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Volatile sampling by headspace techniques

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ABSTRACT

We review the use of static headspace (S-HS) and dynamic headspace (D-HS) techniques for the extraction of volatiles from different matrices. We present fundamentals and the most relevant advances in instrumentation, together with detailed discussion on the most important parameters affecting HS sampling. We also describe some of the most recent and outstanding applications, classified according to the type of matrix – among them, the use of ionic liquids as solvents for S-HS, the coupling of D-HS to comprehensive two-dimensional gas chromatography, the development of novel miniaturized devices for D-HS sampling and increasing interest in approaches based on HS-mass spectrometry (HS-MS) for fast, unbiased sample classification. We also review multi-step strategies for accurate quantitation of volatiles in samples with noticeable matrix effects. To conclude, we show that HS sampling is a versatile, rapid, efficient, green technique for volatile extraction, free of interferences.

Contents

1. Introduction 85
2. Headspace (HS) techniques 86
   2.1. Static headspace 86
      2.1.1. Fundamentals 86
      2.1.2. Instrumentation 86
      2.1.3. S-HS parameters 86
      2.1.4. Applications 87
   2.2. Dynamic headspace 90
      2.2.1. Fundamentals 90
      2.2.2. Instrumentation 90
      2.2.3. D-HS parameters 90
      2.2.4. Applications 91
   2.3. Multi-step headspace extraction (MHE) 96
   2.4. HS-MS 96
3. Conclusions and future trends 97
   Acknowledgements 97
   References 97

1. Introduction

The analysis of volatile composition is of great interest in different fields, such as flavor and fragrance characterization, food and beverage authentication, environmental analysis, and quality control (QC) of samples of different natures. In most applications involving the analysis of real samples, complex mixtures of volatiles are usually found at low concentrations together with other non-volatile matrix components. Therefore, their chromatographic analysis, usually carried out by gas chromatography coupled to mass spectrometry (GC-MS), requires a prior sampling step, in which volatiles are isolated from the matrix and, if possible, preconcentrated. Different techniques based on solvent extraction emerged in recent years for volatile sampling [1–3]. However, the undeniable advantages of headspace (HS)-based methods, in static or dynamic mode, as environment-friendly, easy to implement and versatile procedures, promoted their application in different fields. Moreover, and in line with the current trend on the development

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of fast, non-separative methodologies for sample characterization, the potential of the direct coupling HS-MS also attracted considerable attention.

In this review, we review and discuss the most significant literature on HS extraction from the period 2005–15.

2. Headspace (HS) techniques

The term "headspace" (HS) refers to the gas phase (in equilibrium or not with the matrix) above a solid or liquid sample, when this is placed in a closed container (usually a vial sealed with a septum). HS sampling is usually classified into two types: static (S-HS) or dynamic (D-HS).

2.1. Static headspace

In S-HS sampling, this system is heated for a given period of time at a set temperature, and volatiles are distributed between the sample phase and the gas phase until equilibrium is reached. A small fraction of the HS is further removed and, as it is free of non-volatile compounds, it can be directly analyzed by GC. S-HS sampling can also be carried out under non-equilibrium conditions, as long as the operating parameters are carefully set for reproducible analysis.

2.1.1. Fundamentals

As described in one of the first comprehensive references on the theory and definitions of HS by Kolb and Ettre [4], equilibrium in S-HS is characterized by the partition coefficient (K), which represents the ratio of analyte concentrations in the sample condensed phase (C_s) and the gas phase (C_g).

The phase ratio (β) is defined by the ratio of volumes of gas phase (V_g) and sample phase (V_s). The relationship between K and β to HS concentration (C_g) is shown in Equation (1), where C_o is the analyte concentration initially present in the sample:

$$C_g = \frac{C_o}{K+\beta} \tag{1}$$

In a given system and under specific conditions, K and β are constant, and C_g is proportional to C_o. In addition, peak area (A) in chromatography is proportional to analyte concentration (C_g), so the relationship shown in Equation (2) can be established. It is worth noting that a number of HS and GC parameters influence Equation (2), so analytical conditions should remain constant for reproducible analysis:

$$A \propto C_g = \frac{C_o}{K+\beta} \tag{2}$$

However, and according to basic laws of thermodynamics, K is inversely proportional to the vapor pressure of the analyte i (p_i^o), which depends on temperature, and to its mole concentration (x_i) and activity coefficient (γ_i), which depend on the nature of the compound and reflect its interaction with the sample matrix [Equation (3)], so, by decreasing K, an increase in C_g at equilibrium will be obtained, resulting in an improved HS sensitivity:

$$K \propto \frac{1}{p_i^o x_i \gamma_i} \tag{3}$$

By combining some of the equations above, and considering the response factor (RF) for the instrumental contribution to response, a new expression [Equation (4)] is generated to describe the relationship between the GC peak area and the analyte concentration in the sample (C_o), in which p_{total} is the total pressure in the vial:

$$A = \frac{(RF)C_o}{\frac{p_{total}}{p_i^o \gamma} + \beta} \tag{4}$$

2.1.2. Instrumentation

Instrumentation for S-HS is quite simple and, as mentioned above, usually involves the use of a sealed container and a heating system for temperature control of the sample vial. Sampling can be directly carried out using gas-tight syringes, but other devices based on different trapping materials and designs are also used for further concentration of volatiles in high concentration-capacity HS (HCC-HS) techniques, such as solid-phase microextraction (SPME) and single-drop microextraction (SDME). Literature concerning the use of these techniques is extensive [5–7] and is covered in other manuscripts within this Special Issue, so we mention below only some recent examples in which these techniques are compared with S-HS.

S-HS can be carried out manually, but automated devices equipped with temperature control for cold-injection or valve-loop-injection systems are also available. In these cases, the sample vial is pressurized (usually 22.5–30 psig) and vapor is allowed to escape through a valve-sampling loop that has a fixed capacity and is held at a higher temperature than that of the sample vial. After sampling, the valve rotates and a determined flow of carrier gas is supplied into the loop to sweep volatiles towards a transfer line coupled to the GC system [8].

2.1.3. S-HS parameters

The most important parameters affecting S-HS sampling are the temperature of the sample and the sample volume in an HS vial, as HS sensitivity depends upon the combined effect of K and β {for a detailed explanation, see [4]}. Optimization of these variables depends on analyte properties (e.g., volatility, polarity and matrix affinity), but characteristics of the sample matrix (e.g., lability) should also be taken into account.

Regarding temperature control, temperatures in the range 45–150°C, depending on the stability of target compounds and/or the sample matrix, are usually employed. Optimization of equilibrium time (or sampling time if equilibrium is not reached) is also required to ensure that the analysis is performed at equilibrium or to assure reproducibility in HS sampling under selected conditions.

Sensitivity might also be improved using low HS-to-sample volume ratios, mainly for analytes with low solubility in the condensed phase. However, other options, such as the addition of salts to the analyte solution (the so-called "salting-out effect"), and the use of solvents to dissolve the sample, have also been described [4]. In the salting-out effect, the most common approach, the solubility of the hydrophobic analytes in the water solution decreases with increase in ionic strength, so concentration of these compounds in the HS is higher.

The use of other novel solvents, such as room-temperature ionic liquids (RTILs), and different emerging HCC-HS techniques and sample-preparation procedures as a way to enhance S-HS sensitivity were recently reviewed by Snow and Bullock [9], so we compile here only the most significant developments regarding the use of these solvents published since that date.

ILs are low-melting-point salts that exist in liquid phase at relatively low temperatures (generally below 150°C). They are considered environment-friendly solvents and seem to constitute a safe alternative to the use of traditional volatile organic solvents. Considering their high viscosity, ILs are being successfully used as fiber coatings in HS-SPME [10] or as single drops in HS-SDME [11] analysis of samples in different fields. Moreover, it has also been demonstrated that ILs have potentially useful dual-nature properties to be used as solvents in S-HS. They can be simultaneously retentive for both polar and non-polar solutes and can be highly

retentive for specific functional groups. Different applications regarding the use of ILs as solvents for HS-GC analysis of different compounds, mainly in pharmaceutical or environmental areas, have been developed and we discuss them in the following sections. However, research in this field is still limited and the price of ILs is not yet affordable for routine analysis.

Sampling of volatile compounds is affected by the composition of the matrix. It is known that, in aqueous systems, the retention of aroma compounds can be modified by their physicochemical interactions with proteins, polysaccharides or lipids [12,13]. As an example, Samavati et al. [14] studied the partitioning and the release of two volatile compounds (ethyl acetate and diacetyl) from two model systems, one rich in polysaccharides (Tragacanth gum) and the other in oleic acid. The increasing concentrations of these constituents decreased the diffusion rate of aroma compounds through the interface of the solution in both matrices, but a higher retention of target compounds was observed in the model containing oleic acid.

2.1.4. Applications

S-HS is routinely used by scientists in a wide range of disciplines and numerous applications are continually emerging in different fields. Some remarkable studies, grouped by the type of sample, are described below. In addition, Table 1 summarizes, for each of these studies, the main objective and specific experimental conditions used for both S-HS sampling and GC analysis.

2.1.4.1. Pharmaceutical products. S-HS-GC is commonly used in the pharmaceutical industry for identification and control of residual solvents (RSs) [26]. These compounds are analyzed following an official method described in the European Pharmacopoeia [27]. Matrix media include water, in case of water-soluble samples, and organic solvents, such as *N,N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO), in case of water-insoluble samples [28,29]. However, although this method proved to be suitable for most RSs, it is not sensitive enough for the analysis of high-boiling-point compounds, such as DMF, *N,N*-dimethylacetamide and DMSO, which can also be present as RSs in pharmaceutical products [30]. Moreover, due to their low vapor pressure, they possess high partition coefficients in most dilution media, their sensitive detection being challenging [31]. To overcome this drawback, the search for new solvents as dilution medium has attracted great interest. D'Autry et al. [30] proved the utility of liquid paraffin as a new dilution medium for the analysis of these RSs. The optimized method showed lower limits of detection (LODs) (below 1 μg/vial for each compound) than those of Pharmacopoeia, with good accuracy and reproducibility.

As commented above, the extremely low vapor pressure of ILs promoted their use as matrix media in green HS-GC-MS procedures for analysis of RSs in the pharmaceutical field [15–17,32–34]. As an example, Laus et al. [15] showed the utility of using 1-*N*-butyl-3-methylimidazolium dimethyl phosphate ([BMIM] [DMP]) as solvent for the successful HS-GC-MS analysis of DMSO, *N*-methylpyrrolidone, sulfolane, tetralin, and ethylene glycol in a realistic matrix of commonly-used excipients (carboxymethylcellulose, magnesium stearate, guar flour, and corn starch) in pharmaceutical products.

More recently, Ho et al. [17] evaluated the use of ILs as a new class of solvents for the analysis of two kinds of genotoxic impurities (alkyl/aryl halides and nitro-aromatics) in small-molecule drug substances by S-HS-GC coupled to electron-capture detection (ECD). LODs (5–500 ppb of analytes in a drug substance) were up to tens of thousands-fold lower than those obtained using traditional HS-GC diluents such as DMSO. Among the ILs tested, the best results were achieved using 1-*N*-butyl-3-methylimidazolium bis[(trifluoromethyl)sulfonyl]imide {[BMIM][NTf_2]}.

Frink et al. [16] recently developed a new method to determine the water content in solid active pharmaceutical ingredients (APIs) by HS-GC using ILs as both solvent and stationary phase of an open tubular capillary GC column (SLB-IL107). Among the ILs studied, 1-ethyl-3-methylimidazolium tris(penta-fluoroethyl)trifluorophosphate {[EMIM][FAP]} showed the best results regarding solubility of the APIs. Dissolved samples were purged with dry argon to achieve low background-water content for better accuracy. Different HS parameters (initial purge time, equilibrium time and temperature) to improve sensitivity and efficiency of the method were evaluated. Optimal conditions are shown in Table 1. Regarding the detector, a barrier-ion-discharge detector (BID) was compared to a thermal-conductivity detector (TCD). Both were appropriate to determine the low levels of water required, but the BID was more sensitive. This method showed advantages over the well-known Karl Fischer titration method (e.g., the absence of by-side reactions and solubility problems).

2.1.4.2. Foods. S-HS has been proposed by many researchers as a useful tool to determine food quality. As an example, Güler et al. [18] developed a S-HS-GC-MS method to analyze the volatile aromatic compounds of melons from different varieties. Most valuable varieties from a sensory point of view turned out to be those with higher concentrations of esters. Moreover, the correlation of volatile compounds with aroma allowed the distinction among melon varieties.

Determination of residual solvents by HS-GC is also applied in the food field. Ligor and Buszewski [19] compared two different procedures based on SPME-GC-MS and S-HS-GC-MS to determine the composition of RSs of vegetable oils. Results obtained by both methods showed a high correlation ($R^2 = 0.9943$), indicating the feasibility of the S-HS technique for the analysis of these compounds. Moreover, both methods presented several advantages, such as high sensitivity (analyte concentrations down to the ppm or ppb levels), short extraction times (of the order of minutes), easy automation and simplicity.

Recent advances in HS extraction in the food field are towards the improvement of sensitivity and accuracy in quantitative analysis. Pérez-Pavón et al. [35] developed a sensitive method based on the use of HS coupled to a programmable temperature vaporizer (PTV)-GC-MS system for the fast analysis of filbertone in spiked olive oil samples. The use of a PTV inlet with a liner packed with Tenax-TA allowed compounds more volatile than filbertone to be purged during the venting process, whereas this target compound was retained. LODs and limits of quantitation (LOQs) achieved for filbertone by using this method were as low as 0.27 μg L^{-1} and 0.83 μg L^{-1}, respectively.

2.1.4.3. Environmental samples. VOCs emitted by industrial processes, pesticides, and traffic are dangerous to human health or cause harm to the environment. S-HS-GC is one of the techniques of choice to evaluate their presence in different matrices (e.g., air, water and landfill leachates).

Sanjuán-Herráez et al. [20] developed a new methodology based on the use of membranes as receptors of VOCs from indoor air of vehicle-repair shops that were then analyzed by S-HS-GC-MS. Devices were placed in two different sampling sites of these vehicle-repair shops for different exposure times (8–96 h). VOC concentrations varied, depending on the daily activity of the vehicle-repair shop, but mean values were always below the legislation levels. For all compounds, LODs and relative standard deviation (RSD) values of the method were 15–75 ng and from 2.8–9.2%, respectively. This methodology is a green option, which avoids the use of organic solvents and the addition of reagents. A similar methodology was successfully applied to determine the VOCs released at different steps of the wine-making process [36].

Table 1
Some of the most recent applications of S-HS technique for analysis of volatile compounds in different matrices

Sample	Aim	S-HS sampling	Chromatographic conditions	Ref.
Pharmaceutical products				
Drug matrix	Evaluation of ILs as solvents for determination of residual solvents	-Sample volume: 10 μL of a solution of the analytes in DMF + 1 mL of [BMIM] [DMP] and 100 mg of matrix in 20 mL vials; -Equilibration: 200°C (15 min).	Split mode (25:1); Column: DB-624 (60 m × 0.25 mm, 1.4 μm); Oven program: 120°C (150°C for ethylene glycol) (5 min)-15°C min^{-1}-250°C (20 min); MS detector; Interface temperature: 150°C.	[15]
Solid active pharmaceutical ingredients	Development of a procedure to determine residual water content	-Purge time: 2 min; -Equilibration: 125°C (30 min).	Injector temperature: 280°C; Column: SLB-IL107 (30 m × 0.25 mm, 0.2 μm); Oven temperature: Isotherm 100°C (7 min); Detector temperature: 250°C; Split mode: 5:1(for GC-TCD)/100:1 (for GC-BID).	[16]
Small molecule drug substances	Determination of genotoxic impurities	-Sample volume + IL: 500 μL in 10 mL vials; -Equilibration time: 10 min; -Sample loop: 230°C; -Transfer line: 240°C.	Injector temperature: 250°C; Split mode (1:1); Column: VF-624ms (30 m × 0.32 mm, 1.8 μm); Oven program for alkyls/aryls: 100°C-10°C min^{-1}-150°C (10 min)-10°C min^{-1}-280°C (2 min); Oven program for nitroaromatics: 150°C (10 min)-20°C min^{-1}-280°C (15 min); ECD temperature: 300°C.	[17]
Foods				
Mushrooms	Comparison of S-HS (pressure loop system and gas-tight syringe) and SPME for analysis of volatile compounds	S-HS pressure loop system: -Equilibration: 75°C; -Loopfill time 0.1 min; -Vial pressure time 0.35 min. S-HS gas-tight syringe: -Equilibration: 75°C; -stirring speed: 500 rpm.	Injector temperature: 250°C; Split mode (10:1); Column: DB-FFAP (30 m × 0.25 mm, 0.25 μm); Oven program: 50°C (4 min)-15°C min^{-1}-160°C-2°C min^{-1}-200°C; MS detector.	[8]
Two model matrices containing polysaccharides and lipids	Study of the partitioning and release of ethyl acetate and diacetyl	-Sample volume: 10 mL in 25 mL vials; -Equilibration: 20°C (3 h).	Column: EC-5 MS (50 m × 0.25 mm, 0.25 μm); MS detector.	[14]
Melons	-Analysis of the volatile composition -Establishment of relationships aroma vs. volatile composition -Classification of varieties	-Sample amount: 10 g + 3 g NaCl in 20 mL vials; -Equilibration: 45°C (30 min)-75°C (10 min)-5 times stirring-75°C (5 min).	Injector temperature: 200°C; Splitless mode; Column: HP-INNOWAX (30 m × 0.32 mm, 0.25 μm); Oven program: 45°C (1 min)-1.5°C min^{-1}-80°C-10°C min^{-1}-200°C (15 min); MS detector; Interface temperature: 250°C.	[18]
Vegetable oils	Comparison of S-HS and SPME for determination of solvent residues	-Equilibration: 95°C (25 min); -Vial pressurized for 72 s; -Loop temperature: 110°C; -Loop fill time: 2 s; -Loop/transfer line temperature: 96°C; -Sample volume 10 mL in 22 mL vials.	Injector temperature: 185°C; Splitless mode (0.5 s); Column: SB11 (30 m × 0.32 mm, 0.25 μm); Oven program: 40°C (3 min)-4°C min^{-1}-100°C-15°C min^{-1}-150°C (6 min); FID temperature: 200°C.	[19]
Environmental samples				
Air of vehicle repair shops	Analysis of VOCs by using membrane devices	-Vial volume: 10 mL; -Extraction: 150°C, 10 min; -Syringe temperature 150°C, constant air flow purge.	Injector temperature: 200°C; Split mode (1:10); Column: ZB-5MS (30 m × 0.32 mm, 0.25 μm); Oven program: 40°C (9 min)-20°C min^{-1}-200°C (2 min). MS detector.	[20]
Leachates from sanitary landfill	Comparison of S-HS and SPME for determination of five VOX	-Sample volume: 5 mL in 10 mL vials; -Equilibration: 75°C (15 min); -Sample loop volume: 1 mL; -Loop/transfer line temperature: 110°C; -Sample vial pressure: 16 psi; -Loop fill time: 0.03 min; -Injection time: 1 min.	Injector temperature: 250°C; Split mode (75:1); Column: HP-5MS (30 m × 0.25 mm, 0.25 μm); Oven program: 45°C (5 min)-15°C min^{-1}-150°C (1 min); MS detector.	[21]
Sea water	Determination of benzene, toluene, ethylbenzene, xylene (BTEX), and styrene	-Equilibration: 60°C (5 min); -Injection time: 0.5 min; -Loop temperature: 110°C; -Transfer line temperature: 120°C; -Loop fill time: 0.5 min; -Loop equilibration time: 0.10 min; -Injection time: 1 min.	Column: HP5-MS (30 m × 0.25 mm, 0.25 μm); Oven program: 50°C (4 min)-15°C min^{-1}-170°C (5 min); FID and MS detector (Split ratio FID:MS, 2:1).	[22]

(*continued on next page*)

Table 1 (*continued*)

Sample	Aim	S-HS sampling	Chromatographic conditions	Ref.
Fuels				
Motor oils	Analysis of antioxidants	-Equilibration: 95°C (15 min); -Injection volume from HS to PTV 2.4 mL (syringe at 100°C).	PTV: Solvent vent mode; Purge: 60°C, 0.60 min, 150 mL min^{-1}; Injection: 60°C-12°C s^{-1}-325°C (5.44 min); Injection time: 1 min; GC: Split injection (1:10; 325°C); Column: DB-VRX (20 m × 0.18 mm, 1 μm); Oven program: 110°C (1 min)-65°C min^{-1}-175°C-45°C min^{-1}-240°C (2 min); MS detector.	[23]
Bio-oils	Comparison of S-HS derivatization and on fiber derivatization SPME for determination of low-molecular mass aldehydes	-Sample volume: 2 mL in 10 mL vials; -Derivatization conditions: *O*-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine hydrochloride, 85°C, 20 min, 350 r.p.m.	Injector temperature: 260°C; Split mode; Column: VF-1701 (60 m × 0.25 mm, 0.25 μm); Oven program: 80°C-3°C min^{-1}-150°C-40°C min^{-1}-280°C (5 min); MS detector.	[24]
Biological samples				
Urine samples	Determination of aldehydes	-Sample volume: 1 mL in 10 mL vials; -Equilibration: 84°C, 10 min, 750 r.p.m.; -Injection volume from HS to PTV 2.5 mL (syringe at 120°C).	PTV: Initial injector temperature: 50°C ; Initial time: 0.55 min; Vent flow: 20 mL min^{-1}; Vent pressure: 5 psi; Purge: 60°C, 0.50 min; Injection: 60°C-12°C s^{-1}-250°C (2 min) GC: Column: DB-VRX (20 m × 0.18 mm, 1 μm); Oven program: 45°C (2 min)-60°C min^{-1}-175°C-45°C min^{-1}-240°C (0.5 min); MS detector.	[25]

Florez-Menéndez et al. [21] evaluated the use of S-HS and HS-SPME for recovery of five volatile organochlorine compounds (VOX), namely chloroform, 1,1,1-trichloroethane, carbon tetrachloride, trichloroethene and tetrachloroethene, in raw landfill leachates and biologically-cleansed leachates. After optimization of experimental conditions (see Table 1 for optimal parameters), the LODs of both procedures were at the sub-ppb level. HS-SPME was faster than HS (extraction times of 2 min *versus* 15 min); however, HS-GC-MS offered better analytical precision (2.5–3.5%) than HS-SPME-GC-MS (10–16%). Both techniques provided good recoveries for all analytes under study (±5% agreement).

The analysis of pollutants, such as xylene and styrene in water, requires the development of simple, cheap analytical methods with low LODs. The utility of S-HS-GC-MS for analysis of these compounds in sea water was recently demonstrated by Yilmazkan et al. [22]. Moreover, the use of PTV in solvent-vent mode was proposed as a HS injection system for the analysis of different drugs {e.g., ibuprofen [37,38]} and pollutants {e.g., gasoline oxygenates and benzene, toluene, ethylbenzene and xylene [39]} in waters. This device provided better results (high sensitivity, low LODs and good accuracy and precision) than the conventional split/splitless injection modes.

2.1.4.4. Other samples.

2.1.4.4.1. Fuels. HS-GC-MS has been commonly used to identify gaseous components of engine oils [40]. Del Nogal et al. [23] developed a sensitive, accurate method based on S-HS sampling in combination with a GC system equipped with a PTV and an MS detector to analyze antioxidants in engine-oil samples. The method did not require any sample treatment prior to analysis, the use of a PTV in solvent-vent injection mode allowed the pre-concentration of the compounds of interest in a liner filled with Tenax-TA, while venting other species present in the HS, and no matrix effect was observed.

Bio-oil is a dark brown liquid produced after pyrolysis of biomass (e.g., wood sawdust). It is composed of water and hundreds of oxygenated organic compounds. Among them, bio-oil contains several volatile aldehydes, some of them toxic, such as formaldehyde. Tessini et al. [24] developed a method based on a derivatization procedure (use of *O*-(2,3,4,5,6-pentafluorobenzyl) hydroxylamine hydrochloride as derivatization reagent) for the analysis of aldehydes in this product using two different approaches:

- in-solution derivatization and HS extraction; and,
- on-fiber derivatization SPME.

Although both sample treatments allowed quantification of most important aliphatic aldehydes in bio-oil, the SPME approach was more efficient for preconcentration of analytes on the fiber. However, the main disadvantage of on-fiber derivatization SPME was the brief life-time of the fibers (20 bio-oil samples).

2.1.4.4.2. Polymer products. Polymers contain low-molecular-weight residual compounds, by-products of polymerization, additives and degradation products that migrate from the polymers into the surrounding environment [41]. These volatile compounds can be analyzed by HS-GC-MS, and the use of this technique is proposed by the American Society for Testing Materials (ASTM International) for their qualitative analysis [42].

2.1.4.4.3. Biological samples. A HS-GC-MS method based on the use of a PTV has been optimized using experimental design for the quantitative determination of aldehydes in urine [25]. Good linearity, low LOQs (0.12–0.24 μg L^{-1}) and appropriate accuracy (recoveries of 86–120%) were achieved. This method turned out to be a good alternative to more complex, tedious extraction and preconcentration techniques [e.g., SPE and hollow-fiber liquid-phase

microextraction (HF-LPME)] for the analysis of these endogenous compounds in urine samples.

2.2. Dynamic headspace

D-HS techniques, unlike S-HS, have the common characteristics of using a flow of inert gas for continuous extraction of volatile compounds from a sample and their further preconcentration into an adsorbent or cryogenic trap. In its more general form of application, the so-called "purge and trap" (P&T) technique, the flow of gas is bubbled through the bulk of the sample rather than passed over the matrix, so increasing volatile recovery. Release of volatile compounds from this trap, generally carried out by increasing the temperature, allows their transfer into the chromatographic system for further analysis.

As for other sampling techniques, after a single HS step, only partial recoveries are achieved for most volatiles. In many applications, such as those aimed at sample characterization or classification, these data are enough as a first estimation of the quantitative volatile composition of the samples under study. However, when accurate determination of C_o is intended in solid or semi-solid samples with noticeable matrix effects, and for which matrix-matched or standard-addition calibrations are not feasible, multi-step HS extraction (MHE) approaches based on stepped HS extraction are usually employed [4]. In MHE, as successive HS aliquots are removed, after an infinite number of extraction steps, all volatiles are exhaustively extracted. In practice, MHE approaches rely on a limited number of consecutive extractions, after which extrapolation models are applied to determine C_o.

Due to the common application of the D-HS technique in the MHE mode, sub-section 2.2.1. describes the fundamentals of both techniques, whereas applications of MHE are discussed in sub-section 2.3.

2.2.1. Fundamentals

According to Kolb et al. [4,43], volatile sampling by D-HS is based on the following equation:

$$C_i = C_0 \cdot e^{-qt} \tag{5}$$

in which the concentration C_i of an analyte remaining in the sample after a continuous sweeping process depends on the original concentration C_0 and decreases exponentially with time t, q being a constant of proportionality related to the recovery. Chromatographic peak areas A_i and A_0 are proportional to analyte concentrations C_i and C_0, respectively.

When the stepwise mode is selected, and considering peak areas rather than concentrations, Equation (5) becomes Equation (6) for every successive step (i):

$$A_i = A_1 \cdot e^{-k\cdot(i-1)} \tag{6}$$

where A_1 is the peak area obtained in the first extraction step and k, if extraction is carried out in an automated instrument, represents a constant related to some constant instrumental parameters.

If A_0 represents the total peak area associated with the original analyte concentration C_0,

$$A_0 = \Sigma A_i = A_1 \cdot \left(1 + e^{-k} + e^{-2k} + \ldots\right), \tag{7}$$

its value can be estimated from the sum of the geometric progression in Equation (7) as:

$$A_0 = A_1 / \left(1 - e^{-k}\right) \tag{8}$$

Recovery models should provide a relationship between the desorbed amount of analyte and its total amount in the sample, which can be estimated from GC data as the ratio between the experimental peak area (A_i) and the peak area corresponding to the total analyte amount (A_0). The recovery (R) for the first extraction step is calculated in this way as:

$$R = A_1/A_0 = 1 - e^{-k} \tag{9}$$

The model proposed by Kolb et al. [4,43] uses the logarithmic form of Equation (6):

$$\ln A_i = -k\cdot(i-1) + \ln A_1 \tag{10}$$

to obtain k by linear regression. Equation (10) and experimental A_1 values are then used to obtain A_0 and R.

Finally, and if data are linear, Equation (8) can be simplified to obtain total analyte amount using data for only the first two extractions [Equation (11)]. Although valid for practical purposes, more accurate results are expected by using a higher number of data points.

$$A_0 = \frac{A_1}{1 - \left(\frac{A_2}{A_1}\right)} = \frac{A_1^2}{A_1 - A_2} \tag{11}$$

This MHE model, in spite of having been criticized initially, proved to be theoretically correct and experimentally useful, and it allows use of improved statistical methods for the estimation of recovery and total volatile amount (e.g., see [44] in sub-section 2.3).

2.2.2. Instrumentation

Different designs of D-HS extractors/concentrators are commercially available. All include as main parts a sample vessel, a trap and different devices (e.g., flow-pressure regulators, valves, and probes) for regulation and control of purge gas and temperature throughout the whole system. A few extractors also offer the ability to dry purge the trap after the purge step to remove water that may have accompanied target volatiles during this step and which, e.g., can block the flow of gas (if condensed in cold traps), or destabilize the GC stationary phase [45,46]. Furthermore, several instruments allow, after thermal desorption of the retention trap (primary trap), a secondary trapping of volatiles by cryofocusing before injection onto the GC. This is usually achieved in fused-silica traps cooled by liquid nitrogen or CO_2 [47]. The fast injection from these secondary traps, faster than from adsorbent, decreases peak broadening and improves separation and sensitivity [47,48].

Although most D-HS extractors are coupled on-line to GC systems, others are designed for off-line operation, when cartridges or traps with purged volatiles are desorbed in an additional facility [thermal desorption (TD) unit], which is coupled on-line to the GC-MS apparatus. Depending on sample characteristics, this sort of TD unit can also be used for direct D-HS sampling: volatiles are thermally desorbed from the sample and swept by a continuous flow of inert gas into a secondary trap, which is then heated for transfer of volatiles into the GC-MS system [49,50].

2.2.3. D-HS parameters

As in S-HS sampling, different parameters should be optimized in the development of a D-HS method; the purge volume and the extraction temperature are the most important. Sample vessels of different design (needle-sparge vessel, purge tube with frit or fritless purge vessel) should be chosen according to the characteristics of the sample and the mode of extraction selected: surface sweeping or P&T. Dilution in case of high-viscosity samples or addition of antifoaming agents, such as 1-tetradecanol, are also required sometimes [51–53]. As in S-HS, optimal temperature is determined by analyte and matrix characteristics. The flow of inert gas (15–40 mL min^{-1}) and purge time (2–15 min) should be optimized considering the breakthrough volume, defined as the largest

volume per gram of sorbent that can be sampled without significant loss of sample from the trap.

Regarding volatile preconcentration, a wide variety of traps and cartridges with different dimensions, composition (e.g., Tenax, Silica Gel, Chromosorb, graphitized carbons (Carbotrap), or carbon molecular sieves), thermal stability and desorption characteristics are available [54]. Despite several applications relying on the use of multi-bed traps [55–57], single traps made of Tenax sorbent are the most common, due to their applicability to compounds in a wide volatility range, high temperature stability, low water affinity and long shelf life (see Table 2). For every application, desorption temperature and time, usually 220–260°C and 2–15 min, respectively, should be optimized considering analyte and trap properties. Cooling of traps with liquid N_2 or CO_2 are alternatives for preconcentration of very thermolabile compounds.

2.2.4. Applications

2.2.4.1. Food and plant samples. As an example of the large number of papers devoted to the development and validation of D-HS methods for food characterization, Manzini et al. [59] optimized, by experimental design, a P&T followed by TD-GC-MS for the determination of furfurals in 29 *Aceto Balsamico Tradizionale di Modena* vinegars. In addition to other operating variables commonly optimized (e.g., incubation temperature and time, purge volume, dry volume and thermal desorption time), the performance of two different sorbents (Tenax TA and Tenax GR) for furfural trapping were also evaluated. Under optimal conditions (Table 2) and selecting Tenax TA as sorbent, with similar trapping capability to Tenax GR but providing more reproducibility, the method developed showed good reproducibility (RSD < 10%), so it was shown to be simple, fast and highly automated for QC of vinegars.

A number of studies have also evaluated the performance of D-HS compared to other HCC-HS techniques, mainly SPME, for characterization of food aroma with different purposes (e.g., food authentication, QC, and effect of food-processing techniques) (Table 2). In many of these studies, results were also compared with those from sensory methods in an attempt to determine the most odor-active compounds.

Mallia et al. [58] compared P&T and SPME for the analysis of the aroma compounds of three European Protected Designation of Origin (PDO) cheeses (Gruyère, Manchego and Ragusano). As expected, the profiles obtained by using each technique were different, with P&T being particularly suitable for sampling of very volatile compounds (e.g., linear and branched alcohols, and diketones), whereas SPME was more effective for extracting medium and low-volatility compounds (e.g., fatty acids). The composition of cheeses obtained by each technique was also quite distinctive and allowed, after application of statistical analysis, correct classification of cheeses according to their PDO.

In a similar characterization study by Liu et al. [46], the volatile composition, the non-volatile components and the sensory properties of the most common monovarietal white wine (var. Solaris) in Denmark were studied. A total of 79 compounds were determined by P&T-GC-MS. Partial least squares (PLS) regression showed that acetates and ethyl esters of straight-chain fatty acids were associated with floral and fruity odors, whereas other volatiles, such as ethyl esters of branched-chain fatty acids, were less associated with them. From the results of this study, we can also conclude that differences in wine vintage were less significant that differences due to sulfite management by producers.

Rivas-Cañedo et al. [55] compared the performance of P&T and SPME for sampling of volatiles in ground beef subjected to high-pressure processing (HPP) and further three-day refrigerated storage. Despite the volatile profiles of control samples (neither stored nor pressurized) provided by both techniques being comparable, they turned out to be completely different for stored untreated and HPP samples. In the conditions of this study, SPME proved to be a more sensitive technique than P&T for monitoring the changes undergone in meat subjected to different treatments. However, the very significant decrease during storage of some volatiles, such as 2,3-butanedione, was better followed by P&T. The results of this study highlighted that volatile profiles strongly depend on the method of extraction, among other factors, which should be taken into account when experimental results are to be compared with literature data.

Lozano et al. [45] evaluated by sensory and instrumental methods the heat-induced odorants in ultrahigh-temperature (UHT)-processed soy milk. D-HS dilution analysis (DHDA) and solvent-assisted flavor evaporation (SAFE) were selected as complementary techniques to fractionate the wide range of aroma-active volatiles present in this sample (for experimental conditions, see Table 2).

Murat et al. [56] also compared the performance of three different sampling techniques (P&T, SPME and SAFE) followed by GC-MS to select the most suitable HS-sampling method to provide a fraction representative of the odor of pea (*Pisum sativum*) flour. Compared to SAFE and SPME, the P&T technique allowed identification of a higher number of volatiles. SAFE was particularly useful for extraction of very polar compounds, such as alcohols, and SPME for benzene derivatives and terpenes; very volatile compounds (e.g., ethanol, propan-2-ol, and butan-2-one) were extracted by only P&T. SAFE and SPME extracts were perceived to be the most representative of the global odor of pea flour. The fact that several polar compounds with a "green" and "vegetable" odor were poorly recovered or even only extracted by SAFE and SPME could be responsible for these conclusions.

In a review by Bicchi et al. [5] on the techniques used most for sampling volatiles from vegetable matrices, D-HS was shown as the most widely used technique in the plant field, due to its flexibility (e.g., sampled volume and operating conditions) in achieving the required sensitivity. As an example, Sanz et al. [49] developed a method by TD-GC-MS for analysis of volatile components of wild samples of *Lavandula luisieri* collected in Central and Southern Spain. This simple, fast method, with short analysis time and requiring a small sample amount (only 10–20 mg of dry sample), allowed qualitative and quantitative analysis of different plant parts, such as flowers and leaves. Furthermore, multivariate statistical analysis of data for nine selected compounds allowed determination of several patterns of plant composition that were only partly related to the site of collection.

Characterization of food samples for different purposes requires that the dispersion of quantitative data is minimized. Soria et al. [52] optimized P&T as a sampling technique for the GC-MS analysis of the volatile composition of 22 commercial honeys of eight different botanical sources. Some 100 volatiles were determined, including compounds derived from the floral nectar/honeydew source and from processing and storage conditions; 18 of them were reported in honey for the first time. As for precision of quantitative data, this method was also validated: relative data (percentage of total volatile composition) showed lower dispersion than data obtained by the internal standard (IS) method. The use of a single IS for quantitation of volatiles with different properties and/or its incomplete homogenization in honey matrix could explain these results.

In a subsequent study by the same authors [53], statistical analysis was used for the first time to evaluate the dispersion of percent data in the P&T-GC-MS analysis of honey volatiles with the aim of improving their precision. The comparison of experimental and randomly-simulated data by different statistical parameters [i.e., correlation coefficients, principal component analysis (PCA) eigenvalues and loadings] showed that non-random factors significantly contributed to the total dispersion of data. A significant improvement in precision was achieved when considering percent concentration ratios, rather than single percent data, among volatiles with

Table 2
Some of the most recent applications of D-HS technique for analysis of volatile compounds in different matrices

Sample	Aim	D-HS sampling	Chromatographic conditions	Ref.
Foods and plants				
Butter	Comparison of P&T and SPME fractionation techniques	20 g butter; Equilibration: 45°C (5 min); Purge (N_2): 1 h, 30 mL min^{-1}; Trap (Tenax TA) desorption; 250°C (10 min).	Cold fused silica trap: –120°C; Flash heating injection: 1 min at 250°C; HP-Innowax column (60 m × 0.32 mm, 0.5 μm); Oven program: 40°C (8 min)-4°C min^{-1}-210°C (10 min); GC-MS interface temperature: 220°C.	[48]
Lavandula luisieri	TD-GC-MS analysis of volatiles	10–20 mg dry plant; Primary desorption: 180°C (15 min), 20 mL min^{-1} He; Cryofocusing Tenax trap; Secondary desorption: –30°C to 320°C (4 min) at 40°C s^{-1}; Inlet/Outlet splits: 50 mL min^{-1}; Transfer line: 225°C.	SPB-1 capillary column (27 m × 0.25 mm, 0.25 μm); Oven program: 60°C-3°C min^{-1}-180°C-5°C min^{-1}-250°C (5 min); GC-MS interface temperature: 250°C.	[49]
European PDO hard cheeses	Comparison of P&T and SPME fractionation techniques	5 g grated cheese; Equilibration time: 5 min; Purge: 35°C (15 min), 40 mL min^{-1} N_2; Dry purge time: 5 min; Tenax trap at 36°C; Trap desorption: 230°C (4 min).	GC/MS/FID: Cryofocusing: –125°C; Desorption: 230°C (1.5 min); DBWax capillary column (60 m × 0.32 mm, 1 μm); Oven program: 45°C (1 min)-5°C min^{-1}-250°C (12 min); GC-MS interface temperature: 280°C.	[58]
Aseptically packaged soy milk	P&T followed by GC-MS analysis and sensory characterization of heat-induced odorants	10 mL milk; Purge: 50°C (5 min), 50 mL min^{-1} N_2; Purge time: 1, 5 and 25 min (D-HS dilutions); Tenax TA tube desorption: 220°C (10 min).	Cryo-injection: –150 to 260°C (10 min) at 2°C s^{-1}; Stabilwax DA or DB-5 MS column (30 m × 0.25 mm, 0.25 μm); Oven program: 35°C (5/25 min)-10°C min^{-1}-225°C (25 min); GC-MS interface temperature: 280°C.	[45]
Honey samples of different botanical source	-Optimization of a P&T-GC-MS method -Use of statistical analysis for evaluation of dispersion and for improvement of precision of quantitative data -Estimation of recovery by a MHE approach	5 g honey/2 mL H_2O; Purge: 80°C (15 min), 37.5 mL min^{-1} He; Trap (Tenax) desorption: 220°C (5 min); Transfer line: 200°C.	Cryo-injection: –100 to 220°C in 2 min; Supelcowax-10 column (50 m × 0.25 mm, 0.25 μm); Oven program: 45°C (15 min)-3°C min^{-1}-75°C-5°C min^{-1}-180°C (10 min); GC-MS interface temperature: 280°C.	[44, 52,53]
Vinegars	Optimization of a P&T followed by GC-MS method for analysis of furfurals	1 mL vinegar + 0.25 g NaCl; Incubation: 40°C (10 min); Purge: 50 mL min^{-1} N_2, 800 mL; Tenax TA trap; Trap drying: 50°C, 1500 mL, 100 mL min^{-1} N_2; Trap desorption: 50°C-50°C min^{-1}-280°C (5 min).	Cryo-injection: –150°C-12°Cs^{-1}-280°C (1 min); Split ratio: 1:20; CPSil 8CB column (60 m × 0.25 mm, 1 μm); Oven program: 40°C (2 min)-5°C min^{-1}-150°C-10°C min^{-1}-280°C (10 min); GC-MS interface temperature: 290°C.	[59]
Ground beef subjected to high pressure processing	Comparison of D-HS and SPME for fractionation of volatiles	3.5 g cooked meat + anh. Na_2SO_4; Purge: 45°C (20 min), 45 mL min^{-1} He; Vocarb 4000 trap: 35°C; Dry purge: 4 min; Trap desorption: 260°C (2 min); Transfer line: 200°C.	Injection: 220°C; Split ratio: 1:20; ZB-WAX column (60 m × 0.25 mm, 0.50 μm); Oven program: 45°C (16 min)-4°C min^{-1}-110°C (9 min)-15°C min^{-1}-230°C (3 min); GC-MS interface temperature: 280°C.	[55]
Pea (*Pisum sativum*) flour	Comparison of the performance of three extraction methods (P&T, SPME and SAFE) for providing fractions representative of the overall odor of pea flour	35 g of 10% pea flour suspension in H_2O; Purge: 30°C (10 min), 20 mL min^{-1} N_2; Capillary trap (Tenax); Trap desorption: from –130°C (10 min) to 270°C (15 min).	ZB-1 MS column (30 m × 0.25 mm, 1 μm); Oven program: 50°C (1 min)-4°C min^{-1}-160°C-15°C min^{-1}-320°C (10 min); GC-MS interface temperature: 240°C.	[56]
Radix Angelicae Dahuricae	GC × GC-TOF MS study of changes in the volatile composition of sulfur-fumigated and sun-dried samples	Purge temperature: from 30°C (20 min) till 150°C (30 min); Purge time: 15 min; He flow: 40 mL min^{-1}; Capillary trap (Tenax-Silica Gel-Charcoal): 40°C; Trap desorption: 180°C (2 min).	Injector temperature: 250°C (split mode); ^{1}D column: DB-5 MS (30 m × 0.25 mm, 0.25 μm); ^{1}D oven: 50°C (1 min)-6°C min^{-1}-250°C (10 min); ^{2}D column: DB-17 HT (2 m × 0.1 mm, 0.1 μm); ^{2}D oven: 260°C higher than ^{1}D oven; Modulation: 6 s.	[57]
Solaris white wines	P&T followed by GC-MS study of volatile composition	20 mL wine; Purge: 37°C (20 min), 100 mL min^{-1} N_2; Dry purge: 15 min; Trap (Tenax-TA) desorption: 250°C (15 min), 50 mL min^{-1} H_2.	Cold trap (Tenax-TA): from 5°C to 300°C (4 min); Split ratio: 1:10; Transfer line: 225°C; DB-WAX column (30 m × 0.25 mm, 0.25 μm); Oven program: 40°C (10 min)-8°C min^{-1}-240°C (5 min).	[46]

(*continued on next page*)

Table 2 (*continued*)

Sample	Aim	D-HS sampling	Chromatographic conditions	Ref.
Environmental samples				
Water	Evaluation of purge efficiency in the P&T-GC-MS analysis of trihalomethanes	10/25 mL water; Purge flow: 40 mL min^{-1} He; Purge cycles of 11 min; Purge temperature: 25, 35 and 50°C; CO_2 cooled Vocarb 3000 trap: 10°C; Trap desorption: 225°C (4 min); Transfer line: 150°C.	Injector temperature: 250°C; Split ratio: 1:20; DB-624 column (30 m × 0.25 mm, 1.4 µm); Oven program: 40°C (8 min)-45°C min^{-1}-200°C (10 min).	[60]
	P&T-GC-MS analysis of VOCs (including trihalomethanes) in 174 source, tap and bottled waters	Purge: 30°C (11 min), 40 mL min^{-1} He; Trap desorption: 250°C (4 min).	Injector temperature: 140°C; VF-624 MS column (30 m × 0.25 mm, 1.40 µm); Oven temperature: from 35°C (6 min) to elution of all VOCs (>220°C, 6 min).	[61]
	Determination by GC-ICP-MS of CH_3Hg in humic-rich natural water samples	20 mL distillated and ethylated ($NaBEt_4$) water; Purge: room temperature (8 min); Trap (Tenax) desorption: 200°C (15 s).	HP-5 column (15 m × 0.32 mm, 0.25 µm); Oven program: 30°C-30°C min^{-1}-60°C; He: 7 mL min^{-1}.	[62]
	Target and non-target screening of VOCs by D-HS followed by GC × GC-TOF-MS	5 mL H_2O (26°C, 700 rpm); Purge: 300 mL, 15 mL min^{-1} He; Trap (Tenax) temperature: 25°C.	Off-line TD of trap: 30°C (0.5 min)-12°C s^{-1}-300°C (5 min); PTV injector: –130°C (0.5 min)-12°C s^{-1}-250°C (5 min); ^{1}D column: TRB-624 (20 m × 0.25 mm, 1.4 µm); ^{1}D oven: 35°C (5 min)-4°C min^{-1}-105°C-30°C min^{-1}-250°C (4 min); ^{2}D column: Suprawax-280 (1 m × 0.1 mm, 0.1 µm); ^{2}D oven: 40°C (5 min)-4°C min^{-1}-110°C-30°C min^{-1}-270°C (4 min); Modulation: 4 s.	[63]
Sediment, fish tissues and algal cells	Simultaneous determination by MAPTE-GC-MS of five predominant odors in different environmental samples	Purge: 30°C (10 min), 40 mL min^{-1} N_2; Trap (Tenax) desorption: 180°C (4 min); Valve temperature: 250°C; Transfer line: 270°C.	Injector temperature: 270°C; Split ratio: 1:10; HP-5 MS column (30 m × 0.25 mm, 0.25 µm); Oven program: 60°C-15°C min^{-1}-150°C-5°C min^{-1}-220°C; GC-MS interface temperature: 250°C.	[64]
Others				
Active pharmaceutical ingredient	GC-FID determination of residual solvents	N_2 flow: 40 mL min^{-1}; Purge: 40°C (7 min); Tenax/Silica gel/Charcoal trap; Dry purge: 40°C (1 min), 200 mL min^{-1}; Primary desorption: 200°C (2 min), 100 mL min^{-1}.	Focus temperature: –120°C; Secondary desorption: 130°C (1 min); Injector temperature: 160°C; Split ratio: 1:10; Rtx-1MS column (30 m × 0.32 mm, 1 µm); Oven program: 35°C (3 min)-10°C min^{-1}-75°C-30°C min^{-1}-200°C (5 min); Detector temperature: 300°C.	[47]
Urine and blood	P&T-GC-FID/MS analysis of styrene	5 mL urine/blood diluted in H_2O; Purge: 20°C (11 min), 40 mL min^{-1} He; Tenax trap: 20°C; Primary desorption: 180°C (4 min); Transfer line: 180°C.	Capillary silica tube: –100°C; Secondary desorption: 210°C; Injector temperature: 210°C; Oven program: 35°C (3 min)-10°C min^{-1}-75°C-30°C min^{-1}-200°C (5 min); DB-5 column: (50 m × 0.32 mm, 0.52 µm); Oven program: 80°C (8 min)-5°C min^{-1}-120°C (2 min); FID temperature: 250°C.	[65]
Fecal samples	Development of a P&T-GC-MS method for screening of fermentation metabolites	0.25 g fecal sample in 5 mL H_2O; Purge: 70°C (20 min), 40 mL min^{-1} He; Trap (Vocarb) desorption: 250°C (5 min).	AT Aquawax DA column: (30 m × 0.25 mm, 0.25 µm); He flow: 10 mL min^{-1}; Oven program: 35°C (2 min)-5°C min^{-1}-100°C-10°C min^{-1}-240°C (5 min); GC-MS interface temperature: 250°C.	[66]

similar dispersion behavior, as pointed out by PCA. This statistical approach, of general application to any other sample type/extraction technique, may contribute to extend the use of P&T-GC-MS for precise quantitative determination of very volatile compounds.

As mentioned above, most studies on analysis of the volatile mixtures fractionated by P&T are usually carried out by GC-MS. However, the recent development of comprehensive two-dimensional GC-time-of-flight MS (GC × GC-ToF-MS), and its advantages in terms of resolution and sensitivity over one-dimensional GC, have promoted the use of this technique coupled on-line to P&T sampling for the analysis of complex mixtures of volatiles in different matrices.

Cao et al. [57] developed a method by P&T-GC × GC-ToF-MS to investigate for the first time the effect of sulfur fumigation and subsequent drying on the volatile composition of sun-dried Radix Angelicae Dahuricae, a product derived from the dried root of *Angelica dahurica* and extensively used in Chinese herbal medicine. A total of 32 volatiles, including some of the most active components of Radix Angelicae Dahuricae, disappeared after sulfur fumigation of samples, probably due to volatilization and absorption by sulfur dioxide during the heating process following sulfur treatment (Fig. 1). Some 73 new volatiles, including 3-methyl-thiophene, dimethyl trisulfide and methane sulfonic acid ethyl ester, with reported adverse effects on consumers, were also found in sulfur-fumigated samples (Fig. 1). The proposed method using P&T-GC × GC-ToF-MS was shown to be able to detect commercial samples of Radix Angelicae Dahuricae subjected to sulfur-fumigation processes.

2.2.4.2. Environmental samples. P&T-GC-MS methods have been widely reported for analysis of contaminants in environmental samples, mainly in water (Table 2). In addition, many P&T-based methods have become the standardized protocols for analyzing environmental samples (e.g., soil and water) by different regulatory agencies [e.g., US Environmental Protection Agency (US EPA)].

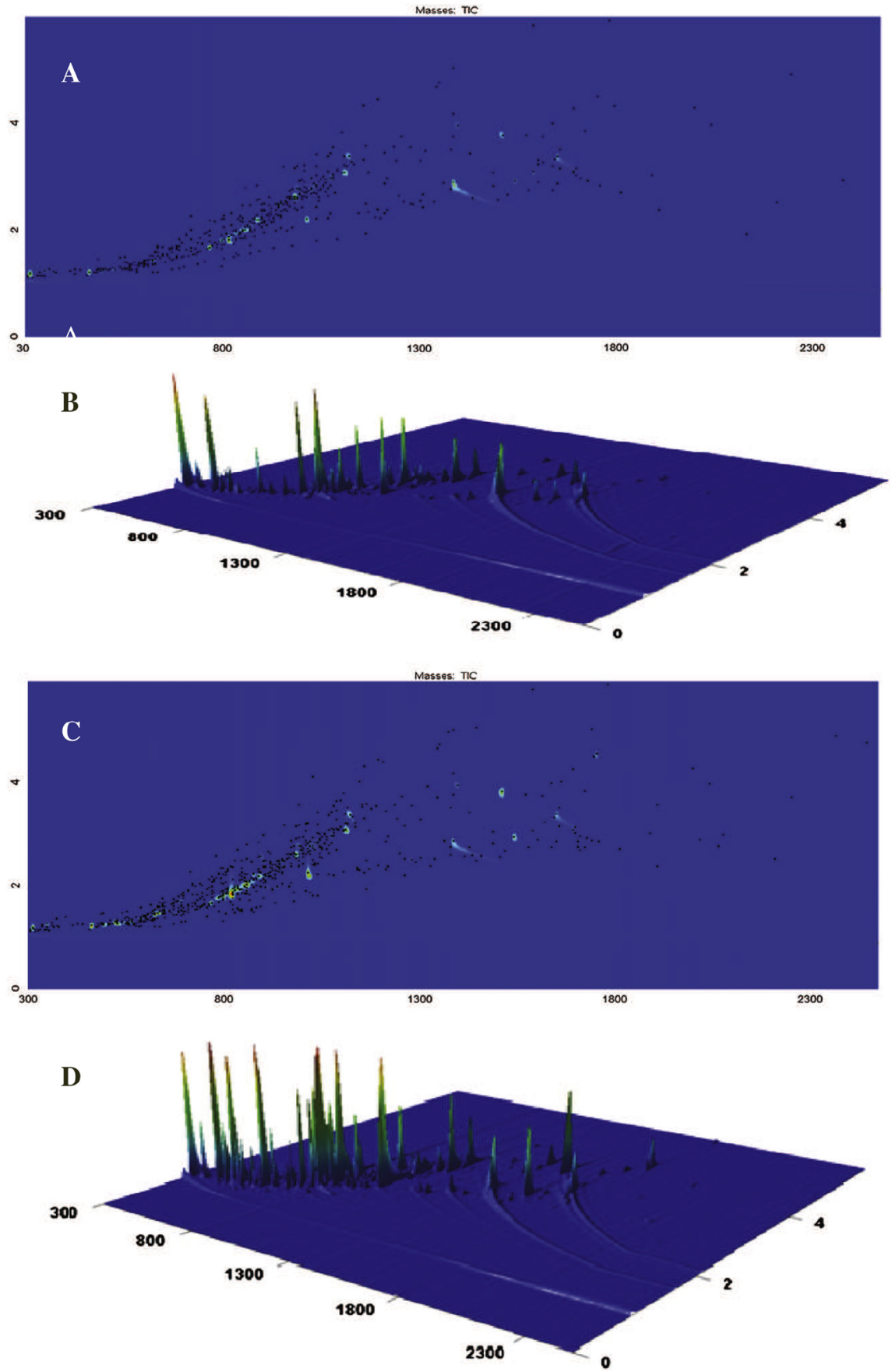

Fig. 1. GC × GC-TOF MS contour plots and three-dimensional chromatograms of sun-dried (A/B) and sulfur-fumigated (C/D) *Radix Angelicae Dahuricae* volatile components. {Reprinted with permission of John Wiley & Sons, Ltd [57]}.

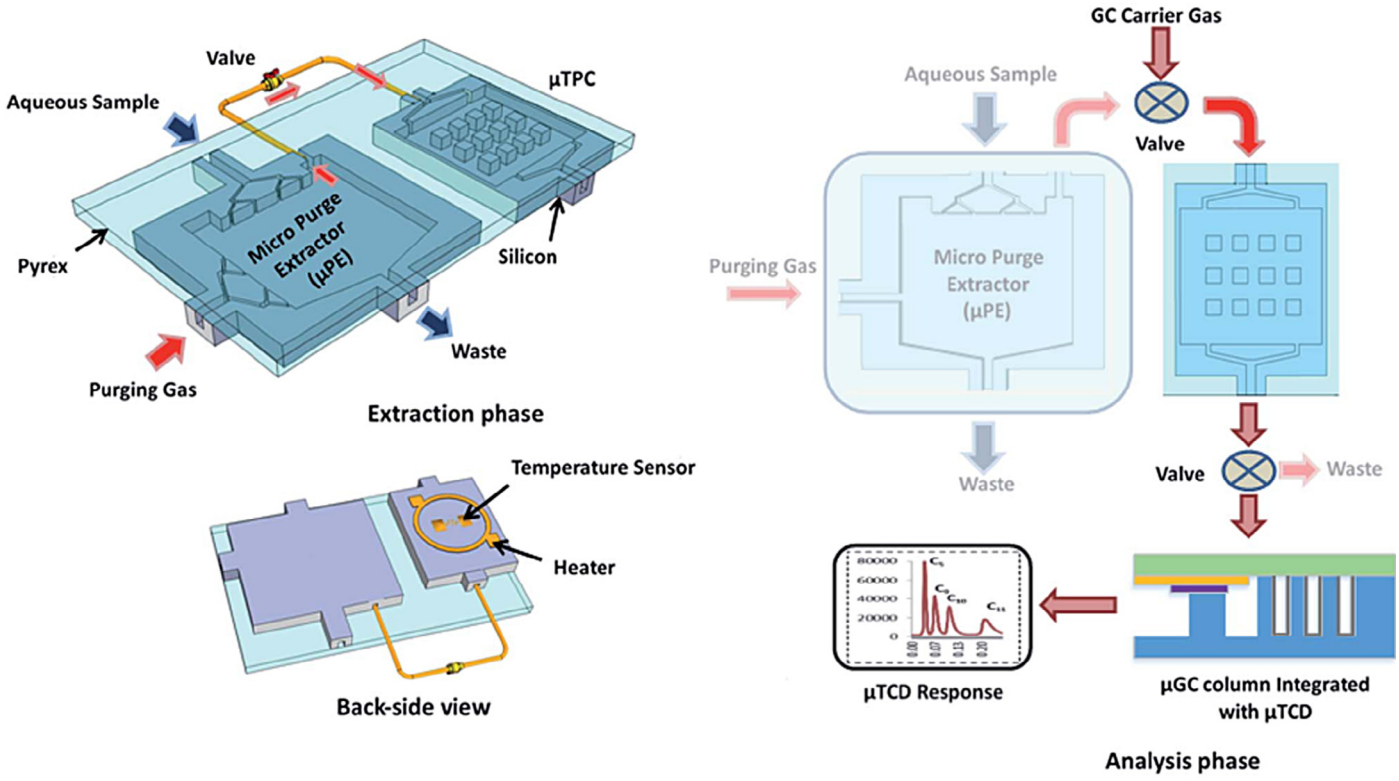

Fig. 2. A purge and trap integrated microGC platform for extraction and analysis of water organic compounds. {Reprinted with permission of the Royal Society of Chemistry [71]}.

Besides a number of papers aimed at the optimization of P&T operating conditions with different purposes [60,61,67,68] (Table 2), several works have also addressed the development of novel devices for improved sampling [69] or developed new analytical approaches based on its coupling on-line to 2D-GC separations [62].

A novel multi-bed, needle-type, extraction device, containing particles of divinylbenzene and activated carbon, for the rapid, simple determination of traces of 23 VOCs in tap water was reported by Ueta el al. [70]. After optimization, the use of this device in combination with purge with N_2 of the water sample achieved the successful recovery of VOCs, without sample heating and/or cryogenic focusing, and with the required sensitivity and repeatability for its application to the analysis of real samples.

Akbar et al. [71] recently developed the first micro-purge extractor (μPE) chip integrated with a micro-scale GC (μGC) system for the extraction and analysis of water organic compounds (WOCs) (Fig. 2). The μPE device consists of two inlets, one for the sample and the other for a pure inert gas to purge target analytes. The chip also contains two outlets, one for water waste and one for directing the purged WOCs to the micro-thermal preconcentrator (μTPC). The trapped compounds, desorbed by resistive heating, are separated on a μGC column and identified using a micro-thermal conductivity detector (μTCD) monolithically integrated with the column. This miniaturized system provided on-site, real-time analysis in less than 1.5 min of concentrations as low as 500 ppb of toluene, chlorobenzene, ethylbenzene and tetrachloroethylene in water.

Herrera López et al. [63] reported an effective full-scan method based on D-HS followed by GC × GC-ToF-MS for screening VOCs in water. A TD unit coupled to a PTV injector was used to deliver VOCs previously extracted and preconcentrated on a Tenax trap into the 2D-GC system. Different operating conditions (i.e., incubation temperature, trap temperature, purge volume, purge flow, transfer heater and sodium-chloride concentration) were optimized to achieve high extraction efficiencies and to increase sensitivity in the analysis of traces of target (non-halogenated, mono-, di-, tri- and tetra-halogenated) VOCs. Optimal parameters are shown in Table 2. In addition to the enhanced separation provided by 2D-GC and the usefulness of data gathered using a ToF-MS analyzer for positive identification of VOCs, combination of both D-HS sampling and GC × GC allowed quantitation of these compounds at the parts per trillion level, with no matrix interferences and with minimum sample preparation in the different waters under study (drinking tap-water and bottled water, river and sea water). Additional advantages such as good linearity and intra- and inter-day reproducibility also made this method suitable for routine analysis.

Although GC-MS is the most extensive technique used for HS analysis, P&T systems have also been coupled to GC with detectors other than MS and have even been used in combination with other chromatographic techniques (e.g., ion chromatography) [72]. Pietilä et al. [62] developed an ethylation-P&T with an isotope-dilution GC-ICP-MS method for the determination of low methyl mercury (CH_3Hg^+) concentrations in humic-rich natural waters. Prior to the analytical determination, samples were subjected to N_2-assisted distillation for separation of CH_3Hg^+ from the interfering matrix and to achieve a low LOD. This sensitive, reproducible methodology, validated with an EPA reference method for accuracy, was found to be reliable for investigating the potential consequences of forest-harvesting practices on biogeochemical cycles and leaching of mercury to natural surface waters.

In the search for a sensitive, effective extraction method for the determination of off-flavors in different environmental samples, Deng et al. [64] developed a rapid, flexible microwave-assisted P&T extraction (MAPTE) device, coupled on-line to GC-MS, for simultaneously determining five predominant odors (dimethyltrisulfide, 2-methylisoborneol, geosmin, β-cyclocitral and β-ionone) in samples of sediment, fish tissue and algal cells. In this easy-to-use extraction/preconcentration device, the rapid heating and large sample throughput provided by microwave-assisted extraction (MAE) is well complemented with the

advantages of P&T as a solvent-free technique, with no matrix interferences and with excellent performance for the extraction of odors. Results obtained in the validation of the method developed (i.e., good linearity and repeatability, and low LODs) proved its potential as a standard methodology for analysis of off-flavors in a variety of environmental matrices.

2.2.4.3. Other samples. P&T sampling, in combination with chromatographic techniques, has also been successfully applied to the analysis of other sample matrices {e.g., APIs [47], urine and blood [65], fecal samples [66]} (Table 2).

2.3. Multi-step headspace extraction (MHE)

In a study by Soria et al. [44] on the volatile composition of honeys determined by P&T-GC-MS (Table 2), performance of six mathematical models applied to data obtained in 2–8 P&T steps was evaluated in terms of fit quality and recovery (R) estimation. Results obtained showed that optimal model depended on the type of compound and that, for those few volatiles for which an approximately constant volatile amount was extracted after the initial P&T steps, estimation of R and C_o was impossible from multistep strategies.

In a similar MHE approach, Ruiz-Bevia et al. [60] studied the purge efficiency in the determination by P&T-GC-MS of trihalomethanes (THMs) present in a wide range of concentrations in water samples. Whereas the least volatile compound, $CHBr_3$, required 7–19 cycles (depending on sample concentration) to be purged quantitatively, $CHCl_3$, the most volatile compound, required only 2–4 extractions. Moreover, it was also concluded that, by applying Novak's model together with Arrhenius-type equations, recovery can be predicted in a purging system under fixed conditions of temperature (T) and sample volume (V_L) if some previous experimental data for other T and V_L are available.

Quantitation of VOCs in solid samples of very different natures {e.g., wheat breadcrumbs [73] and roasted coffee [74]} by MHE approaches has also been described. San Román et al. [8] evaluated MHE for the determination of VOCs responsible for mushroom aroma. Two different HS-injection techniques (pressure-loop system and gas-tight-syringe autosampling system) and HS-SPME were compared. Although the three methods were effective for the analysis of VOCs, HS-SPME offered better results in terms of sensitivity and precision; however, a shorter linear concentration range was obtained. Furthermore, MHE–SPME was found to be the most suitable technique to avoid the matrix effect and to obtain acceptable quantitative results for samples of mushrooms.

Other less common applications of MHE approaches included physicochemical studies. For example, Chai et al. [75] reported a simplified MHE-GC method for the determination of solubility of vinylic monomers in water. In this study, the vapor of the two-phase mixture of monomers and water placed in a closed vial was replaced with inert gas to remove the excess of monomer gradually, till the monomer was no longer present as a separate phase. After application of selected models to corresponding GC data, values for monomer saturation in water could be determined.

2.4. HS-MS

Non-separative approaches based on the direct coupling of a mass spectrometer to S-HS or D-HS extraction, in combination with chemometrics, are gaining increasing importance for the development of fast, economical methods for classification of samples, in particular for QC in the food field [76]. In this sort of strategy, volatile compounds present in the HS of a sample are directly introduced into the ionization source of the MS system. The spectrum thus obtained, resulting from ionization and fragmentation of these volatiles, can be considered a representative "fingerprint" of the sample being analyzed and can be used for classification purposes. The reliability of modern MS systems and the ongoing development of new data-handling strategies, most derived from metabolomics (fingerprinting and profiling), are also contributing to extend use of these "MS-based sensors" or "HS-MS electronic noses" in different fields.

A number of papers have described the development and the application of HS-MS methodologies for QC of olive oils. For example, Peña et al. [77] applied multivariate regression techniques (PLS and PCA) to the sample fingerprints obtained by HS-MS analysis with the aim of generating regression models to detect and to quantify adulteration of virgin olive oils and olive oils with hazelnut oil. The LODs obtained by this method (7% and 15% in refined and virgin olive oils, respectively) were enough to allow the detection of adulterations in commercial olive oils.

Similarly, in a further study, the same authors [78] addressed the usefulness of the HS-MS for evaluating the sensory quality of samples of virgin olive oils. After a training step with oils previously classified according to the official methodology, soft independent modeling of class analogy (SIMCA) was used to create a classification model. Moreover, application of cluster analysis to oil fingerprints allowed discrimination among samples with different negative attributes. The results from this procedure showed an acceptable correlation with those by the expert panel for classification of commercial extra or lampante virgin olive oils.

Cozzolino et al. [79] reported the potential of a HS-MS electronic nose instrument, in combination with chemometrics, for rapid, unbiased prediction of aroma properties (honey, lemon, passion fruit, estery, perfumed floral and stewed apple) in Australian Riesling wine. Although advantageous for the rapid screening of wines before sensory analysis, this methodology lacked the possibility of identification and quantitation of individual compounds responsible for the different aroma notes.

In a study by Gamboa-Santos et al. [80], MS fingerprints gathered by a Headspace ChemSensor system, together with data on vitamin C content and sensorial properties, were evaluated for air-dried carrots previously subjected to different ultrasound (US) or conventional blanching pretreatments. Carrots conventionally blanched at high temperature for a short time showed the highest retention of vitamin C. US-blanched carrots showed an acceptable organoleptic quality similar to that of samples processed by conventional methods. Statistical analysis of MS fingerprints allowed differentiation of carrots with a similar composition and/or blanching treatment, even when indistinguishable by a taste panel of semi-trained judges.

HS analysis of biological samples in combination with computational tools has also been applied for identification of bacteria in biological samples, such as blood [81]. Different data-reduction and pattern-recognition techniques were evaluated to optimize sample classification from data collected using a mass sensor. Thus, combination of Sammon mapping with a radial basis function neural network gave a 100% successful classification rate. These promising results highlight that data-set dimensional reduction via computational methods would be worth considering for rapid medical diagnosis.

As an example of HS-MS approaches in the environmental field, a method for the rapid determination of the total THM index in drinking water was developed by Serrano and Gallego [82]. Once selected ascorbic acid as optimal quenching agent to avoid THM generation from residual chlorine and organic matter during sample manipulation of water, the use of SIMCA before PLS multivariate regression decreased the relative standard error of prediction in estimating the THM index. The results obtained by this fast, straightforward HS-MS method were successfully validated with those provided by a conventional HS-GC-MS method in the analysis of 20 drinking-water samples.

Other approaches based on the use of membrane-introduction MS (MIMS) have also been reported to allow the analysis of VOCs and semi-VOCs mainly from aqueous matrices. These compounds

were fractionated from water by a thin membrane (typically of polydimethylsiloxane) installed between the sample and the ion source of an MS system. Analytes diffused through this membrane and were directly evaporated into the ion source [83]. The combination of both techniques in HS-MIMS resulted in a direct, solvent-free, selective, sensitive method, particularly for wet solid samples, which could also be applied to on-site monitoring of volatiles [84].

3. Conclusions and future trends

The increasing number of developments and applications related to HS techniques in recent years has demonstrated their consolidated potential for routine volatile analysis in different fields. The requirement to avoid organic solvents makes HS sampling advantageous over other traditional methods based on solvent extraction, for the development of green procedures aimed at the analysis of volatile compounds in samples of different natures. Among other strengths, S-HS methods allow sampling of very volatile compounds, otherwise with overlapping solvent peak, and avoid artifacts associated with non-volatile matrix components with a similar polarity to that of the extraction solvent. Moreover, S-HS is a simple, non-destructive technique, so the same sample can be extracted many times in MHE approaches.

The limited sensitivity and the discrimination towards the extraction of not very volatile compounds are generally considered as the main limitations of S-HS methods. D-HS sampling combines the advantages of S-HS with higher sensitivity, especially for extraction of high-volatility compounds. The higher recovery is due to the shift of thermodynamic equilibrium towards the gas phase above the sample, the use of a larger volume of extractant gas phase and the whole volatile fraction extracted being transferred into the GC instrument. Furthermore, sensitivity can be modulated by optimizing the large number of parameters involved in D-HS sampling. This flexibility requires more complex instrumentation and makes maintenance more difficult. However, the availability of automated instrumentation, in which volatile sampling and GC analysis can be carried out simultaneously, has promoted the use of this technique for high-throughput, reproducible analysis of a variety of samples. For example, different standard protocols (e.g., US EPA) rely on the use of the P&T technique for analysis of volatile organic compounds in water.

Regarding both S-HS and D-HS instrumentation, the most recent advances are generally aimed at the development of miniaturized systems or devices for faster, more sensitive determinations. However, their use is still limited and is far from general implementation for routine analysis. The same applies to the large number of applications describing the coupling of HS sampling to 2D-GC techniques that have emerged in the past decade. We expect that the ongoing progress on data handling and quantitation in GC × GC will shortly contribute to exploit fully the potential of coupling both techniques for the analysis of complex mixtures of volatiles in real samples.

Finally, and in line with the current development of non-separative methods and of data-handling strategies, we expect that HS-MS methodologies will continue to be developed for rapid, unbiased sample characterization and classification for different purposes.

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