



Headspace solid-phase microextraction: Fundamentals and recent advances

Carlina Lancioni^a, Cecilia Castells^a, Roberto Candal^b, Marcos Tascon^{b,c,*}

^a Laboratorio de Investigación y Desarrollo de Métodos Analíticos, LIDMA, Facultad de Ciencias Exactas (Universidad Nacional de La Plata, CIC-PBA), 47 y 115, La Plata B1900AJL, Argentina

^b Instituto de Investigación e Ingeniería Ambiental (IIIA-CONICET), Universidad Nacional de San Martín (UNSAM), San Martín, 1650 Buenos Aires, Argentina

^c Centro de Estudios sobre Patrimonios y Ambiente (Escuela de Hábitat y Sostenibilidad -Escuela de Arte y Patrimonio), Universidad Nacional de San Martín (UNSAM), San Martín, 1650 Buenos Aires, Argentina

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ABSTRACT

Solid-phase microextraction (SPME) has become a powerful sample preparation technique which allows to efficiently isolate and enrich analytes from complex matrixes. One of the most widespread SPME modes, consists of the extraction directly from the headspace (HS) which is equilibrated with the sample. In this sense, HS-SPME provides one of the best platforms for sample preparation, especially for the analysis of volatile and semi-volatile organic compounds. Furthermore, this technique has demonstrated to be versatile, sensitive, robust, and environmentally friendly when applied to samples coming from a diverse variety of fields such as bioanalysis, environmental sciences, food and cultural heritage. Moreover, during last years, the implementation of HS-SPME has dramatically grown along with the need to monitor complex systems over time using *in situ* and *in vivo* approaches, taking advantage of its noninvasive nature. In this review article, the authors present the fundamentals of this technique aiming to critically understand its advantages and limitations, highlighting the recent advances published in the last ten years. To this aim, special sections dealing with extractive phase development, technological advances and relevant applications in different fields have been carefully designed. Finally, some thoughts and perspectives about the future of the technique are also discussed.

1. Introduction

Since its inception [1], solid-phase microextraction (SPME) has been conceived as a convenient alternative in sample preparation. SPME not only introduces the concept of microextraction, but also shows clear advantages in front of other classical sample preparation techniques such as liquid extractions (LE) and solid-phase extraction (SPE) [2], showing great enrichment, high simplicity, versatility, and most of the time, reusability in an environmentally friendly manner.

In principle, this non-exhaustive technique is typically defined as an open bed device in which the extraction process is controlled by diffusion of analytes from the sample towards the extractive phase through the boundary layer. The mass transport is driven by the concentration gradient generated among phases. To this end, the sorbent phase will extract the target compounds until system reaches equilibrium, offering efficient analyte enrichment with a simplified analytical workflow [2,3]. In addition, as the extraction is non-exhaustive, due to the extractant phase involves very low-volume or surface, and is limited to the analyte free fraction, the microextraction process does not disturb any physicochemical and/or biological equilibrium of the compound in

the sample, thus, allowing to determine physicochemical distribution or binding constants [4–6].

Furthermore, when thermal desorption is used, the technique is considered solvent-free, fulfilling most of the principles of *green analytical chemistry* [7–9], having outstanding scores in the current developed metrics [10]. Moreover, if additional parameters such as method performance and operational features are introduced, the scores recently discussed about *white analytical chemistry* principles [11] are also exceptional. Having this in mind, one of the most widespread SPME modes is the headspace-SPME (HS-SPME), which consists of the extraction from the HS phase equilibrated with the sample (Fig. 1). HS-SPME provides one of the best platforms for sample preparation, mainly for the analysis of volatile (VOC) and semi-volatile organic compounds (SVOC) [12]. Since there is no direct contact with the sample during extraction, the lifespan of SPME coatings is drastically improved compared to direct immersion into the sample, and the number of matrix interferences by unspecific adsorption is reduced. These features along with the coupling to gas chromatography (GC) through thermal desorption, eliminates the use of solvents, enabling fast and straightforward sample extraction and preconcentration. This analytical procedure simplification not only improves the applicability of HS-SPME but also reduces the number of sample preparation steps, decreasing the overall error of the determina-

* Corresponding author.

E-mail address: mtascon@unsam.edu.ar (M. Tascon).

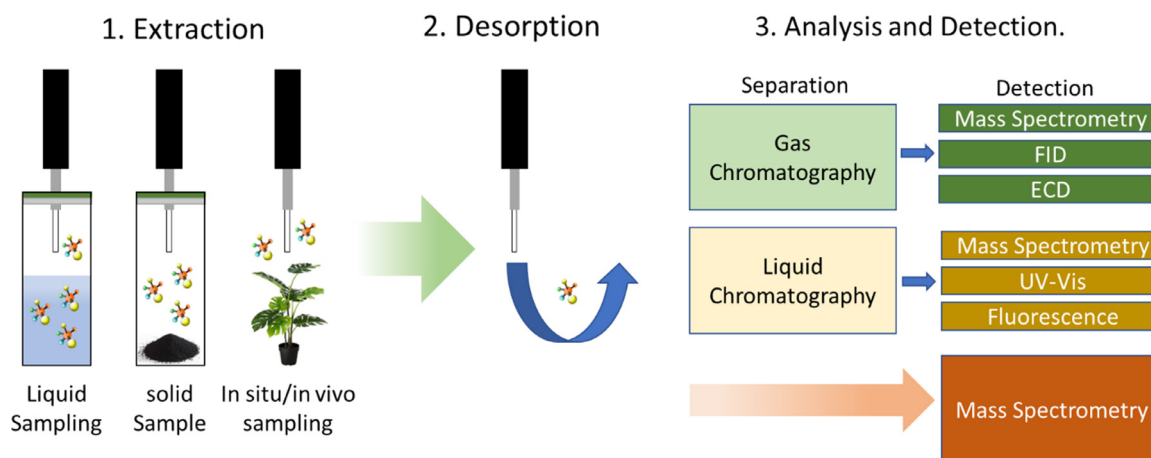


Fig. 1. Scheme of the most common HS-SPME procedures combined with different separation and detection alternatives.

tion. Despite these advantages, HS-SPME coverage of extractable analytes is limited to VOCs and, with slower kinetics, SVOCs, which makes the direct immersion mode more adequate for representative sampling in untargeted analysis [13]. Nevertheless, there is a growing interest in the implementation of HS-SPME for non-invasive *in situ* and/or *in vivo* determinations of VOCs and SVOCs profiles in a wide diversity of fields, namely clinical chemistry [14–17], environmental and agricultural sciences [18,19], food industry [20,21], cultural heritage [22–24], among others. Besides, recent investigations are devoted to improve the extraction kinetics of SVOCs mainly by working under vacuum conditions [25–27] or by the use of thin-film microextraction devices [27,28].

In this context, this review intends to set a sound basis of fundamentals regarding the extraction process and to cover the most recent and, from our point of view, remarkable advances in the field. The later includes, on one hand, fundamental developments describing the impact of new variables on extraction, kinetics or thermodynamic studies of the process, and novel mechanisms of extraction. On the other hand, relevant extraction phases, new technologies and setups, as well as original applications are critically discussed in subsequent sections. In this line, it is worth to mention that representative applications are presented thoroughly, rather than providing an exhaustive summary of publications for each topic. We expect to give readers a review that covers the fundamental concepts of HS-SPME, its relevant recent advances, and future perspectives, which we believe is a key aspect to pave the way towards the development of smarter, greener, and more robust technologies and applications.

2. Fundamentals

The theoretical principles behind HS-SPME are based on the distribution of analytes in a three-phase system schematized in Fig. 2 which includes a condensed phase (solid or liquid sample), a gas phase or HS, and an extractant phase or sorbent (liquid or solid phase) on a solid support. To simplify the mathematical treatment, the sample as well as the coating sorbent will be considered liquid phases.

If sampling time is enough to reach equilibrium, since the total mass of analyte must remain constant and equal to the original amount, it is possible to express that:

$$C_0 V_s = C_e^\infty V_e + C_h^\infty V_h + C_s^\infty V_s \quad (1)$$

where C_0 represents the concentration of the analyte in the sample prior to the extraction; C_e^∞ , C_h^∞ and C_s^∞ denote the analyte concentration once equilibrium has been reached in the extractant phase, the HS and the sample, respectively. Lastly, V_s , V_e and V_h are the sample, extractant phase and HS volumes [3,29].

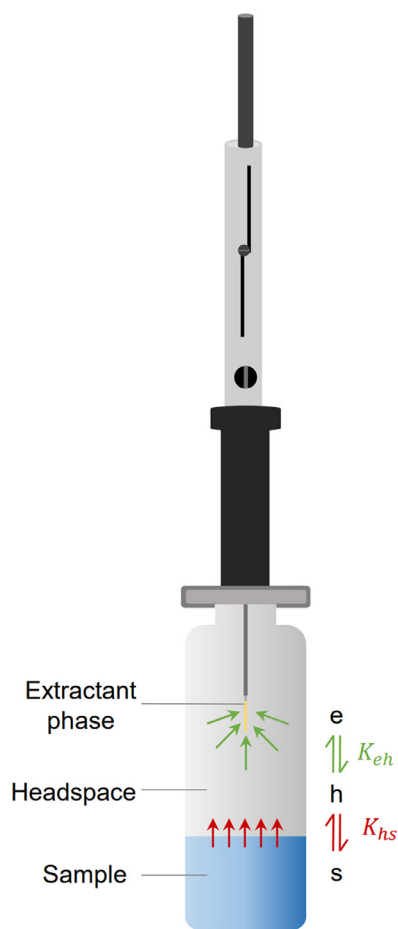


Fig. 2. Scheme of the three-phase system for HS-SPME. In red, the sample-HS distribution of the analyte; in green, the HS-extractant phase distribution of a given analyte. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Considering the definition of extractant phase-HS constant (K_{eh}), and the HS-sample constant (K_{hs}):

$$K_{eh} = \frac{C_e^\infty}{C_h^\infty} \quad (2)$$

$$K_{hs} = \frac{C_h^\infty}{C_s^\infty} \quad (3)$$

the amount of extracted analyte (n) once equilibrium has been reached can be expressed as:

$$n = C_e^\infty V_e = \frac{C_0 K_{eh} K_{hs} V_e V_s}{K_{eh} K_{hs} V_e + K_{hs} V_h + V_s} \quad (4)$$

It is worth to mention this equation remains valid if extractant phase is solid instead of liquid, *i.e.* extraction mechanism is adsorption instead of absorption. The only difference in mathematical expressions relies in the definition of K_{eh} (Eq. (2)), in which C_e^∞ must be replaced by the surface concentration of extracted analyte, S_e^∞ and the coating volume V_e by the active surface area of the extractant phase (A_e).

According to Eq. (4), it is noticeable that parameters affecting HS-SPME extraction efficiency include chemical nature of the sorbent, phase volumes, ionic strength, pH (if analytes are ionizable), addition of organic solvents and temperature.

Regarding temperature, there is a compromise in the behavior between two main processes. This means, an increase of this variable will promote the analyte distribution to the HS from the sample since it is an endothermic process (K_{hs} increases), meanwhile, it will disfavor the analyte distribution from the HS to the extractant phase (extraction) due to the process is exothermic (K_{eh} decreases). Consequently, a temperature optimization is highly encouraged. Alternatively, a heating-cooling strategy, consisting in heating the sample while simultaneously the extractant phase is cooled, the so-called cold fiber HS-SPME, can be considered [3,30–32].

In the abovementioned aspects of this section, only the thermodynamic approach has been discussed. Nevertheless, the kinetics of the process must be considered since it will determine the sampling time needed to reach equilibrium. In other words, all the variables that influence the speed of extraction must be consciously considered. During HS-SPME, analytes firstly have to transport from the bulk sample to the sample-gas interface; secondly, they have to suffer evaporation from the sample surface to the gas phase next to the sample surface; thirdly, transport through the bulk gas phase towards the gas-extractant phase interface has to occur; fourthly, analytes have to suffer sorption by the extractant phase; and lastly, transport to the bulk of the extractant phase has to occur. Among those stages, it is possible to distinguish those involving mass transport which are limiting the kinetic of the extraction process. Even though transport mass takes place in all directions, a one-dimension model will be representative and simpler mathematically. Most of the mass transport theory is based on Fick's second law of diffusion describing mass balance, which can be expressed as:

$$\frac{\partial C(x,t)}{\partial t} = D \frac{\partial^2 C(x,t)}{\partial x^2} \quad (5)$$

where $C(x,t)$ is the concentration of the analyte at a position " x " and time " t ", and D denotes the analyte diffusion coefficient in a stationary medium, which depends on analyte and medium properties, temperature, and pressure. This equation expresses the kinetic dependence on diffusion and distance that the analyte must go across. Since the system is composed of three phases, analogous equations must be written for sample, gas and extractant phase, each of them with defined boundary conditions [29].

Overall mass transfer from sample to extractant phase is typically limited by mass transfer rates from the sample to the HS because of the lower diffusion coefficients in liquids compared to gas (usually 4-5 orders of magnitude) and the larger phase thickness compared to the extractant phase.

Several approaches to accelerate the HS-SPME kinetics can be mentioned: (i) increasing temperature, which decreases media viscosity, increasing D in the sample, (ii) applying agitation, which reduces the concentration gradient in the boundary layer, (iii) increasing sample-HS interface by using large diameter recipient (keeping total volume constant), (iv) enlarging HS-extractant phase interface by using thinner sorbent coatings and larger supports (keeping V_e constant) and (v) applying vacuum conditions during HS-SPME sampling which reduces the

concentration gradient through the bulk HS and increases the diffusion rate in the gas phase.

The latter strategy, is especially important for poorly volatile analytes (or analytes with low Henry constants) which are extracted slower compared to volatile analytes as a consequence of their lower concentration in the HS, [3,29] which results in long equilibration times. The positive effect of reducing HS pressure during sampling was firstly reported by Brunton et al. in 2001 [33] and later confirmed by Darrouzes et al. in 2005 [34] and Groenewold et al. in 2011 [35]. However it was not until 2012 that Psillakis et al. [36] proposed and verified a theoretical model for kinetic dependence on pressure and termed the procedure as vacuum-assisted HS-SPME (Vac-HS-SPME). A deeper insight in this emerging analytical technique as well as its applications will be further discussed in 3.2 and 3.3 sections.

3. Recent advances

3.1. New sorbents for HS-SPME

The successful development of methods involving SPME, requires the knowledge of several aspects of the system under study: 1) physicochemical properties of sample matrix, analyte(s) and possible interfering compounds; 2) selection of appropriate extraction conditions such as operation mode, temperature, exposure time, pH, ionic strength, etc; and 3) sorbent selection, which will be responsible for the performance (sensitivity and selectivity) of the microextraction. Considering the most widely reported geometry for SPME – *i.e.* fiber-, commercially available products include single-phase liquid polymeric materials such as polydimethylsiloxane (PDMS), poly(oxi)ethyleneglycol (PEG) and polyacrylate (PA). Besides, mixed-phase sorbent consisting of solid carboxen (CAR) and/or divinyl benzene (DVB) particles dispersed in PDMS are also commercialized [2,12,37]. It is worth to mention that both kinds of fiber sorbents differ in the extraction mechanisms. On one hand, single-phase coatings are referred as absorbent phases, since analyte retention is a result of attractive forces related to molecules and sorbent polarity match followed by diffusion of these compounds into the polymer bulk (like chromatographic stationary phases). On the other hand, due to mixed-phases consist mainly of porous solid particles embedded in a liquid polymer, also known as "solid sorbents", analyte extraction is based on the adsorption mechanism of van der Waals, π - π or hydrogen-bonding interactions. Therefore, in these coating materials, extraction is highly dependent on particle pore size and surface area.

In Table 1 a summary of commercially available fibers for HS-SPME including thicknesses and recommended uses is provided.

Noteworthy, in last years, there was an increment in commercial options for different SPME geometries using similar sorbents. In this regard, thin film SPME is one of them, consisting of a carbon mesh impregnated with a SPME sorptive phase. Similar to classical SPME fibers, commercially available versions include PDMS, PDMS/CAR, PDMS/DVB. Also, thin films containing PDMS/HLB for balanced affinity of polar and non-polar compounds are offered. Alternatively, SPME arrows are also commercialized, claiming longer lifetime, faster extractions and better sensitivity when compared to classical SPME fibers. Although extractive materials are the same than those included in Table 1, coating thicknesses are in average higher than in fibers, exhibiting better sensitivity due to higher sorbent capacity. It is also worth to mention the devices Hi-Sorb, which consisted of an arrowed device of stainless steel with coating deposited onto a recession. These devices are conceived for coupling to a Thermal Desorption Unit by inserting them in glass tubes, prior to GC-MS analysis. In this line, the sorptive phases are the same than for regular SPME fibers.

Even though commercialized sorbents can be applied to the analysis of a wide variety of analytes in terms of molecular weight, volatility and polarity; great efforts have been made to obtain novel materials able to reduce costs, upgrade lifespan, expand surface area or porosity, improve chemical and/or mechanical stability, provide biocompatibility,

Table 1
Commercially available fibers for HS-SPME and their most relevant applications.

Extraction mechanism	Sorbent	Coating thickness	Recommended application		
			Molecular Weight	Target analytes	
Absorption	PDMS	7 μm	125-600	Non-polar, high molecular weight compounds	
		30 μm	80-500	Non-polar, semi-volatiles compounds	
		100 μm	60-275	Volatile compounds	
	PA	85 μm	80-300	Polar, semivolatile compounds	
Adsorption	PEG	60 μm	40-275	Alcohols and polar compounds	
	DVB-PDMS	65 μm^*	50-300	Volatiles, amines and nitro-aromatic compounds	
		CAR-PDMS	75 μm	30-225	Gases and low molecular weight compounds
			85 μm		
		95 μm			
	DVB/CAR/PDMS	50 $\mu\text{m}/30 \mu\text{m}$	40-275	Volatile and semivolatile	

* Also available with a 10 μm overcoating for direct immersion mode.

Table 2
Summary of different materials and related applications used in HS-SPME.

Sorbent type	Coating/Sorbent and support	Analyte(s)	Matrix	Geometry	Obs	Ref.
Commercially available	(i) PDMS and (ii) PDMS/CAR	Volatile compounds	Matcha processed with different milling techniques	(i) HS-SBSE and (ii) HS-TF-SPME	Thermal desorption GC-QTOF/MS	[76,77]
MIP	Acetaldehyde-imprinted monolith (MMA and EGDMA)	Acetaldehyde	Beverages stored in PET bottles	Fiber HS-SPME	GC/MS	[78]
COF	TpBD-TiO ₂ (TpBD: 1,3,5-trimethylphloroglucinol and benzidine) bonded to titanium wire via TiO ₂ nanotube array	Phthalate esters	Vegetables (tomatoes, cucumber and lettuce)	Fiber HS-SPME	Thermal desorption GC-MS/MS	[79]
IL	1-octyl-3-methylimidazolium hexafluorophosphate on stainless steel wire	Benzene, toluene, ethylbenzene and xylenes	Paints	Fiber HS-SPME	Thermal desorption GC-FID	[64]
PIL	Poly(1-vinyl-3-butylimidazolium) bis[(trifluoromethyl)sulfonyl] imide on fused silica	Five organophosphorus esters	Tap, river, and sewage water	Fiber HS-SPME	GC-FPD	[80]
MOF	MOF-5 on porous copper support	Sulfide compounds (allyl methyl sulfide, dimethyl disulfide, diallyl sulfide, methyl allyl disulfide, diallyl disulfide)	Garlic sprout and Chinese chive	Stir bar HS-SBSE = HSSE	Thermal desorption GC-MS	[81]
ZIF	Acidified ZIF-8/poly(vinyl chloride) on stainless steel	Low molecular weight alkylamines (TMA, TEA)	Wastewater, salmon and mushroom	Arrow HS-SPME	Thermal desorption GC-MS	[82]
Carbon based (graphene)	Graphene aerogel modified with a deep eutectic solvent (support not informed)	Polychlorinated naphthalenes	Sea and river shrimps	Fiber HS-SPME	Thermal desorption GC-MS/MS	[83]
Carbon based (fullerene)	Polymeric C60 fullerene and PDMS on fused silica support	BTEX, naphthalene congeners, and phthalic acid esters acid diesters	Water samples	Fiber HS-SPME	Thermal desorption GC-FID	[84,85]
Carbon based (MWCNT)	MWCNT/polyaniline coating on stainless steel wire	Phthalates (DMP, DEP, DAP, DBP, BBP, DEHP)	White plastic bags and instant cup noodle container	IN-HS-SPME (dynamic extraction)	Thermal desorption GC/MS	[86]
Aptamer based	Composite: AuMNPs@HB-Apt	Polychlorinated biphenyls (PCBs)	Complex environmental matrix (soil)	Magnetic stir bar HS-SBSE = HSSE	Chemical desorption (EtOH) – GC-MS	[87]

MAA = Methacrylic acid // EGDMA = Ethylene glycol dimethacrylate // MOF-5 = Zn₄O(BDC)₃ BDC=1,4-benzodicarboxylate // HB-Apt = hyperbranched aptamer // AuMNPs = Gold Magnetic Nanoparticles (Fe₃O₄@AuMNPs) // ZIF-8: zinc metal and 2-methylimidazololate ligands.

but also increment selectivity and extraction efficiency. In this regard, general properties of emerging materials are detailed below and selected applications evidencing the wide variety of sorbents developed for performing HS-SPME under diverse geometries are summarized in Table 2. It is worth to mention that even though synthesis procedures including inorganic polymerization, electrochemical synthesis, immobilized monoliths, molecular imprinting polymers, etc. exceed the scope of the present review, detailed information can be found elsewhere [38–47].

3.1.1. Molecularly imprinted polymers (MIPs)

MIPs conform a type of synthetic polymeric materials which contain artificially generated binding sites to recognize a target molecule selectively respect to other compounds with similar structures. Contrarily to sorbents designed for wide analyte coverage, MIPs were developed aiming to establish specific compound recognition by creating artificial binding sites. These selective materials are prepared in three simple steps: firstly, a template molecule is integrated physically or chemically

with a functional monomer; secondly, the modified monomer is allowed to react in presence of a cross-linking agent to obtain the polymeric material; finally, the template molecule is removed leaving as a result tridimensional cavities able to accommodate in size and recognize in terms of specific interactions a given molecule or ion. Due to the invaluable selectivity of MIPs sorbents, the application in extraction technologies such as SPE and SPME increased substantially. Regarding SPME diverse geometries such as fibers, in tube and membranes or flat substrates were reported [48–51]. When first MIP-based SPME fiber were manufactured, the main disadvantage was their fragility attributable to the fused silica fiber core; fortunately, that drawback was overcome by changing the fiber support to metallic ones such as aluminum and stainless steel.

3.1.2. Metal organic frameworks (MOFs) and other related frameworks

MOFs, also known as hybrid organic/inorganic frameworks or coordination polymers, are polymeric and crystalline three-dimensional coordination nanomaterials consisting of a porous material composed by a metallic central ion and organic ligands as repeating and bridging units, which are typically mono-, di- tri- or tetravalent ligands. Although metal and ligand dictate the overall physical and chemical properties, MOFs are characterized by uniform pore size, large surface area and outstanding thermal stability. Besides, the easy functionalization of the outer surface and tunable pore size make these materials an excellent alternative in the development of analytical applications as adsorbents for preconcentration by SPE and SPME. Depending on the ligand and metal which conforms the MOF, interactions established with analytes can be diverse: ligands in the framework can provide hydrophobic or π - π stacking between unsaturations, as well as hydrogen bonding sites or dipole-dipole interactions while metal centers offers sites for establishment of Lewis interactions *i.e.* acid-base interactions [46,52,53].

A sub-category of MOFs which has recently gained attention is comprised by zeolitic imidazolate frameworks (ZIF). ZIFs constitute a special class of MOF consisting of imidazolate linkers and metal ions which are topologically isomorphic with conventional aluminosilicate zeolites. Typically, a tetrahedrally coordinated transition metal ion (Zn or Co cations) play the role of silicon and imidazolate anion forms bridges that imitates the role of oxygen, leading to similar structures due to the metal-imidazole-metal angle ($\sim 145^\circ$) in ZIF is similar to the Si-O-Si in conventional zeolites [54–56]. ZIFs displays features of both MOFs and zeolites, *i.e.* high crystallinity and surface area, uniform and versatile pore size, extremely high thermal and chemical stability, for this reason it is not surprising that represent excellent candidates for being used as SPME coatings.

Covalent organic frameworks (COFs) can be defined as an analogous class of MOFs consisting entirely in organic building units, composed exclusively of light elements (B, C, N, O, Si) covalently linked into extended two- and three-dimensional structures that lead to crystalline materials with defined porosity. Because of covalent bonds provide a tool for controlling how repetitive units are assembled, predesigned structures with specific purposes are achievable [41,57]. The challenge relies in overcome the often obtained amorphous or poorly defined materials, a problem known as “crystallization problem” [52,58].

3.1.3. Ionic liquid-based sorbents

Ionic liquids (ILs) are salts composed of an organic cation and an organic or inorganic counter-anion, which are characterized by possessing remarkable properties such as low melting points (below 100°C), negligible vapor pressure at room temperature, high thermal stability and conductivity, good solubility, hydrophobic or hydrophilic properties and environmental friendship. Additionally, desired properties in ILs such as viscosity, chemical stability, and polarities can be easily achievable by modifying the cation or anion type, which in the context of limited selection of commercially available sorbent, represents a promising novelty to extend the applicability of SPME. Commonly used ILs include imidazolium, pyridinium, pyrrolidinium, phosphonium,

sulfonium or ammonium based cations combined with either trifluoromethylsulfonate ($[\text{OTf}]^-$), bis[(trifluoromethyl)sulfonyl]imide $[\text{NTf}_2]^-$, bis(pentafluoroethylsulfonyl)imide $[\text{BETI}]^-$, trifluoroethanoate $[\text{CF}_3\text{CO}_2]^-$ organic anions or with inorganic anions such as halide $[\text{X}]^-$, hexafluorophosphate $[\text{PF}_6]^-$ or tetrafluoroborate $[\text{BF}_4]^-$ [59–63].

Because of all the above described, ILs represent an interesting material as sorbent phase for performing SPME. The first application of ILs as SPME coating was reported in 2005, when they were used to extract benzene, toluene, ethylbenzene and xylenes from HS over water soluble paint samples followed by GC-FID analysis [64]. However, obtained fibers were disposable and the substrate had to be coated with the IL before each extraction. When ILs are physically deposited in the fiber, as in the first report, the IL coating can fell off easily during extraction and desorption steps. Thus, these family of coatings are meant for single analysis. This work made evident the need to immobilize ILs in order to obtain stable and durable SPME devices. Therefore, after the first application, developments were focused on preparation of more robust coatings with longer lifespan and reusability. As a result, efforts have been centered in the synthesis and use of polymeric ionic liquids (PILs) instead of ILs [65]. PILs are polyelectrolytes (polycations, polyanions or polyzwitterions) consisting of repeating units of ILs monomers whose advantages includes enhanced performance in terms of thermal stability, mechanical durability and reusability compared to their precursors, excellent plasticity, and spatial controllability, as well as abundant functional groups. In this sense, it is worth to mention that PILs have greatly enlarged the range of sorbents available for SPME [66–68].

3.1.4. Carbon based nanostructured sorbents

Carbon based nanomaterials such as graphene, carbon nanotubes (CNTs), fullerenes and their functionalized forms, are considered excellent materials for SPME coatings as a consequence of their remarkable physicochemical properties such as large specific surface area, nanosheet morphology, delocalized π -electrons which provides remarkable adsorptive abilities, high heat conductivity, outstanding electrical conductivity as well as thermal and chemical stability [69,70]. Graphene is a carbon allotrope comprised of a single layer of sp^2 -hybridized carbon atoms arranged in six membered rings which are spatially arranged in the form of a honeycomb lattice and is considered the basic structure for all carbon-based nanomaterials. Fullerenes can be described as carbon cages formed by graphene units wrapped together. More specifically, fullerenes are molecules of pentagonal, hexagonal, and heptagonal carbon rings in the form of ellipsoids, hollow spheres or tubes. C_{60} , C_{70} , C_{240} , C_{540} and C_{720} fullerenes have been recognized. CNTs consists in rolled graphene sheets in a circular tube or multiple coaxial tubes resulting from curling single-layer or multilayer graphene in order to form single wall and multiple wall CNTs, respectively which are capped by a structure similar to a fullerene. CNTs length can be up to several centimeters with diameters ranging from a few nanometers to dozens of nanometers [71].

These carbon-based nanomaterials have been employed directly or combined with other materials as SPME coatings in all possible geometries (fiber, hollow fiber, thin-film, stir-bar, in-tube and in-needle SPME) prepared either by chemical bonding, physical deposition, electrochemical deposition, electrophoretic deposition or sol-gel technology [37]. Regarding fullerenes, their applications are limited compared to graphene and CNTs due to their extremely insolubility in both aqueous and organic phases, high cost and low accessibility. Comparing graphene and CNTs some differences in their adsorptive abilities are worth to be mentioned: while the inner layers of CNTs are not accessible to analytes due to steric hindrance both surfaces of graphene are available for adsorption, thus, higher capacity. Moreover, graphene synthesis involves cheap materials and compared to CNTs synthesis do not require the use of special devices or the requirement of difficult processes to remove metal catalysts [72,73]. Besides, graphene is plausible to be easily attached to a support because it is softer and more flexible, the latter a desirable

feature for construction of composite sorbents. Additionally, it possesses a larger number of sites where functionalization can be achieved.

3.1.5. Biologically based sorbents

Biologically based sorbents are highly selective materials with recognition mechanisms which are attained as a result of biological affinity, such as aptamer interactions or immunoaffinity, *i.e.*, antibody-antigen interaction. Aptamers are short artificial single stranded DNA (ssDNA) or RNA (ssRNA) with great affinity to specific target compounds such as proteins, peptides, amino acids, antibiotics, viruses, small ions, low molecular weight organic or inorganic compounds and even entire cells through hydrogen bonding, van der Waals and electrostatic interactions. Their use as sorbents requires the immobilization on a solid support that allows to preserve the aptamer recognizing capacity with chemical and biochemical inertness, mechanical and chemical stability and selected particle size and morphology uniformity. To this aim, several strategies were evaluated employing as solid supports silica, synthetic polymers, sepharose, magnetic particles or beads, gold nanoparticles, hybrid monolithic materials, CNTs and graphene oxides [74,75]. Among the advantages of aptamers, it has to be mentioned the high affinity, specificity, stability with targets and the easiness of preparation and modification at low cost (compared to antibodies). In contrast, the main disadvantage relies in the reusability of the sorbent due to digestion of the aptamer by nucleases and contamination by nonspecific proteins, this aspect has limited their application as SPME coating when employed in the direct immersion mode [37,39].

3.2. Technologies: exploring new strategies to improve HS-SPME

In the development of methods involving sample preparation, the main objectives are centered in minimizing the number of steps and reducing time and solvent consumption while at the same time it is prioritized the reusability, portability, easiness of sample introduction for instrumental analysis, reproducibility, and automation, without losing sensitivity, especially for determination of trace analytes in complex matrices. In this sense, HS-SPME with sample introduction by thermal desorption fulfills most of the abovementioned aspects covering a wide variety of matrixes and analytes by selecting appropriate extractant phase, sorbent geometry and sampling conditions.

A well-known approach called cold fiber SPME (CF-SPME), firstly introduced by Pawliszyn and Zhang [88], allows to maintain the extractant phase at a relatively low temperature while the sample is subjected to high temperatures. In this manner, as discussed in HS-SPME fundamentals, the mass transport coefficient of analytes from the sample to the HS are clearly improved due to the system high temperature, while the low temperature of the fiber increased the distribution coefficients of analytes between the coating and the HS, improving the extraction performance. Devices for performing CF-SPME have been designed based on liquid carbon dioxide as cooling system for SPME fibers. Lately, thermoelectric coolers were designed enabling method automation [89]. This strategy is especially useful for soils and other related solid matrixes, where compounds are highly adsorbed into pores and thermal energy is required to release them.

Other particular situation appears when samples having either labile compounds requiring room temperature extractions or SVOCs are handled; due to extremely long equilibration times are regularly attained. In this sense, approaches dealing with pre-equilibrium conditions may lead to faster extractions in detriment of optimum analysis sensitivity. A strategy that overcomes this issue is the extraction kinetics acceleration, which can be carried out by Vac-HS-SPME.

Although the potential of controlling the pressure variable was disregarded for over a decade, the theoretical basis explaining fundamentals of the technique was established in 2012 [36]. The Vac-HS-SPME theoretical model was based on the fact that evaporation rates can be controlled by mass transfer in the liquid phase, the gas phase or a combination of both contributions. The parameter used to predict the rate-

determining step of the process was the Henry constant, K_H , defined as the ratio of partial pressure to aqueous concentration. It was demonstrated using polycyclic aromatic hydrocarbons that for compounds with high K_H (above than $5 \times 10^{-3} \text{ atm m}^3 \text{ mol}^{-1}$) the evaporation rate is dominated by the resistance of mass transfer in the liquid phase. Contrarily, for compounds with low K_H (below $1.2 \times 10^{-5} \text{ atm m}^3 \text{ mol}^{-1}$) the mass transfer resistance is in the gas phase. Lastly for compounds with K_H between the mentioned values, both mass transfer resistances are important being $\sim 1.6 \times 10^{-4} \text{ atm m}^3 \text{ mol}^{-1}$ the K_H value at which both resistances are equal [36]. That pioneering work demonstrated that Vac-HS-SPME would only accelerate kinetics of analytes with K_H values below $1.6 \times 10^{-4} \text{ atm m}^3 \text{ mol}^{-1}$, *i.e.*, for solutes in which evaporation rate is controlled by the resistance in the gas phase. The explanation for this behavior can be understood taking into consideration that at reduced pressures, diffusion coefficients in gas phase, D_g , are increased (D_g is inversely proportional to the total pressure of the system [90]). Thus, resulting in a faster replenishment of analyte in the headspace formerly depleted by the extractive phase. Additionally, it was proven that the amount of analyte extracted at equilibrium is not affected by sampling under vacuum conditions. As expected, thermodynamic theory establishes that equilibrium concentration is independent on the total pressure since equilibrium constants are not affected by pressure, except if they are significantly high. From a practical point of view, the procedure for performing Vac-HS-SPME is equal to the conventional HS-SPME workflow, with an additional step in which vacuum is performed either before or after sample introduction. Even though it is thought that the procedure is more complex, the simplicity of conventional HS-SPME is preserved; the major disadvantage of the technique relies in the need to construct a sealed recipient capable of maintaining vacuum conditions during microextraction. In this regard, a wide variety of devices for solid and mostly liquid samples have been recently designed, differing in volume and port numbers.

First reported devices consisted of a modified conical flask (Fig. 3A): on one hand a glass tube with a spigot was welded at the neck of the flask for connecting to a vacuum pump; on the other hand an open-cap vial which can be sealed with a PTFE-coated septum was also welded to the top of the neck for a hermetic closure allowing for SPME fiber introduction [34]. In that work, the Vac-HS-SPME technology was applied to the simultaneous quantitative determination of butyl- and phenyltin compounds as ethylated derivatives from aqueous samples. The results were compared to regular HS-SPME under mechanical and magnetic stirring, demonstrating that sampling under reduced pressures yielded higher sensitivities in shorter extraction times. In a previous work [33], volatiles from cooked and raw turkey breast homogenates were determined under regular and reduced vacuum conditions in a device similar to the previously described, which only differs in the way that vacuum is performed inside the container. Instead of welding a tube in the conic flask neck, the vacuum pump was connected via a rubber tubing to a syringe. This procedure resulted in more than 6.6-fold increase of analyte responses compared to the regular pressure procedure.

Several years later, an additional modification to the conical flask device was introduced in order to apply the Vac-HS-SPME technology on solid samples avoiding its exposure during air evacuation (Fig. 3B). Basically, the modification consisted of a 10 mL vial glued to the center of the bottom of the flask with a silicon stopper attached to a stainless-steel wire which was passed through the superior septum to open the vial once vacuum was established. This setup was successfully employed for PAHs [91] and BTEX [92] determination in soils, and also for nicotine analysis in tobacco and hair samples [93]. Alternatively, a series of devices were proposed by Psillakis and collaborators. As a starting point they used a 1000 mL commercial gas-sampling bulb (Fig. 3C) which had the constraint of not allowing the introduction of magnetic stir bars for stirring. This issue that was overcome by constructing 1000 mL and 500 mL lab-made glass containers with three gas-tight ports (Fig. 3D), one port equipped with a spigot for vacuum pump connection, a second port as auxiliary for magnetic stir bar introduction and also for cleaning pur-

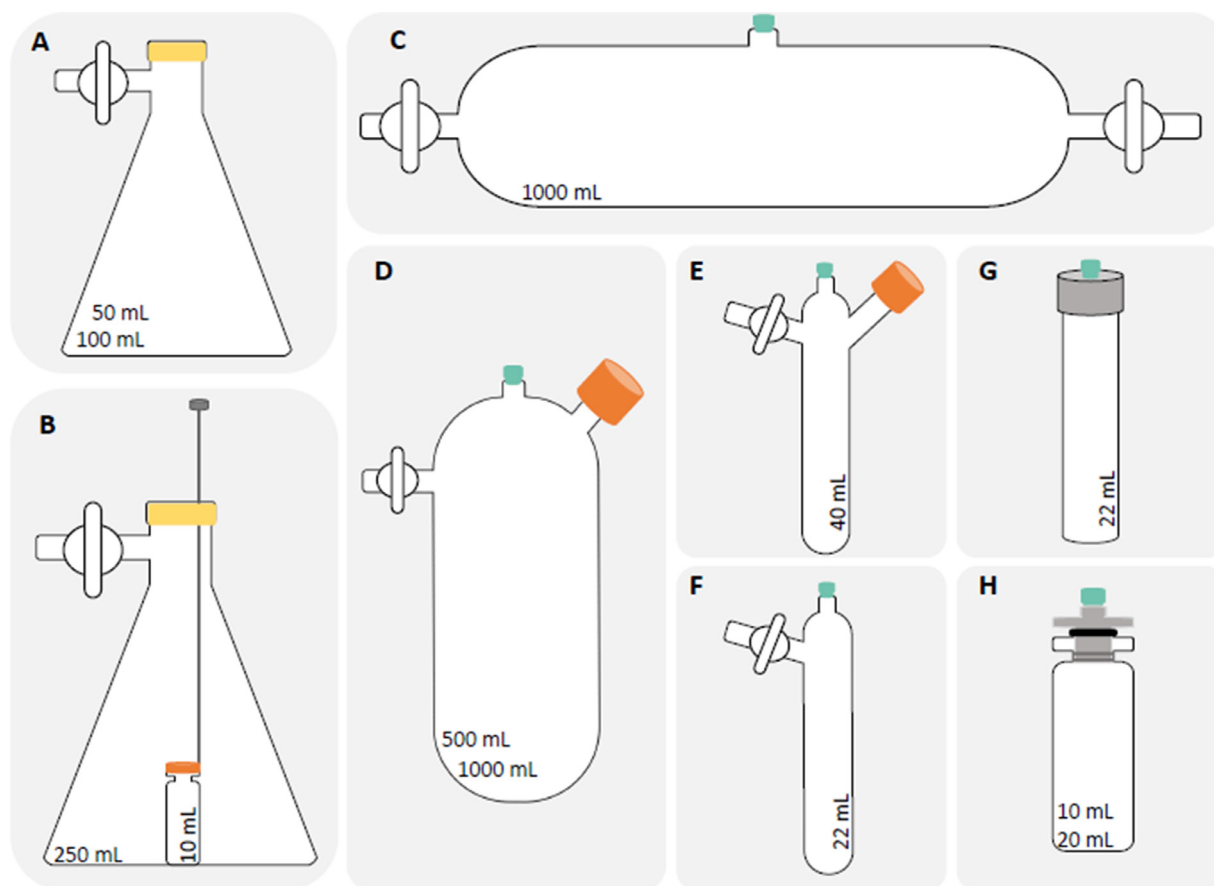


Fig. 3. Scheme of devices reported in literature to perform Vac-HS-SPME.

poses and a third port with a septum for sample introduction and sampling [36,94]. As large volume containers were difficult to manipulate, homogeneous heating was difficult and equilibration times still were time consuming. In this line, the sampler was downsized to a 40 mL or 22 mL by modifying headspace rounded bottom glass vials, reproducing the previous device either keeping the auxiliary port (Fig. 3E) for solid samples [95] or eliminating it for liquid ones [96] (Fig. 3E and F, respectively). Later designs consisted of new PTFE caps equipped with only one-port septum for hermetic closure of commercially available vials with no further modifications (Fig. 3G). The aim was to develop simple and low-cost devices to perform all operations through the septum. The first of two designs included a specially designed O-ring seal screw cap with a hole to attach a GC septum which was molded in a workshop. The sampler performance was verified by Yiantzi et al. [97] on tap and river water in order to quantify polychlorinated biphenyls (PCBs) and also by Glykioti et al. [98] in the determination of earthy-musty odor compounds (2-methylisoborneol and geosmin) found in water samples. The second and latest version of the one-port cap consisted in a modified crimp Mininert® valve developed in 2017 by Trujillo et al. to which the upper part (push/pull buttons and septum) was removed, and a hole was drilled to tightly accommodate a GC septum and an O-ring fitted in the inferior part to guarantee a leak-tight seal (Fig. 3H). This cap can be attached to different volume vials and has the advantage to be easy to reproduce by a turner. Since its introduction, a lot of works were reported including determinations of volatile free fatty acids and phenols in milk and dairy products [99]; rocket fuel unsymmetrical dimethylhydrazine transformation products in lake water and sand [18,100]; haloanisoles in wine [101]; aroma compounds in extra virgin olive [21]; diterpenoidic compounds in frankincense resins for discrimination of *Boswellia* species and origins [102]; simultaneous charac-

terization of both VOCs and SVOCs (monoterpenes, sesquiterpenes and cannabinoids) from *Cannabis sativa* inflorescences; fish volatiles under sub-ambient temperature [103] and characterization of biomarkers in oil source-rock analysis [26].

More recently, Zhu et al. [104] developed a method to improve the mass transport of poor volatile analytes from the sample to the HS called gas-cycle-assisted GCA-HS-SPME. This device is designed to enhance the evaporation rates of analytes from the sample matrix to the headspace. Extraction rates were greatly increased due to the faster evaporation rates of analytes at the sample/headspace interface. Unlike Vac-HS-SPME, where evaporation rates are increased by reducing the HS pressure, in GCA-HS-SPME, evaporation rates are improved by critically increasing the surface area at the liquid sample-HS interface. As a result, extractions were shortened from 70–90 to 5–11 min for a group of semi-volatile organic contaminants from dispersed soil samples.

3.3. Novel applications of HS-SPME

Beyond the classic approach of HS-SPME, where the analyte is distributed among three phases (i.e., liquid or solid sample, headspace and sorbent) until equilibrium is reached in a closed sample vial, there is a growing interest in using this technique to investigate complex systems *in situ* and *in vivo* throughout its volatile and semi-volatile profiles [12,17]. In this manner, the system can be explored without perturbations, or in other words, in a noninvasive way by properly designing, modifying or adapting the devices and setups for such purposes. In this sense, most of the time, novel applications will come along with some technological improvements. However, in this section, the discussion is limited to the application impact. In such context, novel efforts consid-

ering the above-mentioned trends are discussed depending on the field of application. A summary can be found in Table 3.

3.3.1. Environmental

Nowadays, environmental science is not only limited to the determination of pollutants in water and soil but is also devoted to study the impact of organic pollutants on living systems. Monitoring the number and concentration of a wide range of pollutants and endogenous metabolites in biota is crucial for exploring their bioaccumulation and toxicity in environmental toxicology [17,105]. Moreover, the study of the transformations suffered by pollutants in the environment and living systems is also a topic that requires untargeted analytical methods with high sensitivity and excellent recovery of compounds [2,18,106]. In this context, HS-SPME plays an important role as it allows to efficiently monitor traces of volatile and semi-volatile organic pollutants from highly complex matrixes (Table 3). In the last decade, applications of HS-SPME technique have been reported for soil and water samples using targeted and untargeted analysis. In the case of targeted approaches, PAHs and BTEX analysis were the most reported in literature as they exhibit high affinity towards a wide variety of extractant phases [32,95,104,107–109]. In this regard, determinations from soil [32,95] and different aqueous samples such as wastewater [109,110] and natural waters [111] have been recently reported, obtaining in most cases limits of detection ranging from low $\text{ng}\cdot\text{L}^{-1}$ to hundreds of $\text{ng}\cdot\text{L}^{-1}$ [95,109]. In addition, other groups of pollutants have been found in the literature using a HS-SPME approach with different separation and detection such as chlorophenols [18], polychlorinated biphenyls [18,104,110], organophosphonates [112], phthalate esters [104], mercury species [113] and chlorpyrifos [109]. For untargeted strategies, the main goal is to extract VOCs [114] and SVOCs [18,26] with the best coverage of compounds with different physicochemical properties. Hence, fibers with mixed extraction modes such as DVB/CAR/PDMS, DVB/PDMS, hydrophilic-lipophilic balanced coatings, among others, are required. For SVOCs analysis, strategies including vacuum assisted SPME, thin film devices or a combination of both have been recently reported for different environmental applications [18,115]. In this line, Zhakupbekova et al. [116] have developed a method to quantitate trace transformation products of rocket fuel unsymmetrical dimethylhydrazine from sand. The vial containing the sample is kept at -30°C until the vacuum is applied (~ 20 s) to avoid VOCs losses during the process. Then, the sample at vacuum conditions is incubated at higher temperature to enrich the HS. The CAR/PDMS SPME fiber was exposed for extraction and then, thermally desorbed in the GC-MS injector. The LODs were ranged between 0.035 and $3.6 \text{ ng}\cdot\text{g}^{-1}$ for all the target compounds, being about an order of magnitude better than the same procedure without the additional water extraction step and vacuum conditions.

Regarding less conventional environmental matrixes, it is worth to highlight Lin et al. work [113], where a very sensitive method for quantitation and speciation of mercury from rice was established. Rice was primarily digested in basic media and the mercury present was derivatized with a solution of NaBPh_4 . The home-made porous carbon SPME fiber was inserted into the vial and exposed for 20 min. Then, the fiber was thermally desorbed in a GC-DBD-OES instrument for separation and detection of methylmercury, ethyl-mercury and inorganic mercury. Limits of detection of 0.5; 0.75 and $1.0 \text{ ng}\cdot\text{g}^{-1}$ were obtained for inorganic mercury, methylmercury and ethyl-mercury, respectively. Sühning et al. [117] have implemented HS-SPME in combination with internal benchmarking to determine the elimination kinetics of hydrophobic substances classified as unknown or variable composition (UVCB). Internal benchmarking is used to measure the behavior of a target analyte relative to a well-characterized standard, that is also used to feed animals, which will not be eliminated by excretion, biotransformation, or respiration in the duration of the experiment, in this case hexachlorobenzene. After a group of rainbow trout was exposed to cedarwood oil, keeping a group control without exposing, the specimens were sacrificed at different days for kinetic studies. The tissue sample was homogenized, and the

fiber was directly exposed to its HS for extraction. Different elimination kinetics were obtained for the different detected compounds, showing the potential of this technique to monitor such complex systems. In fact, it is also worth mentioning the work performed by Hsieh et al. [107] in which binding constants of a group of PAHs to humic acids are determined. As HS-SPME is a non-exhaustive extraction, the major chemical equilibria are not disturbed, thus, physicochemical constants can be estimated with great accuracy by *in situ* measurements. This demonstrates HS-SPME can not only perform well for analytical purposes but also for biological, environmental, and physicochemical goals.

3.3.2. Bioanalysis

In recent years, along with the development of highly sophisticated separation and detection systems, HS-SPME has gained special attention in bioanalysis. The possibility to perform diagnostics using alternative samples, accessible by less invasive procedures such as exhaled and *in situ* breath [14,15,17], or skin emissions [118–120] has renewed the efforts in the field [17,121–123]. In fact, there is a particular interest in substituting the classical biopsies, where a piece of tissue is taken, for less harmful and invasive options. Thus, SPME emerge as an excellent alternative supporting the *chemical biopsy* concept, and volatile and semi-volatile profiles are of special concern [17,118–120]. Additionally, this technique has been recently implemented for *in vivo* monitoring of VOCs and SVOCs profiles from biological samples such as cancer cell lines and tissue [16,124,125].

Having these highlights in mind, HS-SPME studies related to breath analysis have been continuously increasing in applied to disease diagnosis [125,126] and human exposure to different pollutants [14,15,127,128]. Considering the new coronavirus outbreak, where in many countries result mandatory to wear a face mask, an emerging wearable exhaled breath aerosol (EBA) sampler device was reported. To this end, disposable filtering facepiece masks, e.g. N95 (USA), KN95 (China), containing one or more SPME fiber fixed inside the mask were employed to collect and preconcentrate EBA in a matter of minutes, as can be seen in Fig. 4a [14]. Then, after extraction, the fibers were desorbed and analyzed by DART-MS. Some proof-of-concept experiments have shown acceptable collection and detection of molecules after human exposure to caffeine, tobacco and nasal sprayers. Besides, the in-mask atmosphere is highly moist and thus, non-volatile compounds and water-soluble compounds in microdroplets of EBA could also be un-specifically extracted by the SPME fiber. Nevertheless, the prototype shows some fragility due to the use of SPME fibers and, although it mentioned, there is no clear idea of the reproducibility and quantitative capabilities of the setup. Alternatively, Locatelli et al. [15] have reported the implementation of an array of fabric-phase sorptive extraction (FPSE) devices with different chemistries inserted in a face mask (Fig. 4b). After extraction, the membranes were immersed in methanol for desorption and then, submitted for LC-MS/MS analysis. The experiments have demonstrated the ability of the system to screen in 18 minutes 739 different compounds using an LC-MS/MS. It must be noted that the extraction time was about a full working day (~ 8 h extraction) and the time of sample preparation (desorption and centrifugation) must also be considered for the total time of analysis. Furthermore, the device is used as a passive sampler, reporting average concentrations and not spot concentrations. On one hand, this thin film SPME device [15] has greater surface area and an increased extraction kinetics in comparison to the classical fiber [14]. Also, it provides superior mechanical robustness due to the flexibility and versatility of such devices. On the other hand, from a green analytical perspective [10], the direct coupling of SPME to MS via DART desorption and ionization provides a more environmentally friendly approach, avoiding the use of hazardous organic solvents.

Skin emissions are another attractive niche for HS-SPME development with, up to date, only some preliminary setups with no applications in actual biological problems [17]. Therefore, the topic remains unexplored, having great potential for technology and methodological

Table 3
Summary of recent applications in HS-SPME.

Field of application	Sample	Analytes	SPME phase	Geometry	Setup	Technique	Ref.
Environment	Shrimps	Polichlorinated naphthalenes	Graphene aerogel	Fiber	HS-SPME	GC-MS	[83]
	Water with humic acids	PAHs	65 μm DVB/PDMS	Fiber	Microwave-assisted HS-SPME	GC-MS	[107]
	Soil	PAHs	100 μm PDMS	Fiber	Vac-HS-SPME	GC-MS	[94]
	Wastewater	PAHs, 2,6-diisopropyl naphthalene, chlorpyrifos ethyl and diazinone	85 μm PA	Fiber	HS-SPME	GC-HRMS	[109]
	Soil	PAHs, PCBs and PAEs	100 μm PDMS (PAHs and PCBs) and 65 μm DVB/PDMS (PAEs)	Fiber	Gas-Cycled-Assisted-HS-SPME	GC-FID	[104]
	Wastewater	Pesticides, PAHs, PCBs, BDEs	85 μm PA	Fiber	HS-SPME	GC-HRMS	[110]
	Water	PAHs	Self assembled gold nanoparticles	Fiber	HS-SPME	LC-UV-Vis	[111]
	Vynil floor tiles	Organophosphonates	75 μm CAR/PDMS	Fiber	in situ Vac-HS-SPME	TD-GC-MS	[112]
	Rice	Inorganic mercury, methylmercury, and ethylmercury	Porous carbon	Fiber	HS-SPME	GC-DBD-OES	[113]
	Blood, urine and semen	VOCs	CAR/PDMS	Fiber	HS-SPME	GC-MS	[114]
	Swimming pool water	Chlorinated products	Porous carbon-PDMS	Thin film	HS-SPME	GC-MS	[115]
	Sand	Transformation products of unsymmetrical dimethylhydrazine	85 μm CAR/ PDMS	Fiber	Vac-HS-SPME	GC-MS	[116]
	Bioanalysis	Fish	VOCs	PDMS	Fiber	HS-SPME	GC-MS/MS and GC-HRMS
Skin		VOCs	50/30 μm DVB/ CAR/PDMS	Fiber	in vivo HS-SPME	GC-MS	[118]
Skin		VOCs scent profile	50/30 μm DVB/ CAR/PDMS	Fiber	in vivo HS-SPME	GC-MS	[120]
Adenocarcinoma cell lines		VOCs	30 μm CAR/PDMS	Fiber	in situ HS-SPME	GC-MS	[124]
Lung tissue		VOCs	50/30 μm DVB/ CAR/PDMS	Fiber	in situ HS-SPME	GC-MS	[125]
Exhaled breath		VOCs	75- μm CAR/PDMS and 65- μm DVB/PDMS	Fiber	HS-SPME	GC-MS	[126]
Exhaled breath		VOCs	DVB/CAR/PDMS	Fiber	HS-SPME	GC-MS	[128]
Mycobacteria culture		VOCs	50/30 μm DVB/ CAR/PDMS	Fiber	in situ HS-SPME	GC-MS	[132]
Fungi and bacteria		VOCs	Hydrophilic-lipophilic coating	Thin film	in situ HS-SPME	DART-HRMS	[133]
Food & Agricultural		Olive oil	VOCs	50/30 μm DVB/ CAR/PDMS	Fiber	Vac-HS-SPME	GC-MS
	Fish	VOCs	75- μm CAR/PDMS and 65- μm DVB/PDMS	Fiber	sub-ambient temperature Vac-HS-SPME	GC-MS	[103]
	Soy sauce	VOCs aroma profile	85 μm PA, 100 μm PDMS, 65 μm DVB/PDMS, 75 μm CAR/PDMS and 50/30 μm DVB/CAR/PDMS	Fiber	HS-SPME	GC-Olfactometry and GC-MS	[136]
	Dairy products	VOCs aroma profile	50/30 μm DVB/ CAR/PDMS	Fiber	HS-SPME	GC-IMS	[137]
	Raw beef	VOCs	DVB/PDMS	Fiber	HS-SPME	GC-MS	[138]
	White rice	VOCs	85 μm PA, 100 μm PDMS, 65 μm DVB/PDMS, 75 μm CAR/PDMS and 50/30 μm DVB/CAR/PDMS	Fiber	HS-SPME	GC-MS (SIM mode)	[140]
	Scented rice	Food flavouring compounds	CAR/PDMS, DVB/PDMS, and PDMS	Fiber	HS-SPME	GC-MS (SIM mode)	[140]
	Wine	Semi-volatile additives	85 μm CAR/PDMS	Fiber	HS-SPME	GC-MS	[142]
	Dried onion	VOCs	50/30 μm DVB/ CAR/PDMS	Fiber	HS-SPME	GCxGC-TOF and GC-MS	[144]
	Grapes	VOCs	65- μm DVB/PDMS	Fiber	in vivo HS-SPME	GC-MS	[19]

(continued on next page)

Table 3 (continued)

Field of application	Sample	Analytes	SPME phase	Geometry	Setup	Technique	Ref.
Cultural Heritage	Plastics and rubber materials	VOCs	50/30 μm DVB/CAR/PDMS	Fiber	HS-SPME and <i>in situ</i> HS-SPME	GC-MS	[22]
	Paper	VOCs	50/30 μm DVB/CAR/PDMS	Fiber	HS-SPME	GC-MS	[147]
	Exhibition cases	VOCs	75- μm CAR/PDMS	Fiber	<i>in situ</i> HS-SPME	GC-MS	[24]

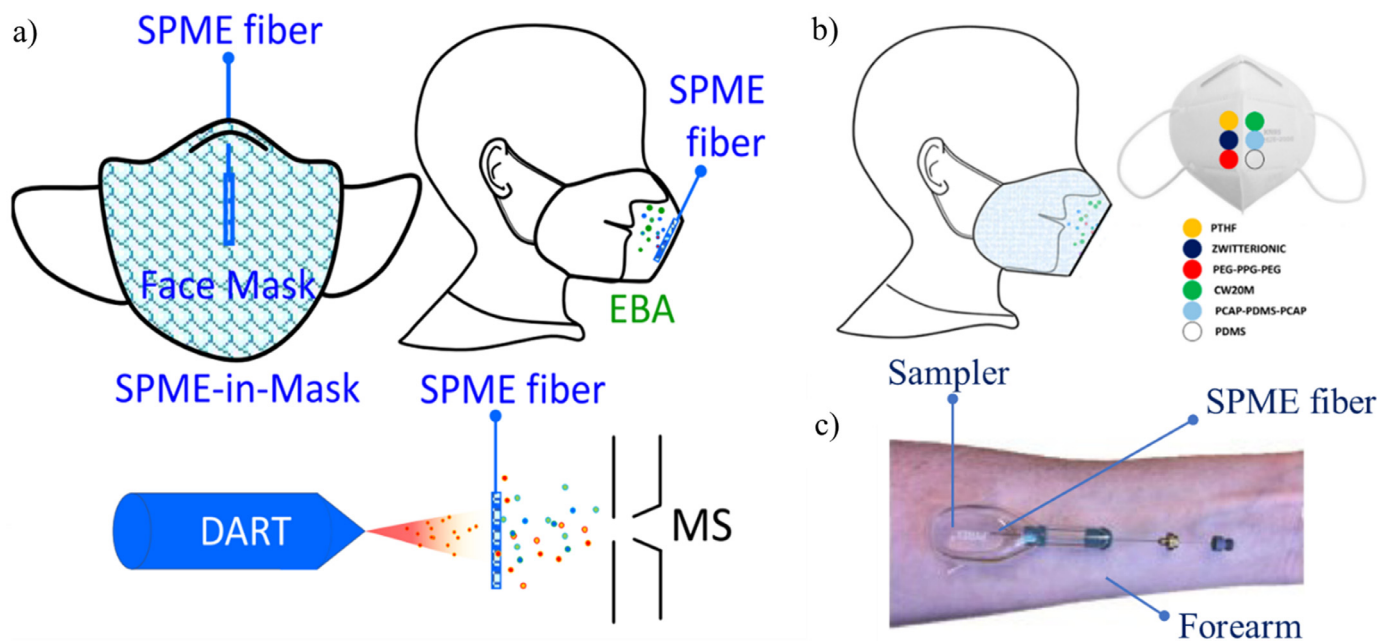


Fig. 4. (a) Face mask HS-SPME setup, sampling and direct analysis by DART-MS, adapted with permission from Ref. [14]. Copyright {2022} American Chemical Society, (b) face mask and HS-SPME array (with different membranes), adapted with permission from Ref. [15]. Copyright {2022} American Chemical Society and, (c) headspace sampling of skin VOCs using HS-SPME placed in a glass funnel, reproduced from Ref. [119] with permission.

development, mainly calibration, quantitation and reproducibility aspects [129–131]. To this end, the pioneer work reported by Zhang et al. [118] involves a chamber, where the arm is sampled, connected to a set of tubes and a pump to make the emanations circulate through a secondary smaller chamber in which the SPME fiber is exposed. In addition, the main chamber is also connected to an independent nitrogen line and a purge valve to eliminate the gases before each experiment. The sampling process consisted in 10 minutes of chamber purging followed by 30 minutes of extraction. Then, the fiber was thermally desorbed in a GC-MS for analysis. By comparison of the obtained data during different seasons, clear differences in the volatile profiles were observed using principal component analysis. Furthermore, various VOCs were also identified with different levels of confidence. Similarly, but locally HS-SPME skin sampling was developed by Duffy et al. [119] to determine differences in volatile profiles before and after acute barrier disruption (Fig. 4c). For such purpose, the DVB/CAR/PDMS SPME fiber was placed within an open glass holder that was affixed to the forearm. In this manner, the HS in contact to the skin is completely enclosed and in contact to the fiber, which is punch through a septum. The optimum extraction time was 15 minutes, and right after, the fiber was immediately thermally desorbed in the GC-MS system allowing for volatile profile differentiation between stages. In a subsequent work from the same group, the system was successfully tested in other applications [17,120].

Finally, another topic that is growing interest in HS-SPME applied to bioanalysis is the study of VOCs and SVOCs profiles in complex and dynamic systems. In this line, the study of cell lines [16,124], bacterial [132] and fungi cultures [133] for diagnosis, monitoring of biological

processes or identification have been carried out. As an example, Filipiak et al. [16] have recently published a work dealing with the analysis of volatile metabolites of A549 cancer cells. The developed setup consists of a thin film microextraction device (TFME) placed in the HS of a 20 mL vial containing 5 mL of the cell culture. It is important to highlight that this kind of devices provide high surface area and faster extraction kinetics [28] when compared with classical fibers. Also, the use of a thermal desorption unit with a cold trap for TFME desorption gives excellent preconcentration factors and band focusing. Different chemistries of TFME devices were tested giving HLB the best results in terms of analyte coverage. As a result, the presence of 40 VOCs was confirmed out of 68 compounds detected. Five metabolites were significantly released by A549 cancer cells, while benzaldehyde was decreased. These results indicate the potential of this technique to study the *volatilome* of complex and active systems. Despite unexplored in this work, the potential of noninvasive rapid extractions in changing systems will enable to study their evolution over time, not only by taking a “picture” of the volatile profile but monitoring the dynamic profiles of each compound at different stages of the biological process.

3.3.3. Food and agricultural safety and quality

HS-SPME has been explored in different applications related to food and agricultural analysis [20,31,134,135]. The presence of very complex matrixes conformed by lipids, proteins, sugars, etc. make HS-SPME an ideal technique over direct immersion SPME, due to the absence of interferences and unspecific adsorption onto the coating that can cause coating fouling and dramatically shorten the lifespan of classical SPME

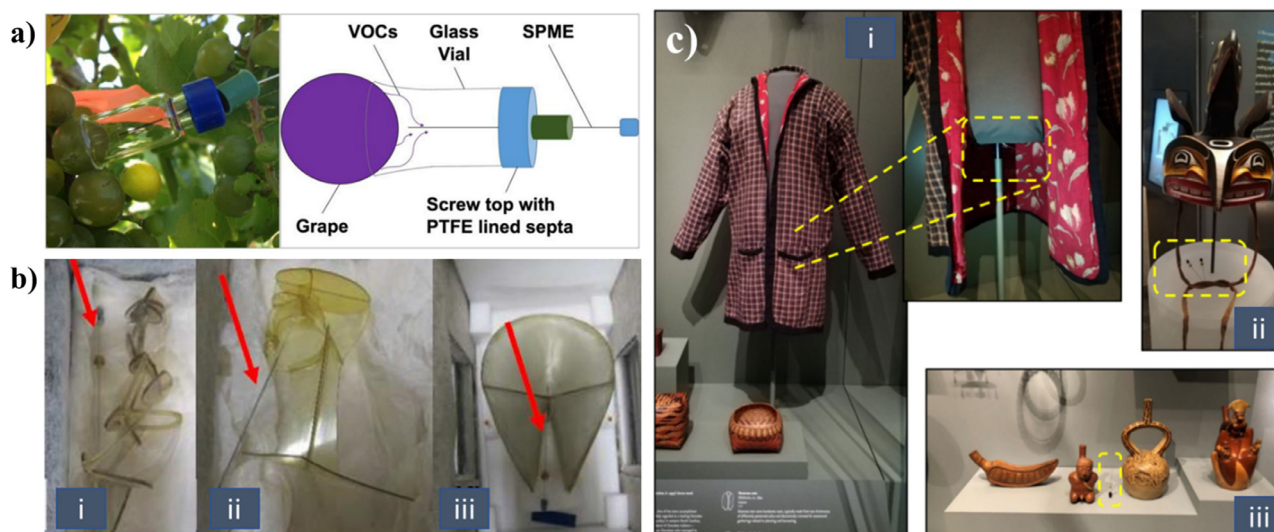


Fig. 5. (a) Single-berry sampling device for *in vivo* and *in situ* VOCs emissions, adapted from Ref. [19] with permissions, (b) Tate plastics-based objects (i) Naum Gabo, Model for the statue of Aphrodite in the ballet 'La Chatte', (ii) Antoine Pevsner, Head and, (iii) Naum Gabo, Model for Spheric Theme, analyzed with the SPME fiber in place (marked by arrow) adapted from Ref. [23] with permissions. (c) On-site HS-SPME sampling locations at (i) Eastern Woodlands wall, SPME fiber mounted into internal Ethafoam® support of Oklahoma Shawnee coat, (ii) Andes wall case, SPME fiber in back of shelf between two Moche stirrup spout ceramic vessels and, (iii) Northwest Coast focal point case, paired SPME fibers in direct contact with efflorescence on cotton ties of Kwakwaka'wakw headdress, wood, paint, cotton fabrics. Adapted from Ref. [24] with permissions.

fibers. Untargeted analysis of volatile bioactive compounds, food adulteration, food quality and safety, and applications related to productive agricultural processes have been extensively reported in literature, and a summary of the most relevant applications can be found in Table 3. Most of them are related to quality assurance and product acceptance (e.g., fragrance [136,137], taste, appearance, shelf life [138], geographical indication [139,140], food adulteration [140–142] and nutritional content [143,144]). However, other research directions are focused on the study of new food properties based on untargeted molecular analysis. To this end, the development of novel HS-SPME strategies hyphenated to sophisticated chromatographic and mass spectrometric systems has become a powerful tool for compound discovery in this field [141,142,145].

Rice et al. [19] have presented a novel concept for non-destructive evaluation of volatiles emitted from ripening grapes using HS-SPME. Even though, the manuscript presented two prototypes, as can be seen in Fig. 5a, the concept of the modified 2 mL vial for *in vivo* monitoring of VOC emissions from single berries is the most innovative. Besides, the single-berry samplers were subjected to vacuum to accelerate the extraction kinetics. To this end, the authors managed to extract the volatile profiles of single specimens and to explore multivariate analysis at different ripening stages of 4 cold-hardy cultivars. Statistical analysis using PCA has shown no significant differences in VOC emission profiles between the two sampling prototypes. Hence, the advances in this work are promising for *in vivo* HS-SPME sampling, where the concept can be extrapolated to other complex systems.

An innovative application of Vac-HS-SPME to the analysis of non-aqueous samples such as olive oil was reported by Mascrez et al. [21]. Air evacuated samples of olive oil have shown an increased extraction kinetics of SVOCs due to the reduction of the gas-phase resistance. However, diffusion coefficient of the analyte in the highly viscous oily phase was another determinant variable to include in the overall dynamics of the extraction system. Additionally, unlike aqueous matrixes, the increasing of temperature will not have a negative impact in HS as oil molecules are much less prone to evaporate. Thus, increasing system temperature during extraction allowed to reduce analytes diffusion coefficients by about 40 %, allowing to increase the mass transfer coefficients between the oily phase and the HS. To conclude, using Vac-HS-SPME, optimum recovery conditions were reached at milder tem-

perature and shorter times when compared with conventional HS-SPME method, namely $\sim 45^{\circ}\text{C}$ for ~ 25 min. Nevertheless, the positive variations were observed for the recovered SVOCs, while for VOCs the behavior remained practically unaltered. In the same line, a follow up work reported by Delbecq et al. [103] shows the implementation of Vac-HS-SPME at low temperatures to extract and preconcentrate analytes from perishable food samples. In this way, although the sample was kept at 5°C for preservation, the evacuated atmosphere improved in most cases the extraction kinetics for a group of VOCs and SVOCs. Also, the efficiency of extraction from a thermodynamic point of view increases, as the affinity constant increases at lower temperatures.

3.3.4. Cultural heritage

In the last decade, the study of VOCs emitted from cultural heritage objects has emerged as an innovative field of application [23,146]. The reasons for which HS-SPME has gained special attention in the field are: i) most of the time, cultural objects cannot be sampled thus, non invasive approaches are encouraged; ii) VOCs and SVOCs emitted can be correlated to material constitution and degradation processes; iii) monitoring of VOCs and SVOCs are also important for preventive conservation purposes of other objects that can be harmed by these emanations and; iv) the amount of VOCs and SVOCs emitted are limited and a preconcentration of them are totally necessary. It is worth to note that even though some approaches using passive samplers and SPE cartridges have already been employed, the spot concentration at a definite time cannot be calculated, making HS-SPME ideal for this purpose. In this context, the main goal of the investigations were focused on the study of volatile degradation profiles (*degradomics*) of different materials such as plastic [22,23], paper [146–148], and rubber [22]. In all cases, classical SPME fibers were used for extraction from the HS of materials at different degradation stages. Thus, a degradation mechanism can be elucidated having as an experimental source of evidence the volatile degradation profile.

Curran et al. [23] have reported the first use of VOCs analysis to study degradation processes of modern polymeric museum artifacts. These objects present serious conservation challenges due to the inherent instability of plastics and the very wide range of materials that can be involved in collections, incorporating different polymers and additives. DVB/CAR/PDMS SPME fibers ($50/30\ \mu\text{m}$) were employed

for the extraction of VOCs emitted from standard samples at different artificial degradation stages and from artifacts at the Tate Museum (Fig. 5b). The authors have determined that not only one VOC but a group of them can be considered for degradation diagnosis. As a result, samples were classified according to the length of degradation time based on HS-SPME-GC-MS monitoring and linear discriminant analysis. For cellulose nitrate, cellulose acetate, cellulose propionate, polyurethane foams and poly(vinyl chloride) samples, classification was achieved with accuracies ranging between 62–83%. More recently, Alvarez-Martin and co-workers [24] have reported the use of HS-SPME-GC-MS for the identification of VOCs in exhibition cases and efflorescence on museum objects exhibited at Smithsonian's National Museum of the American Indian-New York. The extraction consisted of exposing the fiber (CAR/PDMS) inside the exhibition case for 24 h (Fig. 5c). The study has shown great potential in detecting VOCs accumulated in display cases that could lead to the formation of the efflorescence. Noteworthy, the VOCs detected can be emitted either from the exhibition case materials or the cultural objects. The developed protocol also demonstrated reproducible results for shipping the fiber used on experiments to a central facility for GC-MS. However, experiments using more volatile compounds and at standard concentrations should be considered for more accurate results and also to study the limitations of the approach.

4. Future perspectives

Main features of HS-SPME relies on the noninvasive nature of the approach, negligible fiber contamination and degradation, insignificant matrix effects, and excellent reproducibility and robustness. In recent years, these advantages have enabled new fields of application in which *in situ*, *in vivo* and non-invasive approaches are required. Therefore, the context itself is pushing new paradigms, settings new challenges for the future development of this technique. In this regard, fields such as bioanalysis, environmental sciences, food science and, more recently, cultural heritage are demanding higher coverage of analytes at trace levels. In this context, on one hand, vacuum assisted HS-SPME and thin film-microextraction devices emerge as techniques that improve extraction coverage and kinetic of SVOCs. On the other hand, the development of novel materials with higher surface area, alternative geometries, longer lifespans, and balanced polarity coverage is also encouraged. Likewise, the authors still believe there is a lot of room for improvements regarding quantification of analytes from *in vivo* complex systems, where most of the works reported in literature are qualitative. To this end, research focus on calibration methods, automation and, theoretical modelling has an enormous potential for improving qualitative identification, reproducibility, and quantitative figures of merit from an analytical method. In this manner, the implementation of HS-SPME will be strengthened in challenging applications where noninvasive approaches are mandatory.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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