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Solid-phase extraction of organic compounds: A critical review (Part I)

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ABSTRACT

Solid-phase extraction (SPE) is the most widely used method for the extraction, changing of solvents, cleanup, concentration, and fractionation of organic compounds from a number of samples. This procedure is also very useful for desalting proteins and sugar samples. However, most SPE procedures are still poorly developed, with little consideration to the physics involved in the process and are described as largely empirical, labor-intensive, and time-consuming trial-and-error processes, without much systematization.

The objective of this study is to propose a number of contradictions, disagreements, failings, and shortcomings of the SPE procedures found elsewhere. The different arguments introduced in this study attempt to challenge the suitability of this procedure, particularly when it is conducted in the traditional manner (under gravity and at a high flow rate).

The first part of this study focuses on describing the state-of-the-art in SPE and its physical fundamentals.

Contents

Abbreviations: C, Carbon; CNTs, Carbon Nanotubes; DNA, Desoxyiribonucleic Acid; DVD, Divinylbenzene Pyrrolidone; EPA, Environmental Protection Agency; FTIR, Fourier Transform Infrared Spectroscopy; G, Graphene; GO, Graphene Oxide; HEMA, 2-Hydroxyethylmethacrylate; HEPES, 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethane sulfonic acid; HLB, Hydrophilic Lipophilic Balanced Polymers; HPLC, High-Performance Liquid Chromatography; HXLPP, Hypercross Linked Polymeric Sorbent; IMSs, Immunosorbents; LC, Liquid Chromatography; LC/MS, Liquid Chromatography/Mass Spectrometry; LLE, Liquid–Liquid Extraction; LODs, Limits of Detection; MIP, Molecularly Imprinted Polymers; MISPE, Molecularly Imprinted Solid-Phase Extraction; MMIP, Magnetic Molecularly Imprinted Polymers; MNPs, Magnetic Nanoparticles; MSCX, Magnetic Strong Cation Exchange; MSPE, Magnetic Solid-Phase Extraction; MWCNT, Multiwalled Carbon Nanotubes; NMR, Nuclear Magnetic Resonance; PAHs, Polycyclic Aromatic Hydrocarbons; PDDA, Poly(diallyldimethylammonium chloride); PEs, Phthalate Esters; PTFE, Polytetrafluoroethylene; RNA, Ribonucleic Acid; RPLC, Reverse Phase High-Performance Liquid Chromatography; RSD, Relative Standard Deviation; SDB-XC and SDB-RPS, Poly-(styrenedivinylbenzene) copolymers; SPE, Solid-Phase Extraction; SPESs, Solid-Phase Extraction Sorbents; UV/Vis, Ultraviolet/Visible; UHPLC, Ultra High-Performance Liquid Chromatography.

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1. Introduction

Analytical chemistry is a tool to support a number of scientific realms such as forensics and biomedical sciences [1], pharmaceutical science [2], environmental engineering [3], combustion [4], edafology and agronomy [5], food industry [6], epidemiology [7], kinetics [8], and reactivity/photoreactivity studies [9].

Consequently, the effort put into developing efficient analytical procedures is of utmost importance to various scientific disciplines.

Clean-up, preconcentration, and fractioning of samples are some of the most time-consuming steps during the analytical procedure, accounting in average for 61% of the total time required to perform analytical tasks [10]. Besides, they are critical steps, because a significant amount of the target analytes can be lost during these stages and any mistake occurring in collecting and processing an analytical sample could lead to substantial errors in the final results, regardless of the potential excellent performance of the analytical technique in use [11].

Pollutants are usually present in food and environmental samples at very low concentrations (ng/g). Moreover, they are dispersed in highly complex (including thousands of different compounds) and morphologically unstructured matrices with an elevated degree of sample-to-sample variability [4,12]. Therefore, establishing clean-up and preconcentration steps [13,14] has become mandatory and is required by environmental [15] and food legislations, health authorities, and companies operating in the food market [14]. On the other hand, any assessment of efficiency of environmental protection policy needs relevant and reliable data on concentration levels of pollutants (particularly micro-pollutants and emerging pollutants) in the environment.

Environmental pollutants include compounds such as pesticides [16]; pharmaceuticals (antibiotic, analgesic, anti-inflammatory, diuretic, cardiovascular, antiepileptic, and antineoplastic agents, antidepressants, antipsychotics, hormones, drugs, etc.) [17,18]; steroids, xenoestrogens, and other endocrine disrupting compounds [19]; drinking water disinfection by-products; gasoline additives; brominated flame retardants; industrial additives and agents; algal toxins; organotins; chemical warfare agents; and cholesterol and pesticide degradation products [15].

Other compounds of environmental concern are polycyclic aromatic hydrocarbons (PAHs) and their derivatives.

Concerning food industry, contamination by natural or anthropogenic chemicals poses severe risks to human health. Dangerous substances in food include natural toxics such as mycotoxins, phycotoxins, and phytotoxins [20]; environmental contaminants such as polychlorinated dioxins [21] and PAHs [22]; and chemicals such as pesticides and veterinary drugs [23], which must meet the legislative requirements.

Other scientific fields such as combustion require simple and efficient analytical procedures for clean-up and fractionation of organic compounds in very complex matrices such as soot from fossil fuels and biofuels [4,24]. Meanwhile, forensic science needs efficient and sensitive methodologies to detect drugs and poisons at trace levels in clinical samples such as blood, tissues, and urine [25].

Solid-phase extraction (SPE) is the most frequently used procedure for clean-up [15], extraction, class fractionation [26], and preconcentration of trace pollutants from environmental [17], clinical [25], biological, food, and beverage samples [6,27]. SPE is also useful for storing micro-pollutants from environmental samples [28] and desalting proteins and sugar samples [29] because of its simplicity and limited use of organic solvents [28,29]. Other uses of SPE are derivatization [30], concentration of pigments, and changing of solvents [31]. In addition, several Environmental Protection Agency (EPA) methodologies include SPE as the recommended procedure for pretreatment of organic pollutants. Thus, EPA method 1694 [32] recommends SPE through Oasis HLB cartridges for extraction and clean-up pharmaceuticals and personal care products in waters. As regards SPE as a tool for derivatization, there are some relevant examples: Liu et al. [33] used Fe_3O_4/SiO_2/P(MAA-co-EGDMA) [magnetite/silica/poly(methacrylic acid-co-ethylene glycol dimethacrylate)] for the simultaneous extraction and derivatization of heptanal and hexanal in urine. Concerning forensics and clinical sciences, SPE has been successfully used for the extraction and preconcentration of a wide range of substances such as amitriptyline, acetaminophen, cocaine, cholesterol, amobarbital, and androstenedione or caffeine in saliva, nails, meconium, amniotic liquid, vitreous humor, muscle, intestine, liver, and brain tissues [25]. Small samples of brain or liver (1 g), vitreous humor (0.5–1.0 mL), amniotic liquid (1 mL), or intestine (3 g) or small volumes of sweat are sufficient for detection of even trace amounts of drugs such as cocaine.

The first experimental applications of SPE started 50 years ago, although this process was not applied with analytical aims until the mid-1970s [27]. Disposable cartridges for SPE were introduced more than 30 years ago (first cartridges date back to 1978, syringe-format types to 1979, columns for on-line coupling with liquid chromatography (LC) to the early 1980s). SPE development was slow for many years, liquid–liquid extraction (LLE) remaining as the preferred technique for pretreatment of liquid samples, particularly in the environmental field, until the 1980s. Since then, there have been many improvements in the formats of SPE cartridges or disks [34] and a number of new sorbents, such as immunosorbents (IMs) or molecularly imprinted polymers (MIPs), were introduced [35,36].

Besides the development of new materials and sorbents formats, SPE underwent a number of modifications over the last few years, with the majority based on miniaturization and automation [18] of different stages of SPE, which resulted in the development of new extraction techniques such as solid-phase dynamic extraction (SPDE), micro-extraction by packed sorbent (MEPs) [37], matrix solid-phase dispersion (MSPD), stir-bar sorptive extraction (SBSE), solid-phase micro-extraction (SPME), automated headspace dynamic solid-phase extraction [38], and dispersive solid-phase extraction (d-SPE). However, these techniques are beyond the scope of this study, and we focus only on traditional off-line and on-line SPE as well as magnetic SPE.

SPE has been accepted for more than 20 years as the alternative sample preparation method to LLE in many EPA methods for analysis of organic compounds, particularly in drinking water and wastewater. However, some of them are poorly developed with little consideration to the physicochemical processes involved, the optimization procedure being largely empirical and time-consuming trial and error approach [39]. This study attempts to reveal the lack of systematization of SPE optimizing approaches and critically review some of the most important protocols for extraction, clean-up, concentration, and fractionation of organic pollutants from many environmental, food, and biological samples.

2. Physical fundamentals of SPE

The basic SPE procedure consists of loading a solution onto a solid phase (usually a cartridge containing the sorbent) capable of retaining the target analytes, washing away undesired components, and washing off /eluting the desired analytes with another solvents into a collection tube [40]. A typical SPE procedure is shown in Fig. 1.

Conditioning the solid-phase materials consists of passing organic solvents or water through the column to increase the effective surface area and reduce interferences [41]. After drying the sorbent and possibly removing interferences, the interactions between analytes and the solid-phase material are disrupted by flushing small volumes

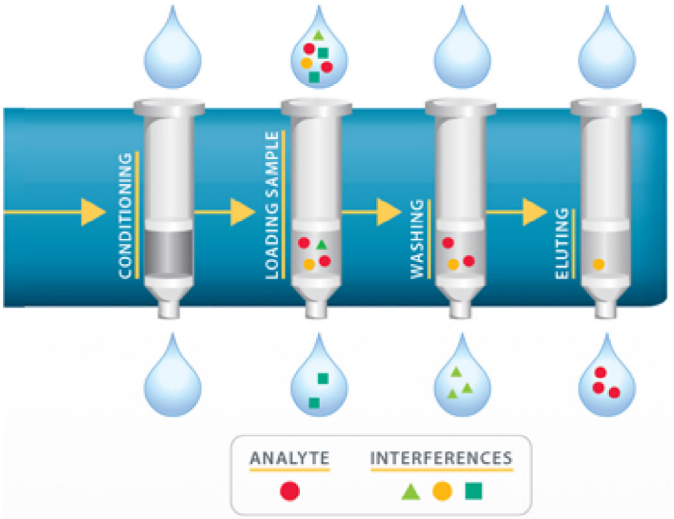

Fig. 1. Typical four-step SPE procedure.

of organic solvents, which leads to desorption of the target analytes from the solid phase [41].

Depending on the nature of the solid phase, a number of solute retention mechanisms are assumed to govern the process.

A common mechanism to describe the SPE process is partition. In this case, the stationary phase can be considered a liquid that is immobilized on a solid support and the principle is similar to that of LLE, involving a partitioning of solutes or distribution processes between the liquid sample and the liquid immobilized on a stationary phase [42].

In general (for any sort of organic solvents), Nernst distribution law (Equation 1) was proposed to describe the mechanism of LLE. The distribution law, derived in 1898 by W. Nernst, relates the distribution of a solute in the organic and aqueous phases. For the equilibrium reaction:

$$A(aq) \leftrightarrow A(org) \tag{1}$$

Nernst distribution law is written as

$$K_{D,A} = \frac{[A]_{org}}{[A]_{aq}} \tag{2}$$

where $K_{D,A}$ is the distribution constant of solute *A*. Strictly, this equation is only valid for pure solvents, but in practice, solvents are saturated with molecules of the other phase. Moreover, the solute *A* can undergo different solvation levels in the two solvents (organic and water). Nevertheless, Equation (1) may be considered valid if the mutual solubilities of the solvents are small, say <1% and the activity factors of the system are constant. If the solute is strongly solvated or at high concentration (mole fraction > 0.1) or if the ionic strength of the aqueous phase is high (>0.1 M) or variable, Equations. 1 and 2 must be corrected for deviations from ideality according to Equation 3 as follows:

$$K^0_{D,A} = \frac{\gamma_{A,org}[A]_{org}}{\gamma_{A,aq}[A]_{aq}} K_{D,A} \tag{3}$$

where γs are the activity coefficients. For aqueous electrolytes, γs vary with the ionic strength of the solution [43].

Liquid/solid adsorption and ion exchange are also possible mechanisms in various separations. In this case, instead of two immiscible liquid phases (as in LLE), SPE involves partitioning between a liquid (sample matrix) and solid (sorbent) phase. The simplest approach consists of considering the stationary phase as a liquid immobilized into the sorbent.

Similar to LC separations, according to this approach, the SPE process consists of an exchange of the molecular species *X* between the mobile phase "*mo*" and the stationary phase (immobilized liquid) "*st*" in the equilibrium

$$X_{mo} \overset{eq}{\longleftrightarrow} X_{st} \tag{4}$$

This equilibrium is characterized by an equilibrium constant *K(X)*, which describes the ratio of the molar concentration of species *X* in the stationary phase ($C_{X,st}$) to the molar concentration of species *X* in the mobile phase ($C_{X,mo}$). *K(X)* is given by

$$K(X) = \frac{C_{X,st}}{C_{X,mo}} \tag{5}$$

As in chromatographic separations, a capacity factor (retention factor) *k*(X) for SPE retention is defined by Equation 6 as

$$k(X) = \frac{t_R}{t_0} \tag{6}$$

where t_R is the time from the start of application of the compound *X* on the solid phase to its elution time and t_0 is the time of elution of an unretained compound (note: index *X* for *k* is frequently omitted, but the retention factor always depends on the compound).

The following important parameters must be defined:

(a) A retention volume $V_R(X)$ is defined for SPE as the volume of mobile phase flowing between the application time of a small sample and their elution.
(b) Retention time, $t_R(X)$.

The following relationship relates both parameters:

$$V_R = t_R U \tag{7}$$

where *U* is the volumetric flow through the SPE device.

A selectivity parameter α that characterizes the ratio of the time between the elution of two different compounds can be defined for SPE as well.

In analogy to chromatography, an equilibrium for the exchange of molecular species *X* between mobile phase and stationary phase is attained when the difference between the chemical potentials $\mu_{j,mo}$,$\mu_{j,st}$ of compound *j* in the two phases is zero:

$$\mu^0_{X,st} + RT\ln a_{X,st} = \mu^0_{X,mo} + RT\ln a_{X,mo} \tag{8}$$

From this, K(X) is given by

$$\ln K(X) = \frac{\left(-\Delta H^0_X + T\Delta S^0_X\right)}{RT} \tag{9}$$

Equation (9) shows that larger values of ΔH^0_X lead to larger values of *K(X)* (for the equilibrium to be displaced toward the products, ΔH^0_X must be negative). However, the detailed contribution of different interactions during the equilibrium process to ΔH^0_X is difficult to assess [30,43].

Consequently, new theories were developed for explaining the reverse phase high-performance liquid chromatography (RPLC) phenomenon (also SPE retention and elution mechanisms). Most of these theories consider the aforementioned two phenomena: partition and/or adsorption onto the stationary phase with different levels of preponderance, depending on the approach.

Thus, current tendencies consider simultaneous contributions from both the retention mechanisms: adsorption on free silanols

and partitioning into the chemically bonded phase [44]. Preponderance corresponds to a mechanism that is largely partitioning, particularly for C_{18} stationary phases and small nonpolar solutes [45], leading to other approaches of RPLC retention mechanism and overcoming the limitations of solvophobic and lipophilic theories [46]. Examples of this are the unified molecular theory model of Martire and Boehm [45] or the statistical mechanical theory [47]. However, both exhibit some flaws and controversies. First, a monomolecular layer cannot be considered a phase in thermodynamics. Another important drawback is the lack of explanation of why retention of analytes on the stationary phase changes when solid-phase particles become saturated by organic modifier [48]. Indeed, silica-bonded alkyl ligands have been shown to act more as an anisotropic interphase than as a bulk liquid phase in RPLC [47].

Adsorption approaches try to account for the influence of alkyl chain nature, their surface density, or the presence or absence of end-capping of the stationary phases [49]. These approaches fail to explain some important experimental observations. Thus, although a correlation between the adsorption equilibrium constant (K) and the carbon content of stationary phases was shown, the value of K increases with increasing carbon content, slope of the curves gradually decreases for carbon contents above 10%, and similar values of K are observed at 13.7% and 17.1% [50]. Therefore, it has been argued that only part of the C_{18} ligands contributes to the retention in RPLC [51]. Other authors claim that this is because when more ligands are present inside the pores of silica particles, both pore volume and surface decrease. Hence, the solid–liquid contact interface becomes smaller [52]. However, they do not explain the very strong retention of molecules highly polarizable as compared to that of nonpolarizable molecules under the same experimental conditions. Besides, this approach fails to explain the change of saturation capacities as a function of bonding density, with the actual nature of the heterogenous adsorption on RPLC packing material remaining unclear [49].

According to Andrade-Eiroa et al. [53], the proposed theories fail to explain most phenomena observed in SPE and RPLC because of the disregarding of the preponderant interactions: electronic and or electromagnetic forces. In literature the most frequently quoted interactions are Gibbs free energy, consisting of cavity energy and interactions energy contributions from van der Waals and H-bond interactions [54]. However, also electronic interactions and ion exchange processes may be relevant, depending on the nature of the analyte [54] and sorbent. Electronic interactions might explain the high retention and improved selectivity observed onto MIPs and carbon-based SPE sorbents. In particular, the imprinted sites of MIPS usually bind analytes by an electrostatic driving force, such as hydrogen bonding, ionic interactions, or π–π bonds [55]. Finally, retention mechanisms onto magnetic nanoparticles (MNPs) are also directly related to electromagnetic forces.

One of the most recent attempts of systematization and grounding of SPE is that by Andrade-Eiroa et al. [24]. The authors claim that the higher the difference between the dielectric constants (relative permittivity) of mobile and stationary phases, the higher the retention of polarizable analytes onto the SPE sorbent. The authors based their theory in the fundamentals of RPLC published in 2011 by Andrade-Eiroa et al. [53]. Authors of the aforementioned study stated that RPLC retention mechanism most likely occurs through polarization of stationary phase (usually dielectric surfaces) submerged in solvents with a very high dielectric constant and high dipole moment (i.e., water and/or acetonitrile) at high pressures as those applied in RPLC systems. The polarized surface interacts with polarizable target analytes causing retention onto the analytical column.

At high pressures as those developed by RPLC systems, according to the mathematical equations developed for modeling the retention times of probe molecules in an RPLC column, interaction between dipole moment of the mobile phase and the pressure inside the column occurs, which increases with the increase of polarizability of the probe molecule, and accounts for most phenomena observed in RPLC. Andrade-Eiroa et al. [53] also considered that this hypothesis could be extended to ions and acid/basic compounds if electrostatic repulsions among target analytes are considered [24].

These statements have been recently confirmed by the conclusions published by Amador-Hernández et al. [56]. In fact, the authors applied an electric field to organic "liquid membrane" supported between two polytetrafluoroethylene (PTFE) modules, acceptor and donor phases, respectively, for isolation and preconcentration of three atrazines from water samples. They studied several supported solvents such as 1,2-dichloroethane (1,2-DCE), dihexyl ether (HEX), and undecane (UND), and finally selected 1,2-DCE as the optimum one. The transfer of triazines through the polarized interface of 1,2-DCE and water seems to be more rapid and the enrichment factor was found to be higher than that achieved through nonpolarized membranes, similarly to the increase of efficiency of preconcentration of species from water samples [56].

However, in SPE, low pressures (atmospheric pressures or even negative pressures) are applied. Consequently, hydrodynamics gains importance and separation of compounds will take place as a function of their solubility rather than their medium polarizability as it occurred in RPLC procedures whereby the analytes are mostly separation as a function of their polarizability [24].

In SPE procedures (Fig. 2), flow through the cartridge takes place under gravity; consequently, hydrostatic pressure (due to the weight to the solvent) in the solvent front (point 2) is high. If, on the contrary, flow were against gravity, hydrostatic pressure in the solvent front would be very low, facilitating the adsorption–desorption equilibrium and fractionation of compounds as a function of their solubility into the mobile phase. This SPE procedure against gravity has been recently used by Andrade-Eiroa et al. [24] in the aim of isolation and fractionation of PAHs and their derivatives from soot extracts. In this case, the procedure is quite similar to that of preparative chromatography, as the mobile phase is passed through the commercial analytical column using a high-performance liquid chromatography (HPLC) pump. However, the application of low pressure (1–5 bar) converts the procedure into an SPE methodology.

Therefore, hydrodynamics may account for the higher efficiency of SPE against gravity over traditional SPE under gravity.

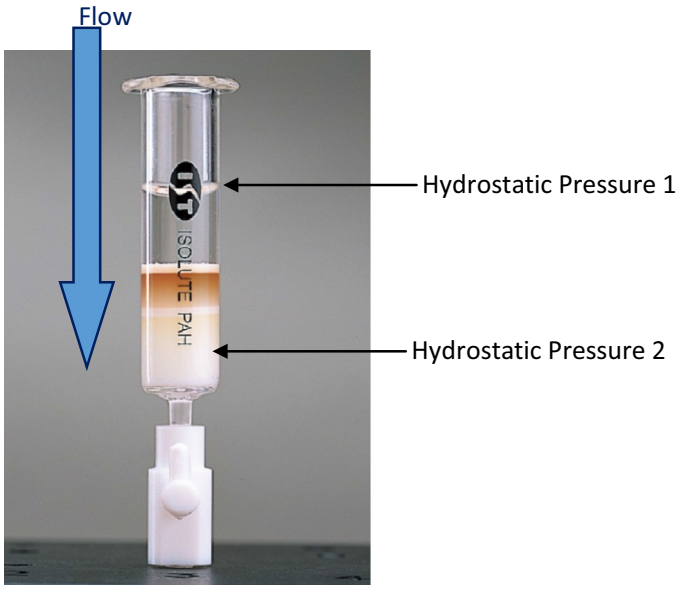

Fig. 2. SPE procedure under gravity (Reproduced with kind permission from Biotage Isolute PAH).

3. Sorbents and formats in SPE

3.1. Sorbents in SPE

A large number of SPE materials and formats are commercially available (Table 1), covering a wide range of analytes and consequently a large variety of applications [36].

In fact, the development of solid-phase extraction sorbents (SPESs) has attracted research attention in different fields, such as materials science, nanotechnology, polymer synthesis, and analytical chemistry, aiming at development of new materials with enhanced selectivity; better sorptive/adsorptive capacity; enhanced thermal, chemical, or mechanical stability; and increased lifetime [68].

Table 1 summarizes the most widely used sorbents and SPE mechanisms. As for LC, different modes are possible depending on the polarity of stationary and mobile phases.

Among the aforementioned materials, the most commonly used SPE sorbents reported in the literature are:

- Alkyl-bonded silicas,
- Copolymer sorbents such as
  - Cross-linked polystyrene divinylbenzene (SDB-XC and SDB-RPS (poly(styrenedivinylbenzene copolymers)) [57],
  - In-house hypercross-linked polymeric sorbent (HXLPP Polar [69]),
  - Hydrophilic lipophilic balanced polymers (Oasis HLB is the most popular of this class [36]). This last sorbent is a

Table 1
Summarizes the most widely used sorbents and SPE mechanisms. As for LC, different modes are possible depending on the polarity of stationary and mobile phases

REVERSE-PHASE	**Polymeric phases** based on Styrene-divinylbenzene Hydrophylic-Lipophilic Balanced phases (Oasis HLB) N-vinyl pirrolidone (Strata-X, Phenomenex) Bond-Elut Plexa (Agilent Technologies) In-house polymeric phases: PANI, PPy, 4-VP-DVB(4-vinylpyridine-divinylbenzene), 4-VIm-DVB, HXLPP (Hypercross linked polymeric sorbent) polar B [36]; cross-linked polystyrene divinylbenzene (SDB-XC (poly(styrenedivinylbenzene)) and SDB-RPS (poly(styrenedivinylbenzene) [57] **Silica-bonded phases** Octadecyl-bonded silica Octyl-bonded silica Butyl-dimethyl bonded silica Phenyl-bonded silica Hisep. Hydrophobic surface enclaved by a hydrophilic network
NORMAL-PHASE	Ciano-bonded silica Diol-bonded silica Graphene Oxide (GO) [58] Amino-bonded silica
ION-EXCHANGE	LC-SAX Quaternary Amine bonded silica with Cl- counterion LC-SCX Sulfonic acid bonded silica with Na^+ counterion [59] LC-WCX Carboxylic acid bonded silica with Na^+ counterion
MIXED-MODE SPE (ION-EXCHANGE+ REVERSED-PHASE)	**Polymeric structures** Polymeric strong cation-exchange — Polymer structure modified by sulfonic acid Polymeric weak cation-exchange — Polymer structure modified by carboxylic acid [60] Polymeric strong anion-exchange — Polymer structure modified by quaternary amine Polymeric weak anion-exchange — Polymer structure modified by secondary amine
ADSORPTION	Silica gel without bonded phase **Alumina-Based Packing – Crystalline, chromatographic grade alumina, irregular particles, 60/325 mesh** Alumina-A Alumina-B Alumina-C **Florisil®-Based Packing–Magnesium silicate, 100/120 mesh particles** LC-Florisil Envi-Florisil **Resin-Based Packing – 80–160 μm spherical particles** Envi-Carb P **Graphitized Carbon-Based Packing – Nonbonded carbon phase** Envi-Carb Envi-Carb C
SIZE EXCLUSION+ADSORPTION	**Graphitic Carbon Nitride (g-C_3N_4)** [61] **Restrict Access Materials (RAMs)**
ADSORPTION+MAGNETIC SPE	**g-C_3N_4/Fe_3O_4** composite materials [62]
MAGNETIC SOLID-PHASE EXTRACTION	**Graphene** [63] **Graphene/Fe_3O_4@polythiophene nanocomposite** [64] **Graphene oxide (GO)/Fe_3O_4 nano-hybrid** [65] **Fe_3O_4/SiO_2/P(MAA-co-EGDMA)** [33] **Conducting Polymers (CPs)** — **Polytiophene** **Polytiophene coated with Fe_3O_4**
ELECTROSTATIC DRIVING FORCE	**Magnetic NPs coated with MIPs** **Molecularly Imprinted Polymers**
IMMUNOSORBENTS (IMSs)	Based on molecular recognition by antibodies [66]
IONIC LIQUIDS	Immobilized onto a silica or polymeric surface [67]

commercially available macroporous copolymer consisting of a balance ratio of two monomer components: lipophilic DVB (divinylbenzenevinylpyrrolidone) and hydrophilic N-vinylpyrrolidone. According to some authors, the hydrophilic component offers good wettability to the resin and high mass transfer rates from aqueous solutions, while the lipophilic one provides reverse phase retention of analytes. The material is designed for sorptive preconcentration of organic compounds with a broad spectrum of polarities in a number of matrices and is stable over the entire range of pH [15,42]. Thus, Azzouz and Ballesteros [12] selected it for the extraction/clean-up of pharmaceuticals, personal care products, and hormones in soils, sediments, and sludge. The following compounds were analyzed: 17α-ethinylestradiol, 17β-ethinylestradiol, estrone, thiamphenicol, pyrimethamine, florfenicol, chloramphenicol, propranolol, metoprolol, carbamazepine, triclosan, clofibric acid, phenylbutazone, niflumic acid, naproxen, mefenanic acid, ketoprofen, ibuprofen, flunixin, diclofenac, paracetamol, and acetylsalicylic acid. Oasis HLB cartridges were also used for clean-up and concentration of PAHs and carbonyl compounds [70].

In order to improve selectivity of the extraction procedure, MIPs, immobilized receptors or antibodies (IMSs), and restricted access materials (RAMs) were introduced 20 years ago [66]. However, applications of IMSs seem to be limited to the pharmaceutical and biomedical trace analyses [71], whereas MIPs would be limited to the selective extraction and clean-up of mainly polar compounds [35]. As regards RAMs, they are efficient only for removing very large molecular interferences (such as humic substances), which cannot be easily trapped by RAMs structure, whereas smaller analytes such as pesticides are retained [15]. On the other hand, IMSs based on molecular recognition by antibodies show high selectivity to target molecules [66]; however, because of their low stability, preparation difficulties, and high cost, their applications are limited to some extent [72].

In spite of all the aforementioned innovations, alkyl-bounded silica phases (especially C_{18} and C_2) as well as the recently introduced OASIS HLB sorbents are the most commonly used sorbents in SPE. In fact, some EPA methods such as 525.1 recommend C_{18} silica adsorbent for the extraction of PAHs from water [73].

3.1.1. *Magnetic sorbents applied to SPE*

In order to overcome the limitations of conventional SPE, besides the aforementioned phases, magnetic or magnetically modified adsorbents were introduced, developed, and used for bioseparation and chemical analysis [74].

One of the first applications of magnetic solids in analytical chemistry was the isolation and extraction of magnetic bacteria from marine sediments. These magnetotactic microorganisms have specific intracellular organelles (magnetosomes) aligned in a chain-like manner, which, in most cases, comprise nanometer-sized, membrane-bound crystals of magnetic iron minerals [75]. Despite this application and the fact that a magnetic MnO_2 adsorbent was already used in 1996 by Towler et al. [76] for the recovery of Ra, Pb, and Pol from seawater, it was not until 1999 when Safarikova et al. [10] introduced the magnetic solid-phase extraction (MSPE), whereby target analytes are preconcentrated from large volumes of samples.

The procedure is based on the use of magnetic or magnetizable adsorbents placed directly into a solution or suspension containing analytes and the application of an external magnetic field (magnet) arranged outside the extraction vessel for rapid separation of the sorbent with the adsorbed analytes from the crude sample matrix [10]. According to many authors, this technique highly simplifies the SPE procedure and enhances the extraction efficiency [77–79].

MNPs show remarkable phenomena such as

(a) Superparamagnetism (that is, the magnetization behavior of these particles above a certain temperature, is identical to that of atomic paramagnets except that an extremely large moment and thus, large susceptibilities are involved) [77],
(b) high field irreversibility,
(c) high saturation field, and
(d) extra anisotropy contributions or shifted loops after field cooling [78].

Frenkel and Dorfman [80] first hypothesized that a particle of ferromagnetic material, below a critical particle size (<15 nm), would consist of a single magnetic domain, that is, a particle that is in a state of uniform magnetization at any field. Direct contact of the MNPs with the analytes is thought to cause selective adsorption of the compounds onto the solid surfaces. Because of their small particle size, MNPs are characterized by high specific surface area, sorption capacity, and adsorption rate. As a consequence, less amounts of sorbent and short equilibrium times are required to extract analytes from large volumes of samples (usually water [79]). Moreover, high selectivity through a retention mechanism of analytes mainly based on hydrogen bonding, dipole–dipole interactions, and π–π interactions is expected [11].

However, a size of several nanometers is often inappropriate to isolate analytes from large volumes of samples, because of the fact that pure iron oxides are prone to aggregate, resulting a loss of their magnetism [79]. In order to overcome these difficulties, the surface of the magnetic core (mainly iron, nickel, cobalt, and their oxides such as magnetite (Fe_3O_4) and maghemite (γ-Fe_3O_4) [81]) is coated with suitable inorganic substances (e.g., silica, alumina, manganese oxide (IV), or graphene [82]) and organic substances (e.g., MIPs [83], chitosan, divinylbenzene, polyamidoamines, or surfactants). A suitable coating for the core increases the durability of the chemical sorbent and prevents its oxidation. Moreover, further modification of the inorganic or organic coating of the core by suitable functional groups enhances the sorption properties of the sorbent [11], particularly when inorganic substances such as silica are, directly or via a second step, functionalized with different molecules such as antibodies, specific receptors, metals, enzymes, and protein alkyl chains [84].

MNPs have been used for decades to improve the separation of chemical species of different natures [82]. In environmental chemistry, MSPE has been used for the isolation of ions, inorganic compounds, and organic compounds (e.g., pesticides, dyes, surfactants, PAHs, drugs, antibiotics, and carcinogenic and mutagenic compounds). Concerning, applications of MSPE in food, we must say that although there is much research focused on isolating contaminants from food samples, many scientific and technical challenges remain to be solved before their practical use in this realm [11]. In spite of limitations of MSPE in the food analysis, some especific magnetic materials have been applied to the extraction of harmful analytes from food samples. Maybe the best example of this is the magnetic strong cation exchange (MSCX) resin prepared by Xu et al. [85] and successfully applied to the extraction of melamine from eggs.

On the contrary, MNPs have also been widely used in the field of biosciences, including biotechnology and medicine, to isolate proteins, peptides, and even cells [82] as well as for isolation, purification, and immobilization of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) from viruses, bacteria, and biological fluids [86].

Magnetic materials have also been applied to the selective extraction of synthetic organic compounds such as plastic softeners and detergents [87].

Magnetic separation has also focused on analyzing drugs, toxins, and steroids and carcinogenic compounds such as ergosterol, sulfonamides, or salicylic acid in different analytical matrices [82].

Particularly interesting is the application of barium alginate caged Fe_3O_4@C_{18} MNPs for preconcentration of PAHs and phthalate esters (PEs) from environmental water samples by Zhang et al. [88].

One of the main advantages of separations based on magnetic solids is their speed [89]. As stated earlier, MNPs are capable of extracting analytes from large volumes of samples efficiently after a short equilibrium time. In addition, the coating of MNPs provides them with specific functionalities and consequently high selectivity toward target analytes. Main advantages of MNPs are that they can be recycled, usually after appropriate rinsing, and the analytes adsorbed can be desorbed by procedures such as sonication [79]. Other advantages when compared with other SPE procedures are easier preparation, simpler sample handling procedure, less solvent consumption, and an increased extraction recovery [85]. In addition, magnetic beads are new potentially useful supports for bead injection analysis [82].

The disadvantage of MNPs is that the stationary phase and thermally unstable components can be partly or completely degraded during desorption procedures at high temperatures. This leads to deterioration in the accuracy and precision of analysis [90]. In fact, at pH < 4.0, degradation of the magnetite present in the magnetic adsorbent can take place, allowing the formation of chelates between Fe(III) and target analytes such as sulfonamides [90]. On the other hand, at pH > 9.0, magnetite particles acquired a negative charge because of the binding of hydroxide groups, causing electrostatic repulsion between the adsorbent and anionic forms of target analytes [91]. This is slightly confusing: it is supposed that magnetite is a magnet and also anion in movement. It is well known that the ion is a charged particle into movement, which behaves like a magnet when it moves in the bulk of the stirred solution and creates a small magnetic field in its vicinity. Although the motion of ions into solutions is similar to the thermal motion of electrons in a conductor with no net current, the net magnetic field being cancelled out, near each moving ion, a very small magnetic field is created. Furthermore, interactions between magnetic fields and electrons or charged moving particles are only possible under certain circumstances ($v \neq 0$ and not parallel or antiparallel to the magnetic field created by the MNP) [92]. However, authors focuses only on electrical repulsions among static charges. Possibly, this is a consequence of not taking electrodynamic phenomenon into account [93]. Of course, electric repulsions can also occur between negatively charged particles on the sorbent and anions in solution, and because electric forces are significantly stronger than magnetic forces, electronic forces predominate. In this case, the following two questions arise: what is the purpose of developing new magnetic materials if magnetic forces are insignificant compared with electronic forces? Why materials capable of strong electronic interactions with analytes are not developed?

Moreover, most target analytes are not charged molecules (most of them are neutral molecules, or with dipole character) and they do not interact with magnetic fields. Even molecules with dense electronic clouds such as PAHs could not interact with magnetic fields because their electrons are strongly retained. Moreover, most neutral organic molecules such as pollutants in water and biological samples are diamagnetic and are immersed into a diamagnetic medium (water with dissolved salts) and as a consequence that they should be slightly repelled by magnetic particles [93]. This might explain why MNPs usually provide similar recoveries to those observed with other SPE materials [94].

These issues should be addressed by analysts working with MNPs for extracting organic pollutants, and they should provide detailed physical fundamentals of this procedure.

3.1.2. *Molecularly imprinted polymers*

MIPs are artificial three-dimensional macromolecular structures capable of mimic natural recognition entities, such as antibodies and biological receptors [95]. These materials have several advantages over natural receptors, such as low cost, easy preparation, high stability at extreme pHs and temperatures, and reusability [96]. Other advantages of MIPs in SPE protocols are their high selectivity and accuracy, and consequently low limits of detection (LODs) [97].

The first use of MIPs was reported by Wulff and Sarhan in 1972 [98], but until 1994 they were not started to be designed, synthesized, and used as SPE sorbents for the selective extraction of target analytes from a number of matrices [99].

MIPs are synthesized by means of a polymerization process, which uses a template molecule and a functional monomer for copolymerization in the presence of a cross-linking agent and initiator in a porogenic solvent (Fig. 3) [100]. For instance, the anti-diazepam MIP is synthesized in the presence of diazepam (the template molecule) and consists of a highly cross-linked porous polymer network. After the polymerization process, the template is removed, leaving a polymer network with strategically positioned functional groups in binding sites that are complementary in size and shape to the template molecule [101]. These binding sites have the potential to rebind with the template molecule or other molecules, with similar molecular structure to the template molecule, in a strong and selective way [102].

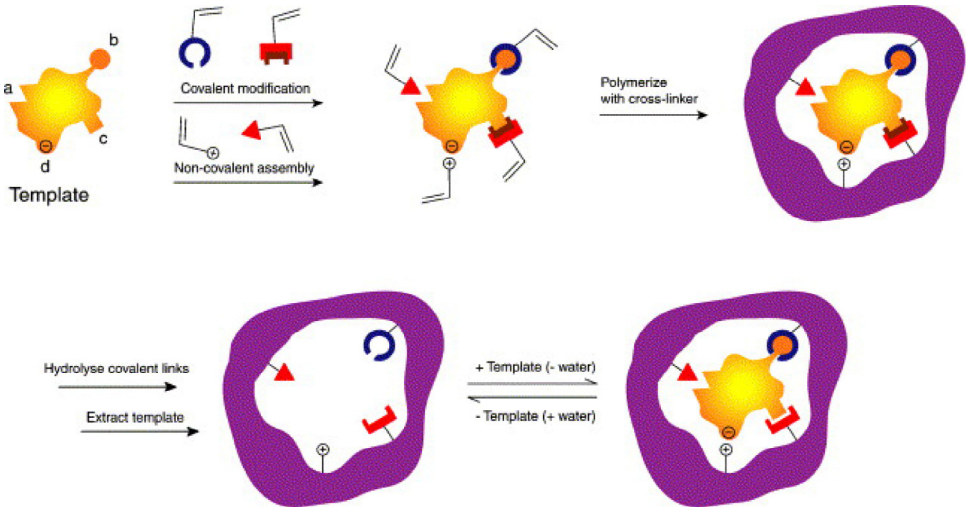

Fig. 3. Synthesis of MIPs [100]. (Reproduced with kind permission of the author.)

Divinylbenzene, ethylene glycol dimethyl acrylate, and pentaerythritol trimethacrylate are the most commonly used cross-linkers, whereas the following functional groups are the main ones used for the synthesis of MIPs: 4-vinylpyridine, 2-vinylpyridine, and methacrylic acid [36].

These sorbents have been used for the extraction of both biological and chemical molecules, including amino acids and proteins [103]; nucleotide derivatives [104]; pesticides from food, soils, and rivers; bisphenol A in river waters; drugs and poisons from plasma, serum, and urine; caffeine from beverages, polyphenols from olive oil wastewaters; uric acid from serum; and α-tocopherol from bay leaves [105]. They became one of the most popular choices for achieving high selectivity during sample preparation of food, biological, or environmental samples [97].

Although many authors claim the high selectivity and advantages of SPE with MIPs (MISPE), some drawbacks have also been reported. Thus, with MIPs synthesized in organic media (most of them), the principal concern when they are applied to the extraction of analytes from aqueous media is the nonspecific hydrophobic interactions. Although several potential solutions have been proposed, nonspecific hydrophobic interactions are difficult to suppress without jeopardizing the specific interactions [106]. Attenuation of nonspecific interactions can be achieved through the use of organic additives and/or detergents such as Tween 20 [107]. Other alternatives for attenuation of nonspecific interactions are introducing hydrophilic comonomers such as 2-hydroxyethyl methacrylate (HEMA) during the synthesis of MIPs [108] or strengthening of the specific interactions between the template and MIP. This has been possible through the use of specifically designed binding monomers capable of stoichiometrically interacting with the template functionalities through stronger interactions [106]. It is important to underline that in this case, electrostatic retentions strengthen the retention and selectivity of the extraction. In this case, loading is carried out in N-(2-hydroxyethyl)piperazine-N′-ethanesulfonic acid buffer, and the increase of specific strong electrostatic interactions between the carboxylate groups of the antibiotics and the urea moiety of the monomer enabled retention of compounds such as derivatives of Penicillin G [109] or fluoroquinolones [35].

Despite the effort put into the reduction of nonspecific interactions in MIPs, the recoveries are sometimes poor. An example of this is the method proposed by Benito-Peña et al. [35], which uses an MIP sorbent for the direct extraction of the fluoroquinolone antibiotics from aqueous samples. In this case, the authors washed the sorbent with acetonitrile/water (0.1 M 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES) buffer, pH 7.5) (10/90, v/v) and eluted the target analytes with 2% trifluoroacetic acid in methanol. Good recoveries (66–100%) and good precision (relative standard deviation (RSD): 2–12%, n = 3) were achieved for danofloxacin, enrofloxacin, oxolinic acid, and flumequine. However, poor recoveries (15–40%, RSD 4–9%, n = 3) were obtained for norfloxacin, ciprofloxacin, lomefloxacin, and sarafloxacin extracted from fortified river water samples.

Recently, magnetic molecularly imprinted polymer (MMIP) has been reported as the ideal sorbent for the determination of fluoroquinolone antibiotics in water samples. It minimizes the preconcentration and elution time as compared with traditional SPE, and has been shown to exhibit very high analytical potential in the separation, purification, and concentration of analytes from large volumes of real water samples at concentration levels about nanograms per liter [110].

3.1.3. Carbon-based nanomaterials in SPE

Of all the allotropic forms of carbon, the following are the ones applied with analytical purposes: fullerenes, carbon nanotubes (CNTs), and graphene oxide/graphene (GO/G) [101].

Carbon-based nanomaterials with giant π-electronic structure have been used as excellent adsorbents in SPE procedures [111]. Particularly, G, an allotrope of C in the form of one-atom thick sheet of hexagonally arranged carbon (i.e., two-dimensional sheet), considered as a large aromatic molecule with a large theoretical specific surface area, has attracted much research attention recently [112].

However, the remarkable tendency of G nanoparticles to aggregate leads to a significant reduction of its surface area and consequently, adsorption efficiency. Moreover, graphene is too light to be recuperated from a suspension even by high-speed centrifugation [113]. As a consequence, some authors consider the modification of graphene as the solution to overcome this difficulty.

GO is a chemically modified graphene which possesses a layered structure and negatively charged surface [114] capable of strong interactions with aromatic compounds. As for G, GO has one atom-thick two-dimensional nanostructure, which confers it to this adsorbent a high specific surface area, without the aggregation problems of G. Nuclear magnetic resonance (NMR) and Fourier transform infrared spectroscopy (FTIR) studies confirm that carboxyl groups exist at the edges of carbon layers and that epoxy and hydroxyl groups were incorporated in the layers of G upon chemical modification [58]. These oxygen-containing groups significantly affect van der Waals interactions between G layers and render it strongly hydrophilic. As a result, hydrophilic and polar substances, such as pigments, heavy metal, ions, phenols, aldehydes, esters, and basic species, could be adsorbed on the surface of GO through hydrogen bonds, anion–π interactions, and electrostatic interactions [115]. In addition, this structure can be easily modified to increase its selectivity by introducing oxygen in its structure [116].

G and GO can also be used for coating magnetic nanomaterials. Thus, magnetic graphene composite absorbent has been recently synthesized to remove trace levels of polybrominated diphenyl ethers (BDEs) in water treatment [117].

In this study, magnetic microspheres of Fe_3O_4 were coated with poly(diallyldimethylammonium chloride (PDDA) via sol–gel approach to obtain polycationic magnetic microspheres (Fe_3O_4@PDDA). Further, Fe_3O_4@PDDA was modified with polyanionic graphene oxide (graphene previously modified by DNA, GO_x@DNA) to increase their stability and adsorption capacity. This adsorbent was applied to the retrieving of BDEs from spiked water samples and river samples from China, showing that Fe_3O_4@PDDA/GO_x@DNA is efficient at 5 ng/mL levels, stable and reusable up to 20 times [117].

Concerning carbon nanotubes (including both single-walled (SWCNTs) and multiwalled ones (MWCNTs)) they have attracted much attention as sorbents of PAHs in water [118]. C_{60} fullerenes have also been used as SPE sorbents for extraction of benzene, toluene, ethylbenzene, and xylene isomers from water samples [119]. According to Serrano and Gallego [119], C_{60} fullerenes interact with nonpolar compounds. However, Jurado-Sánchez et al. [120] stated that C_{60} and C_{70} fullerenes could adsorb only aromatic compounds regardless of their polarity.

3.1.4. Other sorbents used as SPE materials

Among other materials that can be used as SPE sorbents, we mention cigarette filters, which were shown to retain fluoroquinolones from environmental samples (river and tap waters) with recoveries in the range of 76–112% [121].

Coal cinder has also been applied as a sorbent material for extracting esters from environmental matrices. Coal cinder is a solid waste resulting from the coal-burning process in all types of industrial and private boilers and furnaces. Yang et al. [122] used coal cinders to remove phosphorous and other pollutants whereas Wu et al. [123] also used coal cinders to isolate para-, meta-, and ortho-phenylenediamine isomers from hair dyes.

Other studies reveal that coal cinders may also be used as an inexpensive and appropriate adsorption medium for the extraction

of PEs. These compounds were studied by Asadollahzadeh et al. [124] in 2010, who used a carbon nanotube–polypyrrole composite on a stainless steel fiber to extract PEs from aqueous media. On the other hand, Sun et al. [125] evaluated the possibility of using coal cinder as the adsorbent for the extraction of three PEs from landfill leachate (effluent of the landfill flushed by rain in the open air) and lake water samples. LODs of 3.07, 2.07, and 4.06 ng/mL and RSDs of 5.27%, 4.34%, and 7.32% were obtained for dimethyl phthalate (DMP), diethyl phthalate (DEP), and di(2-ethylhexyl) phthalate (DEHP), respectively (concentration = 20 ng/mL, n = 9).

TiO_2 nanotubes were also applied for the concentration of PAHs from water, although this material seems to provide worse recoveries than other SPE sorbents such as carbon-based materials [73].

4. Automated SPE

So far, we have dealt mainly with off-line SPE, but on-line and automated SPE have also become popular and commonly used in the last years.

SPE is frequently used to retain target analytes. Once the analyte is retained by the solid support, it can be either eluted with an appropriate solvent and determined in the eluate or measured directly on the support (with an optosensor). The latter choice provides better detection limits because of the avoidance of the dilution phenomenon involved in the elution process [126].

Automated on-line SPE devices can be classified into homemade manifolds [126] and commercial devices [127]. A semi-automated protocol is also possible. An example of semi-automated protocol was developed by Jurado-Sánchez and applied to the extraction and concentration of C_6-C_{11} perfluoralkyl carboxyl acids and perfluooctane sulfonate in water [119].

4.1. On-line SPE with measurement on the eluate

On-line protocols with measurement on the eluate have become popular because of their advantages such as total automation, high precision, and high sensitivity.

Most on-line SPE procedures consist of SPE columns coupled with LC, MS systems, or spectrophotometric detectors. So far, the on-line configuration most frequently used has been SPE coupled with LC-(tandem) mass spectrometry. Sorbents used include both traditional (alkyl-bonded silica and polymers) and novel RAMs, MIPs, and immobilized receptors or antibodies (IMs) [15].

The most common approach for on-line coupling of SPE with LC is "column switching," which involves the implementation of a small precolumn within the injection loop of a six-port rotary valve [128]. Alternatively, several fully automated sample preparation units for on-line SPE are commercially available, such as LiChrograph OSP-2 (on-line sample preparation unit, Merck, Darmstadt, Germany) or ASPEC XL (Gilson, Middleton, WI, USA). Some of these devices can perform off-line sample clean-up with disposable extraction cartridges, but can also be configured to work as an on-line SPE system using the high-pressure trace enrichment cartridge (TEC) [15].

On-line SPE–LC–MS (fluorimetry or UV/Vis spectrophotometry) is becoming increasingly popular for automation of environmental chemistry [129] and bioanalytical assays [130,131]. For these purposes, usually a small, typically 5- to 20-mm-long and 2- to 4.0-mm i.d. precolumn SPE column/trapping column is connected to a conventional LC or MS analytical column [30] via a switching valve (Fig. 4). Recently SPE columns with i.d. of only 10 or 20 µm have been used aiming at obtaining maximum sensitivity with minimal amount of samples in bioanalytical analysis.

Column-switching configurations can contain various precolumns, switching valves, and pumps. When the switching valve is in "position a," the sample is injected into the SPE column, which has been conditioned by appropriate solvents. The valve is switched to "position b" after elution of the interfering compounds. In the case of SPE coupled with LC, the analytes are eluted from the SPE column in either the back- or straight-flush mode using the chromatographic mobile phase and transferred into the analytical column for being separated before detection. In case of LC coupled to spectrophotometric or fluorimetric detection, the eluted analytes are carried out to the spectrophotometric cells. Afterward, the valve is switched to its initial position (position a). Simultaneously, the SPE column is reactivated and is ready for the injection of the next sample [130].

As compared with off-line SPE, on-line SPE offers a series of advantages and disadvantages. The main advantages of on-line SPE are the following:

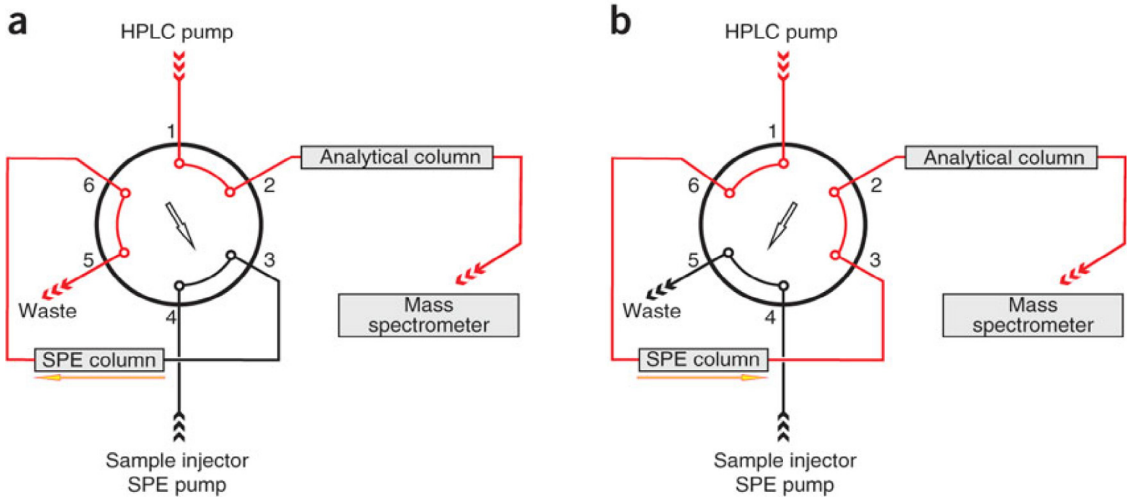

Fig. 4. (a) In the load sample position of the valve (right, 1→2), the sample delivered from the autosampler with the solvent flow from the SPE pump (orange arrow) is flushed onto the SPE column. (b) In the elute sample position of the valve (left, 1→6), the target analyte adsorbed onto the SPE sorbent is eluted by the HPLC mobile phase (orange arrow) and conducted through the second HPLC column to the MS/MS detector [130]. (Reproduced with kind permission of the author.)

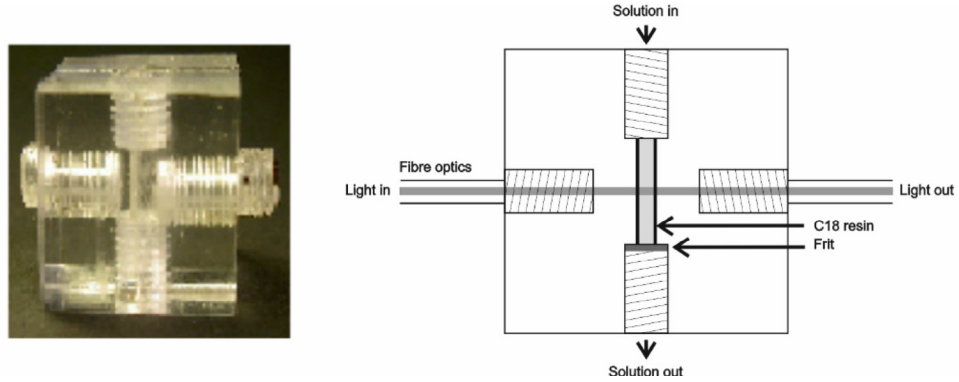

Fig. 5. FIA system for nitrite determination exploiting optosensing detection (with permission of SciWare Systems).

1. On-line SPE technique reduces sample preparation time, and thus, increases the sample throughput [129]. Conditioning, washing, and elution can be performed automatically [132].
2. This technique can decrease the risks of sample contamination and analyte degradation [15].
3. Analyte loss by evaporation (usual in off-line SPE) is reduced or eliminated in on-line SPE.
4. Cartridges can usually be reused [15].
5. On-line SPE improves accuracy
6. It can reduce the risk for the operator to be exposed to infectious materials or toxic solvents [15].
7. In addition, on-line SPE can decrease the solvent consumption and the costs for organic solvent waste disposal [133].
8. In contrast to off-line mode, in on-line mode, the whole extract is transferred to the LC analytical column, and hence the sensitivity is increased, reaching few nanograms per liter and making possible working with even <1 mL of sample [134].

However, on-line SPE methods still face some challenges, one of which is the optimization of preconcentration and elution procedures to achieve an appreciable accuracy in a single run for a class of compounds with different physicochemical properties. In addition, the coupling of on-line SPE with techniques such as ultrahigh-performance liquid chromatography (UHPLC) is not easy because of the high back pressure generated from the high flow rates with a low particle size column (<2 μm) [129]. In addition, on-line SPE has other disadvantages such as the need of expensive equipment, low portability, matrix effects (particularly in MS), absence of extracts for repeating the analysis, degradation of columns, and contamination of sorbents [15].

Although modified silicas are the most frequently used materials, MIPs were also used in on-line SPE procedures. In fact, the first study on MIPs as sorbents in SPE (reported in 1994 by Sellergren [99]) was an on-line SPE procedure. Sellergren [99] used an MIP specific for the on-line SPE determination of the drug pentamidine in spiked urine. The high selectivity of the polymer allowed the drug to be determined directly in the desorption step, thus eliminating the need for a successive chromatographic analysis.

In addition, MIPs can also be used as SPE sorbents in on-line SPE coupled to LC. Thus, since the introduction of this on-line protocol few years ago [135], it has been successfully used to extract tetracycline antibiotics from egg [106], tetracyclines from fish samples [136], and triazines in waters [137].

Other sorbents were also used in the on-line extraction of several analytes. Thus, several on-line SPE methodologies have been applied successfully to the extraction and concentration of polar compounds such as resorcinol, methomyl, phenol, 4-nitrophenol and (4-chloro-2-methyl-phenoxy)acetic acid (MCPA), oxamyl, desisopropylatrazine (DIA), and desethylatrazine (DEA) from spiked Milli-Q waters [67]. A comparison of the efficiencies of several polymer sorbents was made in ref. [68] to recover the aforementioned compounds from spiked Milli-Q waters: N-vinylimidazole-divinylbenzene (NVImDVB), 4-vinylimidazole (4VIm), and two hydrophilic commercial sorbents, OASIS HLB and Strata^{TM}X. Although the authors claim that the more polar/hydrophilic the sorbent, the higher the recoveries of polar compounds, an exhaustive analysis of results reveals that this is not strictly true. Thus, the recovery of polar compounds such as MCPA by using 40% 4VImDVB was 77%, whereas it reached 84% on Strata X (much less polar sorbent than 40% 4VImDVB). Moreover, methomyl (a highly polar compound) was recovered at levels of 61% on 40% 4VImDVB and 73% on Strata X.

4.2. SPE with direct on-column measurement

Rather than eluting the product retained on a preconcentration column or disk and measuring it in the eluate as discussed above, the analyte can be measured directly on the column or disk to obtain better sensitivity and detection limits through decreased dispersion of the target species. This on-column measurement procedure is known as optosensing and is usually carried out combining flow injection analysis and SPE [126]. Although this configuration is not very common in analytical chemistry, we consider it interesting and original.

On-column optosensing measurements can be performed in two ways, namely transmittance and reflectance. The former mode is more commonly used than the latter although it is subject to gross light losses through dispersion across the solid phase. This can be reduced by using very narrow light paths.

Fig. 5 shows a transmittance optosensor developed by SciWare Systems (http://www.sciware-sl.com). The analyte or a derivative is retained by the material packed in a special flow cell having a prismatic channel of width and thickness 2 and 1 mm, respectively.

As the analyte or its derivative reaches the column, it is retained at the top of the packing and its absorbance is monitored by a fiber-optic spectrophotometer.

A proper column packing is required to avoid overpressure or clogging. This problem can be overcome by using filtering membranes containing appropriate extractants, which ensures a high reproducibility when they need to be changed [126].

5. Conclusions

A proper treatment of the fundamentals of the methods is missing in many studies dedicated to the development of SPE procedures,

which do not pay too much attention to the physical phenomena occurring during sorption and elution of the target analytes.

This study focuses on the physical fundamentals of SPE, particularly on the fundamental physical aspects involved in the retention of analytes onto SPE sorbents and proposing an alternative to traditional trial-and-error methodology for optimizing SPE procedures.

Although at present a systematization of the SPE procedures is far off, we provide some principles for achieving a rationalization of the SPE protocols optimization:

1. Accomplishing the SPE procedures against gravity for improving the efficiency of the methodology. In fact, SPE against gravity has shown to significantly increase the efficiency of fractioning of organic compounds from very complex matrices.
2. Using an HPLC pump for passing the flow through the SPE column in the aim of avoiding instability of flow.
3. Monitoring the fractionation procedure with some sort of spectroscopic technique (e.g., PDA or fluorimetry).
4. Commercial columns provided with steel case pipes are recommended to avoid the release of phthalates from plastic cartridges usually used in traditional SPE procedures. Moreover, steel case pipes are required to support medium and high backpressures.

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