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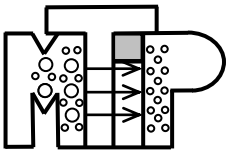

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SOLID PHASE EXTRACTION – PRINCIPLES, TRENDS AND APPLICATIONS

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1. INTRODUCTION

Sample preparation is crucial in the environmental, biomedical, and pharmaceutical analysis and often involves elaborate, time-consuming procedures. Sample preparation typically takes 80% of the total analysis time. A sample clean-up generally includes dilution, precipitation, filtration, and centrifugation. Before chromatographic methods are successfully applied, extraction is usually necessary in order to separate analytes from the interfering matrix components and enrich them [1, 2]. Nevertheless, choosing the appropriate sample preparation method is most important in the qualitative and quantitative determination of target compounds. A wide variety of compounds can be found, ranging from highly lipophilic to moderately polar ones, and exhibiting basic, acidic, or neutral properties. In addition, this step is required for several reasons: to eliminate a possible compound interference, to concentrate and stabilize the target analytes that may be in the sample, and finally to take the sample to the optimal sufficient conditions for the final chromatographic or other analysis [3–5].

Liquid-liquid extraction (LLE) is the most common and widespread sample preparation method which is based on the analyte partitioning between water and an immiscible organic solvent. The solid phase extraction (SPE) is another group of alternative extraction methods. SPE offers numerous applications and was the subject of detailed papers and reviews [1, 3, 6–13]. Generally, during an extraction process an aqueous sample passes through

an immobilized phase and is then extracted by suitable organic solvents. However, limited efficiencies resulting from insufficient retention can be observed for very polar analytes. Nevertheless, in SPE one of the strategies of overcoming the breakthrough volume is changing the type of a sorbent [14–17]. In SPE, the polypropylene cartridge with placed sorption phase is the most often applied design. The analytes to extract are partitioned between a solid phase (bed sorbent) and a liquid - liquid phase (sample). These analytes must have a greater affinity towards the solid phase than towards the sample matrix. Generally, SPE consists of four steps: column preparation, sample loading, column postwash, and sample desorption. The above mentioned prewash step is used for conditioning the stationary phase. Additionally, the postwash is utilized for removing undesirable substances. The target analytes are retained on the appropriate bed sorbent after washing out the interfering compounds. The relevant elution solvents are then used for recovering.

Poole et al. [18] reviewed the experimental determination and models for predicting the sorption isotherms (so-called breakthrough curves) characterizing the relevant packing materials. The breakthrough curves can provide sufficient information for identifying the physicochemical processes involved in the solute transport through the packing materials.

Accordning to Pawliszyn, the solid phase microextraction is defined as a miniaturization and equilibrium technique in which the volume of the extraction phase is exceptionally small in relation to the sample volume [19–21]. A miniaturized extraction (micro-SPE) has several advantages, namely: it is very often easier to make a direct connection with HPLC, GC or CE; a miniaturized device has lower operating costs and is less time consuming, and it can be partly or fully automated, which allows for better reproducibility and *on-line* hyphenation [22–27].

2. THEORETICAL BACKGROUND OF SPE

In SPE, the separation is based on the selective distribution of analytes between the solid packing material and liquid mobile phase. The basis of all extraction procedures is described by Nernst distribution law. A compound distributes itself between two solvents. The system constant is described as the distribution coefficient K_D and presented according to the ratio:

$$K_D = \frac{C_s}{C_m} \quad (T\text{=const.}). \tag{1}$$

In the presented equation C_s and C_m correspond to the compound concentrations in the upper *s* and lower *m* layers, respectively. Analytes to extract are partitioned between a solid phase and a liquid phase (sample)

and must have greater affinity towards the solid phase than for the sample matrix [28].

In a system without chemical reactions, at a constant temperature and pressure, the only processes that can occur depend on the transition of components from one phase to another. The thermodynamic criterion:

$$dG < 0 \ (T, p\text{=const.}) \tag{2}$$

is fulfilled by such systems. In Eq. (2) G, T and p denote the free enthalpy, temperature, and pressure, respectively.

The change in the free enthalpy during the transition is given by Eq. (3):

$$dG = \sum_i \mu_i dn_i \ , \tag{3}$$

where: μ_i – the chemical potential of component and n_i – the number of moles.

When two phases are in equilibrium the chemical potential of the distributed substance is the same in both phases, i.e.:

$$\mu_i^{(s)} + RT \ln a_i^{(s)} = \mu_i^{(m)} + RT \ln a_i^{(m)} \tag{4}$$

where: $\mu_i^{(s)}, \mu_i^{(m)}$ – the standard chemical potentials of the i ingredient in the phases s and m, $a_i^{(s)}$ and $a_i^{(m)}$ – the activities of the components in the respective phase. Thus, the thermodynamic distribution coefficient can be expressed as:

$$K_D = \frac{a_i^{(s)}}{a_i^{(m)}} \tag{5}$$

Eq. (5) is a mathematical representation of the Nernst distribution law.

Since the 1970s, SPE has become a common and effective technique for extracting analytes from complex samples. SPE prepares multiple samples in parallel (typically 12-24) and uses relatively low quantities of solvents as compared to LLE. The procedures can be readily automated. SPE is also regarded as more environmentally friendly because of the lower solvent requirement. Commercially available phases for SPE based on silica and bonded silica have been used for a wide range of analytes.

3. EVALUATION OF FORMATS, SORBENT TYPES AND MODES OF INTERACTION IN SPE

SPE sorbents are commercially available in several forms: contained within cartridges, in columns fashioned like syringe barrels, or in disks. Typical columns are manufactured of polypropylene or glass, and the sorbent is contained in the column by porous frits made of polyethylene or polytetrafluoroethylene (PTFE). A detailed characterization of all of these is provided by Żwir-Ferenc [13]. Generally, sorbents may be deployed as: cartridges (which vary in size from microsized disks in 1 mL syringes up to a 6 mL syringe), discs (which are 47 mm in diameter or the standard

filtration size), the SPE pipette tip, 96-well SPE microtiter plates (which use the 1 mL disks), and also a small column which can be connected *on-line* to an LC system. In the sorbents, appropriate functional groups may be chemically bonded to silica gel.A commonly utilized format is a syringe barrel consisting of a 20 μm frit at the bottom of the barrel, with a relevant sorbent above and an additional frit at the top. The extraction disc is another format.It consists of 8-12 μm sized particles placed in an inert matrix. The silica-based sorbents, having a large variation of functional groups available, are relatively inexpensive and stable within a pH range of approximately 2–7.5. The main advantage of discs is their applicability at higher flow rates. In SPE, the cartridge is the most frequently used design. Several different types and amounts of sorbents are contained between two polyethylene or PTFE frits in polypropylene or glass cartridges which have different column volumes. Another design available in the last few years is the disc, consisting mainly of particle-loaded membranes (PLMs), which are composed of polytetrafluoroethylene microfibrils and enclosed sorbent particles with a diameter of about 8 μm, with particle-embedded glass fiber disc (PEGFDs) as a supporting matrix [29]. Also, a 96-well plate format that simplifies the analysis of a large number of samples is available. SPE cartridges still maintain their lead, but a strong growth of discs has been observed since the 1996 survey. The biggest advantage of the disc format is its ability to accommodate higher flow-rates (and therefore, shorter extraction times), which is most important in the enrichment of organic compounds trace in water. The flow-rate that can be passed through cartridges with their smaller cross-sectional areas is generally lower than the flow-rates used for the discs. The 96-well SPE plates were shown for the first time in 1996 and their recent use is a tribute to their fairly rapid acceptance. Hennion [6] excellently summarized the formats and procedures in SPE. This paper clearly demonstrates that new formats for SPE provide reduced bed masses, high-throughput capabilities, and greater convenience for further method developments.

SPE is performed using either silica-based or polymer-based sorbents.The silica-based bed sorbents are mainly used in the case of nonpolar or medium polar analytes. Additionally, such compounds are extracted from the polar solutions by nonpolar functional groups such as C_1, C_2, C_8, C_{18}, Ph or CN. One of the disadvantages of the most popular reversed phase silica based materials is the presence of residual silanol groups. In HPLC, in order to obtain better efficiency and totally nonpolar sorbents, the trends are to minimize the number of residual silanol groups. Typically a trifunctional silane is used for bonding the *n*-alkyl chains and the endcapping is performed with a trimethylsilane after bonding [30].

The effectiveness of a SPE method depends on several factors such as the cartridge stationary sorbent, pH values, sample pretreatment, organic solvents used for washing and eluting steps, as well as the flow rate during

the different steps. The elution of the analytes is effected by a suitable solvent, leaving the interfering substance on the column. Both strong and weak elution solvents for adsorbed compounds in SPE are described in Table 1.

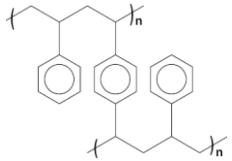
Table 1. Sorbents applied in solid phase extraction.

Type of bed sorbent	Structure of bound ligand	Analyte type	Dissolving solvents	Elution solvents
Reversed phases				
Octadecyl (C_{18})	$-(CH_2)_{17}CH_3$	Slightly-moderately nonpolar-nonpolar	Methanol/water; Acetonitrile/water	Hexane, chloroform (nonpolar analytes); Methanol (polar analytes)
Octadecyl (C_{18}) LightLoad	$-(CH_2)_{17}CH_3$			
Octadecyl (C_{18}) PolarPlus	$-(CH_2)_{17}CH_3$			
Octyl (C_8)	$-(CH_2)_7CH_3$			
Ethyl (C_2)	$-CH_2CH_3$			
Cyclohexyl	$-CH_2CH_2-$			
Phenyl	$-CH_2CH_2CH_2-$			
Normal phases (bonded)				
Cyano (CN)	$-(CH_2)_3CH$	Slightly-moderately polar-strongly polar	Hexane, chloroform, acetone	Methanol
Amino (NH_2)	$-(CH_2)NH_2$			
Diol (COHCOH)	$-(CH_2)_3OCH_2CH-CH_2OHOH$			
Normal phases (adsorption)				
Silica gel	-SiOH	Slightly-moderately polar-strongly polar	Hexane, chloroform	Methanol (dependent on the type of analyte)
Florisil®	Mg_2SiO_3			
Alumina	Al_2O_3			

Table 1, cont.

Ion exchangers (anion and cation exchange)				
Amino (NH2)	$-(CH_2)_3NH_2$	Anion exchange-ionic acid	Water or buffer ($pH=pK_a+2$)	a) buffer ($pH=pK_a+2$) b) pH where sorbent or analyte is neutral c) solvent with high ionic strength
1^o, 2^o-Amino (NH/NH_2)	$-(CH_2)_3NHCH_2CH_2NH_2$			
Quaternary amine (N^+)	$-(CH_2)_2COOH$			
Carboxylic acid (COOH)	$-(CH_2)_3N^+(CH_3)_2$			
Acid (SO_2OH)	$-(CH_2)_3SO_2OH$	Cation exchange-ionic base	Water or buffer ($pH=pK_a-2$)	a) buffer ($pH=pK_a-2$) b) pH where sorbent or analyte is neutral c) solvent with ionic strength
Acid ($ArSO_2OH$)	$-(CH_2)_3- -SO_2OH$			
SE-Sephadex				
Sephadex® G-25	Dextran	-	-	-
Wide-porous				
RP butyl (C_4)	$-(CH_2)_3CH_3$	-	-	-
HI HI-propyl (C_3)	$-(CH_2)_2CH_3$			
IE CBX (carboxylic acid)	-COOH			
PEI (polyethyleneimine)	-(CH2CH2NH)n-			

Table 1, cont.

Polymer-based sorbents				
PS-DVB copolymers (Amberlite XAD-type, PLRP-S resin, Oasis HLB, Porapak RDX)		Polar-strongly compounds	Methanol, water	Methanol, acetonitrile (dependent on the type of analyte)
Graphitized carbon sorbents				
GCBs (Carbopack, Carbograph 1,4,5; Envi-Carb)	-	Neutral, basic and acidic compounds	-	Acetonitrile (acidified organic solvents)
PGC (CARB GR)		Nonpolar and high molecular weight compounds	Methanol, acetonitrile, acetone	-

The eluting solvent strength for normal phase sorbents increases in the reverse order to that characteristic for reversed phase sorbents. Additionally, the reversed phase sorbents should exhibit stability towards both the sample matrix and the elution solvents. SPE, as a selective method, offers countless diverse choices of sorbents, ranging from the traditional reversed-phase sorbents (C_{18}, C_8), normal phase (silica, alumina), ion exchange, to mixed-mode (ion exchange and reversed phase), and functionalized resins based on styrene-divinylbenzene (SDVB) polymers (Table 1) [8, 29]. Among them, the most frequently used groups are silica and bonded silica sorbents, polymer sorbents, graphitized or porous carbon, and new extraction sorbents including molecularly imprinted polymers and immunosorbents [3, 6, 29].

The adsorption stationary phases include unmodified sorption materials such as pure silica, magnesium silicate, alumina and diatomaceous earth (kieselgur). Their hydrogen binding sites are mainly destroyed by water which results in a reduced retention of compounds of interest and poor reproducibility. Meanwhile, polar functional groups such ascyano-, amine- as well as diol- are added to the silica sorbent surface, and thus, one obtains normal phase sorbents which extract the polar analyte from a nonpolar medium by hydrophilic interaction. These are mainly applied in clinical fields for the purification of nonpolar extracts such as hexane of solid matrices. The sorbents for the normal phase are modified with cyano, diol or amino groups, while the sorbents for the reversed phase – with octadecyl, octyl, cyclo or phenyl groups [6, 13].

The ion-exchange bed sorbents are characterized by ionic interactions, as in case of the negatively and positively charged analytes and biological fluids. The optimal conditions including suitable pH values should be assured. Namely, pH should be two units lower (higher) than the pK_a values of the analyte and two pH units higher (lower) than the cation (anion) exchange sorbent pK_a values. It is feasible to select carboxylic acid (pK_a=4.8) or sulphonic acid (pK_a lower than 1) as a weak or strong cation exchange mode, respectively. Nevertheless, among the anion exchange bed sorbents, there are quaternary amines (pK_a higher than 14) or aliphatic aminopropyl functional groups attached to the silica phase (pK_a=9.8) [6, 29].

The molecular recognition mechanisms belong to immunosorbents and molecularly imprinted polymers (MIPs) which are selective and have found applications mainly because of a large interfering substance in the complex matrices. The first ones are composed of biological antibodies that are covalently attached to a silica surface, glass particles, agarose as well as other types of gels. The second ones are formed while utilizing the template molecules that play a role in the target compounds recognition. The disadvantages of the immunosorbents in comparison to MIPs relate to thermal and chemical stability, as well as in the whole pH value range stability, the cost and low reproducibility. The extraction abilities of MIPs are comparable to the reversed phase sorbents [6, 8, 13].

SPE is also performed using polymer-based sorbents. Polymer-based sorbents have different advantages including no need for acidic/basic elution modifiers, no pH limitations (stable from pH 1–14) and high capacity. Polymer-based SPE involves macroporous polymeric media, offering a higher loading capacity compared to conventional functionalized silica SPE media. One example is Strata^{TM}X which has the advantage of having no residual surface silanol groups, unlike the substituent silica sorbents. The most widely used polymeric sorbents are the styrene-divinylbenzene (S-DVB) copolymers (SDB). The absence of silanol groups, resulting in fewer secondary interactions, and the broad range of pH stability of these polymers increases the method development flexibility. To overcome these limitations (i.e. the lack of specific surface area), some highly crosslinked polymers have been developed with greater surface areas (800-1200 m^2g^{-1}) than those of conventional polymeric sorbents (350-500 m^2g^{-1}). Without silanols, only one predominant retention mechanism exists, which results in simpler extraction protocols. In addition, PS-DVB resins typically provide analyte retention greater than the bonded silica. Until recently, however, the disadvantages of the polymers were high level of extractability and undesirable shrink-swell characteristics of PS-DVB copolymers. These phenomena have limited their universal acceptance for trace analysis applications. Another important disadvantage is the fact that these hydrophobic PS-DVB polymers still require a conditioning step with a wetting solvent, and the sorbent has to be kept wet before loading the sample. A new hydrophilic-lipophilic balanced copolymer (HLB) of *N*-vinylpyrrolidone, divinylbenzene and commercial Oasis®HLB (Waters) developed for SPE applications does not show these problems. Oasis HLB sorbent has been reported as the one having good retention for both polar and non-polar compounds [31]. The hydrophilic N-vinylpyrrolidone increases the water wettability of the polymer, and the lipophilic divinylbenzene provides the reversed-phase retention necessary to retain analytes. The sorbent preserves analyte retention even if the bed dries out, which makes it suitable for application in automated (SPE) systems. As a hydrophobic sorbent the copolymer styrene-divinylbenzene possesses retention equal or very often higher than octadecyl-bonded silica (ODS). Recently, despite commercial availability of hydrophilic sorbents (XAD-7, XAD-8, Abselut Nexus, Focus, Oasis HLB, Porapak RDX), there is a high number of home-made sorbents (AN-DVB, MAN-DVB, CMPS-DVB, PANI, PNMA, PDMA, PPy) to be found in literature. A detailed overview of new materials in SPE including the morphological and chemical properties and new developments is reviewed by Fontanals et al. [31]

Empore disks containing C_{18} or PS-DVB are the two main types of disk formats in use. One of the drawbacks of using disks instead of cartridges is the decrease in the breakthrough volume, mainly for more polar compounds. For this reason, disks are used when there is a strong interaction between the analyte and the sorbent [32].

The interactions between the target compounds and the sorption centers on the solid phase include hydrophobic interactions such as Van der Waals

forces and hydrophilic interactions such as dipole-dipole, induced dipole-dipole, hydrogen bonding and π–π interactions (Table 2). Additionally, between the charged groups on the target analyte electrostatic attractions take place, and on the sorbent surface the molecular recognition mechanisms occur. These types of interactions are characterized for reversed phase, normal phase, ion-exchange, immunoaffinity, and molecularly imprinted polymers.

Table 2. Binding energies values of interactions in solid phase extraction.

Primary Interaction Mechanism	Sorbents	Energy of Interaction [kcal/mol]
Dispersion forces (London)	Octadecyl, octyl, ethyl, phenyl, cyclohexyl, styrene-divinylbenzene,	1-10
Polar/Dipole-dipole	Cyano, silica, alumina, Florisil	1-10
Hydrogen bonding	Amino, diol	5-10
Electrostatic	Cation exchange, anion exchange, graphitized carbon	50-200
π–π	Styrene-divinylbenzene, porous graphitized carbon	1-5

The development of effective and selective SPE supports is very important to reduce the interference of the sample matrix. Among different supports, the restricted access material (RAM) is designed specifically for the removal of macromolecules based on the size-exclusion mechanism. Only small molecules are able to penetrate into the pores of RAM and interact with a stationary phase bonded on their inner surface, while large molecules are eluted with the washing solvent. The predominant forces among restricted-access material sorbents are a combination of hydrophobic, ionic, or even affinity interactions due to the analyzed bulky compounds (proteins, lipids) or a suitable hydrophilic sorbent utilization that provides chemical repulsion [33, 34].

The above mentioned reversed phase sorbents have found their application for nonpolar analytes from polar matrices (plasma, whole blood) by hydrophobic interaction. Mainly C_{18} sorbents and their modifications are applied in biomedicine, pharmacology, or toxicology for extraction from different biological matrices. Martin et al. [35] studied the influence of different C_{18} bonded silicas such as SPE sorbents on the extraction abilities in the analysis of acidic and basic compounds. The applied cartridges (1 mL) consisting of 100 mg sorbents included three un-end-capped phases with carbon content ranging from 5 to 16% as well as four end-capped phases with carbon content in the range of 10.5–22%. The best among the studied phases connects those with

intermediate carbon loading. Additionally, the effects of end capping were observed for the basic target analyte (propranolol) because of the silanophilic interactions.
Buszewski et al.[36] prepared new types of silica gel sorbents used for five selected β-receptor antagonist sample preparation methods. They successful prepared silica gels of various porosities chemically modified by the cholesterol ligands. They performed an evaluation of the quality of the formed bed sorbents using spectroscopic methods and elemental analysis. The method development was based on the optimization of sample loading, the washing step, elution conditions, concentration of relevant extracted drugs, and the kind of sorbent. Using optimized conditions, the authors were able to achieve satisfactory recoveries of the analytes from buffers, urine and blood samples.

4. MINIATURIZATION, AUTOMATIZATION AND ROBOTIZATION

Nowadays, nanotechnology is of growing importance in the field of separation science. There are several fabrications of different geometric structures of nanomaterial composites coated on silica gel to be used as the SPE sorbents which provide preconcentration and clean-up for various matrices.
An important advantage of chromatographic methods is their miniaturization and automation [6]. This is also true for the liquid-solid (SPE, SPME) extraction techniques as well as the membrane separations – the so-called extraction disks (Empore, Speedisk). In all these cases, the dominant role is played by the processes of chemical modification of porous and nonporous adsorbents as a carrier for the organic liquid phase. The stationary phases used allow the selective extraction of individual substances in different matrices by specific and nonspecific interactions between the analyte, the surface of the stationary phase (active sites located on its surface) and the mobile phase. SPE is an especially useful extraction method as it enables selective separation both *off-line* and *on-line*. Meanwhile, in the case of *off-line* SPE samples, they are prepared before the chromatographic measurements; the *on-line* SPE is directly connected to the chromatographic system which brings advantages including lower contamination, automation, and complete analysis of the extract in the meaning of higher sensitivity (Fig. 1).

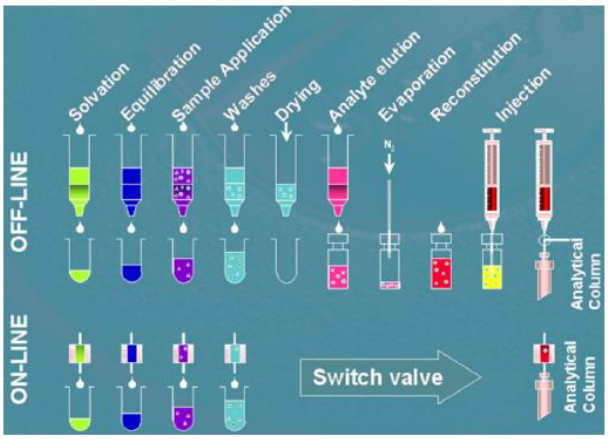


Fig. 1. Schematic illustration of *off-line* and *on-line* SPE methodology. Reprinted from ref. [37] with permission from Elsevier.

Generally, the *on-line* SPE-LC consists of a small precolumn placed in a six-port high-pressure switching valve. During the injection, the sample is preconcentrated on a precolumn with a small dimension (in order to avoid band broadening in space) and pressure resistance. The analytes are eluted onto the analytical column by valve switches. There is also a possibility to use the system without a precolumn in the valve which provides either low or high pressure modes. This format is mostly applied in the analysis of biological fluids (plasma, whole blood, urine) in the presence of restricted access material sorbents [38]. Coupling the SPE with gas chromatography requires a derivatisation and application of small injection volumes. However, several systems have been developed for *on-line* SPE-GC methods using six-port valves in combination with a drying gas, as well as a solvent vapour exit. In a large-volume transfer, the solvent evaporation technique is critical for obtaining sharp peaks [6, 37]. In *on-line* SPE-GC, another concern is to switch the elution solvent from SPE to a suitable solvent to be injected in GC.

The application of fully automated sequential injection SPE procedure coupled to liquid chromatography to determine *in vivo* selected substances used as UV filters is discussed by Leon et al. [39]. They developed and described an analytical method based on the automated procedure for clean-up and preconcentration followed by liquid chromatography-ultraviolet spectrophotometry detection (LC-UV). For such an *on-line* connection of SPE sample processing with LC analysis allowed a six-channel valve as an interface.

Nowadays, *on-line* SPE coupled with HPLC and multidimensional chromatography have been presented not only to increase the analytical selectivity but also to improve the repeatability and reliability of also peptide quantification. One of the latest applications of the *on-line* two-dimensional chromatographic approach for peptide analysis in plasma samples

was introduced by Liu et al. [40]. They utilized reversed phase (RP) and hydrophilic interaction chromatography (HILIC) coupled with *on-line* extraction and quantitative determination of 11 peptides. The final advantages of the applied system were highly reproducible and robust results for over 300 sequentional matrix injections.

Moreover, *on-line* SPE-LC coupled with different detection techniques is a powerful alternative method ofxenobiotics and metabolites analysis in the biological matrices as a support for pharmacokinetic or pharmacodynamic studies. The main advantages are higher throughput, good precision, limited manual processing, as well as low cost and greater sensitivity.

When using *on-line* systems for liquid chromatography, several groups of analytes were separated. Some examples are separated-anti-HIV peptide [41], catecholamine [42], phthalate metabolites [43], river water pollutants [44], amodiaquine, chloroquine, and their metabolites [45], opiates, amphetamine and derivatives, cocaine, methadone and metabolites [46], lamotrigine [47], cyclosporin A [48], valsartan and candesartan [49], herbicides [50], sulfonamide antibiotics, neutral and acidic pesticides [51], remoxipride [52], bisphenol A [53], macrolide antibiotics [54].

On-line SPE–LC–MS is becoming increasingly popular for the automation of bioanalytical assays, especially in the pharmaceutical industry [55]. Total automation, high precision, and high sensitivity are among the most favored features. A generic method for SPE and LC is urgently needed to eliminate the method development for preclinical assays or as a universal starting point for the development of high-quality, high-throughput clinical assays.

An interesting and creative form of sample preparation in multidimensional (MD)-solid phase extraction (tandem-SPE) has appeared. This attractive approach depends on the selectivity of the appropriately chosen bed sorbents or mixed-mode phases to retain the analytes of interest while allowing unretained components to be eliminated from the column form. Additionally, a tandem SPE method is used to eliminate interferences. The combination of two or three different bed sorbents allows for the simultaneous extraction of relevant substances from complex matrices. Such investigations were performed for Oasis HLB SPE cartridge and an HLB μElution SPE plate in the extraction of urinary F_2-isoprostanes [56], C_{18} reverse support and a SCX cation-exchanger for the extraction of atrazine ozonation products in water [57], combination of restricted access materials and molecular imprinted polymers in the extraction of tramadol from human plasma in *off-line* mode [58] and to extract triazines in river water samples using MIP in *on-line* mode [59].

As an alternative, for the first time Kang and his colleagues showed extraordinarily reproducible data for the preparation of a packed-fiber SPE device for the analysis of trace pollutants in the environmental water, as well as a drug and its metabolite in human plasma samples [60–62]. They showed that nanofiber sorbents possess numerous advantages in terms of sensitivity, reproducibility, and limit of detection as well as reducing the

time needed in comparison to commonly used commercially octadecylsilica SPE.

Lafleur and his associates [63] introduced extraction by miniaturized centrifugal SPE platforms for the organic pollutants, mainly polycyclic aromatic hydrocarbons (PAHs), in the environmental samples. They applied fluorescence and absorbance measurements directly on the sorbent material. This device allows for minimizing the sample volume needed as well as simultaneous on-site extraction. Additionally, the advantage of this device is the abilityto reduce the number of sample preparation steps, and the use of organic solvents which is important with regards to "green chemistry".

Conversely, the new methodology of a non-chromatographic determination of ultratrace speciation of vanadium in natural water involved a SPE-flow injection system connected with the electrothermal atomic absorption spectrometry (SPE-FI-ETAAS) was proposed by Kim et al. [64]. For the extraction of V(V) and V(IV) lab-made hybrid mesoporous silica functionalized with 3-aminopropyltriethoxy silane (APS) and mesoporous silica MCM-41 were utilized.

Liu [65] developed a SPE-sweeping-MEKC methodology for the isolation and preconcentration of the neutral steroid compounds – testosterone, progesterone and testosterone propionate – from urine samples. The gold nanoparticle (AuNP) layer-by-layer (LBL)-coated SPE materials successfully concentrated the neutral steroids through hydrophobic interactions with the Au NP-capped silica gel.

Serra and co-workers [66] successfully developed a SPE-multi-syringe flow injection system (SPE-MSFIA). They used a C_{18} membrane disk for the separation between 2,3-diaminonaphthalene (DAN) and the piazselenol complex, which gave better recoveries in comparison with a poly(styrene-co-divinylbenzene) disk.

5. SELECTED APPLICATIONS AND DEVELOPMENTS OF SPE

5.1. MULTI-WELL SPE PLATES-NEW TRENDS IN SPE

To fulfill the need for quick extraction techniques, some recent adaptations of SPE have appeared. SPE has progressed from using individual columns and cartridges to high throughput 96-well plates. This technique uses single blocks or plates with 96 wells that contain discs or packed beds of sorbent particles arranged in an 8-row by 12-column rectangular matrix. A successful application using these plates is described by Henion et al. [67]. A sample throughput of 192 samples of urine for the analysis of estrogen sulfates in 22h followed by LC/MS became possible. At first, the choice of sorbents in plates was limited to several reversed-phase bonded-silica chemistries. Nowadays, a full range of sorbents which match those in the individual cartridge format, is available.

Altun et al. [68] reviewed and described the application of monolithic methacrylate polymer bed in 96-tips as a powerful tool in bioanalytical fields. This approach has some incredibly significant advantages, for example: 96 samples could be prepared in 2-4 min, as well as the reduction of the whole sample-preparation time, good precision and accuracy could be obtained. It will be the future prospect in the fields of bioanalysis and the pharmaceutical industry of the biologically active compounds and metabolites [68].
Nissum et al. [69] introduced a novel in-gel SPE 96-well microplate approach based on the digestion of proteins. This device was composed of two 75-µm-inner diameter and 2.4 mm length capillaries containing C_{18} reversed-phase modified monolithic silica rods, which were surrounded by the support of the direct elution on MALDI-TOF targets. It was applied for the extraction and clean-up of selected peptides [69].

5.2. RESTRICTED ACCESS MATERIALS

Pinkerton et al. [70] were the first to publish the application of internal surface reversed phase (ISRP) for biological samples to obtain two compartments, mainly proteins and analytes of interests. Recently, there has been an increasing number of papers dealing with RAM described [33, 71-73]. The restricted access sorbents are mainly applied in the clinical and toxicologic fields for the extraction of small analytes in the presence of large molecules (e.g. proteins). In the case of highly protein bonding analytes, the recovery rate of classic SPE can be very low because of too weak interactions between the target compounds and bed sorbents. Mainly due to the strong retained proteins on the column, analytes and the stationary phase could not interact normally (Fig. 2).

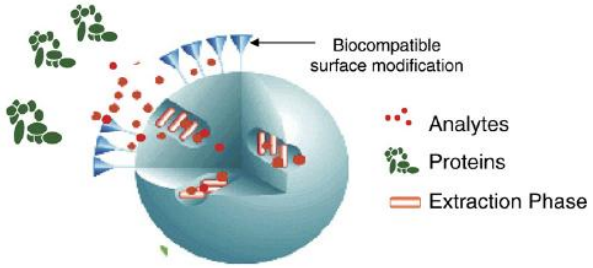


Fig. 2. Schematic illustration of restricted access sorbent. Reprinted from ref. [71] with permission from Springer.

When applying RAM, different types of analytes were extracted from various matrices – naproxen and ibuprofen [74], atropine and sotalol [75], herbicides [76, 77] and even p-acetaminophenol [78] using a combination of RAM-MIP as

a selective recognition. RAM sorbents are applied in combination with *on-line* SPE-LC for the analysis of biological matrices [79].

5.3. IMMUNOSORBENTS

Nowadays, the new extraction sorbents involving reversible and selective antigen-antibody interactions have been synthesized in order to trap also structurally related compounds such as the host-guest complementary complex with steric repulsion contribution; this depends on the size and shape of the analyte of interest. The applied sorbent should provide functional groups for suitable coupling with the appropriate sites, number of antibodies, and hydrophilic to prevent nonspecific interactions with the studied compounds and matrices at once. These requirements have found place in diol and aldehyde activated silica bed sorbents where the applied antibodies are attached via amino groups utilizing Schiff base methods. The multiple interaction mechanism between the antigen-antibody, including ion attraction, hydrogen bonds, hydrophobic attraction as well as Van der Waals forces take place. The first paper describing the immunoaffinity sorbents based on the high selectivity of antigen-antibody interactions was published by Chan in 1987 [80]. They possess several extraordinarily vital advantages such as minimizing the problem of interferences from matrix and extraction of the analytes of interest, hence efficient purification is obtained from complex biological and environmental samples. The preparation of immunoaffinity sorbents for SPE was described by Stevenson [81]. Nevertheless, the development of this type of sorbents with the associated stability in the appropriate range is quite costly and lengthy. On the other hand, an increasing number of papers dealing with the advantages of immunosorbents as unique and powerful biological tools which enable selective extraction of the compound of interest from fixed matrices in one step are described [82].
These sorbents are extremely pricey, and only few of them are commercially available.
Hokkanen et al. [83] described a novel silicon-glass chemistry-based approach to the preparation of an immunoafinity SPE (IA-SPE) device using an immunosorbent in the form of recombinant testosterone-specific compartments immobilized to agarose beads followed by the zone electrophoresis separation.
The immunosorbents have been applied to determine several compounds *off-line* and on-line, using a single antibody or a multi-antibody in a mixed form [81, 82].

5.4. MOLECULARLY IMPRINTED POLYMERS

The development of the molecularly imprinted polymers applied in molecular recognition was another approach for the selective SPE. The molecularly imprinted polymers are made by synthesizing highly crosslinked polymers in

the presence of a template molecule attributed to the formation of functional groups in a specific arrangement within polymer [84–86]. The recognitions placed through the polymer matrix are complementary to the target compound in terms of shape and placing of the functional groups. Afterwards, without an appropriate molecule, the relevant polymer can be utilized as a selective binding matrix for the template (analyte) or structurally related compounds. The polymers bind the template and the suitable ligands form the functional groups in a specific direction. The recognition is due to a shape and different physicochemical properties such as hydrogen bonding, ionic and hydrophobic interactions (Fig. 3).

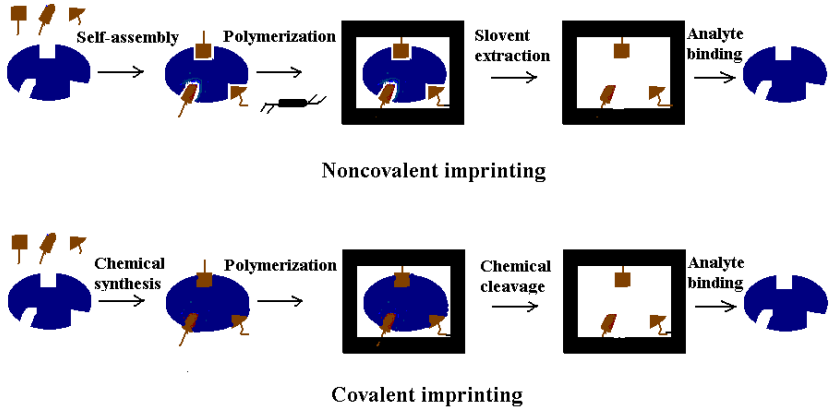


Fig. 3. Schematic illustration of the preparation of molecularly imprinted polymers. Reprinted from ref. [86] with permission from Authors.

Due to the specific recognition offered by MIPs, these materials are applicable in the pharmaceutical, environmental, and even food fields, where binding with high selectivity and affinity is required. Some of the polymers possess both high selectivities and affinity constants, which usually occur in a natural recognition system typical for monoclonal antibodies. In addition, they are suitable as constituents in chemical sensors, and they may also enhance selectivity in SPE. They have some very important advantages, such as ease, cost, time and reproducibility of preparation, sample load capacity, material durability and composition. The recognition sites within the polymer matrix are complementary to the analytes in the shape and positioning of the functional groups. Sellergren [87] was the first to describe the use of MIPs' huge potential as a sorbent for SPE. He synthesized a MIP with the recognition sites for an antiprotozoal drug and evaluated for *on-line* SPE determination in urine samples. As a monomer and cross-linker, methacrylic acid and ethylene glycol dimethacrylatewere used, respectively. Afterwards, these chemical reagents were mostly applied for the synthesis of MIPs for SPE. In 1997, Martin et al. [88] introduced a propranolol-derived MIP as a model compound

utilizing propranolol, three structurally related amino alcohols and two dissimilar acids. Additionally, an ionic modifier (triethylamine) for quantitative recoveries for the elution step was utilized. Khorrami and Rashidpur [80] introduced a completely different cartridge architecture (Fig. 4) which eliminated the need for the sample pre-treatment step in the protein precipitation before performing the extraction. This device was utilized for the extraction of theophylline (THP) from the human serum samples after the fully optimized experimental parameters (type of organic solvent, pH and ionic strength of the aqueous phase, organic to aqueous volume ratio, time of extraction, type and amount of desorbent solvent).

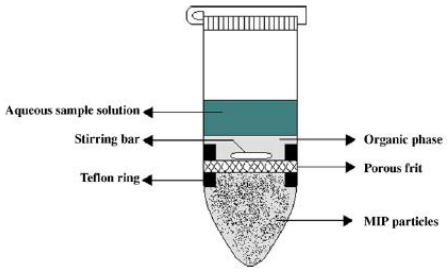


Fig. 4. Schematic illustration of the solvent extraction-molecularly imprinted solid phase extraction (SE-MISPE) cartridge. Reprinted from ref. [80] with permission from Elsevier.

The application of MIP has been numerously reported during the past few years. It has become increasingly attractive in many fields such as chiral separation, chemical sensors, and immunoassays-like analysis as a synthetic antibody. Being used as the sorbent for SPE is one of the most exciting applications of MIP, which provides a simple and effective pretreatment method in complicated samples. In recent years, the molecularly imprinted polymer preparations based on estrogens such as estrone, diethylstilbestrol, and 17 α-ethynylestradiol have been reported. One of the recent studies in this area deals with the utilization of molecularly imprinted SPE in the isolation of steroids (progesterone, testosterone and 17B-estradiol) from human urine samples. The results indicated that this sample preparation method may be used in the quantitative routine analysis of these hormones in biological samples [89]. A very few examples of MISPE applications for the analysis of various samples are listed in Table 3, according to the compound type, sample matrix type and analytical technique [58, 90–98].
A new selective support made of immobilized selected oligonucleotides (DNA or RNA) and named oligosorbents has been recently developed. Aptamer-based sorbents are synthesized and evaluated for the selective extraction of cocaine from human plasma samples [99] or a mycotoxin from complex matrices [100].
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Table 3. Summary of a very few examples MIP-SPE applications in various fields (FM=functional monomer, CL=cross-linker, PM=print molecule, I=initiator).

Analyte	Sample	Sorbent type	Conditioning solvent	Elution solvent	MISPE mode	Final analysis	Reference
Application to bioanalytical and pharmaceutical samples							
Trimethoprim	Human urine	MAA (FM), EDMA (CL),Trimethoprim (PM), AIBN (I)	Ethanol	Methanol (+ 7% TFA)	Off-line	LC/UV	[90]
Tramadol	Human plasma	Tramadol (PM)	-	-	On-line	LC/UV	[58]
Clenbuterol	Liver samples	Bromoclenbuterol (PM)	-	Acidified methanol	Off-line	LC/ECD LC/MS	[91]
Cotinine	Urine samples	Methacrylic acid (FM), Ethylene glycol dimethacrylate (CL), Cotinine (PM)	Methanol water	Acetonitrile-water-TFA (95:2.5:2.5)	Off-line	LC/UV	[92]
Application to environmental samples							
4-Nitrophenol	Environmental water	4-Nitrophenol (FM), EGDMA (CL), 4-Nitrophenol (PM), AIBN (I)	Acetonitrile Acidified water	Acetonitrile	On-line	LC/UV	[93]
Catechol	River water	4-vinylpyridine (FM), EGDMA (CL), Catechol (PM), AIBN (I)	Chloroform	Methanol-acetic acid (4:1)	On-line	DPV	[94]
Trazines	Corn, soil, water	MAA (FM), Propazine (PM)	Toluene	Acetonitrile	Off-line	MEKC	[95]
Cadmium (II)	River water	4-vinylpyridine (FM), EGDMA (CL), Cadmium acetate(PM), AIBN (I)	Buffer solution	HCl, HNO_3, EDTA	Off-line	FAAS	[96]
Application to food samples							
Caffeine and theophylline	Green tea	MAA (FM), EDMA (CL), Caffeine and theophylline (PM), ATBN (I)	Acetonitrile	Methanol-acetic acid (90:10)	Off-line	LC/UV	[97]
Ochratoxin A	Red wine	QMMA (FM), EDMA (CL), Ochratoxin A (PM), AIBN (I)	Methanol water	Methanol-acetic acid (80:20)	On-line	LC/FLD	[98]

5.5. MODERN FORMS OF CARBON USED FOR SPE

Nowadays, the carbon nanotubes (CNTs) such as single-walled and multi-walled carbon nanotubes are being applied in determining nonpolar, medium polar, and polar analytes from aqueous samples. They possess better sorption capacity than C_{18} sorbent towards polar compounds. Moreover, porous immobilized graphitic carbon (PGC) is a new carbon-based sorbent in which graphite is immobilized on the silica structure [101–103]. Nevertheless, also another sorbent material such as the graphitized carbon black (GCB) is characterized by irreversible binding by the target analytes [102, 104–106]. Niu et al. [107] developed SPE disk based on a sheet of single-walled carbon nanotubes (SWCNTs) with successful reproducibility and high extraction efficiency for the enrichment of phthalate esters, bisphenol A (BPA), 4-n-nonylphenol (4-NP), 4-tert-octylphenol (4-OP), and polar chlorophenols from different natural water samples. This new approach was a combination of C18 and GCB properties. The main advantages of a developed activated carbon disk are strong adsorption capacity, high flow rate and simplicity of their preparation.

Conversely, Shi et al. [108] prepared macroporous and heterogeneous ceramic carbon materials (CCMs) for the determination of chlorpromazine in urine samples and monitored by an electrochemical method in less than 3 min. followed by liquid chromatography. The authors claimed that properties possessed by these sorbents might also be useful in the solid phase microextraction, thin-film microextraction, as well as electrochemically controlled solid phase extraction.

Puziy et al. [109] also performed evaluation of the morphology and porous structure of the nanostructured carbons formed, prepared by the template method using zeolite NaY and silica gels, using transmittance electron microscopy (TEM), XRD and nitrogen adsorption. They found that the achieved zeolite-derived carbon can be classified as a micropore material (1.1 nm); however, for the silica gel-derived carbon the size obtained was in the mesopore range (3.4 and 4.8 nm). The developed materials were successfully applied for the preconcentration of chlorophenols with 80–93% recovery at the breakthrough volumes 1700–1300 ml.

Most recently See et al. [110] described the utilization of membrane-protected carbon nanotubes in the view to their integration in the solid phase membrane tip extraction (SPMTE) before their semi-automated dynamic mode analysis by micro-liquid chromatography. They applied MWCNTs enclosed within a home-made cone-shaped polypropylene (PP) membrane, attached to 1000 µl capacity pipette tip, for selected triazine herbicides from river water samples.

5.6. SPE BED ON-CHIP

One of the latest directions in the development and sample throughput advantages of SPE filed, apart of the miniaturization, is the utilization of the microfluidic and on-chip analytical system [111–115]. The microfluidic technology plays a very important role in modern biotechnology and analytical chemistry, mainly due to the shorter separation time and much lower sample consumption. It integrates injection, reaction, separation and detection. Among different sample pretreatment methods carried out on a microchip device, SPE is one of the most important sample preparation technologies. The most valuable issue of combining SPE with a microfluidic device is to immobilize the extraction phase into the microchannels. There are several implementations of SPE microfluidic technology. One of them is focused on the direct coating extraction phase in the inner wall of the microchannel. Kutter et al. [116] prepared such an open-tube shaped channel from a simple glass chip coated with C18. Alongside the common approach of packing beads into a microchamber and forming micro-sized designs in the microchannel [117], the monolithic column has been developed as a new extraction technique [118, 119]. Most recently Liu et al. [96] described the utilization of polymer microfluidic chips integrating SPE and high performance liquid chromatography utilizing in situ photopolymerized polymethacrylate monolith as a bed sorbent. They applied a double-T geometry channel with a short monolithic trap column as a sample clean up and enrichment followed by microfluidic HPLC separations for the peptide analysis (Fig. 5).

Karwa et al. [120] performed the purification, preconcentration and extraction of genomic DNA from *E. coli* utilizing a C_{18} immobilized μ-chip SPE device. They found that the analytes of interest, as polar compounds, are suitable for obtaining a good recovery and high enrichment factor when sorbed into the poly(dimethylsiloxane) microfluidic channel. Octadecylsilica was immobilized onto a PDMS applied sol-gel chemistry mechanism in the presence of an acid and water.

Additionally, Hong et al. [121] introduced the microfluidic channel, prepared with the use of PDMS in the hydroxyl-terminated form, as the extraction phase for electrophoresis separation of amino acid. PDMS-OH microspheres bed was immobilized to the SPE channel by the magnetic field.

Completely different microfluidic device architecture for coupling SPE and micellar electrokinetic chromatography (MEKC) has been introduced by Ramsey et al. [122]. They utilized microcolumns of hydrophobic silane beads packed for the quantitative extraction of rhodamine B.

Some novel procedures are introduced by applying *on-line* sample pretreatment, e.g. Lab-on-Valve (LOV)-bead injection (BI). BI beads are applied for sample pretreatment in terms of trap form for preconcentration, isolation and separation target analytes. The flow-based sorbent extraction

approaches for the *on-line* SPE exploiting bead injection analysis have been meticulously described by Miró et al. [123]. The details on the principles and applications including some interesting approaches can be found in the following references [124-126].

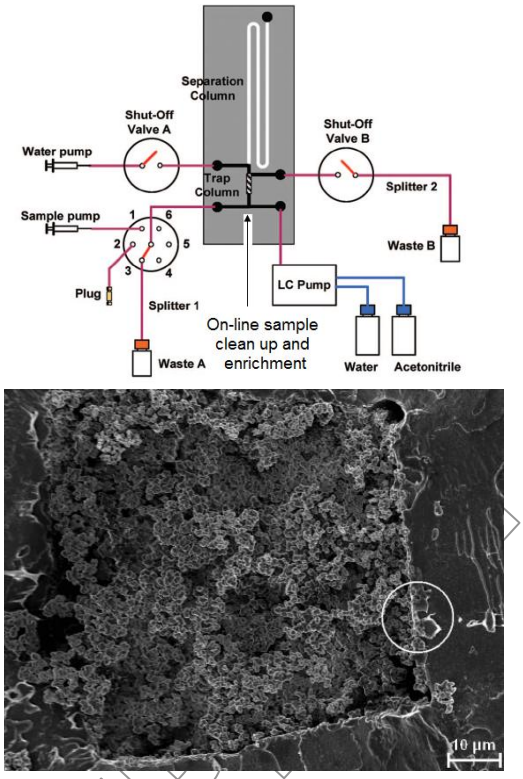

Fig. 5. SPE trap column as a chip design with the SEM image of hydrophobic polymethacrylate monolith covalent attachment to the channel surface. Reprinted from ref. [96] with permission from American Chemical Society.

6. CONCLUSIONS AND FUTURE REMARKS

All the methods proposed appear to be the latest trends in the bioanalytical aim of extraction and analysis of the highest possible number of compounds in one run. Additionally, they strive towards shortening the sample preparation and analysis time and increasing the number of samples which can be determined in a laboratory with one analytical method. The main advantages of the recently used solid phase extraction is the possibility of automation which appeared in better sample throughput, as well as the higher precision and accuracy of the obtained data. Nevertheless, this mode, as a time-saving procedure, provides a memory effect and systematic mistakes can be found. The classic bonded silicas are being displaced by

polymeric sorbents because they cannot effectively trap the most polar compounds. The development of various functionalized polymers and highly crosslinked sorbents would appear to be the next step in the synthesis of new materials for SPE. Nevertheless, new immunosorbents and molecularly imprinted polymers need to be developed. The sample preparation and analysis schedule for the future will include micro devices designed for chip-based connections via closed channels. Additionally, these channels will be integrated with miniaturized formats including HPLC or electrophoretic separations. The application of micro- and nano-scale based extraction and separation techniques will be developed in the future resulting in quick and sensitive analytical methods for the sample preparation and analysis. Generally, the trend is to simplify the manipulations and to reduce the time necessary for the sample preparation. The miniaturization, high-throughput systems with the use of new sorbents and automation of SPE are of interest in clinical, pharmaceutical, environmental and food fields.

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LIST OF ABBREVIATIONS AND SYMBOLS

a_i	Activity of the component
AIBN	Bis-azoisobutyronitrile
APS	3-aminopropyltriethoxy
ASE	Accelerated solvent extraction
Au	Gold
BI	Bead injection

BPA	Bisphenol A
C_m	Compound concentration in the lower layer
C_s	Compound concentration in the upper layer
CCMs	Ceramic carbon materials
CE	Capillary electrophoresis
CNTs	Carbon nanotubes
DAN	2,3-diaminonaphalene
DPV	Differential pulse voltammograms
DVB	Divinylbenzene
E^0	Eluotropic strength
EGDMA	Ethylene glycol dimethacrylate
ETAAS	Electrothermal atomic absorption spectrometry
FAAS	Flame atomic absorption spectrometry
FI	Flow injection
G	Free enthalpy
GC	Gas chromatography
GCBs	Graphitized carbon blacks
HILIC	Hydrophilic interaction chromatography
HLB	Hydrophilic-lipophilic balanced copolymer
HPLC	High performance liquid chromatography
IA	Immunoaffinity
ISRP	Internal surface reversed phase
K_D	Distribution coefficient
LBL	Layer-by-layer
LC	Liquid chromatography
LLE	Liquid-liquid extraction
LLME	Liquid-liquid microextraction
LOV	Lab-on-Valve
MIPs	Moleculary imprinted polymers
MAE	Microwave assisted extraction
MALDI	Matrix-assisted laser desorption ionization
MD	Multidimensional
MEKC	Micellar electrokinetic chromatography
MESI	Membrane extraction with sorbent interface
MISPE	Molecularly imprinted solid phase extraction
MMLLE	Microporous membrane liquid-liquid extraction
MS	Mass spectrometry
MSFIA	Multisyringe flow injection system
MSPD	Matrix solid phase dispersion
MWCNTs	Multi-walled carbon nanotubes
μ_i	Chemical potential of *i* component
n_i	Number of moles
NP	Nanoparticle
NP	Normal phase
4-NP	4-n-nonylphenol
ODS	Octadecyl-bonded silica
4-OP	4-tert-octylphenol
p	Pressure
PAHs	Polycyclic aromatic hydrocarbons
PANI	Polyaniline
PDMA	Polydimethylosiloxane
PDMS	Polydimethylsiloxane
PEGFDs	Particle-embedded glass fiber disk
PFE	Pressurized fluid extraction
PGCs	Porous graphitic carbons

PLMs	Particle-loaded membranes
PME	Polymeric membrane extraction
PNMA	Poly-N-methylaniline
PP	Polypropylene
PPy	Polypyrrole
PS	Polystyrene
PS-DVB	Polystyrene-divinylbenzene
P&T	Purge-and-trap
PTFE	Polytetrefluoroethylene
R	Ideal gas constant (8.314 J/mol K)
RAM	Restricted access material
RP	Reversed phase
S_{H_2O}	Water solubility
SBSE	Stir bar sorptive extraction
SDVB	Styrene-divinylbenzene
SE	Solvent extraction
SEM	Scanning electron microscope
SFE	Supercritical fluid extraction
SLM	Supported liquid membrane extraction
SPE	Solid phase extraction
SPDE	Solid phase dynamic extraction
SPME	Solid phase microextraction
SPMTE	Solid phase membrane tip extraction
SWCNTs	Single-walled carbon nanotubes
σ_v	Standard deviation
T	Temperature
TEA	Triethylamine
TEM	Transmission electron microscope
THP	Theohylline
TOF	Time of flight
UV	Ultraviolet
V	Vanadium
V_B	Breakthrough volume
V_E	Equilibrium volume
V_R	Retention volume
V_0	Total volume