivity.

Biological samples such as blood, plasma, and urine are complex matrices containing a large variety of compounds, from small molecules (e.g., salts, fats and phospholipids) to macromolecules (e.g., proteins), and thus an intensive sample treatment workflow is usually required before the bioanalysis[1,2]. In addition, the low concentration levels of target species (for example, in doping analysis, toxicology or forensic sciences) are increasingly demanding more sensitive analytical methods.

Sample treatment has evolved exponentially in the past two decades in the quest of improved bioanalytical methods. The development of enhanced extraction techniques [3–8], the application of high-performance materials such as sorbents or solvents [9] and the sample preparation automation (in recent years using cutting-edge technologies like 3D printing) [10–13] have been the main driving forces in this evolution. This review article surveys the trends in this field from the perspective of the authors who are leading international research groups working on the advancement in the sample preparation area.

2. Sorbent-based microextraction approaches

The miniaturization of sample preparation has been evolved rapidly over the last three decades. These developments resulted in innovative microextraction approaches , for instance, solid-phase microextraction (SPME)[14], stir-bar sorptive extraction (SBSE) [15] and microextraction by packed sorbent (MEPS) [3]. The introduction of SPME in the early 1990s by Pawliszyn became a historic step towards miniaturization of sorptive phases [16]. SPME and SBSE were initially aimed at the analysis of aqueous samples but both techniques were later used in bioanalysis. In the pharmaceutical industry high throughput and rugged bioanalytical methods are required, yet SPME and SBSE did show some drawbacks such as long extraction times, potential analyte carryover and fiber instability in the case of SPME [17,18]. Furthermore, SPME fibers could be readily used with GC-MS but not with LC-MS while the SBSE is not a fully automated approach. MEPS was developed as an alternative sample preparation approach for biological samples [19]. MEPS is a simple, fully automated, speedy, straightforward and green method, that is easily combined with LC analysis [20,21]. More recently polymeric tablets [MIP-Tabs and GO-Tabs] were introduced by one of the authors [22–24] as a promising sampling and sample preparation tools in bioanalysis. The polymeric tablets have several advantages such as facile fabrication and capability to process sample volumes at will (from nano to milliliters) for selective extraction and biological sample clean-up or enhanced enrichment factors.
MEPS, MIP-Tabs, and GO-Tabs will be discussed in the following two main sections.

2.1. Polymeric Tablets

The Polymeric Tablet is a new microextraction approach based on a polyethylene tablet coated with a thin layer of molecularly imprinted polymer (MIP-Tab), or graphene oxide (GO-Tab) for extraction and enrichment of analytes from plasma or saliva samples (Fig. 1) [22–24]. In these approaches, the surface of polyethylene is modified with sol-gel imprinted polymers or with a mixture of graphene oxide/polyethylene glycol. The as-prepared tablets are soaked/stirred in biological fluids (saliva or plasma) to adsorb the analytes of interest. Finally, the extracted analytes are eluted from the tablet surface and directly injected into the analytical instrument for quantification. The procedure for preparation of the polymeric tablet sorbents is not limited to molecular imprinting or graphene but can be extended to other chemistries, for instance, for the preparation of tablets modified with a layer of graphite or silica and organic derivatives thereof. Furthermore, the tablets can be prepared in different

sizes to be suitable for different applications such as biological, environmental and food analysis. Figure 1 shows photographs of the MIP and GO-Tabs and a schematic illustration of potential analytical applications. The tablets are chemically and mechanically stable.

2.1.1 Applications of tablets in bioanalysis

In an interesting study, the MIP-tablet in combination of LC-MS/MS was utilized for the extraction of amphetamine from human urine samples, and the limit of detection was 1.0 ng/mL. The method featured (i) trueness between 91.0% and 104.0% (ii) precision from 4.8% to 8.5% and, (iii) recovery over 80%. Also, the same tablet could be used for more than twenty extractions. Figure 2 shows a schematic illustration of the preparation of MIP tablets for further amphetamine extraction [23]. As it is shown in Table 1, the MIP-Tablet reduced the sample volume significantly compared to SPME and SBSE (>10 fold) and, minimized the extraction time.

Table 1

Comparison of the analytical performance characteristics between the MIP-Tab and microextraction methods in earlier studies on the determination of amphetamine in human urine.

	SPME	SBSE	DLLME	MEPS	MIP-Tab
Technique	LC-FL	LC-UV	LC-UV	Online-MS	LC-MS/MS
Sample volume (mL)	25	3.0	2.0	0.1	0.2
Linear range (ng/mL)	1000-10000	20-3000	10-3000	20-5000	5-5000
LOD (ng/mL)	250	6.6	8.0	6.0	1.0
LLOQ (ng/mL)	1000	20	10	20	5.0
Extraction time (min)	30-45	20	10	10	3.0
Precision (%RSD)	9-20	8.1	7.8	6.9-17.0	3.3-6.1

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In a further application, the MIP-Tablet was applied to the extraction of methadone from human plasma samples [22]. The extraction relative recovery was 80%, and the coefficient of determination (r^2) for the calibration curve (range: 5-2500 ng/mL) was over 0.999 (n=3), and the method precision (RSD) was between 4 and 8%. Using MIP-tablet, the extraction time was significantly decreased compared to SPME (decreased by 3 fold) and SBSE (decreased

by 9 fold). Additionally, the sample volume was reduced by 5-25 times compared to SPME and SBSE (Table 2).

Table 2

Comparison of LOD, LLOQ, extraction time and precision for the determination of methadone using the MIP-Tab method and compared to earlier studies using SPME and SBSE

Methadone	SPME	SBSE	MIP-Tab
Matrix	Plasma	Urine	Plasma
Sample volume (mL)	1.0	5.0	0.2
Method	GCMS	GCMS	LCMSMS
Linear range (ng/mL)	50-2000	*	5-5000
LOD (ng/mL)	9.0	*	1.0
LLOQ (ng/mL)	30	*	5.0
Extraction time (min)	30	90	10
Precision	5.0	*	4-8

* No reported data.

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In addition, GO-Tabs containing polyethylene glycol (PEG) were applied to the extraction of omeprazole from human saliva samples [24]. PEG was used to improve the interfacial adhesion between the GO nanoparticles and the polyethylene tablet surface. As a result, a layer of GO was immobilized on the surface and within the pores of the polyethylene scaffold. The method validation for omeprazole in saliva showed good relative recoveries and precision [24]. . The GO-Tabs could be reused for at least ten times. GO-Tabs are deemed advanced sorbent materials in sample preparation, with a straightforward synthetic protocol and facile usage along with readily applicability to a plethora of biological specimens. it can be applied in other complex solutions in the near future. In addition the polymeric tablets can be used as sampling tool for saliva.

2.2. MEPS

Microextraction by packed sorbent (MEPS) is a miniaturized and automated mode of SPE. MEPS is usually designed in the syringe format (lab-in-syringe) so the sorbent is either placed inside the syringe barrel or in a special container as a cartridge (Fig. 3). MEPS was developed

for facilitating high-throughput performance in bioanalysis. This approach allows fully automation of the analytical procedure and is, simple, inexpensive and reduces both handling times and sample volume. The value of MEPS is that the integration of the sample preparation with the analytical instrument is made possible. . Another key aspect of MEPS within the framework of green chemistry is that the solvent volume used for the elution of the analytes is small (10-50 µL) and can be injected at-line or on-line into GC/LC instruments without further adjustments [25,26].

In brief, the sample is withdrawn through the syringe solid bed via an autosampler to adsorb the analytes of interest. The solid phase is then washed once or more with a proper washing solution to remove the proteins and other potentially interfering compounds from the biological sample. The final step is the elution of the analytes by a suitable organic solvent (10–50 µL). The MEPS cartridge bed can be packed or coated to provide selective and suitable sampling conditions. It is well known that the sorbent selectivity is an important issue to get a clean extract and a good recovery. A broad variety of sorbents can be used in MEPS, such silica-based (C2, C8, C18), strong cation exchanger (SCX) with sulfonic acid bonded silica, HILIC, polystyrene–divinylbenzene copolymer (PS-DVB), carbon nanomaterial (reduced graphene, graphene oxide), molecular imprinted polymers (MIPs), organic monolithic sorbent, immunosorbents [20,27,28], just to name a few. The chemical moieties of sorbents used in MEPS are schematically shown in Fig. 4.The main asset of MEPS as compared to polymeric tablets and other sorptive microextraction approaches is that a single cartridge could be reused for more than 100 times for plasma or urine samples and more than 400 times for aqueous samples. In addition, MEPS is a flexible technique alike MIP/GO-Tabs and can handle both small sample volumes (10 µL) as well as large volumes (1000 µL).

2.2.1. Extraction protocol

MEPS extraction process consists of four steps that resemble any SPE or sorptive microextraction protocol [25,26]: (i) sample loading, (ii) sample washing, (iii) elution, and (iv) sorbent post-cleaning for cartridge reusing (Fig. 3).

Sample loading

In this step, the sample (usually 50-250 µL) is loaded through the sorbent, once or several-fold depending on the analyte concentration and in particular on the pre-concentration factor that is sought. Generally, four sample-loadings (4 × 100 µL) are recommended for better

performance. The speed of the plunger movement is also a crucial parameter in MEPS, and it can be optimized within the range of 10 and 20 µL per second.

Washing step

The washing step eliminates undesired interfering compounds, and this can be done by water or a mixture of organic solvents/water. The analyte losses at the washing step can be minimized by using an optimized percentage of organic solvent in the washing solution. It is known that there is a direct relationship between analyte breakthrough and the solvent percentage in the washing solution. The use of 5-10% methanol in water (2 × 100 µL) has been recommended as a standard washing solution in MEPS protocols.

Elution step

The elution of the desired analyte(s) is the final step, and this can be performed by using a pure solvent (methanol) or a mix (methanol/acetonitrile/water). In order to obtain high analyte recoveries, the pH of the eluent plays an important role (control charged/uncharged analyte). In addition, an effective elution solution should retrieve the analyte with the smallest possible volume. About 20-50 µL of a proper solvent can elute the analyte from the solid phase by a single step (50 µL directly) or multiple steps (2 × 25 µL).

Post-cleaning step

Carry-over is a well-known weakness in bioanalysis sample preparation methods and thus the implementation of an adequate cleaning step after each extraction protocol is a demanding issue. The cleaning solutions are categorized into two groups; weak and strong rinsing solutions. A weak washing solution can be, for instance, water (80-90%) with 0.1% formic acid or 10-20% of an organic solvent (viz., methanol or isopropanol). In some cases, a strong washing solution is needed, and in such circumstances, 0.2% ammonium hydroxide or 0.2% formic acid in pure methanol or acetonitrile (or a mixture of both) is recommended.

2.2.2. Recent MEPS applications in bioanalysis

Numerous types of drugs serving as local anesthetics, anticancer, beta-blockers, antidepressants, immunosuppressive, neurotransmitters, opiates, cardiac drugs, antibiotics and antipsychotics have been extracted from a variety of biological samples using MEPS [2][25,26,35–44,27,45–54,28–34][55–62][63–65][66–75][76–79][80–88]. Some recent

applications of MEPS in bioanalysis (published between 2017 and 2019) are summarized in Table 3.

Table 3

Recent MEPS applications in bioanalysis (2017-2019)

Analyte	Sorbent	Matrix	Anal. method	Ref
Psychoactive substances	C8/SCX	Saliva	UHPLC–MS/MS	[45]
THC and metabolites		Plasma	GC-MS	[46]
Zonisamide	C18	Plasma	LC-UV	[47]
Microbial Metabolites	C18	Blood	GC-MS	[48]
Trans,trans-muconic acid	SAX	Urine	LC-UV	[55]
trans,trans-muconic acid	MIPs	Urine	LC-UV	[56]
Meropenem, levofloxacin, linezolid	C18	Plasma	UHPLC-PDA	[57]
Drugs of abuse	C8/SCX	Plasma	UHPLC-UV	[58]
Statins	C18	Plasma	UHPLC-MS/MS	[59]
Carbamazepine, naproxen,dexamethasone	IPN Polystyrene Sol-Gel	Urine	LC-UV	[60]
Cocaine and metabolites	C8/SCX	Urine	GC-MS	[61]
AZD6118	C8/SCX	Dog plasma	LC-MS/MS	[62]
Fluoxetine, norfluoxetine, paroxetine	C8	Plasma	LC-FLD	[63]
Lamotrigine	C18	Plasma, saliva	LC-DAD	[64]
Dexamethasone disodium, phosphate dexamethasone	C2, C8, C18	Aqueous humor of patients with uveitis	LC-MS/MS	[65]
Azole drugs	C18	Plasma, urine	LC-DAD	[66]
Lidocaine, prilocaine, ropivacaine	R. graphene	Plasma, saliva	LC-MS/MS	[27]
Pyrethroid, metabolites	C18	Urine	GC-MS	[67]
Quercetin, metabolites	RAX	Rat plasma	UHPLC-MS/MS	[68]
31 new psychoactive substances	C8/SCX	Saliva	UHPLC-MS/MS	[69]
Mandelic acid	MIPs	Urine	LC-UV	[70]
Tetracyclines	Graphene-based sorbents	Milk	CE-UV	[71]
Organophosphorous pesticides	C18	Blood	GC-MS/MS	[72]
Nitroexplosives	C18	Bio fluids	GC-MS	[73]
Dinotefuran	MIPs	Artificial saliva	LC–DAD	[74]
Beta blocker	C18	Urine	LC-FLD	[75]
Local anesthetics	Graphene oxide	Plasma	LC-MS/MS	[28]
Methadone, EDDP	C18	Hair	GC-MS/MS	[76]
Levofloxacin	MIPs	Plasma	UHPLC-UV	[77]

New psychoactive substances	C18	Saliva	GC-MS	[78]
Amphetamine-type stimulants	C18	Urine	GC-MS	[79]
Asthma biomarkers	RAX	Urine	UHPLC-PDA	[80]
Antidepressants	C8/SCX	Urine	UHPLC-PDA	[81]
Mandelic acid	Hybrid metal org. frameworks	Urine	LC-UV	[82]
Ciprofloxacin, enrofloxacin, marbofloxacin	C18	Bovine urine, milk and serum	UHPLC-PDA	[83]
Phenylcarboxylic acid-type microbial metabolites	C18	Blood, serum	GC-MS	[84]
Nitrofurantoin	Green sorbent: Chlorella vulgaris microalgae	Urine	UV-VIS	[85]
Opiates	C8/SCX	Blood	GC-MS/MS	[86]
Antisense oligonucleotide	C8, C18	Plasma	LC-UV	[87]
Lamotrigine (garcinia cambogia)	C18	Rat plasma	LC-DAD	[88]

3. Liquid-based microextraction approaches

Since the introduction of single-drop microextraction (SDME) in 1996 [89][90], liquid-based microextraction (LPME) approaches have been a very active area of research. While all efforts initially were based on SDME, different liquid-phase based alternatives have evolved over more than two decades. These include among others hollow-fibre LPME (HF-LPME) [91], parallel artificial liquid membrane extraction (PALME or 96-well LPME) [92], electromembrane extraction (EME) [93], solvent bar microextraction (SBME) [94], dispersive liquid-liquid microextraction (DLLME) [95] and solidified floating organic drop microextraction [96], and liquid-liquid extraction in micro-chip or millifluidic devices [97]. An overview of the different LPME techniques and their classification has been published recently [98]. The number of articles published on each technique in 2018 is summarized in Table 4 to illustrate the level of activity (Scopus). Major incentives for the development of liquid-based microextraction have been reduction of organic solvent consumption (green chemistry), pre-concentration, scaling of sample preparation to modern analytical instrumentation, improved sample clean up, enhanced selectivity, and automation.

Hollow fibre LPME (HF-LPME) has been explored extensively for bioanalytical applications for two decades. Therefore, only selected articles published in 2018 and 2019 are herein discussed. Articles before 2018 have been reviewed previously [7,8,99]. In HF-LPME target analytes are extracted from the biological sample through a thin film of organic solvent immobilized in the pores in the wall of a porous hollow fibre, and into a few microlitres of acceptor solution in the lumen of the hollow fibre. The thin film of organic solvent is termed supported liquid membrane (SLM), it comprises a few microlitres of organic solvent immiscible with water, and is held in the pores by capillary forces. The acceptor solution is either aqueous or organic. In the former case, HF-LPME is performed in a three-phase system for basic and acidic analytes (many pharmaceuticals are basic compounds). Alternatively, the acceptor is organic for two-phase HF-LPME of neutral analytes.

Recent bioanalytical applications of HF-LPME include extraction of omeprazole, pantoprazole, and lansoprazole (small molecule pharmaceuticals) from human plasma [100]. Plasma samples were buffered to pH 5.0 and 5% (w/v) NaCl was added for optimal extraction, 1-octanol was used as SLM, and borate buffer pH 10.0 was used as acceptor solution. HF-LPME was conducted for 15 minutes with stirring at 750 rpm. The acceptor solutions were analysed by liquid chromatography with UV-detection (LC-UV). The entire

method was validated in the concentration range 0.2-2.0 µg/mL, and data complied with the recommendations set by US FDA for bioanalytical methods.

Bioanalytical applications of HF-LPME are not limited to organic compounds. Thus, in one recent article, lead was extracted from human urine and blood [101]. In this work, the SLM comprised oleic acid containing dicyclohexyl-18-crone-6 to facilitate the efficient transfer of lead, and the acceptor solution was analysed by graphite furnace atomic absorption spectrometry. Recent bioanalytical applications of HF-LPME also report on pharmacokinetic studies of nortriptyline [102], determination of Traditional Chinese medicine main active compounds in blood samples [103], and vanillylmandelic acid (VMA) in human urine [104]. VMA is a clinical biomarker, and the final detection was by voltammetry. The examples above are illustrative for HF-LPME related research; HF-LPME is a general concept, and it is explored for a broad spectrum of applications in areas such as pharmaceutical analysis, clinical analysis, and occupational health. In most bioanalytical applications, HF-LPME is combined with LC, but combinations with electrochemical and spectroscopic techniques are also frequent. Recent HF-LPME research related to bioanalysis also include more fundamental studies, focused on extraction of analytes with very weak base properties [105], three-phase HF-LPME with organic solvents as acceptor phase [106], enhanced mass transfer into a cetyl-alcohol reinforced SLM [107], and use of molecularly imprinted polymer recognition in HF-LPME [108].

The hollow fibres used for HF-LPME are commercially available and can be purchased in bundles. However, there are currently no commercial devices for HF-LPME, and therefore the extraction equipment using a small piece of hollow fibre cut from the bundle, has to be prepared manually for each sample. In 2013, however, commercially available filter plates in 96-well configuration were introduced as an alternative to HF-LPME [109]. In this concept, termed parallel artificial liquid membrane extraction (PALME) or 96-well LPME, a flat membrane filter was used as support for the SLM rather than a hollow fibre. Several papers have been published on 96-well LPME recently, using commercially available 96-well plates. In one article, 96-well LPME was combined with LC-MS/MS for therapeutic monitoring of psychoactive pharmaceuticals [109]. In this paper, all liquid handling was performed with a semi-automated 96-channel pipette system, and venlafaxine, o-desmethylvenlafaxine, citalopram, norfluoxetine, fluvoxamine, fluoxetine, sertraline, and paroxetine were determined in human patient samples. Data on precision, accuracy, and linearity complied with the recommendations of US FDA. In follow-up articles, 96-well LPME was developed

for extraction of designer benzodiazepines, benzodiazepines, and Z-hypnotics in whole blood [110], and for extraction from dried blood spots [111]. In the former article [109], 96-well LPME was combined with UHPLC-MS/MS and 20 illegal drugs were included in the method. Extractions were from 100 µL of whole blood, and detection limits were in the range 0.10 to 5.0 ng/mL. In the latter article [110], dried blood spots (DBS) were placed in the sample plate and 10 mM NaOH solution was added. During 96-well LPME, target drugs from the DBSs were desorbed and subsequently extracted into acceptor solution (20 mM HCOOH). After 60 minutes of extraction, acceptor solutions were analysed by LC-MS/MS. Since 96-well LPME is performed with commercial plates, this concept is mature for routine implementation.

Similar to HF-LPME, there is currently considerable activity in the field of electromembrane extraction (EME). EME is similar to HF-LPME in the sense that target analytes are extracted across a SLM and into acceptor solution. However, while mass transfer in HF-LPME is based on diffusion, mass transfer in EME is by electrokinetic migration. Thus, electrodes are located in the sample and acceptor solution, and are coupled to an external power supply. For extraction of basic analytes, the negatively charged electrode (cathode) is located in the acceptor solution, while the electrical field is reversed for the extraction of acidic analytes. The advantages of EME as compared to HF-LPME include faster mass transfer and the option for selectivity tuning by the external electrical field. EME has been reviewed several times in recent years [6], and only a few articles from 2018 and 2019 are discussed in the following.

Since the introduction in 2006 [6], EME has been explored extensively for the extraction of pharmaceuticals from biological fluids. Pharmaceutical applications have also been published recently, including extraction of triptorelin in rabbit plasma [112], valproic acid in human plasma [113], non-steroidal anti-inflammatory drugs from urine [114], and benzodiazepines from human plasma [115]. New forensic and clinical applications of EME have also been reported recently, such as extraction of 37 different drugs of abuse (mainly benzodiazepines and amphetamines) from human plasma [116], and extraction of polar endogenous metabolites from plasma [117]. In the latter article, 45 polar basic metabolites (log P from −5.7 to 1.5) from various biochemical families were extracted successfully after careful optimization of the SLM and acceptor solution. This paper represents an important step forward for EME, since the system extracted even very polar analytes.

In addition to biomedical applications, there is currently substantial activity related to the fundamental development of EME. Recently, EME was performed without any organic

solvent [118]. In this system, small peptides were extracted into a polyvinylidene difluoride (PVDF) membrane by electrokinetic migration, and subsequently the neuropeptides were measured by matrix-assisted laser desorption mass spectrometry (MALDI-MS). Development of free liquid membranes (not immobilized in a porous membrane) [119], integration of EME into micro-chip systems [120], and 3D printed micro-devices for EME [121] are additional advances reported very recently. EME shows great potential, and is expected to be an active area of research in the near future.

Solvent-bar microextraction (SBME) is close to HF-LPME in terms of principles, operation, and performance. SBME is based on the use of a small piece of hollow fibre holding the SLM and the acceptor solution (solvent bar). The solvent bar is closed in both ends, and is tumbling freely in the sample solution during extraction. Because the acceptor solution is protected by a SLM, the solvent bar is compatible with complex biological fluids, and SBME is often reported for bioanalytical applications. Most of this can be found in recent reviews on SBME [5], and only a few recent papers are summarized here. For bioanalytical applications, SBME in three-phase mode has among others been reported recently for extraction of ephedrine [122] and sarcosine [123] from human urine samples. Extraction of polar analytes is also challenging in SBME, and has been reported recently based on carrier-mediated transfer across the SLM [124] and by using pure tris(2-ethylhexyl) phosphate as SLM solvent [125]. Method optimization in SBME involving several operational parameters and multivariate optimization has been reported [126,127]. Although the consumption of organic solvent is a few microlitres per sample, efforts to use green solvents have been emphasized [128].

As illustrated in Table 4, there is substantial activity in the areas of SDME, DLLME, and solidified floating organic drop microextraction. Especially with DLLME, the current number of research papers per year is very high. Most of this work is within environmental applications, and only very few articles report on direct extraction from complex biological samples. The reason for this is that the microlitre volumes of organic solvent used for extraction is in direct contact with the sample during SDME and DLLME, and the solvent may emulsify and be lost into the biological fluid. From the authors' point of view, LPME has great potential in bioanalysis, and more research in this direction is expected in the near future. While SDME and DLLME are particularly suited for water samples, the membrane-based counterparts (HF-LPME, 96-well LPME, EME, and SBME) are deemed more appropriate for handling complex biological samples. For these approaches, there is a quest for the introduction of commercial products and the development of rugged

mechanized/automatic setups. Work is currently in progress in these two directions. Development of applications, for which standard methods are inappropriate, should also be prioritized to facilitate the implementation of liquid-based microextraction in bioanalysis.

Table 4

Number of liquid-based microextraction articles indexed by Scopus in 2018

	Bioanalysis applications	Other applications	Total
Hollow-fibre liquid-phase microextraction	16	30	46
Electromembrane extraction	15	19	34
Solvent-bar microextraction	9	15	24
Single-drop microextraction	2	29	31
Dispersive liquid-liquid microextraction	6	317	323
Solidified floating drop microextraction	2	12	14

4. High-performance materials as extractant phases

The analytical performance of the extractant phases becomes crucial when their amount/volume is reduced due to the downscaling of the traditional extraction approaches. The performance includes not only the extraction capacity but also the selectivity and feasibility (for example, easiness of derivatization, handling or dispersion). This section provides a general overview of the potential of high-performance and non-conventional sorptive and liquid materials used for bioanalytical sample preparation.

4.1 Novel sorbents

Although silica-based and polymeric microparticles are still employed in classical and miniaturized extraction techniques, new sorbents are being continuously proposed [9, 128].

4.1.1 Nanomaterials (NMs)

The nanometric size of these materials provides an exceptional increase of the specific superfice area, which positively affects to both the thermodynamics and kinetics of the extraction [130]. The various types of NMs and their role as sorbents for sample preparation in bioanalysis has been already reviewed [9], and therefore, only some recent approaches will be commented on.

Nanometric sorbents exhibit a higher packing density than micrometric particles which hinders a smooth sample flow through. This aspect becomes even more critical when carbon nanoparticles are used because they tend to aggregate. To avoid this problem, NMs can be embedded in a support or directly dispersed in the sample. As it was previously indicated, graphene oxide tablets, obtained by chemically bonding of carbon-based NM to in lab-made polyethylene disks, have been successfully applied to the determination of drugs in saliva with absolute extraction recoveries as high as 90 % [24]. If the sample is intended to flow through the sorbent, thus favouring the interaction with the target analytes, the NMs can be embedded in a monolithic rod [131].

The aggregation tendency of carbon NMS, however, can be exploited when carbon nanohorns are employed because they tend to form ordered and stable aggregates called dahlia. These dahlias can be further self-assembled into superior porousstructures, which can be deposited over paper [132] thus generating thin-film sorptive phases as those shown in Figure 5. The paper-based phases can be easily adapted to pipette tip extraction in a disposable format, making sample processing easier.

Inorganic NMs involve metal and metal oxides nanoparticles. Among them, magnetic nanoparticles have found particular application in sample treatment in the bioanalytical context as recently overviewed [129].

4.1.2 Synthetic polymers

Although particulate polymers are used in standard SPE and SPME procedures other formats like electrospun fibers, fabric phases (FPs) or polymeric nanocomposites have been recently harnessed to the analysis of complex biological samples

Electrospun fibers are easily obtained starting from a polymeric precursor, and they can be used as non-packed fibers or as a polymeric mat (membrane) [133,134]. Polystyrene electrospun fibers have been for example used for the extraction of dexamethasone and betamethasone from urine [135]. Composite fibers [136], obtained by the dispersion of metal organic frameworks in the polymeric precursor, have also been proposed for the extraction of some drugs and metabolites from human plasma.

Fabric phases (FPs) [137] are obtained by the sol-gel coating of a fabric that produces flat materials of high porosity and sorption capacity. FPs have been used for the extraction of

drugs [138] and pollutants [139] from biological samples, and they have been recently suggested as promising sorptive phases in metabolomic studies [140].

The polymers can also be combined with NMs to form polymeric nanocomposites [141].

4.1.3 Natural polymers

Environmental protection and the design of green materials is one of the driving forces of the sample treatment evolution. In the last years, this environmental concern has been fostered by the proposal of new sorbents of natural origin, including cellulosic or lignocellulosic materials.

Vakh et al. have recently reported the synthesis of cotton disks containing cation exchange bead microparticles (the actual sorbent) for the isolation of ofloxacin from serum and urine samples [142]. However, if the raw cotton is intended to be used as a sorptive phase, some chemical moieties must be introduced in the surface to promote the interaction with the analytes. Pyrolysis is the most straightforward modification process as it is reagentless, only requiring the heating of cotton at high temperatures in an inert atmosphere. Following this protocol carbon fibers are generated and this environmentally friendly material has been proven most appropriate for the extraction of chlorophenols from urine samples [143]. Paper, another cellulosic material, has also been proposed as a sorptive phase in bioanalysis [144,145]. Preliminary bioanalytical applications of other natural sorbents like cork [146] and bract [147] have been just reported.

Natural polymers can also be used for enhancing the selectivity of the microextraction procedures, which is a crucial property in those approaches with minute amount of sorptive phase. In addition to the consolidated molecularly imprinted polymer technology [148], some natural biopolymers like antibodies have been extensively used. Antibodies, however, must be *in vivo* produced and they can be only obtained towards molecules that induce an immunogenic response. These potential biomaterials have been complemented by other biomolecules like aptamers (nucleic acids) [149,150], proteins (selected by reverse docking) [151] and enzymes [152].

4.2 Non-conventional solvents

Although classical solvents are still useful in the bioanalytical context [153], the performance of new alternatives with unique properties and green chemical properties is in constant

scrutiny. The potential of ionic liquids, which have been consolidated as extractive phases in the last decade, is now supplemented with other solvents like switchable and deep eutectic solvents.

4.2.1 Ionic liquids

Ionic liquids (ILs) are a broad class of semi-organic salts, which are liquids in a temperature range from 200-700 ºC even when they are entirely composed of ions. Although ILs are well-established solvents in the microextraction context[154], some innovative approaches, like magnetomotive ionic liquids, have been recently developed. These solvents, usually known as magnetic ILs (MILs), respond to an external magnetic field thanks to the incorporation of a paramagnetic component (typically a transition metal or lanthanide ion) within their structure. Magnetic ILs find application in diverse areas of analytical sciences [155] such as sample preparation [156], and especially in DLPME as demonstrated by Anderson's team. For example, MIL-based DLPME have been used for the rapid isolation of estrogens from urine [157]. Also, MILs can be easily adapted to SDME just by using a magnetic rod to support the solvent during the extraction. Recently, the use of magnetic rods fixed to the pins of a commercial extraction blade for 96-well plate system using conventional pipette tips has been proposed for high-throughput extraction and simultaneous processing of multiple samples [158]. This strategy, applied initially to environmental samples, could be transferred to the bioanalytical context.

MILs can be used for the isolation of compounds of different physicochemical properties. However, in bioanalysis, MILs have found a particular application for the extraction of DNA from complex samples like cell lysates [159]. The selectivity of the extraction (primarily related to the length of the DNA strain to be extracted) directly depends on the type of MIL, but if the MIL is well chosen the selective extraction of DNA in the presence of other biomolecules like proteins is feasible. Also, DNA extraction by MILs preserves the nucleic acids from being degraded by the nucleases typically occurring in biological samples [160]. Anderson et al. have also made DNA extraction using MILs compatible with the polymerase chain reaction (PCR) by the design of a buffer that mitigate the negative effect of MIL over the PCR [161].

4.2.2 Deep eutectic solvents

Deep eutectic solvents (DES) are a new class of solvents that share with ILs some properties but are different enough to be considered a different material. Moreover, DES are less toxic than ILs and their preparation is cheaper and easier. DES are synthesized by the combination of a solid H-bond acceptor (HBA) and an H-bond donor (HBD), which results in a substance with a lower melting point than the individual precursors. HBA are typically quaternary ammonium salts with the choline moiety or chloride counter ion usually acting as hydrogen acceptors while HBD can be composed of carboxylic acids, secondary or tertiary amines and (poly)alcohols. DES are considered eco-friendlier than IL, and they can also be biocompatible. This aspect is particularly marked in natural DES, which are built using natural precursors such as amino acids, sugars, organic acids, or choline derivatives [162]. DES have clear potential in analytical sciences [163], and their solvent related properties can be exploited for sample treatment [164].

DES have been proposed as the acceptor phase in HF-LPME for the extraction of steroidal hormones from urine and plasma [165], providing enrichment factors as high as 421. Also, Shemirani *et al.* reported the combination of DES with magnetic carbon nanotubes to fabricate a magnetic composite solvent that can be applied in headspace SDME [166] following a similar approach to that described above for MILs. This composite was harnessed to the extraction of volatile aromatic hydrocarbons from urine.

DES can also be used in DLLME. If the DES is not hydrophobic enough, an emulsifier must be added to induce a biphasic system. The efficient extraction (enrichment factors, in the range from 25-40) of several antidepressants from plasma samples has been reported by Asghari and co-workers following this workflow [167]. The same research group has applied a relatively hydrophobic DES, thus avoiding the use of an emulsifier, for the extraction (enrichment factors in the range 47-50) of amphetamine and methamphetamine from plasma samples[168].

It has been demonstrated that , the analytes themselves can participate in the DES formation. For example, the extraction of some acidic anti-inflammatory drugs has been accomplished by the H-bonding between menthol (HBA) and the oxygen of the carboxylic group of the analytes[169].

The versatility of DES in bioanalysis is demonstrated by the fact that they have been reported as solvents for the extraction of compounds as diverse as DNA [170] or Cr (VI) [171] in biological specimens.

4.2.3 Switchable solvents

The term switchable solvent (SS) refers to those solvents able to shift between two states of different properties in response to an external stimulus. Jessop *et al.* described the potential of these solvents in 2008 in industrial processes [172] while Lasarte *et al.* adapted SS to the analytical sample preparation context in 2014 [173]. The use of SS is an excellent alternative to conventional solvents under the DLLME format because the use of a disperser solvent is here avoided. The first SS proposed was CO_2-responsive in such a way that the SS becomes miscible with water at a high concentration of CO_2, being the process completely reversible when the solution was purged with N_2. This behaviour, which could be exploited for homogeneous extraction, is difficult to miniaturize. The volatile character of some SS causes losses of the extractant phase during the N_2 purge, and these losses are critical when the volume of SS is meagre due to the miniaturization of the extraction. This problem can be avoided if the switch between both states of opposite polarity is done by a simple pH change.

Secondary and tertiary amines have been successfully applied as SS for the extraction of drugs [174–176] from urine and plasma because most of them are basic compounds with low polarity under alkaline conditions. This aspect assures the efficient transfer of the analytes during the formation of the biphasic system which is the moment at which the extraction takes place. However, the extraction of charged species can also be achieved by the simple addition of an ion-pairing agent to the sample [177]. The characteristics of amine-based SS make them compatible with both liquid and gas chromatography, thus expanding the application scope of SS.

Fatty acids also have a switchable behaviour, although in this case, phase separation is achieved at acidic conditions. Vakh *et al.* designed a fully automated system to implement effervescence extraction in combination with fatty-acids SS for the determination of ofloxacin in human urine [178]. An excess of Na_2CO_3 is used to induce the solubilization of the SS in the sample while the addition of sulphuric acid removes the carbonate in the form of CO_2. The release of gas, which is the base of effervescence extraction [179], enhances the mass transfer and, in this case, it is also mandatory to generate the biphasic system.

5. Role of 3D printing in microextraction for bioanalytical applications

Additive manufacturing, also called 3D printing, has made tremendous strides over the past couple of years as an emerging industrial technology and the last core element of the so-called

Industry 4.0 because of the feasibility of in-house creation and transfer of computer-aid-design (CAD) or Standard Tessellation Language (STL.) files across institutions through the internet [180]. Interest of 3D printing has been also grown in the field of bioanalytical research to leverage the unique features that this technology offers in the field of miniaturization [181], (bio)sensing [182], sample preparation [183] and separation science [184]. Readers are referred to a number of comprehensive and authoritative reviews illustrating the opportunities of 3D printed devices for bioanalytical applications [10–13]. Fuse deposition modelling (FDM), stereolitography (SLA), digital light processing (DLP) and photopolymer inkjet printing (PIP) using photopolymerized resins or filaments are the four main 3D printing approaches available in custom-grade printers that have paved the way for fast prototyping and fabrication of enabling platforms [180,181,185]. The wide variety of printing techniques and range of materials available, including biocompatible polymers, facilitates the user-friendly tailoring and fit for purpose of the functional and morphological features of the design by the bio(analytical) chemist. A comparative appraisal of the performance of various printing technologies in terms of print characterization, minimum features available, versatility and cost has been recently published by Breadmore and co-workers [186].

Initial developments focused on the 3D printing of scaffolds, modular components and portable platforms with intricate geometries that were subsequently applied to bioanalytical assays and biosensing schemes [180]. For example, bespoke holders and housing have been 3D printed to accommodate disposable dialysis or ultrafiltration membranes for protein-ligand (metal) studies [187,188] or size-tailorable chambers for dynamic HF-LPME of drugs in urine[189]. In another example, unibody platforms with multiple inlets and outlets and incorporating sample preparation proved useful for immunoassays using paramagnetic modified nanoparticles conjugated with either antibodies or target species for identification of biomarkers in cell lines [190] or microorganisms (including preconcentration and genomic DNA purification) in blood [191].

Aiming at the miniaturization of bioanalytical systems, researchers have devoted a considerable amount of effort to one-step printing of millifluidic devices enabling parallel analysis or processing of several biological samples simultaneously. Acceptance of 3D printing in the field of (micro)fluidics is linked to the creative flexibility and rigidity of the fluidic devices as compared to soft lithographic counterparts [10–13,180,182–186]. The Spence research group demonstrated the feasibility of simple multi-channel PIP devices with

printed threaded inlets/outlets and O-rings to accommodate commercially available cell-culture (transwell) insert wells equipped with porous semipermeable membranes [192]. In fact, the same flow-based device proved appropriate for a plethora of semi-automatic passive-diffusion bioassays (see Fig. 6A) by merely replacing the cell types that might be seeded on the membrane: (i) cell viability [192], (ii) ATP release from erythrocytes [193], (iii) in-vitro drug dosing and investigation of the metabolism of chemotherapeutics [194], and (iv) biomimetic profiling of drug pharmacokinetics [195], though cells were excluded in this study. News avenues are also opened for customization of 3D printed organ-on-chip prototypes by resorting to bioprinting of biological materials, such as agarose, DNA or even cells to mimic cell environments and study supramolecular interactions [11].

The beauty of 3D printing is that entirely new formats and configurations of fluidic devices that cannot easily be fabricated with milling approaches or soft lithography, such as serpentine and spiral-shaped channels, and at much lower expenditures -without the need of clean room facilities- are now possible. In the field of microextraction and sample handling in on-line flow-through format, unique (fluidic) structures have been fabricated by using: (i) the photopolymerized resin itself or after chemical functionalization as a sorptive material [183], (ii) square-channel cross-sectional devices to hold magnets in sorptive magnetic microextraction of emerging contaminants in urine [196], (iii) in-situ printing of microporous membranes by a commercially available composite filament composed of polyvinyl alcohol that can be after printing easily removed with water, thus creating an integrated polymeric barrier [197], or (iv) conductive polylactic acid filaments for printing of electroactive sample containers for electromembrane microextraction [121]. An elegant proof-of-concept bioanalytical application of a one-step 3D printed by FDM multimaterial millifluidic platform has been reported by Li *et al.* that integrates two printed dialytic membranes that allow concentration of drugs from urine while excluding protein and salts followed by electrokinetic separation on the very same millifluidic device (see Fig 6B) [198].

By combining the flexibility of 3D printing schemes and the user-friendly programming of advanced flow methodologies, the fourth generation of flow injection analysis, the so-called 3D printed μFIA, has been recently launched [199]. In fact, a single monolithic structure (termed Lab-on-a-Valve) with integrated optical and electrochemical detection has proven appropriate for automating intricate assays and analysis of real biological samples, such as human serum. Multiple unit operations were accommodated in the very same device without need of platform reconfiguration (see Fig 6C). Two representative examples include (i)

dynamic membrane-based passive-diffusion fingerprinting with on-line photometric analysis of diffusate species, and (ii) on-line micro-solid-phase extraction on-chip with disposable titanium dioxide microparticles for removal of phospholipids [199].

New research directions of 3D printing in the bioanalytical arena gear toward (i) in-house fabrication of blended mixtures of photopolymerized materials to avoid dependence on proprietary resins [200], (ii) improve the printer resolution for (bio)fabrication of truly microfluidic platforms [200,201] and (iii) exploit multi-material printers for integrating unit operations and detection in a single printed device[198]. It should be however noted that the majority of papers in the field of 3D printing only reported proof-of-concept studies, indicating a lack of bioanalytical methods integrating 3D prints that at present can handle troublesome and high matrix samples.

6. CONCLUSIONS

Sample treatment and handling continues to be an essential but undervalued step in bioanalytical procedures for the quality of the analytical data. Nonetheless, sample preparation approaches have made great strides over the past decade in terms of miniaturization and automation so as to become an integrated part of the analytical systems. The development of new extraction phases and formats, both in the solid and liquid phase microextraction context, is still an active research area for analysis of small volumes of plasma, oral fluids and urine samples, along with doping testing. In fact, the decrease of the amount/volume of phases in microextraction makes the use of novel materials with higher surface area and extraction capacities necessary, and thus innovation in this field is strongly dependent upon nanotechnological advances.

The present review discussed two miniaturized forms of SPE (MEPS and MIP-Tabs) that can be attractive to those working with biological samples. Compared with SPE, both techniques use 10–100 times less sample volume and reagents. The MEPS format is also amenable to full automation using online sample handling robotic arms and autosamplers. MIP-Tabs can be applied generally to selectively extract and enrich analytes from small volumes of plasma and urine samples. The tablets can also be used as sampling tool for oral fluids and drug and doping testing.

This review also demonstrates that 3D printing has opened up new avenues in the field of sample preparation by fast prototyping of polymeric or metallic scaffolds for holding sorptive phases or membrane barriers or using the pristine photopolymerized resins as sorbent materials or diffusive layers after appropriate treatment. However, overly simplistic

aqueous/sample models have been selected up to date as a proof of concept applicability, whereby real applicability of complex biological samples is expected to be undertaken in the near future.

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Legends to Figures

Fig. 1

The prepared Tabs and their applications

Fig. 2

Preparation of MIP-tablets (Reprinted with permission from [23]).

Fig. 3

MEPS tools and performance steps.

Fig. 4

Schematic of some sorbent structures used in MEPS

Fig. 5

Pipette tip extraction using paper coated with SWCNHs suprastructures as sorptive phase.

Fig. 6

Diagrammatic description of illustrative 3D-printed millifluidic devices incorporating microextraction approaches for bioanalytical applications. A) Multi-well platform by PIP accommodating membrane inserts for semi-automatic drug permeation studies. Reprinted with permission from [195]. Copyright (2016) American Chemical Society. B) Multimaterial device with 3D printed polymeric membranes by FDM for on-chip electrophoretic analysis of drugs in urine. Reprinted with permission from [198]. Copyright (2019) American Chemical Society. C) One-step unibody 3D printed Lab-on-Valve by SLA for multiple unit operations (dilution, derivatization, passive diffusion across membranes and sorptive extraction on-chip). Reprinted with permission from [199]. Copyright (2019) American Chemical Society.

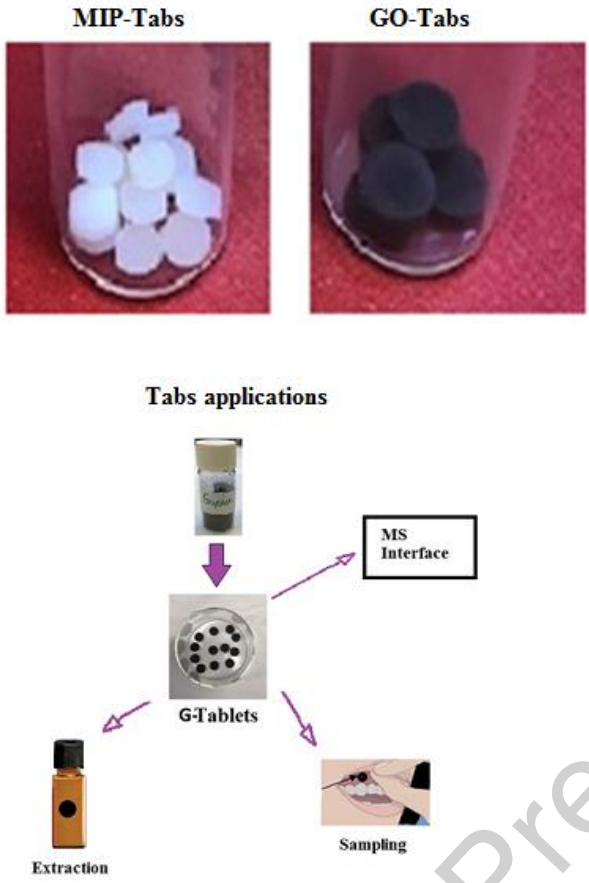


Fig. 1. The prepared Tabs and their applications

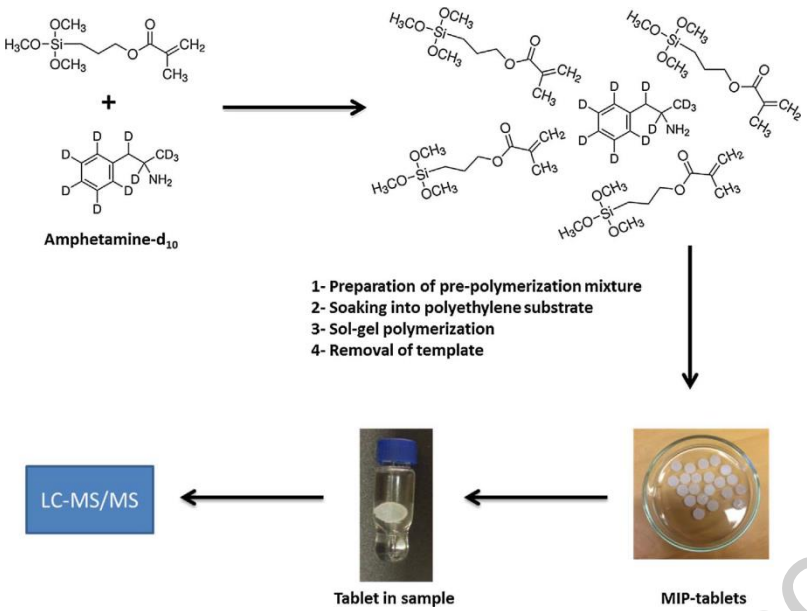


Fig. 2. Preparation of MIP-tablets [13].

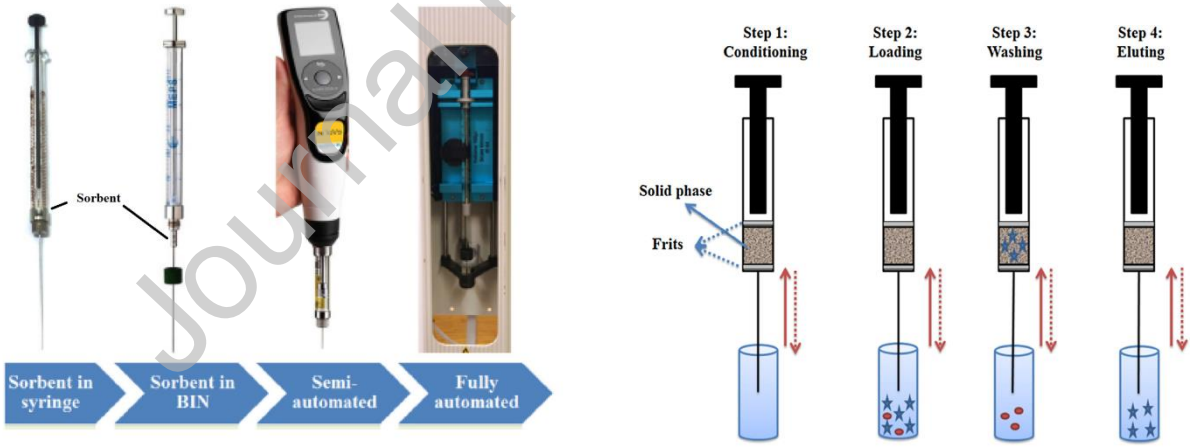


Fig. 3. MEPS tools and performance steps.

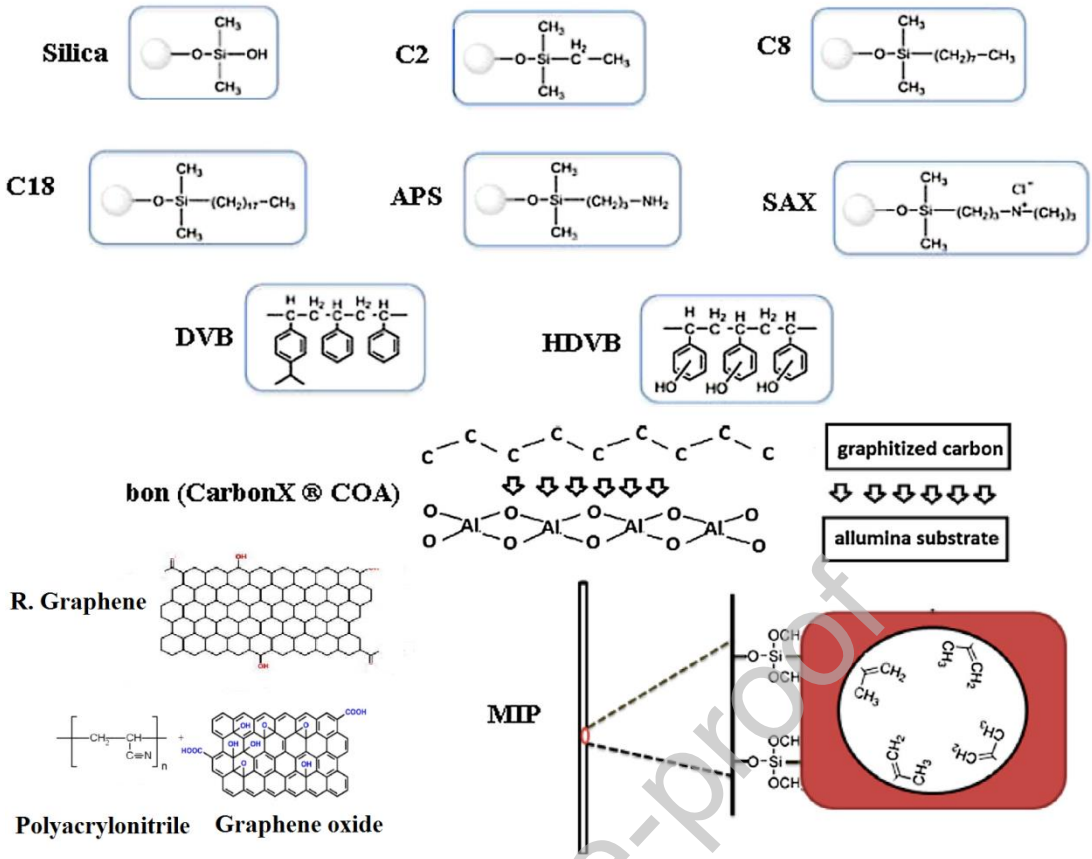


Fig. 4. Schematic of some sorbent structures used in MEPS

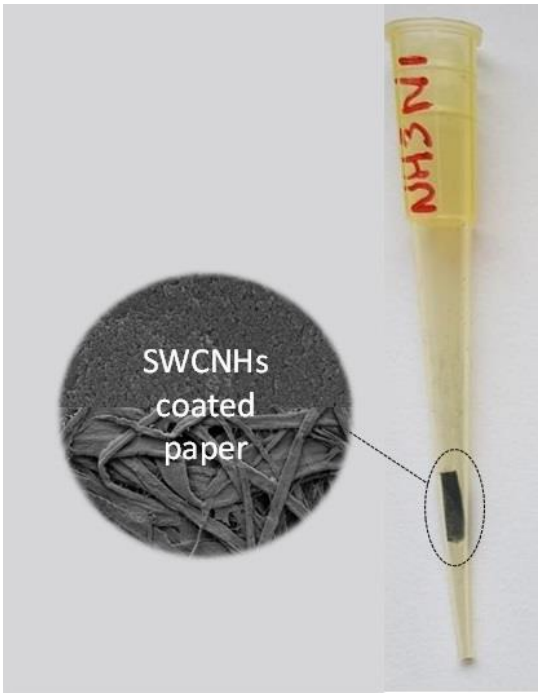
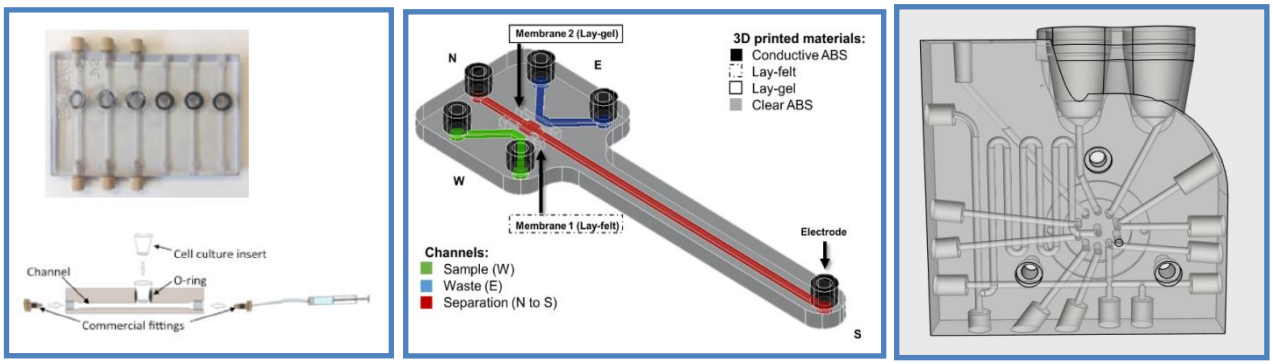


Fig. 5. Pipette tip extraction using paper coated with SWCNHs suprastructures as sorptive phase.



(A) (B) (C)

Fig. 6

Diagrammatic description of illustrative 3D-printed millifluidic devices incorporating microextraction approaches for bioanalytical applications. A) Multi-well platform by PIP accommodating membrane inserts for semi-automatic drug permeation studies. Reprinted with permission from [195]. Copyright (2016) American Chemical Society. B) Multimaterial device with 3D printed polymeric membranes by FDM for on-chip electrophoretic analysis of drugs in urine. Reprinted with permission from [199]. Copyright (2019) American Chemical Society. C) One-step unibody 3D printed Lab-on-Valve by SLA for multiple unit operations (dilution, derivatization, passive diffusion across membranes and sorptive extraction on-chip). Reprinted with permission from [200]. Copyright (2019) American Chemical Society.